2015

SWEDRES | SVARM

Consumption of antibiotics and occurrence of antibiotic resistance in Sweden

Folkhälsomyndigheten
PUBLIC HEALTH AGENCY OF SWEDEN

SVA NATIONAL VETERINARY INSTITUTE

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

Published by:

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Suggested citation:

Swedres-Svarm 2015. Consumption of antibiotics and occurrence of antibiotic resistance in Sweden. Solna/Uppsala ISSN 1650-6332

Print & Layout: Åtta.45 Tryckeri

Cover by Ingvar Westerdahl/Thomas Isaksson

ISSN 1650-6332
ISBN 978-91-7603-546-7 (pdf)
ISBN 978-91-7603-547-4 (print)
Article no. at Folkhälsomyndigheten 15099

This title and previous Swedres and Svarm reports are available for downloading at www.folkhalsomyndigheten.se/publicerat-material/ or www.sva.se.

The title can also be ordered from the webshop at: www.folkhalsomyndigheten.se/publicerat-material/ or Department of Animal Health and Antimicrobial Strategies, National Veterinary Institute, SE-751 89 Uppsala, Sweden
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Preface

This 2015 Swedish report from the monitoring of antibiotic resistance and antibiotic consumption in human and veterinary medicine, Swedres-Svarm, is an integrated report from the Public Health Agency of Sweden and the National Veterinary Institute with data from humans, animals, and food. The data from public health, human and veterinary medicine have been jointly published in Swedres-Svarm since 2002, and data from the sectors have been fully integrated under common sections in the report since 2012.

The importance of a 'One Health' approach is being acknowledged internationally, and awareness of the urgency of jointly dealing with antibiotic resistance and health care-associated infections is increasing.

A good example of international collaboration is the development of the Global Antimicrobial Resistance Surveillance System (GLASS) by the World Health Organization with support from Sweden. Early implementation of the system has recently started in several countries worldwide, including Sweden. In addition, the Unit for Antibiotics and Infection Control at the Public Health Agency of Sweden has recently been designated as a WHO Collaborating Centre for antimicrobial resistance containment with the assignment to further support development and implementation of GLASS and support capacity building in the WHO Member States.

A new national strategy for Sweden regarding antibiotic resistance was approved by the government in April this year. A 'One Health' approach is emphasized, as well as the importance of strengthened surveillance, effective preventive measures, responsible use of antibiotics, increased knowledge and development of new antibiotics, and diagnostic methods as well as other strategies for combating antibiotic resistance. Also, increased knowledge of antibiotics, resistance and countermeasures in society, governance, supporting structures and systems, and international collaboration are stressed. A national coordinating mechanism for governmental authorities will be important in implementing this strategy. This group is led by the Public Health Agency of Sweden in collaboration with the Swedish Board of Agriculture, and is comprised of representatives from 23 governmental authorities and organizations.

Although the current situation in Sweden, in both the public health and veterinary sectors, is favorable from a global perspective, this year's report shows trends of concern in human medicine both for methicillin-resistant Staphylococcus aureus (MRSA) and for carbapenem-resistant Enterobacteriaceae. In part, these trends can be explained by the increased number of refugees who arrived in Sweden last year. Of more concern, though, is the increasing risk in general of introduction and spread of carbapenem- resistant or extended spectrum beta-lactamase (ESBL) producing Enterobacteriaceae, in high-risk health care departments, such as neonatal intensive care. Efforts to prevent or reduce the consequences of these risks need to be prioritized.

In the veterinary sector, MRSA is rare in both farm and companion animals, and carbapenem-resistant Enterobacteriaceae has not been reported.

Finally, we would like to thank Barbro Olsson-Liljequist, who has contributed to this report since it was first published in 2001. She has worked within this field for more than thirty years, and she will share some historical perspectives in this edition of Swedres-Svarm.

Solna and Uppsala 2016-06-14

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Acknowledgements

The analyses of the antibiotic consumption was made in close collaboration with the external group of antibiotic sales data of the Public Health Agency of Sweden: Ingrid Brännström, Jonatan Dahlqvist, Mats Erntell, Annika Hahlin, Mikael Hoffmann and Anastasia Nyman.

Data on antibiotic use in relation to number of admissions and number of patient days in somatic hospital care during 2010-2015 were kindly provided by pharmacists in local Strama-groups. Strama collaboration group of the Public Health Agency of Sweden.

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

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

Kerstin Ortman and Hanna Arosenius at Eurofins Food & Agro, Skara who kindly provided SVA with clinical isolates and susceptibility results from clinical submissions from animals.

Lotta Persson, Sofie Jonasson and Eva Fallström for kindly providing samples from wild hedgehogs.

The National Food Administration for collecting samples of intestinal content from healty animals at slaughter for the studies of indicator bacteria.

Environmental departments in several municipalites for collecting samples of fresh meat from retail for ESBL-screening.

Content

Sammanfattning/Summary

Sammanfattning

När det gäller antibiotikaresistens hos bakterier från människor och djur har Sverige fortfarande en gynnsam situation, ur ett internationellt perspektiv. Detta stöder att vi har effektiva strategier för att främja rationell användning av antibiotika och begränsa spridningen av antibiotikaresistens. Trots det ökar de flesta typer av resistens som övervakas. Den trenden har pågått sedan den nationella övervakningen startade i slutet av 90-talet.

De viktigaste resultaten i årets rapport är en kraftig ökning av MRSA och fler fall av $ESBL_{CARBA}$ hos människor. Ökningen av MRSA är associerad med det stora antalet människor på flykt som togs emot under 2015. Ökningen av $ESBL_{CARBA}$ bedöms dock som mer oroande eftersom det ökar risken för att resistenstypen ska introduceras bland känsliga patienter, till exempel på neonatalavdelningar, vilket kan få allvarliga konsekvenser. Ökningen av MRSA har inte lett till någon ökad smittspridning på sjukhus och framtida risk för detta bedöms som liten. MRSA är ovanliga hos såväl lantbrukets djur som hos sällskapsdjur och $ESBL_{CARBA}$ har inte påvisats.

Förbrukning av antibiotika

Antibiotikaförbrukning inom humanmedicin

Den totala antibiotikaförsäljningen (öppenvård och slutenvård) minskade med 1,3 procent (från 12,8 till 12,6 DDD per tusen invånare och dag) under 2015 jämfört med 2014.

Öppenvård

I öppenvården (inkluderar all antibiotika försålt på recept) minskade försäljningen med 1,6 procent, från 328 till 323 recept per tusen invånare och år. Minskningen sågs i alla åldersgrupper förutom i åldersgruppen 65 år och äldre där försäljningen låg kvar på samma nivå som under 2014.

Antibiotikaförsäljningen minskade i 15 av 21 län. Skillnaden mellan länen är stor: från 352 recept per tusen invånare och år i Stockholm till 252 i Västerbotten. Minskningen omfattade de flesta antibiotikagrupper med undantag för två urinvägsantibiotika, pivmecillinam och nitrofurantoin, samt för penicillin med klavulansyra. Betalaktamaskänsliga penicilliner tillsammans med tetracykliner var de antibiotika som förskrevs mest på recept under 2015.

Antibiotika som ofta används mot luftvägsinfektioner (LVI) är den grupp som försäljs mest på recept, och under 2015 minskade försäljningen med 1,6 procent.

Behandlingen av nedre urinvägsinfektioner (UVI) hos kvinnor ser ut att följa de nationella behandlingsrekommendationerna. Under 2015 minskade den totala försäljningen av UVI-antibiotika till kvinnor 18–79 år något (1,9 procent) jämfört med 2014. Under året fortsatte också den positiva trend som setts under de senaste åren med en ökad försäljning av förstahandspreparaten pivmecillinam och nitrofurantoin, i stället för de breda och mer resistansdrivande preparaten trimetoprim och fluorokinoloner.

Fluorokinoloner är fortfarande det preparat som används mest bland UVI-antibiotika till män i åldersgruppen 65 år och äldre. Under 2015 fortsatte denna försäljning att minska med 3,0 procent jämfört med året innan medan försäljningen av pivmecillinam och nitrofurantoin ökade (13,2 respektive 0,6 procent).

Försäljningen av antibiotika som är förskrivet av tandläkare står för 6 procent av totala antibiotikaförsäljningen på recept. Under 2015 minskade försäljningen med 3,0 procent jämfört med 2014, från 23,6 till 22,9 recept per tusen invånare och år (J01 inklusive metronidazol P01AB01).

Slutenvård

Den totala antibiotikaförbrukningen på svenska sjukhus låg under 2015 kvar på samma nivå som 2014 (mätt som DDD per hundra vårddagar och DDD per hundra vårdtillfällen). Under de senaste åren har användningen av penicilliner med betalaktamashämmare ökat kraftigt och 2015 var ökningen 8,4 procent jämfört med året innan. Användningen av karbapenemer har ökat marginellt. Karbapenemer och piperacillin med tazobaktam används också oftare och det kan bero på att fler infektioner är orsakade av bakterier med ESBL (extended spectrum betalaktamases). Sett över en längre tid har försäljningen av antibiotika på slutenvårdsrekvisition (alla sjukhus inklusive viss förbrukning inom äldreboenden och andra vårdenheter) gått från en hög användning av breda preparat till främst smala antibiotikaterapier. Sedan 2008 är betalaktamasresistenta penicilliner (J01CF) och betalaktamaskänsliga penicilliner (J01CE) de antibiotikagrupper som försäljs mest på slutenvårdsrekvisition.

Antibiotikaförbrukning inom veterinärmedicin

Efter omregleringen av apoteksmarknaden 2009 finns indikationer på ett visst bortfall i statistiken över försäljning av antibiotika för djur. Bortfallet berör troligen främst läkemedel för injektion, men då dessa utgör minst 70 procent av den totala förbrukningen kan trender från 2010 inte fullt ut bedömas.

Den rapporterade försäljningen av antibiotika för djur uppgick 2015 till 10 468 kilogram. Motsvarande siffra för 2010 var 14 117 kilogram. Den totala förbrukningen av antibiotika för djur har minskat sedan mitten av nittiotalet, och det är troligt att det är en sann minskning även från 2010. Cirka 55 procent av försäljningen 2015 var bensylpenicillin.

Läkemedel för medicinering av enskilda djur via munnen och för medicinering av grupper av djur via foder och vatten påverkas troligen inte nämnvärt av problemen med bortfall av data. En påtaglig nedåtgående trend ses mellan 2010 och 2015 för båda dessa typer av antibiotikaprodukter (35 respektive 41 procent) och för flertalet antibiotikaklasser.

Jämförelse av försäljning inom human- och veterinärmedicin

Under 2015 såldes 61,2 och 10,2 ton antibiotika inom human- respektive veterinärmedicin (exklusive intrammammarier). Mätt som milligram aktiv substans per skattad kilogram biomassa var förbrukningen 94,4 respektive 12,7 milligram per kilogram. Försäljning inom humanmedicin dominerade för alla antibiotikaklasser utom trimetoprim-sulfa och aminoglykosider.

Anmälningspliktig resistens

ESBL-producerande Enterobacteriaceae

År 2015 rapporterades totalt 9 584 fall av Enterobacteriaceae med betalaktamaser med utvidgat spektrum (ESBL) hos människa, vilket var en ökning med 8 procent jämfört med året innan. Ökningen sågs i 17 av 21 län och regioner, och som tidigare år var Escherichia coli den vanligaste arten och förekom i 86 procent av fallen. Klebsiella pneumoniae var näst vanligast med 9 procent. De flesta fynden av ESBL gjordes i urinprov. År 2015 anmäldes 578 fall av invasiva infektioner med ESBL-producerande bakterier, jämfört med 520 året innan.

ESBL-typen $ESBL_{CARBA}$ är även resistent mot karbapenemer, och bakterier med denna resistens blev under 2012 anmälningspliktiga för både den behandlande läkaren och laboratoriet som gör fyndet. Totalt 115 nya fall upptäcktes 2015 (46 2014), och de två vanligaste enzymtyperna var OXA-48 och NDM. Under året inträffade en inhemsk smittspridning på en neonatalavdelning med nio fall, och ytterligare en smittspridning på ett sjukhus där tre personer var inblandade. Dessa extremt resistenta bakterier är hittills ovanliga i Sverige men det är mycket viktigt att upptäcka dem tidigt och förhindra spridningen inom vården, eftersom det finns få eller inga behandlingsalternativ vid en eventuell infektion.

Bakterier som bildar ESBL är ovanliga hos djur i Sverige, med undantag för slaktkycklingar. Under 2015 undersöktes förekomsten av ESBL-bildande E. coli i tarm- och köttprov från gris och nötkreatur samt i tarmprov från slaktkyckling. Sådana bakterier hittades i 1 procent av tarmproven från gris respektive nöt men inte i några av köttproven. Förekomsten hos slaktkyckling är dock högre och ESBL-bildande E. coli isolerades från 39 procent av tarmproven. Förändringar i odlingsmetoden gör dock att denna siffra inte kan jämföras direkt med tidigare års uppgifter.

MRSA

Totalt anmäldes 3 882 nya fall hos människa av meticillinresistenta Staphylococcus aureus (MRSA) 2015, vilket är en ökning med 33 procent från året innan. Ökningen beror till stor del på det stora antalet asylsökande som tagits emot och förklaras av att många kommer från länder med en högre förekomst av MRSA än genomsnittet i Sverige, men också av att de provtas oftare än övriga befolkningen eftersom de har fler kontakter med sjukvården. Flera län eller regioner provtar också asylsökande rutinmässigt för multiresistenta bakterier i samband med hälsoundersökning och vård på sjukhus.

En knapp majoritet av alla MRSA fall var smittade utomlands. Samhällsförvärvad smitta var vanligare bland de inhemskt smittade fallen (75 procent) än bland de utomlands smittade (48 procent), medan sjukhusförvärvad smitta var vanligare bland importerade fall (19 procent) än bland inhemska (6 procent). Invasiva infektioner med MRSA rapporterades hos 36 personer under 2015.

Förekomsten av MRSA hos djur i Sverige är fortfarande låg vilket begränsar risken för spridning till människor. Under året isolerades MRSA sporadiskt från djurslagen häst, hund, katt och nötkreatur. Hos en stor del av undersökta igelkottar i en screeningstudie påvisades MRSA med *mecC*. Hos hundar och katter dominerar samma typer av MRSA som hos människor, vilket tyder på att människor är smittkällan. Hos hästar är lantbruksdjurstypen MRSA CC398 vanligast.

MRSP

Under 2015 skedde en ökning av anmälda fall av meticillinresistenta Staphylococcus pseudintermedius (MRSP) hos djur. Totalt anmäldes 60 fall av MRSP vilket kan jämföras med 39 fall 2014 och 33 fall 2013. Därmed har ett trendbrott skett då antalet fall som årligen anmäls tidigare har minskat från rekordåret 2009 då 130 fall anmäldes. Antalet fall har länge varit kopplat till framförallt en specifik klon, den såkallade ST71-t02-SCCmecII-III, och den tidigare nedåtgående trenden verkar framförallt ha varit kopplad till minskad förekomst av denna klon. Det verkar nu som en ny variant av MRSP tillhörande ST258 står för ökningen då den utgjorde 33 procent (ST71 utgjorde ca 32 procent) av alla anmälda fall under 2015 från att tidigare endast ha förekommit sporadiskt.

MRSP är inte anmälningspliktig vid förekomst hos människa.

PNSP

År 2012 förändrades definitionen för anmälningsplikt av Streptococcus pneumoniae med nedsatt känslighet för penicillin (PNSP) hos människa till att gälla enbart isolat med MIC av penicillin som är större än 1 milligram per liter. Detta har medfört en kraftig minskning av antalet anmälda fall och 2015 anmäldes totalt 59 fall.

VRE

År 2015 anmäldes 157 nya fall av vankomycinresistenta enterokocker (VRE) hos människa, och 2014 anmäldes 402 fall varav över hälften tillhörde ett utbrott i Gävleborg. Merparten av isolaten 2015 var Enterococcus faecium, och i motsats till 2014 är nu vanA -genen (95 fall) vanligare än vanB-genen (39 fall). Totalt 12 sjukvårdsrelaterade utbrott rapporterades under året i nio län, alla med E. faecium, varav 9 med vanA och 3 med vanB. Endast en invasiv infektion med VRE rapporterades under 2015.

Förekomsten av VRE hos slaktkyckling har minskat signifikant sedan 2010 när senaste undersökningen gjordes. Under 2015 kunde VRE isoleras från elva procent av proven, alla var E. faecium med vanA.

Resistens hos zoonotiska smittämnen

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

Campylobacter-stammar från djur i Sverige är oftast känsliga för relevanta antibiotika och exempelvis är resistens mot erytromycin mycket ovanligt.

Vanligtvis behandlas inte infektioner orsakade av Salmonella eller Campylobacter med antibiotika, varken hos människor eller hos djur. Hos människa resistensbestäms därför endast en liten andel av isolaten, varav de flesta gäller allvarliga infektioner. Se vidare avsnittet ”Zoonotiska aspekter” för respektive bakterie.

Resistens hos kliniska isolat från människor

Arton laboratorier rapporterade endast data efterfrågade av EARS-Net, och tio rapporterade alla blododlingsfynd. Escherichia coli förekom i cirka 20 procent av de positiva blododlingarna och Staphylococcus aureus i 10 procent. De övriga sex bakteriearterna som ingår i övervakningen utgjorde en avsevärt mindre andel av fynden. Hos E. coli och Klebsiella pneumoniae har andelen cefalosporinresistenta (till största delen orsakad av ESBL-produktion) isolat ökat varje år och uppgick till 6 respektive 4 procent 2015. Andelen MRSA av drygt 3 500 rapporterade fall av S. aureus var mindre än en procent, vilket är lågt ur ett europeiskt perspektiv. Inga Enterococcus faecium eller Enterococcus faecalis rapporterades som resistenta mot vankomycin i EARS-Net-övervakningen 2015. Andelen PNSP av de knappt 900 fallen av S. pneumoniae var 7 procent.

I ResNet, ett övervakningsprogram för andra provtyper än blod där samma bakteriearter (utom Acinetobacter spp) som i EARS-Net ingår, låg andelen resistenta bakterieisolat på likartade nivåer.

För vissa bakteriearter finns speciella övervakningsprogram och/eller speciallaboratorier som kan utföra analyserna. Det gäller dels Clostridium difficile, och dels bakteriearterna Neisseria gonorrhoeae, Neisseria meningitidis och Mycobacterium tuberculosis.

2015 anmäldes 7 112 fall med Clostridium difficile infektion, en ökning med 9 procent från föregående år. Inga isolat med nedsatt känslighet för metronidazol eller vankomycin, de viktigaste behandlingalternativen, hittades.

Under 2015 anmäldes 1 677 fall av gonorré. Resistens mot cefixime var som tidigare 2 procent och ingen resistens mot ceftriaxon påvisades. Det är mycket positivt eftersom ceftriaxone är det sista tillgängliga medlet för empirisk behandling av gonorré.

Resistens hos kliniska isolat från djur

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

Indikatorbakterier från friska djur

Resistens hos E. coli från tarmfloran hos friska djur kan användas som indikator för utbredningen av antibiotikaresistens hos bakteriefloran i en djurpopulation och indirekt på omfattningen av antibiotikaanvändning till djuren. I Sverige är förekomsten av resistens hos dessa indikatorbakterier låg hos de flesta undersökta djurslag och situationen är gynnsam i ett internationellt perspektiv. På senare år har dock en ökande trend setts vad det gäller resistens mot vissa antibiotikum bland E. coli från friska grisar.

Summary

The situation in Sweden regarding antibiotic resistance in bacteria from humans and animals is still favorable from an international perspective. This confirms that our strategies to promote rational use of antibiotics and to limit the spread of antibiotic resistance are effective. Despite this, most of the monitored types of antibiotic resistance are increasing. This trend has been going on since national surveillance began in the late 90s.

The key findings in this year's report is a sharp increase in MRSA and an increasing number of cases of $ESBL_{CARBA}$. The increase of MRSA is associated with the large number of refugees who have arrived during the year. The increase in $ESBL_{CARBA}$ is considered more worrying, though, as it increases the risk of introduction of $ESBL_{CARBA}$ among vulnerable patients, such as in neonatal units, which can have serious consequences. The increase in MRSA has not led to increased spread of infection in hospitals and future risk of this is considered small. In the veterinary sector, MRSA is rare in both farm and companion animals, and $ESBL_{CARBA}$ has not been reported.

Consumption of antibiotics

Antibiotic consumption in humans

The total consumption (including outpatient and hospital care) of antibiotics decreased by 1.3 percent in 2015 compared to 2014 (from 12.8 to 12.6 DDD per 1 000 inhabitants per day).

Outpatient care

In outpatient care (including prescription sales), antibiotic sales decreased by 1.6 percent, from 328 prescriptions per 1 000 inhabitants in 2014 to 323 prescriptions in 2015. This decrease was seen in all age groups except the elderly (65 years and older), in which the sales remained stable from the previous year. The decrease encompasses most antibiotic groups with the exception of nitrofurantoin, pivmecillinam, and combinations of penicillins.

Beta-lactamase–sensitive penicillins, along with tetracyclines, were the most commonly used antibiotics in outpatient care in 2015. Antibiotics commonly used to treat respiratory tract infections (RTIs) were the most frequently prescribed antibiotics. Among these substances, we also found the greatest decrease in sales over the years and during 2015 the sales continued to decrease by 1.6 percent.

In 2015, there was a decrease in the number of antibiotic prescriptions in 15 out of 21 counties. There are still significant regional differences within Sweden, and the number of prescriptions per 1 000 inhabitants ranges from 352 in Stockholm County to 252 in Västerbotten County.

Treatment of lower urinary tract infections (UTIs) in women appears to follow national treatment recommendations. In 2015, the total sale of antibiotics commonly used to treat UTIs in women aged 18–79 years slightly decreased (1.9 percent) compared to 2014. There was an increased usage of the recommended drugs pivmecillinam and nitrofurantoin and a reduction in the sale of trimethoprim (13.2 percent) and fluoroquinolones (0.6 percent).

The total sales of antibiotics commonly used to treat UTIs in men 65 years and older remained stable from 2014 to 2015 (152 prescriptions per 1 000 men per year). Fluoroquinolones are still the most commonly used antibiotics for treating UTIs in this population. During 2015, the sales of fluoroquinolones decreased by 3.0 percent compared to 2014 while the sales of pivmecillinam and nitrofurantoin increased by 11.1 percent and 7.9 percent (measured as prescriptions per 1 000 men per year).

The sales of J01 and metronidazole (P01AB01) prescribed by dentists decreased by 3.0 percent in 2015 compared to 2014 – from 23.6 to 22.9 prescriptions per 1 000 inhabitants.

Hospital care

The total consumption of antibiotics in Swedish acute care hospitals was at almost the same level in 2015 as in 2014, measured as DDD per 100 patient days and as DDD per 100 admissions. Penicillins with enzyme inhibitors have increased significantly in recent years, and carbapenems have increased marginally with these agents replacing the cephalosporins in many situations. In 2015, penicillins with enzyme inhibitors increased by 8.4 percent when measured as DDD per 100 patient-days compared to 2014. This increase is probably the result of an increased number of infections with ESBL (extended spectrum beta-lactamase)-producing bacteria. When analyzing the total antibiotic sales on requisition (consumption in all hospitals, including parts of nursing homes, and other care units) from 2000 to 2015, a clear shift from high use of broad-spectrum antibiotics to narrow-spectrum antibiotics can be seen.

Sales of antibiotics for animals

Until 2009, statistics on sales of antibiotics for animals was assumed to be complete. Since, the Swedish pharmacy market has been reregulated and there have been indications that the data on sales from Swedish pharmacies are less complete. This problem probably mainly affects the sales of antibiotics for parenteral use but as such drugs are at least 70% of the overall consumption the magnitude of overall trends from 2010 cannot be assessed with full certainty.

In 2015, the total reported sales of antibiotics for animals were 10 468 kg. In 2010, the corresponding figure was 14 117 kg. The overall consumption of antibiotics has decreased gradually since the mid-nineties, and there is most likely a true decrease also since 2010. About 55% of the total sales in 2015 were benzylpenicillin.

Products for oral medication of individual animals and oral medication of groups of animals via feed or water are less likely to be affected by the lack of completeness. Major downward trends are noted 2010 to 2015 for both these categories, (35 and 41%, respectively) and for most substance classes.

Comparing consumption of antibiotics in human and veterinary medicine

In 2015, a total of 61.2 and 10.2 tonnes of antibiotics were consumed in human and veterinary medicine (excluding intramammaries), respectively. When measured as mg active substance per kg estimated biomass, the corresponding figures were 94.4 and 12.7 mg per kg. Consumption in human medicine by far outweighs consumption in veterinary medicine for most classes, except for trimethoprim-sulphonamides and aminoglycosides.

Notifiable resistance

ESBL

A total of 9 584 human cases of extended spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae were reported in 2015, an increase of 8% compared to 2014, and increases occurred in 17 counties. The most commonly reported species was *Escherichia coli* with 86% of all cases followed by *Klebsiella pneumoniae* with 9%. Most ESBL-producing bacteria were found in urine samples (56%). Invasive infections with ESBL-producing bacteria increased from 520 cases in 2014 to 578 cases in 2015.

A special type of ESBLs, so-called $ESBL_{CARBA}$, is resistant to carbapenems as well as other classes of betalacam-antibiotics. Bacteria with this extended resistance mechanism became notifiable for both clinicians and laboratories in 2012. One hundred fifteen new cases were detected in 2015, and the two most common types of enzymes were OXA-48 and NDM. One domestic outbreak involving nine persons at a neonatal unit and a cluster with three persons at a hospital were reported in 2015. Because the treatment alternatives for these infections are few if any, it is necessary to have an active surveillance of these new and extremely resistant bacteria in order to detect them at an early stage and thereby hinder their spread within the health care system.

ESBL-producing Enterobacteriaceae are, with the exception of broilers, rare among animals in Sweden. In 2015, the occurrence of ESBL-producing *E. coli* in intestinal and meat samples from pigs and cattle and from intestinal samples from broilers was investigated with screening methods. Such bacteria were isolated from 1% of the intestinal samples from both pigs and cattle but not from any meat samples. The occurrence among broilers is higher and ESBL-producing *E. coli* was isolated from 39% of the intestinal samples. Changes in the screening methodology hinder any direct comparisons with the figures from previous years.

MRSA

The total number of human cases of methicillin-resistant *Staphylococcus aureus* (MRSA) was 3882 in 2015, an increase of 33% compared to 2014. This increase is mainly comprised of cases among persons seeking asylum, likely due both to a higher prevalence, increased need for medical care and increased sampling in this group. No increased spread of MRSA in hospitals has been reported in connection with this increase among persons seeking asylum, nor a progressive increase in domestic cases of MRSA in the general population. According to the systematically reviewed notification reports, a slight majority of the infections were acquired abroad. Community-acquired infections dominated among domestic cases (75%) but were less frequent among imported cases (48%). Hospital-acquired infections were comparatively more common in imported cases (19%) than among domestic cases (6%), indicating continued good compliance to basic hygiene principles among healthcare staff in Sweden. Thirty-six invasive isolates of MRSA were reported in 2015.

The occurrence of MRSA in animals in Sweden is still low which limits spread from animals to humans. MRSA was found sporadically in the animal species horse, dog, cat and cattle in 2014. In a major part of hedgehogs sampled in a screening study, was MRSA with *mecC* detected. In companion animals, the same types of MRSA as in humans dominate, indicating a human source of MRSA in these animals. In horses, livestock-associated MRSA CC398 is the most common type.

MRSP

In 2014 an increase of methicillin resistant *Staphylococcus pseudintermedius* (MRSP) cases was noticed for the first time since 2009. The increase of cases continued in 2015 with 60 cases notified all, except one case from a cat, where connected to dogs. It is also possible that a clonal shift of MRSP has occurred in Sweden. In 2015, 33% of all cases belonged to ST258, which only have occurred sporadically in the years before, while the previous dominant clone belonging to ST71 continued to decrease in occurence. MRSP in humans is not notifiable.

PNSP

In 2012, the definition for *Streptococcus pneumoniae* with reduced susceptibility to penicillin (PNSP) was changed to include only isolates with an MIC (minimal inhibitor concentration) of penicillin > 1 mg/L, and this resulted in a dramatic decrease in reported cases. A total of 59 new cases of PNSP were reported in 2015.

VRE

In 2015, a total of 157 new cases of vancomycin-resistant enterococci (VRE) were reported, which was a decrease compared to 2014 when 402 cases were reported. More than half of the cases 2014 were connected to a large outbreak in Gävleborg County. In 2015 most of the isolates were *Enterococcus faecium*, and in contrast to 2014 the resistance gene *vanA* was more common than the *vanB* gene. Twelve healthcare-related outbreaks were reported from nine counties, all with *E. faecium*, nine carrying the *vanA* gene and three carrying the *vanB* gene. One invasive VRE infection was reported in 2015.

Occurrence of VRE in broilers has decreased significantly since 2010 when the last investigation was done. In 2015, VRE could be isolated from 11% of the samples, and all were *E. faecium* with *vanA*.

Zoonotic pathogens

Salmonella is rare in animals in Sweden and few incidents involve antibiotic resistant strains. Strains with ESBL-resistance has never been found and resistance to fluoroquinolones is rare. Isolates from human invasive infections are markedly more resistant, which makes animals in Sweden an unlikely source for these infections.

Campylobacter from animals in Sweden are mostly susceptible and for example resistance to erythromycin is most uncommon.

Infections, either in humans or in animals, caused by *Salmonella* and *Campylobacter* are usually not treated with antibiotics. In humans, only a small proportion are tested for susceptibility, most of these isolates are related to serious infections. See the section "Zoonotic aspects" of each bacterium.

Human clinical isolates

EARS-Net surveillance

Eighteen laboratories reported only data requested by the EARS-Net, while 10 laboratories reported data on all positive blood cultures. *Escherichia coli* was the most frequently found pathogen in blood cultures at 20% followed by *Staphylococcus aureus* at 10%. The six other pathogens in the EARS-Net system were all much less frequently found. In *E. coli* and *K. pneumoniae*, the levels of resistance to third-generation cephalosporins had increased to 6 and 4%, respectively. MRSA isolates accounted for less than one percent of all invasive *S. aureus*, which is low from a European perspective. The rate of non-susceptibility to penicillins in *Streptococcus pneumoniae* (referred to as PNSP) was higher than in previous years at 7% in 2015.

In ResNet, a surveillance program for other sample types than blood where the same bacterial species as in EARS-Net are included, except *Acinetobacter* spp, the proportion of resistant bacterial isolates were at similar levels.

Other bacterial species are included in special surveillance programmes and are often referred to special laboratories, like *Clostridium difficile* and *Mycobacterium tuberculosis*, and *Neisseria gonorrhoeae* and *N. meningitidis*.

In 2015, 7 112 new CDI cases were reported corresponding to an incidence of 72 cases per 100 000 inhabitants, a reduction compared with 2014 of 9%.

No isolates with a decreased susceptibility against metronidazole or vancomycin were found in 2015.

In 2015, 1 677 cases of gonorrhea were reported. Resistance to cefixime remained at 2 percent and no resistance to ceftriaxone was detected. This is very positive because ceftriaxone is the last available agent for empirical treatment of gonorrhoea.

Animal clinical isolates

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

Indicator bacteria from healthy animals

Antibiotic resistance in *Escherichia coli* from the intestinal flora of healthy animals serve as indicator for presence of resistance in an animal population. Also, the prevalence of acquired resistance in such commensal bacteria indirectly indicates the magnitude of the selective pressure from use of antibiotics in an animal population. Prevalence of resistance in indicator bacteria from animals in Sweden is low and the situation is favorable in an international perspective. In the latest years there has however been an increasing trend regarding resistance against certain antibiotics among *E. coli* from healthy pigs.

Guidance for readers

The Swedres-Svarm report is the result of a cooperation between the Public Health Agency of Sweden and the National Veterinary Institute with the aim to present data relating to both humans and animals on the use of antibiotics and on antibiotic resistance in a joint report.

Data on occurrence of notifiable diseases caused by resistant bacteria as well as data on resistance in zoonotic bacteria and in bacteria from clinical submissions are presented. In addition, data on resistance in so called indicator bacteria from healthy animals and from food of animal origin are presented.

Data on resistance in bacteria from humans are obtained from several sources and national programs and compiled by the Public Health Agency of Sweden in Swedres. In contrast, data on animals and food, compiled by the National Veterinary Institute, are from the national monitoring program in the veterinary field Svarm. This program is specifically designed to monitor resistance in bacteria from animals and food and is organized and run at the National Veterinary Institute. Data in the veterinary field also emanate from other sources, such as the SvarmPat project and specific research projects. For details on data sources see Background material and references.

Embedded files in the PDF-file version of the report

To provide flexibility for those using the data for creating presentations the data from most of the tables and figures can now also be accessed from an embedded Excel-file. This new functionality has only been tested with Adobe Acrobat Reader. Embedded files are indicated with paper clips.

Antibiotic consumption

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

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

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

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

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

Antibiotic resistance

Swedres - Humans

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

Svarm - Animals and food

The vast majority of data on resistance in Svarm are from MIC determinations performed at the National Veterinary Institute using broth microdilution following the standards of the Clinical and Laboratory Standards Institute (CLSI, 2013). MICs for isolates of zoonotic and indicator bacteria are interpreted by ECOFFs from EUCAST (www.eucast.org) and also, clinical isolates from animals are classified by ECOFFs when such values are available. Interpretive criteria used are given in the section Materials and methods, resistance in bacteria from animals.

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

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

Indicator bacteria in animals

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

Presentation of MIC distributions in bacteria from animals

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

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

Multidrug resistance

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

Example of a table with MIC distributions

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

Abbreviations of generic antibiotic names

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

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

Abbreviations

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

Consumption of antibiotics

Total consumption of antibiotics in humans

In 2015, the total consumption of antibiotics (J01 excl. methenamine) in Sweden (outpatient care and hospital care) decreased by 1.3% compared with 2014 (12.8 to 12.6 DDD per 1 000 inhabitants and day). The total consumption differs within the country, from 14.1 per 1 000 inhabitants and day in Stockholm County to 10.4 in Jämtland County. The overall consumption in Sweden has decreased by 13% since 2000, from 14.5 to 12.6 DDD per 1 000 inhabitants and day, Figure 1.1.

Eighty-seven percent of all antibiotic consumption in Sweden 2015 were sold on prescriptions in outpatient care.

Beta-lactamase sensitive penicillins and tetracyclines were the two most used antibiotic classes in Sweden during 2015, Figure 1.2.

FIGURE 1.1. Consumption of antibiotics (J01 excl. methenamine) in outpatient care (sales on prescriptions) and in hospital care (sales on requisition including hospitals and parts of nursing homes) in Sweden and per county, 2000-2015, DDD/1 000 inhabitants and day. The data are sorted according to the consumption in 2015.

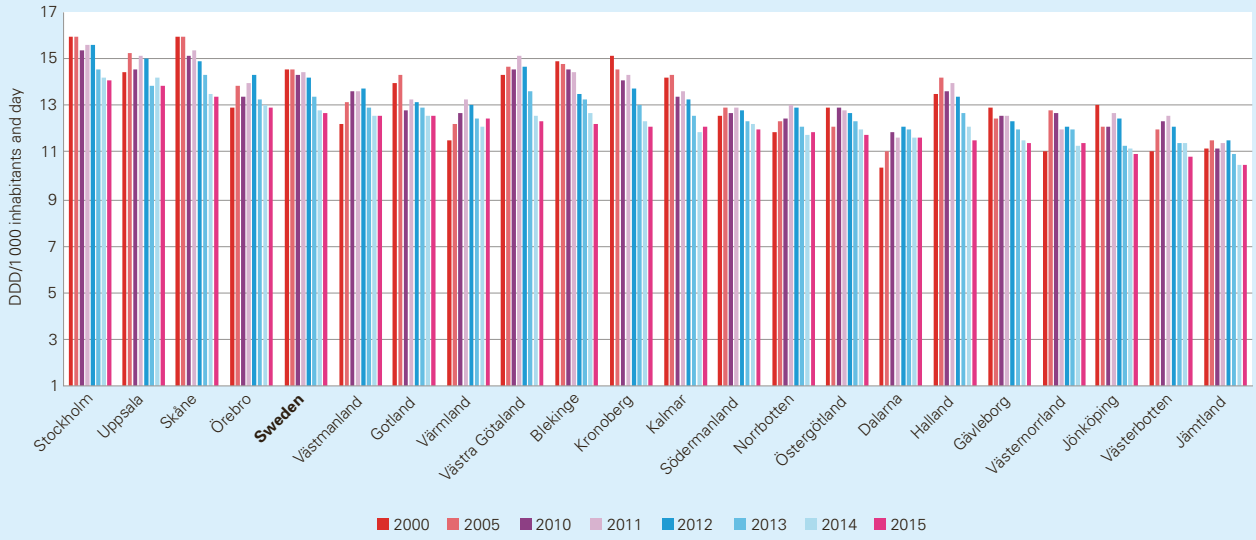
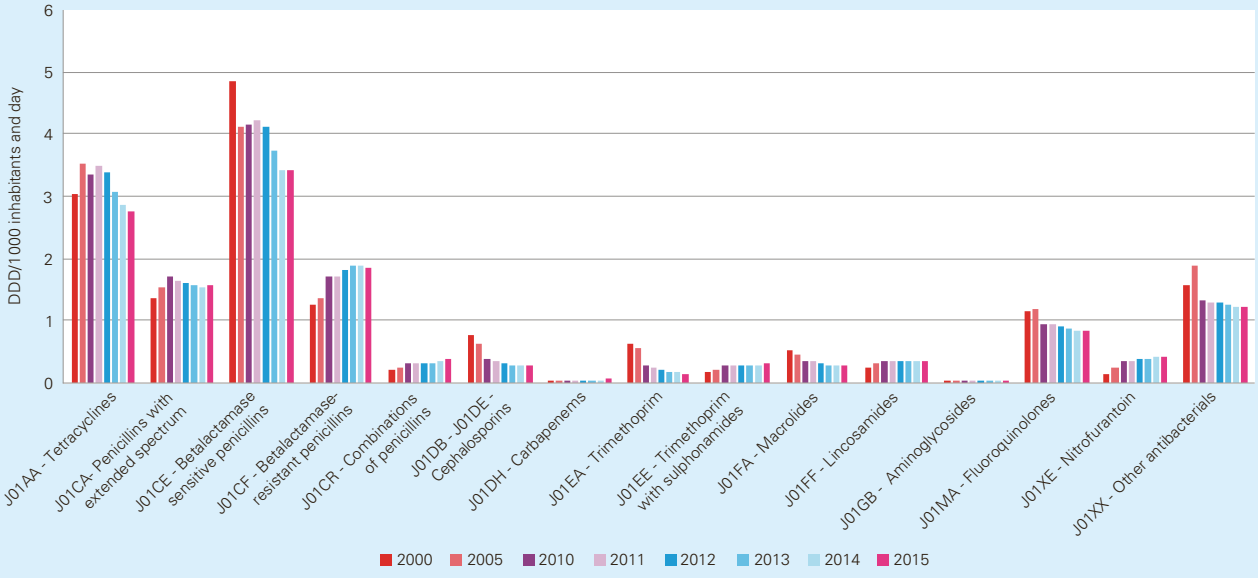


FIGURE 1.2. Antibiotics (ATC-5) in outpatient care (sales on prescriptions) and hospital care (sales on requisition including hospitals and parts of nursing homes) in 2000-2015, DDD/1 000 inhabitants and day.



Antibiotics in outpatient care

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

Sales of antibiotics in outpatient care has continued to decrease (1.6%) during 2015, from 328 in 2014 to 323 prescriptions per 1 000 inhabitants and year. The decrease in 2015 was seen in all age groups except the elderly (65 years and older) where the sales was stable at the same level as the year before, Figure 1.3.

Since 1992, the total sales of antibiotics on prescriptions has decreased by 42%. The greatest decrease during these years has been in the 0-4 years age group, where sales decreased by 74%, from 1328 in 1992 to 349 prescriptions per 1 000 inhabitants and year in 2015. In addition, less seasonal variation in sales of antibiotics is seen over the years. This also indicates a more rational consumption and less misuse of antibiotic for cold or flu.

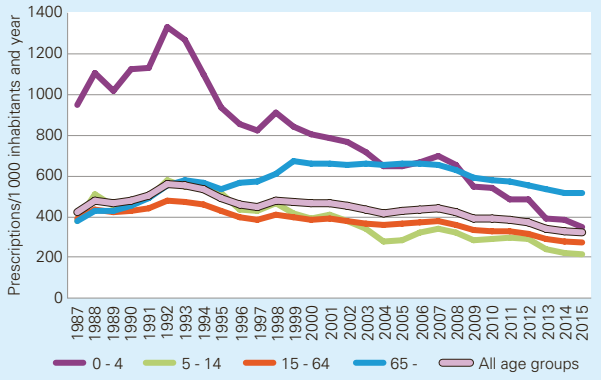
The age group 65 years and older has the highest use of antibiotics in Sweden, as measured by prescriptions per 1 000 inhabitants and year, Figure 1.3. As mentioned in the chapter "Guidance for readers", some of the antibiotic use among elderly people is not included in the statistics for outpatient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

The decrease in sales in outpatient care during 2015 encompasses all antibiotic groups except nitrofurantoin (J01XE), penicillins with enzyme inhibitor (J01CR) and pivmecillinam (J01CA08), Figure 1.4.

Beta-lactamase sensitive penicillins (J01CE) and tetracyclines (J01AA) were the most commonly sold antibiotics in 2015, Figure 1.4 and Table 1.1. Doxycycline (J01AA02) is the most frequently sold tetracycline and represents 73% of the sales in this group as measured by prescriptions per 1 000 inhabitants and year.

In summary, a decrease in the sales are seen in most age groups and in most of the antibiotic groups during 2015, Figure 1.4 and Table 1.1. The figures will be discussed further in the following chapters.

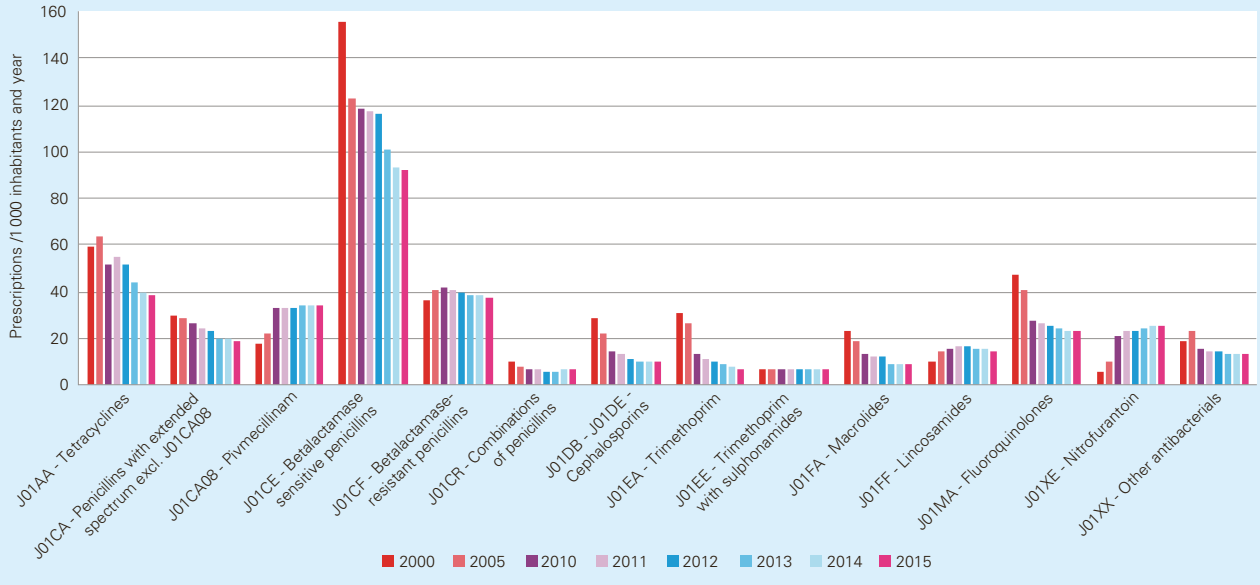
FIGURE 1.3. The sales of antibiotics for systemic use in out-patient care (sales on prescriptions) 1987-2015, prescriptions/1 000 inhabitants and year, both sexes, different age groups.



Gender differences

Out of all antibiotics prescribed in Sweden during 2015, 60% were prescribed to females and 40% to males. This proportion has almost been constant over time and the decrease in antibiotic sales during the last years has been seen in both sexes equally. During 2015, the antibiotic sales decreased by 2.0% to men and 1.7% to women. The greatest differences between genders occurred in the age groups 20-39 years (20-24, 25-29, 30-34 and 35-39). In these age groups 65-69% of the total antibiotic sales were to women, Figure 1.5. In these

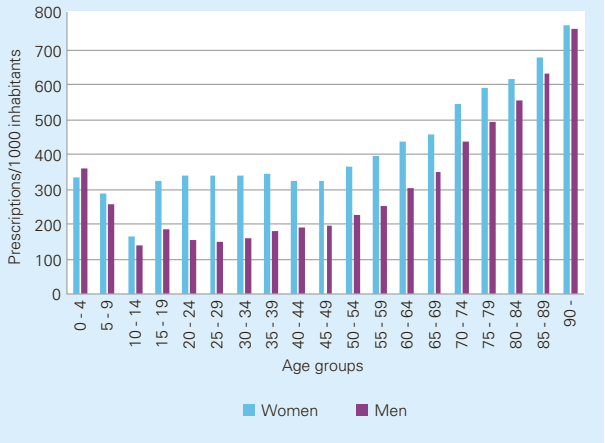
FIGURE 1.4. Sales of antibiotics in outpatient care (includes sales on prescriptions) 2000-2015, prescriptions/1 000 inhabitants and year, both sexes, all ages. The data are sorted according to ATC codes.



age groups the main differences is among antibiotics commonly used to treat urinary tract infections (UTI) which are predominantly sold to women.

In 2015, women were prescribed 383 antibiotic prescriptions/1 000 inhabitants and year while men were prescribed 254.

FIGURE 1.5. The sales of antibiotics for systemic use in out-patient care (sales on prescriptions) in 2015, prescriptions/1 000 inhabitants and year, gender and different age groups.

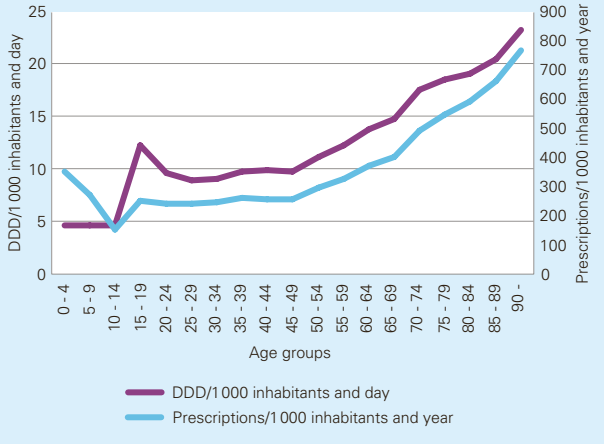


Antibiotics commonly used to treat respiratory tract infections, urinary tract infections and skin and soft tissue infections

Antibiotic sales in different age groups

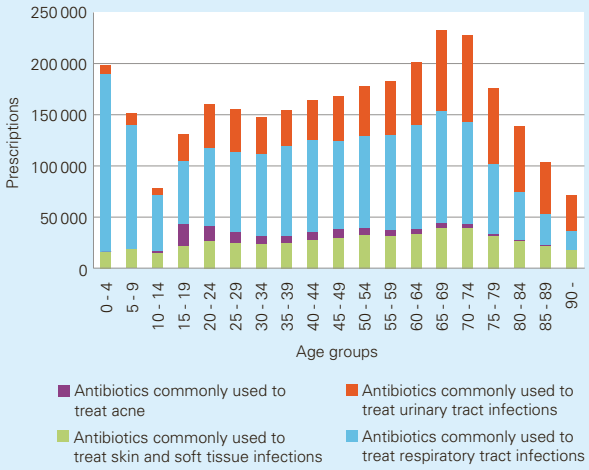
The antibiotic use is greatest in the age groups 65 years and older, both as measured by prescriptions/1 000 inhabitants and year and by DDD/1 000 inhabitants and day, Figure 1.6. However, even though the antibiotic use is high among children and elderly, other age groups represent a significant share of the total antibiotic sales, Figure 1.7.

FIGURE 1.6. Sales of antibiotics (J01 excl. methenamine) in outpatient care (sales on prescriptions) in different age groups. Measured by both prescriptions/1 000 inhabitants and year and as DDD/1 000 inhabitants and day, in 2015.



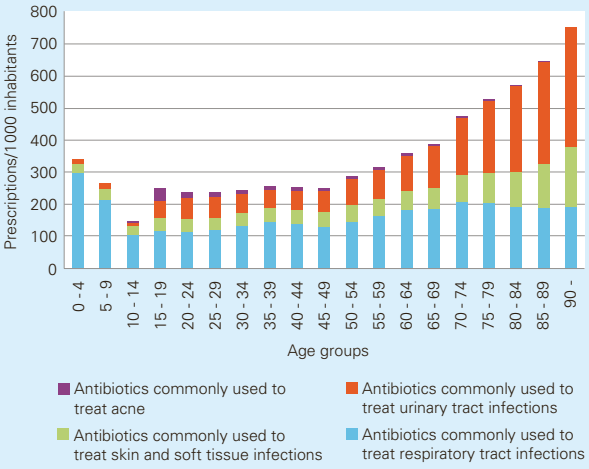
Figures 1.7 and 1.8 illustrate the sales of different antibiotics in different age groups. In children, antibiotics commonly used to treat respiratory tract infections (RTI) are the most frequently prescribed antibiotics and represents 90% of the total antibiotic sales. In the older age groups antibiotic commonly used to treat UTI are as common as antibiotics commonly used to treat RTI. In contrast, in the age group 15-19 years, antibiotics commonly used to treat acne represent a larger proportion. This kind of antibiotics are prescribed with long treatment duration, hence the peak seen in Figure 1.6 for this age group measured as DDD per 1 000 inhabitants and day.

FIGURE 1.7. Antibiotics commonly used to treat: respiratory tract infections (J01AA02[a], J01CE02, J01CA04, J01CR02, J01DB-DE and J01FA), urinary tract infections (J01CA08, J01EA01, J01MA02, J01MA06 and J01XE01), skin and soft tissue infections (J01FF01 and J01CF05), acne (J01AA02[b], J01AA04, J01AA06 and J01AA07), both sexes, different age groups, prescriptions in 2015.



[a] Excluding packages containing more than 50 tablets.
[b] Including packages containing more than 50 tablets.

FIGURE 1.8. Antibiotics commonly used to treat: respiratory tract infections (J01AA02[a], J01CE02, J01CA04, J01CR02, J01DB-DE and J01FA), urinary tract infections (J01CA08, J01EA01, J01MA02, J01MA06 and J01XE01), skin and soft tissue infections (J01FF01 and J01CF05), acne (J01AA02[b], J01AA04, J01AA06 and J01AA07), both sexes, different age groups, prescriptions/1 000 inhabitants in 2015.



[a] Excluding packages containing more than 50 tablets.
[b] Including packages containing more than 50 tablets.

TABLE 1.1. Antibiotics in outpatient care, classes of antibiotics and age groups. DDD/1 000 inhabitants and day, prescriptions/1 000 inhabitants and year and user/1 000 inhabitants and year.

Age groups (years)	DDD/1 000 and day								Prescriptions/1 000 and year								User/1 000 and year							
	2008	2009	2010	2011	2012	2013	2014	2015	2008	2009	2010	2011	2012	2013	2014	2015	2008	2009	2010	2011	2012	2013	2014	2015
Tetracyclines (J01AA)																								
0-6	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0
7-19	3.25	3.31	3.40	3.48	3.29	3.06	2.82	1.99	32.0	31.6	32.5	35.1	31.2	27.6	25.1	17.4	19.5	19.2	20.1	22.9	19.6	16.8	15.5	14.6
20-64	3.56	3.30	3.35	3.54	3.43	3.10	2.92	2.78	64.5	56.2	56.3	60.2	56.5	47.7	43.1	41.4	50.3	43.6	43.8	47.2	43.8	36.4	32.9	31.6
65-79	3.99	3.64	3.60	3.78	3.75	3.36	3.06	3.02	90.6	79.9	78.0	81.1	80.0	68.9	60.4	59.9	68.8	61.2	60.1	62.1	61.3	52.5	46.2	44.9
80-	2.77	2.43	2.32	2.35	2.41	2.15	1.97	2.06	71.7	62.2	58.6	58.8	59.8	52.5	45.7	48.0	57.1	49.7	46.8	47.2	47.7	41.9	36.3	38.4
All age groups	3.28	3.08	3.11	3.25	3.15	2.85	2.66	2.55	58.3	51.7	51.6	54.7	52.0	44.4	39.8	38.7	44.1	38.8	38.9	41.7	39.2	33.1	29.8	28.8
Penicillins with extended spectrum (J01CA) excl. Pivmecillinam (J01CA08)																								
0-6	1.70	1.52	1.62	1.35	1.32	1.07	1.08	1.04	90.8	72.7	73.3	59.1	54.9	43.8	43.7	42.3	69.0	56.5	57.4	45.3	42.1	33.6	33.5	30.3
7-19	0.43	0.39	0.43	0.43	0.37	0.32	0.31	0.32	13.6	11.8	12.4	12.0	10.1	8.5	8.2	8.5	11.7	10.1	10.6	10.1	8.3	6.9	6.7	6.4
20-64	0.82	0.72	0.73	0.69	0.64	0.59	0.56	0.55	20.6	18.2	18.0	16.9	15.4	13.9	13.2	13.1	17.4	15.4	15.3	14.1	12.6	11.2	10.5	10.2
65-79	1.75	1.67	1.62	1.59	1.55	1.50	1.44	1.45	45.0	41.7	40.2	38.7	37.0	34.3	32.4	32.6	35.8	32.8	31.9	30.6	29.2	26.8	25.2	24.6
80-	1.82	1.76	1.74	1.75	1.77	1.73	1.71	1.81	46.5	44.0	42.1	41.0	39.7	37.7	36.8	38.1	37.9	35.4	34.1	33.2	32.3	30.4	29.4	30.1
All age groups	1.01	0.93	0.94	0.89	0.85	0.79	0.76	0.76	30.5	26.9	26.9	24.4	22.7	20.1	19.3	19.0	23.9	21.1	21.1	19.3	17.7	15.6	15.0	14.5
Pivmecillinam (J01CA08)																								
0-6	0.01	0.01	0.02	0.01	0.01	0.01	0.01	0.01	0.7	0.8	1.1	1.0	1.0	1.0	1.0	0.8	0.6	0.8	1.0	1.0	0.9	0.9	1.0	1.0
7-19	0.24	0.24	0.24	0.22	0.21	0.20	0.20	0.13	15.5	16.1	15.9	15.7	14.4	13.8	13.4	9.2	13.5	13.9	13.9	13.5	12.5	12.0	11.7	10.9
20-64	0.45	0.45	0.46	0.45	0.44	0.46	0.48	0.47	27.8	28.2	28.6	29.2	28.7	29.5	29.8	29.4	23.2	23.6	24.0	24.3	23.8	24.3	24.6	24.1
65-79	0.98	0.98	0.97	0.95	0.93	0.98	1.00	1.01	57.7	57.9	57.5	58.7	57.3	59.3	59.5	59.4	44.1	43.7	43.3	44.0	42.8	44.0	44.2	43.1
80-	1.94	1.92	1.90	1.79	1.75	1.83	1.92	1.91	116.6	115.8	115.0	112.6	109.3	112.3	114.7	114.1	85.5	83.9	83.1	81.4	78.4	80.5	82.1	81.4
All age groups	0.53	0.54	0.53	0.52	0.51	0.53	0.55	0.55	32.2	32.8	33.0	33.5	32.8	33.7	34.0	33.7	25.8	26.0	26.2	26.4	25.7	26.3	26.5	26.0
Beta-lactamase sensitive penicillins (J01CE)																								
0-6	4.13	3.56	3.71	3.52	3.78	3.07	2.82	2.54	343.7	287.4	290.6	271.1	285.9	226.3	211.5	196.1	244.4	211.8	218.7	198.8	205.6	169.8	159.2	146.4
7-19	3.63	3.46	3.52	3.61	3.47	2.92	2.66	2.48	135.0	123.3	124.6	127.5	124.1	103.6	94.0	94.7	109.6	100.9	102.1	103.5	99.1	83.9	75.7	73.3
20-64	4.43	4.05	3.99	4.09	3.95	3.55	3.24	3.22	108.5	98.2	96.8	98.6	95.1	84.8	77.6	77.2	91.6	84.3	83.4	85.0	81.4	72.7	66.2	65.3
65-79	4.40	4.16	4.01	4.18	3.96	3.86	3.58	3.62	104.1	97.8	94.5	98.4	93.9	89.9	83.4	84.4	87.4	83.2	81.0	84.4	80.3	76.4	70.4	69.5
80-	3.50	3.38	3.29	3.33	3.34	3.24	3.07	3.17	85.7	81.7	79.5	80.4	81.0	78.3	73.9	76.7	72.7	69.9	68.3	69.5	69.6	67.4	63.3	65.1
All age groups	4.25	3.96	3.93	3.99	3.88	3.49	3.21	3.19	130.0	118.6	118.4	117.7	115.7	101.1	93.1	92.1	104.9	96.2	96.1	96.2	93.5	82.7	75.8	73.9
Beta-lactamase resistant penicillins (J01CF)																								
0-6	0.33	0.31	0.30	0.28	0.29	0.26	0.26	0.23	32.8	30.8	29.4	28.0	29.0	26.1	26.2	24.4	25.6	24.3	23.4	22.0	22.9	20.4	20.6	19.5
7-19	0.80	0.79	0.77	0.76	0.77	0.78	0.77	0.68	31.9	31.2	31.0	30.0	28.5	27.8	27.4	25.6	26.0	25.4	25.5	24.6	23.1	22.6	22.2	20.9
20-64	1.22	1.20	1.18	1.19	1.27	1.31	1.30	1.26	34.8	34.0	34.2	33.9	33.0	32.2	32.1	30.8	27.4	26.9	27.4	27.0	26.3	25.6	25.5	24.3
65-79	2.63	2.55	2.52	2.51	2.67	2.77	2.74	2.69	62.5	60.8	60.0	58.5	58.1	57.1	56.2	54.9	40.9	39.9	40.3	39.5	38.6	38.1	37.3	35.4
80-	4.99	4.92	4.92	4.69	4.85	5.11	5.18	5.22	122.1	119.4	113.2	106.2	103.2	103.2	102.6	101.6	67.1	65.5	66.8	64.8	63.2	63.4	62.8	61.2
All age groups	1.46	1.45	1.43	1.42	1.51	1.56	1.56	1.54	42.3	41.7	41.3	40.3	39.5	38.7	38.5	37.4	30.8	30.2	30.6	29.9	29.2	28.5	28.2	26.9
Combinations of penicillins (J01CR)																								
0-6	0.67	0.52	0.39	0.28	0.26	0.21	0.21	0.18	46,4	33.7	25.3	17.8	16.7	13.9	13.5	12.0	31.9	24.0	17.9	12.3	11.1	8.8	8.3	7.2
7-19	0.20	0.18	0.17	0.16	0.14	0.14	0.14	0.14	6,0	5.4	4.9	4.7	4.0	3.9	4.0	4.2	4.5	4.1	3.8	3.6	3.0	2.8	2.7	2.7
20-64	0.22	0.21	0.22	0.22	0.22	0.22	0.24	0.25	4,7	4.4	4.7	4.7	4.7	4.7	5.0	5.1	4.1	3.8	4.0	4.0	3.9	3.9	4.0	4.1
65-79	0.27	0.29	0.31	0.32	0.34	0.34	0.37	0.40	5,5	5.7	6.1	6.3	6.7	6.8	7.5	8.2	4.3	4.6	4.8	5.0	5.1	5.2	5.6	6.0
80-	0.20	0.22	0.24	0.27	0.29	0.32	0.35	0.39	4,1	4.3	4.8	5.2	5.8	6.2	6.7	7.6	3.2	3.4	3.9	4.1	4.3	4.6	5.0	5.8
All age groups	0.26	0.24	0.24	0.24	0.23	0.23	0.25	0.26	8,3	7.2	6.7	6.1	6.0	5.8	6.1	6.2	6.3	5.5	5.2	4.7	4.6	4.4	4.5	4.5
Cephalosporins (J01DB-DE)																								
0-6	0.46	0.36	0.34	0.32	0.32	0.27	0.27	0.24	43.6	34.1	33.2	31.6	29.2	25.7	26.9	25.1	34.9	28.2	27.7	25.6	24.1	21.2	22.2	20.7
7-19	0.26	0.21	0.20	0.18	0.16	0.15	0.13	0.13	18.4	14.9	13.8	12.8	11.6	10.4	9.3	9.5	15.6	12.7	11.6	10.7	9.6	8.5	7.6	7.2
20-64	0.26	0.20	0.18	0.15	0.14	0.12	0.11	0.11	14.6	11.5	10.3	9.2	8.2	7.3	6.7	6.6	12.3	9.7	8.7	7.7	6.8	6.0	5.5	5.3
65-79	0.39	0.31	0.29	0.23	0.20	0.19	0.17	0.18	19.1	14.9	13.9	12.6	11.0	10.4	9.4	9.7	14.8	11.5	10.6	9.5	8.2	7.8	7.0	6.9
80-	0.54	0.41	0.38	0.34	0.32	0.31	0.29	0.29	29.4	22.7	21.6	19.9	18.5	17.6	17.0	17.4	23.0	17.9	16.6	15.5	14.2	13.4	13.1	13.2
All age groups	0.31	0.25	0.23	0.20	0.18	0.16	0.14	0.14	19.0	15.2	14.1	12.8	11.5	10.4	9.8	9.6	15.4	12.3	11.4	10.3	9.2	8.3	7.8	7.5

Age groups (years)	DDD/1 000 and day								Prescriptions/1 000 and year								User/1 000 and year							
	2008	2009	2010	2011	2012	2013	2014	2015	2008	2009	2010	2011	2012	2013	2014	2015	2008	2009	2010	2011	2012	2013	2014	2015
Trimethoprim (J01EA)																								
0-6	0.10	0.09	0.09	0.08	0.08	0.07	0.07	0.06	14.0	12.6	12.2	11.3	11.0	10.0	9.2	8.1	10.1	9.7	9.5	8.8	8.4	7.6	6.9	6.1
7-19	0.15	0.11	0.10	0.08	0.06	0.05	0.04	0.04	8.9	7.0	5.9	4.8	3.9	3.3	2.8	2.4	7.7	6.0	5.1	4.1	3.3	2.7	2.2	1.8
20-64	0.26	0.20	0.17	0.15	0.13	0.11	0.10	0.09	12.7	9.4	7.8	6.5	5.4	4.5	3.9	3.3	10.5	7.7	6.4	5.2	4.3	3.5	3.0	2.5
65-79	0.76	0.61	0.57	0.50	0.43	0.39	0.34	0.31	34.7	27.5	24.3	20.9	17.7	15.5	13.5	11.8	25.1	19.6	17.3	14.6	12.3	10.7	9.2	8.1
80-	1.58	1.30	1.23	1.08	0.94	0.83	0.71	0.69	84.7	69.6	63.6	56.4	49.1	41.5	35.5	32.7	49.3	38.6	34.5	29.4	24.6	21.4	18.8	17.1
All age groups	0.36	0.29	0.26	0.23	0.20	0.17	0.15	0.14	18.8	14.9	13.1	11.2	9.7	8.3	7.2	6.4	13.9	10.7	9.3	7.9	6.7	5.7	4.9	4.3
Trimethoprim with sulphonamides (J01EE)																								
0-6	0.14	0.13	0.12	0.10	0.10	0.09	0.09	0.08	16.7	14.8	13.7	11.8	11.8	10.2	9.6	8.6	12.4	10.7	10.0	8.2	7.6	6.2	5.7	4.8
7-19	0.10	0.11	0.10	0.10	0.10	0.10	0.10	0.10	4.2	4.3	4.0	4.1	3.9	3.8	3.8	4.1	2.6	2.6	2.4	2.5	2.2	2.1	2.0	1.9
20-64	0.17	0.18	0.19	0.19	0.19	0.20	0.20	0.21	3.6	3.8	4.0	4.2	4.3	4.6	4.8	4.8	2.4	2.5	2.6	2.7	2.6	2.6	2.7	2.6
65-79	0.48	0.52	0.52	0.54	0.54	0.56	0.57	0.60	11.3	11.7	12.1	12.2	12.2	12.4	13.0	13.2	7.9	8.2	8.5	8.5	8.3	8.4	8.6	8.4
80-	0.43	0.43	0.46	0.46	0.47	0.51	0.51	0.53	13.1	12.5	13.1	12.5	12.6	13.0	13.2	13.1	10.0	9.7	10.1	9.8	9.5	9.7	9.9	9.7
All age groups	0.21	0.22	0.23	0.24	0.24	0.25	0.25	0.26	6.5	6.6	6.8	6.7	6.6	6.7	6.8	6.8	4.3	4.3	4.3	4.2	4.1	4.0	4.0	3.9
Macrolides (J01FA)																								
0-6	0.68	0.51	0.53	0.51	0.39	0.26	0.26	0.23	29.9	22.4	23.1	22.2	18.1	12.1	12.4	11.2	24.0	18.1	18.7	18.3	14.8	9.5	9.7	8.5
7-19	0.38	0.31	0.33	0.40	0.32	0.24	0.22	0.19	15.4	12.7	13.8	15.4	13.2	8.3	8.6	7.8	11.7	9.7	10.7	12.1	10.0	5.8	6.1	5.7
20-64	0.33	0.28	0.28	0.28	0.30	0.27	0.24	0.23	14.3	12.0	11.9	10.4	11.4	8.7	9.1	8.9	11.3	9.5	9.5	8.3	8.8	6.4	6.8	6.5
65-79	0.34	0.32	0.30	0.32	0.32	0.33	0.30	0.30	12.4	11.1	10.3	9.3	10.4	8.7	9.0	9.0	9.3	8.2	7.6	6.7	7.4	5.6	5.9	5.7
80-	0.23	0.23	0.21	0.20	0.19	0.20	0.19	0.21	8.4	7.4	6.9	6.0	6.4	5.7	5.8	6.5	6.4	5.5	5.3	4.4	4.8	4.0	4.0	4.2
All age groups	0.36	0.31	0.31	0.32	0.31	0.27	0.25	0.24	15.3	12.8	12.8	11.9	11.9	8.9	9.2	9.0	11.9	9.9	10.0	9.3	9.1	6.3	6.7	6.3
Lincosamides (J01FF)																								
0-6	0.02	0.02	0.02	0.02	0.03	0.02	0.02	0.02	5.0	5.2	5.0	5.3	6.5	5.0	5.1	4.5	3.8	3.8	3.9	4.0	4.9	3.7	3.6	3.3
7-19	0.12	0.12	0.12	0.12	0.12	0.11	0.11	0.09	8.4	8.2	8.1	8.0	7.9	7.4	7.3	6.3	6.8	6.6	6.5	6.5	6.5	5.9	5.7	5.4
20-64	0.32	0.31	0.31	0.32	0.32	0.31	0.31	0.30	16.3	15.7	15.6	16.0	15.8	15.4	14.7	14.5	12.7	12.4	12.4	12.7	12.5	12.2	11.5	11.3
65-79	0.61	0.61	0.59	0.59	0.58	0.58	0.56	0.57	26.2	25.4	25.0	24.6	24.2	24.3	22.9	23.0	17.3	17.1	16.9	16.8	16.8	16.8	15.7	15.3
80-	0.76	0.72	0.73	0.71	0.70	0.71	0.73	0.72	33.2	31.0	31.7	30.8	30.2	29.9	29.9	30.2	19.3	18.8	19.2	19.0	18.7	18.9	18.9	18.6
All age groups	0.33	0.32	0.32	0.33	0.32	0.32	0.32	0.32	16.4	15.9	15.9	16.0	16.0	15.6	14.9	14.8	12.0	11.7	11.7	11.9	11.9	11.6	11.0	10.8
Fluoroquinolones (J01MA)																								
0-6	0.01	0.01	0.01	0.01	0.01	0.02	0.02	0.01	0.7	0.7	0.8	0.7	0.7	0.9	0.8	0.7	0.4	0.4	0.5	0.4	0.5	0.5	0.4	0.5
7-19	0.12	0.12	0.12	0.12	0.11	0.11	0.10	0.08	4.8	4.3	4.3	4.3	4.0	3.6	3.4	2.8	3.8	3.5	3.5	3.4	3.2	2.9	2.7	3.0
20-64	0.78	0.72	0.68	0.68	0.65	0.62	0.59	0.57	27.0	23.8	22.9	21.9	20.8	19.7	18.9	18.4	19.5	17.3	16.7	15.9	15.1	14.4	13.8	13.3
65-79	1.90	1.84	1.79	1.77	1.73	1.64	1.61	1.58	70.8	65.6	63.8	61.1	58.8	55.7	54.8	53.6	48.3	44.9	43.9	41.8	40.4	38.6	37.6	35.6
80-	2.41	2.25	2.26	2.18	2.08	2.00	1.95	1.91	98.5	88.2	87.3	82.0	77.6	73.7	72.5	71.0	68.4	61.4	60.9	57.8	54.9	52.6	51.4	49.8
All age groups	0.84	0.80	0.78	0.77	0.75	0.71	0.69	0.68	30.6	27.8	27.1	26.1	25.0	23.8	23.3	22.9	21.7	19.6	19.2	18.4	17.7	16.9	16.4	15.9
Nitrofurantoin (J01XE)																								
0-6	0.06	0.06	0.06	0.06	0.05	0.05	0.06	0.05	6.2	6.9	7.2	7.3	7.0	7.1	7.2	6.8	4.3	5.0	5.1	5.1	5.0	5.1	5.2	5.2
7-19	0.13	0.15	0.14	0.14	0.13	0.13	0.13	0.09	6.6	9.2	10.6	10.8	10.4	10.1	9.8	7.1	5.7	7.9	9.0	9.2	8.9	8.6	8.3	7.8
20-64	0.24	0.27	0.27	0.28	0.29	0.30	0.31	0.31	11.1	15.3	17.8	19.1	19.8	20.5	21.1	20.9	9.1	12.5	14.6	15.6	16.1	16.6	17.0	16.7
65-79	0.55	0.62	0.61	0.64	0.67	0.72	0.74	0.76	24.2	32.6	37.3	39.9	41.5	44.0	44.9	45.2	18.1	24.0	27.5	29.3	30.3	31.9	32.5	31.7
80-	0.95	1.05	1.06	1.12	1.15	1.23	1.30	1.35	47.7	61.7	70.6	76.0	77.4	80.6	84.0	87.0	31.3	40.3	45.6	47.8	49.0	51.6	53.8	53.8
All age groups	0.29	0.32	0.32	0.34	0.35	0.37	0.38	0.38	13.6	18.5	21.3	22.8	23.5	24.5	25.1	25.2	10.5	14.1	16.3	17.3	17.8	18.4	18.9	18.6
All agents (J01 excl. Methenamine)																								
0-6	8.32	7.11	7.21	6.55	6.66	5.43	5.15	4.70	630.8	522.4	515.0	467.6	471.9	382.4	367.2	340.9	342.4	299.5	300.7	273.3	274.4	232.0	222.7	206.4
7-19	9.83	9.52	9.65	9.83	9.27	8.33	7.75	6.48	301.4	280.8	282.5	286.1	268.0	232.7	217.8	200.0	194.6	182.5	183.8	185.5	173.2	152.1	141.8	136.1
20-64	13.09	12.14	12.03	12.25	11.98	11.19	10.62	10.38	361.7	331.8	329.9	331.7	320.0	294.4	280.8	275.2	224.7	209.1	207.8	208.9	200.7	184.9	175.8	171.3
65-79	19.16	18.23	17.78	18.00	17.76	17.28	16.55	16.54	566.6	535.0	525.3	524.7	510.7	489.2	468.7	466.3	297.5	282.9	278.6	278.9	270.6	258.1	246.5	238.9
80-	22.24	21.13	20.85	20.38	20.34	20.22	19.95	20.34	765.1	723.5	710.9	690.7	673.0	654.2	640.3	645.9	357.7	340.2	336.1	330.9	323.2	314.7	307.8	306.7
All age groups	13.53	12.76	12.68	12.76	12.51	11.74	11.20	11.04	423.1	391.9	390.3	385.3	373.9	342.7	328.0	322.8	245.1	228.3	227.5	226.3	218.7	201.0	191.7	186.0

Antibiotics commonly used to treat respiratory tract infections

Antibiotics commonly used to treat respiratory tract infections (RTI) are overall the most frequently prescribed antibiotics in Sweden. Among these substances we also find the greatest decrease over time in terms of number of prescriptions per 1 000 inhabitants and year, from 294 in 2000 to 164 in 2015. During 2015 the sales continued to decrease with 1.6%. Measuring as DDD per 1 000 inhabitants and day the sale of these agents has decreased by 33.2% since year 2000, from 8.8 to 5.9.

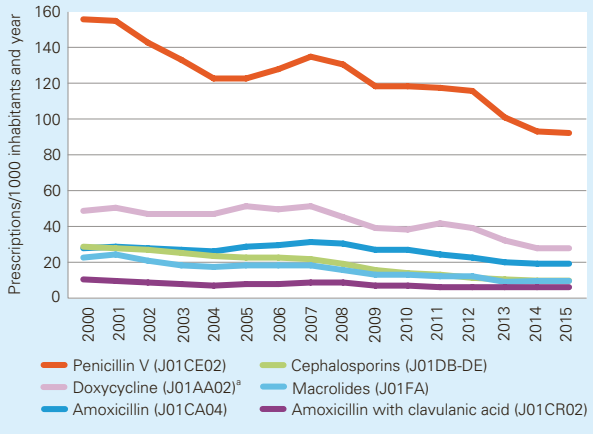
Narrow spectrum penicillin, penicillin V, is the recommended first line antibiotic for treatment of community acquired RTI in Sweden (Medical Products Agency & Strama, 2008) and is the most frequently prescribed antibiotic in outpatient care. The sales of penicillin V decreased by 1.1% in 2015 compared to 2014, Figure 1.9. and Table 1.1.

Tetracyclines are the second most frequently prescribed antibiotics in outpatient care. The sales of tetracyclins commonly used to treat respiratory tract infections (packages containing less than 50 tablets) continued to decrease in 2015 compared to 2014 (1.7%). The decrease in sales of doxycycline seen during the last three years may indicate an improved compliance to national treatment recommendations (Medical Products Agency & Strama, 2008) where it is stated that acute bronchitis (including *Mycoplasma pneumoniae*) should generally not be treated with antibiotics.

Even though the total sales of antibiotics commonly used to treat RTI decreased during 2015 the sales of amoxicillin with clavulanic acid increased by 1.5%. The increased sales of amoxicillin with clavulanic acid might be a consequence of an increased number of urinary tract infections caused by ESBL producing bacteria, where amoxicillin with clavulanic acid could possibly be an oral treatment alternative (Public Health Agency of Sweden, 2014). In addition, amoxicillin with clavulanic acid has since 2013 been part of initial sensitivity testing against Enterobacteriaceae for patients with uncomplicated UTI. This might have affected the prescription rate of amoxicillin with clavulanic for this indication (RAF, 2014).

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

FIGURE 1.9. Sales of antibiotics commonly used to treat respiratory tract infections in outpatient care (sales on prescriptions), 2000-2015, prescriptions/1 000 inhabitants and year, both sexes, all ages.

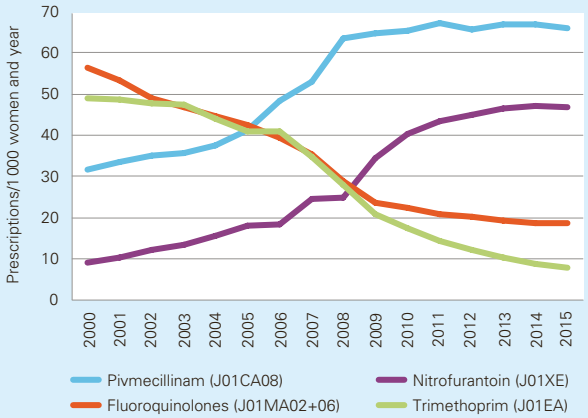


[a] Excludes packages containing more than 50 tablets

Antibiotics commonly used to treat urinary tract infections in women

National treatment recommendations for lower urinary tract infections in women over 18 years (Medical Products Agency & Strama, 2007), recommends pivmecillinam and nitrofurantoin before trimethoprim, and prescribers are also encouraged to minimize the use of fluoroquinolones because of the resistance situation. In 2015, the total sales of antibiotics commonly used to treat UTI in women aged 18-79 years decreased by 1.9% compared with 2014. However, the same positive trend as previous years, with increased use of the first-line drugs pivmecillinam and nitrofurantoin and reduced sales of trimethoprim (13.2%) and fluoroquinolones (0.6%), was also seen, Figure 1.10.

FIGURE 1.10. Sales of antibiotics commonly used to treat lower urinary tract infections in women (sales on prescriptions), 18-79 years, 2000-2015, prescriptions/1 000 women and year.



The total sales of these antibiotics have decreased slowly over the years; by 4.8% since 2000, as measured by prescriptions per 1 000 women and year. However, if measured by DDD per 1 000 women and day, the sales have decreased by 13% since 2000. This suggest shorter treatment durations for this condition with time, which is also according to recommendations.

Antibiotics commonly used to treat UTI are mostly prescribed to the age group 65 years and older, Figure 1.8. In this age group the total sales have decreased by 21.8% since 2000,

as measured by prescriptions per 1 000 women and year. As mentioned in the chapter "Guidance for readers", some of the antibiotic use among elderly people is not included in the statistics and a possible underestimation in the age group 65 years and older can therefore not be ruled out. Nevertheless, the great decrease in the age group 65 years and older indicates increased compliance to recommendations. Many elderly have asymptomatic bacteria in urine (ABU) and should not normally be treated with antibiotics (Medical Products Agency & Strama, 2007). Information and education at local and national level regarding treatment recommendation and ABU might be one explanation for the great decrease in sales over time in this age group. The same trend is seen in men, see below.

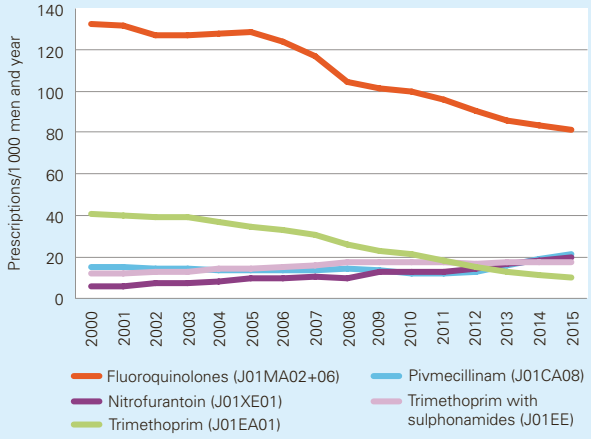
Antibiotics commonly used to treat urinary tract infections in men

The total sales of antibiotics commonly used to treat UTI in men 65 years and older has decreased by 27.8% since 2000. In 2015, however, the sales remained stable at the same level as in 2014 (152 prescriptions/1 000 men and year).

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

The sales of fluoroquinolones to men aged 65 years and older has decreased significantly since 2000 (39.4%), as measured by prescriptions per 1 000 men and year. The decrease continued in 2015 by 3.0% compared with 2014. During the last years, sales of pivmecillinam and nitrofurantoin have increased. In 2015, the sales of these two antibiotics increased by 11.1% and 7.9% respectively, as measured by prescriptions per 1 000 men and year, compared with 2014, Figure 1.11.

FIGURE 1.11. Sales of antibiotics commonly used to treat UTI in men 65 years and older 2000-2015, measured as prescriptions/1 000 men and year.

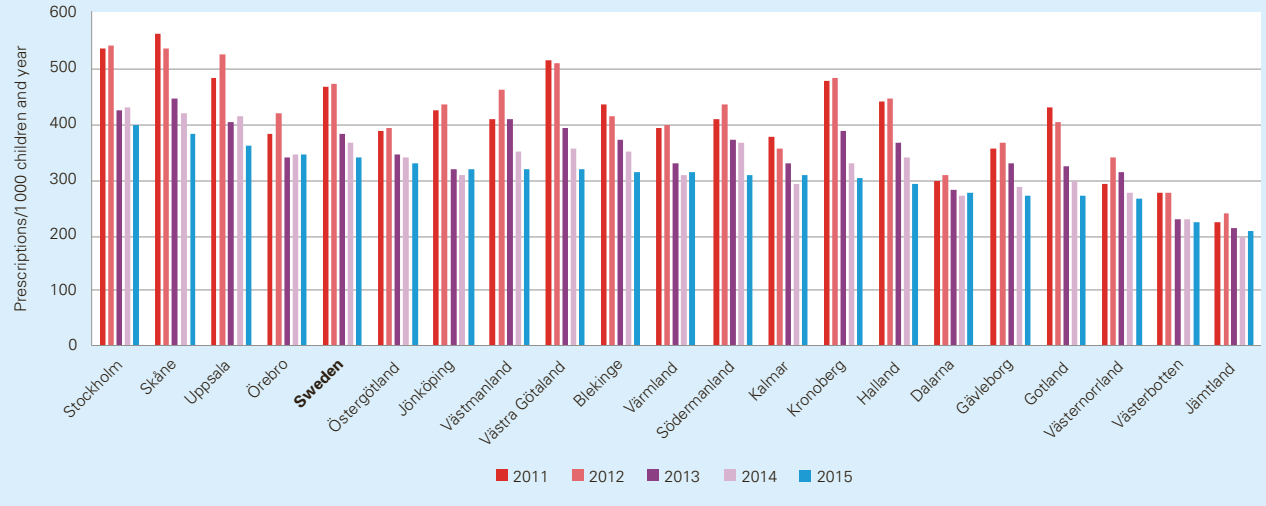


Antibiotic consumption in children

The total sales of antibiotics to children aged 0-6 years have decreased by 54.6% since 2000 (from 746 to 339 prescriptions per 1 000 children and year). Between 2014 to 2015, the sales decreased by 8.6%. A decrease was seen in 16 out of 21 counties. There are still great national variations in antibiotic sales to children 0-6 years, from 397.2 prescriptions per 1 000 children and year in Stockholm County to 206.5 in Jämtland County, Figure 1.12. The great variation between the counties might suggest antibiotic overuse in some counties.

The reduction in sales during 2015 includes the majority of the available antibiotic agents, Table 1.1. Different kinds of penicillins are the most commonly prescribed antibiotics in this age group and penicillin V (J01CE02), amoxicillin (J01CA04) and flucloxacillin (J01CF05) represent 57.7% , 11.9% and 7.3% respectively of the total sales in 2015, Table 1.1.

FIGURE 1.12. Sales of antibiotics (J01 excl. methenamine) on prescriptions to children 0-6 years, per county and in Sweden, prescriptions/1 000 children and year. The data are sorted according to the use in 2015.



The Swedish HALT study – diagnose linked antibiotic prescription data in long-term care facilities

Prevention of healthcare-associated infections (HAI) and the spread of resistant bacteria is a major patient safety issue. In addition, antibiotic stewardship helps decrease the development of antibiotic resistance. Both these core concepts rely on a loop of monitoring, feedback and improvement of local practices. In Sweden, the elderly population has the highest consumption of antibiotics. To target the antibiotic use and optimize it in this population is very important in order to contain antibiotic resistance.

The Swedish HALT project is an annual point prevalence survey that aims to support prevention of health care associated infections and improve the use of antibiotics in assisted living facilities. The aim is also to develop a standardized tool that makes it possible to follow trends in the prevalence of HAIs and antibiotic use at local, regional and national level. This is in order to identify priorities for national and local interventions and support monitoring of their implementation, to improve resident safety and the quality of care in Swedish LTCFs.

Swedish HALT is a national adaptation of the ECDC HALT project (healthcare-associated infections in long-term care facilities). The original protocol has been adjusted to be more applicable to national conditions, for example regarding the included diagnoses, treatment alternatives and types of care facilities. Risk factors, like wounds urine and vascular catheters, are collected for all participants. This makes it possible to evaluate prescribing of antibiotics in relation to various symptoms of HAI and how the presence of risk factors correlates to the prevalence of infections. The national adaptation of the protocol simplified reporting for participating facilities and thereby encouraged a wider participation in the survey. A national IT-tool for data collection and feedback in the Swedish HALT survey has also been developed. The tool is a module integrated in a nationwide quality register for health and social care, Senior alert (www.senioralert.se).

The HALT project is managed by the Public Health Agency of Sweden, and the first national HALT survey was performed in 2014.

Method

All assisted living facilities in all 290 municipalities in Sweden were invited to participate in the Swedish HALT 2014 and 2015. All municipalities that signed up to participate were invited to a one day train-the-trainer course, and 1-2 persons were invited per municipality.

The survey was performed at any day during a two week period. The survey was performed by record audits, and were in most cases performed by a nurse working at the facility.

Signs and symptoms of HAIs were recorded in the IT-tool, and the HAIs were then defined as confirmed or not confirmed by algorithms based on CDC/SHEA and McGeer criteria. All antibiotic treatments on the day of the survey were recorded. For the antibiotic treatments the following information were reported: Diagnosis, treatment duration, therapeutic or prophylactic prescription, administration route, where the antibiotic was prescribed (at hospital or at the facility), by whom the antibiotic was prescribed, end date for the treatment, if a bacterial culture was taken before treatment, or if a urine dip-stick was taken before treatment of urinary tract infections (UTI).

Results Swedish HALT 2015

From a handful of participating nursing homes in the ECDC HALT project 2010 and 2013, the national HALT survey in 2015 comprised of 105 municipalities with more than 1 000 reporting units and 13 406 included residents.

In 2015, the total prevalence of residents with a confirmed HAI at long-term care facilities for elderly was 2.2%. The prevalence differs between genders. Among women the prevalence was 1.9% and among men 2.7%. Skin and soft tissue infections (SSTI) were the most commonly recorded HAI (37.8% out of all HAI) followed by UTIs (31.3% out of all HAI), Figure 1.

FIGURE 1. Distribution of types of HAI (relative frequency) in the included LTCFs, by unit type, Swedish HALT 2015. n= number of HAI.

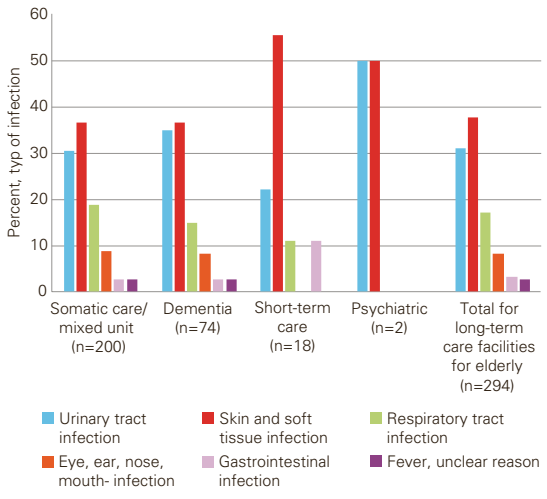
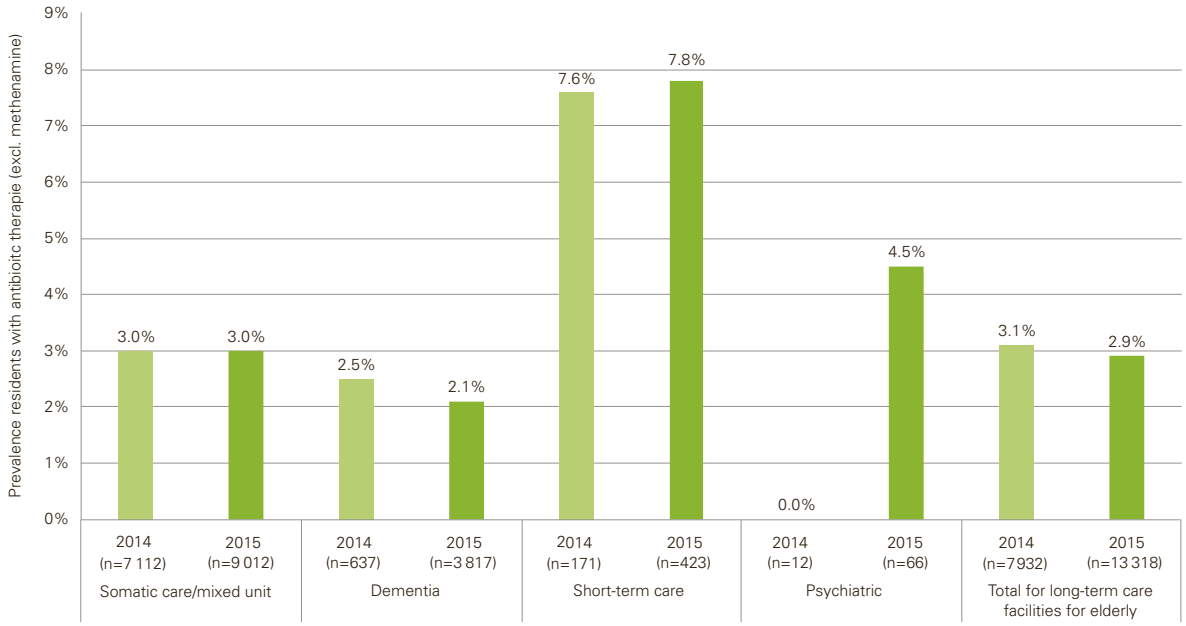


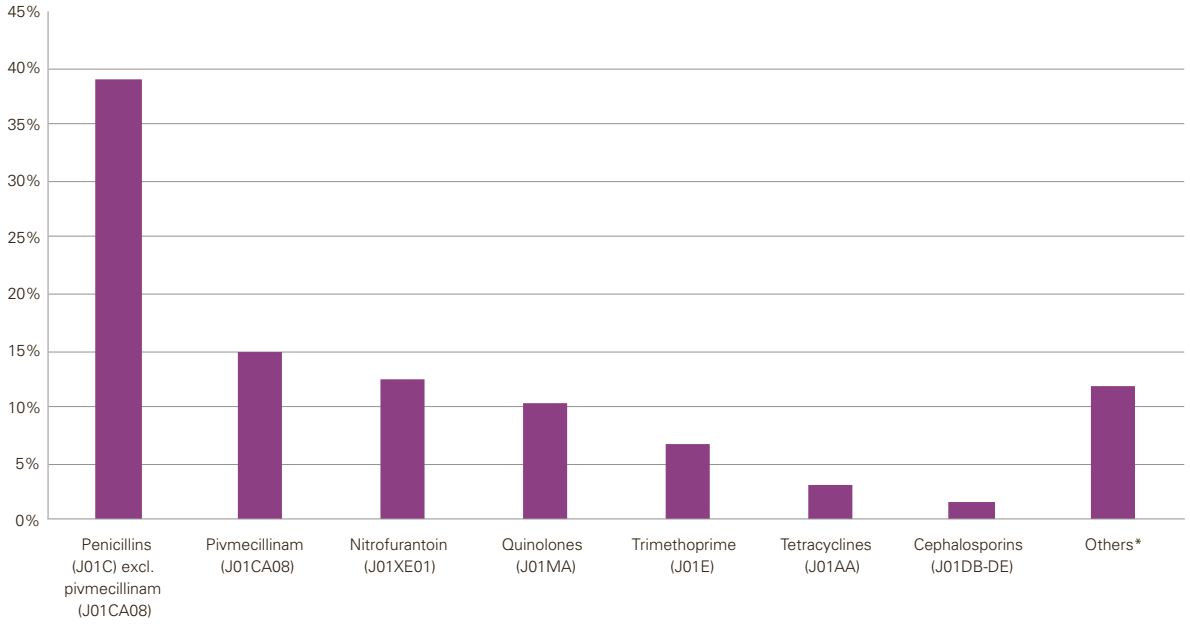
FIGURE 2. Prevalence of eligible LTCF residents receiving at least one antibiotic treatment (J01 excl. methenamine), by unit type. n= number of includes residents at respectively unit type.



The total prevalence of residents with an antibiotic treatment (J01 excluding methenamine) in long-term care facilities for the elderly was 2.9%. The greatest prevalence was measured at short-term care units, where 7.8% were treated with at least one course of antibiotics, Figure 2. A little more than 55% of all the antibiotic prescriptions at the short-term care units were prescribed at hospitals. The proportion of antibiotics prescribed at hospitals was lower for the unit type somatic care/mixed unit and dementia care, 22% respectively 16%.

Penicillins followed by nitrofurantoin and quinolones were the most commonly prescribed antibiotics in HALT 2015, Figure 3.

FIGURE 3. Distribution of antibiotics (J01 excl. methenamine), number of therapies.

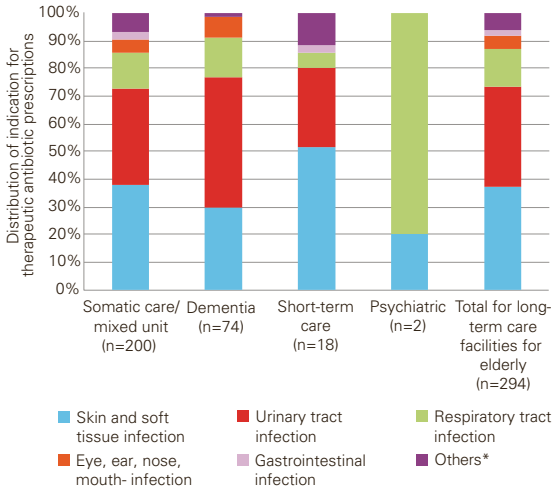


* others=ATC-codes J01XD, J01XA, A07AA09, J02AC01 and D01BA02.

The most common indication for the therapeutic antibiotic prescriptions at long-term care facilities for elderly people was SSTI (37%), followed by UTI (36%). Respiratory tract infections were the third most common indication and represented 13%. The distribution varied between different types of units, Figure 4.

As mentioned above, UTIs were the most common indication for antibiotic treatment. Out of all UTIs cystitis was the most common diagnosis (74%), followed by "other or no specific urinary diagnosis" (22%) and pyelonephritis (4%).

FIGURE 4. Distribution of indication for therapeutic antibiotic prescriptions per unit type. n= number of recorded therapeutic antibiotic prescriptions.

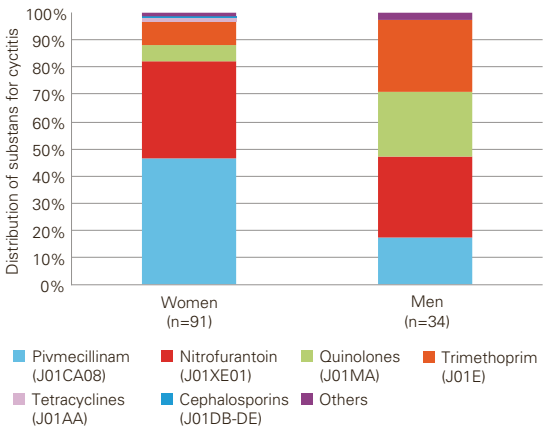


* Other= systemic infection, fever with unknown reason and other indication.

Treatment of women with cystitis seemed to follow national treatment guidelines and more than 80% out of all antibiotic therapies for cystitis were first line antibiotics (pivmecillinam J01CA08 and nitrofurantoin J01XE01). The distribution of antibiotic substances differs between the sexes. Men are more often treated with quinolones for cystitis, and pivmecillinam and nitrofurantoin represents less than 50% in this group, Figure 5.

Read more about the Swedish HALT study and results at the Public Health Agency's webpage (www.folkhalsomyndigheten.se/HALT).

FIGURE 5. Distribution of substances for the indication cystitis, per gender. n= number of recorded therapies for cystitis.



Discussion

The collaboration with Senior alert has established a link to all the 300 regional authorities providing social care and assisted living in Sweden. The development of the Web-based reporting tool has made it easy for staff to register infections, prescribed antibiotics and risk factors. It also made it possible to evaluate prescribing of antibiotics in relation to various symptoms of HAI and how the presence of risk factors correlates to the prevalence of infections. The reporting tool secured the possibility to extract data from the reporting module, so that participating facilities got instant feedback on their results.

The results from the participating facilities are important for identifying areas for targeted improvement and for raising awareness about risk factors. The results are also shared with regional groups for antibiotic stewardship, as a way to highlight the current use of antibiotics and improve prescribing. Over time, the survey will be an important tool in benchmarking and follow-up of long-term efforts to promote patient safety and optimal use of antibiotics in long-term care facilities.

FIGURE 1.13. Proportion of children 0-6 years treated with at least one course of antibiotics (J01 excl. methenamine) in 2013-2015 (user/1 000 children and year).

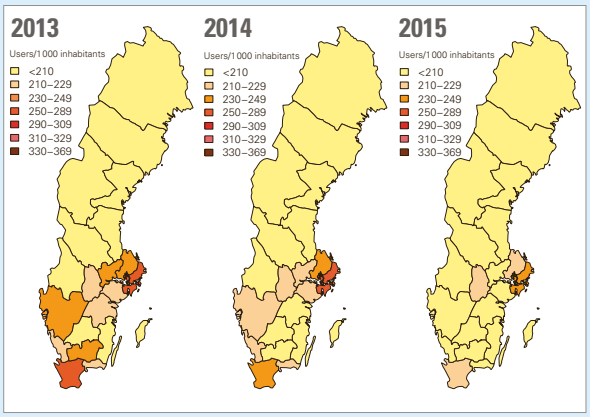
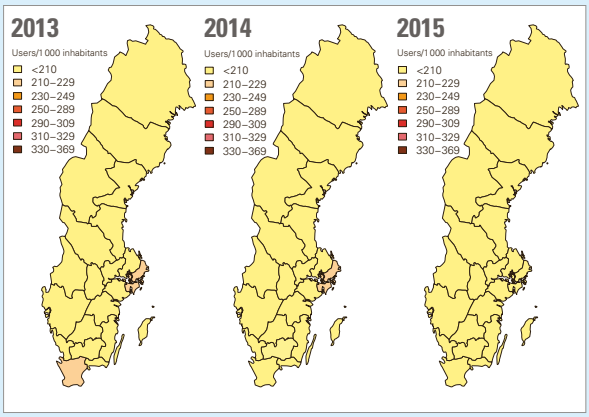


FIGURE 1.14. Proportion of people treated with at least one course of antibiotics (J01 excl. methenamine) in 2013-2015 (user/1 000 inhabitants and year).



The great decrease in antibiotic sales to children, seen over time, can be explained by a more appropriate antibiotic use in Sweden. New recommendations for treatment of acute otitis media were launched by Strama and the Swedish Medical Products Agency in 2010 (Medical Products Agency & Strama, 2010). The new recommendations have been attracting attention from professionals and the public which may have influenced the antibiotic use in young children.

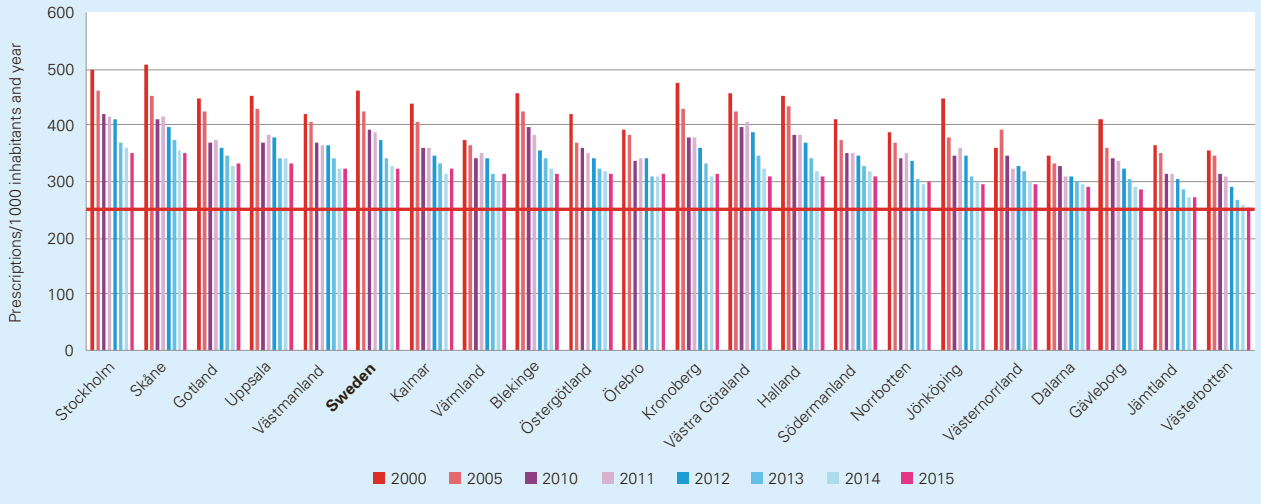
In Sweden, the proportion of children (0-6 years) treated with at least one course of antibiotics was 20.6%, which is less than in 2014, Table 1.1. The proportion decreased in 18 out of 21 counties during 2015 and it ranges within the country, from 238 users per 1 000 children in Stockholm County to 133 users per 1 000 children in Jämtland County, Figure 1.13.

County data

In 2015, 18.6% of the Swedish population was treated with at least one course of antibiotics, which is marginally less than in 2015 when 19.2% was treated, Table 1.1. However, the proportion of people treated with antibiotics varies within Sweden, from 20.4% in Stockholm County to 14.6% in Västerbotten County. The antibiotic use is greatest in big cities and their surroundings. In total, the proportion of patients treated decreased in 17 out of 21 counties in 2015, Figure 1.14.

In 2015, the average sales of antibiotics in outpatient care measured as prescriptions per 1 000 inhabitants in Sweden was 323. To reach the Swedish long term target of 250 prescriptions per 1 000 inhabitants and year the antibiotic use in Sweden still must be reduced by 22.6%, Figure 1.15.

FIGURE 1.15. Sales of antibiotics in outpatient care 2000-2015, prescriptions/1 000 inhabitants and year. The red line indicates the Swedish long term target of 250 prescriptions/1 000 inhabitants and year. The data are sorted according to the sales in 2015.



In 2015, a reduced number of prescriptions per 1 000 inhabitants was seen in 15 out of 21 counties, Figure 1.15. One reason for the great decrease in antibiotic sales in all counties in Sweden during the latest years might be the patient safety initiative, that started in 2011 and continued until the end of 2014. This was a governmental performance-based initiative partly focusing on optimizing the antibiotic use through financial incentives. Read more about the agreement and evaluation on antibiotic use in relation to the initiative in Swedres-Svarm 2014 chapter "National campaign for improved patient safety" (Swedres-Svarm 2014, 2015).

However, there are still great regional differences between different parts of Sweden and prescriptions per 1 000 inhabitants range from 352 in Stockholm County to 252 in Västerbotten County, Figure 1.15. The greatest decrease, measured as a percentage, during 2015 was seen in Halland, Södermanland, Västra Götaland and Uppsala counties.

The great variation between counties is probably not explained by differences in morbidity (Hedin K, Andre M, et al. 2006), but more likely explained by overuse of antibiotics. Factors influencing antibiotic prescription at Swedish healthcare centers has been investigated in a study, see results in the report "*Vad påverkar allmänläkare vid förskrivning av antibiotika?*" on the webpage of the Public Health Agency of Sweden (Public Health Agency of Sweden, 2014).

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

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

1. At least 80% of antibiotics commonly used to treat respiratory tract infections in children aged 0-6 years should be penicillin V (J01CE02). The numerator is penicillin V (J01CE02) and the denominator is amoxicillin (J01CA04), penicillin V (J01CE02), amoxicillin-clavulanate (J01CR02), cephalosporins (J01DB-DE) and macrolides (J01FA).

In 2015 the proportion of penicillin V was 69% on a national level, which is the same as in 2014. Värmland County had the greatest proportion, 78%, and Kronoberg County the lowest, 65%, Figure 1.16. In total, 12 out of 21 counties increased this proportion in 2015 compared to 2014. The great decrease in use of penicillin V to children during the latest years, from 351 prescriptions/1 000 inhabitants and year in 2007 to 196 in 2015, needs to be considered when analyzing this indicator.

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

In Sweden the average proportion was 13% in 2015. Västernorrland County had the highest proportion (16%) and Östergötland County the lowest proportion (12%), Figure 1.17.

FIGURE 1.16. Proportion penicillin V of antibiotics commonly used to treat respiratory tract infections in children 0-6 years, per county, 2014-2015. The red line indicates Strama´s goal at minimum 80% penicillin V.

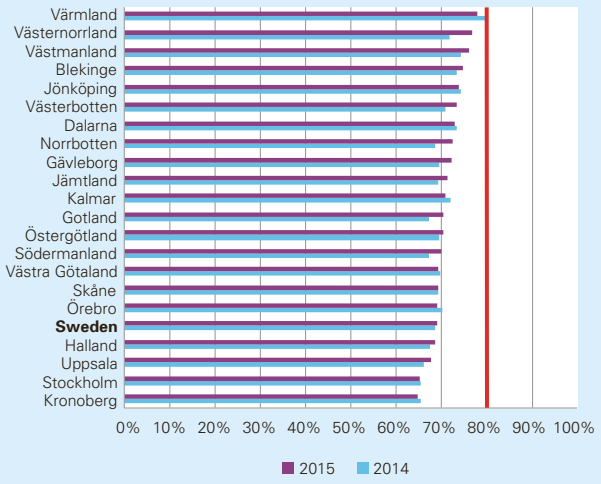
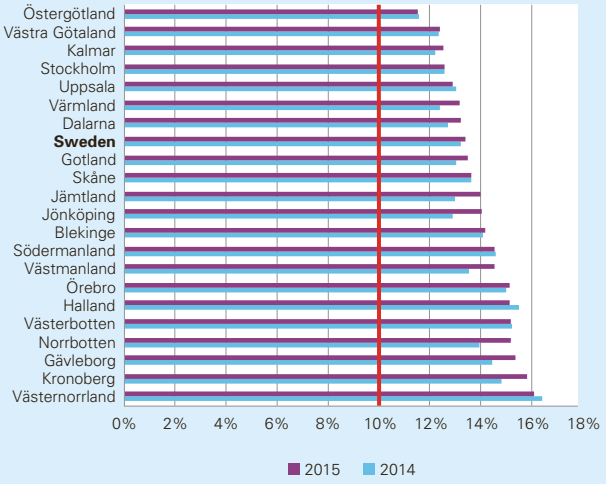


FIGURE 1.17. Proportion of fluoroquinolones of antibiotics commonly used to treat urinary tract infections in women 18-79 years, per county, 2014-2015. The red line indicates Strama´s goal of maximum 10% fluoroquinolones.



Antibiotics in dentistry

The sales of antibiotic prescribed by dentists decreased by 3% in 2015 compared with 2014, from 23.6 to 22.9 prescriptions per 1 000 inhabitants and year for J01 and metronidazole (P01AB01), Figure 1.18. Penicillin V (J01CE02) is the most commonly prescribed antibiotic followed by amoxicillin (J01CA) and clindamycin (J01FFA01). These antibiotic substances represent 73%, 9% and 9% respectively of all antibiotics prescribed by dentists. However, the greatest decrease in 2015 was seen for erythromycin (6%) and metronidazol (6%), measured as prescriptions per 1 000 inhabitants and year. Amoxicillin has decreased by 32% between 2012 and 2015, this might be due to the new stricter treatment recommendations for the use of prophylaxis which were implemented in 2012. A big increase was seen for clindamycin between 2001 and 2011. Since 2012, the trend has reversed and the prescribing of clindamycin has decreased each year hereafter.

The age group 65-74 years stands for the highest consumption of antibiotics (J01 and P01AB01) prescribed by dentists, followed by the age groups 75-84 years and 45-64 years. The antibiotic consumption peaked in 2007 and has thereafter decreased in all age groups (50-33%), Figure 1.19.

Dentists account for approximately 6% of all antibiotics prescribed in outpatient care in Sweden. The proportion varies between 4% in some counties to 7% in others. The total sales of antibiotics (J01 and metronidazole), measured as prescriptions per 1 000 inhabitants and year, decreased in 13 out of 21 counties in 2015 compared with 2014. Corresponding to outpatient care, there are great differences between the counties. In 2015 dentists in Stockholm County prescribed the most (28.5 prescriptions/1 000 inhabitants) and Västerbotten County the least (13.4 prescriptions/1 000 inhabitants), Figure 1.20.

FIGURE 1.18. Sales of antibiotics prescribed by dentists in outpatient care, 2010-2015.

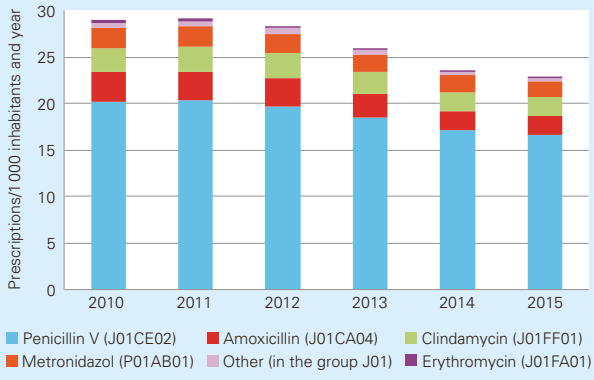


FIGURE 1.19. Sales of antibiotics (J01 and P01AB01) prescribed by dentists in outpatient care, 2000-2015, different age groups.

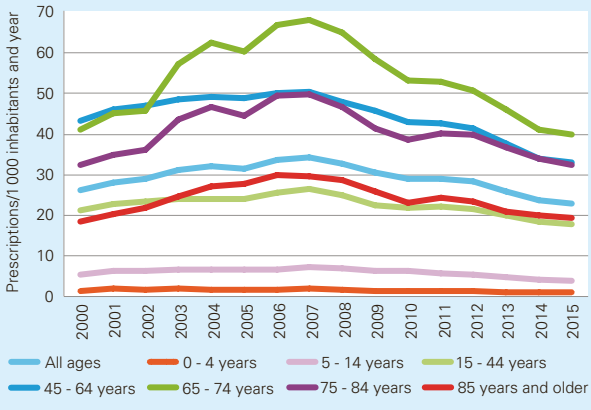
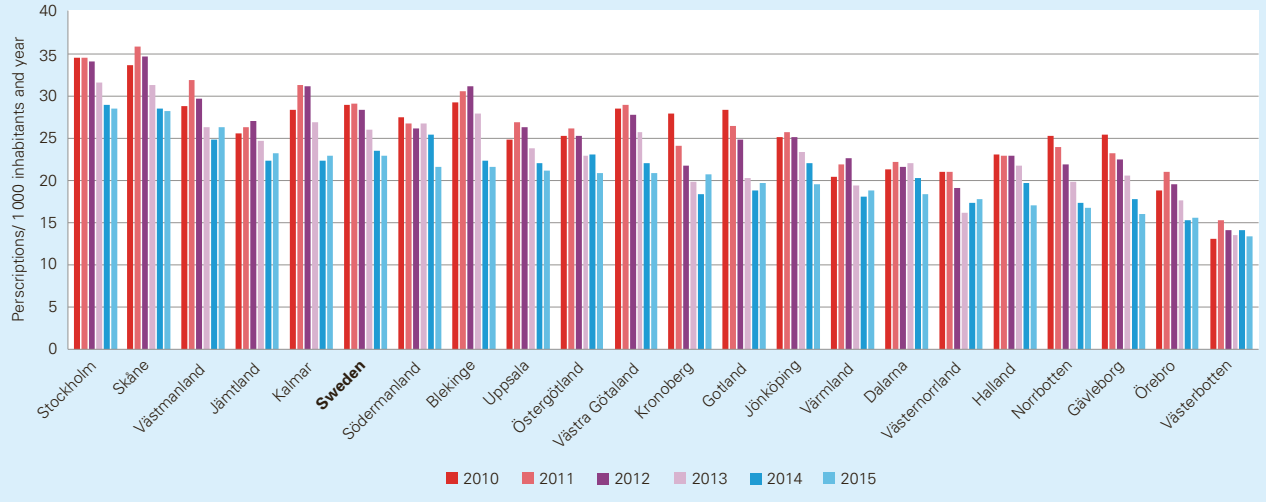


FIGURE 1.20. Sales of antibiotics prescribed by dentists in outpatient care per county, 2010-2015, Antibiotics for systemic use (J01) and metronidazol (P01AB01).



Antibiotics in hospital care

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

Hospital care includes data from all Swedish acute care hospitals as well as data from those nursing homes and other care givers that order their antibiotics through requisition. It varies between nursing homes if they buy antibiotics through requisition or by prescriptions to individual residents. If antibiotics are bought on prescription, data are included in primary health care data, presented in the previous section. The way of retrieving antibiotics to nursing homes varies among counties, but on a national level the proportion of antibiotics in hospital care sold to acute care hospitals is about 75%. In some counties almost 100% of all antibiotics are bought by acute care hospitals and in other counties this proportion is as low as 60%.

Antibiotic consumption in Swedish acute care hospitals

When analyzing data from acute care hospitals, the consumption was at almost the same level in 2015 compared with 2014, measured as DDD/100 patient-days and as DDD/100 admissions, Table 1.2.

Figure 1.21 shows the most frequent groups of antibiotics used in hospital care. The consumption of cephalosporins did not change during last year, and stayed at almost the same level as in 2014. Beta-lactamase sensitive penicillins, penicillins with enzyme inhibitor, carbapenems and vancomycin continues to increase as in previous years, while aminoglycosides, fluoroquinolones and beta-lactamase resistant penicillins decreased.

FIGURE 1.21. Antibiotic groups often used within hospital care 2011-2015 DDD/100 patient-days in Swedish acute care hospitals.

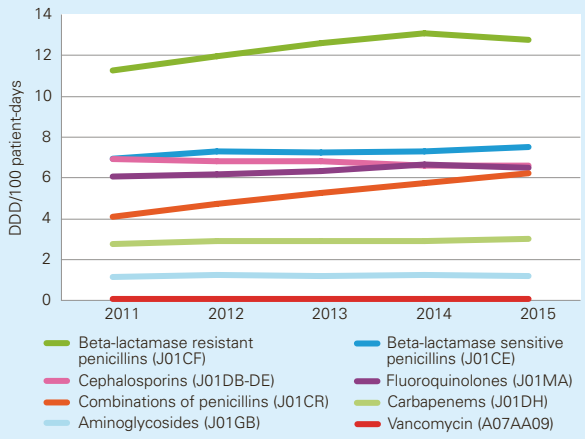


TABLE 1.2. DDD/100 patient-days and DDD/100 admissions in somatic medical care in Swedish acute care hospitals 2011-2015.

	DDD/100 admissions					DDD/100 patient-days				
	2011	2012	2013	2014	2015[a]	2011	2012	2013	2014	2015[a]
Tetracyclines (J01AA)	23.0	24.2	23.6	24.1	23.7	5.0	5.5	5.3	5.4	5.3
Penicillins with extended spectrum (J01CA)	29.7	30.6	31.8	33.1	33.1	6.5	6.9	7.2	7.4	7.4
Betalactamase sensitive penicillins (J01CE)	31.7	32.4	32.2	32.5	33.5	6.9	7.3	7.3	7.3	7.5
Betalactamase resistent penicillins (J01CF)	51.4	53.0	55.9	58.4	57.0	11.3	12.0	12.6	13.1	12.8
Combinations of penicillins (J01CR)	18.7	20.9	23.5	25.6	27.8	4.1	4.7	5.3	5.7	6.2
Cephalosporins (J01DB-DE)	31.5	30.2	30.3	29.5	29.4	6.9	6.8	6.8	6.6	6.6
Carbapenems (J01DH)	12.6	13.0	13.0	13.1	13.4	2.8	2.9	2.9	2.9	3.0
Trimethoprim (J01EA)	3.5	2.6	2.0	1.8	1.7	0.8	0.6	0.4	0.4	0.4
Trimethoprim with sulphonamides (J01EE)	10.6	10.5	10.5	10.6	10.5	2.3	2.4	2.4	2.4	2.3
Macrolides (J01FA)	5.0	4.3	4.5	4.4	4.8	1.1	1.0	1.0	1.0	1.1
Lincosamides (J01FF)	7.9	8.4	8.8	8.7	8.3	1.7	1.9	2.0	1.9	1.9
Aminoglycosides (J01GB)	5.2	5.5	5.2	5.4	5.2	1.1	1.2	1.2	1.2	1.2
Fluoroquinolones (J01MA)	27.7	27.3	28.1	29.7	29.0	6.1	6.2	6.3	6.7	6.5
Glycopeptides (J01XA)	4.2	4.3	4.3	4.5	4.6	0.9	1.0	1.0	1.0	1.0
Imidazole derivates (J01XD)	6.3	5.9	5.4	4.6	4.3	1.4	1.3	1.2	1.0	1.0
Nitrofurantoin (J01XE)	2.2	2.1	2.3	2.4	2.2	0.5	0.5	0.5	0.5	0.5
Vancomycin (A07AA09)	0.3	0.3	0.3	0.3	0.4	0.1	0.1	0.1	0.1	0.1
Pivmecillinam (J01CA08)	7.9	8.1	8.5	9.2	8.9	1.7	1.8	1.9	2.1	2.0
Piperacillin and tazobactam (J01CR05)	13.3	15.1	17.3	20.3	21.6	2.9	3.4	3.9	4.6	4.8
Moxifloxacin (J01MA14)	2.0	2.2	2.2	2.5	2.4	0.4	0.5	0.5	0.6	0.5
Methenamine (J01XX05)	2.6	2.4	2.4	2.5	2.4	0.6	0.5	0.5	0.6	0.5
Linezolid (J01XX08)	0.4	0.4	0.5	0.6	0.7	0.1	0.1	0.1	0.1	0.2
All agents (J01)	274.4	278.3	284.4	292.7	292.5	60.1	62.8	64.1	65.6	65.5

[a] Denominator data from 2014.

The use of penicillins with enzyme inhibitor have increased substantially in recent years, while the use of carbapenems has increased to a lesser extent. These agents have in many situations replaced the cephalosporins. Piperacillin with tazobactam accounts for the majority of the sales of penicillins with enzyme inhibitor (J01CR) in acute care hospitals. In 2015 penicillins with enzyme inhibitor increased with 8.4% measured as DDD per 100 patient-days compared to 2014. The corresponding figure for carbapenems was 2.5%. The increase of these substances is probably a result of an increased number of infections with ESBL. Invasive infections caused by ESBL-producing *Escherichia coli* and *Klebsiella pneumonia* have increased, but the proportion of pathogens resistant to third-generation cephalosporins causing invasive infections is still very low in an European and international perspective. To minimize the selection of ESBL producing bacteria, a decreased use of 2nd and 3rd generation's cephalosporins is recommended in Sweden. Due to the decrease in the consumption of cephalosporins, the beta-lactamase resistant penicillins (J01CF) is since 2008 the largest group of antibiotics in Swedish acute care hospitals, even though it decreased some (2.5%) during the last year compared to 2014. A large proportion of the use consists of surgical prophylaxis (even though the hospital use in Sweden to a large extent has gone from a multi-dose to a single-dose prophylaxis). The use of fluoroquinolones (J01MA) accounts for 10% of all antibiotics in acute care hospitals. The use has been at almost the same level since 2008, and only decreased marginally (2.3%) in 2015 compared to 2014. One reason for why the fluoroquinolones are not increasing might be that the resistance is already quite extensive.

According to available data, antibiotic consumption in Swedish acute care hospitals shows a wide variation between the counties in the use of narrow-spectrum penicillins, ranging from 5% to 20% of the total hospital consumption measured as DDDs, Figure 1.22. There are, however, great differences in dosages of penicillin G between the counties. DDD is 3.6g and in Sweden the dosage varies from 1g three times a day to 3g three times a day. Type of hospital and patient composition may also influence the statistics and should be taken into account when comparing these data. Uppsala, Stockholm, Västerbotten, Västra Götaland, Skåne, Östergötland and Örebro counties all have tertiary referral hospitals.

The proportion of cephalosporins of the total antibiotic sales varied between counties, from 3.5% to 14.4%. The corresponding figures for fluoroquinolones were 8.3% to 13.8%, and 2.5% to 13.9% for piperacillin-tazobactam, and 2.4% to 7.6% for carbapenems, Figure 1.23. Taken together, the percentage of broad spectrum antibiotics (fluoroquinolones, cephalosporins, piperacillin with tazobactam and carbapenems) of all antibiotics in Swedish acute care hospitals varied from 27.9% in Värmland County to 36.2% in Östergötland County. In conclusion, there are major differences regarding the distribution of which group of broad spectrum antibiotics that is used, but the overall consumption of broad spectrum antibiotics is quite similar.

FIGURE 1.22. Percentage of narrow spectrum penicillins (penicillin V and G, J01CE) of all antibiotics in Swedish acute care hospitals 2015, per county.

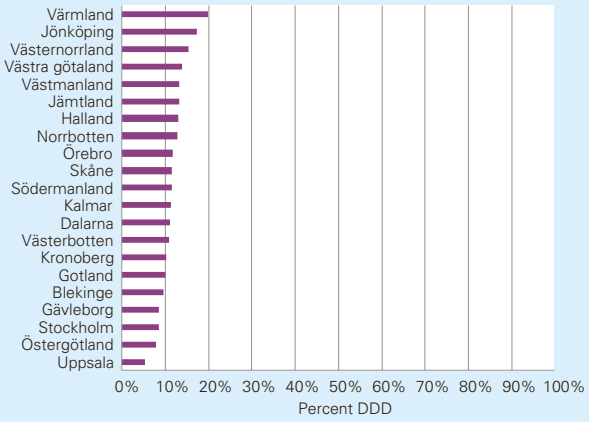


FIGURE 1.23. Percentage of broad spectrum antibiotics (fluoroquinolones, cephalosporins, piperacillin with tazobactam and carbapenems) of all antibiotics in Swedish acute care hospitals 2015, per county.

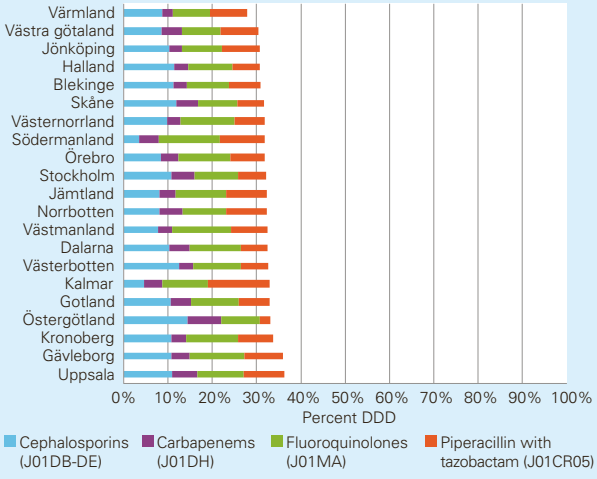
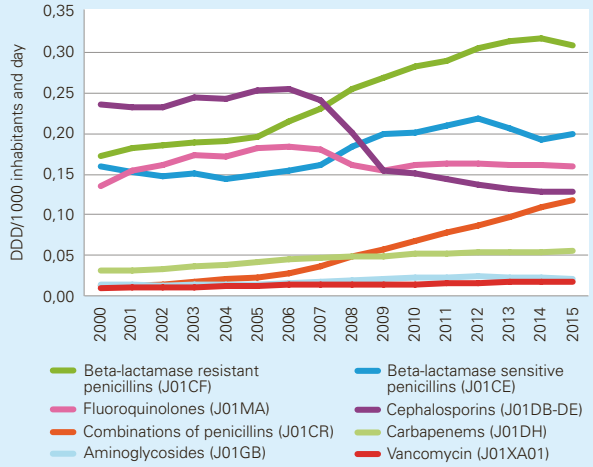


TABLE 1.3. Antibiotic consumption in hospital care 2000-2015, DDD/1 000 inhabitants and day.

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
J01 excl. methenamine	1.18	1.22	1.25	1.33	1.36	1.43	1.49	1.55	1.52	1.48	1.52	1.59	1.63	1.60	1.60	1.59
Methenamine (J01XX05)	0.03	0.03	0.03	0.05	0.07	0.07	0.07	0.07	0.05	0.03	0.03	0.02	0.02	0.02	0.02	0.02
Total J01	1.21	1.25	1.27	1.37	1.43	1.50	1.56	1.62	1.57	1.52	1.55	1.61	1.65	1.62	1.62	1.60

FIGURE 1.24. Antibiotic groups often used within hospital care 2000-2015, DDD/1 000 inhabitants and day.



Antibiotic consumption in hospitals

The total antibiotic sales on requisition have increased in Sweden during 2000-2007 and has since then been on a quite stable level. During the last year the consumption decreased some and the levels for 2015 are slightly lower than those in 2014. Even though we have not seen any increase since 2012, the consumption has still increased with 34% since the year 2000, from 1.18 to 1.59 DDD/1 000 inhabitants and day, Table 1.3.

Figure 1.24 is the same as Figure 1.21, the only difference is that this one includes all sales on requisition (hospitals, nursing homes and other units orders of antibiotics on requisition). The figure shows the clear shift from high use of broad spectrum antibiotics to narrow spectrum antibiotics. The consumption of cephalosporins, fluoroquinolones, aminoglycosides and vancomycin did not change during the last year. Beta-lactamase resistant penicillins decreased during the last year, while penicillins with enzyme inhibitor and carbapenems continued to increase like in previous years. Beta-lactamase sensitive penicillins also increased during 2015 after having decreased the two previous years.

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

Adverse reactions related to antibiotic use

Spontaneously reported drug-related adverse reactions are continuously entered into BiSi, a national database administered by the Swedish Medical Products Agency. The reports originate from health care professionals. The antibiotic related adverse reactions in the last five years, 2011-2015, 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=1 025), gastrointestinal disorders (n=299), hepato-biliary disorders (n=112), general disorders (n=170), blood disorders (n=81), neurological reactions (n=124), respiratory disorders (n=139), immune system disorders (n=176), musculoskeletal disorders (n=91), psychiatric disorder (n=48) and renal and urinary disorders (n=72), immune system disorders (n=176).

The majority of the reports (57%) concern female patients, which is corresponding to the gender difference seen in the antibiotic use.

The 10 antibiotic substances most commonly associated with adverse reactions, in the last 5 years unadjusted for consumption and regardless of the cause of the report are presented in Table 1.4.

TABLE 1.4. Most reported adverse drug reactions related to antibiotic agents to the Swedish Medical Products Agency 2011-2015.

Antibiotic	Total number of adverse drug reaction reports 2011 to 2015	Number of 'serious' reports	Number of fatal cases
Ciprofloxacin	222	131	3
Flucloxacillin	208	138	11
Phenoxymethyl-penicillin	199	86	0
Sulfamethoxazole and trimethoprim	140	85	1
Clindamycin	149	80	2
Nitrofurantoin	140	80	2
Amoxicillin	124	57	0
Doxycycline	92	40	0
Cefotaxime	93	49	3
Piperacillin and enzyme inhibitor	105	62	0

TABLE 1.5. Number of most frequently spontaneously reported adverse events for fluoroquinolones and nitrofurantoin, during the period 2011-2015.

	2011	2012	2013	2014	2015	2011-2015
Fluoroquinolones (J01MA)						
Total no of reports	25	19	28	46	54	172
Number of reactions						
Musculoskeletal	3	4	10	12	12	41
tendinitis	2	3	3	1	5	14
tendon rupture	3	3	3	1	2	12
Skin- and subcutaneous tissue	5	4	5	13	20	47
Psychiatric disorders	4	0	7	7	4	22
Nitrofurantoin (J01XE01)						
Total no of reports	25	30	20	21	40	136
Number of reactions						
Respiratory system	4	16	8	7	9	44
dyspnoea	1	4	5	4	5	19
interstitial pneumonia	0	2	1	0	3	6
pulmonary fibrosis	0	3	0	3	0	6
Skin- and subcutaneous tissue	10	17	6	4	18	55
General disorders	6	3	10	2	6	27
fever	3	2	4	1	6	16

We have previously reported that amended treatment recommendations resulted in changed prescription patterns for uncomplicated urinary tract infections. Due to the low number of reports and the fact that data are based on spontaneous reporting, no clear conclusions can be made regarding the selected reported adverse events for fluoroquinolones and nitrofurantoin in Table 1.5.

Sales of antibiotics for animals

Statistics on total sales of antibiotics for use in animals in Sweden are available since 1980. For a review of data from 1980-2000, see Svarm 2000 and for the following years the relevant Svarm- and Swedres-Svarm-reports. Data are derived from sales statistics. The sales represent an approximation of the use of antibiotics, assuming that the amount sold is also used during the observation period. Details on data source and inclusion criteria are given in Materials and methods, sales of antibiotics.

For Comments on trends by animal species, information from different sources is used to supplement the sales data.

Completeness of data

Until 2009, statistics on sales of antibiotics were assumed to be complete. Since, the Swedish pharmacy market has been reregulated. In 2011, it was noted that the information on sales of products with special license was less complete than in previous years and between 2012 and 2014, efforts have been made to obtain sales data for the main products sold with special license also from pharmaceutical companies. The system has been adjusted and it is assumed that the sales of this type of products is no less complete than before the reregulation.

Concerns have also been raised that data on sales of veterinary medicinal products with a general marketing authorisation from recent years are less complete than before the reregulation. It is assumed that the problem mainly or only concerns products sold on requisition to veterinarians (i.e. for use in their practice), which mostly are injectables. The difference in sales of seven selected products to pharmacies and from pharmacies to animal owners and veterinarians, expressed as kg active substance, were 8, 12 and 6% for 2013, 2014 and 2015, respectively. The estimate was limited to products for injection with general marketing authorisation in Sweden. Other types of products are less likely to be affected by the observed lack of completeness. For further information on the lack of completeness of data from recent years, see Materials and methods, consumption of antimicrobials.

Most of the trends identified in the data presented below have been observed before 2010. There are known explanations relating to e.g. changes in prescribing behaviour or improved animal health that support the view that there is a true decrease in antibiotic consumption. The exception is sales of benzylpenicillin where sales have decreased between 2010 and 2014.

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

Trends in animal populations

Changes in the numbers of animals may affect trends in statistics on consumption of antibiotics. Compared to 2010, the number of pigs slaughtered in 2015 has decreased by 13%, while the number of broilers has increased by 22%. The number of dairy cows was relatively unchanged during the same period. The number of horses was 363 000 in 2010. The number of dogs was 784 000 in 2012 and 729 000 in 2006. Further details on animal numbers and sources are found in Demographics and denominator data in this report.

Overall sales

Of the overall sales expressed as kg active substance, more than 90% are products formulated for treatment of individual animals (injectables, tablets, intramammaries) and less than 10% for treatment of groups or flocks (premixes, oral powders, solutions for in water medication). In 2015, the total reported sales from Swedish pharmacies of antibiotics for animals was 10 468 kg, of which 55% was benzylpenicillin. The corresponding overall figures for 2005 and 2010 were 16 389 kg and 14 117 kg, respectively. For information on sales of benzylpencillin, see Table 1.6. When interpreting the figures, the mentioned decrease in numbers of pigs slaughtered as well as the uncertainty of data from recent years must be borne in mind. Clearly, there is a true decrease

over time but as data from recent years are uncertain its magnitude cannot be estimated.

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

Sales of antibiotics for parenteral use

The sales of antibiotic products formulated for injection is presented in Table 1.6. Trends from 2010-2015 are uncertain as there is a lack of completeness in data (see Completeness of data). A slight increase in sales of penicillins from 2014 to 2015 can probably be explained by the apparent higher completeness in 2015.

Sales of injectable fluoroquinolones have decreased by 82% since 2010. In January 2013, a regulation limiting veterinarians' right to prescribe fluoroquinolones and third and fourth generation cephalosporins entered into force (SJVFS 2013:42). Antibiotics in these classes may only be prescribed for animals if a microbiological investigation shows that alternative choices cannot be expected to be effective. Exceptions are for example acute life threatening infections. The decrease in sales of these antibiotics is much larger than the estimated lack of completeness mentioned above, and the reduction from 2012 to 2013 was 34%. Further, an increase in sales of injectable trimethoprim-sulphonamides in 2013 probably reflects a switch to this class in situations when fluoroquinolones would have been used before the regulation. In 2014 and 2015, sales of trimethoprim-sulphonamides have been of similar magnitude as in 2013. Taken together, the sales data indicate that the regulation has accelerated an ongoing trend in reduction of sales of injectable fluoroquinolones.

Sales of antibiotics for oral medication of individual animals

The sales of products formulated for oral medication of individual animals are presented in Table 1.7. For this category, the completeness of data is likely to be high and trends can be assessed.

For all classes except trimethoprim-sulphonamides and aminoglycosides, this category of antibiotics consists of tablets sold for companion animals. The aminoglycosides also include products authorised for farm animals while from 2012, the trimethoprim-sulphonamides only include products authorised for oral use in horses.

The sales of fluoroquinolones have decreased gradually since 2005. A more pronounced decrease is noted after 2012 (- 56% to 2015). This is probably a reflection of the above mentioned regulation restricting veterinarians' prescribing of fluoroquinolones.

Major downward trends from 2010-2015 are noted for all classes. For further comments see Comments on trends by animal species, Horses and Dogs.

TABLE 1.6. Yearly sales of antibiotic drugs for parenteral use (injections), expressed as kg active substance. Figures are uncertain because of indications of lack of completeness.

ATCvet code	Antibiotic class	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
QJ01AA	Tetracyclines	548	564	588	557	527	492	471	422	424	396	335
QJ01BA	Amphenicols								0	3	7	11
QJ01CA, QJ01CR	Aminopenicillins	142	134	142	143	152	144	146	143	131	145	165
QJ01CE, -R, QJ51	Benzylpenicillin	7493	7778	7505	7674	7641	7492	6627	6290	5901	5455	5800
QJ01DD	Cephalosporins	26	26	26	25	21	13	13	8	4	2	4
QJ01G, -R,	Aminoglycosides	362	345	343	318	301	272	246	210	104	145	144
QJ01E	Trimethoprim & sulphonamides	825	804	685	691	669	685	667	699	857	849	825
QJ01F	Macrolides & lincosamides	225	241	216	136	118	101	95	95	95	90	90
QJ01MA	Fluoroquinolones	123	132	125	118	113	105	83	69	29	25	19
QJ01XX92, - 94	Pleuromutilins	29	39	36	36	28	17	13	14	17	13	10
Total		**9773**	**10064**	**9666**	**9699**	**9568**	**9322**	**8362**	**7950**	**7565**	**7125**	**7402**

TABLE 1.7. Yearly sales of antibiotic drugs for oral medication of individual animals, expressed as kg active substance.

ATCvet code	Antibiotic class	2005	2006	2007	2008	2009	2010	2012	2013	2014	2015
QJ01AA	Tetracyclines	75	45	44	47	48	46	50	47	38	31
QJ01CA, QJ01CR	Aminopenicillins	769	775	756	681	650	598	501	500	460	445
QJ01DB	Cephalosporins	984	1186	924	792	714	562	402	325	297	263
QA07AA	Aminoglycosides	115	131	126	131	118	109	102	77	61	100
QA07AB, QJ01E	Trimethoprim & sulphonamides	2260	2189	2179	2028	1838	1670	1442	1169	1164	1081
QJ01FF	Lincosamides	176	176	194	216	214	210	178	164	159	144
QJ01MA	Fluoroquinolones	57	59	52	46	46	39	32	22	18	14
Total		**4436**	**4559**	**4276**	**3941**	**3630**	**3234**	**2706**	**2304**	**2198**	**2079**

Sales of antibiotics for oral medication of groups of animals

Data on sales of antibiotics formulated for medication of groups of animals are given in Table 1.8. Data for 1984 are given as historical reference. As for products for oral medication of individual animals, completeness is assumed to be high. Today, the sales of products for medication of groups of animals are 3% of what it was on average before 1986 (counting the sum of veterinary medicines and growth promoters, average for 1980, 1982 and 1984: 28 961 kg).

Products for medication of groups of animals are mainly for treatment of pigs. There has been an overall decrease in sales of such products since 2010 (Table 1.8). Expressed as g active substance per pig produced, sales of products for group medication were 0.66 and 0.33 g/pig in 2005 and 2015, respectively. The sales of pleuromutilins have decreased since the mid 90s and were 63% lower in 2015 than in 2005. 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 consumption figures. There is a continued drop in sales of tetracyclines for group medication, but sales of macrolides seems to have stagnated (see also Consumption by animal species, Pigs).

Sales of antibiotics for intramammary use

In 2015, a total sales from pharmacies of 88 059 dose applicators for use in lactating cows were reported. In 2014, the corresponding figure was 93 090. An error was discovered in the figures reported in 2014 (79 790 dose applicators) and that explains the difference between this figure and the one reported in Swedres-Svarm 2014. There are two products of this type on the Swedish market, one with only procaine benzylpenicillin and one with procaine benzylpenicillin combined with dihydrostreptomycin.

The sales of intramammary products for use at drying off were 227 096 dose applicators in 2015 compared to 231 520 in 2014. On the Swedish market, there are two products of this type, both containing prodrugs of benzylpenicillin in combination with either framycetin or dihydrostreptomycin.

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

Comments on trends by animal species

Dairy cows

Växa Sweden publishes a yearly report related to the livestock organisations' work to improve animal health and welfare in dairy cows (Växa Sverige, 2016). For statistics on incidence of antibiotic treatments of dairy cows enrolled in the Swedish milk recording scheme, data are retrieved from a database with veterinary reported disease events and treatments (Jansson Mörk, 2010).

According to Växa Sweden (2016), the by far most common indication for treatment of dairy cattle is mastitis. In Sweden, mastitis is generally treated systemically and any changes in treatment incidence, treatment length or choice of antibiotic for this condition will have a noticeable influence on the statistics on sales of antibiotics. The reported incidence of treatment of clinical mastitis in dairy cows has decreased over the last ten years and was 9.8 recorded treatments per 100 completed/interrupted lactations in 2014/2015. Treatment with benzylpenicillin was by far the most common (around 90%).

TABLE 1.8. Yearly sales of antibiotic drugs authorised for group treatment and of ionophoric anticoccidials sold, expressed as kg active substance.

ATCvet code	Antibiotic class	1984 →	2005	2006	2007	2008	2009	2010	2011[a]	2012	2013	2014	2015
QA07A	Intestinal anti-infectives		163	170	158	106	107	119	77	75	76	80	91
QJ01A	Tetracyclines	12300	934	903	1217	1040	594	575	552	408	463	352	317
QJ01C	Penicillins incl. aminopenicillins			11	28	111	266	164	36	5	13	30	31
QJ01EW	Sulphonamides & trimethoprim												42
QJ01F	Macrolides & lincosamides	607	680	837	1 107	744	657	427	361	359	305	235	251
QJ01MA	Fluoroquinolones		5	5	3	5	5	4	2	6	1	2	1
QJ01MQ	Quinoxalines[b]	9900											
QJ01XX91	Streptogramins[b]	8800											
QJ01XX92, -94	Pleuromutilins		309	420	471	536	370	157	127	85	109	101	113
QP51AA	Nitroimidazoles	1440											
	Feed additives[c]	700											
Total		**33747**	**2091**	**2346**	**2984**	**2543**	**1999**	**1447**	**1154**	**937**	**968**	**800**	**845**
QP51AH	Ionophoric antibiotics (coccidiostats)[d]	7900	11095	12335	12527	13376	12471	15325	14693	12860	15965	15800	18204

[a] For some classes, data on sales of products sold with special licence may be incomplete for 2011 (indicated in red). Drugs with special licence prescription include colistin, tetracyclines, aminopenicillins and small quantities of benzylpenicillin; [b] Years 1980-1984 sold as feed additives, thereafter on veterinary prescription at therapeutic dosages until 1997; [c] Feed additives other than quinoxalines and streptogramins: avoparcin, bacitracin, nitrovin, oleandomycin and spiramycin; [d] Figures are from the Feed Control of the Board of Agriculture (www.sjv.se). Figures for 2013 and 2014 have been updated.

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

Pigs

Most of the sales of antibiotics for pigs are dispensed by pharmacies (on prescription) directly to the animal owner, i.e. sales of products intended for use in pigs on requisition by a veterinarian are not common. Data are therefore not likely to be affected by the lack of completeness discussed above (see Completeness of data).

In 2010 and 2015 the sales of antibiotics for pigs was 3 369 and 2 126 kg active substance, respectively, or 12.8 and 12.1 mg/kg slaughtered pig. Of the total sales in kg active substance during 2015, 77% were products for use in individual animals, and of these 60% were products containing benzylpenicillin. Colistin is used for treatment of weaning diarrhoea in herds with acute problems. In 2015, the sales corresponded to 0.4 mg/kg pig slaughtered. The total sales of fluoroquinolones for pigs was only 1.5 kg active substance and there were no sales of third generation cephalosporins for pigs.

The overall sales have been stable over the last five years but the sales of products for individual medication have increased and products for group medication have decreased (see Consumption of antibiotics for group medication). A shift from products for medication of groups of animals via feed or water towards medication of individual animals, preferably with narrow spectrum substances such as benzylpenicillin is observed over the last ten years. This is well in line with guidance on appropriate use of antibiotics (Läkemedelsverket 2012).

Poultry

Antibiotics are rarely used for treatment of bacterial diseases in commercially reared *Gallus gallus*. Localized outbreaks can therefore have a major influence on the sales in a specific year. Over the last five years, the yearly sales of fluoroquinolones for slaughter chickens and hens have been below or much below 0.5 kg. In 2015, there were no reported sales of fluoroquinolones for chickens, hens or turkeys. Cephalosporins or colistin are never used.

From 2011, the Swedish poultry meat association requests all treatments of broilers, parents and grandparents to be reported as part of the Poultry health control programme. According to the reports, a total of 28 of 3 191 broiler flocks (0.9%) were treated in 2015. This corresponds to 0.16 mg active substance/kg slaughtered chicken. In all but one case, the flocks were treated with amoxicillin or phenoxymethylpenicillin. In addition, grandparent and parent flocks (244 flocks in total) were treated on 37 occasions, mostly with phenoxymethylpenicillin.

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

Horses

More than half of the sales of trimethoprim-sulphonamides are products for oral use in horses (paste or powder). The sales of such products increased steadily until 2006 but from 2010, there has been a decrease by 30%. Among the indications for trimethoprim-sulphonamides in horses are reproductive disorders and various conditions in foals. Between 2009 and 2013, the number of mares covered and number of foals born has decreased (Anonymous, 2014). Thus, it is probable that the decrease in sales of trimethoprim-sulphonamides is partly explained by the lower number of mares covered and a lower number of foals born. In 2013, guidelines for use of antibiotics in horses were published by the Swedish Veterinary Association. It is possible that this guidance, together with an overall strong focus on the need for antibiotic stewardship in human and veterinary medicine has also contributed to the observed decrease.

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

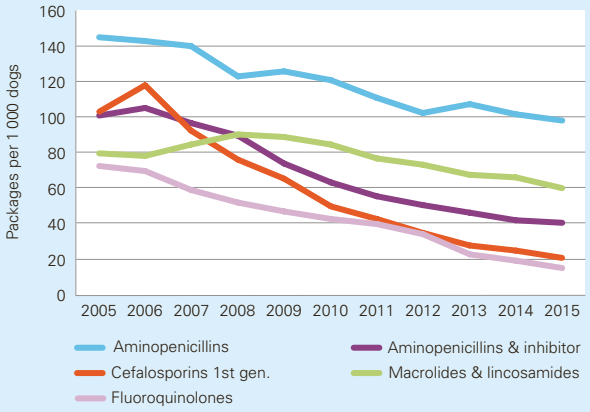
Dogs

Data on outpatient sales of antibiotics authorised for medication of dogs have a high degree of completeness. In 2015, the overall sales of veterinary products for oral medication of dogs was 804 kg compared to 1 348 kg in 2010 and 1 967 kg in 2005. Aminopenicillins, first generation cephalosporins and lincosamides were by far the classes with largest consumption in 2015 (288, 254 and 136 kg, respectively).

The figures above refer to sales of veterinary products only. In 2006, the total number of all prescriptions of antibiotics for oral use in dogs, i.e. both veterinary antibiotics and those authorised for use in humans, corresponded to 563 packages per 1000 dogs. Since then, the number of prescriptions has decreased to 260 packages per 1 000 dogs (-53%). Trends over time for the five largest classes (90% of the total sales) are illustrated in Figure 1.25. The most prominent changes relative to 2006 are noted for cephalosporins (-83%), fluoroquinolones (-79%) and amino-penicillins with clavulanic acid (-62%).

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

FIGURE 1.25. Sales of the five largest antibiotic classes among antibiotics for oral medication of dogs expressed as packages per 1 000 dogs (2015). Data include antibiotics authorised for veterinary use as well as antibiotics for human use.



Comparison of antibiotic consumption in human and veterinary medicine

Data included and calculations

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

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

Comparison of consumption in tonnes active substance

In 2015, a total of 61.2 and 10.2 tons of antibiotics in included ATC classes were consumed in human and veterinary medicine, respectively. It should be noted that there is a lack of completeness of the sales of antibiotics for animals (See Completeness of data in Sales of antibiotics for animals). Figure 1.26 displays the consumption of beta-lactam antibiotics. These substances are by far the most consumed antibiotics in both human and veterinary medicine and also represent the largest amounts measured as kilograms. Penicillins ((Q) J01C) represent most of the amount in kg active substance of antibiotics for both humans and animals; 77 and 62%, respectively. The substances shown in Figure 1.27 are consumed in smaller quantities (n.b. the difference in indexation of the x-axis between the figures), but given their chemical and pharmacological properties, their impact on the emergence of antibiotic resistance and the environment is probably more pronounced than that of the penicillins. In the figures, only antibiotics consumed in a total quantity exceeding 1 000 kg during 2015 are included. The only class where consumption in animals outweighs human consumption is trimethoprim-sulphonamides, of which more than half are products only authorised for use in horses.

FIGURE 1.26. Consumption of beta-lactam antibiotics in human and veterinary medicine, kg active substance, 2015. Please note the difference in indexation of the x-axis between figures 1.26 and 1.27.

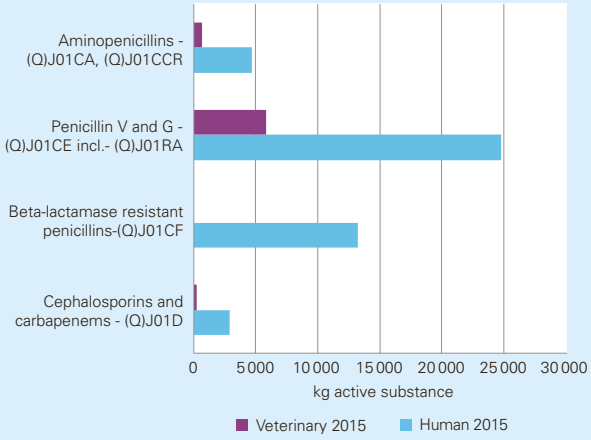
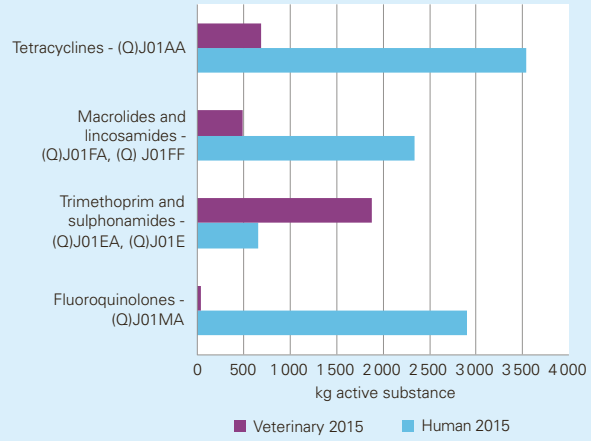


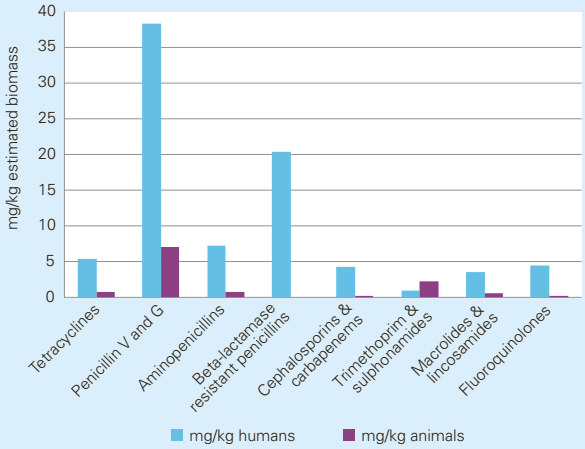
FIGURE 1.27. Consumption of fluoroquinolones, macrolides, lincosamides, trimethoprim and suphonamides, and tetracyclines in human and veterinary medicine, kg active substance, 2015. Please note the difference in indexation of the x-axis between Figure 1.26 and 1.27.



Comparison of consumption expressed as mg per kg estimated biomass

In 2015, the consumption was 94.4 and 12.7 mg active substance per kg estimated biomass in human and veterinary medicine, respectively. In Figure 1.28 a comparison of consumption of antibiotics for use in humans and animals are shown expressed as mg per estimated kg biomass. Data on the total consumption do not take the heterogeneity of the likelihood of exposure within the population into account. This is especially true for data on consumption for use in animals, as certain substances may only or mainly be sold for use in one particular animal species. This means that the selective pressure in a particular subset of the population (i.e. a particular animal species) can be far larger than in the total population. Nevertheless, in Figure 1.28 the largest difference is noted for the fluoroquinolones where consumption in humans is 107 times higher than in animals.

FIGURE 1.28. Consumption of antibiotics in humans and animals expressed as mg active substance per estimated kg biomass in 2015. Only classes where the total consumption exceeded 1 000 kg active substance are shown.



Antibiotic resistance

Notifiable diseases

For humans four bacterial types of antibiotic resistance are included in the Swedish Communicable Diseases Act. These are *Staphylococcus aureus* with resistance to methicillin and other betalactam antibiotics (MRSA), *Streptococcus pneumoniae* with reduced susceptibility or resistance to penicillin (PNSP), *Enterococcus faecalis* and *Enterococcus faecium* with resistance to vancomycin (*vanA* or *vanB*, VRE), and Enterobacteriaceae carrying ESBL or $ESBL_{CARBA}$. As in previous years, the reports of ESBLs have outnumbered the other three types manifold.

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

Increased number of persons arriving in Sweden and seeking asylum

During 2015 more than 160 000 persons seeking asylum were received in Sweden. The most common countries of origin were Syria (51 338), Afghanistan (41 564), and Iraq (20 857). This has been associated with a marked increase in the reported cases of MRSA and in an increase in the reported cases of $ESBL_{CARBA}$. Refer to the respective resistance types for further information.

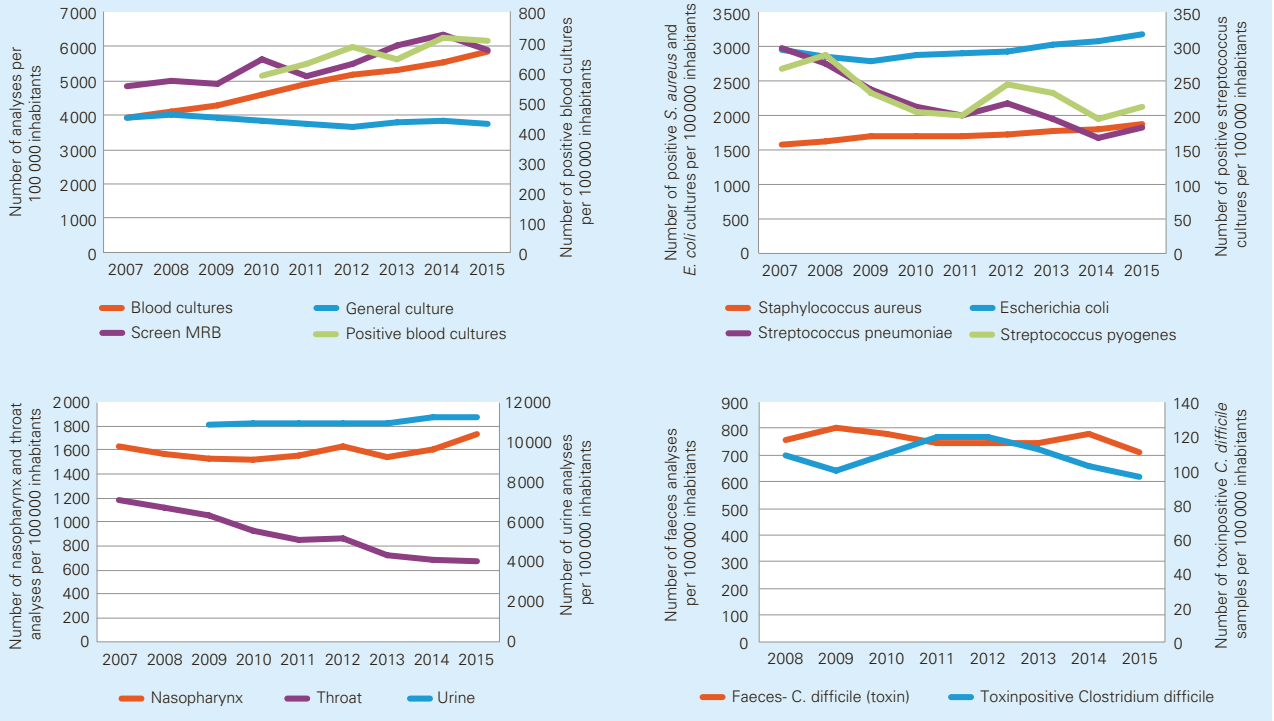
Overview of sampling and culture results in humans

Denominator data has been collected since 2001 on a voluntary basis from the microbiology laboratories in Sweden and reported each year in Swedres-Svarm as background data. The reporting laboratories, this year 24 out of 25, cover more than 95 percent of the population. Some modifications of the data collection has been made during the years, for instance were analyses of toxinpositive *C.difficile* included year 2008, urine cultures analyses included year 2009 and positive blood culture analyses included year 2010. Complete data for 2015 are given in the section Demographics and denominator data.

In the following figure 2.1 the annual numbers of requested analyses per 100 000 inhabitants are presented for: blood culture, MRB screening culture, general culture, throat culture, nasopharynx culture, urine culture, and *C. difficile*. Number of positive blood cultures per 100 000 inhabitants and number of isolated *S. aureus*, *E. coli*, *S. pneumoniae*, and *S. pyogenes* in all specimen types per 100 000 inhabitants are also given.

The trend for blood cultures, and MRB screening cultures requested annually per 100 000 inhabitants have increased continuously, except for MRB-screen which decreasesed the

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



Next-generation sequencing as a tool for epidemiological and resistance investigations

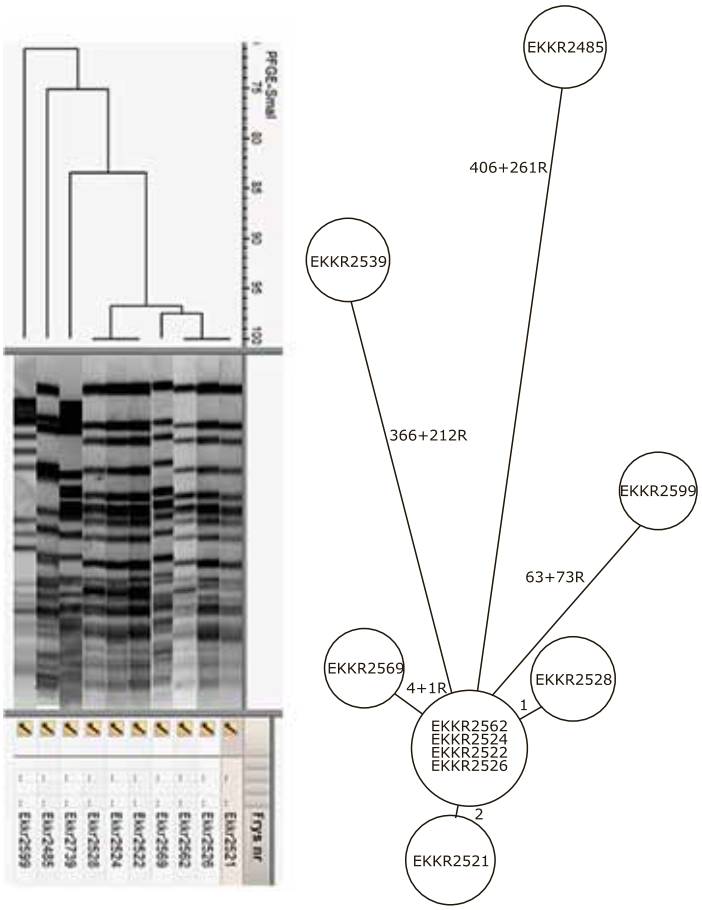
Background

The technological developments within next-generation sequencing (NGS) have enabled generation of large amounts of nucleic acid sequence data in short turnaround times and at a low cost. Although little impact has been seen to date on the diagnosis and treatment of patients with an infectious disease, the technology has greatly improved contact tracing investigations, surveillance programmes and monitoring of antimicrobial resistance mechanisms.

The relatively small genome of most infectious agents enables truly cost effective analysis by whole genome sequencing (WGS). The data generated from one WGS analysis of a microbiological sample can be used to answer a wide range of questions.

In terms of monitoring occurrence of resistance genes NGS has been used both in virology and bacteriology. The limitations are set by knowing the genetic sequence or mutations that confer resistance to an antimicrobial or antiviral drug. Once the infectious agent has been sequenced the genome can be matched against a database of known resistance genes or mutations to identify resistant genotypes. As not all mechanisms of resistance are known or linked to a genetic marker, phenotypic susceptibility testing is still important to carry out. A conflicting result between a positive genotype and a negative phenotype can be explained by several factors, like mutations in the promoter regions of resistance genes or single nucleotide polymorphisms (SNPs) that reduce or completely remove the activity of a resistance mechanism, these are mutations that apply mostly to enzyme mediated resistance mechanisms, like extended spectrum beta lactamases. Resistance mechanisms that are mediated by more than one gene or SNP are more complex to monitor solely by determining the genotype. For such advanced mechanisms like porin-mediated permeability and proton efflux pumps, phenotypic analysis of susceptibility has to be performed for diagnostic purposes until the genetic factors involved in that specific resistance mechanism are fully elucidated.

FIGURE 1. Comparison of PFGE and WGS analysis of related and unrelated isolates of *E. faecium* sequence type 117.



Rapid identification and control of outbreaks is another area where NGS has had a large impact. The most common methods to study inter-strain relationships are MLST, core genome MLST or whole genome/core genome SNP analysis. Depending on the setting and questions that need to be answered, different approaches can be used. An amplicon based (multiplex PCR of only the genes included in the MLST scheme) MLST is the most cost effective method but also the method with least discrimination. If more resolution is needed, a core genome MLST can be performed, this approach requires sequencing of the whole genome as well as a well characterized reference genome(s) to define a core genome (i.e. a set of genes shared by all analyzed strains) and a unique typing nomenclature. By having a well-defined nomenclature, whole genome MLST enables easy sharing and comparison of results. If the requirements for establishing a whole genome MLST are not met, inter-strain relationships can be studied by using whole genome or core genome SNP analysis which has the same or greater discriminatory power as a core genome MLST but inter laboratory sharing of data is not standardized.

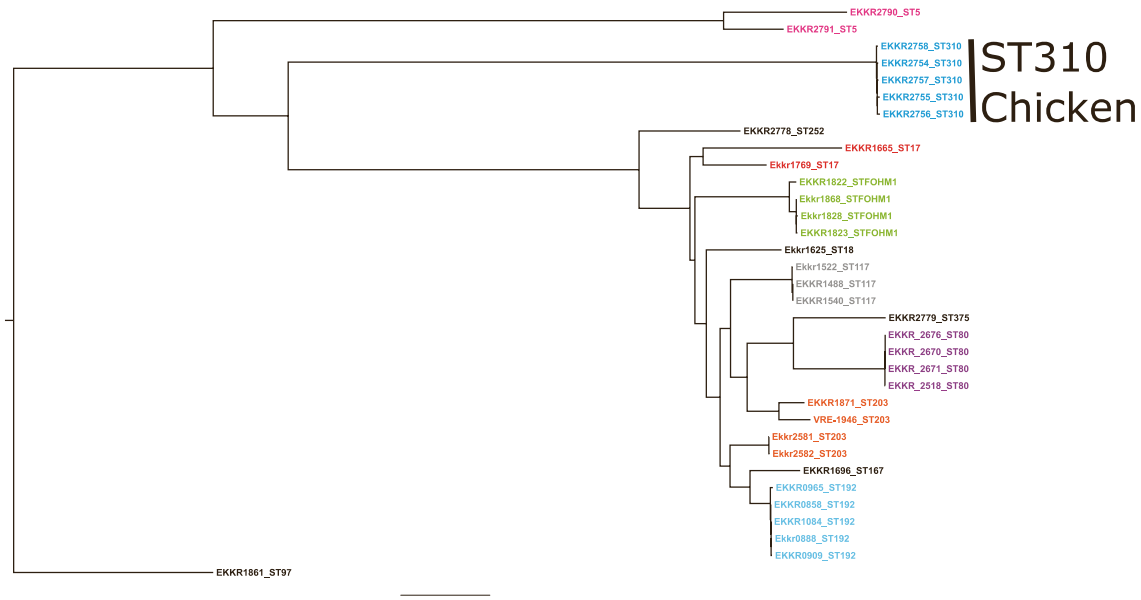
In Sweden several of the above mentioned methods have been applied to improve surveillance programs and contact tracing in outbreak investigations. A practical example of this, is the surveillance program of vancomycin resistant enterococci (VRE), which monitors the situation of VRE within Swedish hospitals. VRE is associated with hospital-acquired infections, they are naturally resistant to many antibiotics and have a high ability to acquire resistance which gives them a survival advantage in hospitals. WGS has been introduced within the VRE surveillance program to replace more time-and labor intensive methods for molecular typing and detection of resistance gene such as Pulsed-field gel electrophoresis (PFGE) and PCRs. When comparing PFGE data with WGS data, we see high concordance between the methods in determining the genetic relationship of the bacterial strains, both methods give similar results in regard to ruling isolates in or out of possible outbreaks (Figure 1).

Further advantages gained by shifting to WGS and SNP-analysis is the ability to perform in silico PCR and determine the presence or absence of antibiotic resistance genes that would normally have required additional laboratory analysis. The increase in discriminatory power obtained by preforming WGS rather than PFGE also enables sharing of results between laboratories. For example, by comparing our VRE genome data to Danish VRE data we could confirm that an international transmission was the origin of a small VRE outbreak in southern Sweden.

Practical example

WGS has also been used to compare human and animal isolates of VRE. *E. faecium* isolates from broilers were compared to previously sequenced human isolates, investigating both the presence of the gene responsible for vancomycin resistance and the gene recently described to putatively mediate elevated MIC towards narasin (Nilsson et al 2016). The main scope was to determine the presence of the gene that putatively mediates an elevated MIC towards narasin as a marker for isolates (or rather plasmids) with a broiler association. No such association was however found in the 250 VRE isolates from humans that had been sequenced (Figure 2). The narasin gene was however found in human isolates of *E. faecalis*. Genetically the two species of Enterococci are rather different and WGS cannot at this time be used to establish

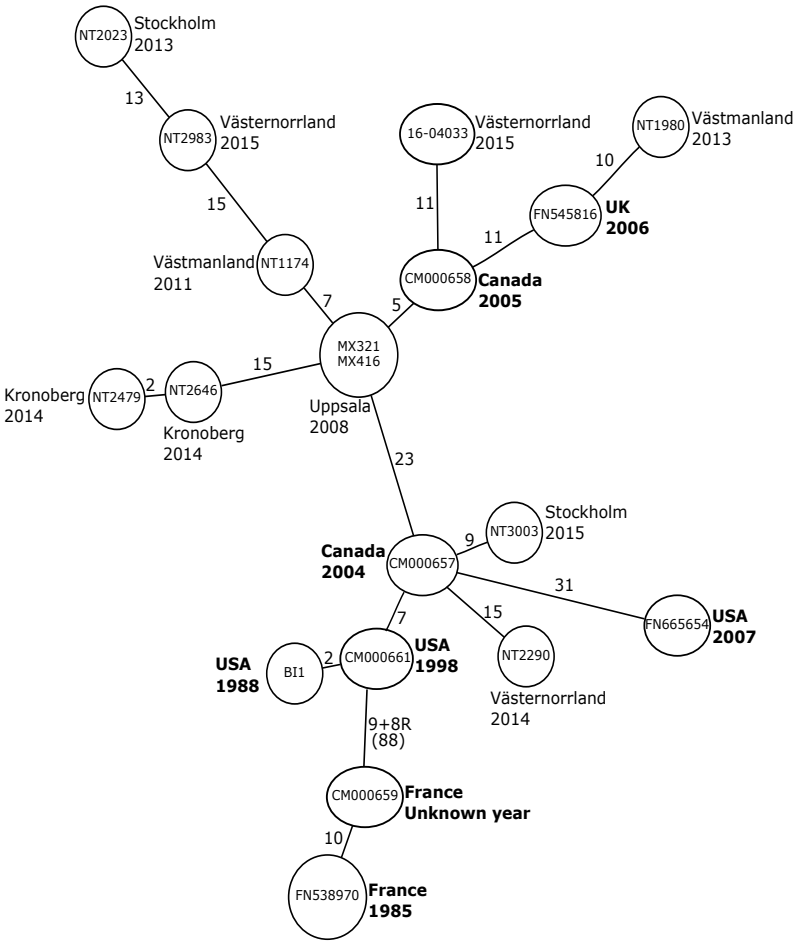
FIGURE 2. Approximate maximum likelihood tree showing the relationship between human and chicken isolates of *E. faecium*.



if a plasmid transfer between animal isolates of *E. faecium* and human isolates of *E. faecalis* has occurred. These issues will probably be answered in a near future using WGS, but the advances in technology also brings into question if plasmid transfer between non-related strains and species should be investigated during outbreak situations.

The study of inter-strain relationship of *C. difficile* ribotype 027 is another practical example of how WGS has been used to answer questions of public health relevance. *C. difficile* PCR ribotype 027, is a hyper virulent type associated with a more severe clinical presentation, higher relapse rate, increased mortality and resistance to multiple antibiotics (Kuijper et al 2006). Outbreaks of this specific type have occurred across Europe and North America and the incidence of ribotype 027 has increased since the beginning of the year 2000. Since the start of the Swedish national surveillance program in 2009 we have observed sporadic cases of *C. difficile* ribotype 027 and one known outbreak in the County of Kronoberg in 2014. To assess whether the Swedish cases are related or the result of independent import events, we performed WGS on a selection of isolates and compared them to publicly available genomes of *C. difficile* ribotype 027. The result of the core genome SNP analysis is shown in Figure 3 as a minimum spanning tree. The relatively large genetic differences between Swedish type 027 isolates indicate that transmission within or between Swedish counties is a rare event. Thus, except from the known outbreak in Kronoberg County in 2014, we conclude that most isolates so far have been independent import cases (the identical isolates from Uppsala County in 2008 were collected from the same patient).

FIGURE 3. Minimal spanning tree showing the relationship of Swedish and international strains of *C.difficile* ribotype 027. The relatively large genetic differences between Swedish strains indicate that transmission within or between Swedish counties is unlikely. SNP differences are shown over the branches, recombination events are marked as R and the total number of SNPs is shown in parenthesis. The length of the branches is not relative to the relationship distance.



Reference:

Kuijper EJ, Coignard B, Tull P. Emergence of Clostridium difficile-associated disease in North America and Europe. Clin Microbiol Infect. 2006;12 Suppl 6:2-18.

Nilsson O, Myrenås M, Ågren J. Transferable genes putatively conferring elevated minimum inhibitory concentrations of narasin in Enterococcus faecium from Swedish broilers. Vet Microbiol. 2016; 184 80-83

last years. Part of this decrease is associated with the ending of a large outbreak of VRE. The trends for number of positive blood cultures, and isolated *E. coli* and *S. aureus*, regardless of specimen type, were also increasing. Throat cultures and the isolation of *S. pyogenes* has decreased the past years, likely due to an increased use of near patient testing for streptococcal tonsillitis. Though for *S. pyogenes* there is an increased number of isolates the last year.

ESBL-producing Enterobacteriaceae

ESBL-producing Enterobacteriaceae in humans

Background

ESBL-producing Enterobacteriaceae has been notifiable by clinical laboratories according to the Communicable Diseases Act since February 2007. As there is no clinical reporting, information on ESBL cases is limited to data on age, gender and sample type. From 2010, the definition of ESBL included not only classical ESBLs (=$ESBL_A$), which are inhibited by clavulanic acid, but also plasmid-mediated AmpC-beta-lactamases (= $ESBL_M$) and metallo-betalactamases/carbapenemases (= $ESBL_{CARBA}$). In March 2012 the notifications of bacteria with $ESBL_{CARBA}$ were extended to include both a laboratory and a clinical report, additionally contact tracing became mandatory.

TABLE 2.1. Distribution of species among human cases of ESBL-producing Enterobacteriaceae 2015.

Species	Number of cases	Proportion, %
Escherichia coli	8 462	85.6
Klebsiella pneumoniae	850	8.6
Proteus mirabilis	95	1.0
Shigella species	47	0.5
Citrobacter species	37	0.4
Salmonella species	7	0.1
Enterobacreiaceae (not specified or species not reported)	386	3.9
Total number reported	**9 884**[a]	

[a] In 276 patients two or more ESBL-producing species were reported resulting in a higher number of isolates than number of cases reported.

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

A total of 9 584 cases were notified in 2015, an increase with 8% compared to 2014. Since 2007 the number of cases has increased continuously each year with 8-33%. The national incidence was 97 cases per 100 000 inhabitants. An increased incidence was seen in 17 out of 21 Swedish counties, with the highest incidence found in Jönköping county (143 cases per 100 000 inhabitants; Figure 2.2). There was almost a three-fold difference in incidence between the counties. In part the large variation in incidence between counties could be explained by different screening and contact tracing practices.

The most commonly reported species was *Escherichia coli* found in 86% of all cases, followed by *Klebsiella pneumoniae* with 9% (Table 2.1). ESBL-producing *Shigella* species and *Salmonella* species were reported in 47 and 7 cases respectively in 2015.

ESBL-producing bacteria were most often found in urine samples (56%). The second and third most common sources were fecal and rectal samples with 21% and 13% respectively. Sampling from feces and rectum for screening purposes has increased in recent years. Isolates from blood and wound samples constituted four percent and two percent, respectively, and isolates were from other samples in five percent of the cases. During 2015, 578 cases with ESBL-producing bacteria were reported as invasive infections (576 in blood and 2 in liquor). This is an increase of 11% compared to 2014 when 520 persons were reported. Among these, 473 were new cases for 2015 and 105 were known carriers of ESBL, notified during the previous years. For details on the frequencies of antibiotic resistance among clinical samples, especially blood and urine samples, please see below in chapter: Resistance in clinical isolates from humans.

FIGURE 2.2. The incidence (cases per 100 000 inhabitants) of ESBL-producing Enterobacteriaceae in Swedish counties 2011-2015, arranged according to incidence figures 2015.

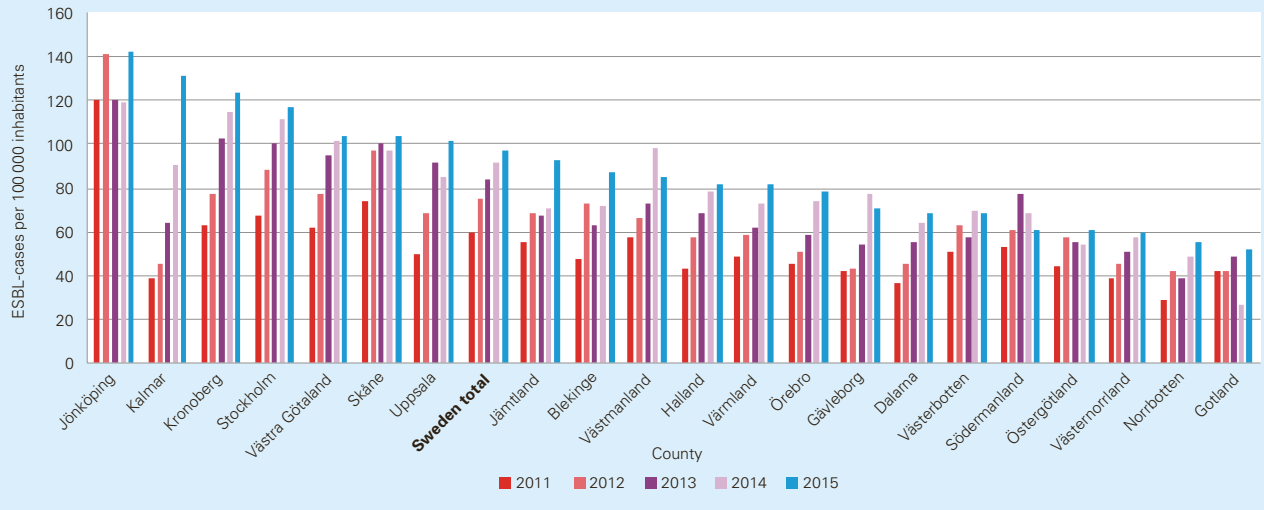
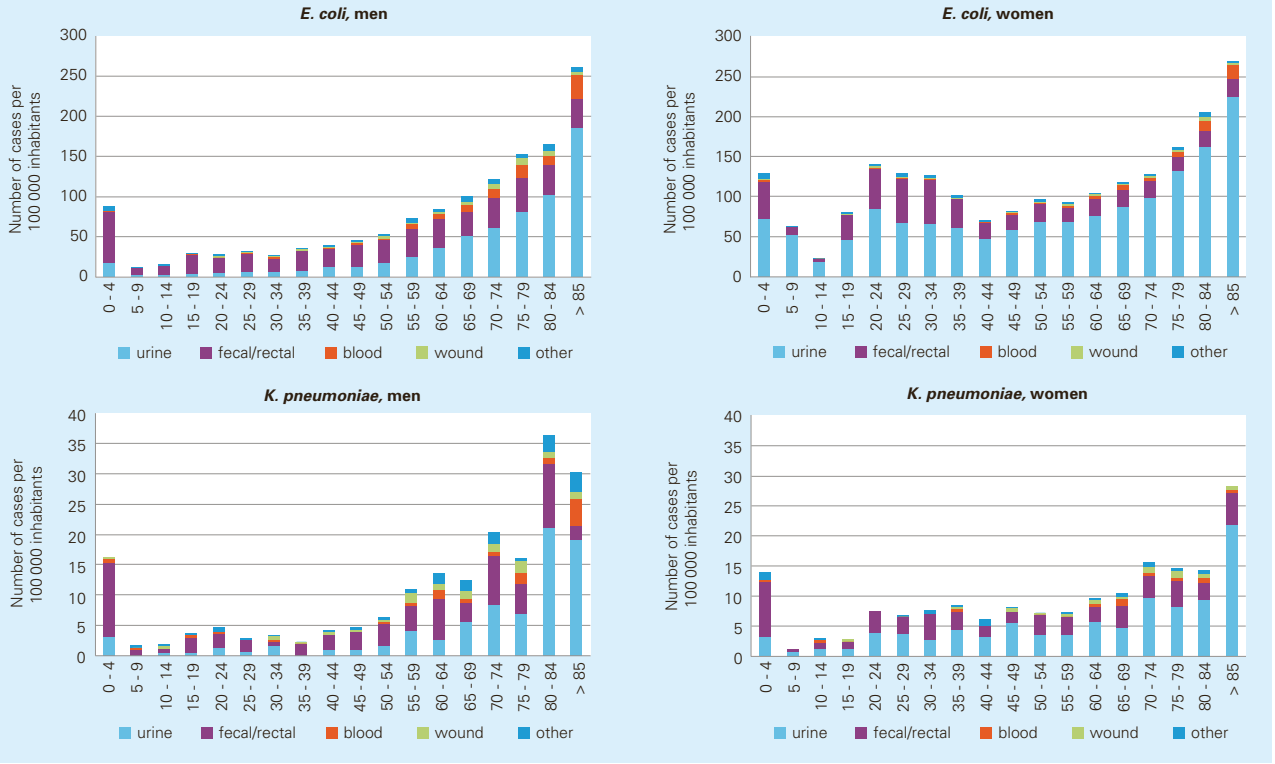


FIGURE 2.3. Age, gender and sample type distribution of human cases of ESBL-producing *E. coli* and *K. pneumoniae* 2015.



The incidence in age and gender groups for both *E. coli* and *K. pneumoniae* reflects the expected occurrence of urinary tract infection in the different groups (Figure 2.3). ESBL-producing *E. coli* were derived from women in 65% of the cases. They had a median age of 47 years compared to 59 years for men. The *K. pneumoniae* ESBL cases were more equally distributed between sexes, with median ages of 54 years for women and 61 years for men.

Outbreak investigations

In 2015, one food-related outbreak with ESBL-producing *Shigella* was reported. The outbreak was linked to fresh coriander and affected 42 persons. Clusters with both ESBL-producing *K. pneumoniae* and *E. coli* have been noted at neonatal units during 2015. A cluster with ESBL-producing *E. coli* affecting nine persons at a nursing home was also reported 2015.

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

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

The rationale behind the strengthened notification was that ESBL$_{CARBA}$, pose an even greater threat because of the further limited treatment options. ESBL$_{CARBA}$ of clinical importance belong to one of three kinds, either KPC (*K. pneumoniae* Carbapenemase)/IMI (imipenem-hydrolyzing β-lactamase), MBLs (Metallo-betalactamases, i.e. NDM, VIM and IMP) or certain OXA-enzymes. In Sweden, all enzymes with carbapenemase activity are denoted ESBL$_{CARBA}$ (Giske et al., 2009).

In 2015, 115 new cases with an ESBL$_{CARBA}$-producing Enterobacteriaceae were reported, compared to 46 new cases in 2014. Cases were reported from sixteen Swedish counties with more than half of the cases being reported from Stockholm and Västra Götaland. Twenty three cases were reported as domestic and ninety cases were acquired abroad. (Figures 2.4). The five most common countries for imported infections were Syria (19 cases), Turkey (11), India (7), Greece (5) and Spain (5). The relatively large number

FIGURE 2.4. Number of human cases of ESBL$_{CARBA}$ annually notified in Sweden, 2007-2015.

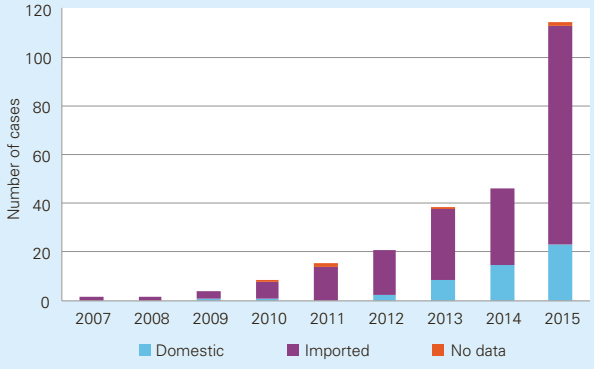
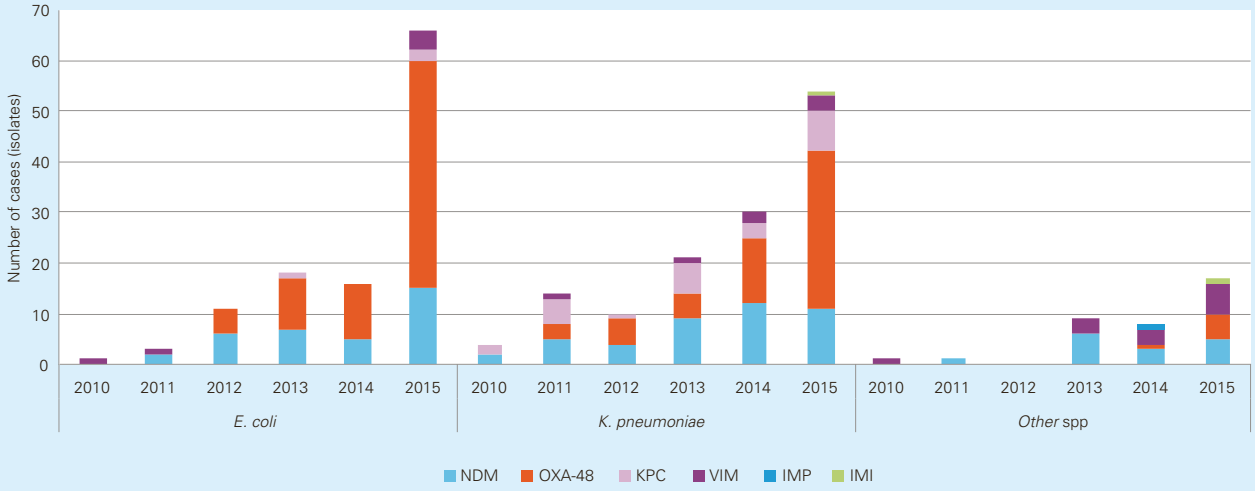


FIGURE 2.5. Number of isolates of different species with different ESBL-enzymes among human cases with $ESBL_{CARBA}$ in Enterobacteriaceae in Sweden 2010-2015. In samples from 30 cases (2013-2015) two or more $ESBL_{CARBA}$-producing species were reported resulting in a higher number of isolates than number of cases reported. In samples from nine patients (2013-2015) two different enzyme types were detected in the same sample.

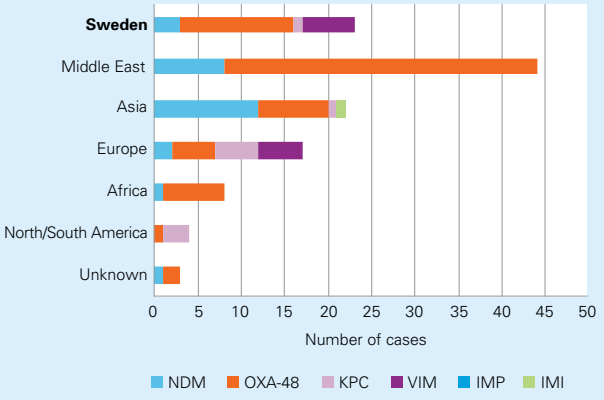


of cases acquired in Syria suggests an association with the large number of refugees arriving in Sweden during 2015. A majority of the domestic cases, eleven cases, were detected by screening, six were found by contact tracing and five due to clinical symptoms. Of the imported cases, seventy-three were detected through targeted screening, thirteen due to clinical symptoms and three by contact tracing. For one of the domestic cases and one of the imported cases no reason for detection was given. The way of acquisition for the domestic cases were related to hospital care (13 cases), community acquired (3) and by household contacts (2). For five domestic cases there was no information of acquisition. Among the imported cases hospital acquired infection dominated (64 cases). The other ways of acquisition for the imported cases in 2015 were, infections related to healthcare/care outside hospital (7 cases), community acquired infections (6), household contacts (1) and for two cases the infection was stated to be food-and waterborne related. For ten of the imported cases there was no information of acquisition.

The $ESBL_{CARBA}$-producing Enterobacteriaceae were identified in fecal/rectal samples (82 cases), urine (14), wound (4), respiratory samples (3), blood (3), and for nine cases sample material was missing. Five cases of invasive infection with $ESBL_{CARBA}$ were notified in 2015. For two of the invasive cases, $ESBL_{CARBA}$ was first isolated from a fecal sample. More than half of the cases were male (59%) and the median ages were 43 and 44 years for women and men, respectively.

In 2015 the most common carbapenemase-producing Enterobacteriaceae was *E. coli* (64 isolates) followed by *K. pneumoniae* (53 isolates). Genes coding for carbapenem resistance have also been detected in several other species of

FIGURE 2.6. $ESBL_{CARBA}$ subtypes isolated from human cases of $ESBL_{CARBA}$ notified in Sweden 2015, presented in relation to region of acquisition.



Enterobacteriaceae (Figure 2.5). In 2015 an isolate producing imipenem-hydrolyzing β-lactamase (IMI) was identified. The IMI-producing carbapenem-resistant Enterobacter species isolate was recovered from a fecal sample from a patient hospitalised abroad. The dominating enzyme type in 2015 was OXA-48 and this enzyme was detected in *E. coli* and *K. pneumoniae* isolates, in most cases together with CTX-M (=$ESBL_A$) and/ or pAmpC CIT (=$ESBL_M$) enzymes. In Figure 2.6 all $ESBL_{CARBA}$ enzymes isolated from cases notified in Sweden 2015 are presented in relation to region of acquisition. All isolates with $ESBL_{CARBA}$ were multi-resistant, leaving very few options for antibiotic treatment.

ESBL-producing Enterobacteriaceae in animals

Farm animals

In Svarm, active screening for ESBL-producing *E. coli* (including plasmid-mediated AmpC) in healthy farm animals using samples collected at slaughter for the studies of indicator bacteria has been performed since 2008. The proportions of faecal samples positive for $ESBL_A$ or $ESBL_M$ in screenings of healthy animals and of meat in Sweden are shown in Table 2.2.

During 2015, samples of intestinal contents from healthy pigs (n=303) and healthy cattle (n=103) as well as samples of pig meat (n=286) and cattle meat (n=289) at retail were screened for *E. coli* resistant to ESCs and carbapenems. Furthermore, samples of intestinal contents from healthy broilers (n=100) were screened for *E. coli* resistant to ESCs. Isolates with reduced susceptibility were further investigated by molecular methods for presence of transferrable genes coding for ESC resistance (for details see Material and methods, resistance in bacteria from animals). In Sweden, carbapenemase producing Enterobacteriaceae ($ESBL_{CARBA}$) in animals are notifiable but not classical ESBLs ($ESBL_A$) or plasmid-mediated AmpC ($ESBL_M$).

In 2015, $ESBL_A$ or $ESBL_M$ were detected in 39 (39%) of the samples of intestinal contents from broilers, in 4 (1%) of the samples of intestinal contents from pigs and in 1 (1%) of the samples from pig meat but neither in the samples of intestinal contents from cattle nor in samples of cattle meat. $ESBL_{CARBA}$ was not isolated from any samples.

Two of the isolates from intestinal contents of pigs and the isolate from pig meat carried the gene $bla_{CTX\text{-}M\text{-}55}$ ($ESBL_A$). The other two isolates from intestinal contents of pigs carried the gene $bla_{CTX\text{-}M\text{-}15}$ ($ESBL_A$) and $bla_{CMY\text{-}2}$ ($ESBL_M$) respectively. The low occurrence of $ESBL_A$ and $ESBL_M$ in pigs, pig meat, cattle and cattle meat is in accordance with previous investigations (Svarm 2011 and Swedres-Svarm 2013).

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

Animal species	Matrix	Year	No. of samples	No. samples with ESC resistance	No. samples with $ESBL_A$ or $ESBL_M$	% samples with $ESBL_A$ or $ESBL_M$	Beta-lactamase (No. isolates)						
							CTX-M-1	CTX-M-3	CTX-M-15	CTX-M-55	TEM-52	SHV	CMY-2
Broilers	Intestine	2015	100	40	39[a]	39[a]	18[a]						22[a]
Broilers	Intestine	2014	200	72	71	36	1						70[b]
Broilers	Intestine	2013	100	45	40	40					2		38[b]
Broilers	Meat	2013	59	31	30	51							30[b]
Broilers	Intestine	2012	200	102	97	49							97[b]
Broilers	Meat	2012	97	41	40	41							40[b]
Broilers	Intestine	2011	100	57	54	54	3						51
Broilers	Intestine	2010	200	77	68	34	12						56
Broilers	Meat	2010	100	49	44	44	4						40
Cattle	Intestine	2015	103	5	0	0							
Cattle	Meat	2015	289	0	0	0							
Calves	Intestine	2013	202	3	1	<1			1				
Calves	Intestine	2012	742	81	9	1	1		4				4
Calves	Intestine	2009	256	11	0	0							
Pigs	Intestine	2015	303	35	4	1			1	2			1
Pigs	Meat	2015	286	1	1	<1				1			
Pigs	Intestine	2011	184	9	3	2		1	1		1		
Pigs	Meat	2011	100	0	0	0							
Pigs	Intestine	2008	452	9	0	0							
Pigs	Meat	2008	50	0	0	0							
Turkeys	Intestine	2014	60	12	0	0							
Turkeys	Intestine	2013	55	16	0	0							
Laying hens	Intestine	2012	69	11	9	13	3						6
Dogs	Faeces	2012	84	6	1	1							1[b]
Horses	Faeces	2010	431	9	6	1						6	

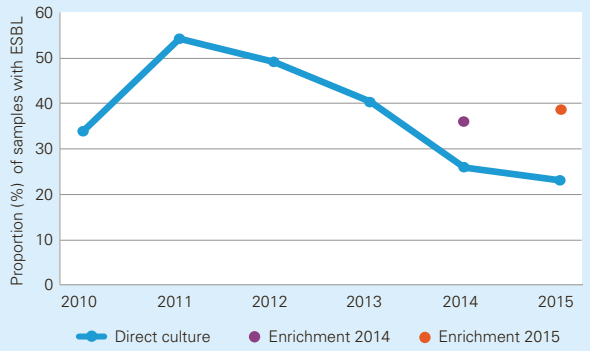
[a] One isolate carried both an $ESBL_A$ and an $ESBL_M$ gene.
[b] CIT-group, all isolates from broilers or broiler meat with a CIT-group enzyme in other years possessed the gene $bla_{CMY\text{-}2}$.

TABLE 2.3. Clinical isolates of different bacterial species of Enterobacteriaceae, producing $ESBL_A$ or $ESBL_M$ enzymes, from companion animals and horses submitted 2008-2015.

Animal species	Resistance gene	Bacterial species	2008	2009	2010	2011	2012	2013	2014	2015
Cats	CTX-M-14	*Kluyvera* sp.				1				
	CTX-M-15	*Enterobacter cloacae*								1
	CTX-M-15	*Escherichia coli*			1					
	CTX-M-15	*Klebsiella pneumoniae*			1	1				
	TEM-52	*Escherichia coli*								1
	CMY-2	*Escherichia coli*		1[a]	1					
	CMY-16	*Escherichia coli*							1	
	unknown	*Escherichia coli*				1				
	Total all genes			**1**	**3**	**3**			**1**	**2**
Dogs	CTX-M-1	*Enterobacter cloacae*							4	
	CTX-M-1	*Escherichia coli*			1		1	1	3	
	CTX-M-2	*Escherichia coli*				1				
	CTX-M-3	*Enterobacter* spp.						1		
	CTX-M-3	*Escherichia coli*						2		1
	CTX-M-9	*Escherichia coli*				1	2	1	1	
	CTX-M-14	*Escherichia coli*								5
	CTX-M-14	*Klebsiella pneumoniae*								1
	CTX-M-15	*Enterobacter cloacae*								2
	CTX-M-15	*Enterobacter* spp.		1	2	1	2	1	6	
	CTX-M-15	*Escherichia coli*	1			2	3	2		2
	CTX-M-15	*Klebsiella pneumoniae*		1						1
	CTX-M-27	*Escherichia coli*				3		1	1	1
	CTX-M-55	*Escherichia coli*								1
	CTX-M-57	*Escherichia coli*								1
	SHV-12	*Escherichia coli*							2	
	CMY-2	*Escherichia coli*			1	9	4	5	5	6
	CMY-2	*Klebsiella pneumoniae*								1
	CMY-2	*Proteus mirabillis*				1				2
	unknown	*Escherichia coli*		1	1					
	Total all genes		**1**	**3**	**5**	**18**	**12**	**14**	**22**	**24**
Horses	CTX-M-1	*Enterobacter cloacae*								1
	CTX-M-1	*Enterobacter* spp.						1		
	CTX-M-1	*Escherichia coli*		2	9	8	3	3	2	3
	CTX-M-1	*Klebsiella oxytoca*							1	
	CTX-M-1	*Serratia odorifera*			1					
	CTX-M-9	*Escherichia coli*							1	
	CTX-M-14	*Escherichia coli*				1				1
	CTX-M-15	*Escherichia coli*		1	1					
	CTX-M-15	*Klebsiella pneumoniae*		1						3
	SHV-12	*Citrobacter braakii*			1					
	SHV-12	*Enterobacter amnigenus*							1	
	SHV-12	*Enterobacter cloacae*							1	2
	SHV-12	*Enterobacter* spp.		1	3	5	3	3		
	SHV-12	*Escherichia coli*	2		2	2				
	SHV-12	*Escherichia hermanii*			1					
	SHV-12	*Klebsiella oxytoca*						2		1
	SHV-12	*Klebsiella pneumoniae*							1	
	unknown	*Enterobacter cloacae*							1	3
	unknown	*Escherichia coli*			1					
	unknown	*Klebsiella pneumoniae*			5					
	Total all genes		**2**	**5**	**24**	**16**	**6**	**9**	**8**	**14**

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

FIGURE 2.7. Proportion (%) of samples from broilers positive for $ESBL_A$ or $ESBL_M$ from 2010 to 2015.



About half of the isolates (21/39) from broilers carried the gene bla_{CMY-2} ($ESBL_M$) and all but one of the remaining isolates carried the gene $bla_{CTX-M-1}$ ($ESBL_A$, n=17). The last isolate carried both bla_{CMY-2} and $bla_{CTX-M-1}$. In previous years, isolates with bla_{CMY-2} have dominated among ESBL-producing *E. coli* from broilers even if isolates carrying the gene $bla_{CTX-M-1}$ was common also in 2010, especially in samples collected during the spring of 2010 (Svarm 2010). Apart from the obvious resistance to betalactams and that all but one of the isolates carrying $bla_{CTX-M-1}$ showed additional resistant to sulphonamides, resistance was generally uncommon among the isolates of ESBL-producing *E. coli* from broilers.

Due to changes in methodology, it is not correct to assess the change over time of the overall proportion of samples positive for ESC resistant *E. coli*. However, the samples of intestinal contents from broilers in 2014 and 2015 were also cultured in duplicate according to the method used from 2010-2013 (i.e. by direct culturing on MacConkey agar with cefotaxime: for details on methodology see Material and methods, resistance in bacteria from animals). Using that method, ESC resistant *E. coli* were isolated from 23 (23%) of the samples from 2015 (Figure 2.7). This means a slight numerical decrease since 2014 in the proportion of samples that are positive for ESC resistant *E. coli* using direct culturing on selective media but the difference is not significant ($p=0.57$, X^2). The decrease is however part of an ongoing trend since 2011, where for example the difference between 2013 and 2014 is significant ($p=0.01$, X^2).

Companion animals and horses

In Svarm, there are no continuous active screening for ESBL-producing Enterobacteriaceae in healthy companion animals or horses. The results of the screenings for ESC resistant *E. coli* that has been performed are shown in Table 2.2.

During 2015, a total of 40 isolates of Enterobacteriaceae with phenotypic resistance to ESCs were confirmed to produce $ESBL_A$ or $ESBL_M$ at SVA (Table 2.3). The isolates were from cats (n=2), dogs (n=24) and horses (n=14), and the majority was isolated from wounds or from the urogenital tract. Numerically, this is a small increase in the number of ESBL-producing Enterobacteriaceae since 2014. The proportion of submitted isolates that were confirmed to produce $ESBL_A$ or $ESBL_M$ was however the same as previous years as the total number of isolates sent to SVA for confirmation has also increased. Most likely, the increased number of submitted isolates reflects an increased awareness of the problem among clinicians. In addition, funding from the Swedish Board of Agriculture has enabled SVA to perform confirmation of suspected ESC resistance in isolates of Enterobacteriaceae free of charge for referring laboratories.

Zoonotic aspects on ESBL-producing Enterobacteriaceae

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

The available data from Sweden show that ESBL-producing bacteria are rare in animals in Sweden with the exception of poultry where *E. coli* with $ESBL_A$ or $ESBL_M$ resistance is found in a large proportion of birds. The majority of isolates from humans in Sweden is however not of the same types of $ESBL_A$ or $ESBL_M$ as in broilers. Furthermore, a recent Swedish study investigating the potential overlap between clinical human isolates and isolates from healthy farm animals and food concluded that food on the Swedish market was a limited source for ESBLs for humans (Börjesson et al., 2016). Nevertheless, continued vigilance towards development of reservoirs of ESBL-producing Enterobacteriaceae in animals is warranted.

Methicillin resistant Staphylococcus aureus (MRSA)

MRSA in humans

Background

MRSA has been mandatory notifiable since the year 2000. Infection control programmes have been developed and implemented locally under supervision of the County Medical Officers (CMO) and infection control teams. These programmes are based on early case-finding through extensive screening of patients with risk factors and contact tracing combined with infection control measures such as isolation of MRSA positive cases and intensive campaigns on basic hygiene

FIGURE 2.8. Number of human cases of MRSA notified annually as domestic and imported, respectively, 2011-2015.

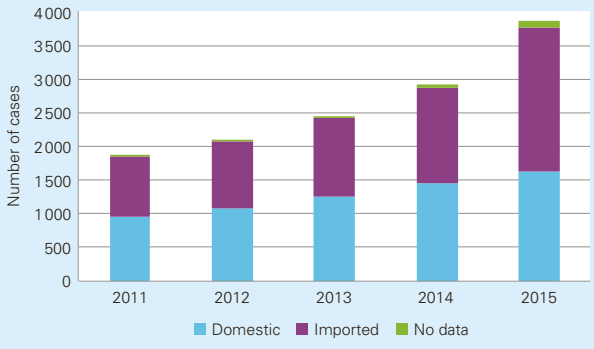


TABLE 2.4. MRSA in humans by county 2011-2015. Number of cases according to the Communicable Disease Act and incidence.

County	2011		2012		2013		2014		2015	
	No	Inc[a]	No	Inc[a]	No	Inc[a]	No	Inc[a]	No	Inc[a]
Blekinge	17	11	24	16	32	21	37	24	49	31
Dalarna	38	14	33	12	35	13	61	22	121	43
Gotland	9	16	11	19	15	26	17	30	10	17
Gävleborg	36	13	35	13	51	18	50	18	74	26
Halland	51	17	47	15	58	19	55	18	137	44
Jämtland	19	15	33	26	54	43	51	40	57	45
Jönköping	61	18	82	24	126	37	118	34	195	56
Kalmar	45	19	72	31	82	35	140	59	175	74
Kronoberg	40	22	40	22	54	29	89	47	110	57
Norrbotten	20	8.0	31	12	39	16	73	29	69	28
Skåne	369	29	384	30	394	31	488	38	727	56
Stockholm	502	24	589	28	623	29	685	31	835	37
Södermanland	34	12	32	12	50	18	66	24	59	21
Uppsala	42	12	80	23	76	22	98	28	95	27
Värmland	48	18	40	15	80	29	66	24	166	60
Västerbotten	20	8.0	21	8.1	34	13	40	15	69	26
Västernorrland	24	10	35	14	40	17	56	23	94	39
Västmanland	28	11	31	12	50	19	68	26	60	23
Västra Götaland	347	22	360	22	439	27	463	28	536	33
Örebro	44	16	55	19	50	18	106	37	111	38
Östergötland	71	16	62	14	72	16	94	21	133	30
Total	**1 884**	**20**	**2 097**	**22**	**2 454**	**25**	**2 921**	**30**	**3 882**	**39**

[a]=Incidence (cases per 100 000 inhabitants)

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

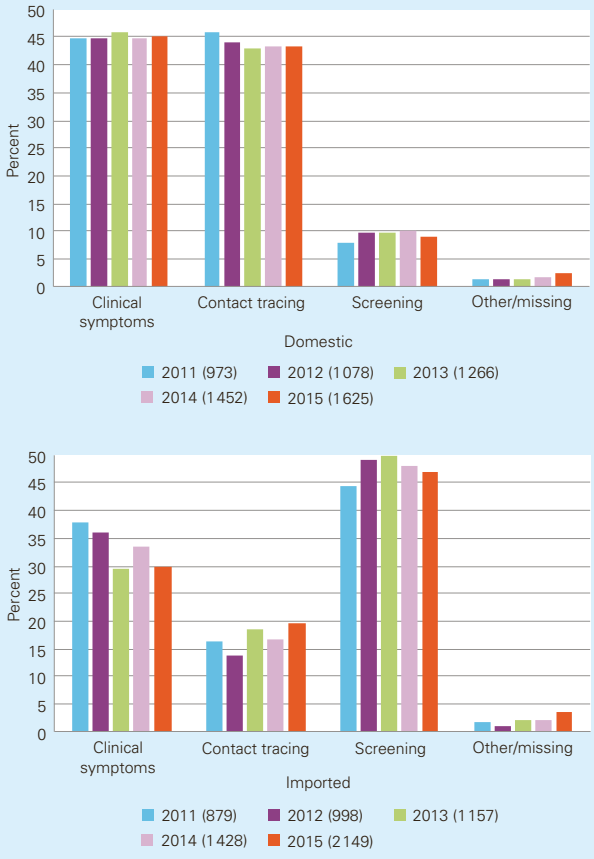
Notifications of MRSA according to the Communicable Disease Act

In 2015 a total of 3 882 cases of MRSA were notified, an increase by 961 cases (33%) compared to 2014 (Figure 2.8). The average national incidence was 39 cases per 100 000 inhabitants with markedly higher than average incidence in the counties of Kalmar, Värmland, Kronoberg, Jönköping, and Skåne, Table 2.4.

In 2015, 42% (n=1 625) of all reported MRSA were domestic cases and 55% (n=2 149) were acquired abroad. Syria (541 cases), Iraq (240), Afghanistan (119), Eritrea (81) and Philippines (67) made up the five most common countries for imported MRSA. For approximately three percent (108 cases) country of infection was missing ("No data").

A majority of of the domestic cases were reported as patients with clinical symptoms and cases identified by contact tracing, and these proportions have remained stable over the years (Fig 2.9A). For imported cases, screening remains as the largest reported indication for sampling followed by clinical symptoms and contact tracing (Fig 2.9B). The majority of samples from investigations of clinical symptoms were wound samples (69%). Invasive MRSA infection was reported in 36 cases 2015 compared to 39 cases 2014. Thirty of those were newly notified cases 2015 and six occurred in patients already known to carry MRSA in previous years.

FIGURE 2.9, A AND B. Indications for sampling of domestic (A, top) and imported (B, bottom) MRSA cases in humans in Sweden 2011-2015. Number of reported human cases each year is shown in brackets.



Epidemiological classification of the acquisition of MRSA was based on information in the clinical notifications and from subsequent investigations by the CMOs, Figures 2.9, A and B. Community-acquired infections continues to be the most common way of acquisition among domestic and imported cases in 2015, Figure 2.10 A and 2.10 B. A higher proportion of hospital acquired MRSA was noted in imported cases, than among domestic cases. The number of domestic cases with hospital acquired MRSA stayed nearly the same from 109 cases in 2014 to 105 cases in 2015. The proportion of cases with MRSA acquired in healthcare/care outside hospital were the same for both domestic as well as imported cases. One fourth of the imported cases with MRSA had no information on acquisition.

Among the domestic MRSA cases 2015, the incidence was highest in the age group 0-6 years, followed by the age group 80 years and older (Figure 2.11). The incidence of MRSA among the very old and the very young was substantially higher (≥ 28) than in the other age groups. In the other age groups the incidence remained at a low but slightly increasing level, in 2015 reaching 11-14. Among children (0-6 years), the infants (0 years) had by far the highest incidence (Figure 2.12). Infant MRSA cases were mainly detected through contact tracing (49%), 29% by screening and 22% by clinical symptoms. Of 199 cases among infants, 30 (15%) were hospital related, 18 of these were part of 3 neonatal outbreaks comprising 3 or more cases, 157 cases (79%) were community acquired.

FIGURE 2.10, A AND B. Epidemiological classification of human cases of MRSA, A, top: domestic, and B, bottom: imported, Sweden 2011-2015. Number of reported cases each year is shown in brackets.

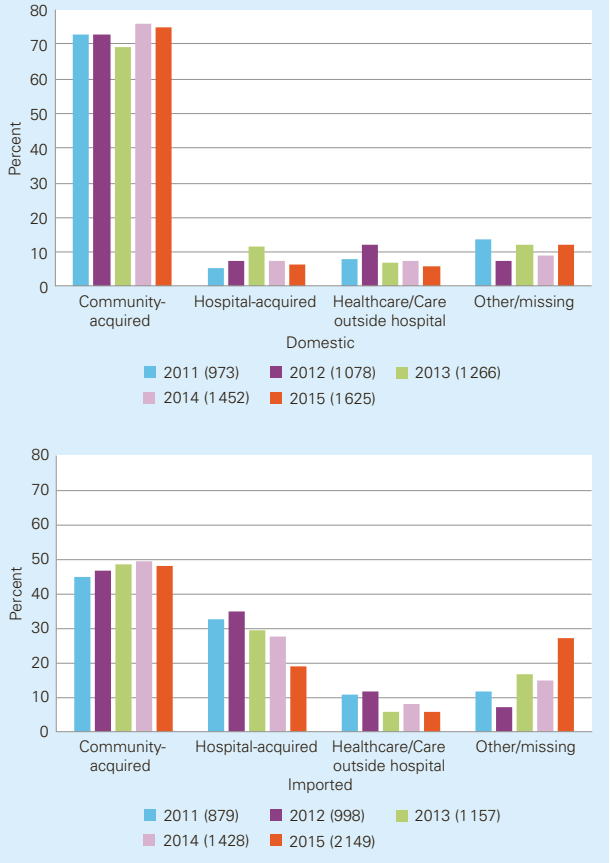


FIGURE 2.11. Incidence per age group of all notified domestic human cases of MRSA in Sweden 2011-2015.

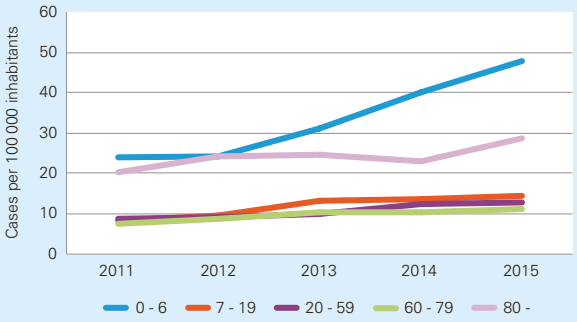
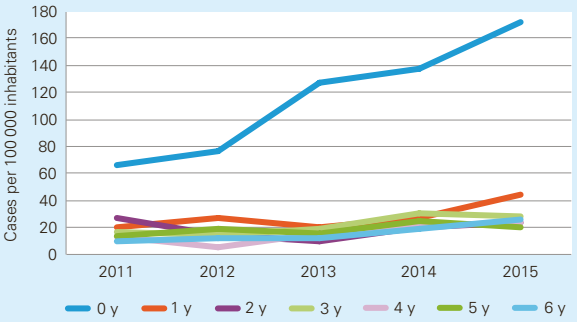


FIGURE 2.12. Incidence of notified domestic human cases of MRSA in the age group 0-6 years in Sweden 2011-2015.



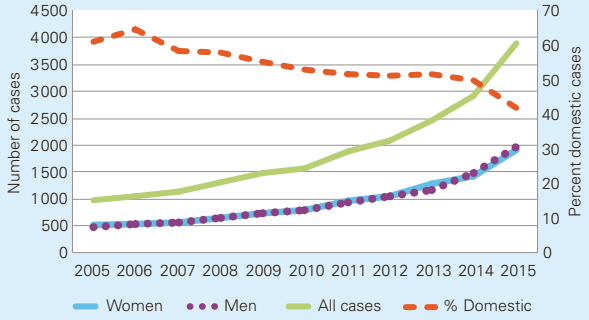
Analysis of the increase of MRSA

In 2015 the number of MRSA cases increased by 33% compared to 2014, Figure 2.13. From August there was a marked increase in the number of reported cases per month (data not shown). This increase is mainly comprised of cases among persons seeking asylum, likely due both to a higher prevalence, increased need for medical care and increased sampling in this group.

No increased spread of MRSA in hospitals has been reported in connection with this increase among persons seeking asylum, nor a progressive increase in domestic cases of MRSA in the general population. The increase in cases of MRSA is seen mainly among the younger age groups 0-14 years, 15-24 years and 25-44 years for both women and men.

Even if the number of domestic cases have increased from 595 to 1625 year 2005 to 2015 the proportion of domestic cases decreased from 61% to 42%.

FIGURE 2.13. MRSA in humans 2005-2015. Number of cases among men, women and all cases. Proportion of domestically acquired cases is shown on the right axis.



Outbreak investigations

During 2015, thirteen outbreaks (three or more cases/outbreak) were reported in eight different counties. These outbreaks comprised 105 cases, representing 3% of all cases of MRSA in 2015. The three most common *spa*-types were t230, t11717 and t2958. Eight outbreaks were reported from healthcare institutions outside hospitals, whereas five were hospital outbreaks.

Epidemiological typing of MRSA

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

In 2015, *spa*-typing results were available for MRSA isolates from 94% of the notified cases. All but 20 of the 3 654 isolates were typable, and a total of 464 *spa*-types were recorded. In 2015, 48% (n=1 769) of the cases had an MRSA with a top ten *spa*-type, Figure 2.14 A. Seven of these *spa*-types have been among the top ten during 2011-2015; t223, t044, t127, t002, t008, t690 and t019. Three of the top ten *spa*-types in 2011, t437, t015 and t790, were not seen among the top ten in 2015. Figure 2.14 B shows the proportions per year of each of the top ten *spa*-types in 2015. Among these *spa*-types t223, t044, t304, t127, t386 and t688 have become more prevalent, and t002, t008 and t019 less prevalent.

FIGURE 2.14, A AND B. The most common *spa*-types and their association with PVL among human cases of MRSA in 2011-2015. A: Number of cases. B: Proportion (%) of *spa*-type.

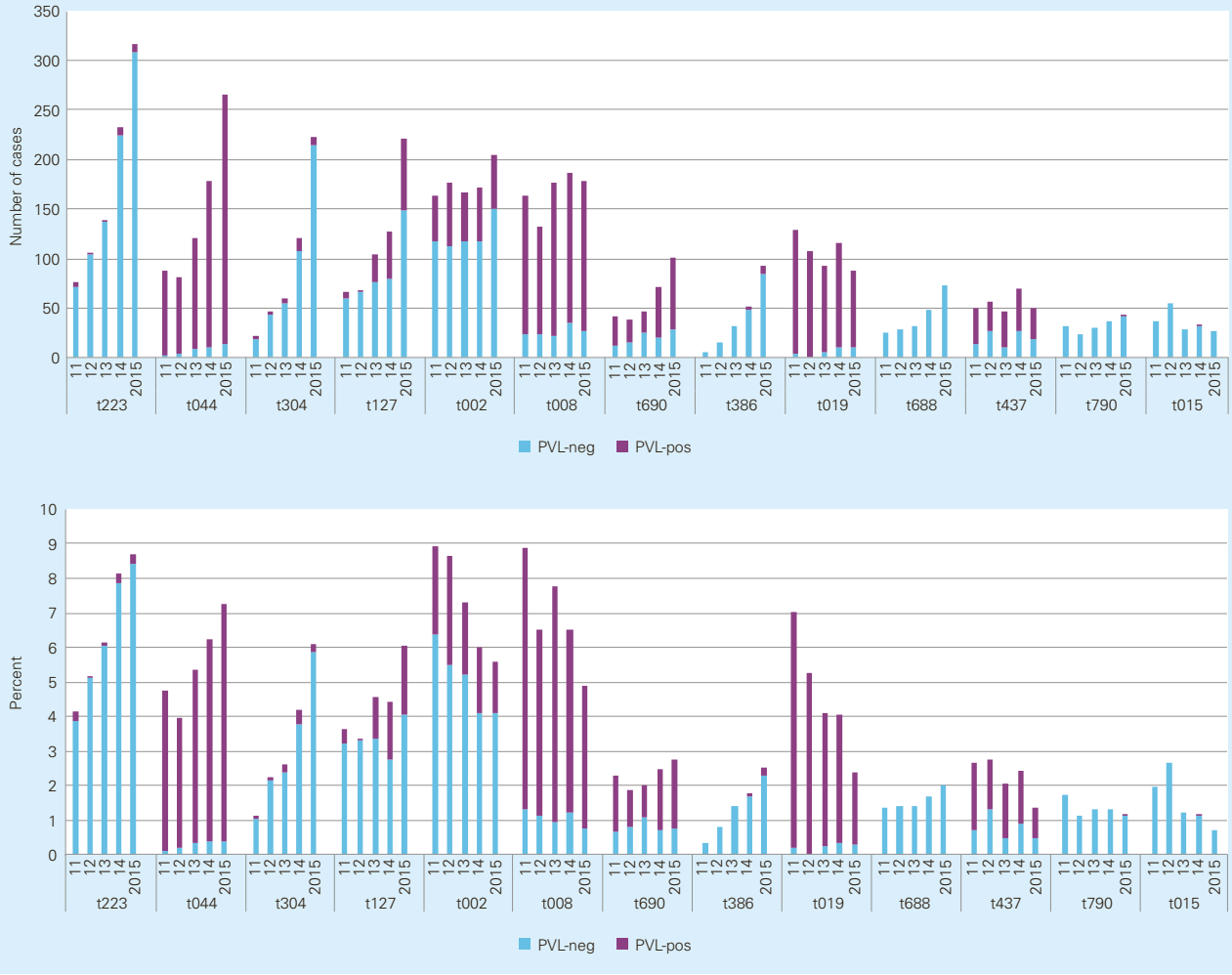


TABLE 2.5. The ten most common *spa*-types among MRSA from notified human cases with domestically acquired MRSA and MRSA acquired abroad (imported), respectively, for 2015. Number of notifications per *spa*-type and percent PVL-positive isolates are shown.

Domestic			Imported		
***spa*-type**	**No.**	**PVL-pos (%)**	***spa*-type**	**No.**	**PVL-pos (%)**
t223	114	2	t223	197	4
t002	113	27	t044	149	95
t044	106	95	t304	140	3
t127	98	23	t127	115	40
t008	89	81	t008	89	89
t304	73	5	t002	88	26
t019	41	85	t690	67	73
t688	39	0	t386	56	9
t386	34	12	t019	45	89
t690	30	70	t1339	39	31

Table 2.5 shows the top ten *spa*-types seen among isolates from cases with domestically acquired MRSA (n=737) and MRSA acquired abroad (imported, n=985), respectively, for 2015. The one *spa*-type seen only among the top ten in the domestic group was t688, and the one seen only among the top ten in the imported group was t1339.

MRSA in animals

In Sweden, MRSA in animals was first verified in 2006 and was made notifiable in 2008. During 2015, 12 new cases of MRSA were detected; 7 dogs, 2 cats, 2 horses and 1 dairy cow. In addition, MRSA was detected in 34 hedgehogs in a screening study (In focus MRSA with *mecC* in wild hedgehogs). Up to and including 2015, a total of 126 cases in animals have been confirmed (Tables 2.6 and 2.7 and In focus MRSA with *mecC* in wild hedgehogs). Most cases in domestic animals were detected in passive monitoring when animals with clinical infections were sampled. From such samples, isolates of *S. aureus* with resistance to oxacillin or cefoxitin were further analysed with confirmatory tests. Screening studies for active monitoring have been performed in pigs, cattle, horses, dogs and hedgehogs during different years (see below).

Farm animals

Screening studies in pigs have been performed five times since 2006, with only one positive sample from pigs at slaughter in 2010. The most recent screening was performed in all 39 nucleus and multiplying herds in 2014. Other herd types have not been investigated since 2010. Therefore, information about the occurrence of MRSA in the majority of Swedish pig herds is currently not complete.

In dairy cattle, active monitoring of selected isolates of beta-lactamase producing *S. aureus* from milk samples has been ongoing since 2010, and 850 isolates have been tested up to and including 2015. One isolate from each submission of beta-lactamase producing *S. aureus*, if present, is tested. In this monitoring, PVL-negative MRSA with *mecC* was detected four times in 2010-2011 (Unnerstad et al., 2013), and once in 2013 and 2015, respectively. PVL-positive MRSA with *mecA* was detected in 2012 and PVL-negative MRSA with *mecA* in 2014. During 2013, 513 isolates without beta-lactamase production were part of the monitoring as well, without any findings of MRSA. The above mentioned monitoring is performed on isolates with anonymized origin. In addition, PVL-positive MRSA with *mecA* was isolated from several animals in a dairy herd in 2012 (Zoonotic aspects on MRSA, MRSA in dairy cattle, below).

Companion animals and horses

In dogs, cats and horses, there was no active monitoring of MRSA during 2015. Screenings in dogs were performed in 2006 and 2012 without detection of MRSA. Screening studies in horses have been performed twice, in 2007 and 2010, with only one positive sample in 2007. In 2015, MRSA was detected in clinical samples, mostly from wound infections, from seven dogs, two cats and two horses.

Since the first finding of MRSA in companion animals, *spa*-type t032 has been most common, but during the most recent years the *spa*-types have been more varied (Table 2.7). In isolates from horses, *spa*-type t011, CC398, has dominated. All isolates from both companion animals and horses have been PVL-negative.

Wild animals

MRSA with *mecC* has been detected in hedgehogs in Sweden. In 2012, two MRSA-isolates were confirmed retrospectively from hedgehogs sent in for post mortem investigation in 2003 and 2011. The isolate from 2003 is the first known isolate of MRSA from animals in Sweden, although not confirmed until 2012. During 2015, a screening study in hedgehogs was performed and MRSA was isolated from 35 out of 55 sampled animals (In focus MRSA with *mecC* in wild hedgehogs).

Zoonotic aspects on MRSA

Zoonotic transmission of MRSA occurs by direct or indirect contacts, making farmers, animal owners, veterinarians and other persons in close contact with animals the population at risk. MRSA is reported globally in farm animals, companion animals and horses. During the last ten years, the zoonotic aspects on MRSA in farm animals, mostly in pigs but also in veal calves, broilers and dairy cows, has widened due to spread of livestock-associated MRSA (LA-MRSA), mostly of clonal complex (CC) 398 in many countries. There is also a risk of spread of MRSA from humans to animals which has long been assumed to occur in companion animals. It is also possible that MRSA may be introduced in livestock farms through humans.

LA-MRSA in pigs

Internationally, LA-MRSA, mostly CC398, dominates in farm animals and can be of importance for the overall human MRSA burden in countries with low prevalence of MRSA in humans (EFSA, 2009). In countries with high prevalence of MRSA CC398 in pigs, the pig population constitutes a reservoir of MRSA with continuous transmission to people in close contact with pigs. In the screening study in nucleus and multiplying pig herds in 2014, MRSA was not detected in Swedish pigs, indicating a favourable situation. However, continuous monitoring is of importance as the situation can change rapidly, for example through import of live animals. Under current conditions, import of live pigs to Sweden is restrictive and traded animals are tested for MRSA before introduction to a pig herd.

MRSA CC398 also occurs among horses and *spa*-type t011, belonging to CC398, is by far the most common type among Swedish horses (Table 2.6). The likelihood of horses as a source of spread of MRSA to pigs is not known under Swedish conditions, but such transmission may be possible, for instance with humans that handle both horses and pigs as vectors.

Domestically acquired MRSA CC398 was detected in six humans in 2012 and in five in 2013. In 2014, the occurrence doubled to 12 human cases, but this increase has not continued, with 10 cases in 2015. The low number of domestically aquired MRSA CC398 in humans in Sweden may indicate that MRSA is not widespread in Swedish pigs, since high occurrence in the pig population would lead to transmission to humans in contact with pigs. The 10 isolates of domestically acquired MRSA CC398 from human cases in 2015 were of *spa*-types t011 and t034. In addition, 9 human cases with MRSA CC398 aquired abroad were detected in 2015. These isolates were of *spa*-types t011, t034, t571 and t899. The epidemiological information on human cases is scarce, and possible animal contact is not known.

MRSA in dairy cattle

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

In 2012, PVL-positive MRSA of *spa*-type t002 was isolated from a dairy farmer and from several of the dairy cows and a few other cattle on the farm. Since MRSA of this *spa*-type is common among humans in Sweden, it is likely that transmission has occurred from the farmer to cows. Hygienic measures were implemented on the farm in order to reduce the risk of transmission and several of the MRSA-positive cows were culled. This reduced the number of colonized or infected animals, but MRSA was still detected in cattle or in bulk milk on the farm in 2013, 2014 and 2015.

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

In different years, MRSA with *mecC* (see below) has been isolated from milk samples. All isolates were from samples with anonymized origin and therefore the source and transmission of MRSA cannot be investigated.

MRSA with *mecC*

Isolates of MRSA with *mecC* were first reported internationally from dairy cows and humans in 2011 (García-Álvarez et al., 2011, Shore et al., 2011, Ito et al., 2012). MRSA with *mecC* has been detected in samples from both animals and humans in Sweden. In animals, such MRSA isolates have been detected in milk from dairy cows (*spa*-types t524, t9111 and t843), from three cats (*spa*-types t978 and t843) and from two dogs (*spa*-types t373 and t843) (Tables 2.6 and 2.7). MRSA with *mecC* has also been isolated from 39 Swedish hedgehogs (In focus MRSA with *mecC* in wild hedgehogs).

In humans, MRSA with *mecC* has been isolated from 76 cases 2011-2015. In total, 16 *spa*-types were seen among human isolates. The two most common were t373 (20 cases) and t843 (22 cases).

MRSA in companion animals

MRSA isolated from dogs and cats often belong to *spa*-types seen in MRSA from humans. This supports the view that humans often constitute the source of MRSA in companion animals (EFSA, 2009; CVMP, 2009). After transmission to a companion animal, the animal may serve as vector for indirect transmission to other humans. The magnitude of companion animals as vectors for spread between humans is however not known. The most common *spa*-type among Swedish dogs and cats has been t032. This type was one of the ten most common *spa*-types among human MRSA isolates in Sweden up to 2011, but in 2015 it was only found in 25 isolates. In later years, isolates with other *spa*-types have been detected in dogs, some of these types being common in humans.

Conclusions

The MRSA situation in Sweden is still favourable both in humans and in animals. If this situation is preserved in animals, a reservoir of MRSA in animals with risk of spread from animals to humans can be prevented. Biosecurity, with caution in trade of live animals and measures to prevent introduction by indirect routes, is important for preventing introduction and spread of MRSA in animal populations. Cautions to prevent transmission from humans to animals are also of importance, since human types of MRSA may be established also in animal populations.

TABLE 2.6. Large animals. Isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) in Swedish horses, pigs and cows up to and including 2015. All isolates were positive for the *mecA* or *mecC* and *nuc* genes by molecular methods. Shaded areas indicate MIC above EUCAST ECOFF.

Animal species	Year	Clinical background/ Sampling site	Antibiotic													*spa*-type	*mec*-gene
			Oxa[a]	Fox	Pen	Cet	Cli	Ery	Tet	Fus	Gen	Kan	Cip	Tmp	Chl		
Horse	2007	screening	>16	-	>4	1	≤0.25	0.5	64	0.5	>64	>32	1	>32	8	t011	*mecA*
Horse	2008	post-op wound	>16	>16	>4	1	≤0.25	0.5	32	0.5	64	>32	1	>32	8	t011	*mecA*
Horse	2008	post-op wound	>16	>16	>4	2	≤0.25	1	32	1	>64	>32	1	>32	8	t011	*mecA*
Horse	2008	post-op wound	16	>16	>4	2	≤0.25	1	32	0.5	>64	>32	0.5	>32	8	t011	*mecA*
Horse	2008	post-op wound	>16	>16	>4	2	≤0.25	0.5	32	0.25	>64	>32	0.5	>32	8	t011	*mecA*
Horse	2008	screening	>16	16	>4	2	≤0.25	1	32	0.5	64	>32	0.5	>32	8	t011	*mecA*
Horse	2008	post-op wound	>16	8	>4	2	≤0.25	1	64	1	>64	>32	1	>32	16	t011	*mecA*
Horse	2008	post-op wound	2	>16	4	4	≤0.25	≤0.25	32	0.12	4	32	0.25	>32	4	t011	*mecA*
Horse	2009	wound	16	>16	>4	>8	≤0.25	0.5	64	0.25	16	>32	0.25	>32	8	t011	*mecA*
Horse	2009	post-op wound	16	>16	4	1	≤0.25	0.5	32	0.25	64	>32	1	>32	8	t011	*mecA*
Horse	2010	post-op wound	>16	>16	>4	8	0.5	2	64	1	>64	>32	1	>32	16	t011	*mecA*
Horse	2010	post-op wound	>16	>16	>4	4	≤0.25	1	32	0.5	>64	>32	0.5	>32	8	t064	*mecA*
Horse	2010	post-op wound	>16	>16	>4	8	≤0.25	0.5	64	0.25	64	>32	0.25	>32	8	t011	*mecA*
Horse	2010	wound	>16	>16	>4	4	≤0.25	0.5	32	0.5	>64	>32	0.25	>32	8	t011	*mecA*
Horse	2010	post-op wound	>16	>16	>4	2	≤0.25	1	32	0.5	16	>32	0.25	>32	8	t064	*mecA*
Horse	2010	post-op wound	>16	-	>4	4	≤0.25	0.5	64	0.25	>64	>32	0.25	>32	8	t011	*mecA*
Horse	2011	post-op wound	16	>16	>4	1	≤0.25	≤0.25	32	0.12	32	>32	0.25	>32	4	t011	*mecA*
Horse	2011	skin infection	>16	>16	>4	2	≤0.25	≤0.25	64	0.5	≤0.5	4	0.25	1	8	t011	*mecA*
Horse	2012	wound	>16	>16	>4	8	1	1	64	0.25	>64	>32	0.5	>32	8	t011	*mecA*
Horse	2012	wound	16	-	>4	1	≤0.25	0.5	32	0.25	32	>32	0.25	>32	4	t011	*mecA*
Horse	2013	abscess	>16	4	>4	>8	≤0.25	1	64	1	>64	>32	1	>32	16	t011	*mecA*
Horse	2014	wound	>16	>16	>4	4	≤0.25	1	64	0.25	64	>32	0.25	>32	8	t011	*mecA*
Horse	2014	post-op wound	>16	>16	>4	1	≤0.25	≤0.25	32	0.12	16	>32	0.25	>32	8	t011	*mecA*
Horse	2014	wound	>16	>16	>4	1	≤0.25	≤0.25	32	≤0.06	8	>32	0.25	>32	8	t011	*mecA*
Horse	2014	wound	>16	>16	>4	4	≤0.25	≤0.25	32	0.12	64	>32	0.25	>32	8	t011	*mecA*
Horse	2014	wound	>16	>16	>4	4	≤0.25	≤0.25	32	≤0.06	64	>32	0.25	>32	8	t011	*mecA*
Horse	2014	unknown	>16	>16	>4	2	≤0.25	≤0.25	32	0.12	32	>32	0.25	>32	8	t011	*mecA*
Horse	2014	post-op wound	>16	>16	>4	2	≤0.25	≤0.25	32	0.12	64	>32	0.12	>32	8	t011	*mecA*
Horse	2014	umbilical wound	>16	>16	>4	2	≤0.25	≤0.25	16	≤0.06	64	>32	0.25	>32	8	t011	*mecA*
Horse	2014	post-op wound	16	>16	>4	4	≤0.25	≤0.25	32	≤0.06	64	>32	>4	>32	8	t011	*mecA*
Horse	2015	post-op wound	>16	>16	>4	4	≤0.25	≤0.25	32	0.12	16	>32	>4	>32	8	t011	*mecA*
Horse	2015	post-op wound	16	>16	>4	2	≤0.25	≤0.25	32	0.25	32	>32	0.25	>32	8	t1451	*mecA*
Pig	2010	snout	>16	>16	>4	>8	0.5	1	64	0.5	>64	>32	0.25	>32	16	t011	*mecA*
Cow	2010	milk screening	4	16	2	1	≤0.25	≤0.25	≤0.5	0.25	≤0.5	2	0.5	2	8	t524	*mecC*
Cow	2010	milk screening	4	16	1	1	≤0.25	0.5	≤0.5	0.5	≤0.5	2	0.25	1	4	t524	*mecC*
Cow	2010	milk screening	16	>16	>4	4	≤0.25	0.5	≤0.5	0.25	≤0.5	2	0.5	2	8	t524	*mecC*
Cow	2011	milk screening	2	>16	2	2	≤0.25	0.5	≤0.5	0.12	≤0.5	4	0.25	1	8	t9111	*mecC*
Cow	2012	milk screening	>16	>16	2	0.5	≤0.25	0.5	≤0.5	0.25	≤0.5	2	0.25	2	8	t002	*mecA*
Cow	2012	milk	>16	16	>4	1	≤0.25	1	≤0.5	0.5	1	8	0.5	2	8	t002	*mecA*
Cow	2013	milk screening	1	8	0.5	0.5	≤0.25	1	≤0.5	0.5	≤0.5	4	0.5	2	8	t843	*mecC*
Cow	2014	milk screening	>16	>16	>4	2	≤0.25	>32	16	0.25	≤0.5	>32	0.25	2	8	t127	*mecA*
Cow	2015	milk screening	1	4	0.25	0.25	≤0.25	≤0.25	≤0.5	0.12	≤0.5	8	0.5	1	8	t843	*mecC*

[a] Tested with 2% NaCl.

TABLE 2.7. Companion animals. Isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) in Swedish dogs and cats up to and including 2015. All isolates were positive for the *mecA* or *mecC* and *nuc* genes by molecular methods. Shaded areas indicate MIC above EUCAST ECOFF.

Animal species	Year	Clinical background/ Sampling site	Antibiotic													*spa*-type	*mec*-gene
			Oxa[a]	Fox	Pen	Cet	Cli	Ery	Tet	Fus	Gen	Kan	Cip	Tmp	Chl		
Dog	2006	post-op wound	>16	>16	>4	8	≤0.25	0.5	≤0.5	0.5	≤0.5	2	>4	1	8	t032	*mecA*
Dog	2006	post-op wound	>16	>16	>4	8	≤0.25	0.5	≤0.5	0.5	≤0.5	2	>4	1	8	t032	*mecA*
Dog	2006	post-op wound	>16	8	>4	>8	≤0.25	0.5	≤0.5	0.25	1	4	>4	2	8	t032	*mecA*
Dog	2007	post-op wound	>16	>16	>4	>8	≤0.25	0.5	≤0.5	0.5	≤0.5	4	>4	2	8	t032	*mecA*
Dog	2007	abscess	>16	>16	>4	>8	≤0.25	0.5	≤0.5	0.5	≤0.5	2	>4	1	8	t032	*mecA*
Dog	2007	post-op wound	>16	>16	>4	>8	0.5	0.5	2	-	1	2	>4	2	4	t032	*mecA*
Dog	2007	post-op wound	>16	16	>4	8	≤0.25	0.5	≤0.5	0.25	≤0.5	2	>4	1	8	t032	*mecA*
Dog	2007	unknown	>16	16	>4	>8	≤0.25	0.5	≤0.5	0.25	≤0.5	4	>4	2	8	t032	*mecA*
Dog	2008	wound	>16	>16	>4	>8	≤0.25	1	≤0.5	0.25	1	2	>4	2	8	t032	*mecA*
Dog	2008	unknown	>16	>16	>4	>8	≤0.25	≤0.25	≤0.5	0.5	1	2	>4	1	8	t032	*mecA*
Dog	2008	unknown	>16	>16	>4	>8	≤0.25	1	≤0.5	0.25	1	2	>4	2	8	t032	*mecA*
Dog	2008	unknown	>16	>16	>4	>8	0.5	>32	≤0.5	0.5	32	>32	>4	>32	16	t127	*mecA*
Dog	2009	post-op wound	8	>16	>4	>8	≤0.25	0.5	≤0.5	0.25	≤0.5	2	>4	2	8	t032	*mecA*
Dog	2009	wound	>16	>16	>4	>8	0.5	1	1	0.5	1	4	>4	4	16	t032	*mecA*
Dog	2010	wound	>16	>16	>4	>8	>32	>32	≤0.5	0.5	1	>32	>4	2	16	t002	*mecA*
Dog	2010	ear	8	-	>4	>8	≤0.25	0.5	≤0.5	0.5	≤0.5	2	>4	1	8	t032	*mecA*
Dog	2010	unknown	>16	16	>4	8	≤0.25	>32	≤0.5	0.5	≤0.5	2	>4	8	4	t020	*mecA*
Dog	2010	skin	16	16	>4	1	≤0.25	≤0.25	≤0.5	8	1	2	0.5	2	8	t002	*mecA*
Dog	2013	wound	4	>16	>4	1	≤0.25	>32	16	0.25	2	>32	0.25	2	8	t127	*mecA*
Dog	2013	wound	16	>16	>4	2	≤0.25	1	≤0.5	0.5	≤0.5	2	0.5	4	8	t304	*mecA*
Dog	2013	wound	>16	>16	>4	2	≤0.25	1	≤0.5	0.25	≤0.5	4	0.5	2	8	t127	*mecA*
Dog	2013	unknown	>16	>16	>4	>8	0.5	1	1	1	1	4	>4	4	8	t032	*mecA*
Dog	2013	wound	16	>16	>4	2	≤0.25	0.5	≤0.5	0.5	≤0.5	2	0.5	>32	8	t223	*mecA*
Dog	2014	wound	16	>16	>4	2	≤0.25	1	16	0.5	1	8	0.5	4	8	t325	*mecA*
Dog	2014	unknown	>16	>16	>4	8	≤0.25	≤0.25	≤0.5	≤0.06	≤0.5	2	>4	1	8	t032	*mecA*
Dog	2014	unknown	>16	>16	>4	1	≤0.25	>32	≤0.5	≤0.06	≤0.5	2	0.25	1	8	t002	*mecA*
Dog	2015	wound	8	16	>4	2	0.5	≤0.25	≤0.5	0.5	≤0.5	2	0.25	≤0.5	8	t373	*mecC*
Dog	2015	abscess	>16	>16	>4	4	≤0.25	>32	32	≤0.06	≤0.5	>32	0.25	1	8	t127	*mecA*
Dog	2015	wound	2	16	1	0.5	≤0.25	≤0.25	≤0.5	0.12	≤0.5	4	0.25	1	8	t843	*mecC*
Dog	2015	wound	>16	>16	>4	2	≤0.25	>32	16	0.12	≤0.5	>32	0.12	2	4	t127	*medA*
Dog	2015	wound	>16	>16	>4	2	≤0.25	>32	16	0.25	≤0.5	>32	0.5	2	8	t948	*mecA*
Dog	2015	post-op wound	>16	>16	>4	4	≤0.25	>32	16	0.5	≤0.5	>32	0.25	2	8	t127	*mecA*
Dog	2015	unknown	>16	>16	>4	2	≤0.25	>32	16	0.12	≤0.5	>32	0.25	1	4	t177	*mecA*
Cat	2009	urine	>16	>16	>4	>8	≤0.25	0.5	≤0.5	0.25	≤0.5	0.5	>4	4	4	t032	*mecA*
Cat	2009	unknown	>16	>16	>4	>8	≤0.25	0.5	≤0.5	0.5	1	1	>4	2	8	t032	*mecA*
Cat	2010	ear	>16	-	>4	>8	≤0.25	0.5	≤0.5	1	≤0.5	2	>4	1	8	t032	*mecA*
Cat	2010	nose	>16	16	>4	>8	≤0.25	≤0.25	≤0.5	0.25	≤0.5	1	>4	1	8	t032	*mecA*
Cat	2011	skin infection	>16	>16	>4	>8	≤0.25	≤0.25	≤0.5	0.25	≤0.5	2	>4	1	8	t022	*mecA*
Cat	2012	wound	>16	>16	>4	>8	≤0.25	≤0.25	≤0.5	0.25	≤0.5	4	>4	2	8	t032	*mecA*
Cat	2012	wound	>16	>16	>4	>8	0.5	1	1	1	1	4	>4	2	16	t032	*mecA*
Cat[b]	2013	wound															
Cat	2014	wound	8	>16	1	2	≤0.25	≤0.25	≤0.5	0.25	≤0.5	2	0.25	0.5	8	t978	*mecC*
Cat	2014	unknown	8	>16	2	1	≤0.25	≤0.25	≤0.5	≤0.06	≤0.5	1	0.25	0.5	8	t978	*mecC*
Cat	2015	wound	4	16	1	1	≤0.25	≤0.25	≤0.5	≤0.06	≤0.5	0.5	0.25	1	8	t843	*mecC*
Cat	2015	post-op wound	8	16	>4	1	≤0.25	0.5	≤0.5	0.12	≤0.5	2	0.25	1	8	t933	*mecA*

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

MRSA with *mecC* in wild hedgehogs

Background

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important cause of infections in humans since the 1980ies (Moellering 2012). In the last decade MRSA has emerged also among animals, notably among animals raised for food-production (Vanderhaeghen et al., 2010).

Previously methicillin resistance in MRSA from humans and animals was only known to be mediated by the *mecA* gene but in 2011 a divergent homologue, *mecC*, was reported from cattle and humans in England, Scotland and Denmark (Garcia-Alvarez et al., 2011).

Since then MRSA *mecC* has been reported in humans in several other European countries but this variant is not a common cause of human infections (Paterson et al., 2014). MRSA *mecC* has also been reported from several other domesticated animal species including sheep, dogs and cats (Paterson et al., 2014).

The origins of MRSA *mecC* are not clear although the epidemiological information available indicate that an animal reservoir is likely (Paterson et al., 2014). MRSA *mecC* has also been found in diverse wild animal species (Paterson et al., 2014) and it has been hypothesized that this variant could have evolved in wildlife (Monecke et al., 2013).

In Sweden, MRSA *mecC* is a rare finding in humans and in 2015 only eleven cases were confirmed (see Notifiable diseases: MRSA). In animals altogether six cases have been confirmed in cattle, two in dogs and three in cats (see Notifiable diseases: MRSA) In previos years MRSA *mecC* has also been found in five hedgehogs examined post mortem at SVA (Swedres-Svarm 2014). The earliest finding was from a hedgehog examined 2003. These random findings of MRSA *mecC* in hedgehogs initiated the present study aiming to more systematically investigate the occurrence of MRSA in wild hedgehogs.

Study design

During 2015, 49 hedgehogs were sampled at three wildlife rescue centers located in the counties Gotland, Skåne and Västra Götaland. The centers take care of weakened wildlife found in the surrounding area and provide basic healthcare to animals with the aim to release animals that recuperate. In addition, six hedgehogs from other parts of Sweden sent for postmortem examination to SVA were sampled. Samples for bacteriological culture were collected by sterile cotton swabs from nostrils, oral cavity and the perineal area.

TABLE. Resistance phenotypes of 35 MRSA *mecC* isolated from hedgehogs 2015. Phenotypes of previously isolated MRSA *mecC*s from hedgehogs are included for comparison. ECOFFs (mg/L) are indicated and shaded fields denote MIC above the ECOFF.

Number of solates (year)	MIC (mg/L)												
	Oxa	Fox	Pen	Cet	Cli	Ery	Tet	Fus	Gen	Kan	Cip	Tmp	Chl
	>2	>4	>0.12	>1	>0.25	>1	>1	>0.5	>2	>8	>1	>2	>16
7 (2015)	0.5-2	8->16	1-4	0.5-1	≤0.25	≤0.25	≤0.5	≤0.06-0.25	≤0.5-1	0.5-2	0.12-0.25	≤0.5-1	4-8
16 (2015)	4-16	16->16	1->4	1	≤0.25	≤0.25	≤0.5	≤0.06-0.25	≤0.5	0.5-8	0.25-0.5	≤0.5-1	1-8
5 (2015)	4-16	16->16	2->4	2-4	≤0.25	≤0.25	≤0.5	≤0.06-0.5	≤0.5	1-4	0.25-0.5	≤0,5-1	8
1 (2015)	16	16	>4	2	≤0.25	≤0.25	≤0.5	1	≤0.5	0.5	0.25	≤0.5	8
1 (2015)	>16	>16	>4	>8	16	0.5	≤0.5	8	2	8	0.5	1	8
1 (2015)	16	>16	2	>8	16	4	≤0.5	4	8	32	2	1	8
2 (2015)	16->16	>16	2	>8	16	2	≤0.5	2-4	4-8	32	1	1	8
2 (2015)	>16	>16	4->4	>8	4-16	4	16-32	2-4	4-8	32->32	2-4	1	8
Isolates from previous years													
1 (2003)	16	16	2	2	≤0.25	1	≤0.5	1	1	8	0.5	4	8
1 (2011)	4	16	2	1	0.5	1	≤0.5	1	1	8	0.5	2	8
1 (2014)	16	>16	2	1	≤0.25	≤0.25	≤0.5	≤0.06	≤0.5	2	0.25	1	8
1 (2014)	16	>16	2	2	≤0.25	≤0.25	≤0.5	≤0.06	≤0.5	2	0.25	≤0.5	8
1 (2014)	16	>16	2	2	≤0.25	≤0.25	≤0.5	0.5	≤0.5	4	0.5	1	16

Pooled samples were cultivated for MRSA on MRSA 2 Brilliance agar (Oxoid, UK) after selective pre-enrichment in tryptic soy broth (TSB) with 4% NaCl supplemented with 10 mg/mL aztreonam. Putative isolates of MRSA from Brilliance plates were confirmed with an in house multiplex PCR targeting the genes *mecA*, *mecC* and *nuc*. Isolates confirmed as MRSA were tested for susceptibility to relevant antimicrobials (Table) by determination of the minimum inhibitory concentration (MIC) by micro-dilution according to CLSI (CLSI, 2013) and using VetMIC panels (SVA, Sweden).

Results and Discussion

MRSA was isolated from 35 (64%) of the 55 hedgehogs sampled. All isolates carried the *mecC* gene. Twenty-eight isolates (80%) from 2015 were resistant only to beta-lactams but seven isolates were resistant also to other antimicrobials (Table). Six of these were multiresistant and were in addition to beta-lactams also resistant to macrolides, lincosamides and aminoglycosides. Three of these isolates were resistant also to fluoroquinolones. All isolates had cefoxitin MIC above the ECOFF but seven isolates had oxacillin MIC below the ECOFF (Table). This is in agreement with the observation that oxacillin is an unreliable indicator for MRSA *mecC* (Skov et al., 2013).

The resons for the surprisingly high occurrence of MRSA *mecC* in hedgehogs is not known. Spread of MRSA within rescue centers could be an explanation but in this study the animals were sampled on arrival and thus had minimal contact with the facilities at the rescue centers before being sampled. Moreover, to avoid spread of infections at rescue centers, strict hygienic routines are practiced. Also, on postmortem examinations at SVA, MRSA *mecC* has been isolated from hedgehogs without known connections to rescue centers. This indicates that MRSA *mecC* occurs also without a putative nosocomial spread at rescue centers.

From a public health perspective the findings are likely of minor importance. Most people never come in direct contact with hedgehogs and MRSA *mecC* is rarely isolated from humans in Sweden. It is however of great importance that persons handling hedgehogs at rescue centers or elsewhere are aware of the risk that the animals can be carrying MRSA and should take relevant precautionary actions to avoid contamination.

From a scientific perspective the findings are however most interesting and the possibility that hedgehogs, or other wildlife, are natural reservoirs of MRSA *mecC* should be further investigated.

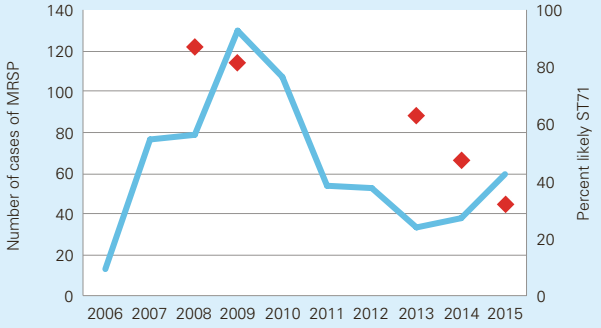
Methicillin-resistant *Staphylococcus pseudintermedius* (MRSP)

MRSP in animals

During 2010-2013 there was a decrease of cases of methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) reported to the Swedish Board of Agriculture, from 130 cases in 2009 to 33 cases in 2013 (Figure 2.15). In 2014 a small increase was observed with 39 cases. In 2015 the numbers of cases increased even further with 60 cases reported to the Board of Agriculture. All but one case, from a cat, were related to dogs, and 58 of the 60 isolates were available at SVA for further typing. The origin of isolates was unknown in 8 of the cases, 22 were from skin including ears, 18 were from wounds, and the remaining 12 were isolated from various sites.

Twenty-four of the isolates could by typed by sequencing the *spa*-gene, and belonged to *spa*-types t02 (n = 8), t05 (n = 1), t06 (n = 6), t10 (n = 2), t21 (n = 2), t51 (n = 2) and two isolates belonged to a new *spa*-type. The new *spa*-type appears to have a deletion in the first repeat of the *spa*-gene, but was besides this identical with t08. The remaining 34 isolates were untypable using *spa* and were therefore subjected to MLST. Of the 34 isolates characterized with MLST, 3 isolates belonged to ST71, 20 isolates to ST258, 2 isolates to ST265, while the remaining 9 isolates belonged to different singletons. Based on the combined results of *spa* and MLST it is likely that 32% of all MRSP isolates belonged to the European clone ST71-J-t02-II-III, described by Perreten et al. (2010). Compared to 2014 the number of isolates belonging to ST258 increased from 4 isolates to 20 isolates in 2015, thus constituting the same proportion as ST71 isolates in 2015. Isolates belonging to ST258 have been described as an emerging clone in Denmark and Norway (Osland et al., 2012; Damborg et al., 2013) and it appears that it has now been established in Sweden.

FIGURE 2.15. Number of cases with methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) in Sweden notified to the Swedish Board of Agriculture 2008-2015. In 2006-2007 the numbers represent the isolates that were sent to SVA and confirmed as *mecA*-positive. Red rhombs represent the percent of isolates likely belonging to the European clone ST71, complete data only available for 2008-2009 and 2013-2015.



All isolates were defined as multiresistant, but 78% were susceptible to fusidic acid, 71% to gentamicin and 100% to nitrofurantoin. The occurrence of ST71 isolates resistant to fusidic acid and tetracycline increased from 3% and 0% in 2014 to 5% and 37% in 2015, respectively. Isolates belonging to ST258 were all susceptible to gentamicin, but 100% were resistant to trimethoprim-sulfa and 85% to tetracycline.

Zoonotic aspects on MRSP

Staphylococcus pseudintermedius may act as an opportunistic pathogen in humans and there are several reports in the literature of infections in humans with a varying degree of severity. However, MRSP is not generally considered to be a zoonotic pathogen.

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

VRE in humans

Background

Vancomycin resistant enterococci (VRE) are important causes of nosocomial infections in many parts of the world, usually involving high-risk populations such as immunocompromised and intensive care patients. Like MRSA, VRE were made notifiable according to the Swedish Communicable Disease Act in the year 2000 and since 2004 contact tracing is mandatory. The following presentation is based on data collected in the national web-based notification system SmiNet. During the last 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 relevant epidemiologic information from investigations around each case in collaboration with the CMOs. From 2000 to 2006 only low numbers (18-35 per year) of VRE-cases were reported in Sweden. In 2007 an increase of VRE-cases were reported from Stockholm County. This was the beginning of an outbreak with *Enterococcus faecium vanB* that would last until 2011. The total number of cases in this outbreak was 872. The next large outbreak of *E. faecium* with *vanB* occurred in Västernorrland County (2010-2011) with an estimated number of 100 cases. In 2012 at least two outbreaks caused by two different strains of *E. faecium* with *vanA* genes contributed to the increase in this type of VRE. In September 2013 a new outbreak caused by a strain of *E. faecium* with *vanB* occurred in Gävleborg County. It lasted to the end of 2014 and affected a total of 314 patients. These outbreaks led to extensive infection control measures to limit and eradicate the outbreak strains.

A potential clone shift of methicillin-resistant *Staphylococcus pseudintermedius* from ST71 to ST258

Since 2006 methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) has established itself as a significant clinical problem in Swedish veterinary medicine, especially among dogs. From the first sporadic cases in 2006 MRSP increased rapidly reaching its peak in 2009 with 130 cases reported to the Swedish Board of Agriculture. The rapid increase was mainly due to spread of isolates belonging to the multi-locus sequence type ST71. This increase and domination of one clonal lineage belonging to ST71 mimicked the picture of MRSP described in the rest of Europe (Perreten et al., 2010). However, after 2009 a decreasing trend was observed in Sweden with only 33 cases reported in 2013. The decrease was primarily due to the decreasing number of cases related to ST71, and as the fraction of cases related to MRSP ST71 decreased an increase in diversity were noticed. The decline in cases halted in 2014 when 39 cases were observed and in 2015 this increasing trend continued with 60 cases being reported.

In Sweden, SVA has mainly relied on using the *spa*-typing scheme described by Moodley et al. (2010) to characterize MRSP isolates. However, as the number of isolates likely belonging to ST71 decreased the number of isolates that were untypable using spa increased. In 2014 it was concluded that 47% of isolates belonged to the ST71 clonal lineage, based on *spa*-type, and 35% of isolates were untypable using *spa*-typing. Due to this SVA implemented the seven locus MLST scheme described by Solyman et al. (2013) in 2014. Using MLST it was shown that 20 isolates (33%) out of 58 available isolates from 2015 belonged to ST258. The ST258 were also identified in 2014 when 4 out of 34 isolates available for typing (12%) belonged to this sequence type. While based mainly on *spa*-typing it was concluded that a total of 19 isolates (32%) likely belonged to ST71 in 2015.

Interestingly, there are clear differences in resistance phenotypes of the ST71 and ST258 lineages. With all isolates of ST258 being susceptible to gentamicin and a clear majority being resistant to tetracycline, while basically the opposite is the situation for ST71 isolates (Table). Resistance to fusidic acid is also more common in ST258 isolates compared to ST71.

The increasing trend of isolates belonging to ST258 might therefore indicate that a clonal shift is occurring in Sweden in regards to MRSP. A similar shift with increasing occurrence of ST258 and an overall increasing diversity of MRSP has also been reported in a study from The Netherlands (Duim et al., 2015). The authors of the study also observed that isolates belonging to the ST258 had emerged after 2007. In contrast to most other European countries, Norway has had a lower fraction of MRSP cases related to ST71 and overall a more diverse picture (Osland et al., 2012). However, ST258 has been described as an emerging clone in Norway, and also in Denmark (Osland et al., 2012; Damborg et al., 2013). Furthermore, ST258 has been described in relation to clinical cases in dogs in France and Italy (Haenni et al., 2014; Rota et al., 2015).

TABLE. Percent resistant isolates among verified MRSP isolates at SVA during 2014 and 2015, in related to MLSTs

	MLST		
Antibiotic	**ST258 (%)**	**ST71[a] (%)**	**Other STs (%)**
Oxacillin	88	95	93
Cephalothin	8	90	7
Fusidic acid	21	5	34
Erythromycin	83	95	90
Clindamycin	63	95	86
Gentamicin	0	83	55
Nitrofurantoin	0	0	0
Tetracycline	88	25	59
Trim-Sulph[b]	100	93	62

[a] Based on spa-typing, [b] trimethoprim sulphametoxazole, tested in concentration ratio 1/20

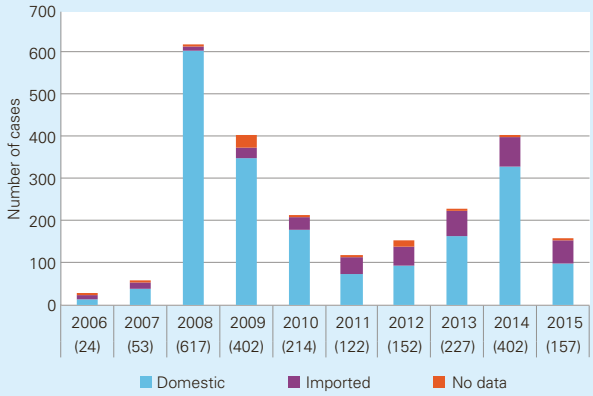
The reason for the observed clonal shift from one dominating clonal lineage, the ST71, to two common clonal lineages, the ST71 and ST258, is unknown. It is also something that warrants further studies and it is therfore important to continue monitoring MRSP cases in animals.

Notifications of VRE according to the Communicable Disease Act

In 2015 a total of 157 cases were reported, a decrease compared to 2014 when 402 cases were reported (Table 2.8). VRE cases were reported from 12 of the 21 Swedish counties. The average national incidence of VRE was 1.6 with higher than average incidence figures in Örebro (5.2), Gävleborg (3.2), Stockholm (2.5), Uppsala (2.3), Kronoberg (2.1), Skåne (1.9) and Kalmar (1.7) counties. Of all cases, 97 (62%) were reported as domestic (Figure 2.16), and of those 86 were healthcare related. In 59 cases (38%) VRE had been acquired abroad. The most common countries for imported VRE infection were Serbia (8 cases), Bosnia and Herzegovina (6), Turkey (5) and USA (4). Fifty-five (93%) of the imported cases were healthcare related.

The domestic VRE cases were detected through contact tracing (71%), screening (15%) or clinical symptoms (7%). For six of the domestic cases, indication for sampling was not stated. The majority of the imported cases (81%) were detected through screening, seven percent due to clinical symptoms and seven percent due to contact tracing. Accordingly a majority of the isolates (87%) in the first laboratory notifications were from feces and rectum, and only ten percent from urine, wound or other clinical samples. The VRE cases were equally distributed between sexes, with median ages of 74 years for women and 72 years for men. The median age was lower for imported (68 years) than for domestic cases.

FIGURE 2.16. Human cases of VRE in Sweden 2006-2015, notified as domestic and imported, respectively. Numbers of reported cases are shown in brackets.



In 2015, isolates from 133 cases carried *E. faecium* and isolates from 12 cases *E. faecalis*. In samples from three cases both *E. faecium* and *E. faecalis* could be isolated. In contrast to 2014, the dominating resistance gene 2015 was *vanA* (Table 2.9). One invasive VRE infection was reported in 2015 in a person already known to carry VRE in a previous year.

Epidmiological typing of VRE in outbreakes

For enterococci PFGE is still used as the standard typing method. Isolates from notified cases in all counties from 2007 and onwards have been analysed, and comparisons with isolates from previous years have also been performed. From this national strain collection and PFGE database it has been shown that the *E. faecium* with *vanB* gene causing the outbreak situation 2007-2010 had not been detected before 2007. This strain was named SE-EfmB-0701 to indicate species (Efm), resistance gene (B), year of detection (07) and a serial number (01). The extensive outbreak 2010-2011 in Västernorrland County was caused by a strain with the PFGE-type SE-EfmB-1001. The large outbreak in Gävleborg County in 2013-2014 was caused by a strain typed as SE-EfmB-1308. During these years other smaller hospital-related outbreaks make the baseline of reported cases while the larger outbreaks contributes to the peaks. To date *E. faecium* with *vanA-gene* have caused more but smaller hospital-related outbreaks while *E. faecium* with *vanB* have caused fewer outbreaks but with more cases.

In 2015, twelve healthcare related outbreaks of *E. faecium* were reported from nine counties. Nine outbreaks with *vanA* gene and three with *vanB* gene, comprising 3-11 cases each, and six cases respectively. The number of hospital-related outbreaks this year are similar to what has been reported the last three years.

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

VRE in animals

During 2015, samples of intestinal contents from healthy broilers (n=100) were screened for vancomycin resistant enterococci (VRE) by culture on vancomycin supplemented media (16 mg/L). Presumed enterococci were species identified with MALDI-TOF MS and subsequently typed with

TABLE 2.8. VRE-notifications according to the Communicable Disease Act 2008-2015 by species and *van*-gene.

Species and R-gene	2008	2009	2010	2011	2012	2013	2014	2015
E. faecium vanA	96	61	63	39	97	93	110	95
E. faecium vanB	505	326	135	70	26	126	281	39
E. faecalis vanA	4	6	3	8	5	1	3	7
E. faecalis vanB			1	2			5	2
Not specified	12	9	12	3	24	7	6	18
Total	**617**	**402**	**214**	**122**	**152**	**227[a]**	**402[a,b,c]**	**157[a,b,c]**

[a]In one case in 2013, in two cases 2014 and in two cases 2015 a strain of *E. faecium* with both *vanA* and *vanB* gene was detected. [b]In one case in 2014 both *E. faecium vanB* and *E. faecalis vanB* could be isolated. [c]In two cases in 2015 both *E. faecium vanA* and *E. faecalis vanA* could be isolated.

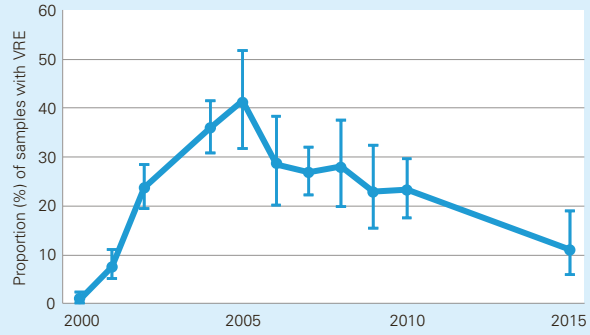
whole genome sequencing (WGS) (for details see Material and methods, resistance in bacteria from animals).

Vancomycin resistant *E. faecium* with the *vanA* gene was isolated from 11 (11%) of the samples (Figure 2.17). This is the lowest occurrence observed since 2001 and when tested with Pearson's X^2 test the difference between 2010 and 2015 was statistically significant (p=0.001). The reason(s) for this decrease in occurrence is however not known.

All VRE isolates in 2015 were resistant to vancomycin (MIC >128 mg/L), narasin (MIC = 4-8 mg/L) and erythromycin (MIC = 8-32 mg/L) but susceptible to all other substances tested. Typing with WGS showed that all but one of the isolates belonged to ST310 which has previously been described to dominate among broilers in Sweden (Nilsson et al., 2009). The remaining isolate differed in one allele and belonged to a new sequence type.

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

FIGURE 2.17. Proportion (%) of samples of intestinal content from healthy broilers positive for VRE from 2000 to 2002, 2004 to 2010, and 2015 when cultured on vancomycin supplemented media (16 mg/L), 95% confidence intervals indicated. Number of samples cultured each year is between 99 and 351.



Zoonotic aspects on VRE

Occurrence of *E. faecium* with the *vanA* gene has decreased but such bacteria are still present among Swedish broilers and there is a potential risk for transfer of these VRE to humans. Due to different outbreaks, the proportion of *E. faecium* with the *van*A gene among VRE from humans has varied over the years. In 2015 this variant comprised almost 2/3 of the cases. However, in previous studies comparing PFGE-patterns of VRE isolates from humans and broilers no common type has been found. Furthermore, all VRE isolates from both humans and broilers in 2015 were typed with whole genome sequencing (WGS) but nor with this method was any common types identified. Moreover, the recently described gene that putatively mediate elevated MIC of narasin (Nilsson et al., 2016) was used as a marker for plasmids with a broiler association and it was screened for among VRE isolates from humans in 2015. No isolate with that gene was detected. Accordingly, there are no indications that the presence of VRE in broilers in Sweden has affected the situation in Swedish healthcare.

Streptococcus pneumoniae with reduced susceptibility to penicillin (PNSP)

PNSP in humans

Background

Streptococcus pneumoniae with reduced susceptibility to penicillin (PNSP, defined as MIC ≥ 0.5 mg/L) became notifiable according to the Communicable Disease Act in 1996. In May 2012, a revised case definition was introduced, stating that only PNSP with MIC of penicillin >1 mg/L were now notifiable and the identified cases subjected to contact tracing. However, in order to follow and evaluate the effect of vaccination against pneumococcal disease and to identify emerging spreading antibiotic resistant pneumococcal clones, the Public Health Agency of Sweden has continued to collect and perform serotyping on PNSP isolates according to the previous definition (below).

Notifications according to the Communicable Disease Act

In 2015 a total of 59 PNSP (MIC >1mg/L) cases were reported in Sweden. Fifty-one percent of the cases had been infected domestically and thirty-one percent of the cases in a foreign country. For the remaining 11 cases no country of acquisition was given. The incidence of PNSP (MIC >1mg/L) in Sweden 2015 was 0.6 cases per 100 000 inhabitants. Among age groups PNSP is most common in group 0-4 years (42% in 2015), independent of year observed. Of the reported cases in 2015, 56% have been male, 44% female. PNSP (MIC >1mg/L) were reported from 16 of 21 Swedish counties, with Stockholm (12 cases), Dalarna (7), Västmanland (5) and Skåne (5) accounting for 49% of all notifications. The remaining 12 counties reported 1-4 cases each. PNSP, were most often found in cultures from the nasopharynx. In 37 cases (63%) the detection of PNSP was due to clinical infection. Six cases were detected through contact tracing and five cases through targeted screening. In the remaining cases another reason for sampling was stated (2 cases) or the information was missing (9).

Serotype distribution of pneumococcal isolates with MIC ≥ 0,5

To be able to follow the trend of pneumococci with a reduced susceptibility to penicillin during the years, we have continued our surveillance of PNSP, i e pneumococci with MIC ≥0,5mg/L. In 2015, 314 pneuomococcal isolates with an MIC ≥ 0,5mg/L were collected which is an increase compared to 2014 (n=237) The serotype distribution for these 314 isolates were, in descending order: 19F (21%), non-typable (NT; 15%), 35B (10%), 6B (7%), 19A (7%), 23F (6%), 14 (4%), 11A (4%), 9V (3%), 15C (3%), 9N (3%), and 15B (3%). Of the serotyped isolates, 54% constituted types included in the 13-valent vaccine compared to 60% and 54% in 2013 and 2014, respectively. One isolate of serotype 19F was isolated from an invasive case (blood) with an MIC > 1mg/L.

Sales of polymyxins and occurrence of the *mcr-1* gene in bacteria from humans, animals and food in Sweden

For many decades, the use of polymyxins in human medicine was mainly limited to topical and ophtalmological applications due to side-effects associated with parenteral treatment. Today, colistin (polymyxin E) has emerged as a last-resort drug for systemic treatment of severe infections caused by multiresistant Gram-negative bacteria. In veterinary medicine in many countries, colistin has been widely used for decades for oral treatment of infections in farm animals caused by Enterobacteriaceae (Catry et al., 2015). In spite of this, reported occurrence of resistance to colistin among Enterobacteriaceae from animals has mostly been low and until recently, there were no reports on transferrable resistance to colistin, neither in bacteria from animals, nor from humans (Catry et al., 2015).

In November 2015, Liu et al. (2015) reported on findings of a plasmid mediated, transferrable gene, *mcr-1*, conveying resistance to colistin. The gene was found in China in comparatively high frequency (around 20%) among *Escherichia coli* from pigs as well as pig and chicken meat and in low frequency among Enterobacteriaceae from human beings (around 1%). Since, a number of reports have documented presence of *mcr-1* among Enterobacteriaceae from various sources in most continents (Skov and Monnet 2016). Compared to a situation with only mutational (non-transferrable) resistance, occurrence of transferrable resistance in animal microbiota increases the risk of spread of resistance between animals, and from animals to humans. Specific surveillance of occurrence of *mcr-1* among bacteria from humans and animals is therefore needed.

Human beings

The total sales of colistin for systemic use (J01XB01) in Sweden has increased over the last years. However, the consumption is low and in 2015 the sales was 0.005 DDD/1 000 inhabitants and day. Polymyxin B is also included in topical ophtalmological or otological formulations in combination with hydrocortisone (S03CA04). The total sales of such products have decreased by 10% since 2000. In 2015, the total sales of topical products with hydrocortisone in combinations with polymyxin B were 38 packages per 1 000 inhabitants and year.

Two isolates with the *mcr-1* gene, both *E. coli* from humans, have been identified in Sweden up until March 7, 2016. One of the isolates, which also carried an $ESBL_A$ gene of type CTX-M, was identified in a research study of MRB-carriage post travel to foreign countries performed at Karolinska Institutet and the other in the national microbiological surveillance program for enterohaemorrhagic *E. coli* (ehec) at The Public Health Agency of Sweden. The *mcr-1* gene was in both of the cases identified in isolates from stool samples of individuals who had been traveling in Asia and were considered as asymptomatic carriage within the fecal flora.

From January 1, 2009 until March 7, 2016 a total of 2 095 isolates of Enterobacteriaceae with reduced susceptibility to cephalosporins have been tested for antibiotic susceptibility to colistin. Of these, 24 isolates (13 *E. coli* and 11 *Klebsiella pneumoniae*) had MIC > 2 mg/L and were tested for the presence of *mcr-1*, but none of these isolates carried the gene.

The above material includes all carbapenemase producing isolates ($ESBL_{CARBA}$) identified in Sweden that since 2011 are routinely sent to The Public Health Agency for molecular and phenotypic antimicrobial susceptibility characterization, including MIC of colistin. Moreover, since December 2015, all $ESBL_{CARBA}$ isolates are whole genome sequenced and genetically screened for the presence of *mcr-1* irrespective of MIC of colistin. Also included in the above are national biannual collections of ESBL-producing Enterobacteriaceae.

Animals and food

In Sweden, colistin is authorised for use in pigs for oral treatment of weaning diarrhea (QA07AA10). In 2013, sales corresponding to 0.13 mg active substance per population correction unit (i.e. kg estimated live biomass) were reported for Sweden, compared to the average of countries reporting in the EU/EEA of 10.2 mg per population correction unit (calculated from data presented in EMA, 2015).

Polymyxin B is authorized for topical otological use in dogs and cats (QS02CA01). Furthermore, products authorized for use in humans for topical ophtalmological or otological use are prescribed "off-label" for use in animals (S03CA04). In 2015, a total of 20 635 packages of topical products with polymyxin B was sold for use in animals; mainly for dogs and cats but also for other companion animals and occasionally for horses. The sales for dogs was 75% of the total sales, corresponding to around 20 packages per 1000 dogs and year.

Within the frame of Svarm, *E. coli* from the intestines of randomly selected healthy farm animals sampled at slaughter have been tested for susceptibility to colistin since 2010 (see Indicator bacteria and Materials and methods, resistance in bacteria from animals). Other

TABLE. Materials from the monitoring in Svarm, number of isolates with MIC of colistin of >2 mg/L and results of PCR for *mcr-1*.

Bacterial species	Type of material	Years	N of isolates tested for susceptibility	N of isolates with MIC of colistin >2 mg/L	Result of PCR for *mcr-1*
E. coli	healthy animals[a]	2010-2015	1 598	1	negative
E. coli	meat[b]	2010-2012	189	1	negative
E. coli	screening[c]	2010-2015	606	3	negative
Salmonella enterica	mixed	2013-2015	241	8	negative[d]

[a] Indicator E. coli: 465 isolates from pigs, 572 from chickens, 284 from cattle, 114 from turkeys and 61 from hens; [b] mainly chicken-meat; [c] from samples cultured on media selective for ESBL or cabapenemases; [d] 7 isolates tested, 1 isolate from a cat could not be retrieved.

materials routinely tested for colistin susceptibility are *E. coli* isolated from samples of healthy animals on screening plates for *E. coli* producing ESBL or carbapenemase, and *Salmonella enterica*. For more information on these materials, see Materials and methods, resistance in bacteria from animals and the relevant sections in this and previous reports from Swedres-Svarm.

All isolates from the above materials for which a MIC of colistin of >2 mg/L was recorded were retrieved and tested for the presence of *mcr-1* with PCR according to the protocol provided by the European Union reference laboratory for antimicrobial resistance. In addition, a miscellaneous collection of 40 isolates of relevant species of Enterobacteriaceae, isolated from various animals, and where the MIC of colistin was >2 mg/L, were also tested for *mcr-1*.

The materials derived from the monitoring in Svarm and results obtained are shown in Table. All tested isolates were negative for *mcr-1*, including the miscellaneous collection of 40 isolates mentioned above.

Isolates of *E. coli* from clinical submissions of samples from various animals to SVA are resistant to colistin at a low frequency (5% or below; see section on Clinical isolates from animals). These isolates are not routinely stored for retrospective analysis and could not be further investigated.

The existence of a collection of isolates where sampling and testing for antibiotic susceptibility has been performed in a standardized way made it possible to rapidly investigate the possible occurrence of transferrable colistin resistance mediated by *mcr-1* in materials where the denominator is known. Such resistance could not be demonstrated in this retrospective investigation. However, as noted by Perrin-Guyomard et al. (2016), the power of the European monitoring of indicator bacteria to detect early emergence of resistance is likely to be low. It is possible that such resistance would first be noted in isolates from clinical submissions from animals, where there is higher likelihood of previous exposure to antibiotics. Swedish diagnostic laboratories handling samples from farm animals have therefore been asked to submit all isolates of *E. coli* and selected other species of Enterobacteriaceae with elevated MICs of colistin for further investigation.

Conclusions

So far, occurrence of *mcr-1* in Enterobacteriaceae from humans and animals in Sweden appears to be rare. Surveillance continues, and the Public health agency of Sweden, SVA and other relevant authorities follow the scientific development in close collaboration.

Zoonotic pathogens

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

Salmonella

Salmonella from human clinical specimens

Infection with *Salmonella* in humans is a notifiable disease in Sweden, and the focus is on epidemiological typing mainly of domestic cases in order to facilitate contact tracing. Antibiotic susceptibility testing on isolates from faecal cultures has only been done by a few local laboratories, thus the following data is on blood isolates. Since the majority of *Salmonella* strains isolated in Sweden come from persons who were infected while travelling abroad, their resistance patterns reflect the situation at their geographical origin.

Blood culture isolates of *Salmonella* are always tested for antibiotic resistance, and in 2015 we used the complete data set of positive blood cultures from 10 laboratories (see background information) as the source of information on antibiotic susceptibility. A total of 52 isolates of *Salmonella* were found among approximately 20 000 blood cultures, Table 3.1. The most common serovars were *Salmonella* ser. Enteritidis (ten cases), *Salmonella* ser. Typhi and *Salmonella* ser. Paratyphi A with six cases each. 35 of the cases were reported as travel associated with the most common countries being Bangladesh (5), Thailand (4) and India (3).

Salmonella in animals

Findings of *Salmonella* in animals are notifiable in Sweden. In Svarm, antibiotic susceptibility is determined in one isolate from each warm-blooded animal species (wild and domesticated) involved in incidents notified 2015. Isolates from incidents previously notified but still under restrictions in 2015 are also included. In incidents involving more than one serovar, one isolate of each serovar is tested. As from 2014 phage typing is not performed on isolates of *Salmonella* from animals. For details on methodology see Materials and methods, resistance in bacteria from animals.

All animals 2015

Altogether, 54 isolates were tested of which 24 were *S.* Typhimurium (Table 3.2). Distributions of MICs and resistance in all isolates are presented in Table 3.3 and for the subset *S.* Typhimurium in Table 3.4. The majority of isolates (89%) were susceptible to all antibiotics tested, but six isolates (11%) were resistant to at least one substance and three isolates (6%) were multiresistant (Table 3.5). Resistance in *S.* Typhimurium is overall low but varies over the years studied due to occurrence of multiresistant strains in individual years (Figure 3.2).

Two isolates were phenotypically resistant to colistin (Table 3.3) but both were negative for the *mcr-1* gene on testing with PCR. No isolate was resistant to extended spectrum cephalosporins (ESC).

The three multiresistant isolates were *S.* Typhimurium from cattle (Table 3.5). All three isolates were resistant to ampicillin, streptomycin and sulphonamide and two also to trimethoprim.

TABLE 3.1. *Salmonella* from blood cultures in Sweden 2015. Data collected from reporting laboratories covering approximately 45 % of the Swedish population.

Salmonella serovar	No of isolates	No of isolates tested for Cip	No of Cip-R	No of isolates tested for Tsu	No of Tsu-R	Travel associated countries reported (no)
Salmonella ser. Enteritidis	10	9	4	10	0	Ivory Coast (1), Makedonia (1), Sri Lanka (1), Tunisia (1), Turkey (1)
Salmonella ser. Typhi	6	6	4	6	1	Bangladesh (2), India (2), Irak (1), Pakistan (1)
Salmonella ser. Paratyphi A	6	3	3	6	0	Bangladesh (3), India (1), Pakistan (1), Southeast Asia (1)
Salmonella other serovars	30	18	5	23	4	Thailand (4), Tanzania (2), Angola (1), China (1), Egypt (1), Gambia (1), Germany (1), Ghana (1), India (1), Mexico (1), Montenegro (1), Nigeria (1), Senegal (1), United Arab Emirates (1)
Total	**52**	**36**	**16**	**45**	**5**	

TABLE 3.2. Number of *Salmonella enterica* isolates from animals tested for antibiotic susceptibility, 2015.

Serovar	Cattle	Pigs	Sheep	Poultry	Horses	Dogs	Cats	Wild birds	Total
S. Aarhus	1								**1**
S. Agona	1	1							**2**
S. Derby						1			**1**
S. Dublin	6								**6**
S. Duesseldorf	2								**2**
S. enterica subsp. diarizonae (IIIb)			3						**3**
S. Epinay				2					**2**
S. Hessarek				1					**1**
S. Kottbus							1		**1**
S. Livingstone	1			2					**3**
S. Mbandaka				1					**1**
S. Meleagridis				2					**2**
S. Newport						1			**1**
S. Reading		1		2					**3**
S. Typhimurium	4	1		7	2		10		**24**
S. Typhimurium 4,5,12:-:1,5								**1**	**1**
Total	**15**	**3**	**3**	**17**	**2**	**2**	**11**	**1**	**54**
Percent of total	28%	6%	6%	31%	4%	4%	20%	2%	

Farm animals 2000-2015

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 2000-2015, isolates from the vast majority of notified incidents in farm animals were tested in Svarm, in total 655 isolates. About half of the isolates, 317 (48%), were *S.* Typhimurium and of these 37% were from pigs, 32% from cattle, 29% from poultry and 2% from sheep.

The majority (73%) of *S.* Typhimurium isolates from the incidents in farm animals were susceptible to all antibiotics

TABLE 3.3. Distribution of MICs and resistance (%) in *Salmonella enterica* (n=54) from all animals, 2015.

Antibiotic	Resistance %	Distribution (%) of MICs (mg/L)																		
		≤0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	>1024
Ampicillin	6								94.4								5.6			
Cefotaxime	0			7.4	50.0	42.6														
Ceftazidime	0						61.1	37.0	1.9											
Chloramphenicol	0									18.5	75.9	5.6								
Ciprofloxacin	2		20.4	48.1	29.6				1.9											
Colistin	4[a]							20.4	50.0	25.9		3.7								
Florfenicol	0										74.1	25.9								
Gentamicin	0						9.3	70.4	20.4											
Kanamycin	0											96.3	3.7							
Nalidixic acid	0								1.9	9.3	81.5	5.6	1.9							
Streptomycin	6									1.9	5.6	27.8	59.3			1.9	3.7			
Sulphamethoxazole	6													35.2	53.7	5.6				5.6
Tetracycline	0								92.6	7.4										
Trimethoprim	4					1.9	57.4	31.5	5.6					3.7						

[a] Transmissible resistance genes (*mcr-1*) not found.

TABLE 3.4. Distribution of MICs and resistance (%) in *Salmonella* Typhimurium (n=24) from all animals, 2015.

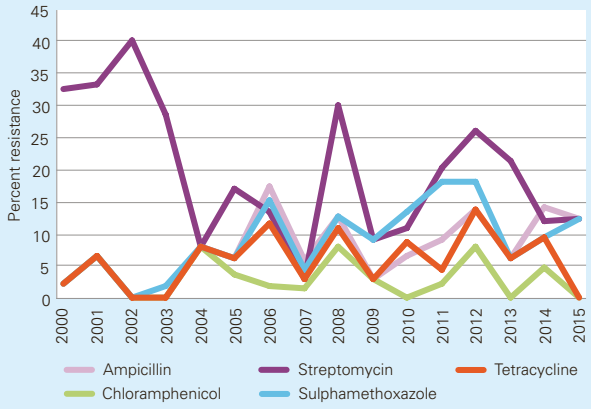
Antibiotic	Resistance %	Distribution (%) of MICs (mg/L)																	
		≤0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	>1024
Ampicillin	13								87.5								12.5			
Cefotaxime	0			4.2	62.5	33.3														
Ceftazidime	0						66.7	33.3												
Chloramphenicol	0									16.7	83.3									
Ciprofloxacin	0		16.7	45.8	37.5															
Colistin	0							12.5	58.3	29.2										
Florfenicol	0										100									
Gentamicin	0						8.3	79.2	12.5											
Kanamycin	0											100.0								
Nalidixic acid	0								4.2	12.5	75.0	8.3								
Streptomycin	13											20.8	66.7			4.2	8.3			
Sulphamethoxazole	13													25.0	54.2	8.3				12.5
Tetracycline	0								91.7	8.3										
Trimethoprim	8						62.5	25.0	4.2					8.3						

TABLE 3.5. MICs (mg/L) in the three isolates of *Salmonella enterica* resistant to three or more antibiotics, 2015. Shaded fields indicate resistance.

Source	Serovar	Amp	Ctx	Caz	Cip	Nal	Chl	Flf	Col	Gen	Kan	Str	Sul	Tet	Tmp
Cattle	*S.* Typhimurium	>128	0.06	0.5	0.03	4	4	≤4	2	0.5	≤8	256	>1024	≤1	0.25
Cattle	*S.* Typhimurium	>128	0.12	≤0.25	0.03	8	4	≤4	2	0.5	≤8	256	>1024	≤1	>16
Cattle	*S.* Typhimurium	>128	0.06	≤0.25	0.03	4	4	≤4	≤0.5	0.5	≤8	128	>1024	≤1	>16

tested but 37 (12%) were multiresistant (Table 3.6). The most common traits were resistance to ampicillin, streptomycin, tetracycline, sulphonamide, chloramphenicol and florfenicol. Resistance to third generation cephalosporins was not found and resistance to ciprofloxacin was confirmed in isolates from only five incidents. Six isolates (2%) of other serovars than Typhimurium were multiresistant.

FIGURE 3.1. Resistance (%) in *Salmonella* Typhimurium from all animals, 2000-2015. The number of isolates each year varies (n=24-85).



The 37 multiresistant isolates of *S.* Typhimurium in the period 2000-15 were from 35 separate incidents of which 24 involved cattle, 6 pigs, 2 poultry and 1 incident involved both pigs and cattle. Of the two remaining incidents, one was in sheep and one in ducks in a hobby flock. Three incidents in 2004 and two in 2015 involved cattle and were epidemiologically linked through trade of calves. An epidemiological link was also suspected between four incidents 2007-2008 involving cattle, pigs and sheep. There were no known links between the other incidents.

In 2015 monophasic *S.* Typhimurium I (O 4,5,12:i- /O 4,5:i:- / O 4:i:-) was not isolated from farm animals. However, nine incidents of monophasic *S.* Typhimurium were confirmed in farm animals since this variant was first found in Swedish animals in 2006 (Table 3.6). Three incidents involved cattle, three incidents pigs, one incident ducks, and one incident involved both cattle and poultry. In five incidents isolates had the resistance phenotype ampicillin, streptomycin, sulphonamide and tetracycline (Table 3.6). Monophasic *S.* Typhimurium was also isolated from three dogs and two wild birds. Epidemiological links were confirmed between some of the incidents of monophasic *Salmonella*.

TABLE 3.6. Resistance phenotypes of *Salmonella* Typhimurium (n=317) from incidents in farm animals, 2000-2015. All isolates were tested for susceptibility to ampicillin, florfenicol, gentamicin, chloramphenicol, ciprofloxacin, nalidixic acid, streptomycin, sulphamethoxazole, tetracycline, trimethoprim and to ceftiofur or cefotaxime.

		Phagetype																						
Phenotype	**Source**	**1**	**7**	**9**	**10**	**12**	**15[a]**	**39**	**40**	**41**	**99**	**104**	**110[b]**	**120**	**125**	**126**	**146**	**193**	**195**	**NST**	**NT**	**monophasic**	**Not typed**	**Sum**
AmpStrSulTetNalChlFlf	**Pigs**											1												1
AmpStrSulTetChlFlfGen	**Cattle**																						1	1
AmpStrSulTetChlFlf	**Cattle**											6		1									3	10
AmpStrSulTetChlFlf	**Pigs**											4											1	5
AmpStrSulTetChlFlf	**Sheep**											1												1
AmpStrSulTetChl	**Cattle**											1												1
AmpStrSulTetNal	**Cattle**																						3	3
AmpStrSulTet	**Cattle**													1							2	2		5
AmpStrSulTet	**Pigs**																					1		1
AmpStrSulTet	**Poultry**																				1	2		3
AmpStrSulTmp	**Cattle**																						2	2
AmpStrSul	**Cattle**													1								1	1	3
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
SulTmp	**Cattle**																1			1				2
Amp	**Poultry**																			2				2
Gen	**Poultry**																			1				1
Nal	**Pigs**					1																		1
Str	**Cattle**											1		1		1				4			1	8
Str	**Pigs**								4	3		2		1						4	1		2	17
Str	**Poultry**									2										3				5
Tet	**Pigs**																						1	1
Susceptible	**Cattle**	4			2		1	1	1	6		2		5	1	1				27	1	1	11	64
Susceptible	**Pigs**	1	1			2			33	5	1	1		8					1	18	2		15	88
Susceptible	**Poultry**	1		1		1			5	1			1	2				1	1	43	4		16	77
Susceptible	**Sheep**	1																					3	4
Sum		**7**	**1**	**1**	**2**	**4**	**3**	**1**	**44**	**19**	**1**	**22**	**1**	**20**	**1**	**2**	**1**	**1**	**2**	**104**	**11**	**9**	**60**	**317**

Zoonotic aspects on *Salmonella*

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

Compiled data on occurrence and susceptibility of *Salmonella* from humans in Sweden is largely lacking. It is therefore not possible to comprehensively relate the situation in Swedish animals to the situation in humans. However, of the most common serovars from human invasive infections in 2015 (Table 3.1) *S.* Typhi and *S.* Paratyphi A are serovars that are not associated with animals. Also, other serovars from human invasive infections, e.g. *S.* Enteritidis, are rare in animals in Sweden.

Moreover, a large proportion (43%) of the human isolates from the reporting laboratories were resistant to ciprofloxacin. This high rate is in contrast to the rare findings of ciprofloxacin resistance in *Salmonella* from animals in Sweden. Taken together, this strongly suggests that *Salmonella* causing human invasive infections rarely originate from Swedish animals.

Campylobacter

Campylobacter in humans

Data on antibiotic resistance in *Campylobacter* from humans is largely lacking. A total of 36 cases of *Campylobacter* was reported during 2015 from 10 laboratories delivering data from blood cultures. Resistance to ciprofloxacin was found in 12 cases and none of the isolates tested was resistant to erythromycin.

Campylobacter in animals

Campylobacter spp. were isolated from samples of intestinal contents from slaughter pigs and cattle collected at abattoirs for isolation of indicator bacteria. Isolates were identified as *Campylobacter jejuni* or *Campylobacter coli* by MALDI-TOF MS. For details on methodology see Materials and methods, resistance in bacteria from animals.

All isolates from pigs were *C. coli* and of 141 cultured samples 108 were positive. Of the 108 isolates, 31 were susceptible to the 6 tested antibiotics. There was no resistance recorded against erythromycin, gentamicin or tetracycline (Table 3.7). Combined resistance to fluoroquinolones (ciprofloxacin and nalidixic acid) and streptomycin was the most common phenotype (n=26).

The rising tendency of resistance to quinolones (ciprofloxacin and nalidixic acid) continues (Figure 3.2). Neither quinolones nor fluoroquinolones are authorised or used for treatment of groups of pigs via feed or water in Sweden. Additionally a regulation has restricted prescription of fluoroquinolones to animals in Sweden since 2013 (see Sales of antibiotics in animals). In 2015 the sales of fluoroquinolones for pigs was only 1.5 kg, corresponding to 0.59 mg/slaughtered pig. Fluoroquinolones are mostly used in piglets and to a lesser extent in other age categories (Sjölund et al., 2015). Selection for quinolone resistance in *Campylobacter* therefore probably occurs in younger pigs before they are moved to the finishing stage.

Occurrence of streptomycin resistance in *C. coli* is remarkably high (55%). Streptomycin resistance in *C. coli* from Swedish pigs is difficult to explain in the context of selection by use since streptomycin is rarely used in pigs in recent years. Neither is co-selection by use of other substance likely since 51% of the streptomycin resistant isolates were resistant only to this antibiotic.

Of 103 cultured samples from cattle, 23 were positive for *C. jejuni* (Table 3.8) and of these 20 were susceptible to all 6 tested antibiotics. No comparison is made with previous data because of the low number of isolates obtained this year. Instead, data from cattle from 2013 are included in Table 3.9.

FIGURE 3.2. Ciprofloxacin and nalidixic acid resistance (%) in *Campylobacter coli* from pigs years 1999, 2003, 2005, 2008, 2011 and 2015 and streptomycin resistance from 2008, 2011 and 2015. In years 1999, 2003 and 2005 enrofloxacin was tested instead of ciprofloxacin. The number of isolates per year has varied (n=83-108).

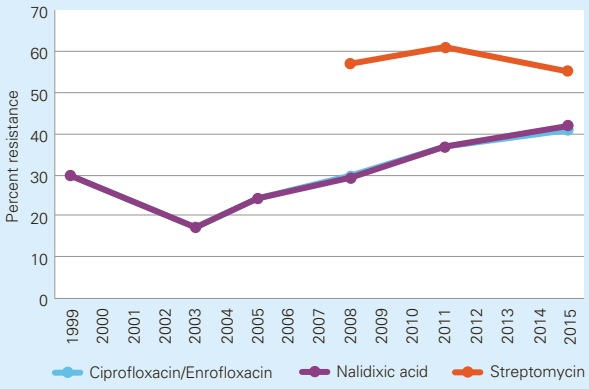


TABLE 3.7. Distribution of MICs and resistance (%) for *Campylobacter coli* from slaughter pigs, 2015.

Antibiotic	Resistance (%) n=108	Distribution (%) of MICs (mg/L) ≤0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Ciprofloxacin	41	41.7	17.6				7.4	22.2	10.2	0.9			
Erythromycin	0				76.9	23.1							
Gentamicin	0		1.9	57.4	39.8	0.9							
Nalidixic acid	42					0.9	18.5	33.3	5.6	0.9	9.3	31.5	
Streptomycin	55				0.9	11.1	33.3	1.9		6.5	46.3		
Tetracycline	2			96.3	0.9	0.9				0.9	0.9		

TABLE 3.8. Distribution of MICs and resistance (%) for *Campylobacter jejuni* from cattle, 2015.

Antibiotic	Resistance (%) n=23	Distribution (%) of MICs (mg/L) ≤0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Ciprofloxacin	9	87.0	4.3					8.7					
Erythromycin	0				100.0								
Gentamicin	0		43.5	56.5									
Nalidixic acid	9					8.7	56.5	26.1				8.7	
Streptomycin	0			13.0	78.3	8.7							
Tetracycline	4			95.7					4.3				

TABLE 3.9. Resistance (%) in *Campylobacter coli* from slaughter pigs 2015. Data on *Campylobacter jejuni* from other animal species and from other years from previous Swedres-Svarm reports are given for comparison.

Antibiotic	ECOFF (mg/L) *C. coli*	ECOFF (mg/L) *C. jejuni*	Resistance (%) Pigs *C. coli* **2015** (n=108)	Broilers *C. jejuni* **2014** (n=102)	Broiler meat *C. jejuni* **2011-2013** (n=111)	Cattle *C. jejuni* **2013** (n=109)
Ciprofloxacin	>0.5	>0.5	41	4	20	21
Erythromycin	>8	>4	0	0	2	0
Gentamicin	>2	>2	0	0	0	2
Nalidixic acid	>16	>16	42	8	20	23
Streptomycin	>4	>4	55	1	0	5
Tetracycline	>2	>1	2	1	4	6

Zoonotic aspects on *Campylobacter*

This year the majority of the isolates from animals were *C. coli* from pigs. *Campylobacter coli* can cause disease in humans but most *Campylobacter* infections in humans are caused by *C. jejuni*. Data on *C. jejuni* from earlier reports are presented in Table 3.9.

Comparison between data for *Campylobacter* from animals and humans is hampered because the investigated human isolates are too few and 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. Resistance to erythromycin, the drug of choice for treatment of human campylobacteriosis, has only been found in two isolates from Swedish broiler meat (Svarm 2013) and never in isolates coming directly from animals in Sweden.

Clinical isolates from humans

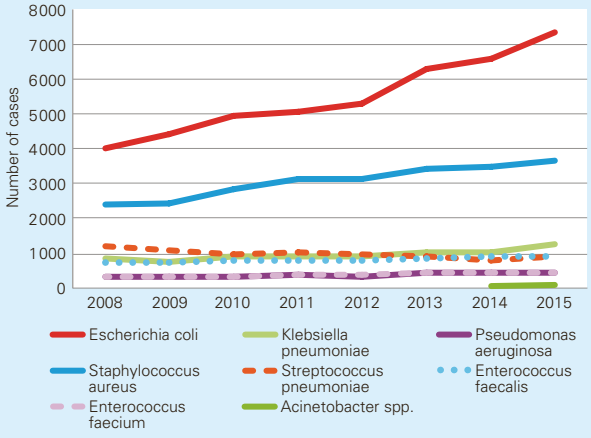
Swedish surveillance of antibiotic resistance is based on the routine testing of clinical samples in microbiology laboratories. In these laboratories the majority of tests for antibiotic susceptibility are performed using the standardized disk diffusion method. From 2011 and onwards all laboratories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

Two sets of data are included in the surveillance programme. The first set is found under the heading Isolates from blood cultures reported to ECDC/EARS-Net. The data on susceptibility testing of consecutive invasive (blood) isolates are collected from eighteen laboratories in 2015, together representing approximately 90% of the Swedish population. Results on eight important bacterial pathogens are requested by and reported to ECDC. These data form the Swedish part of EARS-Net, the European Antimicrobial Resistance Surveillance Network.

As part of the surveillance of bacteria from blood cultures, ten of these Swedish laboratories, with coverage of approximately 45% of the Swedish population, also deliver data on invasive isolates from all their positive blood cultures. This enables a further insight into clinically important bacterial species other than those reported to ECDC/EARS-Net. These results are presented under the heading Resistance in other bacterial species from blood cultures. From these laboratories *E. coli* was the most frequently found pathogen in blood cultures at 20% followed by *S. aureus* at 10%, this is also reflected in the reporting to EARS-Net, Figure 4.1.

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

FIGURE 4.1. Yearly number of bloodstream infections by seven pathogens reported to EARS-Net from Sweden 2008-2015 by participating laboratories.



Isolates from blood cultures reported to ECDC/EARS-Net

Background

In 1998 when EARSS (the European Antimicrobial Resistance Surveillance System) started, two bacterial pathogens were included, *Staphylococcus aureus* representing hospital-related infections, and *Streptococcus pneumoniae* representing community-acquired infections. Data on both pathogens was derived from cases with invasive disease (positive blood cultures). After three years the EARSS programme was ready to include new pathogens. The natural choice was to include *Escherichia coli*, which is by far the most common bacterial pathogen in invasive infections (not counting the normal skin flora bacterial species like CoNS), and also the two enterococcal species *E. faecalis* and *E. faecium*. A third step was taken in 2005 when *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were added, and by that time most of the European countries were participating in EARSS. In 2014 *Acinetobacter* species was added to the programme.

EARSS turned into EARS-Net

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

A summary of the data reported from Sweden 2008-2015 is presented in Figure 4.1 in which numbers of cases are shown, and in Table 4.1 where the proportions of resistance to certain antibiotics are included. The numbers of isolates of *E. coli* and *S. aureus* were much greater than the numbers for other pathogens, but they also showed increasing trends over the years, whereas the numbers of the other five pathogens were relatively stable.

Results and comments

In general the proportions of resistance to clinically important antibiotics were low, and this has been the typical situation for Sweden and its neighbouring Nordic countries all through the EARSS/EARS-Net history (www.ecdc.europa.eu/en/activities/surveillance/EARS-Net/database/). However, increasing trends of resistance to third-generation cephalosporins are seen for both *E. coli* and *K. pneumoniae*. This increase is due to an increasing prevalence of ESBL-producing isolates, whereas the mechanism for resistance to ceftazidime in *P. aeruginosa* is not ESBL-production (Figure 4.2). In *E. coli* and *K. pneumoniae* the levels of cephalosporin resistance has reached 6.1% and 4.3%, respectively (Table 4.1). Resistance to fluoroquinolones is now on a level of 11.7% in *E. coli* and 6.4% in *K. pneumoniae*. During 2015, 15 participating laboratories reported 74 cases of *Acinetobacter* species, with resistance to carbapenems at 1.6% (one case).

TABLE 4.1. Antibiotic resistance in isolates from bloodstream infections of eight pathogens included in EARSS/EARS-Net surveillance during the years 2008-2015.

		2008		2009		2010		2011		2012		2013		2014		2015	
Species	**Antibiotic**	**n**	**% R**	**n**	**% R**	**n**	**% R**	**n**	**% R**	**n**	**% R**	**n**	**% R**	**n tested**	**% R[a]**	**n tested**	**% R[a]**
Escherichia coli	Total nr of isolates	4 028		4 423		4 991		5 066		5 336		6 323		6 586		7 352	
	Ctx		2.3		2.9		3.2		4.0		4.4		4.9	6 576	5.4	6 808	6.1
	Imp/Mer		0.0		0.0		0.0		0.0		0.0		0.0	6 321	0.0	6 484	0.0
	Gen/Tob		2.3		3.3		4.5		5.1		5.5		4.5	6 577	6.3	7 128	6.1
	Fluoroquinolones		14.4		13.7		14.0		10.4		9.9		9.9	5 170	11.7	6 521	11.7
	Ptz[b]		nd		nd		nd		nd		nd		nd	6 285	2.3	6 745	2.9
Klebsiella pneumoniae	Total nr of isolates	826		755		908		934		933		1 028		1 009		1 257	
	Ctx		2.3		1.8		2.3		2.2		2.6		3.1	951	4.0	1 171	4.3
	Imp/Mer		0.0		0.0		0.0		0.0		0.0		0.0	984	0.2	1 157	0.4
	Gen/Tob		1.1		1.0		2.0		2.1		2.1		2.0	1 008	3.2	1 235	3.8
	Fluoroquinolones		12.9		12.2		8.5		5.0		4.6		4.4	766	5.1	1 129	6.4
	Ptz[b]		nd		nd		nd		nd		nd		nd	964	9.3	1 168	4.1
Pseudomonas aeruginosa	Total nr of isolates	309		326		337		402		350		428		432		468	
	Caz		5.2		6.9		5.9		5.2		6.0		6.5	437	5.5	398	4.5
	Imp/Mer		4.0		7.7		6.7		7.2		6.9		6.3	432	7.6	419	6.2
	Gen/Tob		0		0		3.0		1.0		1.4		2.3	445	1.8	433	2.1
	Fluoroquinolones		7.6		10.1		10.1		7.0		9.1		7.9	345	7.5	390	6.2
	Ptz[b]		nd		nd		nd		nd		nd		nd	442	5.0	102	5.5
Staphylococcus aureus	Total nr of isolates	2 409		2 457		2 856		3 143		3 268		3 209		3 519		3 683	
	Oxa/Fox		0.7		1.0		0.5		0.8		0.7		1.2	3 511	0.9	3 053	0.7
	Van		0.0		0.0		0.0		0.0		0.0		0.0	1 026	0.0	781	0.0
Streptococcus pneumoniae	Total nr of isolates	1 213		1 060		960		1 019		992		861		797		912	
	Pen (I+R)		2.0		3.3		3.8		3.5		5.0		6.6	797	6.3	741	6.6
	Ery		5.2		3.9		3.9		4.5		5.1		5.8	793	6.2	785	6.2
Enterococcus faecalis	Total nr of isolates	720		718		776		824		779		851		912		897	
	Van		0.0		0.0		0.0		0.0		0.0		0.0	894	0.0	770	0.0
	Gen (HLAR)		20.1		18.6		15.2		16.6		14.1		13.3	673	15.6	621	15.8
Enterococcus faecium	Total nr of isolates	333		311		339		406		391		431		457		430	
	Van		1.5		0.5		0.3		0.0		0.0		1.4	456	0.7	356	0.0
	Gen (HLAR)		24.8		24.1		21.8		22.0		18.4		20.4	351	22.5	283	20.5
Acinetobacter species[c]	Total nr of isolates													59		74	
	Imp/Mer		nd		nd		nd		nd		nd		nd	59	3.4	61	1.6

[a] From 2014 the resistance is expressed as % of isolates tested
[b] Ptz was included from 2014
[c] *Acinetobacter* species was included from 2014

Standardization and surveillance of AST/AMR in humans in Sweden – from collecting strains to data mining. A thirty year experience

Introduction

Looking back at my more than forty years of work in the field of susceptibility and resistance to antibiotics gives a lot of perspective and thoughts on the amazing developments we have achieved.

Some people might say that it seems boring to work within the same area for such a long time. On the contrary, I have always regarded it as a privilege to have been allowed to focus on this subject which has an almost infinite number of important and interesting aspects.

Looking back, it is obvious that the studies on antibiotic susceptibility and resistance were always performed according to the state of art at that particular time. However, increasing knowledge and better understanding of the biological nature of bacterial populations and their susceptibility or resistance to antibiotics, as well as the continuous development of new antibacterial substances, necessitated new approaches to investigations.

In this historical review I will share with you the development of standardization and surveillance of antibiotic resistance (AMR), based on a long term experience as a national coordinator of surveillance of AMR in Sweden.

Development of new antibiotics was the driving force

Already during the 1950´s and 1960´s, most of the antibacterial compounds which we know and still use, were detected, developed for large scale production, and taken into clinical use. Thus, when I entered the scene in the early 1970´s the floor was already set. Also, it was already a well-known fact that some bacterial strains or even whole bacterial species had the ability to resist the actions of some antibacterial compounds. In response to this, the pharmaceutical industry constantly developed new chemical compounds. These were, however, most often derivatives of the already existing compounds but with improved properties in terms of antibacterial spectrum, stability to bacterial resistance mechanisms, or improved pharmacokinetic properties. There are numerous examples of these strategies, such as the variety of compounds belonging to the groups of penicillins, cephalosporins, macrolides, tetracyclines, aminoglycosides or fluoroquinolones.

In order to launch these new antibacterial compounds on the market they needed to be carefully investigated and evaluated, so that guidelines for routine testing in clinical laboratories could be established. Such evaluation studies were often designed by scientists on behalf of the recently formed Swedish Reference Group for Antibiotics (SRGA, in Swedish Referensgruppen för antibiotikafrågor, RAF), but supported by the pharmaceutical industry. They were carried out in Sweden as well as in a number of western countries in which the big pharmaceutical companies were represented, and the experimental results were often summarized at international scientific conferences. Although not designed to be of epidemiological relevance for antibiotic resistance, these studies were nevertheless used for describing "the situation" of antibiotic resistance in a hospital, a city, a country, or a region.

In countries with more restricted policies for prescribing antibiotics, such as Sweden, it was inevitable that there would be conflicting interests between, on the one hand, clinical microbiologists performing the necessary studies of new antibiotics and, on the other hand, the pharmaceutical industry having high expectations of the introduction of these new antibiotics into the daily testing in clinical laboratories and their subsequent use in clinical practice.

Collections of strains were required

Even in the early days there was a requirement, not the least from editors of scientific journals, that studies on antibiotic susceptibility were performed using reference methodology. By definition, the reference method for antibiotic susceptibility testing (AST) was a dilution method, in which the antibiotic to be tested was serially diluted in either nutrient broth or agar. The dilution method required strict standardization of every step of the procedure, which of course is a good thing, but it meant that this method could not be used for daily testing by patient care clinical laboratories due to the extremely laborious technique. Dilution methods were thus used mainly by reference laboratories, but even in these laboratories they were mostly applied for specifically designed studies. A common example would be the evaluation of a new antibiotic together with older comparators of the same class of compounds, on a rather restricted collection of strains that was already available. The alternative would be to collect new clinical isolates through the kind supply from clinical laboratories, as in the following example.

One of the more ambitious programmes in this context in Sweden was the surveys of antibiotic susceptibility of four respiratory tract pathogens, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae and Streptococcus pyogenes*, collected from five different geographical areas of Sweden in 1983, 1986 and 1990 (Kallings et al., 1983; Olsson-Liljequist et al., 1992). The extra workload put on the local clinical laboratories, the logistics in collecting and sending strains to the central laboratory, and the enormous amount of work in performing agar dilution MICs of six different antibiotics on a total of 1500 bacterial strains required generous financial support from one or several pharmaceutical

companies to be accomplished. From a scientific point of view, what was achieved was snapshots of resistance rates to a few relevant antibiotics among the respiratory tract pathogens over a couple of years. What was totally missed in this and similar programmes was, however, the quality assurance aspect of the daily work in the clinical laboratories. Also, the long term trends in AMR were not obtained using this kind of "privately" sponsored activities.

Quantitative or qualitative data?

Susceptibility testing is performed by one of two methods, named dilution or diffusion methods. They differ in the way the antibiotic to be tested is presented to the bacteria.

In dilution methods the antibiotic is diluted either in broth or in agar medium, and the dilutions normally used are so called doubling or two-step dilutions. Bacteria are added, and after incubation they show either growth or no growth at these concentrations. The lowest concentration able to inhibit growth is defined as the Minimum Inhibitory Concentration, MIC. The dilution method has always been considered to be quantitative, yet the term semi-quantitative would be more appropriate.

In the diffusion method the antibiotic to be tested is contained in a paper disk (or a tablet), and when put on the surface of a previously seeded agar plate the antibiotic diffuses radially into the surrounding agar, creating a continuous gradient of antibiotic concentrations. In short, following incubation there will be either a circular zone of no growth around the disk (= some degree of susceptibility in the bacterial isolate), or there will be bacterial growth up to the disk, i.e. no inhibition of growth (= resistant bacteria). When the diameter of the inhibition zone is measured (mm) one will get a quantitative measure of the susceptibility. However, most often the inhibition zones are interpreted into SIR categories, and thus these results are regarded as qualitative.

Standardization of antibiotic susceptibility testing (AST) in Sweden

An AST result must be based on standardized technology, and it should be interpreted by means of scientifically sound guidelines to be of any value in the clinical situation. As of today, countries in Europe and in the rest of the world are able to use the professional guidelines and documents presented by EUCAST, the European Committee on Antimicrobial Susceptibility Testing. However, it has been a long journey to reach this far.

Fortunately, Sweden has had a number of pioneers who have contributed to the development and standardization of AST and to the understanding of the nature of susceptibility and resistance to antibacterial agents. A few milestones along the way have been: a) standardization of the technical details of the disk diffusion method being outlined already in the 1960´s by Ericsson & Sherris (1971), b) the multi-species regression line analysis being replaced by species related breakpoints for definition of susceptibility (S) or resistance (R) through the extensive work of the methodology group of SRGA (Olsson-Liljequist & Forsgren, 1997; Ringertz et al., 1997; Olsson-Liljequist et al., 1997; Kahlmeter et al., 1997), and c) the accumulated knowledge of SRGA being transferred to the EUCAST Steering Committee under the successful leadership of Kahlmeter and coworkers during the first decade of the 2000 century.

Surveillance of AMR – what, how and whither?

This was the title of one of the numerous articles focussing on surveillance of AMR and written by a distinguished Working Party (Bax et al., 2001). The authors aimed at defining good surveillance, discussed how to perform it and for what purpose it should be done. They made a thorough inventory of all the components of surveillance programmes with all their problems and pitfalls. However, their final conclusions did not provide any simple and straight ways forward.

A more positive standpoint was taken by O´Brien & Stelling (2011) when they advocated the use of patient care microbiology data as the basis for continuous AMR surveillance for public health purposes. One of the key factors for this becoming a potential success story was the computerisation of laboratories, which facilitated data acquisition for more types of analyses. The WHO has made available a free software program called WHONET, which enables any laboratory to put its reports, including its quantitative AST results (disk diffusion zones in mm or MICs in mg/L) into a personal computer database for its local surveillance and also to merge its data easily with electronic data files of other WHONET laboratories into multicentre files for higher-level analyses.

Collecting data, not strains, for surveillance in Sweden

Clinical laboratories in Sweden have been very active and introduced computerized laboratory systems early , giving an advantage when taking part in surveillance studies at local and national levels. The active and enthusiastic role of the SRGA Methodology group in regularly educating the key persons among the laboratory workers from all laboratories, ensured the collection of high-quality AST results for analyses of quality as well as prevalence of AMR.

The idea of a routine based surveillance system, at least for the most common bacterial pathogens, was developed from the concept of normally distributed bacterial populations with regard to susceptibility to antibiotics (inhibition zones measured in mm), which are often clearly separated from zones of resistant bacteria. Laboratories have been asked once a year to present data of 100 consecutive clinical isolates each of 4-6 bacterial pathogens, tested against 4-6 relevant antibiotics. In the beginning of the 1990´s the data was reported manually (on paper forms), and computers were used only for summarizing and presenting the results. But the development was rapid, and a

few years later electronic data files were delivered. This was a big leap forward but still not the most effective way of reporting.

Next step was taken in the beginning of the 2000´s when the web application ResNet was introduced. Laboratories continued with their yearly exercises of testing 100 isolates of an agreed set of pathogens and antibiotics, and they were able to enter their cumulated results into ResNet, giving both a local and a nationwide presentation. With the ResNet application we now have 20 years of quality assured data on *Streptococcus pneumoniae* and 15 years of data on *Escherichia coli* and *Staphylococcus aureus*, not to mention many other bacterial species.

EARS-Net, a surveillance network in Europe

Based on the high-quality work by Swedish clinical laboratories and the active networking introduced by RAF-M, the Swedish participation in the European Antimicrobial Resistance Surveillance System (EARSS, (founded in 1998) was a natural consequence. EARSS took on its task as a non-profit network for AMR surveillance for public health action by carefully considering the potential problems and pitfalls involved. It started with 15 countries who agreed to focus on one type of isolates, bacteria grown from blood samples because these would hopefully be processed in similar ways in all countries, and only two pathogens, *Staphylococcus aureus* and *Streptococcus pneumoniae*. By doing so the network would find its form and working plan and would eventually grow. Today the network is administered by the European Center for Disease prevention and Control (EARS-Net at ECDC) and nearly all countries in the European Union are involved. The number of bacterial pathogens has grown to eight, now also including *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa and Acinetobacter* species.

Swedish data are collected and checked for accuracy and quality by the Swedish coordinator before being transferred to ECDC, and the Swedish participation has always been considered important for the success of the surveillance network.

The future and other important issues

Nothing is so good that it cannot be done better, and this goes for AMR surveillance as well. There are things to hope and wish for, and others that need to be considered and not forgotten. Some of them are:

-Higher degree of automation in transferring complete sets of data. In Sweden the answer to this challenge is SVEBAR, a system that captures all microbiology data from clinical laboratories with an in-built early warning system and functions for processing and analysing anonymized data for national surveillance.

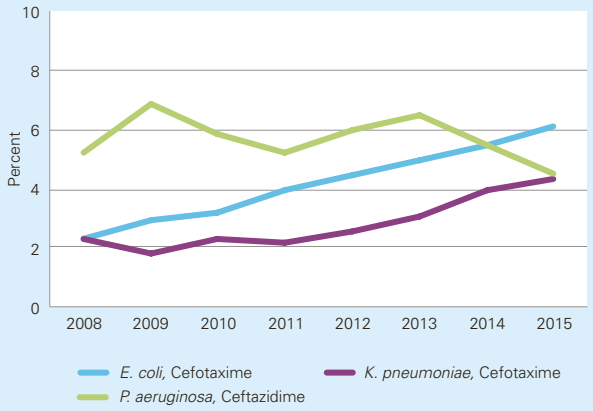
-A proposal to make it mandatory to send specimens to a clinical laboratory for species identification and AST before antibiotic treatment is started. By doing so the results from the microbiological investigations would represent both in-patients and out-patients as completely as possible and should present a better tool for empiric treatment.

-The question whether susceptibility testing as it is done today should be replaced by techniques for detection and verification of resistance mechanisms needs to be kept in mind. It might be tempting to use the new possibilities with whole genome sequencing (WGS) also for extraction of data on resistance genes or mutations. The argument for being conservative and stick to the phenotypic methods is that they will detect not only the already known resistance mechanisms but also the potentially new ones.

-The alarming global situation of AMR warrants the urgent need for availability of basic microbiological tests including AST to medical care in all countries. This would help in educating health care workers and the public in rational use of antibiotics.

By Barbro Olsson-Liljequist

FIGURE 4.2. Proportion of resistance to third generation cephalosporins in *E. coli, K. pneumoniae* and *P. aeruginosa* in invasive, human isolates. Swedish data in EARS-Net 2008-2015, from participating laboratories, covering approximately 90% of the population.



2013 was the first year that MRSA exceeded 1%, and the highest level noted for PNSP, at 6.6% I+R, in Sweden ever since the start of EARSS/EARS-Net. In 2015, the MRSA frequency was again below 1% (0.7%) while pneumococci with reduced susceptibility to penicillin (I+R) reached the same level as in 2013 (6.6%). For the two enterococcal species there were no cases of VRE reported for *E. faecium* and still no report of VRE for *E. faecalis*. High-level aminoglycoside resistance (HLAR) was found in both species at 15.8-20.5% just as previous years.

Resistance in other bacterial species from blood cultures

Streptococcus pyogenes, Streptococcus agalactiae and *Haemophilus influenzae*

Data on all positive blood cultures were obtained from ten laboratories. Their total catchment population is at present 4.5 million, thus representing around 45 % of the Swedish population. From these laboratories data on all bacterial pathogens consecutively isolated from blood cultures are retrieved, not only those specified by EARS-Net. In previous SWEDRES reports (2008-2014) data for *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Haemophilus influenzae* were presented, and they are summarized in Table 4.2 together with the most recent data from 2015.

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

TABLE 4.2. Antibiotic resistance in invasive isolates of *Streptococcus pyogenes, Streptococcus agalactiae* and *Haemophilus influenzae* during eight years (2008-2015).

		2008 (n=11 115)[a]		2009 (n=11 416)		2010 (n=12 296)		2011 (n=16 969)		2012 (n=18 117)		2013 (n=18 367)		2014 (n=12 609)		2015 (n=19 608)	
Species	**Antibiotic**	**n (% of tot)**	**% R**	**n (% of tot)**	**% R**	**n (% of tot)**	**% R**	**n (% of tot)**	**% R**	**n (% of tot)**	**% R**	**n (% of tot)**	**% R**	**n (% of tot) n tested**	**% R[b]**	**n (% of tot) n tested**	**% R[b]**
Streptococcus pyogenes: n (% of total)		196 (1.8)		134 (1.2)		118 (1.0)		188 (1.1)		257 (1.4)		297 (1.6)		149 (1.2)		213 (1.1)	
	Ery		0.5		2.2		1.7		3.2		2.3		4.0	149	2.0	211	0.5
	Tet		14.6		9.7		12.7		13.3		12.5		7.7	141	7.8	170	6.5
Streptococcus agalactiae: n (% of total)		107 (1.0)		131 (1.1)		166 (1.4)		206 (1.2)		197 (1.1)		205 (1.1)		184 (1.5)		206 (1.1)	
	Ery		6.5		6.9		7.8		6.8		13.2		12.7	184	13.6	204	9.8
	Kli		6.5		3.8		5.4		5.8		13.7		9.3	158	10.1	206	10.2
Haemophilus influenzae: n (% of total)		63 (0.6)		49 (0.4)		75 (0.6)		76 (0.5)		103 (0.6)		87 (0.5)		70 (0.6)		107 (0.5)	
	Amp		25.4		20.4		9.3		18.4		20.4		25	61	14.8	92	23.9
	Ctx		nd		nd		nd		2.5		1.9		0.0	58	0.0	92	4.3
	Tsu		14.3		14.3		13.3		15.8		22.3		17.2	70	21.4	97	21.6

[a] Total number of positive blood isolates from participating laboratories
[b] From 2014 the resistance is expressed as % resistance of isolates tested

Surveillance of antibiotic resistance in humans – uses, interpretation of data, and sources of bias

European recommendations for surveillance of antimicrobial resistance have been described by Cornaglia et al. (1). In Sweden surveillance relies on clinical samples for the diagnosis of infections, except for mandatory reporting (ESBL, $ESBL_{CARBA}$, MRSA, PNSP, and VRE) where screening and contact tracing is also done. This sampling strategy is the basis for the following discussion.

Uses

Clinical cultures and antimicrobial susceptibility testing (AST) are necessary for patient care. They are needed to guide treatment for individual patients. The results will, in addition, provide feedback to physicians, and add to their experience in diagnosing infectious diseases. All of this is important to achieve rational use of antibiotics.

Basing surveillance on clinical cultures and AST introduces a host of possible bias, but there are few cost-effective alternatives. So most surveillance programs use results from routine diagnostics. This is true for all major surveillance systems.

It is often said "surveillance for action" and the spectrum of actions range from immediate warning for spectacular and unusual resistance to the development and regular evaluation of empirical (blind) therapy recommendations.

When cultures are rarely taken and then only for serious cases, the resulting resistance rates will be artificially high. Blood cultures taken for suspected blood stream infections are thought to be excellent targets for surveillance since they represent the really ill patients who are supposedly cultured. However, this is not the case. Tradition, economical restrictions, diagnostic availability and general differences in health care systems influence how patients are sampled.

Monitoring trends for selected species-antibiotic combinations in clinically important infections is necessary to be able to describe the extent of the problem, the burden of disease. This is needed to prioritize in which areas to take action first in dealing with resistance.

Additionally, surveillance should be used to evaluate the effects of various interventions to counteract resistance development.

In some countries it is mandatory to report certain types of resistance, e.g. MRSA. This simplifies monitoring of local, regional, and national trends. For this type of especially problematic resistance surveillance systems with early inbuilt warnings can be useful.

In Sweden surveillance of resistance and surveillance of the quality of AST of all contributing laboratories has been combined. This is done by collecting data on disc diffusion inhibition zones of defined species – antibiotic combinations and comparing distributions between laboratories, with reference material, and the breakpoints used.

Sources of bias

Sampling strategy

Uncomplicated cases are not sampled as frequently as complicated. The latter are more often caused by resistant bacteria. This leads to higher resistance than is representative for consecutive cases of the disease. The resistance rate will represent a worst-case scenario, representative of patients with difficult to treat, complicated infections. *E. coli* from urinary tract infections in general practice and in a urology ward will result in very different resistance rates. Contrary to popular belief, *E. coli* causing urinary tract infections in general practice and from blood cultures from most hospitals in Sweden have very similar resistance rates. As expected, in some tertiary care hospitals resistance rates are higher than rates from general practice from the same area.

Repeated sampling of patients colonized or infected with bacteria with resistance of special importance (community control or hospital infection control), is an important cause of falsely high resistance. Carriers of resistant bacteria may be sampled repeatedly to check if colonization is still present. For patients with resistant bacteria in high-risk units, such as intensive care and neonatal wards cultures are requested more frequently, both to guide treatment and to assess colonization with resistant bacteria.

Some surveillance systems exclude all duplicate results from the patient to deal with repeated sampling. If surveillance reports monthly rates, the patient is allowed to participate once a month and so forth.

The effect of this has been studied in a Swedish setting, where sampling frequency is high compared to most other countries (2). In large materials of *Escherichia coli* and *Staphylococcus aureus*, resistance rates were calculated every 7, 14, and 30 days, 6 months and per year.

The difference in rates did not change to any great extent but the pattern obtained with including one sample per patient over the tested time periods were reproducible and distinctive. For *E. coli* vs. ampicillin rates were higher when based on the inclusion of only one organism

per patient per year whereas for *S. aureus* and clindamycin the rates based on a yearly analysis were lower than those based on for example monthly analysis.

Laboratory algorithms for AST may introduce severe bias in antimicrobial resistance rates.

To conserve resources laboratories test limited panels of antimicrobials. All isolates of a species from a certain sample type will be tested against the standard panel. For highly resistant isolates, the panel is extended to comprise more antibiotics. Thus, the standard antibiotics and antibiotics for more difficult situations are tested against different subsets of isolates. Moreover, commonly newer, more active antibiotics in a group is tested only when the isolate is resistant to the older variants. Both of these strategies will give falsely high proportion of resistance.

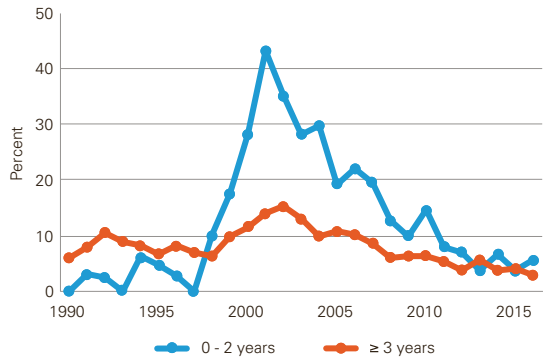
Irrespective of species, isolates resistant to one drug are more likely to be resistant to any other drug than are susceptible isolates. Thus, trimethoprim resistance in *E. coli* was 38.4% among ampicillin-resistant vs. 3.9% among ampicillin-susceptible isolates, and erythromycin resistance in *S. pneumoniae* was 41% among doxycycline-resistant vs. 1% among doxycycline-susceptible isolates. In all five species investigated, there was significant associated resistance among unrelated agents, highlighting the fact that resistance development occurs primarily among bacteria already resistant to one or more antimicrobial agents (3).

Shifts in clones predominating in the population

Clonal outbreaks of bacteria will also skew resistance rates. If the outbreak is with a resistant organism, rates increase and if an outbreak is with a very sensitive organism this will dilute resistance rates. Both phenomena have been noticed regarding erythromycin resistance in *Streptococcus pyogenes*.

Outbreaks can cause rapid changes regarding antibiotic resistance. One example from Sweden is the rapid increase in resistance to fusidic acid among children (0-12 years) when a strain causing impetigo was introduced and spread, Figure (4). The increase was only seen in children, which was the age group affected by impetigo.

FIGURE. *Staphylococcus aureus* with fusidic acid resistance (%), 1990 – 2016 in small children (0 – 2 years) and older persons (≥3 years). An epidemic of bullous impetigo among toddlers explains the sudden increase in fusidic acid resistance.



Interpretation

It is reasonable to include only one sample from a patient within the period on which rates are based. The algorithm used for excluding repeat sampling should be stated. Some algorithms are simple and others more complicated building on more knowns than just the patient identity (time, organism type (spa-type etc), sample type, only organisms with the same resistance pattern are excluded etc). It is also reasonable to report on

- Sample size (number of people, number of cultures). Refrain from reporting percent rates unless the sample size is at least one hundred.
- Describe the population on which surveillance was based (hospital vs. community; type of ward; homes for elderly people)
- Describe samples selection. Complicated infections and patients over represented vs. samples representative for a more general population
- Outbreaks?
- Screening algorithms?
- Population changes (major movements of refugees have been known to influence rates)?
- Age
- AST algorithms in participating laboratories?

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The annual resistance surveillance and quality control programme (ResNet)

Background

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

In 2015 six pathogens were included in the program, and the results on these pathogens are presented and analyzed in the following texts and graphs to illustrate trends.

Escherichia coli

Escherichia coli, mainly derived from urinary tract infections, have been included in the national surveillance programme regularly since 1996 and every year since 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 2015, 24 laboratories delivered data as requested, and a total of 5905 isolates were included in the analysis (Figure 4.3).

The resistance levels for all tested antibiotics decreased slightly during 2015 with exception for mecillinam. Ampicillin was substituted for amoxicillin-clavulanic acid from 2015.

Cefadroxil resistance is used as an indicator for presence of genes coding for ESBLs (5.2%). It should be noted that ciprofloxacin 5µg is now the recommended disk for detecting fluoroquinolone resistance, and the resistance rate 8.6% represents resistance (R, not I+R as was the case when nalidixic acid was used) calculated from the zone breakpoint R <19 mm correlating to the clinical MIC-breakpoint R >1 mg/L.

FIGURE 4.3. Proportion (%) resistant *E. coli* isolates from urine, 2001-2015. Resistance (R) to fluoroquinolones was tested by nalidixic acid (screening for I+R) 2002-2011, and by ciprofloxacin from 2011 and onwards. Ampicillin was substituted with amoxicillin-clavulanic acid from 2015. Zone breakpoints relevant at the time of testing were always used.

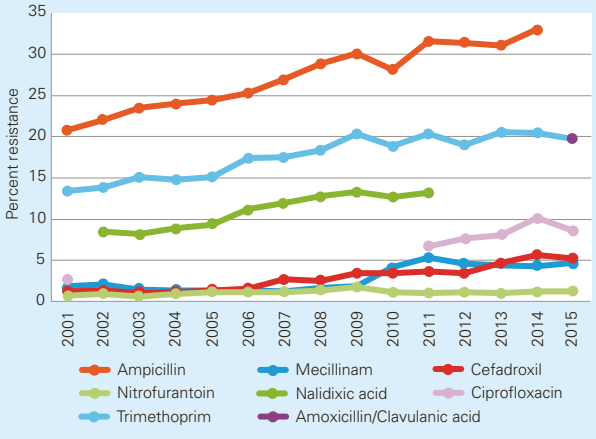
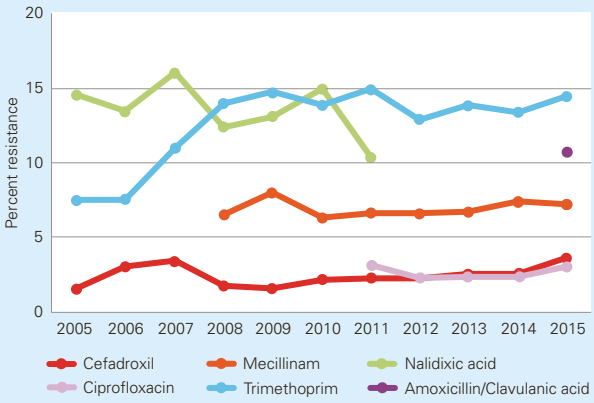


FIGURE 4.4. Proportion (%) resistant *K. pneumoniae* isolates from urine, 2005-2015. Resistance (R) to fluoroquinolones was tested by nalidixic acid (screening for I+R) 2005-2011, and by ciprofloxacin from 2011 and onwards. Amoxicillin-clavulanic acid was included from 2015. Zone breakpoints relevant at the time of testing were always used.



Klebsiella pneumoniae

Klebsiella pneumoniae is important for health care associated infections. Isolates mainly derived from urine samples have been included in the surveillance programme since 2005. In 2015, 24 laboratories delivered data according to EUCAST methodology, and 2 712 isolates were included in the analysis (Figure 4.4). The results indicate that the rates of resistance to all tested antibiotics increased 2015 except for a slight decrease in the resistance to mecillinam. Amoxicillin-clavulanic acid was included in the surveillance programme from 2015.

Pseudomonas aeruginosa

Pseudomonas aeruginosa has been included in the surveillance programme on a yearly basis since 2006, with the exception of 2008. Laboratories have been asked to test 100 consecutive isolates of *P. aeruginosa* with the exclusion of respiratory isolates. In 2015, 24 laboratories delivered data, and 2 560 isolates were included in the analysis (Figure 4.5). Aminoglycoside resistance (gentamicin and/or tobramycin tested) is around 1%. Four beta-lactam antibiotics were tested; one cephalosporin, one penicillin-inhibitor combination, and two carbapenems. For all of them, the rates of resistance have been more or less stable since 2010. For the carbapenems, resistance to imipenem continues to be higher (7.5%) than to meropenem (4.7%) in 2015. Resistance to ciprofloxacin show a slight increase (8.9%).

FIGURE 4.5. Proportion, %, resistant *P. aeruginosa* isolates for four groups of antibiotics tested, 2006-2015 (no data collected in 2008). Zone breakpoints relevant at the time of testing were always used.

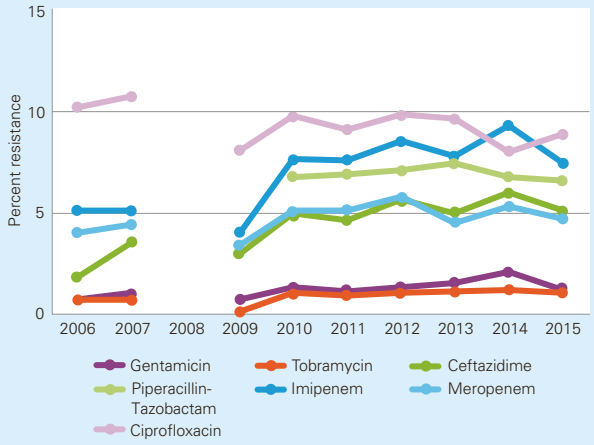
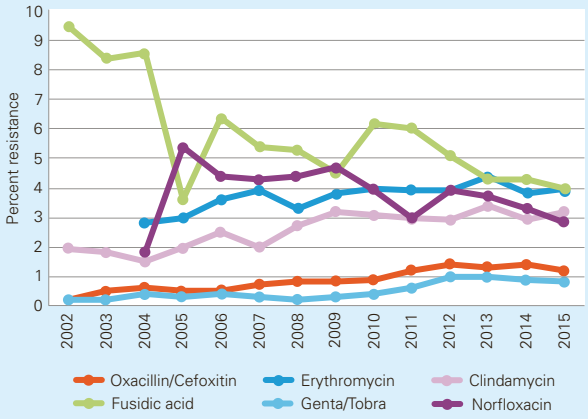


FIGURE 4.6. Proportion (%) resistant *S. aureus* isolates from skin and soft tissue infections 2002-2015. In 2005 only results from infections in elderly (> 65 years) patients were reported.



Staphylococcus aureus

Staphylococcus aureus from skin and soft tissue infections has been included in the annual surveillance programme since 1994. In 2015, 24 laboratories delivered data. All laboratories used the EUCAST methodology, and a total of 4 792 isolates were included in the analysis (Figure 4.6).

The frequency of MRSA in skin and soft tissue infections (SSTI) (cefoxitin used as test compound) has increased slowly and reached an average value of 1.2% in 2015. The average resistance proportions for fusidic acid and norfloxacin indicates a slight decreasing trend while clindamycin and erythromycin resistance displayed a minor increase. Resistance to aminoglycosides was still only 1%.

Streptococcus pneumoniae

Isolates collected and tested in the surveillance programme were mainly derived from nasopharyngeal cultures. The clinical laboratories have tested isolates for susceptibility to penicillin (by means of oxacillin 1 µg screen disk), erythromycin, clindamycin (since 2004), tetracycline, trimethoprim-sulfamethoxazole, and norfloxacin (since 2005, used as indicator for fluoroquinolone resistance) using the disk diffusion method. In 2015, 23 laboratories delivered data, and 2 397 isolates were included in the analysis (Figure 4.7). During the first 15 years of surveillance there had been a slow increase in the proportions of resistance for all tested antibiotics. In 2015 the increase in resistance continued for oxacillin, tetracyclin and trimethoprim-sulfamethoxazole while a decreasing trend was shown for norfloxacin, clindamycin and erythromycin.

FIGURE 4.7. Proportion (%) resistant *S. pneumoniae* isolates from respiratory tract specimens 1994-2015.

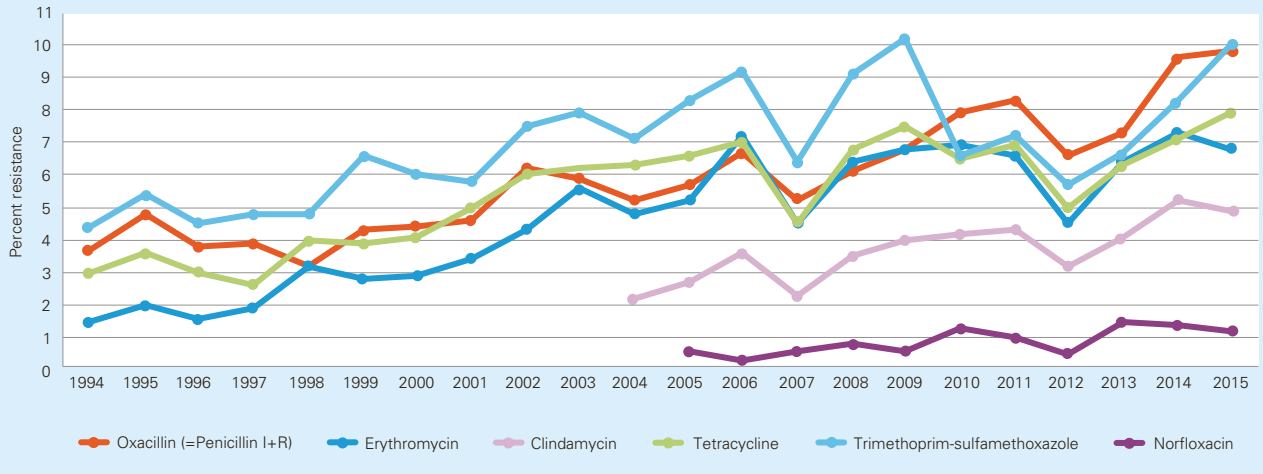
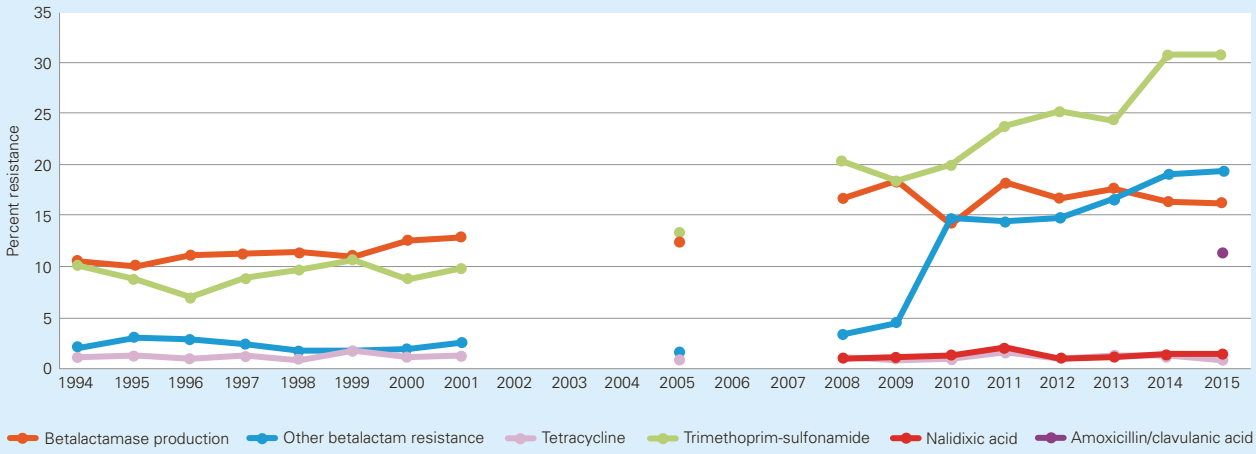


FIGURE 4.8. Proportion (%) resistant isolates of *H. influenzae* from respiratory tract specimens 1994-2015 (no data collected in 2002-2004, 2006-2007). In 2010-2015 beta-lactamase producing isolates were separated from isolates with other beta-lactam resistance mechanisms by use of penicillin G1 unit disk using the following interpretation: 6 mm = beta-lactamase production, 7-11 mm = other beta-lactam resistance.



Haemophilus influenzae

Haemophilus influenzae was re-introduced into the yearly surveillance programme on antibiotic resistance in 2008 after several years with no data collections. In 2015, 24 laboratories delivered data according to the new EUCAST methodology, and 2 608 isolates were included in the analysis (Figure 4.8).

In 2010 methodological changes were introduced (for description see www.nordicast.org) which made results for beta-lactam resistance more difficult to interpret. This was resolved by adjusting the reporting routines. Laboratories were asked to report 6 mm inhibition zones of penicillin G 1 for all beta-lactamase producing isolates, regardless of the actual zone diameter. Other mechanisms of beta-lactam resistance were then assumed if zones of penicillin G 1 unit disk measured 7-11 mm, allowing for a rough estimation of the frequencies of resistance due to other mechanisms of beta-lactam resistance (BLNAR). By doing so the results since 2010 indicate a dramatic increase in BLNAR. However, disk diffusion results must always be verified by MIC determination, and useful interpretation tables for treatment options are issued and updated yearly by NordicAST. Amoxicillin-clavulanic acid was included in the surveillance programme from 2015.

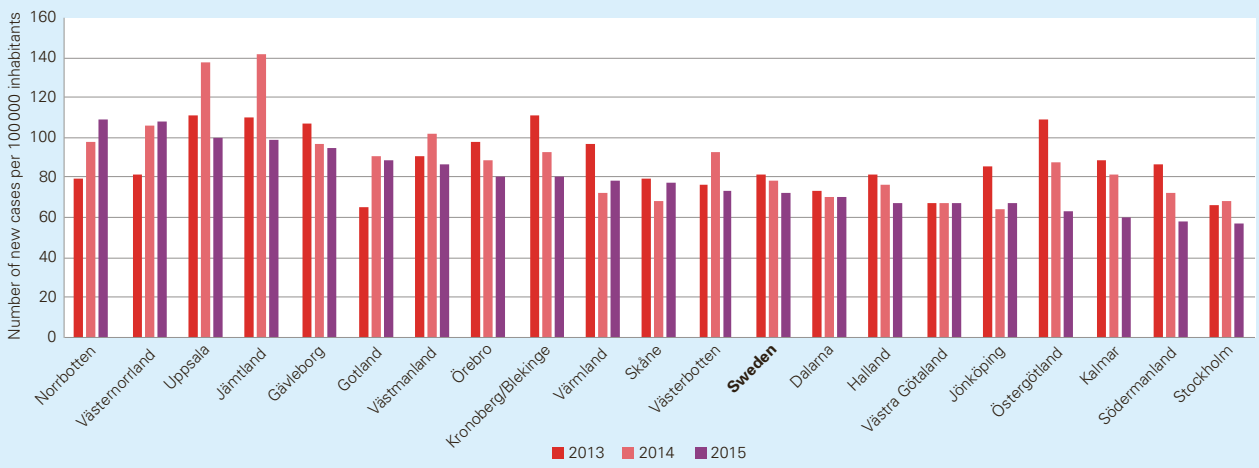
The high increase in resistance to trimethoprim-sulfamethoxazole seen in 2014 levelled out during 2015. The increase in resistance due to BLNAR seen from 2013 continues, while the resistance correlating beta-lactamase production is continuously decreasing. Tetracycline resistance was still rare (0.8%) as was resistance to fluoroquinolones (1.4%), detected by the nalidixic acid screening disk.

Clostridium difficile

The *Clostridium difficile* surveillance programme in Sweden

The national surveillance program for *Clostridium difficile* includes both a voluntary laboratory reporting system of all new cases of *C. difficile* infection (CDI) and a determination of resistance and epidemiological typing of isolates from

FIGURE 4.9. Incidence of new cases of CDI (cases per 100 000 inhabitants) in Swedish counties 2013-2015, arranged in descending order according to incidence rates for 2015.



the clinical microbiology laboratories. All *C. difficile* strains isolated during week no. 11 and 39 were sent to the Public Health Agency of Sweden for typing by PCR ribotyping and antibiotic susceptibility testing. Primarily metronidazole and vancomycin resistance was monitored, i.e. the recommended treatment choices for CDI. However, since use of antibiotics is a risk factor for acquiring CDI we also tested for susceptibility to other antibiotics as an indicator of selective pressure, currently moxifloxacin, clindamycin and erythromycin. All isolates were tested using E-test on fastidious Mueller Hinton agar.

Incidence of CDI and distribution of resistant *Clostridium difficile* isolates in 2015

In 2015, 7 112 new CDI cases were reported corresponding to an incidence of 72 cases per 100 000 inhabitants Thus, the incidence continued to decrease, compared to 2014 by 9% (Figure 4.9). The mean incidence of new CDI cases per 10 000 patient-days for 2015 was 11 cases/10 000 patient-days (patient-days data is from 2014), a reduction of 8% compared to the incidence in 2014 wich was 12 cases/10 000 patient-days (Figure 4.10).

FIGURE 4.10. Incidence of new cases of CDI (cases per 10 000 patient-days) in Swedish counties 2013-2015, arranged in descending order according to incidence rates for 2015. (Incidence of cases for 2015 is calculated using patient-days for 2014).

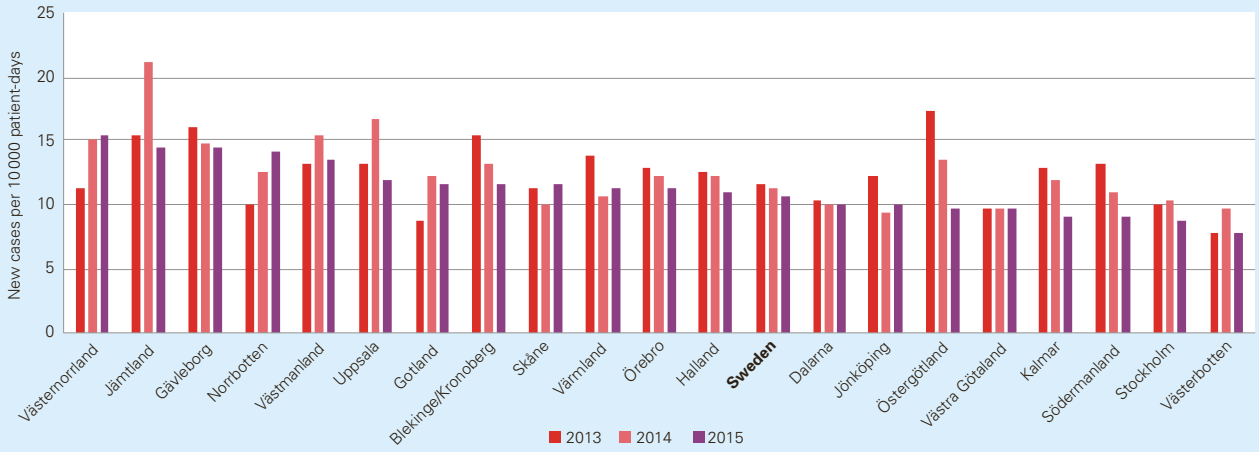
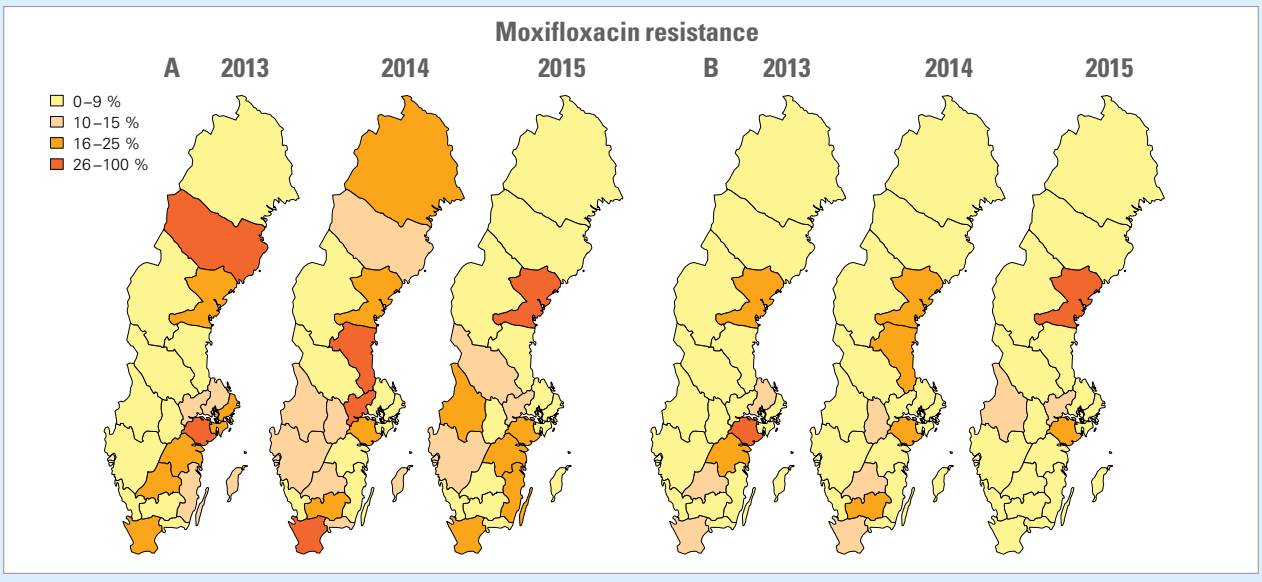


FIGURE 4.11. Proportion of *Clostridium difficile* isolates with A) resistance to moxifloxacin per county 2013-2015 and B) resistance to moxifloxacin, erythromycin and clindamycin per county 2013-2015



No isolates with a decreased susceptibility against the treatment options metronidazole or vancomycin were found in 2015. The proportions of *C. difficile* isolates resistant to the indicator antibiotics erythromycin, moxifloxacin and clindamycin decreased slightly during 2015 (Table 4.3). In the past three years the percentage of moxifloxacin isolates found has decreased in most counties, only two counties, Västernorrland and Värmland, show a constant increase in the proportion of moxifloxacin resistant isolates found since 2013 (Fig 4.11 A). Västernorrland is also the only county showing an increase in the percentage of MDR isolates (Fig 4.11 B) (resistance against clindamycin, erythromycin and

moxifloxacin, MIC >16 mg/L, >2 mg/L and >4 mg/L respectively). The counties that have had a percentage of MDR isolates larger than 20% in a year during the last three year period had an overrepresentation of one PCR ribotype. Type 001 was found in Västernorrland, type 012 in Gävleborg and Östergötland, 017 in Skåne and 231 in Södermanland. These four PCR ribotypes 001, 012, 017 and 231 account for 80% of the MDR isolates in Sweden during the period 2013-2015 Previous geographic clustering of these types indicate that outbreaks have occurred as has been reported for MDR isolates of type 017, 027 and 046.

TABLE 4.3. *Clostridium difficile* types susceptible to clindamycin, erythromycin and moxifloxacin in Sweden 2015 (n=413)

Antibiotic	Type	%R 2015 (2014)	Distribution (no. of strains) per MIC (mg/L)												
			0,05	0,064	0,125	0,25	0,5	1	2	4	8	16	32	64	>256
Clindamycin	001	30 (21)						3	12	6					9
	002	0 (4)					1	4	20	6					
	010	53 (71)					1		3	2	1				8
	012	86 (89)								1					6
	014	2 (7)					2	4	23	13	1	1			1
	017	75 (100)							1						3
	020	4 (9)					2	4	14	4		1			1
	027	67 (50)							1						2
	078	17 (27)						2	7	7	3				4
	231	100 (100)													2
	Other	8 (4)			2		14	54	88	40	7	4	1	1	16
	Total	**13 (18)**			**2**		**20**	**71**	**169**	**79**	**12**	**6**	**1**	**1**	**52**
Erythromycin	001	30 (21)					3	15	3						9
	002	0 (7)				1	5	20	5						
	010	53 (71)				1		4	2					1	7
	012	100 (94)													7
	014	2 (2)				2	7	25	10						1
	017	75 (100)					1								3
	020	4 (5)				1	7	11	6						1
	027	67 (67)						1							2
	078	57 (46)					1	7	2	1					12
	231	100 (100)												1	1
	Other	8 (4)		3	5	11	68	84	38	1					17
	Total	**15 (19)**		**3**	**5**	**16**	**92**	**167**	**66**	**2**				**2**	**60**
Moxifloxacin	001	27 (18)					1	8	12	1			8		
	002	6 (0)					1	13	11	4			2		
	010	33 (43)						1	9		1		4		
	012	29 (56)						3	1	1			2		
	014	7 (0)					2	12	26	2			3		
	017	100 (75)											4		
	020	20 (14)					1	7	15	1			2		
	027	33 (83)						1		1			1		
	078	22 (19)						9	8	1			5		
	231	100 (100)											2		
	Other	4 (3)	1			1	12	70	121	14		1	7		
	Total	**11 (18)**	**1**			**1**	**17**	**124**	**203**	**25**	**1**	**1**	**40**		

The following MIC-breakpoints were used: Clindamycin R >16mg/mL, Erythromycin R >2 mg/mL and Moxifloxacin R >4 mg/mL.

Neisseria gonorrhoeae

Notifications according to the Swedish Communicable Diseases Act

Gonorrhoea is a notifiable infection and in 2015, 1677 cases (17.0 cases per 100 000 inhabitants) of gonococcal infections were reported to the Public Health Agency of Sweden. Most of these cases were identified in the three largest counties of Sweden, which comprise the cities Stockholm, Gothenburg, and Malmö, respectively. The clinical isolates described in the present report were referred for characterization to the Swedish Reference Laboratory for Pathogenic Neisseria (an external body of the Public Health Agency of Sweden), Department of Laboratory Medicine, Clinical Microbiology, Örebro University Hospital, Örebro. In 2015, in total 462 *N. gonorrhoeae* isolates were fully characterized at this laboratory.

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

The results for 2015 are compared with those from 2007 to 2014 in Table 4.4. Briefly, the levels of resistance to antibiotics previously used as first-line treatment for gonorrhoea (penicillins and ciprofloxacin) remain high. The level of resistance to azithromycin also remains high, at 10% in 2015. Fortunately, in 2015 the resistance to cefixime remained low (2%; which is identical compared to 2014) and, for the first time since 2009, no resistance to ceftriaxone was identified. This is exceedingly promising because ceftriaxone is the last remaining option for empirical antibiotic monotherapy of gonorrhoea. Similar decreases in the resistance to these extended-spectrum cephalosporins have been indicated in some additional European countries. The reasons for this decline are still unknown, however, most likely the European recommendations to use ceftriaxone (500 mg) plus azithromycin (2 g) in the empiric first-line treatment have been effective. No gonococcal isolates resistant to spectinomycin have yet been detected in Sweden. However, the availability of spectinomycin is limited (in Sweden as in most countries globally), and it is not suitable for treatment of pharyngeal gonorrhoea.

Neisseria meningitidis

Notifications according to the Swedish Communicable Diseases Act

Invasive meningococcal disease is a notifiable disease, and in 2015 a total of 53 clinical cases (0.53 cases per 100 000 inhabitants) of the disease were reported. In total, 47 clinical invasive isolates from blood, cerebrospinal fluid or puncture (one per patient) were analysed at the Swedish Reference Laboratory for Pathogenic Neisseria (an external body of the Public Health Agency of Sweden [previously Swedish Institute for Communicable Disease Control, SMI]), Department of Laboratory Medicine, Clinical Microbiology, Örebro University Hospital.

Antibiotic susceptibility testing was performed according to standardized and quality assured methodology using Etest for determination of MIC values for penicillin G, cefotaxime, meropenem, chloramphenicol, ciprofloxacin and rifampicin. Production of β-lactamase was examined by nitrocefin discs.

Four (8.5%) isolates had an intermediate susceptibility to penicillin G (MIC>0.064 mg/L), however, no isolate was resistant (highest MIC of penicillin G was exactly on the resistance breakpoint, i.e. MIC=0.25 mg/L). All isolates (100%) were susceptible to cefotaxime (MIC values of <0.002-0.016 mg/L), meropenem (MICs: 0.002-0.016 mg/L), chloramphenicol (MICs: 0.25-1 mg/L), ciprofloxacin (MICs: 0.002-0.006 mg/L), and rifampicin (MICs: 0.002-0.032 mg/L). None of the isolates obtained in 2015 produced β-lactamase, and in fact no β-lactamase-producing meningococcal isolate has ever been identified in Sweden.

TABLE 4.4. Antibiotic resistance rates (%) and β-lactamase production of Swedish *Neisseria gonorrhoeae* strains 2007-2015

	2007 (n=406)	2008 (n=447)	2009 (n=384)	2010 (n=618)	2011 (n=805)	2012 (n=877)	2013 (n=967)	2014 (n=384)	2015 (n=462)
Ampicillin	30	28	44	31	24	23	18	28	22
Cefixime	<1	1	5	6	8	10	4	2	2
Ceftriaxone	0	<1	0	2	2	1	<1 (0.3)	<1 (0.3)	0
Azithromycin	7	13	6	12	11	10	13	9	10
Ciprofloxacin	70	63	75	56	55	62	53	60	53
Spectinomycin	0	0	0	0	0	0	0	0	0

Mycobacterium tuberculosis

During 2015 in total 835 cases of tuberculosis (TB) were reported compared to 684 cases during 2014 which is an increase of 22%. Out of the 835 cases 14 was already on TB treatment when arriving in Sweden.

The number and proportion of culture confirmed cases were 697 (83%) compared to 527 (77%) in 2014. *Mycobacterium tuberculosis* was identified in 687 cases; *Mycobacterium africanum* in four cases and *Mycobacterium bovis* in six cases. The proportions of cases diagnosed with isoniazid resistant TB in 2015 were 12.4% (85/687) and with MDR-TB 3.2% (22/687). One of the MDR-cases was classified as XDR-TB.

Isolates of *M. tuberculosis* resistant to at least one of the four first line drugs (isoniazid, rifampicin, ethambutol or pyrazinamid) were identified in 111 patients corresponding to 16% of the 687 with culture confirmed TB, see Table 4.5. As always the most common resistance found was against isoniazid.

Among the cases born in Sweden 13% (10/76) of those with culture confirmed diagnosis had some kind of resistant TB; one with MDR-TB and nine with only isoniazid-resistance.

Of the cases reported in Sweden 90% were born in another country. In total 611 in this group had a culture confirmed TB and 96 (16%) had some kind of resistance out of which 21 had MDR-TB.

For 32 of the 687 we have information on previous treatment for TB after 1950 since when effective medication has been available. Out of these 32 cases 25% (8/32) had some resistance and five were cases of MDR-TB. It is likely that more cases have received treatment earlier but there are no data on this.

Of the 22 cases with MDR-TB one was of Swedish origin and the majority (14/21) came to Sweden 2013 or later. In total 16 of the 22 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 664 of the 687 isolates so far. This is done to help detect clusters which could indicate ongoing spread in Sweden. Of all 835 reported cases, 97 were considered to have been infected in Sweden. Among culture confirmed cases with unique strains but still considered as infected in Sweden, the majority were elderly most likely infected in their youth.

The proportion of patients with *M. tuberculosis* resistant against isoniazid has increased in 2015 and we have seen more cases of MDR-TB and one XDR-TB. Even if there has been an increase in the number of MDR-cases the proportion is not as high as in 2010 and 2011.

TABLE 4.5. Drug resistant tuberculosis in Sweden 2006-2015.

Year of diagnosis	2006		2007		2008		2009		2010		2011		2012		2013		2014		2015	
Culture confirmed *M. tuberculosis*	395		361		434		510		523		473		498		522		522		687	
	No	**%**	**No**	**%**	**No**	**%**	**No**	**%**	**No**	**%**	**No**	**%**	**No**	**%**	**No**	**%**	**No**	**%**	**No**	**%**
Any resistance	43	10.9	49	13.6	57	13.1	58	11.4	68	13	73	15.4	60	12	58	10.7	65	12.4	111	16
Isoniazid	38	9.6	46	12.7	51	11.8	51	10	57	10.9	57	12	49	9.8	44	8.4	51	9.8	85	12.4
Rifampicin	6	1.5	15	4.2	15	3.5	14	2.7	20	3.8	19	4	15	3	10	1.9	18	3.4	26	3.8
Ethambutol	1	0.3	7	1.9	6	1.4	7	1.4	12	2.3	10	2.1	12	2.4	8	1.5	15	2.9	20	2.9
Pyrazinamid	6	1.5	11	3	18	4.1	15	2.9	20	3.8	27	5.7	23	4.6	14	2.7	23	4.4	24	3.5
Isoniazid + rifampicin (MDR)	3	0.8	15	4.2	14	3.2	13	2.5	18	3.4	17	3.6	14	2.8	8	1.5	15	2.9	22	3.2

Clinical isolates from animals

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

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

Pigs

Escherichia coli

Isolates of *Escherichia coli* are from clinical submissions of faecal samples or samples taken post mortem from the gastro-intestinal tract. During the latest years, the number of samples submitted has decreased and the sampling strategy has probably changed to some extent. This may influence the proportion of resistant isolates. Some of the isolates are tested by PCR for genes coding for the virulence factors enterotoxin (LT), heat-stable enterotoxin a and b (STa and STb), verocytotoxin (VT2e) and adhesion factors F4, F5, F6, F18 and F41. However, isolates may be susceptibility tested regardless of presence of virulence factors.

As in previous years, resistance to ampicillin, streptomycin, tetracycline and trimethoprim-sulphamethoxazole were the most common resistance traits (Table 5.1). Resistance to ampicillin and to trimethoprim-sulphamethoxazole has increased considerably the last years but the increase has ceased in 2015 (Figure 5.1).

Multiresistance occurred in 25% (21/84) of the isolates in 2015 and has varied over the years (42% in 2014, 38% in 2013 and 24% in 2012). According to a regulation from 2013, susceptibility testing is generally required before ordination of fluoroquinolones for animals. Due to this, sampling may be biased towards isolates from herds with therapeutic failure with trimethoprim-sulphonamides, since fluoroquinolones may be an alternative for treatment of *E. coli* diarrhoea. Co-resistance between trimethoprim-sulphonamides and other antibiotics is common.

The combination of resistance to ampicillin, streptomycin and trimethoprim-sulphametoxazole was the most common trait in multiresistant isolates in 2015, as in previous years. Three isolates were resistant to six antibiotics, two isolates were resistant to five and four isolates to four antibiotics.

FIGURE 5.1. Resistance (%) in *Escherichia coli* from pigs 1992-2015. Clinical isolates from faecal samples or from samples taken post mortem from the gastro-intestinal tract. The number of isolates each year varies (n=74-482).

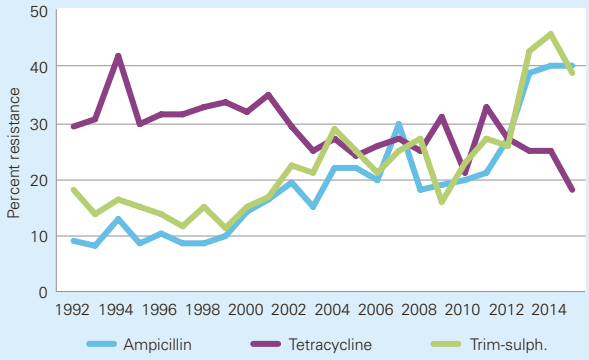


TABLE 5.1. Distribution of MICs and resistance (%) in *Escherichia coli* from pigs 2015. Clinical isolates from faecal samples or from samples taken post mortem from the gastro-intestinal tract.

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)										
	2015 n=84	≤0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Ampicillin	40					54.8	4.8			40.5		
Cefotaxime	0		100									
Colistin	0				95.2	4.8						
Enrofloxacin	7	92.9	3.6	2.4				1.2				
Gentamicin	0					100						
Neomycin	11						89.3			2.4	8.3	
Nitrofurantoin	0							54.8	41.7	1.2	2.4	
Streptomycin	26							70.2	3.6	3.6	8.3	14.3
Tetracycline	18					82.1			2.4	15.5		
Trim-Sulph.[a]	39			59.5	1.2			39.3				

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

Brachyspira hyodysenteriae

Isolates of *Brachyspira hyodysenteriae* are from clinical submissions of faecal samples. Analysis of antibiotic susceptibility data from isolates of *B. hyodysenteriae* from Sweden 1990-2010 has resulted in a proposal for epidemiological cut-off values for the antibiotics tested at SVA (Pringle et al., 2012). In Table 5.2 these values are used and historical data have been adjusted. With the epidemiological cut-off value >0.25 mg/L for tiamulin, some isolates are classified as resistant. However, with the previously used clinical breakpoint >2 mg/L, no isolate was classified as clinically resistant. The 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 of *Brachyspira pilosicoli* are from clinical submissions of faecal samples. ECOFFs for *B. pilosicoli* are not available for the antibiotics tested. As guide for the choice of antibiotic for treatment of spirochaetal diarrhoea, a clinical breakpoint for tiamulin of >2 mg/L and for tylosin of >16 mg/L are used at SVA. With these breakpoints, 12% of the isolates are resistant to tiamulin and 57% to tylosin (Table 5.3). If the same epidemiological cut-off value as for *B. hyodysenteriae* is used, 28% of the isolates are resistant to tiamulin.

Actinobacillus pleuropneumoniae

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

Pasteurella spp.

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

Isolates from 2013-2015 (n=121) were species identified by MALDI-TOF MS and are *Pasteurella multocida*. Isolates from earlier years were species identified with biochemical methods. Most of these isolates are *P. multocida*, but species identification is in some cases uncertain. Cut-off values as given in Table 7.11 for *P. multocida* are used in Table 5.5 for all isolates.

TABLE 5.2. Resistance (%) in *Brachyspira hyodysenteriae* from pigs 2005-2015 and distribution of MICs for isolates from 2009-2015. Clinical isolates from faecal samples.

Antibiotic	Resistance (%)			Distribution (%) of MICs (mg/L)												
	2005-06 n=54[a]	2007-08 n=38[c]	2009-15 n=69[e]	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Doxycycline	9	3	3			20.3	66.7	10.1		2.9							
Tiamulin	7	18	6		40.6	39.1	14.5	2.9	2.9								
Tylosin	81	76	58								24.6	15.9	1.4			1.4	56.5
Tylvalosin	NA[b]	93[d]	57				1.4	15.9	26.1	2.9	11.6	27.5	11.6		2.9		
Valnemulin	0	18	3	81.2	15.9			2.9									

[a] 29 isolates 2005, 25 isolates 2006; [b] Not analysed; [c] 23 isolates 2007, 15 isolates 2008; [d] 15 isolates tested; [e] 24 isolates 2009, 9 isolates 2010, 7 isolates 2011, 7 isolates 2012, 8 isolates 2013, 7 isolates 2014, 7 isolates 2015;

TABLE 5.3 Distribution of MICs for *Brachyspira pilosicoli* from pigs 2005-2015, n=296. Clinical isolates from faecal samples. The number of isolates each year varies (n=7-67).

Antibiotic	Distribution (%) of MICs (mg/L)													
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Doxycycline			39.2	49.0	4.4	2.7	4.4	0.3						
Tiamulin		34.1	26.4	11.8	8.1	6.1	1.7	0.7	2.4	8.8				
Tylosin							5.4	20.6	12.8	4.1	4.4	3.7	5.1	43.9
Tylvalosin[a]				0.8	12.0	27.1	25.6	4.5	1.5	3.8	12.8	12.0		
Valnemulin	46.3	19.6	5.7	9.5	7.4	4.1	2.4	1.4	3.7					

[a] 133 isolates tested.

TABLE 5.4. Distribution of MICs and resistance (%) in *Actinobacillus pleuropneumoniae* from pigs 2005-2015. Clinical isolates from post mortem investigations of lungs. The number of isolates each year varies (n=16-57).

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)														
	2005-2015 n=359	≤0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Ampicillin	0							100								
Chloramphenicol	0								100							
Ciprofloxacin	0	11.7	54.6	33.7												
Florfenicol	<1									99.7		0.3				
Gentamicin	0							0.3	8.4	79.9	11.4					
Nalidixic acid	0							2.5	59.9	37.3	0.3					
Penicillin	0		0.3	1.1	8.9	62.7	27.0									
Streptomycin	NR[a]								0.3		1.9	45.4	50.7	1.7		
Tetracycline	<1							99.7	0.3							
Trimethoprim	0				18.1	62.1	16.7	2.2	0.8							

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

TABLE 5.5. Distribution of MICs and resistance (%) in *Pasteurella* spp. from pigs 2005-2015. Clinical isolates from the respiratory tract, isolated from nasal swabs or from post mortem investigations of lungs. The number of isolates each year varies (n=7-95).

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)															
	2005-2015 n=259	≤0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Ampicillin	0								100								
Chloramphenicol	0[a]									100							
Ciprofloxacin	0[b]	21.6	58.8	18.6	1.0												
Enrofloxacin	0[c]					98.8	1.2										
Florfenicol	1[d]										98.8	1.2					
Gentamicin	1									73.4	21.2	4.6	0.4	0.4			
Nalidixic acid	0[b]								50.5	40.2	8.2		1.0				
Penicillin	0					52.5	42.9	4.6									
Streptomycin	NR[e]										3.1	44.4	34.7	13.1	4.6		
Tetracycline	0								98.5	1.5							
Trim/Sulph	1[f]							96.6	0.7	0.7	0.7	1.4					

[a] 104 isolates tested; [b] 97 isolates tested [c] 162 isolates tested; [d] 255 isolates tested; [e] Not relevant since the genus has inherently low susceptibility to streptomycin;
[f] 145 isolates tested, concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphamethoxazole).

Cattle

Escherichia coli from faecal samples

Isolates of *E. coli* are from the gastro-intestinal tract of calves. Most of the isolates are probably from calves no more than a few weeks old, i.e. during a period when resistance in enteric bacteria often is high in cattle. Resistance is high to tetracycline, streptomycin and ampicillin (Table 5.6 and Figure 5.2), as in previous years. Multiresistance occurred in 56% (20/36) of the isolates from 2015, compared to 76% in 2014, 70% in 2013 and 50% in 2012.

One isolate from 2015 had a MIC of cefotaxime above the ECOFF but did not have an ESBL or AmpC phenotype when tested further. One isolate from 2015 had a MIC of colistin above the ECOFF but was not available for further PCR test for detection of the *mcr-1* gene.

Escherichia coli from milk samples

Isolates of *E. coli* are from clinical submissions of milk samples from dairy cows. It is likely that most sampled cows had clinical mastitis. According to a regulation from 2013, susceptibility testing is generally required before ordination of fluoroquinolones for use in animals. As a consequence of this the number of isolates of *E. coli* from milk samples that are susceptibility tested each year was higher between 2013 and 2015 compared to previous years. Although antibiotic treatment

is not always indicated for *E. coli* mastitis, fluoroquinolones may be the clinically most effective group of antibiotics if treatment is required.

In the material from 2015, 25% (28/113) of the isolates were resistant to at least one antibiotic. Resistance to ampicillin, streptomycin, tetracycline or trimethoprim-sulphamethoxazole was most common as in previous years (Table 5.7). Multiresistance occurred in 15% (17/113) of all isolates. Resistance to ampicillin, streptomycin and trimethoprim-sulphamethoxazole were the most common traits and 10% of all isolates were resistant to all three of these antibiotics. One isolate was resistant to five antibiotics and one to six.

Three isolates had MICs of cefotaxime above the ECOFF. Two of these isolates had AmpC phenotypes when tested further, but no genes conferring transferable extended spectrum

FIGURE 5.2. Resistance (%) in *Escherichia coli* from cattle 2007-2015. Clinical isolates from faecal samples or from samples taken post mortem from the gastro-intestinal tract. The number of isolates each year varies (n=12-58).

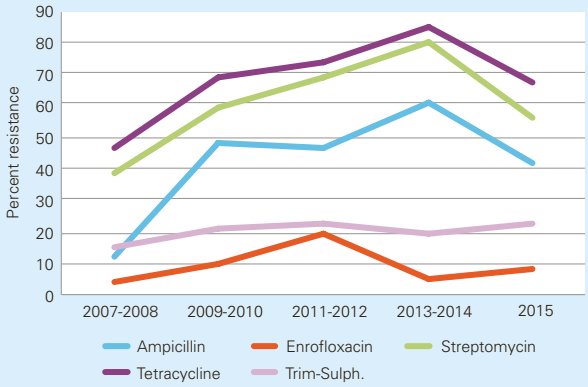


TABLE 5.6. Distributions of MICs and resistance (%) in *Escherichia coli* from cattle 2015. Clinical isolates from faecal samples or from samples taken post mortem from the gastro-intestinal tract.

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)										
	2015 n=36	≤0.12	0.25	0.5	1	2	4	8	16	32	64	>32
Ampicillin	42					38.9	19.4			41.7		
Cefotaxime	3[b]		97.2	2.8								
Colistin	3[c]				91.7	5.6			2.8			
Enrofloxacin	8	91.6	5.6	2.8								
Gentamicin	3					97.2	2.7					
Neomycin	19						77.8	2.8	5.6	5.6	8.3	
Nitrofurantoin	0							58.3	36.1	2.8	2.8	
Streptomycin	56							44.4			5.6	50.0
Tetracycline	67					33.3				66.7		
Trim/Sulph.[a]	22			75.0	2.8			22.2				

[a] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphamethoxazole); [b] The isolate with MIC 0.5 mg/L was further tested and did not show an ESBL or AmpC phenotype. [c] The isolate with MIC 16 mg/L was not available for PCR detection of the *mcr-1* gene.

TABLE 5.7. Resistance (%) in *Escherichia coli* from dairy cows 2013-2015. Distribution of MICs from 2015. Clinical isolates from milk.

Antibiotic	Resistance (%)			Distribution (%) of MICs (mg/L)										
	2013 n=142	2014 n=95	2015 n=113	≤0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Ampicillin	14	20	20					57.5	22.1			20.4		
Cefotaxime	NA[b]	NA	3[c]		97.3	0.9	0.9	0.9						
Ceftiofur	1	0	NA											
Colistin	NA	NA	<1[d]				89.4	9.7	0.9					
Enrofloxacin	5	6	2	98.2		1.8								
Gentamicin	0	0	0					100						
Neomycin	4	1	<1						99.1				0.9	
Nitrofurantoin	NA	NA	0							47.8	49.6	1.8	0.9	
Streptomycin	16	25	20							72.6	7.1		0.9	19.5
Tetracycline	9	19	11					89.4			0.9	9.7		
Trim-Sulph.[a]	11	17	12			88.5				11.5				

[a] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphametoxazole); [b] Not analysed; [c] The isolates with MICs 1 and 2 were further tested with PCR but genes for ESBL or transferrable AmpC were not detected. The isolate with MIC 0.5 mg/L was further tested and did not show an ESBL or AmpC phenotype; [d] The isolate was not available for PCR detection of the *mcr-1* gene.

cephalosporin (ESC) resistance were detected when tested with PCR. One isolate did not have an ESBL or AmpC phenotype when tested further. One isolate had MIC of colistin above the ECOFF, but was not available for analysis of the *mcr-1* gene.

Klebsiella pneumoniae from milk samples

Isolates of *Klebsiella pneumoniae* are from clinical submissions of milk samples from dairy cows. Resistance was uncommon and 78% of isolates was susceptible to all tested antibiotics, excluding ampicillin. Resistance to streptomycin was the most common resistance trait (Table 5.8). Multiresistance did not occur in isolates from 2015.

Pasteurella spp.

Isolates of *Pasteurella* spp. are from nasal swabs from calves with respiratory disease or from post mortem investigations of lungs. Isolates from 2013-2015 were species identified by MALDI-TOF MS and are *Pasteurella multocida*. Isolates from earlier years were species identified with biochemical methods. Most of these isolates are also *P. multocida*, but species identification is in some cases uncertain. Cut-off values as given in table 7.11 for *P. multocida* are used in Table 5.9 for all isolates.

Antibiotic resistance was rare among isolates of *Pasteurella* spp. (Table 5.9) and penicillin is considered the substance of choice for treatment of pneumonia in cattle in Sweden. Isolates of beta-lactamase producing *Pasteurella* spp. have been confirmed in one herd in 2003 and beta-lactamase producing *Mannheimia haemolytica* in one herd in 2010 and one herd in 2015.

TABLE 5.8. Resistance (%) in *Klebsiella pneumoniae* from dairy cows 2013-2015 and distributions of MICs 2014. Clinical isolates from milk.

Antibiotic	Resistance (%)			Distribution (%) of MICs (mg/L)										
	2013 n=41	2014 n=39	2015 n=41	≤0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Ampicillin	NR[b]	NR	NR							2.4		97.6		
Cefotaxime	NA[c]	NA	0		100									
Ceftiofur	1	0	NA											
Colistin	NA	NA	0				85.4	14.6						
Enrofloxacin	5	6	2	97.6			2.4							
Gentamicin	0	0	0					100						
Neomycin	4	1	0						100					
Nitrofurantoin	NA	NA	NR							4.9	4.9	43.9	41.5	4.9
Streptomycin	16	25	15							82.9	2.4	2.4	9.8	2.4
Tetracycline	9	19	10					87.8	2.4			9.8		
Trim-Sulph.[a]	11	17	0			97.6	2.4							

[a] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphamethoxazole); [b] Not relevant as the genus has inherently low susceptibility to the substance; [c] Not analysed.

TABLE 5.9. Distribution of MICs and resistance (%) in *Pasteurella* spp. from calves 2005-2015. Clinical isolates from the respiratory tract, isolated from nasal swabs or from post mortem investigations of lungs.

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)								
	2005-2015 n=239	≤0.06	0.12	0.25	0.5	1	2	4	8	16	>16
Ampicillin	0					100					
Enrofloxacin	0[b]		97.1	2.9							
Florfenicol	0							100			
Penicillin	0		54.3	39.5	6.2						
Tetracycline	0					96.5	3.5				
Trim/Sulph.[a]	0				97.3	1.5	0.9	0.3			

[a] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphamethoxazole); [b] 314 isolates tested.

TABLE 5.10. Distribution of MICs and resistance (%) in *Staphylococcus aureus* isolated from sheep in 2013-2014. Clinical isolates from milk.

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)														
	2013-2014 n=30	≤0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Cephalothin	0				6.6	86.7	6.7									
Ciprofloxacin	0			3.3	56.7	40.0										
Chloramphenicol	0									36.7	63.3					
Clindamycin	0					100										
Erythromycin	0					96.7	3.3									
Fucidic acid	0			23.3	70.0	3.3	3.3									
Gentamicin	0						100									
Kanamycin	0						23.3	53.3	23.3							
Penicillin	0[a]															
Tetracycline	0						96.7	3.3								
Trimethoprim	0						10.0	73.3	16.7							

[a] Denotes beta-lactamase production.

Sheep

Staphylococcus aureus from milk samples

Isolates of *Staphylococcus aureus* are from milk samples from sheep. Samples were collected within a field study in 2013-2014.

Isolates of *S. aureus* from sheep are generally susceptible for the antibiotics tested (Table 5.10). None of the tested isolates produced beta-lactamase. Penicillin is considered the substance of choice for treatment of clinical mastitis in sheep but subclinical mastitis is generally not treated with antibiotics.

According to phenotypic results and PCR of some of the isolates, MRSA was not detected in this material.

Farmed fish

Aeromonas salmonicida subsp. *achromogenes*

Isolates of *Aeromonas salmonicida* subsp. *achromogenes* are from clinical submissions of farmed fish. Most isolates are from brown trout or Arctic char. Data from 2009-2015 are compiled and presented as distributions of MICs in Table 5.11. Epidemiological cut-off values (ECVs) of >4 mg/L and >1 mg/L for florfenicol and oxytetracycline, respectively, according to CLSI are used (CLSI, 2014b). One isolate was resistant to florfenicol and two to tetracycline. A bimodal distribution with deviating high MICs of nalidixic acid indicate the presence of acquired resistance to this antibiotic as well.

Flavobacterium columnare

Isolates of *Flavobacterium columnare* are from clinical submissions of farmed fish. Most isolates are from brown trout or Arctic char. Data from 2009-2015 are compiled and presented as distributions of MICs in Table 5.11. ECOFFs for *F. columnare* are not available.

Flavobacterium psycrophilum

Isolates of *Flavobacterium psycrophilum* are from clinical submissions of farmed fish. Most isolates are from rainbow trout. Recently, Smith et al. (2014) proposed epidemiological cut-offs for florfenicol, oxolinic acid and oxytetracycline for

TABLE 5.11. Distribution of MICs for *Aeromonas salmonicida* subsp. *achromogenes* (n=70) and *Flavobacterium columnare* (n=44) from farmed fish 2009-2015.

Bacterial species	Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)							
		2009-2015	≤0.5	1	2	4	8	16	32	64	>64
Aeromonas salmonicida subsp. *achromogenes*	Florfenicol	1			97.1	1.4		1.4			
	Nalidixic acid[a]		81.7	1.7					1.7	6.7	8.3
	Tetracycline	3	94.3	2.9		1.4		1.4			
Flavobacterium columnare	Florfenicol				100						
	Nalidixic acid[b]		77.4	12.9	3.2	3.2				3.2	
	Tetracycline		97.7	2.3							

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

F. psycrophilum. These are used in the distributions in Table 5.12. Resistance to oxolinic acid and oxyteracycline was high in this material.

In Figure 5.3. resistance to tetracycline and quinolones (nalidixic acid or oxolinic acid) in *F. psycrophilum* 2005-2015 is shown. A three years moving average is used. There is a marked increase in resistance to these antibiotics. There is a limited therapeutic use of oxolinic acid as well as of tetracycline in aquaculture in Sweden. The antibiotic mostly used is florfenicol (Svarm 2011). The reason for the observed increases in resistance is not known.

FIGURE 5.3. Resistance (%) in *Flavobacterium psycrophilum* from farmed fish 2005-2015 with a three years moving average. The number of isolates each year varies (n=12-62).

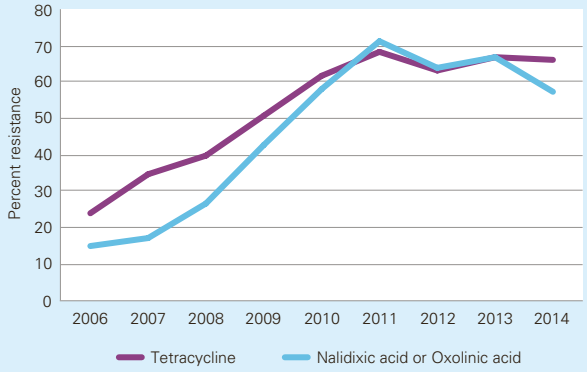


TABLE 5.12. Distributions of MICs and resistance (%) in *Flavobacterium psycrophilum* from farmed fish 2015.

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)											
	2015 n=31	≤0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8
Florfenicol	0						6.5	38.7	45.2	9.7			
Oxolinic acid	48				3.2	41.9	6.5			48.4			
Oxytetracycline	74				22.6	3.2	3.2		12.9	12.9	38.7	6.5	

Horses

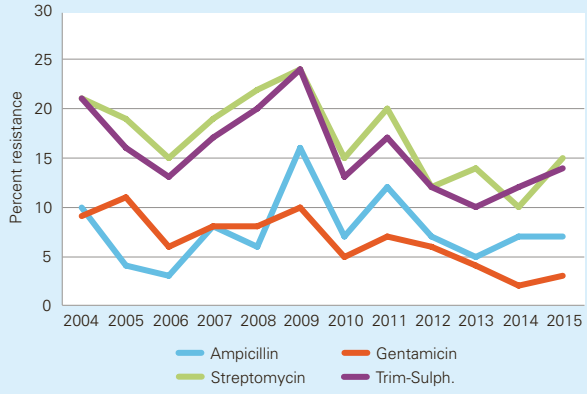
Escherichia coli

Isolates of *Escherichia coli* are from clinical submissions of the genital tract of mares. As in previous years, resistance to trimethoprim-sulphamethoxazole and streptomycin was most common in 2015 (Table 5.13). Since 2004, the rate of resistance has differed somewhat between the years, but there seems to be a generally declining trend (Figure 5.4).

Multiresistance was detected in 6% (12/188) of the isolates, which is comparable to the figures in 2013 and 2014 (4-5%). Seven of the multiresistant isolates were resistant to three antibiotics and two to four antibiotics, but no specific resistance phenotype was observed. One isolate was resistant to five antibiotics; ampicillin, gentamicin, streptomycin, tetracycline and trimethoprim-sulphamethoxazole. Two isolates were resistant to six antibiotics; both to ampicillin, gentamicin, streptomycin, tetracycline and trimethoprim-sulphamethoxazole, and one isolate also to enrofloxacin and the other to cefotaxime.

Two isolates were resistant to cefotaxime. Genes conferring transferable ESC resistance were detected in both these isolates. For more information of ESBL in horses, see ESBL-producing Enterobacteriaceae in animals.

FIGURE 5.4. Resistance (%) in clinical isolates of *Escherichia coli* from the genital tract of mares 2004-2015. The number of isolates each year varies (n=124-273).



Seven isolates were resistant to colistin (MIC >2 mg/L), but the isolates were not available for PCR detection of the *mcr-1* gene.

SvarmPat – monitoring of resistance in pathogens from farm animals

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

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

In 2015, a half day seminar at The Veterinary Congress in Uppsala in November was held to acknowledge that the SvarmPat programme has been running for 10 years. The seminar included short presentations of several topics that have been studied in SvarmPat over the years.

Selected studies within SvarmPat in 2015:

Milk samples in dairy cows

- Screening for MRSA in milk samples from dairy cows started in 2010 and is still ongoing. Selected isolates of beta-lactamase producing *Staphylococcus aureus* from routine submissions to SVA are investigated for methicillin resistance. During 2010-2015, 850 isolates were tested and MRSA with *mecC* was confirmed in 3 isolates from 2010, 1 from 2011, 1 from 2013 and 1 from 2015, and MRSA with *mecA* was confirmed in 1 isolate from 2012 and 1 from 2014. In addition, 500 isolates of *S. aureus* without beta-lactamase production was tested in 2013, but MRSA was not detected. See Notifiable diseases, MRSA in animals.
- Continuous monitoring of bacterial findings in clinical mastitis in dairy cows started in 2013. Randomly collected milk samples from dairy cows with clinical mastitis are cultured and isolated bacteria are susceptibility tested. Mastitis is an important disease in dairy cows. Most bacteria causing mastitis in dairy cows in Sweden are sensitive to penicillin and penicillin is the drug of choice if antibiotic treatment is needed. It is, however, desirable to continuously monitor the bacterial panorama and the resistance situation. The most commonly found bacterial species are *S. aureus*, *Streptococcus dysgalactiae*, *Escherichia coli* followed by *Streptococcus uberis*.

Respiratory tract samples from pigs, cattle and sheep

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

Enteric samples from pigs

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

Enteric and environmental samples from broilers

- The occurrence of ESBL-producing *E. coli* in broilers, laying hens and turkeys are monitored and the epidemiology of this resistance is studied in several projects and the work is partly financed by SvarmPat. See Notifiable diseases, ESBL-producing Enterobacteriaceae.

TABLE 5.13. Distributions of MICs and resistance (%) in *Escherichia coli* from horses in 2015. Clinical isolates from the genital tract of mares.

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)										
	2015 n=188	≤0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Ampicillin	7					58.0	32.4	2.1		7.4		
Cefotaxime	1[a]		98.9				1.1					
Colistin	4[b]				88.3	8.0	2.1	1.1	0.5			
Enrofloxacin	5	94.7	4.3	0.5				0.5				
Gentamicin	3					96.8	0.5	0.5	0.5	1.6		
Neomycin	0						99.4	0.5				
Nitrofurantoin	0							74.5	25.0	0.5		
Streptomycin	15							79.8	5.3	2.7	1.6	10.6
Tetracycline	6					90.4	3.2	0.5		5.9		
Trim-Sulph.[c]	14			85.6				14.4				

[a] Genes conferring transferable ESC resistance were detected in the 2 isolates resistant to cefoxatime; [b] The 7 isolates resistant to colistin were not available for PCR detection of the *mcr-1* gene; [c] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim sulphametoxazole).

TABLE 5.14. Distribution of MICs and resistance (%) in *Streptococcus zooepidemicus* from horses in 2015. Clinical isolates from the respiratory tract.

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)												
	2015 n=82	<0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Cephalothin	0						100							
Clindamycin	12					87.8	11.0	1.2						
Erythromycin	0					100								
Gentamicin	NR[a]						3.7	1.2	9.8	85.4				
Nitrofurantoin	0										100			
Penicillin	0	100												
Tetracycline	NR				1.2	1.2	3.7	43.9	37.8	12.2				
Trim-Sulph.[b]	7				76.8	15.9	2.4			4.9				

[a] Not relevant, the genus has inherently low susceptibility to the antibiotic; [b] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim-sulphamethoxazole).

Streptococcus zooepidemicus

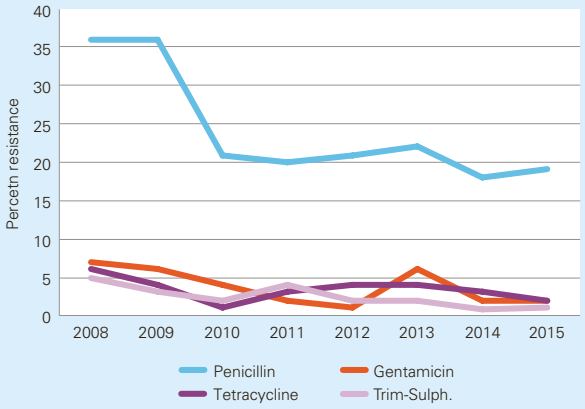
Isolates of *Streptococcus zooepidemicus* are from clinical submissions of the respiratory tract. Resistance was rare in 2015 (Table 5.14) and *S. zooepidemicus* has remained uniformly susceptible over the years studied.

Streptococcus zooepidemicus has a low inherent susceptibility to aminoglycosides (e.g. gentamicin) and tetracyclines. The MICs of gentamicin were above concentrations obtained during systemic therapy.

Staphylococcus aureus

Isolates of *Staphylococcus aureus* are from clinical submissions of samples from skin lesions, excluding wounds and abscesses. Table 5.15 presents the distribution of MICs and resistance in isolates from 2015. The proportions of resistance to gentamicin, penicillin, tetracycline and trimethoprim-sulphamethoxazole over the last eight years are shown in Figure 5.5. Resistance to penicillin due to beta-lactamase

FIGURE 5.5. Resistance (%) in clinical isolates of *Staphylococcus aureus* from skin of horses 2008-2015. The number of isolates each year varies (n=96-145).



production dominates. In 2008-2009, 36% of the tested isolates were resistant to penicillin, but for the last six years the figures have stabilised to around 20%.

Multiresistance was detected in 4% (5/116) of the isolates. Six of the isolates were resistant to three antibiotics and one to four antibiotics.

Three isolates were resistant to oxacillin (MIC of >1 mg/L), but were negative when analysed for *mecA* and *mecC* genes (PCR), i.e. not MRSA. Of the two isolates resistant to cefoxitin one isolate was not available for further testing. The other was one of the isolates resistant also to oxacillin and negative for *mecA* and *mecC*. For more information on MRSA isolated from horses, see Notifiable diseases, Methicillin-resistant *Staphylococcus aures* in animals.

TABLE 5.15. Distribution of MICs and resistance (%) in *Staphylococcus aureus* from horses 2015. Clinical isolates from the skin.

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)										
	2015 n=116	≤0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Cefoxitin	2[a]			1.7	0.9	36.2	59.5	0.9	0.9			
Cephalothin	3				97.4	2.6						
Clindamycin	5			94.8	3.4	1.7						
Erythromycin	1			96.6	2.6		0.9					
Fusidic acid	24			75.9	19.0	3.4	1.7					
Gentamicin	2				94.8	3.4		1.7				
Nitrofurantoin	1								96.6	2.6	0.9	
Oxacillin	3[b]		37.1	36.2	24.1	2.6						
Penicillin	19[c]											
Tetracycline	2		62.1	30.2	6.0	0.9	0.9					
Trim-Sulph.[d]	<1		95.7	3.4	0.9							

[a] Two resistant isolates, one negative for *mecA/mecC*-genes and the other not available for analyse; [b] Three resistant isolates, all negative for mecA/mecC; [c] Denotes beta-lactamase production; [d] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim-sulphamethoxazole).

Dogs

Escherichia coli

Isolates of *Escherichia coli* are from clinical submissions of urine, submitted either as urine or cultures on dip-slides or other agar plates. As in previous years, resistance to ampicillin was the most common trait in 2015 (Table 5.16). The proportions of resistance to ampicillin, enrofloxacin and trimethoprim-sulphamethoxazole have been slightly declining since 2005 (Figure 5.6).

Multiresistance was detected in 7% (81/1 112) of the isolates. Fifty-four of the multiresistant isolates were resistant to three antibiotics, seventeen to four antibiotics, four to five, five to six and one to seven antibiotics. The most common phenotype, 40% (32/81), was resistance to ampicillin, streptomycin and trimethoprim-sulphamethoxazole.

Isolates of *E. coli* with MIC of cefotaxime >0.25 mg/L (n=20), where further analysed for ESBL-production. Genes conferring transferable ESC resistance were detected in four of the isolates. For more information, see ESBL-producing Enterobacteriaceae in animals.

Twenty-four isolates were resistant to colistin (MIC >2 mg/L), but the isolates were not available for PCR detection of the *mcr-1* gene.

FIGURE 5.6. Resistance (%) in clinical isolates of *Escherichia coli* from urine of dogs, 2005-2015. The number of isolates each year varies (n=304-1112).

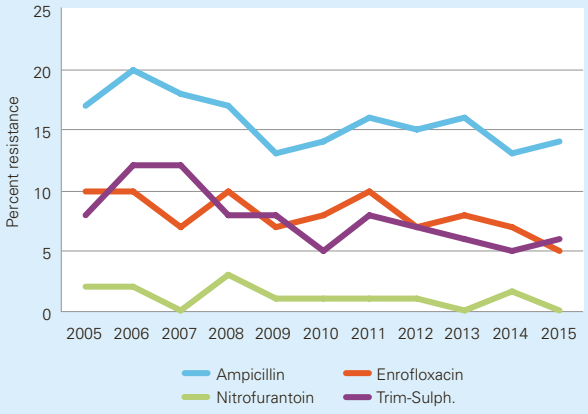


TABLE 5.16. Distribution of MICs and resistance (%) in *Escherichia coli* from dogs 2015. Clinical isolates from urine.

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)										
	2015 n=1 112	≤0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Ampicillin	14					54.4	30.4	1.0	0.4	13.8		
Cefotaxime	2[a]		98.2	1.0	0.2	0.2	0.4					
Colistin	2[b]				85.8	12.1	1.6	0.2	0.4			
Enrofloxacin	5	95.0	2.1	1.4	0.4	0.2	0.1	0.8				
Gentamicin	<1					99.4	0.3	0.1	0.1	0.2		
Neomycin	1						99.0	0.2	0.1	0.2	0.5	
Nitrofurantoin	1							70.4	28.1	1.1	0.3	0.1
Streptomycin	10							85.3	4.9	1.2	2.0	6.7
Tetracycline	5					94.3	0.6		0.4	4.7		
Trim-Sulph.[c]	6			93.6	0.3	0.2		5.9				

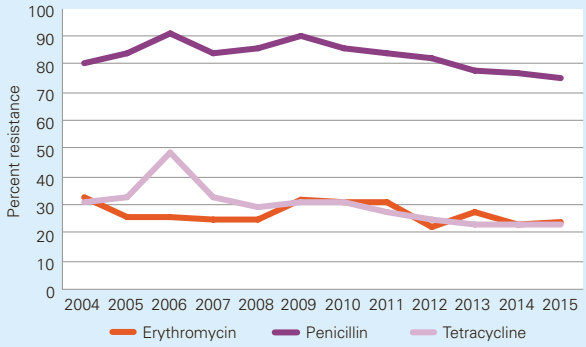
[a] Of 20 isolates with MIC >0.25 mg/L were genes conferring transferable ESC resistance detected in 4 isolates; [b] The 24 isolates resistant to colistin were not availabe for PCR detection of the *mcr-1* gene; [c] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim-sulphamethoxazole).

Staphylococcus pseudintermedius

Isolates of *Staphylococcus pseudintermedius* are from clinical submissions of samples from skin lesions, excluding wounds and abscesses. As in previous years, occurrence of penicillin resistance due to beta-lactamase production was high (75%) in 2015. However, since 2009 the figures have gradually declined, from 91% to 75% (Table 5.17 and Figure 5.7).

Multiresistance is common in *S. pseudintermedius*. Between 2009 and 2014 the figures on multiresistance reported in Svarm for the included isolates have varied from 26 to 36% (see previous Swedres-Svarm reports). In 2015 the corresponding figure was 27% (108/393). Seventy-six percent (82/108) of the isolates were resistant to penicillin, clindamycin and erythromycin, which was the most common multiresistant phenotype. This phenotype was also present in all the isolates resistant to four or more antibiotics, most commonly combined with resistance to tetracycline, 30% (32/108) and/or fusidic acid, 27% (29/108). One fourth (27/108) of the multiresistant isolates were resistance to five antibiotics.

FIGURE 5.7. Resistance (%) in clinical isolates of *Staphylococcus pseudintermedius* from skin of dogs 2004-2015. The number of isolates each year varies (n=89-566).



Six isolates with oxacillin MIC >0.5 mg/L were further analysed with PCR. Five isolates were found to be MRSP and one was negative. For more information on MRSP isolated from dogs, see Notifiable diseases, Methicillin-resistant *Staphylococcus pseudintermedius* in animals.

TABLE 5.17. Distribution of MICs and resistance (%) in *Staphylococcus pseudintermedius* from clinical submissions of skin samples in dogs 2015.

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)										
	2015 n=393	≤0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Cephalothin	1				98.7	1.3						
Clindamycin	22			77.6	2.0	1.0	19.3					
Erythromycin	24			76.1	1.0	0.3	22.6					
Fusidic acid	20			70.5	9.2	3.1	17.3					
Gentamicin	1				98.2	1.0	0.8					
Nitrofurantoin	<1								98.7	1.0	0.3	
Oxacillin	2[a]		77.1	21.4	1.0	0.5						
Penicillin	75[b]											
Tetracycline	23		75.8	1.3		0.5	0.3	22.1				
Trim-Sulph.[c]	13		45.8	40.5	9.7	0.8		2.3				

[a] Five of the 6 isolates with MIC >0.5 mg/L were positive for *mecA*, i.e. MRSP; [b] Denotes beta-lactamase production; [c] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphamethoxazole).

Staphylococcus schleiferi

Isolates of *Staphylococcus schleiferi* are from clinical submissions of samples from the external ear canal, skin lesions or wounds. No further identification to separate *S. schleiferi* in subspecies (subsp. *schleiferi* and subsp *coagulans*) was carried out.

The proportion of resistance in the presented isolates of *S. schleiferi* (Table 5.18) is lower than in isolates of *S. pseudintermedius* from dogs (Table 5.17), but also lower compared to *S. aureus* from horses (Table 5.15) and *S. felis* from cats (Table 5.22). For example, the occurence of beta-lactamase production in the tested *S. schleiferi* isolates was only 4%, compared to 75% in *S. pseudintermedius*, 19% in *S. aureus* and 18% in *S. felis*.

Pseudomonas aeruginosa

Isolates of *Pseudomonas aeruginosa* are from clinical submissions of the external ear canal. *Pseudomonas aeruginosa* is inherently resistant to trimethoprim-sulphonamides, tetracyclines and aminopenicillins (including combinations with clavulanic acid). Svarm data prior to 2014 cover *P. aeruginosa* isolates of the described category tested with polymyxin B, and all tested isolates have been sensitive to the antibiotic throughout the years. In 2014 polymyxin B was replaced by colistin as representative for polymyxins. In 2015 less than 1% (3/355) of the tested isolates were resistant to colistin, but those isolates were not available for further analyses. The proportion of resistande to enrofloxacin has declined from 25% in 2009 to 10% in 2015. Resistance to gentamicin has also declined, from 5% in 2009 to zero in 2015 (Table 5.19).

Pasturella spp.

Isolates of *Pasteurella* spp. are from clinical submissions of various locations, but mainly from wound or skin, external ear canal and the respiratory tract. *Pasteurella canis* was the most commonly detected species among the included isolates (n=194), while *P. multocida* was the second most common (n=46). As shown in Table 5.20, resistance to antibiotics among the tested *P. canis* isolates is rare. Furthermore, all *P. multocida* isolates were susceptible to all the tested antibiotics (data not shown).

The same cut-off values for resistance were used of *P. canis* and for *P. multocida*.

TABLE 5.18. Distribution of MICs and resistance (%) in *Staphylococcus schleiferi* isolated from various locations in dogs 2015.

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)										
	2015 n=201	≤0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Cephalothin	0				100							
Clindamycin	4			95.7	1.9		2.4					
Erythromycin	4			95.7	1.9		2.4					
Fusidic acid	10			74.3	16.2	5.2	4.3					
Gentamicin	0				98.1	1.9						
Nitrofurantoin	0								98.6	1.4		
Oxacillin	0		92.4	7.6								
Penicillin	4[a]											
Tetracycline	3		90.0	5.2	1.4		0.5	2.9				
Trim-Sulph.[b]	<1		98.6	1.0				0.5				

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

TABLE 5.19. Distribution of MICs and resistance (%) in *Pseudomonas aeruginosa* from dogs 2015. Clinical isolates from the external ear canal.

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)									
	2015 n=355	≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Enrofloxacin	10	0.8	2.3	15.2	49.0	22.5	4.2	5.9			
Colistin	1					80.6	16.1	0.3	0.6		
Gentamicin	0					93.0	5.4	1.7			

TABLE 5.20. Distribution of MICs and resistance (%) in *Pasteurella canis*. Clinical isolates from dogs 2014-2015.

Antibiotic	Resistance (%)		Distribution (%) of MICs (mg/L)									
	2014 n=207	2015 n=194	≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	0	0				100						
Enrofloxacin	1	<1	99.0	0.5	0.5							
Gentamicin	0	0					98.5	1.5				
Penicillin	<1	0	98.1	2.1								
Tetracycline	<1	0				100						
Trim-Sulph[a]	0	0			99.0	1.0						

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

Cats

Escherichia coli

Isolates are from clinical submissions of urine, submitted either as urine or cultures from dip-slides or other agar plates. Resistance to ampicillin was the most common trait in 2015 (Table 5.21 and Figure 5.8). Since 2007, the proportions of resistance have fluctuated somewhat over the years studied but overall are stable (Figure 5.8).

Of the *E. coli* isolates tested in 2015, 5% (25/455) was multiresistant. Of the 25 multiresistant isolates 15 were resistant to 3 antibiotics, 8 to 4 and 2 to 5 antibiotics. No specific resistance phenotype dominated.

Six *E. coli* isolates were resistant to cefotaxime (MIC >0.25 mg/L). Genes conferring transferable ESC resistance were detected in one of these isolates. For more information see ESBL-producing Enterobacteriaceae in animals.

Nine isolates were resistant to colistin (MIC >2 mg/L), but the isolates were not available for PCR detection of the *mcr-1* gene.

FIGURE 5.8. Resistance (%) in clinical isolates of *Escherichia coli* from urine of cats, 2007-2015. The number of isolates each year varies (n=131-461).

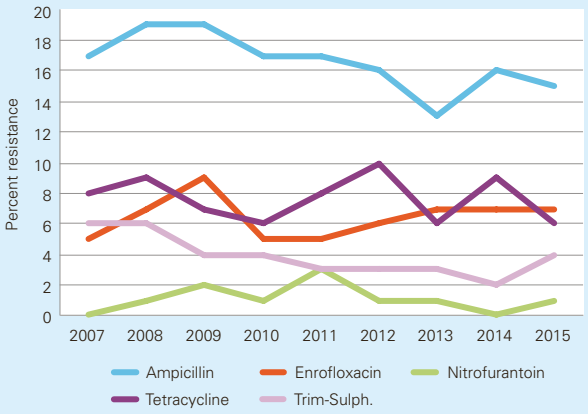


TABLE 5.21. Distribution of MICs and resistance (%) in *Escherichia coli* isolated from cats 2015. Clinical isolates from urine.

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)										
	2015 n=455	≤0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Ampicillin	15					64.2	19.3	1.1	1.1	14.3		
Cefotaxime	1[a]		98.7	0.9	0.2	0.2						
Colistin	2[b]				86.4	11.6	1.8		0.2			
Enrofloxacin	7	93.4	2.4	2.4	0.4	0.4		0.9				
Gentamicin	1					98.9	0.7			0.4		
Neomycin	1						99.3			0.4	0.2	
Nitrofurantoin	<1							73.6	25.1	0.4	0.7	0.2
Streptomycin	7							89.2	3.3	1.5	1.4	4.6
Tetracycline	6					92.7	0.7	0.2		6.4		
Trim-Sulph.[c]	4			96.0			0.4	3.5				

[a] Of 6 isolates with MIC >0.25 mg/L were genes conferring transferable ESC resistance detected in 1 isolate; [b] The 9 isolates resistant to colistin were not available for PCR detection of the *mcr-1* gene; [c] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim-sulphamethoxazole).

Staphylococcus felis

Isolates of *Staphylococcus felis* are from clinical submissions of samples from various locations in cats, but mainly external ear canal or other skin locations, urine or wounds.

The proportions of resistance to the tested antibiotics in *S. felis* (Table 5.22) are comparable to those of *S. aureus* isolates from horses (Table 5.16), except for fusidic acid. Compared to the proportions of resistance of *S. pseudintermedius* in dogs (Table 5.18) the figures are lower for *S. felis*. For example resistance to penicillin due to beta-lactamase production was 18% in *S. felis* (cats), but 75% in *S. pseudintermedius* (dogs).

Four percent (10/244) of the isolates were multiresistant. Of these, eight isolates were resistant to three antibiotics and two isolates to four antibiotics. The most common phenotype was resistance to erythromycin, klindamycin and penicillin (8/10).

Pasturella spp.

Isolates of *Pasteurella* spp. are from clinical submissions of samples from various locations in cats, but mainly from wounds, skin lesions, abscesses, external ear canal and the respiratory tract. *Pasteurella multocida* (mostly subsp. *multocida*, but also some subsp. *septica* and *gallicida*) was the most commonly detected *Pasteurella* spp. in the presented material (n=340). *Pasteurella dagmatis* was the second most common species (n=22).

The proportion of resistance to antibiotics used in pets was low in the tested *P. multocida* isolates (Table 5.23). All isolates of *P. dagmatis* were susceptible to the tested antibiotics (data not shown). The same cut-off values for resistance were sused for *P. dagmatis* and *P. multocida*.

TABLE 5.22. Distribution of MICs and resistance (%) in *Staphylococcus felis* isolated from various locations in cats 2015.

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)										
	2015 n=227	≤0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Cephalothin	2				97.8	2.2						
Clindamycin	6			94.3	0.9	0.4	4.4					
Erythromycin	10			89.9	2.6		7.5	0.4				
Fusidic acid	1			87.7	11.0	0.4	0.9					
Gentamicin	1				97.4	1.3	1.3					
Nitrofurantoin	0								98.2	1.8		
Oxacillin	0		97.4	2.6								
Penicillin	18[a]											
Tetracycline	1		97.8	1.3				0.9				
Trim-Sulph.[b]	0		96.4	3.5								

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

TABLE 5.23. Distribution of MICs and resistance (%) in *Pasteurella multocida*. Clinical isolates from cats 2014-2015.

Antibiotic	Resistance (%)		Distribution (%) of MICs (mg/L)									
	2014 n=244	2015 n=340	≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	0	0				100						
Enrofloxacin	2	1	98.0	0.6	0.3	0.9	0.3					
Gentamicin	2	1					38.2	55.3	5.0	0.3	1.2	
Penicillin	0	0	82.6	16.7	0.6							
Tetracycline	<1	0				98.8	1.2					
Trim-Sulph.[a]	3	4			93.8	1.8	0.6	0.3	3.5			

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

Indicator bacteria from animals

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

In 2015, indicator bacteria from pigs and cattle were studied. Samples of intestinal contents were collected at slaughter and cultured for *E. coli*. In addition, samples from pigs and cattle were also screened for *E. coli* resistant to extended spectrum cephalosporins (ESC) by selective culture on media supplemented with cefotaxime. For details on methodology see Material and methods, resistance in bacteria from animals.

Escherichia coli from pigs

Escherichia coli was isolated from 200 (99%) of 202 samples cultured. The majority of the isolates (68%) was susceptible to all antibiotics tested, but one third of the isolates was resistant to one antibiotic or more (Table 6.1 and 6.2). Resistance to sulphonamides (25%), ampicillin (21%) and trimethoprim (20%) were the most common traits. Thirty-nine isolates (20%) were multiresistant, i.e. resistant to three or more antibiotics. All but two of these had resistance to sulphonamides and ampicillin in their phenotype. Resistance to trimethoprim was also a common trait in these isolates.

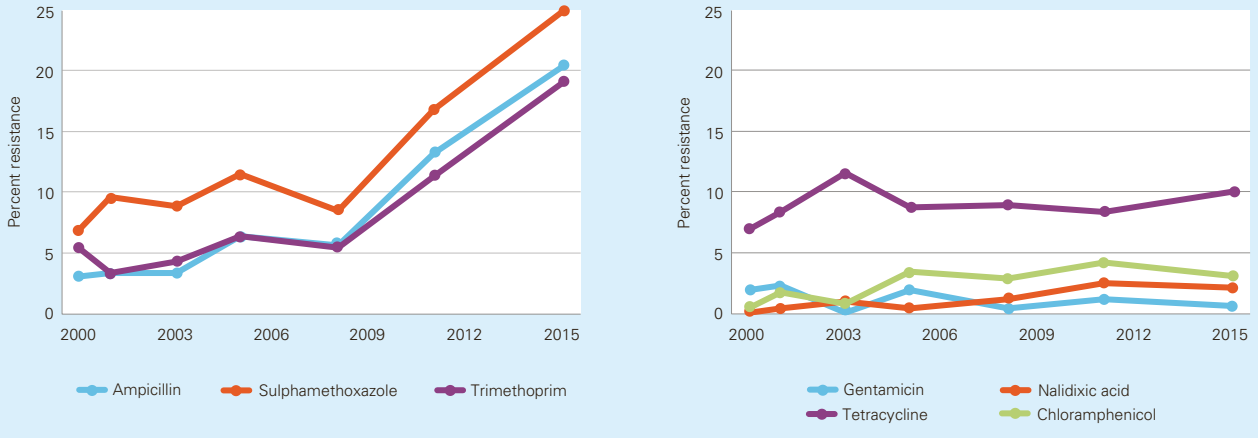
Levels of resistance in *E. coli* from pigs are low in an international perspective. For some antibiotics, levels of resistance have been stable over the years studied whereas resistance to other substances appears to have increased during the last years (Figure 6.1). Resistance to ampicillin, sulphonamides and trimethoprim in *E. coli* from pigs has increased considerably from 6, 9 and 5%, respectively, in 2008 to 21, 25, 20%, respectively, in 2015. Resistance to these three antibiotics has also increased in *E. coli* from diagnostic submissions during the last years (Table 5.1, Resistance in clinical isolates from animals).

The reasons for this increase is not known. Even if the total sales of antibiotics for pigs, measured as mg/kg slaughtered pig, was stable during 2010-2014 (Swedres-Svarm 2014), the sales of trimethoprim-sulphonamides for parenteral use has increased. However, as the sales of trimethoprim-sulphonamides for Swedish farm animals is low in an international comparison, an increased selective pressure cannot fully explain the observed increase in resistance. Co-selection by these three, as well as by other, substances is also likely to occur since the resistance traits often are linked and frequently occur in multiresistant isolates. Spread of multiresistant clones and/or plasmids are other potential reasons for the increased occurrence of these resistances.

Of the randomly selected isolates two were resistant to cefotaxime (MIC of 0.5 mg/L) on initial testing. Further phenotypical testing however showed that these isolates were not ESC resistant.

On screening for resistance to ESC, *E. coli* resistant to cefotaxime were isolated from 35 (12%) of 303 samples. Thirty-one isolates were of the AmpC type (MIC of 1-4 mg/L) but transferable genes for resistance to ESC were not found and resistance in these isolates is likely caused by mutational hyperproduction of AmpC beta-lactamases. In four isolates (1%), transferrable genes for resistance to ESC were found (MIC >4 mg/L). Two had $bla_{\text{CTX-M-55}}$, one $bla_{\text{CTX-M-15}}$ and one $bla_{\text{CMY-2}}$. For details and comments see section Resistance as notifiable disease.

FIGURE 6.1. Percent resistance in *Escherichia coli* from pigs 2000-2015. The number of isolates each year varies (n=167-390).



Escherichia coli from cattle

Escherichia coli was isolated from 101 (98%) of 103 samples cultured. The vast majority of isolates (97%) were susceptible to all antibiotics tested and only 3 isolates (3%) were resistant to one substance or more (Table 6.1 and 6.2). One isolate was resistant to colistin (MIC = 16 mg/L) but was negative for *mcr-1* when tested with molecular methods. No isolates were multiresistant, i.e. resistant to three or more antibiotics.

Low levels of resistance in *E. coli* from healthy cattle are in agreement with the previous studies of indicator *E. coli* from cattle in Svarm. More than 90% of the isolates have been susceptible to all antibiotics tested and resistance to any single substance has never exceeded 5% (Svarm 2009 and Swedres-Svarm 2013). This indicates a low selection pressure from use of antibiotics in the categories of cattle studied, i.e. calves older than six months and dairy cows. The findings are in stark contrast to the high levels of resistance in clinical isolates of *E. coli*, see Resistance in clinical isolates from animals. The difference is probably due to the fact that the clinical isolates mostly are from younger calves and most likely from herds with disease problems.

On screening for resistance to ESC, *E. coli* resistant to cefotaxime (MIC of 1-2 mg/L) was isolated from 5 (5%) of the 103 samples. All isolates were of the AmpC type but transferable genes for resistance to ESC were not found and resistance in these isolates is likely caused by mutational hyperproduction of AmpC beta-lactamases. For details and comments see section Resistance as notifiable disease.

TABLE 6.1. Resistance (%) and multiresistance (%) in indicator *Escherichia coli* from pigs and cattle, 2015. Data on indicator *E. coli* from previous Svarm-reports are given for comparison.

		Resistance (%)									
Antibiotic	**ECOFF (mg/L)**	**Pigs**	**Cattle**	**Broilers**	**Turkeys**	**Broiler meat**	**Laying hens**	**Pig meat**	**Sheep**	**Horses**	**Dogs**
		2015 n=200	**2015** n=101	**2014** n=197	**2014** n=59	**2012** n=92	**2012** n=61	**2011** n=20	**2006-09** n=115	**2010-11** n=274	**2012** n=74
Ampicillin	>8	21	1	9	25	18	3	30	2	2	9
Azithromycin	16	<1	1	0	0	-	-	-	-	-	-
Cefotaxime	>0.25	1	0	0	2	0	2	0	0	0	1
Ceftazidime	>0.5	0	0	0	2	-	-	-	-	-	-
Chloramphenicol	>16	3	0	0	3	0	0	0	0	<1	0
Ciprofloxacin	>0.06	3	0	11	3	4	5	10	<1	<1	3
Colistin	>2	0	1	0	0	1	0	0	-	<1	0
Gentamicin	>2	<1	0	0	0	3	2	0	3	<1	0
Meropenem	>0.12	0	0	0	0	-	-	-	-	-	-
Nalidixic acid	>16	2	0	11	2	4	5	0	0	<1	0
Sulphamethoxazole	>64	25	2	13	17	16	8	10	7	15	4
Tetracycline	>8	10	1	10	24	14	13	0	<1	2	8
Tigecycline	>1	0	0	0	0	-	-	-	-	-	-
Trimethoprim	>2	20	0	8	5	7	5	10	2	16	1
Multiresistance[a]											
Susceptible to all above		68	96	75	44	66	80	70	89	83	84
Resistant to 1		9	2	14	43	18	7	10	9	2	8
Resistant to 2		4	2	3	4	7	7	5	2	12	7
Resistant to 3		14		2	10	3	7	15	<1	2	
Resistant to >3		6		6		5				<1	<1

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

TABLE 6.2. Distribution of MICs and resistance (%) in *Escherichia coli* from intestinal content from pigs (n=200) and cattle (n=101), 2015.

Antibiotic	Source	Resistance	Distribution (%) of MICs (mg/L)																
		%	≤0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	>1024
Ampicillin	Cattle	1							5.9	46.5	44.6	2				1				
	Pigs	21							4.5	43.5	31	0.5				20.5				
Azithromycin	Cattle	1								2	41.6	54.5	1	1						
	Pigs	<1								3.5	47	48.5	0.5	0.5						
Cefotaxime	Cattle	0					100													
	Pigs	1[a]					99	1												
Ceftazidime	Cattle	0						100												
	Pigs	0						100												
Chloramphenicol	Cattle	0										100								
	Pigs	3										96	1	2		0.5	0.5			
Ciprofloxacin	Cattle	0	95	5																
	Pigs	3	94.5	3		1	1.5													
Colistin	Cattle	1[b]							99				1							
	Pigs	0							100											
Gentamicin	Cattle	0						79.2	18.8	2										
	Pigs	<1						78.5	18.5	2.5			0.5							
Meropenem	Cattle	0		100																
	Pigs	0		99.5	0.5															
Nalidixic acid	Cattle	0									100									
	Pigs	2									97	1			1.5	0.5				
Sulphamethoxazole	Cattle	2										15.8	54.5	27.7						2
	Pigs	25										5	30.5	32.5	7	1	0.5		0.5	23
Tetracycline	Cattle	1								97	2					1				
	Pigs	10								90					6	4				
Tigecycline	Cattle	0					99	1												
	Pigs	0					99.5	0.5												
Trimethoprim	Cattle	0					52.5	41.6	5.9											
	Pigs	20					39	38.5	3					0.5	19					
			≤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] MIC below ECOFF on further phenotypical testing. [b] Isolate negative for *mcr-1*

Background data, material, metods and references

Demographics and denominator data

Human beings

TABLE 7.1. Population by county and age group. December 31st 2015.

	0-6 years	7-19 years	20-64 years	65-79 years	80 years-	All ages
Stockholm	204 541	271 330	1 329 281	259 927	85 176	2 198 044
Uppsala	29 240	41 554	206 201	48 243	15 454	348 942
Södermanland	22 699	35 428	153 929	46 430	15 509	280 666
Östergötland	36 148	52 498	253 587	65 271	23 751	442 105
Jönköping	28 890	43 274	192 675	50 992	19 944	344 262
Kronoberg	15 566	23 248	105 872	28 522	11 367	189 128
Kalmar	17 163	26 381	129 518	41 888	15 194	235 598
Gotland	4 074	6 195	31 995	10 268	3 427	57 255
Blekinge	11 736	18 186	84 631	26 522	9 520	154 157
Skåne	111 896	152 867	745 584	183 228	66 182	1 288 908
Halland	25 818	39 339	172 321	48 637	17 178	310 665
Västra Götaland	137 492	193 910	951 061	228 566	83 423	1 632 012
Värmland	20 028	30 909	153 431	46 219	17 628	274 691
Örebro	23 769	34 564	162 292	44 932	15 563	288 150
Västmanland	20 932	31 311	146 900	41 696	14 749	261 703
Dalarna	20 970	32 697	152 888	48 473	17 358	278 903
Gävleborg	20 668	32 835	154 934	48 381	16 679	279 991
Västernorrland	17 986	28 763	133 896	42 028	14 888	243 061
Jämtland	9 596	14 618	70 716	21 261	7 693	126 765
Västerbotten	20 650	29 992	151 819	39 440	14 213	262 362
Norrbotten	17 509	28 012	141 671	42 552	14 512	249 987
Sweden	**817 371**	**1 167 911**	**5 625 202**	**1 413 476**	**499 408**	**9 747 355**

TABLE 7.2. Population in Sweden 2002-2015. Numbers represent the population by December 31st 2015.

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Population	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	9 555 893	9 644 864	9 747 355

TABLE 7.3. Number of admissions and patient-days in somatic medical care in Sweden, 2011-2014. Data represent production by acute care hospitals in the counties.

Year	Admissions	Patient-days
2011	1 455 286	6 644 028
2012	1 460 774	6 472 380
2013	1 432 377	6 359 117
2014	1 410 705	6 294 497

TABLE 7.4. Number of admissions and patient-days in somatic medical care 2014. Data represent production by acute care hospitals in the counties.

County	Admissions	Patient-days
Blekinge	24 067	119 158
Dalarna	45 624	194 563
Gotland	10 066	42 506
Gävleborg	36 842	160 563
Halland	43 412	186 770
Jämtland	17 511	82 699
Jönköping	55 466	233 926
Kalmar	42 274	159 485
Kronoberg	25 795	118 572
Norrbotten	37 332	183 310
Skåne	186 896	856 658
Stockholm	277 882	1 096 957
Södermanland	36 167	178 628
Uppsala	56 027	286 449
Värmland	40 777	188 107
Västerbotten	48 912	237 385
Västernorrland	36 716	167 332
Västmanland	37 461	171 208
Västra götaland	240 543	1 139 107
Örebro	43 893	210 051
Östergötland	67 042	281 063
Sweden	**1 410 705**	**6 294 497**

TABLE 7.5. Denominator data from the microbiological laboratories 2015.

Laboratory	Number of analyses 2015									Number of positive samples 2015	Number of positive cultures 2015				
	Blood (pair of bottles)	Cerebro-spinal fluid (CFS)	Nasopharynx	Throat	General culture	Screen MRB	Urine	Faeces SSYC	Faeces *Clostridium difficile* (toxin)	Blood (pair of bottles)	*Staphylococcus aureus*	*Streptococcus pneumoniae*	*Streptococcus pyogenes*	*Escherichia coli*	*Clostridium difficile* (toxinpositive)
Aleris Medilab	1 161	0	9 275	3 503	9 912	21 578	41 610	8 256	1 397	122	4 853	1 328	806	11 236	199
Borås	20 390	182	5 061	1 809	6 319	2 902	23 256	4 528	1 700	2 407	4 572	301	514	7 092	133
Eskilstuna (Unilabs)	16 758	151	7 054	2 551	8 436	3 427	29 156	6 122	1 757	1 225	4 666	741	595	7 691	236
Falun	19 141	190	4 611	1 460	11 835	7 496	33 580	3 869	2 049	1 886	5 684	601	577	9 115	291
Gävle	15 181	248	3 292	836	11 678	5 947	26 233	3 003	1 938	2 091	5 234	411	404	8 843	367
Göteborg	45 865	1 397	2 193	2 844	18 712	32 475	66 146	10 457	4 379	5 611	10 729	592	1 071	15 555	708
Halmstad	14 811	114	3 231	2 055	8 323	10 915	27 165	5 564	1 927	1 999	4 830	613	545	8 276	295
Jönköping	24 443	305	7 701	3 192	17 657	24 431	39 768	7 185	3 142	3 103	8 511	752	905	11 877	443
Kalmar	13 864	140	4 033	1 736	8 412	3 408	29 212	4 465	1 523	1 841	5 033	638	611	10 053	176
Karlskrona/ Växjö	22 597	147	7 220	2 657	10 713	8 864	38 314	6 582	3 374	2 700	5 895	893	817	11 533	466
Karlstad	21 076[a]	387	5 039	2 327	13 628	9 452	38 605	4 101	2 158	4 059[a]	7 028	552	668	10 628	254
Karolinska Stockholm	95 616	2 537	31 390	8 791	80 908	255 824	162 124	20 777	11 558	12 151	32 592	2 464	3 095	43 176	1 143
Linköping	26 051	921	7 492	2 568	22 218	9 171	48 933	5 841	3 143	2 744	9 263	699	939	15 203	398
Lund/ Malmö	75 285	1 684	20 028	11 759	31 585	51 033	165 689	24 837	9 775	9 221	22 930	1 962	3 065	45 388	1 386
Skövde (Unilabs)	14 866	172	4 503	2 967	12 511	9 827	55 042	8 531	2 208	1 463	8 070	508	782	16 016	267
S:t Göran (Unilabs)	14 381	79	8 312	2 194	10 505	44 882	48 201	8 541	1 508	1 137	5 806	733	814	11 742	166
Sunderby Luleå	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sundsvall	15 173	154	2 083	1 292	6 830	5 783	25 252	3 649	NA	2 156	3 881	549	385	8 866	NA
NÄL Trollhättan	20 065	277	2 481	1 244	8 675	15 102	31 082	3 680	1 958	2 178	4 675	270	329	8 907	288
Umeå	17 320	521	4 054	1 864	9 037	8 963	31 644	4 484	1 857	1 426	5 119	493	613	9 901	324
Uppsala	21 479	836	7 461	2 167	16 740	12 972	34 627	5 004	3 462	2 525	6 624	621	667	9 044	493
Visby	4 522	27	2 401	428	3 102	NP	6 941	921	468	498	1 631	342	110	2 100	84
Västerås	15 133	182	3 483	1 658	9 704	3 339	28 340	3 909	2 131	2 268	3 999	361	513	9 039	314
Örebro	18 070	374	11 439	1 929	16 340	9 608	33 853	5 342	2 877	1 874	6 550	1 340	1 107	8 623	349
Östersund	7 485	130	2 714	1 090	7 949	3 230	17 985	2 298	1 185	1 746	3 247	434	NP	5 709	170
Total	**560 733**	**11 155**	**166 551**	**64 921**	**361 729**	**560 629**	**1 082 758**	**161 946**	**67 474**	**68 431**	**181 422**	**18 198**	**19 932**	**305 613**	**8 950**

[a]not pair; NA, data not available; NP, not performed

Animals

Agricultural statistics are provided by Statistics Sweden in collaboration with the Board of Agriculture. The Board of Agriculture maintains a statistical database accessible online (www.jordbruksverket.se). The statistics are also published annually as a Yearbook of Agricultural Statistics and continuously as Statistical Messages (SM). 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 table 7.10, the average herdsize is given. In brief, the number of dairy cows and pigs has decreased notably over the last three decades while during the same time, herd size has increased. In the same period, the number of beef cows, sheep and chickens reared for slaughter has increased.

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

TABLE 7.6. Number of livestock and horses (in thousands) 1980-2015. From the statistical database of the Board of Agriculture and Statistical message JO 24 SM 1101.

Animal Species	1980[a]	1985[a]	1990	1995	2000	2005	2010	2013	2014	2015
Cattle										
Dairy cows	656	646	576	482	428	393	348	346	344	338
Beef cows	71	59	75	157	167	177	197	193	186	184
Other cattle >1 year	614	570	544	596	589	527	513	499	490	487
Calves <1 year	595	563	524	542	500	509	479	468	472	466
Total, cattle	1 935	1 837	1 718	1 777	1 684	1 605	1 537	1 506	1 492	1 475
Sheep										
Ewes and rams	161	173	162	195	198	222	273	286	287	289
Lambs	231	252	244	266	234	249	292	297	301	306
Total, sheep	392	425	406	462	432	471	565	585	588	595
Pigs										
Boars & sows	290	260	230	245	206	188	156	150	145	142
Fattening pigs >20 kg[b]	1 254	1 127	1 025	1 300	1 146	1 085	937	851	857	830
Piglets <20kg[c]	1 170	1 113	1 009	769	566	539	427	397	376	384
Total, pigs	2 714	2 500	2 264	2 313	1 918	1 811	1 520	1 397	1 378	1 356
Laying hens										
Hens	5 937	6 548	6 392	6 100	5 670	5 065	6 061	6 874	6 549	7 571
Chickens reared for laying	2 636	2 159	2 176	1 812	1 654	1 697	1 647	1 708	1 713	1 842
Total, hens	8 573	8 708	8 568	7 912	7 324	6 762	7 707	8 582	8 262	9 413
Turkeys										
Total, turkeys						122	130	80		
Horses										
Total, horses						283[d]	363			

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

TABLE 7.7. Number of holdings with animals of different types, 1980-2015. The statistical database of the Board of Agriculture.

Animal Species	1980	1985	1990	1995	2000	2005	2010	2013	2014	2015
Cattle										
Dairy cows	44 143	35 063	25 921	17 743	12 676	8 548	5 619	4 668	4 394	4 161
Beef cows	12 436	10 310	10 883	17 069	13 861	12 821	12 190	11 092	10 663	10 405
Other cattle >1 year	63 179	52 652	42 696	39 160	30 457	24 808	20 295	17 824	17 094	16 432
Calves <1 year	62 314	52 001	41 986	36 542	27 733	22 888	18 494	16 306	15 706	15 186
Total holdings with cattle	70 503	58 872	47 292	41 990	32 063	26 179	21 586	18 962	18 210	17 466
Sheep	10 238	10 595	9 749	10 037	8 089	7 653	8 657	8 869	8 912	9 110
Pigs	26 122	19 937	14 301	10 753	4 809	2 794	1 695	1 281	1 282	1 228
Laying hens	23 603	17 531	12 900	9 593	5 678	4 916	3 703	4 149	3 878	2 927
Chickens reared for laying	5 093	2 714	1 875	1 405	715	634	487	629	760	730
Broilers						234	181	242	260	263
Turkeys						383	102	126		
Horses						56 000[a]	78 000			

[a] Data from 2004.

TABLE 7.8. Number of animals slaughtered (in thousands) at slaughterhouses, 1980-2015. From the statistical database of the Board of Agriculture.

Animal Species	1980	1985	1990	1995	2000	2005	2010	2013	2014	2015
Cattle										
Cattle >1 year	574	584	523	502	490	433	425	391	405	406
Calves < 1 year	130	152	70	30	39	33	27	27	26	22
Total, cattle	704	736	593	532	529	466	453	418	431	428
Sheep	302	328	280	189	202	206	255	281	258	256
Pigs	4 153	4 283	3 653	3 743	3 251	3 160	2 936	2 556	2 553	2 560
Broilers	40 466[a]	36 410[a]	38 577[a]	61 313	68 617	73 458	78 507	83 265	89 681	95 974
Turkeys							495	452	420	475

[a] Data supplied by the National Food Administration.

TABLE 7.9. Quantity of livestock slaughtered (in 1 000 tonnes) at slaughterhouses, 1990-2015. From the statistical database of the Board of Agriculture.

Animal Species	1990	1995	2000	2005	2010	2013	2014	2015
Cattle								
Cattle >1 year	139.5	140.1	145.4	131.4	133.5	121.9	127.5	129.7
Calves < 1 year	6.8	3.2	4.4	4.5	4.3	4.2	4.1	3.5
Total. cattle	146.3	143.3	149.8	135.9	137.8	126.1	131.5	133.1
Sheep	5.0	3.5	3.9	4.1	5.0	3.9	4.1	4.2
Pigs	293.1	308.8	277.0	275.1	263.5	234.6	235.3	233.5
Broilers	44.0[a]	73.6[a]	89.9	96.2	112.0	116.8	128.7	137.7
Turkeys					3.2	2.9	3.3	3.8

[a] Data supplied by the National Food Administration.

TABLE 7.10. Average number of animals per holding 1995-2015. From statistical messages JO 20 SM 1401 and JO SM 1502.

Animal Species	1995	2000	2005	2010[a]	2013[a]	2014[a, b]	2015[a, b]
Cattle							
Dairy cows	27.2	33.7	46.0	61.9	73.7	78.4	81.3
Beef cows	9.2	12.0	13.8	16.2	17.0	17.5	17.7
Sheep	19.5	24.8	29.2	31.7	32.4	32.2	31.8
Boars and sows	30.8	62.5	105.6	156.0	190.1	186.0	186.3
Fattening pigs	157.0	293.8	471.0	664.0	795.0	791.1	845.5
Laying hens	640.0	995.0	470.6	1 638.0	1 657.0	1 689.0	2 587.0

[a] The definition of holdings included changed from 2010; [b] Data for 2014 and 2015 are estimated from a sample and therefore have a larger uncertainty

Materials and methods, consumption of antibiotics

Legal framework and distribution of medicines

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

Medicinal products with antibiotics as active substance are only dispensed through pharmacies, which are supplied by drug wholesalers or manufacturers. In outpatient care, antibiotic drugs (including medicated feed in veterinary use) may only be sold on prescriptions, ApoDos or requisitions. Prescribers (veterinarians or doctors) are not permitted to own a pharmacy or to otherwise sell medicinal products for profit. Veterinarians may deliver products to the animal caretaker in relation to examination of a case for self-cost (no profit). In hospital care, both for humans and animals, antibiotic drugs are usually bought on requisitions from pharmacies, but some counties manage drug supplies to human hospitals by themselves.

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

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

The ATC classification system and defined daily doses (DDD)

Since 1988, the Anatomical Therapeutic Chemical (ATC) and ATCvet classification system recommended by the WHO is used in Sweden for national drug statistics. For drugs sold for use in humans, to facilitate drug utilisation studies from a medical point of view, the concept of defined daily dose (DDD) is used as a unit of comparison in drug statistics. The DDD for a drug is established on the basis of the assumed average dose per day for the drug given to adults for its main indication. If possible, the DDD is given as the amount of active substance. The DDDs are usually equal for all dosage forms of a preparation. The statistical data systems of the Swedish eHealth Agency are upgraded yearly according to the recommendations made by the WHO Collaborating Centre for Drug Statistics methodology in Oslo, Norway. The DDDs used in this report are shown in Table 7.11. The sales of drugs are presented as number of DDDs per 1 000 inhabitants and day (DDD/1 000 and day), which give an estimate of the proportion of the population daily exposed to a particular drug. This figure is a rough estimate and should be interpreted with caution.

Antimicrobial consumption in humans

Swedish national statistics on drug utilization

Since 1975, the National Corporation of Swedish Pharmacies regularly produce 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 on 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/1 000 inhabitants and day or number of prescriptions/1 000 inhabitants.

Hospital care data includes drugs delivered by all hospital pharmacies to the hospital departments (se bellow chapter Completeness of data). The sales are expressed as cash value, number of packages and number of defined daily doses.

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

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

Completeness of data

Concerns have been raised that after the reregulation, the statistics on sales of medical products to hospitals in Sweden is less complete than before. In Sweden, pharmacies are required by law to report sales statistics to the Swedish eHealth Agency. However, after the reregulation of the pharmacy market, counties can choose to manage drug supplies to hospitals by themselves. If so, the counties are not required to report data to the national database. Since October 2013, three counties have chosen to organize their own drug supplies organization for hospitals.

Definitions of DDD 2015

TABLE 7.11. DDD for all antibiotic substances (J01) sold in Sweden in 2015. Substances are sorted according to ATC-code.

	DDD (g)		DDD (g)
J01AA02 – doxycycline	0.1	J01EA01 - trimethoprim	0.4
J01AA04 – lymecycline	0.6	J01EC02 - sulfadiazin	0.6
J01AA06 - oxitetracycline	1	J01EE01 - sulfamethoxazol and trimethoprim	1.92
J01AA07 - tetracycline	1	J01FA01 - erythromycin	1
J01AA12 - tigecycline	0.1	J01FA01- erythromycin erythylsuccinat tablets	2
J01BA01 - chloramphenicol	3	J01FA06 - roxithromycin	0.3
J01CA01 - ampicillin	2	J01FA09 - clarithromycin - oral	0.5
J01CA04 - amoxicillin	1	J01FA10 - azithromycin - parenteral	0.5
J01CA08 - pivmecillinam	0.6	J01FA10 - azithromycin - oral	0.3
J01CE01 - benzylpenicillin	3.6	J01FA15 - telithromycin	0.8
J01CE02 - fenoximethylpenicillin	2	J01FF01 - clindamycin - parenteral	1.8
J01CF02 - cloxacillin	2	J01FF01 - clindamycin - oral	1.2
J01CF05 - flucloxacillin	2	J01GB01 - tobramycin - parenteral	0.24
J01CR02 - amoxicillin and enzyme inhibitor-oral	1	J01GB01 - tobramycin - oral inhalation solution	0.3
J01CR05 - piperacillin and enzyme inhibitor	14	J01GB01 - tobramycin - oral inhalation powder	0.112
J01DB01 - cefalexin	2	J01GB03 - gentamicin	0.24
J01DB03 - cefalotin	4	J01GB06 - amikacin	1
J01DB05 - cefadroxil	2	J01GB07 - netilmicin	0.35
J01DC02 - cefuroxime- parenteral	3	J01MA01 - ofloxacin	0.4
J01DC02 - cefuroxime - oral	0.5	J01MA02 - ciprofloxacin - parenteral	0.5
J01DC08 - loracarbef	0.6	J01MA02 - ciprofloxacin - oral	1
J01DD01 - cefotaxime	4	J01MA06 - norfloxacin	0.8
J01DD02 - ceftazidime	4	J01MA12 - levofloxacin	0.5
J01DD04 - ceftriaxon	2	J01MA14 - moxifloxacin	0.4
J01DD08 - cefixime	0.4	J01XA01 - vancomycin	2
J01DD14 - ceftibuten	0.4	J01XA02 - teicoplanin	0.4
J01DE01 - cefepime	2	J01XB01 - colistin	3 MU
J01DF01 - aztreonam - parenteral	4	J01XC01 - fusidic acid	1.5
J01DF01 - aztreonam - inhalation	0.225	J01XD01 - metronidazole	1.5
J01DH02 - meropenem	2	J01XE01 - nitrofurantoin	0.2
J01DH03 - ertapenem	1	J01XX04 - spectinomycin	3
J01DH51 - imipenem and enzyme inhibitor	2		

Therefore, no national database with complete sales statistics is available at this time. Efforts have been made to complement the data from the Swedish eHealth Agency with data from counties. At this time only one of the three counties does not report data to the Swedish eHealth Agency.

Data sources and inclusion criteria

Data on sales of antibiotics in outpatient care is obtained from the Swedish eHealth Agency. For the overall statistics, the data include all antimicrobial products marketed in Sweden in the ATC classes J01 and J02. The data includes all sales of these products, even if the antimicrobial (J01 and J02) is prescribed by a veterinarian. Measures used are defined daily doses per 1 000 inhabitants and day (DDD/1 000 inhabitants and day) and prescriptions per 1 000 inhabitants and year. Every purchase of a medicine prescribed in outpatient care is also recorded in the Prescribed Drug Register, held by the Swedish National Board of Health and Welfare. This register provides the opportunity to link each prescription to an individual, which makes it possible to investigate the actual number of individuals or the fraction of the population treated with a specific medicine.

Antibiotic consumption in hospital care is measured as DDD/1 000 inhabitants and day and DDD/100 patient-days

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

The Swedish Prescribed Drug Register

Since July 2005, the Swedish National Board of Health and Welfare supplies an individually based register on all drugs prescribed and dispensed in outpatient care. Among others this data gives information on the number of individuals treated with at least one course of antibiotics during a specific period of time, i.e. number of users per 1 000 inhabitants and year (Users/1 000/year). It is also possible to follow the number of purchases per person.

Number of admissions and patient-days

Each of the 21 county councils in Sweden deliver once a year data to the National Patient Register kept by The National Board on Health and Welfare. Administrative data within hospital care include, among others, date of admission, date of discharge and length of stay. Data for 2015 is not available until August 2016, denominator data from 2014 are therefore used in some figures in this report. The number of admissions and patient-days in Swedish somatic medical care (produced by acute care hospitals) 2011-2014 is shown in Table 7.3. The National Board of Health and Welfare keeps a searchable database at the web, http://www.socialstyrelsen.se/statistik.

Sales of antibiotics for animals

Data sources, inclusion criteria and analysis

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

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

In rare cases, premixes mixed in medicated feed may be delivered from feed mills without the sales being recorded by a pharmacy. Examination of the reports by all feed mills to the SBA shows that this happened only once during 2005-2009 (a total quantity of 40 kg active substance).

The ionophoric antibiotics are presently regulated as feed additives and not sold through pharmacies. However, the SBA collects figures on sales of ionophores from the feed mills as a part of the feed control system. As the source differs, data on ionophores are given only in the table on sales of products for mixing in feed or water in Table 1.8.

Completeness of data

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

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

In 2015, seven of the originally included products were marketed during the whole year. For these products, the difference in sales expressed as kg active substance to and from pharmacies was 8, 12 and 6% for 2013, 2014 and 2015, respectively. The above estimate was limited to products for injection with general marketing authorisation in Sweden. Other types of products are less likely to be affected by the observed lack of completeness.

Products sold with special licence

Previously, most antibiotic 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. Between 2012 and 2014, efforts were made to identify

companies who might have statistics on sales of products sold with special licence to the Swedish market. Whenever the information on number of packages sold per product-packtype from the Swedish eHealth Agency was lower than that obtained from pharmaceutical companies, the figure was adjusted. This means that for some products, the figures may represent a slight overestimate of sales from pharmacies as they may include products kept in stock. The reporting system has been adjusted and it is assumed that from 2015, data from the eHealth Agency on sales of products with special licence is no less complete than for products with general marketing authorisation.

Materials and methods, resistance in bacteria from humans

Antibiotic susceptibility testing

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

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

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

National surveillance of antibiotic resistance

Surveillance regulated in the Communicable Disease Act

Statutory notifications of certain communicable diseases are regulated in the Communicable Disease Act (SFS 2004:168, SFS 2004:255). With the exception of certain sexually transmitted infection (STI), and from 2007 ESBL-producing Enterobacteriaceae, both the clinician caring for a patient with a notifiable disease (clinical notification) and the laboratory diagnosing the pathogen causing the disease (laboratory notification) are obliged to notify. This double notification significantly enhances the sensitivity of the surveillance system. Notification shall be done within 24 hours, in duplicate to the County Medical Officer for Communicable Disease Control (smittskyddsläkare) and to the Swedish Public Health Agency. Notifications, with the exception of STI, are done with full person identification. The clinical notification shall also include information on the likely source and route of infection, as well as other information of epidemiological importance.

Infections (or colonisation) with different antibiotic resistant pathogens are included in the list of notifiable diseases. *Streptococcus pneumoniae* with bensylpenicillin MIC > 0.5 mg/L (PNSP) have been notifiable since 1996 (MIC > 1 mg/L from 2012). Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant (*vanA* and *vanB*) *Enterococcus faecalis* and *Enterococcus faecium* (VRE) have been notifiable since 2000.

Since 1st February 2007 ESBL-producing Enterobacteriaceae were made notifiable by laboratory notifications. The definition of an ESBL was extended in 2009 to include not only ESBLs inhibited by clavulanic acid (now referred to as $ESBL_A$) but also plasmid-mediated AmpC enzymes ($ESBL_M$) and carbapenemase enzymes ($ESBL_{CARBA}$).

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

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

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

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

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

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

In 1994 a model for the concomitant surveillance of antibiotic resistance and quality assurance of antibiotic susceptibility testing was devised. In Sweden there are at present 26 clinical microbiology laboratories, each covering a county (or part of county) of Sweden. The demographics of the laboratories, their geographic areas and their corresponding populations are well characterized. The antibiotic susceptibility testing methods of the laboratories have been standardized through the combined work of the former SRGA-M (since 2011 replaced by NordicAST) and the microbiology laboratories.

Each year the laboratories are asked to collect quantitative data (zone diameters) for defined antibiotics in 100-200 consecutive clinical isolates of a defined set of bacterial species. Since 1994, *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Haemophilus influenzae* have been part of this yearly program. Since 2001 *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* have been part of these surveys. The number of antibiotics tested for each pathogen has varied between 4 and 6.

From 2002, the web-based software (ResNet) will receive the aggregated data from the laboratories and, following approval of registered data by one of two web administrators, instantly displayed it in the form of resistance frequencies on the geographical areas on a map of Sweden. Behind each resistance frequency the distribution of zone diameters together with the relevant demographic data are directly accessible. 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). Laboratories can view their own data and link information to websites of their own local health care system.

EARS-Net

The European network of national surveillance systems of antimicrobial resistance (EARSS) performed on-going surveillance of invasive infections of *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli*, and *Enterococcus faecalis/faecium*, and monitors variations in antibiotic resistance over time and place. From 2005 invasive isolates of *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* are also part of the scheme. In 2014 *Acinetobacter* species was added to the programme.

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

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

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

Surveillance of invasive isolates additional to EARS-Net data

Data on invasive isolates on all positive blood cultures were obtained from ten laboratories in 2015 that are using the same laboratory information system (ADBakt). Their total catchment population is at present 4.5 million, thus representing 45% of the Swedish population. From these laboratories data for the pathogens specified by the EARS-net network are retrieved, but also data on all other bacterial pathogens consecutively isolated from blood cultures. In the SWEDRES reports from 2007 data for *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Haemophilus influenzae* are presented as well as data for *Salmonella* and *Campylobacter*.

Sentinel surveillance

A national surveillance programme for *Clostridium difficile* was initiated by SMI in 2009. The programme included both a voluntary laboratory reporting system of all new cases of *Clostridium difficile* infection (CDI) through SmiNet2 and a determination of resistance and epidemiological typing of isolates from the clinical microbiology laboratories. All C. difficile strains isolated during weeks number 11 and 39 were sent to SMI for typing by PCR ribotyping and antibiotic susceptibility testing.

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

Materials and methods, resistance in bacteria from animals

Sampling strategy

Antibiotic resistance as notifiable diseases

ESBL

Clinical isolates from cats, dogs, and horses were submitted to the Dept. of Animal Health and Antimicrobial Strategies, SVA as bacterial strains.

Screening for $ESBL_{A,}$ $ESBL_{M}$ and $ESBL_{CARBA}$-producing *Escherichia coli* was performed on caecal samples from healthy pigs and faecal samples from healthy cattle as well as on samples of pig and cattle meat. Furthermore, screening for $ESBL_{A}$ and $ESBL_{M}$-producing *Escherichia coli* was performed on caecal samples from healthy broilers

Samples from pigs were collected at slaughter under the supervision of the National Food Agency (SLV) at six abattoirs that together processed more than 85% of the total number of pigs slaughtered in Sweden 2015. At each abattoir, a proportional number of samples in relation to the slaughter volume were collected throughout the year. Samples were sent to SVA for culture within one week after collection and in the meantime kept refrigerated. The number of samples collected at each abattoir was proportional to the annual volume of pigs slaughtered at an abattoir and each sample represented a unique herd. By these measures, bacterial isolates included were from randomly selected healthy pigs of Swedish herds. Each isolate was from a unique herd.

Samples from cattle, older than six months, were collected at slaughter for a prevalence study of EHEC at fourteen abattoirs. Samples were collected during January, February and April.

Samples from Swedish pig and cattle meat were collected throughout the year by municipal environmental departments in nine different cities in Sweden. In each city, a proportional number of samples in relation to the human population was collected.

Samples from broilers were from the Swedish Campylobacter programme in which whole caeca are collected from each batch of broilers slaughtered. From these samples, 50 were selected by convenience in March-April and 50 in September-October. Each sample was from a unique flock but not always from a unique production site. Samples cultured were collected at six abattoirs that in 2015 accounted for approximately 98% of the total volume of broilers slaughtered. The number of samples from each abattoir was roughly proportional to the annual slaughter volume of the abattoir.

MRSA and MRSP

Clinical isolates from cats, dogs, and horses were submitted to the Dept. of Animal Health and Antimicrobial Strategies, SVA as bacterial strains.

Findings of MRSA and MRSP in animals are notifiable in Sweden and hitherto the majority of isolates from notified incidents has been confirmed using molecular methods at SVA.

Monitoring of MRSA in dairy cattle was performed by screening isolates of beta-lactamase producing *Staphylococcus aureus* from routine submissions of milk samples sent to SVA. From each submission where beta-lactamase producing *S. aureus* was found, one isolate, selected by convenience, was tested.

VRE

Screening for VRE was performed on the same samples of intestinal content from caecas of healthy broilers as for screening for ESBL (see above).

Zoonotic pathogens

Salmonella

Salmonellosis in animals is a notifiable disease in Sweden and isolates from each notified incident are confirmed at SVA. Data presented in this report are from susceptibility testing of these isolates. The summary for each year includes one isolate of each serovar from each warm-blooded animal species in notified incidents. An exception is isolates from cats from which a subset of isolates are selected by convenience. In addition, isolates from incidents previously notified and still under restrictions are included in the yearly statistics. Also included are isolates obtained in the salmonella surveillance programme from samples collected at slaughter (carcass swabs, neck skins and lymph nodes).

Campylobacter

Screening for *Campylobacter coli* in caecum from pigs and *Campylobacter jejuni* in faeces from cattle were performed on the same samples as for ESBL (see above).

Clinical isolates from animals

Clinical isolates included are from routine bacteriological examinations of clinical submissions or post-mortem examinations. Part of the isolates of *Actinobacillus pleuropneumoniae* from pigs and part of the isolates of *Pasteurella* spp. from calves are, however, isolated from samples collected in surveys initiated within the SvarmPat programme. Isolates of *Staphylococcus aureus* from sheep are isolated in a field study.

In pigs, isolates of *E. coli* are from the gastro-intestinal tract and isolates of *Brachyspira* spp. from faecal samples. Isolates of *Pasteurella* spp. from pigs are isolated from nasal swabs collected within a control programme for atrophic rhinitis in nucleus and multiplying herds or from tissue samples from lungs taken post mortem. Isolates of *A. pleuropneumoniae* in pigs emanate from tissue samples from lungs sampled post mortem.

In cattle, isolates of *E. coli* are from samples from the gastro-intestinal tract or from milk samples. Isolates of *Klebsiella pneumoniae* are from milk samples. Isolates of *Pasteurella* spp. are from the respiratory tract.

In sheep, isolates of *S. aureus* are from milk samples.

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

In dogs, isolates of *E. coli* are from urine, *Staphylococcus pseudintermedius* from skin samples, *Staphylococcus schleiferi* from external ear canal, skin or wound, *Pseudomonas aeruginosa* from the external ear canal and *Pasteurella* spp. from various locations (mainly wound, skin, external ear canal or the respiratory tract).

In cats, isolates of *E. coli* are from urine samples, *Staphylococcus felis* from various organs (mainly external ear canal, other skin locations, urine or wound) and *Pasteurella* spp. from various locations (mainly wound, skin, abscesses, external ear canal or the respiratory tract).

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

Indicator bacteria

The samples from intestinal content from healthy pigs and cattle that were screened for $ESBL_A$, $ESBL_M$ and $ESBL_{CARBA}$-producing *E. coli* were also used to isolate indicator *E. coli*. However, only 202 of the samples from pigs were cultured for indicator *E. coli* and these samples were evenly distributed over the year.

Isolation and identification of bacteria

Antibiotic resistance as notifiable diseases

ESBL

$ESBL_A$, $ESBL_M$ and $ESBL_{CARBA}$-producing *E. coli* were isolated by culture on MacConkey agar (Oxoid) with cefotaxime (1 mg/L), CHROMID CARBA agar (bioMérieux) and CHROMID OXA 48 agar (bioMérieux) after incubation overnight at 37°C, with prior enrichment in buffered peptone water (BPW).

Intestinal samples

Briefly, 1 g of intestinal content was diluted in 9 ml BPW and incubated at 37°C overnight. From the BPW solution 10 µL was spread each on a plate of MacConkey agar with cefotaxime (1 mg/L), CHROMID CARBA agar and CHROMID OXA 48 agar. The plates were incubated overnight at 44°C (MacConkey agar) or 37°C (chromagar).

Additionally from all samples from broilers, before incubation 100 µL from the BPW solution was, spread on MacConkey agar with cefotaxime (1 mg/L) and incubated overnight at 37°C.

One lactose positive colony with morphology typical for *E. coli* growing on MacConkey agar with cefotaxime was subcultured on horse-blood agar (5% v/v) and further tested for ESBL detection.

Meat samples

Briefly, 25 g of surface meat was homogenized in 225 ml BPW and incubated at 37°C overnight. From the BPW homogenizate 10 µL per agar plate was spread on MacConkey agar with cefotaxime (1 mg/L), CHROMID CARBA agar and CHROMID OXA 48 agar and incubated overnight at 44°C for MacConkey agar and 37°C for the chromagar.

MRSA

In the screening for MRSA among isolates of beta-lactamase producing *S. aureus* from dairy cows, isolates were tested for presence of *mecA* and *mecC* with PCR (see below). If positive for *mecA* or *mecC*, the isolate was susceptibility tested using microdilution (see below).

VRE

After the initial dilution in BPW (see screening for ESBL above), 100 µL was spread on Slanetz-Bartley agar with vancomycin (16 mg/L) and incubated for 48 hours at 37°C.

One colony, randomly chosen, were sub-cultured on bile-esculin agar and blood agar (37°C, 24 h). Colonies with morphology consistent with enterococci, and with a positive reaction on bile-esculin agar were identified to species level by MALDI-TOF MS. Mass spectra were compared against the MALDI Biotyper database using the MALDI Biotyper 3.0 Realtime Classification (RTC) software (Bruker Daltonik GmbH, Bremen, Germany). If available, one isolate of *E. faecium* and one isolate of *E. faecalis* were tested for antibiotic susceptibility.

Zoonotic pathogens

Salmonella

Salmonella was isolated and identified at the Dept. of Microbiology, SVA or at regional laboratories in accordance with standard procedures. All samples within official control programmes are cultured according to the procedures detailed by the MSRV (ISO-EN 6579:2002/ Amd 1:2007). Confirmatory identification and serotyping was performed according to the procedures of Kaufmann and White.

Isolates of *Salmonella* Enteritidis are phage-typed by The Public Health Agency of Sweden, Solna using the Colindale scheme. As from 2013 other serovars are not phagetyped.

Campylobacter

Campylobacter coli from pigs were isolated and identified at SVA. Briefly, samples were cultured direct on Preston selective agar at 42°C for 48 h in an microaerophilic environment. Isolates were selected based on colony morphology and microscopic appearance including motility. All isolates were species identified by MALDI-TOF-MS.

Campylobacter jejuni from cattle were isolated and identified as *C. coli* from pigs with the exception that samples were enriched in Preston enrichment broth 42°C for 24 h before culture on Preston agar.

Clinical isolates from animals

Most clinical isolates were isolated and identified with accredited methodology, following standard procedures at SVA. Part of the isolates of *Pasteurella* spp. from pigs and cattle and part of the isolates of *E. coli* from cattle were isolated and identified following standard procedures at a regional laboratory.

Indicator bacteria

Escherichia coli

After the initial dilution in BPW and incubation (see screening for ESBL above), 10 µL was spread on MacConkey agar and incubated overnight at 44°C.

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

Susceptibility testing

Microdilution

At SVA, bacteria from animals are tested for antibiotic susceptibility with accredited methodology using dilution methods in cation adjusted Mueller-Hinton broth (CAMHB) (Difco). Tests are performed following the standards for microdilution of the Clinical and Laboratory Standards Institute (CLSI, 2013). The microdilution panels used, VetMIC, are produced at Section of Substrate Production, SVA and Sensititre are produced at Trek diagnostics LTD. Different panels are used depending on the bacterial species tested and the purpose of the investigation (monitoring or clinical diagnostics). Minimum inhibitory concentration (MIC) is recorded as the lowest concentration of an antibiotic that inhibits bacterial growth.

Some adaptations from the CLSI standard are employed. For *Pasteurella* spp. three different protocols are used at SVA. Either the tests are made by dilution in CAMHB supplemented with 5-10% horse serum followed by incubation in aerobic atmosphere, 37°C for 16-18 hours, or by dilution in Haemophilus test medium (HTM) followed by incubation in CO_2, 37°C for 16-18 hours. Also dilution in CAMHB supplemented with 5-10% horse serum and incubation in CO_2, 37°C for 16-18 hours was used. For testing of *A. pleuropneumoniae* dilution in HTM broth was used followed by incubation in CO_2 at 37°C for 16-18 hours. Also, *S. equi* subsp. *zooepidemicus* was tested using CAMHB supplemented with 5-10% horse serum followed by incubation at 37°C for 16-18 hours.

Susceptibility of *Campylobacter* spp. was tested according to the CLSI standard M45-3rd EditionA2 for fastidious bacteria (CLSI, 2015b).

Susceptibility of *Brachyspira hyodysenteriae* and *B. pilosicoli*, was tested by a broth dilution method described by Karlsson et al. (2003), in tissue culture trays with 48 wells per plate. The wells were filled with 0.5 mL of a suspension of bacteria in brain heart infusion broth (BHI) with 10% foetal calf serum ($1x10^6$-$5x10^6$ CFU/ml) and incubated in an anaerobic atmosphere at 37°C for four days on a shaker.

Bacteria from fish are tested for antibiotic susceptibility by broth microdilution adapted for aquatic bacteria according to CLSI (2014a).

Phenotypic confirmatory tests for production of extended spectrum beta-lactamases (ESBLs) in *E. coli* were performed with and without clavulanic acid in Sensititre EUVSEC2 microdilution panels and interpreted according to EUCAST (Table 7.12).

Genotyping

Suspected isolates of MRSA were confirmed by detection of the *nuc*, *mecA* and *mecC* genes applying real-time PCR as described by Pichon et al. (2012). *Spa*-typing, a single locus sequence typing method using the polymorphic region X of the protein A gene, was performed on all isolates confirmed as MRSA, according to Harmsen et al. (2003) and the specific *spa*-type was determined using BioNumerics® (Applied Maths). MRSP *spa*-typing was performed according to Moodley et al. (2009) and MLST according to the MLST Scheme at http://pubmlst.org/spseudintermedius/.

PCR was performed for identification of $ESBL_M$ (Perez-Perez and Hanson, 2002), $ESBL_A$ (Woodford et al., 2006), genes coding OXA-1 group, TEM-groups and SHV-groups (Fang et al., 2008) and $ESBL_{CARBA}$ (Poirel et al., 2011).

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

Quality assurance system

Laboratories performing antibiotic susceptibility testing at SVA are accredited according to SS-EN ISO/IEC 17025 by the Swedish Board for Accreditation and Conformity Assessment (SWEDAC) to perform antibiotic susceptibility tests with microdilution methods. In addition, Dept. of Micobiology is accredited for isolation and identification of animal pathogens and of *Salmonella* according to the same standard.

For susceptibility tests of zoonotic, pathogen and indicator bacteria, *Escherichia coli* ATCC 25922, *Enterococcus faecalis* ATCC 29212, *Staphylococcus aureus* CCUG 15915 (analogue to ATCC 29213) and *Campylobacter jejuni* CCUG 11284 (analogue to *Campylobacter jejuni* ATCC 33560) were included as quality controls. Relevant control strains were also included and evaluated at least once weekly for animal pathogens. For testing of *Brachyspira*, the *B. hyodysenteriae* type strain B78^T ATCC 27164^T was used for quality control.

Dept. of Animal Health and Antimicrobial Strategies participates in two proficiency tests for antibiotic susceptibility testing. These are arranged by the European Union Reference Laboratory - Antimicrobial Resistance and as a national ring trial. Likewise, Dept. of Microbiology participates in proficiency tests concerning isolation and identification of *Salmonella* and general clinical veterinary bacteriology and susceptibility tests.

Data handling

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

Cut-off values for resistance

For interpretation of MICs from susceptibility testing of zoonotic bacteria (*Salmonella* and *Campylobacter*) and indicator bacteria (*Escherichia coli* and enterococci) epidemiological cut-off values (ECOFF) issued by EUCAST (www.eucast.org) or values suggested by the European Food Safety Authority are used. For some antibiotics, values based on MIC distributions obtained in Svarm are used. This applies e.g. for narasin in *E. faecium* where the ECOFF (>4 mg/L) cuts through the resistant MIC population for some animal categories (e.g. broilers) in a manner not in agreement with the concept of wild-type distributions.

ECOFFs are used when available also for clinical isolates from animals. When ECOFFs are not available, or the range of concentrations tested precludes use of a recommended value, values based on MIC distributions obtained in Svarm are used but clinical breakpoints issued by CLSI (CLSI, 2015a) or epidemiological cut-offs (ECVs) issued by CLSI (CLSI, 2014b) are also taken into consideration.

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

TABLE 7.12. Cut-off values (mg/L) for resistance. Values in red are current (March 2016) EUCAST epidemiological cut-off values (ECOFFs), blue underlined values deviate from ECOFFs, red underlined values are CLSI epidemiological cut-off values (ECVs) and for values in black, ECOFFs are not defined.

Antbiotic	*Actinobacillus pleuropneumoniae*	*Aeromonas salmonicida*	*Brachyspira hyodysenteriae*	*Campylobacter jejuni*	*Campylobacter coli*	*Enterococcus faecium*	*Escherichia coli* (indicator)	*Escherichia coli* (pathogen)	*Flavobacterium psycrophilum*	*Klebsiella pneumoniae*	*Pasteurella multocida*	*Pseudomonas aeruginosa*	*Salmonella enterica*	*Staphylococcus pseudintermedius, S. felis, S. schleiferi*	*Staphylococcus aureus*	*Streptococcus zooepidemicus*
Ampicillin	>1			>8	>8	>4	>8	>8			>1		>8			
Azithromycin							>16									
Bacitracin[a]						>32										
Cefepime							0.12									
Cefotaxime							>0.25	>0.25		>0.25			>0.5			
Cefoxitin															>4	
Ceftazidime							>0.5									
Ceftiofur								>1		>1						
Cephalothin														>1	>1	>2
Chloramphenicol	>2					>32	>16	>16			>2		>16		>16	
Ciprofloxacin	>0.06			>0.5	>0.5		>0.06				>0.06		>0.06		>1	
Clindamycin														>0.5	>0.5[d]	>0.5
Colistin							>2	>2		>2		>4	>2			
Doxycycline			>0.5													
Enrofloxacin							>0.12	>0.12		>0.12	>0.25	>2				
Ertapenem							>0.06									
Erythromycin				>4	>8	>4								>0.5	>1	>0.5
Florfenicol	>4	>4						>16	>2		>4		>16			
Fusidic acid														>1	>0.5	
Gentamicin	>8			>2	>2	>32	>2	>2		>2	>8	>8	>2	>2	>2	
Imipenem							0.5									
Kanamycin						>1024							>16		>8	
Linezolid						>4										
Meropenem							>0.12									
Nalidixic acid	>16			>16	>16		>16				>16		>16			
Narasin						>2										
Neomycin								>8		>8			>4			
Nitrofurantoin								>64						>32		>32
Oxacillin														>0.5	>1[d]	
Oxolinic acid									>0.25							
Penicillin	>0.5										>0.5			[c]	[c]	>0.06
Streptomycin				>4	>4	>128		>16		>16			>16			
Sulphametoxazole							>64						>256			
Temocillin							>32									
Tetracycline	>1	>1		>1	>2	>4	>8	>8	>0.12	>8	>2		>8	>1	>1	>4
Tiamulin			>0.25													
Tigecycline							>0.5									
Trimethoprim	>4						>2						>2		>2	
Trim & sulpha[b]								>1		>1	>4			>0.5	>0.5	>0.5
Tylosin			>16													
Tylvalosin			>1													
Valnemulin			>0.12													
Vancomycin						>4										
Virginiamycin						>4										

[a] MIC in U/mL; [b] Concentration of trimethoprim given, tested with sulphamethoxazole in concentration ratio 1/20; [c] beta-lactamase production; [d] EUCAST ECOFFs are used for MRSA (clindamycin >0.25 mg/L and oxacillin >2 mg/L).

Svarm 2000-2015

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

TABLE 7.13. *Salmonella enterica*, number of isolates 2000-2015.

Source	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Warm-blooded animals	67	52	49	101	68	105	101	112	122	117	82	71	71	86	77	54
Cold-blooded animals										17						

TABLE 7.14. *Campylobacter* spp., number of isolates 2000-2015.

Source	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Cattle		67					68							109		23
Pigs		98		105		100	46		97			83				108
Broilers		50	100		100				38		100		100		102	
Broiler meat														111		
Meat (different sources)		74														
Water		19														

TABLE 7.15. Indicator *Escherichia coli*, number of isolates 2000-2015.

Source	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Cattle	293						314			223				197		101
Pigs	260	308		303		390		342	349			167				200
Pig meat									19			20				
Broilers	274	296	306		300			296			181		194		197	
Broiler meat											77		92			
Laying hens													61			
Turkeys														55	59	
Horses											274					
Dogs							257						74			
Willow grouse						19										
Wild boars		87														
Sheep									115							

TABLE 7.16. Indicator *Enterococcus faecalis* and *E. faecium*, number of isolates 2000-2015 *E. faecalis/E. faecium*.

Source	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Cattle	22/71						13/98			10/24				11/42		
Pigs	56/48	52/106		87/71		55/47			68/39			22/22				
Pig meat									17/3			29				
Broilers	24/151	49/204	57/189		48/163			28/197			35/136		44/136		27/187	
Broiler meat											81/17		78/10			
Laying hens													20/36			
Horses											34/27					
Dogs							135/29									
Wild boars		12/35														
Sheep									24/15							

TABLE 7.17. Clinical isolates from animals, number of isolates 2000-2015..

Animal species & bacterial species	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Cattle																
Escherichia coli (enteric)			220		87	39	24			40	15	15	58	30	29	36
Escherichia coli (uterine)														60		
Escherichia coli (udder)				169										142	95	113
Klebsiella spp. (udder)				44			24							41	39	41
Pasteurella spp.	254			100				27	32	14	27	80	37	39	39	46
Staphylococcus aureus (udder)		100	100			96			87						74	
Streptococcus dysgalactiae (udder)			100													
Streptococcus uberis (udder)			100													
Fusobacterium necrophorum										41						
Pigs																
Actinobacillus pleuropneumoniae	18							84	39	24	39	57	33	36	37	33
Brachyspira hyodysenteriae	50	75	109	100		31	26	23	15	24	9	7	7	8	7	7
Brachyspira pilosicoli				93		57	72	44	31	24	13	16	17	12	13	7
Escherichia coli (enteric)	399	82	340	340	386	325	298	93	83	102	94	91	74	142	118	84
Pasteurella spp.		75						38	25	24	10	17	24	95	19	7
Staphylococcus hyicus					20											
Streptococcus equisimilis												82				
Poultry (laying hens)																
Escherichia coli (infection)								70								
Sheep																
Staphylococcus aureus (udder)								25								30
Fusobacterium necrophorum										24						
Mannheimia haemolytica and *Bibersteinia trehalosi*															44	
Fish																
Aeromonas salmonicida subsp. *achrom.*								67	20	23	8	14	5	10	9	1
Flavobacterium columnare								30	16	10	5	8	3	5	9	4
Flavobacterium psychrophilum								42	27	24	21	27	31	23	61	31
Horses																
Actinobacillus spp.		40														
Escherichia coli (genital)	323	103	166	188	188	161	124	273	174	210	236	174	196	140	229	188
Rhodococcus equi	73	20			187											
Streptococcus zooepidemicus	301	174	163	150	185	175	174	180	159	152	43	131	140	123	129	82
Staphylococcus aureus										308	131	135	145	139	132	116
Dogs																
Escherichia coli (urinary)	185	183	204	234	247	304	366	425	503	599	803	661	407	840	943	1 112
Pasteurella canis															207	194
Pasteurella multocida					231										29	46
Pseudomonas aeruginosa				234						261	313	353	178	309	389	355
Staphylococcus pseudintermedius	145	156	133	102	159	126	89	220	258	381	444	388	229	566	513	393
Staphylococcus schleiferi															297	201
Cats																
Escherichia coli (urinary)			46	52	55	74	95	131	170	245	236	274	310	404	461	455
Beta-hemolytic streptococci												184				
Pasteurella dagmatis															20	22
Pasteurella multocida															244	340
Staphylococcus felis															244	227

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SWEDRES|SVARM 2015

This report describes the monitoring of antibiotic resistance and antibiotic usage in human and veterinary medicine.

The situation in Sweden regarding antibiotic resistance in bacteria from humans and animals is favourable when seen in an international perspective. This confirms that the Swedish strategies to promote rational use and to contain antibiotic resistance have been effective. The total sales of antibiotics in humans has continued to decrease and positive trends regarding choices of antibiotics have also continued in 2015. Downward trends are also noted for sales of antibiotics for animals. Key findings this year is a sharp increase in MRSA and an increase of $ESBL_{CARBA}$ in humans. The increase of MRSA is associated with the large number of refugees who have arrived 2015. The increase in $ESBL_{CARBA}$ is considered more worrying as it increases the risk of introduction of $ESBL_{CARBA}$ among vulnerable patients, such as in neonatal units, which can have serious consequences. The increase in MRSA has not led to increased spread of infection in hospitals and future risk of this is considered small. In the veterinary sector, MRSA is rare in both farm and companion animals, and $ESBL_{CARBA}$ has not been reported.

Focus areas:

- Swedish HALT study- diagnose linked antibiotic prescription data in long-term care facilities
- Next-generation sequencing as a tool for epidemiological and resistance investigations
- MRSA with *mecC* in wild hedgehogs
- A potential clone shift of methicillin-resistant *Staphylococcus pseudintermedius* from ST71 to ST258
- Sales of polymyxins and occurrence of the mcr-1 gene in bacteria from humans, animals and food in Sweden
- Standardization and surveillance of AST/AMR in humans in Sweden – from collecting strains to data mining. A thirty year experience
- Surveillance of antibiotic resistance in humans - uses, interpretation of data, and sources of bias
- SvarmPat – monitoring of resistance in pathogens from farm animals

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

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