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Consumption of antibiotics and occurrence of antibiotic resistance in Sweden

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

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Preface

The 2016 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. This report is a result of the successful collaboration between the public health and veterinary sectors in Sweden.

The very word "antibiotics" is almost a contradiction. It is derived from the Greek and means "against life". However, antibiotics make up a life-saving class of drugs and have shaped modern human and veterinary medicine. The life that the word refers to is the life of bacteria, and the power of these drugs lies in their ability to stop and eventually kill bacteria. However, we are slowly losing more and more ways to keep bacterial infections at bay due to antibiotic resistance, globally as well as in Sweden. It is therefore imperative that we not only monitor the development of antibiotic resistance and continue to develop the tools at hand, but also to follow the actual use of antibiotics.

In this joint report, we present the latest data on resistance and antibiotic use monitoring in Sweden. In addition to chapters focusing on either human or veterinary medicine, there is also an important chapter on comparative analysis. Only by working together, across various disciplines, will we have a chance to face the complex challenge that antibiotic-resistant bacteria pose. In addition to this, the key to long-term success is international collaboration. The United Nations, the World Health Organization, and the World Organization of Animal Health (OIE) have all presented actions plans and strategies for the joint battle against antibiotic resistance. This is also echoed by action plans and strategies presented by the Swedish government with broad support in the Swedish Parliament.

During 2016, the Unit for Antibiotics and Infection Control at the Public Health Agency of Sweden was a designated WHO Collaborating Centre for Antibiotic Resistance Containment. The activities of the Collaborating Centre include support for country-level capacity building to promote local and national use of surveillance data and to facilitate participation and implementation of the Global AMR Surveillance System (GLASS). We also acknowledge the initiative by the OIE to collect data on the global use of antibiotics in animals. These kinds of comparisons increase transparency and enable the international community to motivate more states to join the collaboration against antibiotic resistance and misuse of antibiotics.

The use of antibiotics in Swedish farm animals continues to be at a steady, low level. The first examples in Sweden of tiamulin-resistant *Brachyspira hyodysenteriae* have been identified in some pig production facilities. In contrast, no plasmid-borne colistin resistance genes have been found in either fresh or archived veterinary isolates. This demonstrates the usefulness of regular surveillance to understand the dynamics of resistance. To further strengthen the surveillance capacity in Sweden, a new laboratory network was formed by the National Veterinary Institute in collaboration with major veterinary clinics.

Antibiotic resistance is a consequence of the use and, more importantly, the misuse of antibiotics. Only through broad partnerships can we slow and hopefully prevent the rise of ever more dangerous multi-resistant bacteria.

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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.

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Thank you also to environmental departments in several municipalities 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. Antibiotikaanvändningen i Sverige har under de senaste årtiondena minskat inom både humanmedicin och veterinärmedicin. Dessutom har användningen av bredspektrumantibiotika minskat till fördel för antibiotika med smalare spektrum. 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 avtagande ökningstakt av MRSA jämfört med 2015, fler inhemska fall av $ESBL_{CARBA}$ bland Enterobacteriaceae hos människor och fortsatt minskande förekomst av Clostridum difficile infektion. Ökningen av $ESBL_{CARBA}$ bedöms som 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 risken för detta bedöms som liten även i framtiden. MRSA är ovanliga hos både lantbrukets djur och sällskapsdjur, och $ESBL_{CARBA}$ har inte påvisats.

Förbrukning av antibiotika

Antibiotikaförbrukning inom humanmedicin

Den totala antibiotikaförsäljningen (öppenvård och slutenvård) minskade med 1,6 procent (från 12,7 till 12,5 DDD per tusen invånare och dag) under 2016 jämfört med 2015.

Öppenvård

I öppenvården (inkluderar all antibiotika försålt på recept) minskade försäljningen med 1,6 procent, från 323 till 318 recept per tusen invånare och år. I barngrupperna (0-4 år och 5-14 år) ökade dock antibiotikaförsäljningen under 2016 med 4,4 respektive 2,1 procent. Ökningen i dessa åldersgrupper sågs under hela året, förutom under första kvartalet där försäljningen minskade något. I åldersgrupperna 15-64 år och 65 år och äldre fortsatte antibiotikaförsäljningen att minska likt föregående år.

Antibiotikaförsäljningen minskade i 13 av 21 län. Skillnaden mellan länen är stor: från 345 recept per tusen invånare och år i Stockholm till 252 i Västerbotten.

Minskningen omfattade de flesta antibiotikagrupper med undantag för pivmecillinam, betalaktamaskänsliga penicilliner, penicillin med klavulansyra, trimetoprim med sulfonamider och nitrofurantoin. Betalaktamaskänsliga penicilliner tillsammans med tetracykliner var de antibiotika som förskrevs mest på recept under 2016.

Antibiotika som ofta används mot luftvägsinfektioner är den grupp som försäljs mest på recept och det är inom denna grupp av antibiotika som den största minskningen över tid skett. Under 2016 ökade dock försäljningen med 1,3 procent.

Behandlingen av nedre urinvägsinfektioner (UVI) hos kvinnor ser ut att följa de nationella behandlingsrekommendationerna. Under 2016 minskade den totala försäljningen av UVI-antibiotika till kvinnor 18–79 år något (1,9 procent) jämfört med 2015. 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.

Positiva trender ses också när det gäller UVI-antibiotika till män 65 år och äldre. Den totala försäljningen av antibiotika som ofta används mot UVI till män 65 år och äldre minskade med 0,9 procent jämfört med 2015. Under 2016 fortsatte försäljningen av fluorokinoloner till denna grupp att minska med 3,1 procent jämfört med året innan medan försäljningen av pivmecillinam och nitrofurantoin ökade (8,3 respektive 3,6 procent).

Försäljningen av antibiotika som är förskrivet av tandläkare står för 6 procent av den totala antibiotikaförsäljningen på recept. Under 2016 minskade försäljningen med 3,0 procent jämfört med 2015, från 22,9 till 22,2 recept per tusen invånare och år (J01 inklusive metronidazol P01AB01).

Slutenvård

Den totala antibiotikaförbrukningen på svenska sjukhus minskade något under 2016 jämfört med 2015 (mätt som DDD per hundra vårddagar och DDD per hundra vårdtillfällen). Under de senaste åren har användningen av penicilliner med betalaktamashämmare och karbapenemer ökat kraftigt. Under 2016 fortsatte användningen av penicilliner med betalaktamashämmare att öka (12 procent) jämfört med året innan, försäljningen av karbapenemer minskade dock något för första gången på flera år under 2016. Att karbapenemer och piperacillin med tazobaktam används i större utsträckning än tidigare kan bero på att fler infektioner är orsakade av bakterier med ESBL (extended spectrum betalactamases). 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 och betalaktamaskänsliga penicilliner de antibiotikagrupper som försäljs mest på slutenvårdsrekvisition i Sverige.

Antibiotikaförbrukning inom veterinärmedicin

Den rapporterade försäljningen av antibiotika för djur uppgick 2016 till 10 543 kilogram varav 57 procent var bensylpenicillin. Motsvarande värden för 2007 var 17 106 kilogram och 44 procent bensylpenicillin.

Den totala försäljningen av antibiotika för djur har minskat med cirka två tredjedelar sedan 1986 då användningen av tillväxtbefrämjande antibiotika upphörde, korrigerat för att antalet av vissa djurarter har minskat över tid. Under 90-talet minskade användningen av antibiotika som läkemedel till hela djurgrupper, och under det senaste decenniet ses också en minskad användning av antibiotika för behandling av enstaka djur.

Jämförelse av försäljning inom human- och veterinärmedicin

Under 2016 såldes 62,1 respektive 10,4 ton antibiotika för allmänbehandling inom human- och veterinärmedicin. Mätt som milligram aktiv substans per skattad kilogram biomassa var förbrukningen 93,8 respektive 13,4 milligram per kilogram. Försäljning inom humanmedicin dominerade för alla antibiotikaklasser utom trimetoprim-sulfa och aminoglykosider.

Under 2016 såldes 362 antibiotikaförpackningar per tusen människor jämfört med 263 förpackningar per tusen hundar (öppenvård). Förskrivningsmönstret för människa och hund är olika. Inom humansjukvården dominerar vanligt penicillin och penicillinasstabila penicilliner, men inom hundsjukvården förskrivs mest aminopenicilliner med eller utan klavulansyra.

Anmälningspliktig resistens

ESBL-producerande Enterobacteriaceae

År 2016 rapporterades totalt 10 659 fall av Enterobacteriaceae med betalaktamaser med utvidgat spektrum (ESBL) hos människa, vilket var en ökning med 11 procent jämfört med året innan. Ökningen sågs i 15 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 2016 anmäldes 609 fall av invasiva infektioner med ESBL-producerande bakterier, jämfört med 578 året innan.

ESBL-typen $ESBL_{CARBA}$ innebär även resistens mot karbapenemer, och Enterobacteriaceae med denna resistens blev under 2012 anmälningspliktiga för både den behandlande läkaren och laboratoriet som gör fyndet. Totalt 126 nya fall upptäcktes 2016 (115 fall 2015), och de två vanligaste enzymtyperna var OXA-48 och NDM. Under året har två anhopningar av E. coli med NDM-5 med totalt 12 fall påvisats med helgenomsekvensering. Flera av fallen är inhemska och i flertalet fall saknas epidemiologiska kopplingar mellan fallen. Dessa extremt resistenta bakterier är hittills ovanliga i Sverige men det är mycket viktigt att upptäcka dem tidigt och förebygga 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 2016 undersöktes förekomsten av ESBL-bildande E. coli i tarm- och köttprov från slaktkyckling samt i tarmprov från kalkon med selektiva metoder. Sådana bakterier hittades i 42 procent av tarmproven från slaktkyckling och i 44 procent av köttproven med svenskt ursprung. Förekomsten i tarmprov är jämförbar med föregående år. Det är dock svårt att göra direkta jämförelser längre bak i tiden samt för förekomst i kött på grund av förändringar i odlingsmetoderna. För första gången i Svarm hittades även ESBL-bildande E. coli i ett av tarmproven från kalkon (1 procent).

MRSA

Totalt anmäldes 4 402 nya fall av meticillinresistenta Staphylococcus aureus (MRSA) hos människa 2016, vilket är en ökning med 13 procent från året innan. Det innebär att ökningstakten för MRSA avtog under året. Den kraftiga ökningen 2015 berodde på det stora antalet asylsökande som togs emot, varav många kom från länder med en högre förekomst av MRSA än genomsnittet i Sverige. Provtagningen i den gruppen är också större än i den övriga befolkningen eftersom de har fler kontakter med sjukvården.

En majoritet av alla MRSA-fall var smittade utomlands. Samhällsförvärvad smitta var vanligare bland de inhemskt smittade fallen (76 procent) än bland de utomlands smittade (58 procent), medan sjukhusförvärvad smitta var vanligare bland importerade fall (16 procent) än bland inhemska (4,6 procent). Invasiva infektioner med MRSA rapporterades hos 44 personer under 2016.

Förekomsten av MRSA hos djur i Sverige är fortfarande låg, vilket begränsar risken för spridning till människor. Under året isolerades MRSA sporadiskt från djurslagen hund och katt. MRSA med *mecC* påvisades hos ett flertal getter och får i ett utbrott i en djurpark. 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 2016 var antalet anmälda fall av meticillinresistenta Staphylococcus pseudintermedius (MRSP) hos djur på samma nivå som 2015. Totalt anmäldes 55 fall av MRSP, vilket kan jämföras med 60 fall 2015 och 39 fall 2014. Antalet fall har länge varit kopplat till framför allt en specifik klon, den så kallade ST71-t02- SCCmecII-III, och denna variant är fortfarande vanligt förekommande. Dock har läget blivit mer varierande med flera olika genotyper detekterade i Sverige. Noterbart är att endast 9 procent av fallen var kopplade till ST258 som utgjorde 33 procent av alla fallen 2015, samt att en ny variant, ST551, var kopplad till 11 procent av fallen.

MRSP är inte anmälningspliktig vid förekomst hos människa.

PNSP

År 2016 anmäldes 67 fall hos människa, varav 2 fall var invasiva, jämfört med 2015 då 59 fall av Streptococcus pneumoniae med nedsatt känslighet för penicillin (PNSP) anmäldes. Antalet fall per år är betydligt lägre efter 2012, då gränsen för vilka fall som skulle rapporteras höjdes.

VRE

År 2016 anmäldes 165 nya fall av vankomycinresistenta enterokocker (VRE) hos människa, och 2015 anmäldes 157 fall. Enterococcus faecium med vanA-gen (126 fall) var vanligare än vanB-genen (24 fall). Inga stora spridningar på sjukhus förekom under 2016. Under år med stora spridningar på sjukhus har vanB-genen dominerat. Ett invasivt isolat av VRE rapporterades 2016.

Resistens hos zoonotiska smittämnen

Salmonella är ovanligt hos djur i Sverige och isolerade stammar är oftast känsliga för antibiotika. Överförbar resistens mot tredje generationens cefalosporiner har aldrig påvisats hos isolat från djur i Sverige, och resistens mot antibiotikagruppen fluorokinoloner är mycket ovanlig. Salmonella från svenska djur är en osannolik källa till invasiva infektioner hos människor. För det första rör det sig vanligen om olika typer av stammar, och för det andra är kinolonresistens vanlig hos dessa humana isolat till skillnad från isolat från djur.

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

Vanligtvis behandlas inte infektioner som orsakas 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 ” Comparative analysis” för respektive bakterie.

Resistens hos kliniska isolat från människor

I årets Swedres-Svarm sammanställs data från kliniska odlingar från Svebar. Det är ett system som automatiskt samlar in alla odlingsresultat från de 15 laboratorier som deltar. Till skillnad från tidigare års data kommer nu upprepade resultat från samma individ att räknas med. Det kommer medföra vissa skillnader i resistensnivå, särskilt för bakteriearter med litet antal isolat och för ovanliga resistenstyper.

Följande resultat gäller invasiva isolat från EARS-Net. Resistensnivåerna gällande kliniska isolat i ResNet var generellt något lägre. Hos E. coli och K. pneumoniae har andelen cefalosporinresistenta (till största delen orsakad av ESBL-produktion) isolat ökat varje år och uppgick till ca 7,8 respektive 4 procent 2016. Andelen MRSA av ca 2 700 rapporterade fall av S. aureus var 2,3 procent, vilket är lågt ur ett europeiskt perspektiv. För E. faecium var andelen resistenta mot vankomycin 0,4 procent. Andelen PNSP av de cirka 1400 testade isolaten av S. pneumoniae var ca 7 procent.

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

Under 2016 rapporterades 6613 nya fall av C. difficile infektion, vilket motsvarar en incidens av 66 fall per 100 000 invånare och år. Det är en fortsatt minskning med 8 % jämfört med 2015.

Inga isolat med resistens mot metronidazol eller vankomycin hittades 2016.

Under 2016 anmäldes 1778 fall av gonorré. Andelen med resistens mot cefixim var 1 procent och ingen resistens mot ceftriaxon påvisades. Det är mycket positivt eftersom ceftriaxon 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 i tarmfloran hos friska djur kan användas som indikator för utbredningen av antibiotikaresistens hos bakteriefloran i en djurpopulation och indirekt som indikator 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 ur ett internationellt perspektiv.

Summary

The situation in Sweden regarding antibiotic resistance in bacteria from humans and animals is still favourable from an international perspective. This confirms that our strategies to promote the rational use of antibiotics and to limit the spread of antibiotic resistance are effective. In the last decades the consumption of antibiotics in Sweden has decreased in both human and veterinary medicine. In addition, the sales of broad-spectrum antibiotics have decreased while the use of narrow-spectrum antibiotics has increased. Despite this, most of the monitored types of antibiotic resistance have continued to increase since national surveillance began in the late 1990s.

The key findings in this year's report are a lower rate of increase for methicillin-resistant *Staphylococcus aureus* (MRSA) compared to the previous year, an increasing number of community-acquired cases of carbapenemase-producing Enterobacteriaceae ($ESBL_{CARBA}$) in humans, and a continuing decrease in the occurrence of *Clostridium difficile* infections. The increase in $ESBL_{CARBA}$ is considered worrying because it increases the risk of introducing $ESBL_{CARBA}$ among vulnerable patients, such as infants in neonatal units, which can have serious consequences. The increase in MRSA has not led to an increased spread of infection in hospitals, and future risk of such spread 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 1.6% in 2016 compared to 2015 (from 12.7 to 12.5 DDD per 1 000 inhabitants and day).

Outpatient care

In outpatient care (including prescription sales), antibiotic sales decreased by 1.6% from 323 prescriptions per 1 000 inhabitants in 2015 to 318 prescriptions in 2016. However, in the age groups 0–4 years and 5–14 years the sales increased by 4.4% and 2.1%, respectively. The increase was seen during the whole year, except from the first quarter (January–March) when the sales slightly decreased. In the age groups 15–64 years and 65 years and older the sales continued to decrease as in previous years.

In 2016, there was a decrease in the number of antibiotic prescriptions in 13 out of Sweden's 21 counties. There are still significant regional differences within Sweden, and the number of prescriptions per 1 000 inhabitants ranges from 345 in Stockholm County to 252 in Västerbotten County.

The decrease encompasses most antibiotic groups with the exception of pivmecillinam, beta-lactamase-sensitive penicillins, penicillins combined with beta-lactamase inhibitors, trimethoprim with sulfonamides, and nitrofurantoin.

Beta-lactamase-sensitive penicillins, along with tetracyclines, were the most commonly used antibiotics in outpatient care in 2016. Antibiotics commonly used to treat respiratory tract infections were the most frequently prescribed antibiotics. Among these substances, we have observed the greatest decrease in sales over the years. However, in 2016 the sales of these drugs increased by 1.3%.

Treatment of lower urinary tract infections (UTIs) in women appears to be following national treatment recommendations. In 2016, the total sale of antibiotics commonly used to treat UTIs in women aged 18–79 years decreased by 1.9% compared to 2015. There was increased use of the recommended drugs pivmecillinam and nitrofurantoin and reduced use of trimethoprim and fluoroquinolones.

Positive trends are also seen when it comes to UTI antibiotics to men. The total sales of antibiotics commonly used to treat UTIs in men 65 years and older decreased by 0.9% compared to 2015. In 2016, the sales of fluoroquinolones decreased by 3.1% compared to 2015, while the sales of pivmecillinam and nitrofurantoin increased by 8.3% and 3.6% (measured as prescriptions per 1 000 men and year), respectively.

Dentists account for approximately 6% of all antibiotics prescribed in outpatient care in Sweden. The sales of J01 and metronidazole (P01AB01) prescribed by dentists decreased by 3.0% in 2016 compared to 2015 – from 22.9 to 22.2 prescriptions per 1 000 inhabitants.

Hospital care

The total consumption of antibiotics in Swedish acute care hospitals was slightly lower in 2016 compared to 2015, measured as both DDD per 100 patient days and as DDD per 100 admissions. The use of penicillins with enzyme inhibitors and carbapenems has increased significantly in recent years. In 2016 the consumption of penicillins with enzyme inhibitors continued to increase by 12% when measured as DDD per 100 patient-days compared to 2015. Although, the consumption of carbapenems decreased for the first time in many years in 2016 compared to 2015. These two agents have to a large extent replaced cephalosporins in many situations. The increase of these two substances is probably a result of an increased number of infections with ESBL-producing bacteria. When analysing the total antibiotic sales on requisition (consumption in all hospitals, including parts of nursing homes and other care units) from 2000 to 2016, a clear shift from high use of broad-spectrum antibiotics to narrow-spectrum antibiotics can be seen.

Sales of antibiotics for animals

In 2016, reported sales of antibiotics for animals were 10 543 kg, of which 57% were for benzylpenicillin. The corresponding figures for 2007 were 17 106 kg and 44%, respectively.

Since the withdrawal of growth-promoting antibiotics from the market in 1986, the total sales of antibiotics have decreased by two thirds when corrected for different population sizes over time. During the 1990s, sales of veterinary products for medication of groups of animals decreased, and in the past decade there has also been a decrease in sales of products for use in individual animals.

Comparing consumption of antibiotics in human and veterinary medicine

In 2016, a total of 62.1 tonnes of antibiotics were sold for human use and 10.4 tonnes were sold for animal use. Measured as milligrams of active substance per kilogram biomass, the consumption was 93.8 and 13.4 milligrams per kilogram, respectively. Consumption by humans still dominates for all classes of antibiotics except for trimethoprim-sulphonamides and aminoglycosides.

In 2016, the consumption of antibiotics by humans in outpatient care was 362 packages per 1 000 individuals. The corresponding figure for dogs was 263 packages per 1 000 individuals. The consumption pattern was also different. In outpatient care of humans, simple penicillins and penicillinase-stable penicillins dominated, while for dogs aminopenicillins with or without clavulanic acid were the most prescribed.

Notifiable resistance

ESBL

A total of 10 659 human cases of extended spectrum beta-lactamase (ESBL)- producing Enterobacteriaceae were reported in 2016, an increase of 11% compared to 2015, and increases occurred in 15 of Sweden's 21 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. Invasive infections with ESBL-producing bacteria increased from 578 cases in 2015 to 609 cases in 2016.

A special type of ESBLs, so-called $ESBL_{CARBA}$, confers resistance to carbapenems as well as other classes of betalactam antibiotics. Bacteria with this extended resistance mechanism became notifiable for both clinicians and laboratories in 2012. A total of 126 new cases were detected in 2016 compared to 115 cases 2015, and the two most common types of enzymes were OXA-48 and NDM. During the year, two clusters involving a total 12 cases of *E. coli* with NDM-5 were identified using whole-genome typing. Several of these cases were domestically acquired, but for the majority of cases epidemiological data linking cases are missing. Because the treatment alternatives for these infections are few if any, it is necessary to undertake active surveillance of these new and extremely resistant bacteria in order to detect them at an early stage and thereby prevent their spread within the health care system.

ESBL-producing Enterobacteriaceae are, with the exception of broilers, rare among animals in Sweden. In 2016, the occurrence of ESBL-producing *E. coli* in intestinal and meat samples from broilers and from intestinal samples from turkeys was investigated with screening methods. Such bacteria were isolated from 42% of the intestinal samples and 44% of the meat samples from broilers of Swedish origin. The occurrence in intestinal samples from broilers was comparable with 2015. Changes in the screening methodology prevent any direct comparisons with the figures from previous years and for the occurrence in meat. For the first time in Svarm, ESBL-producing *E. coli* was also detected in one (1%) of the intestinal samples from turkeys.

MRSA

The total number of reported human cases of MRSA was 4 402 in 2016, an increase of 13% compared to 2015. The rate of increase was lower than the previous year. The increase seen during 2015 was mainly comprised of cases among persons seeking asylum and was likely due to higher prevalence, increased need for medical care, and increased sampling in this group.

The majority of the MRSA infections were acquired abroad. Community-acquired infections dominated among domestic cases (76%) but were less frequent among imported cases (58%). Hospital-acquired infections were comparatively more common in imported cases (16%) than among domestic cases (4.6%). Forty-four invasive isolates of MRSA were reported in 2016.

The occurrence of MRSA in animals in Sweden is still low, which limits the spread from animals to humans. MRSA was found sporadically in dogs and cats in 2016, and MRSA with *mecC* was detected in samples from several goats and sheep in an outbreak at a zoo. 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.

MRSP

In 2016, the number of notified cases of methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) was on the same level as 2015. In total, 55 cases were notified in 2016, which can be compared to 60 cases in 2015 and 39 cases in 2014. All cases except two were related to dogs. The picture of MRSP is becoming more diverse compared to earlier years, although the ST71-t02-SCCmecII-III lineage is still common. The emerging clone ST258 only constituted 9% of cases in 2016 compared to 33% of notified cases in 2015. Furthermore, a new MLST variant, ST551, was identified in 11% of cases in 2016. MRSP in humans is not notifiable.

PNSP

Sixty-seven cases of pneumococci with reduced susceptibility to penicillin (PNSP, defined as MIC > 1 mg/L) were reported in humans in 2016, and in 2015 there were 59 reported cases. Two invasive cases were reported.

VRE

In 2016, a total of 165 new cases of vancomycin-resistant enterococci (VRE) were reported in humans compared to 157 cases in 2015. *Enterococcus faecium* carrying the resistance gene *vanA* (126 cases) was more common than those carrying *vanB* (24 cases). In 2016 there were no large hospital outbreaks reported. During years with large hospital outbreaks, *vanB* has been the most common resistance gene.

One invasive VRE infection was reported in 2016.

Zoonotic pathogens

Salmonella is rare in animals in Sweden, and few incidents involve antibiotic-resistant strains. Strains with ESBL resistance have never been found in isolates from animals in Sweden, 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 resistance to erythromycin, for example, 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 of isolates are tested for susceptibility, and most of these are related to serious infections. See the "Comparative analysis" section of each bacterium.

Human clinical isolates

In this Swedres-Svarm report all data on clinical isolates from humans have been collected through Svebar. This is an automated system that collects all culture results from participating laboratories. Currently 15 laboratories deliver data to Svebar. In contrast to previous years, the data for this year will contain all culture results from different individuals, e.g. duplicate findings from blood cultures. This will result in some differences in resistance levels, especially for species isolated less frequently and for unusual resistance types.

The following results are for invasive isolates from EARS-Net. In general the level of resistance was lower for clinical isolates reported to ResNet. In *E. coli* and *K. pneumoniae*, the levels of resistance to third-generation cephalosporins has increased continually, and is now approximately 8% and 4%, respectively. MRSA isolates accounted for 2.3% of invasive *S. aureus*, which is low from a European perspective. For *Enterococcus faecium* the rate of vancomycin resistance was 0.4 %. The rate of non-susceptibility to penicillins in *Streptococcus pneumoniae* (referred to as PNSP) was 7% in 2016.

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

In 2016, 6 613 new CDI cases were reported corresponding to an incidence of 66 cases per 100 000 inhabitants, a continued reduction of 8% compared with 2015.

No isolates with a decreased susceptibility against metronidazole or vancomycin were found in 2016.

In 2016, 1 778 cases of gonorrhea were reported. Resistance to cefixime was 1%, and no resistance to ceftriaxone was detected. This is a very positive result because ceftriaxone is the last available agent for the 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 benzylpenicillin, but penicillin resistance is common in *Staphylococcus pseudintermedius* from dogs and occurs in *S. aureus* from horses and *Staphylococcus felis* from cats. Resistance in *E. coli* occurs in all animals but is most prominent in enteric isolates from young calves. Susceptibility testing for guidance in antibiotic therapy is warranted, especially for staphylococci and *E. coli*.

Indicator bacteria from healthy animals

Antibiotic resistance in *E. coli* from the intestinal flora of healthy animals serves as an indicator for the presence of resistance in an animal population. The prevalence of acquired resistance in such commensal bacteria also indirectly indicates the magnitude of the selective pressure from the use of antibiotics in an animal population. The prevalence of resistance in indicator bacteria from animals in Sweden is low, and the situation is favourable in an international perspective.

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 data, material, methods and references.

Embedded files in the PDF-file version of the report

The data from many of the tables and figures in Swedres-Svarm can be accessed from embedded Excel-files. To access the embedded files, indicated with paperclips, we recommend using Adobe Acrobat Reader.

Antibiotic consumption

Antibiotics 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.

Data regarding antibiotic consumption in long-term care facilities are originated from a national point prevalence survey called Swedish HALT. The survey is an annual survey performed during week 46-47. All antibiotic treatments on the day of the survey were recorded.

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). Results 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.

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

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*)
LSS	The law regulating support and service to persons with certain functional disabilities
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	*Staphylococcus aureus* protein A gene
SSTI	Skin and soft tissue infection
ST	Sequence type
Strama	Swedish strategic programme against antibiotic resistance
Svarm	Swedish antibiotic resistance monitoring
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 in humans

Total consumption of antibiotics

In 2016, the total consumption of antibiotics (J01 excl. methenamine) in Sweden (outpatient care and hospital care) decreased by 1.6% compared with 2015 (12.7 to 12.5 DDD per 1 000 inhabitants and day). The total consumption differs within the country, from 14.0 per 1 000 inhabitants and day in Uppsala County to 10.4 in Jämtland County. The overall consumption in Sweden has decreased by 13.7% since 2000, from 14.5 to 12.5 DDD per 1 000 inhabitants and day, Figure 1.1.

Eighty-seven percent of all antibiotic consumption in Sweden 2016 were sold on prescriptions in outpatient care.

Beta-lactamase sensitive penicillins and tetracyclines were the two most used antibiotic classes in Sweden during 2016, 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, 2000-2016, DDD/1 000 inhabitants and day. The data are sorted according to the consumption in 2016.

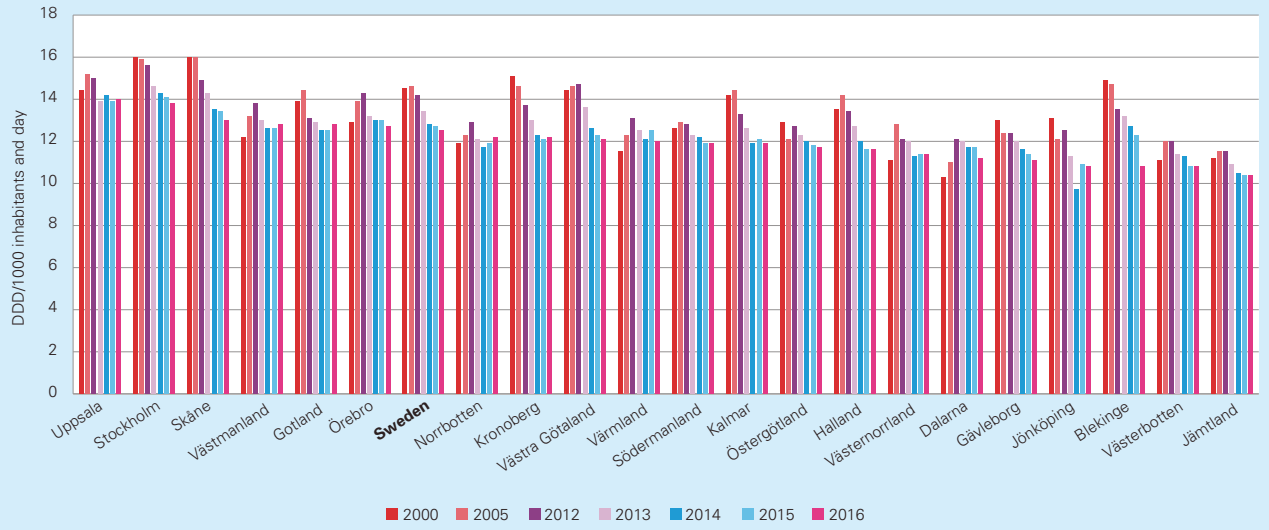
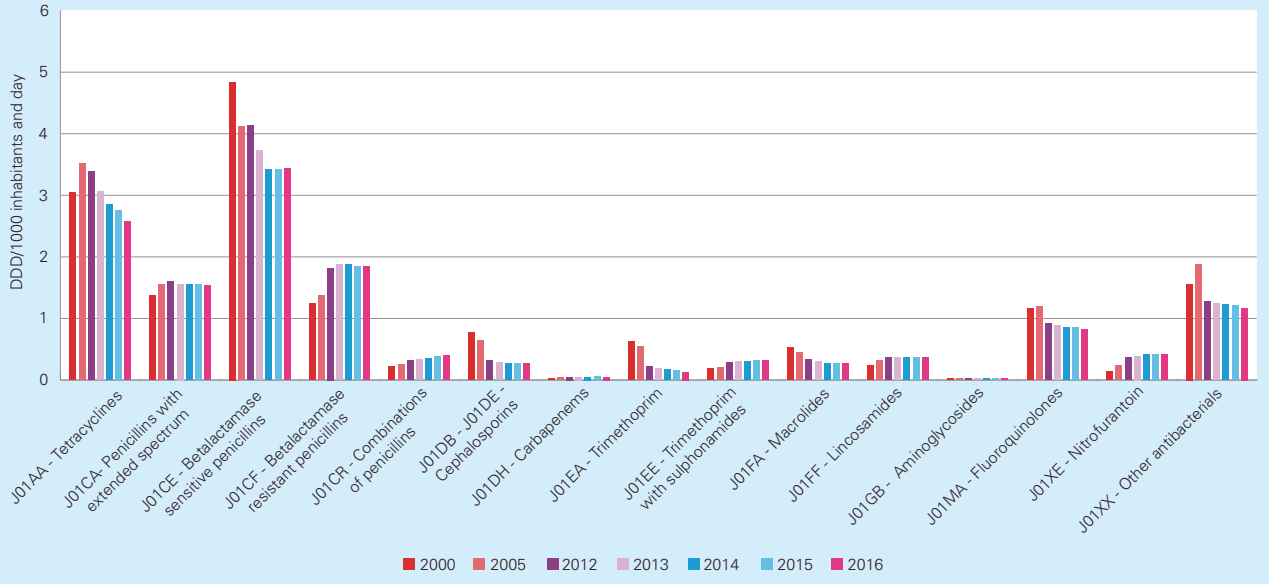


FIGURE 1.2. Antibiotics (ATC-5) in outpatient care (sales on prescriptions) and hospital care (sales on requisition including hospitals and parts of nursing homes) in 2000-2016, DDD/1 000 inhabitants and day. The data are sorted according to ATC codes.



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. About 64% out of all antibiotic sold on prescriptions in Sweden 2016 were prescribed in primary health care (including private and public healthcare centers).

The total sales of antibiotics in outpatient care has continued to decrease (1.6%) in 2016, from 323 in 2015 to 318 prescriptions per 1 000 inhabitants and year. In the age groups 0-4 years and 5-14 years, the antibiotic sales increased by 4.4% respectively 2.1% during the last year (read more about the increase in the chapter Antibiotic consumption in children). In the age groups 15-64 years and 65 years and older, the sales continued to decrease (2.7% respectively 3.0%), Figure 1.3.

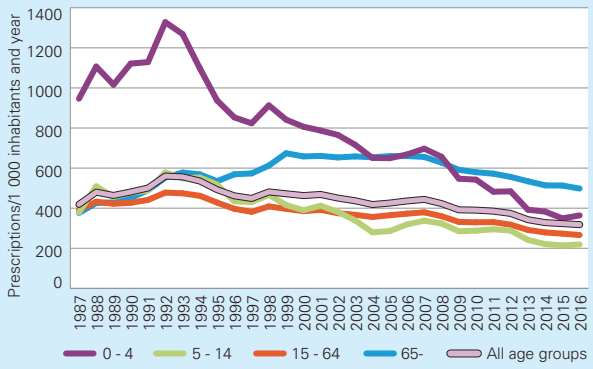
Since 1992, the total sales of antibiotics on prescriptions has decreased by 43%. The greatest decrease during these years has been in the 0-4 years age group, where sales decreased by 73%, from 1 328 in 1992 to 364 prescriptions per 1 000 children and year in 2016. In addition, less seasonal variation in sales of antibiotics is seen over the years. This 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 2016 encompasses most antibiotic groups with the exception of pivmecillinam (J01CA08), beta-lactamase sensitive penicillins (J01CE), penicillins combined with beta-lactamase inhibitors (J01CR), trimethoprim with sulphonamides (J01EE) and nitrofurantoin (J01XE), Figure 1.4.

Beta-lactamase sensitive penicillins (J01CE) and tetracyclines (J01AA) were the most commonly sold antibiotics in 2016, Figure 1.4 and Table 1.1. Doxycycline (J01AA02) is the most frequently sold tetracycline and represents 72% of the sales in this group as measured by prescriptions per 1 000 inhabitants and year.

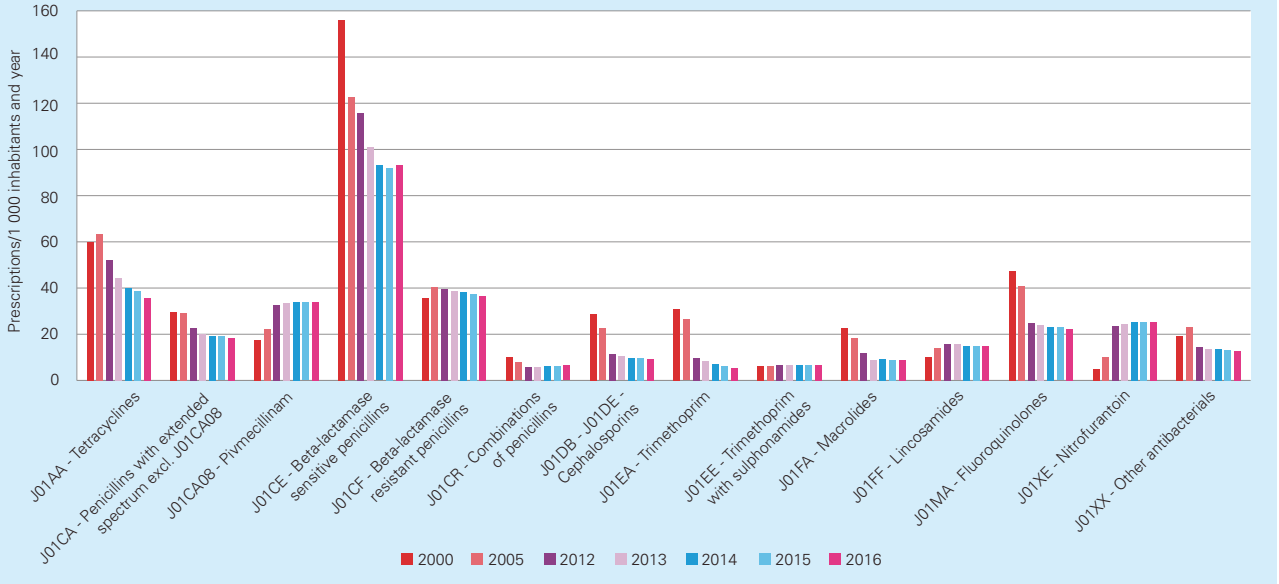
FIGURE 1.3. The sales of antibiotics for systemic use in out-patient care (sales on prescriptions) 1987- 2016, prescriptions/1 000 inhabitants and year, both sexes, different age groups.



Gender differences

Out of all antibiotics prescribed in Sweden during 2016, 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 2016, the antibiotic sales decreased by 2.0% to men and 1.7% to women. The greatest differences between genders occurred in the age groups 20-34 years (20-

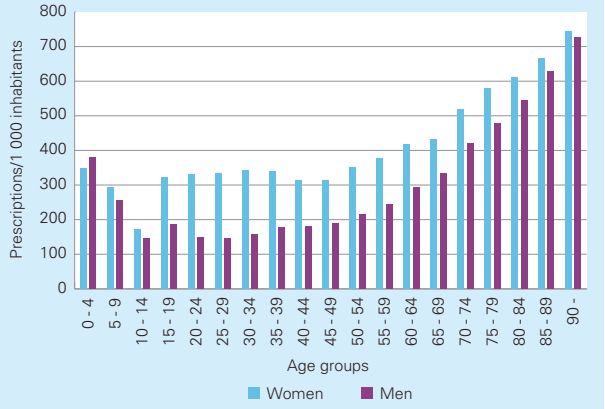
FIGURE 1.4. Sales of antibiotics in outpatient care (includes sales on prescriptions) 2000-2016, prescriptions/1 000 inhabitants and year, both sexes, all ages. The data are sorted according to ATC codes.



24, 25-29 and 30-34). In these age groups 68-70% of the total antibiotic sales were to women, Figure 1.5. In these age groups the main differences is among antibiotics commonly used to treat urinary tract infections (UTI) which are predominantly sold to women.

In 2016, women were prescribed 375 antibiotic prescriptions/1 000 inhabitants and year while men were prescribed 250.

FIGURE 1.5. The sales of antibiotics for systemic use in out-patient care (sales on prescriptions) in 2016, prescriptions/1 000 inhabitants and year, gender and different age groups.

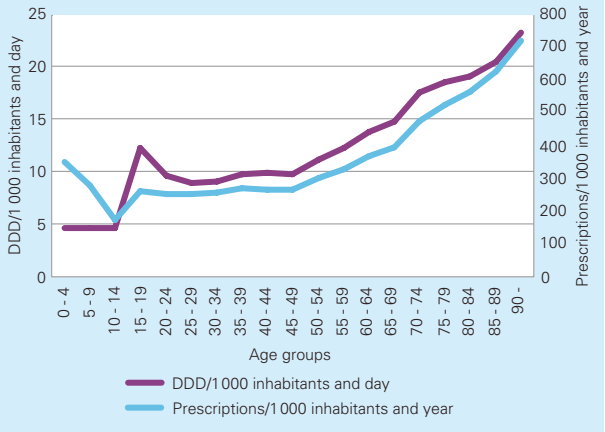


Antibiotics commonly used to treat respiratory tract infections, urinary tract infections and skin and soft tissue infections

Antibiotic sales in different age groups

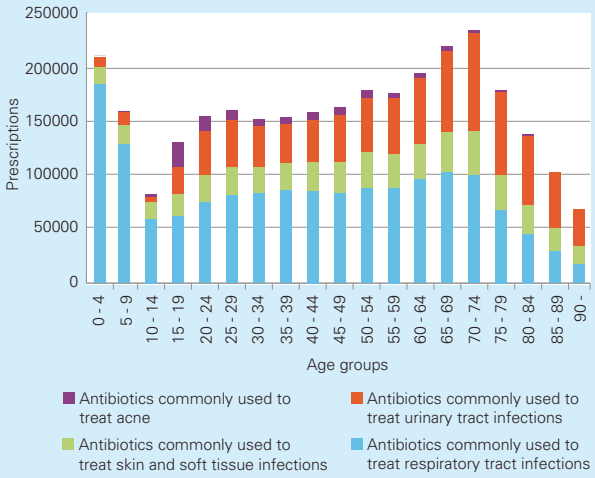
The antibiotic use is greatest in the age group 65 years and older, both as measured by prescriptions/1 000 inhabitants and year and by DDD/1 000 inhabitants and day, Figure 1.6. However, even though the antibiotic use is high among children and elderly, other age groups represent a significant share 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 2016.



In children, antibiotics commonly used to treat respiratory tract infections (RTI) are the most frequently prescribed antibiotics and represents 88% 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, Figure 1.7. 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 RTI, UTI, SSTI and Acne, both sexes, different age groups, prescriptions in 2016.



Antibiotics commonly used to treat RTI=J01AA02[a], J01CE02, J01CA04, J01CR02, J01DB-DE and J01FA. Antibiotics commonly used to treat UTI=J01CA08, J01EA01, J01MA02, J01MA06 and J01XE01. Antibiotics commonly used to treat SSTI=J01FF01 and J01CF05. Antibiotics commonly used to treat acne=J01AA02[b], J01AA04, J01AA06 and J01AA07.

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

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 161 in 2016. Although, in 2016 the sales of these substances increased with 1.3%. The Increase encompasses penicillin V (1.3%) and amoxicillin with clavulanic acid (4%).

Narrow spectrum penicillin, penicillin V, is the recommended first line antibiotic for treatment of community acquired RTI in Sweden (Medical Products Agency & Strama, 2008) and is the most frequently prescribed antibiotic in outpatient care, Figure 1.8. and Table 1.1.

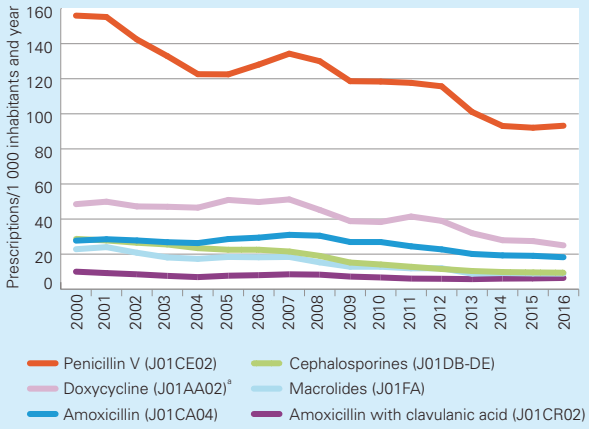
Tetracyclines are the second most frequently prescribed antibiotics in outpatient care. The sales of tetracyclines commonly used to treat respiratory tract infections (packages containing less than 50 tablets) continued to decrease in 2016 compared to 2015 (9%). The decrease in sales of doxycycline seen during the last four years may indicate an

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				
	2012	2013	2014	2015	2016	2012	2013	2014	2015	2016	2012	2013	2014	2015	2016
Tetracyclines (J01AA)															
0-6	0.00	0.00	0.00	0.00	0.00	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.1
7-19	3.29	3.06	2.82	1.99	2.09	31.2	27.6	25.1	17.4	17.6	19.6	16.8	15.5	14.6	14.8
20-64	3.43	3.10	2.92	2.78	2.55	56.5	47.7	43.1	41.4	37.5	43.8	36.4	32.9	31.6	29.1
65-79	3.75	3.36	3.06	3.02	2.78	80.0	68.9	60.4	59.9	54.3	61.3	52.5	46.2	44.9	41.6
80-	2.41	2.15	1.97	2.06	1.90	59.8	52.5	45.7	48.0	43.8	47.7	41.9	36.3	38.4	35.2
All age groups	3.15	2.85	2.66	2.55	2.40	52.0	44.4	39.8	38.7	35.6	39.2	33.1	29.8	28.8	26.8
Penicillins with extended spectrum (J01CA) excl. Pivmecillinam (J01CA08)															
0-6	1.32	1.07	1.08	1.04	1.06	54.9	43.8	43.7	42.3	42.6	42.1	33.6	33.5	30.3	30.2
7-19	0.37	0.32	0.31	0.32	0.32	10.1	8.5	8.2	8.5	8.4	8.3	6.9	6.7	6.4	6.4
20-64	0.64	0.59	0.56	0.55	0.53	15.4	13.9	13.2	13.1	12.2	12.6	11.2	10.5	10.2	9.6
65-79	1.55	1.50	1.44	1.45	1.42	37.0	34.3	32.4	32.6	31.1	29.2	26.8	25.2	24.6	23.9
80-	1.77	1.73	1.71	1.81	1.75	39.7	37.7	36.8	38.1	36.2	32.3	30.4	29.4	30.1	28.7
All age groups	0.85	0.79	0.76	0.76	0.74	22.7	20.1	19.3	19.0	18.2	17.7	15.6	15.0	14.5	13.9
Pivmecillinam (J01CA08)															
0-6	0.01	0.01	0.01	0.01	0.01	1.0	1.0	1.0	0.8	1.0	0.9	0.9	1.0	1.0	1.1
7-19	0.21	0.20	0.20	0.13	0.14	14.4	13.8	13.4	9.2	9.4	12.5	12.0	11.7	10.9	11.1
20-64	0.44	0.46	0.48	0.47	0.47	28.7	29.5	29.8	29.4	29.5	23.8	24.3	24.6	24.1	24.3
65-79	0.93	0.98	1.00	1.01	1.02	57.3	59.3	59.5	59.4	59.1	42.8	44.0	44.2	43.1	43.7
80-	1.75	1.83	1.92	1.91	1.94	109.3	112.3	114.7	114.1	114.2	78.4	80.5	82.1	81.4	81.6
All age groups	0.51	0.53	0.55	0.55	0.56	32.8	33.7	34.0	33.7	33.8	25.7	26.3	26.5	26.0	26.2
Beta-lactamase sensitive penicillins (J01CE)															
0-6	3.78	3.07	2.82	2.54	2.86	285.9	226.3	211.5	196.1	211.8	205.6	169.8	159.2	146.4	155.7
7-19	3.47	2.92	2.66	2.48	2.59	124.1	103.6	94.0	94.7	98.7	99.1	83.9	75.7	73.3	77.0
20-64	3.95	3.55	3.24	3.22	3.19	95.1	84.8	77.6	77.2	76.5	81.4	72.7	66.2	65.3	65.2
65-79	3.96	3.86	3.58	3.62	3.51	93.9	89.9	83.4	84.4	81.4	80.3	76.4	70.4	69.5	68.1
80-	3.34	3.24	3.07	3.17	3.05	81.0	78.3	73.9	76.7	73.4	69.6	67.4	63.3	65.1	62.3
All age groups	3.88	3.49	3.21	3.19	3.20	115.7	101.1	93.1	92.1	93.2	93.5	82.7	75.8	73.9	74.8
Beta-lactamase resistant penicillins (J01CF)															
0-6	0.29	0.26	0.26	0.23	0.23	29.0	26.1	26.2	24.4	23.6	22.9	20.4	20.6	19.5	19.0
7-19	0.77	0.78	0.77	0.68	0.67	28.5	27.8	27.4	25.6	24.7	23.1	22.6	22.2	20.9	20.4
20-64	1.27	1.31	1.30	1.26	1.25	33.0	32.2	32.1	30.8	30.3	26.3	25.6	25.5	24.3	24.1
65-79	2.67	2.77	2.74	2.69	2.64	58.1	57.1	56.2	54.9	53.4	38.6	38.1	37.3	35.4	35.4
80-	4.85	5.11	5.18	5.22	5.26	103.2	103.2	102.6	101.6	100.4	63.2	63.4	62.8	61.2	61.2
All age groups	1.51	1.56	1.56	1.54	1.53	39.5	38.7	38.5	37.4	36.7	29.2	28.5	28.2	26.9	26.7
Combinations of penicillins (J01CR)															
0-6	0.26	0.21	0.21	0.18	0.18	16.7	13.9	13.5	12.0	12.0	11.1	8.8	8.3	7.2	6.9
7-19	0.14	0.14	0.14	0.14	0.15	4.0	3.9	4.0	4.2	4.3	3.0	2.8	2.7	2.7	2.7
20-64	0.22	0.22	0.24	0.25	0.25	4.7	4.7	5.0	5.1	5.3	3.9	3.9	4.0	4.1	4.3
65-79	0.34	0.34	0.37	0.40	0.44	6.7	6.8	7.5	8.2	8.8	5.1	5.2	5.6	6.0	6.4
80-	0.29	0.32	0.35	0.39	0.44	5.8	6.2	6.7	7.6	8.8	4.3	4.6	5.0	5.8	6.5
All age groups	0.23	0.23	0.25	0.26	0.27	6.0	5.8	6.1	6.2	6.5	4.6	4.4	4.5	4.5	4.7
Cephalosporins (J01DB-DE)															
0-6	0.32	0.27	0.27	0.24	0.24	29.2	25.7	26.9	25.1	24.7	24.1	21.2	22.2	20.7	20.0
7-19	0.16	0.15	0.13	0.13	0.13	11.6	10.4	9.3	9.5	9.5	9.6	8.5	7.6	7.2	7.1
20-64	0.14	0.12	0.11	0.11	0.11	8.2	7.3	6.7	6.6	6.4	6.8	6.0	5.5	5.3	5.1
65-79	0.20	0.19	0.17	0.18	0.17	11.0	10.4	9.4	9.7	9.4	8.2	7.8	7.0	6.9	6.9
80-	0.32	0.31	0.29	0.29	0.30	18.5	17.6	17.0	17.4	17.6	14.2	13.4	13.1	13.2	13.2
All age groups	0.18	0.16	0.14	0.14	0.14	11.5	10.4	9.8	9.6	9.4	9.2	8.3	7.8	7.5	7.3

Age groups (years)	DDD/ 1 000 and day					Prescriptions/1 000 and year					User/1 000 and year				
	2012	2013	2014	2015	2016	2012	2013	2014	2015	2016	2012	2013	2014	2015	2016
Trimethoprim (J01EA)															
0-6	0.08	0.07	0.07	0.06	0.06	11.0	10.0	9.2	8.1	7.6	8.4	7.6	6.9	6.1	5.6
7-19	0.06	0.05	0.04	0.04	0.03	3.9	3.3	2.8	2.4	2.0	3.3	2.7	2.2	1.8	1.6
20-64	0.13	0.11	0.10	0.09	0.07	5.4	4.5	3.9	3.3	2.6	4.3	3.5	3.0	2.5	1.9
65-79	0.43	0.39	0.34	0.31	0.25	17.7	15.5	13.5	11.8	9.5	12.3	10.7	9.2	8.1	6.5
80-	0.94	0.83	0.71	0.69	0.62	49.1	41.5	35.5	32.7	30.3	24.6	21.4	18.8	17.1	14.2
All age groups	0.20	0.17	0.15	0.14	0.12	9.7	8.3	7.2	6.4	5.4	6.7	5.7	4.9	4.3	3.5
Trimethoprim with sulphonamides (J01EE)															
0-6	0.10	0.09	0.09	0.08	0.07	11.8	10.2	9.6	8.6	7.8	7.6	6.2	5.7	4.8	4.6
7-19	0.10	0.10	0.10	0.10	0.10	3.9	3.8	3.8	4.1	4.1	2.2	2.1	2.0	1.9	1.8
20-64	0.19	0.20	0.20	0.21	0.20	4.3	4.6	4.8	4.8	4.9	2.6	2.6	2.7	2.6	2.7
65-79	0.54	0.56	0.57	0.60	0.62	12.2	12.4	13.0	13.2	13.7	8.3	8.4	8.6	8.4	8.9
80-	0.47	0.51	0.51	0.53	0.55	12.6	13.0	13.2	13.1	14.0	9.5	9.7	9.9	9.7	10.3
All age groups	0.24	0.25	0.25	0.26	0.26	6.6	6.7	6.8	6.8	6.9	4.1	4.0	4.0	3.9	4.0
Macrolides (J01FA)															
0-6	0.39	0.26	0.26	0.23	0.25	18.1	12.1	12.4	11.2	12.0	14.8	9.5	9.7	8.5	9.0
7-19	0.32	0.24	0.22	0.19	0.21	13.2	8.3	8.6	7.8	8.2	10.0	5.8	6.1	5.7	6.1
20-64	0.30	0.27	0.24	0.23	0.23	11.4	8.7	9.1	8.9	8.4	8.8	6.4	6.8	6.5	6.3
65-79	0.32	0.33	0.30	0.30	0.29	10.4	8.7	9.0	9.0	8.3	7.4	5.6	5.9	5.7	5.4
80-	0.19	0.20	0.19	0.21	0.22	6.4	5.7	5.8	6.5	6.3	4.8	4.0	4.0	4.2	4.0
All age groups	0.31	0.27	0.25	0.24	0.24	11.9	8.9	9.2	9.0	8.9	9.1	6.3	6.7	6.3	6.2
Lincosamides (J01FF)															
0-6	0.03	0.02	0.02	0.02	0.02	6.5	5.0	5.1	4.5	4.8	4.9	3.7	3.6	3.3	3.7
7-19	0.12	0.11	0.11	0.09	0.09	7.9	7.4	7.3	6.3	6.3	6.5	5.9	5.7	5.4	5.7
20-64	0.32	0.31	0.31	0.30	0.30	15.8	15.4	14.7	14.5	14.3	12.5	12.2	11.5	11.3	11.4
65-79	0.58	0.58	0.56	0.57	0.56	24.2	24.3	22.9	23.0	22.5	16.8	16.8	15.7	15.3	15.6
80-	0.70	0.71	0.73	0.72	0.72	30.2	29.9	29.9	30.2	30.0	18.7	18.9	18.9	18.6	18.8
All age groups	0.32	0.32	0.32	0.32	0.32	16.0	15.6	14.9	14.8	14.8	11.9	11.6	11.0	10.8	10.9
Fluoroquinolones (J01MA)															
0-6	0.01	0.02	0.02	0.01	0.02	0.7	0.9	0.8	0.7	0.8	0.5	0.5	0.4	0.5	0.5
7-19	0.11	0.11	0.10	0.08	0.07	4.0	3.6	3.4	2.8	2.3	3.2	2.9	2.7	3.0	2.5
20-64	0.65	0.62	0.59	0.57	0.55	20.8	19.7	18.9	18.4	17.6	15.1	14.4	13.8	13.3	12.8
65-79	1.73	1.64	1.61	1.58	1.53	58.8	55.7	54.8	53.6	51.7	40.4	38.6	37.6	35.6	35.2
80-	2.08	2.00	1.95	1.91	1.90	77.6	73.7	72.5	71.0	70.1	54.9	52.6	51.4	49.8	49.1
All age groups	0.75	0.71	0.69	0.68	0.66	25.0	23.8	23.3	22.9	22.1	17.7	16.9	16.4	15.9	15.5
Nitrofurantoin (J01XE)															
0-6	0.05	0.05	0.06	0.05	0.05	7.0	7.1	7.2	6.8	7.1	5.0	5.1	5.2	5.2	5.5
7-19	0.13	0.13	0.13	0.09	0.09	10.4	10.1	9.8	7.1	7.1	8.9	8.6	8.3	7.8	7.7
20-64	0.29	0.30	0.31	0.31	0.31	19.8	20.5	21.1	20.9	20.9	16.1	16.6	17.0	16.7	16.8
65-79	0.67	0.72	0.74	0.76	0.76	41.5	44.0	44.9	45.2	45.2	30.3	31.9	32.5	31.7	32.2
80-	1.15	1.23	1.30	1.35	1.38	77.4	80.6	84.0	87.0	87.7	49.0	51.6	53.8	53.8	53.1
All age groups	0.35	0.37	0.38	0.38	0.39	23.5	24.5	25.1	25.2	25.3	17.8	18.4	18.9	18.6	18.7
All agents (J01 excl. Methenamine)															
0-6	6.66	5.43	5.15	4.70	5.06	471.9	382.4	367.2	340.9	356.1	274.4	232.0	222.7	206.4	213.2
7-19	9.27	8.33	7.75	6.48	6.71	268.0	232.7	217.8	200.0	203.1	173.2	152.1	141.8	136.1	138.9
20-64	11.98	11.19	10.62	10.38	10.04	320.0	294.4	280.8	275.2	267.2	200.7	184.9	175.8	171.3	168.4
65-79	17.76	17.28	16.55	16.54	16.06	510.7	489.2	468.7	466.3	450.0	270.6	258.1	246.5	238.9	235.4
80-	20.34	20.22	19.95	20.34	20.10	673.0	654.2	640.3	645.9	634.7	323.2	314.7	307.8	306.7	301.2
All age groups	12.51	11.74	11.20	11.04	10.86	373.9	342.7	328.0	322.8	317.7	218.7	201.0	191.7	186.0	184.5

FIGURE 1.8 Sales of antibiotics commonly used to treat respiratory tract infections in outpatient care (sales on prescriptions), 2000-2016, prescriptions/1 000 inhabitants and year, both sexes, all ages.



[a] Doxycycline (J01AA02) excl.package with more than 50 tablets.

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.

The increased sales of amoxicillin with clavulanic acid seen during the last three years 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).

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 over time.

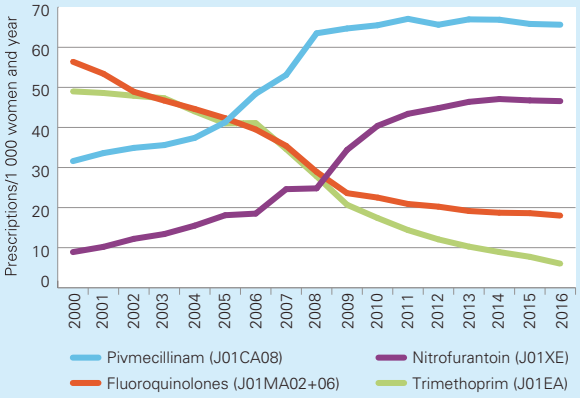
Antibiotics commonly used to treat urinary tract infections in women

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 2016, the total sales of antibiotics commonly used to treat UTI in women aged 18-79 years decreased by 1.9% compared with 2016. However, the same positive trend as previous years, with increased use of the first-line drugs pivmecillinam and nitrofurantoin and reduced sales of trimethoprim (22.2%) and fluoroquinolones (3.3%), was also seen, Figure 1.9.

The total sales of these antibiotics have decreased slowly over the years; by 6.7% 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 16.3% 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 1.7. In this age group the total sales have decreased by 23.5% 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 the 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 regarding men, see below.

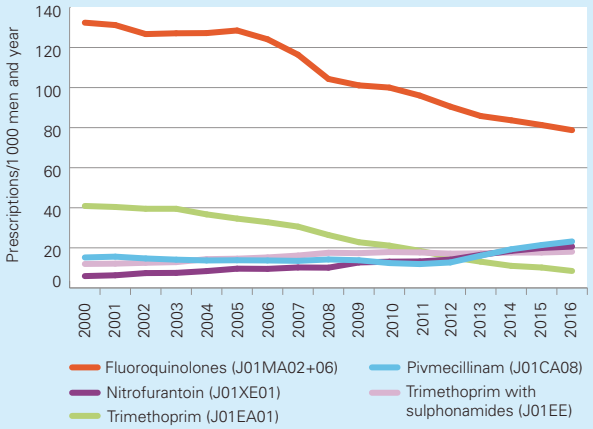
FIGURE 1.9 Sales of antibiotics commonly used to treat lower urinary tract infections in women (sales on prescriptions), 18-79 years, 2000-2016, prescriptions/1 000 women and year.



Antibiotics commonly used to treat urinary tract infections in men

The total sales of antibiotics commonly used to treat UTI in men 65 years and older has decreased by 27.7% since 2000. In 2016, the sales continued to decrease by 0.9% compared to 2015 (from 150 prescriptions/1 000 men and year to 149).

FIGURE 1.10 Sales of antibiotics commonly used to treat UTI in men 65 years and older 2000-2016, measured as 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 (40.5%), as measured by prescriptions per 1 000 men and year. The decrease continued in 2016 by 3.1% compared with 2015. During the last years, sales of pivmecillinam and nitrofurantoin have increased. In 2016, the sales of these two antibiotics increased by 8.3% and 3.6% respectively, as measured by prescriptions per 1 000 men and year, compared with 2015, Figure 1.10.

Antibiotic consumption in children

In 2016 the total sales of antibiotics to children aged 0-6 years increased by 4.5%, from 339 to 356 prescriptions per 1 000 children and year. An increase was seen in quarter two, three and four compared to the same periods in 2015. It was the sales of antibiotics commonly used to treat RTI that increased the most, Table 1.2. Penicillin V and erythromycin were the two substances that increased the most, eight percent respectively.

TABLE 1.2. The sales of antibiotics to children 0-6 years in outpatient care, for different periods in 2016 compared to the same periods in 2015. The sales is measured as prescriptions/ 1 000 children and year. The difference between 2016 and 2015 is measured as percentage.

	J01 excl. Methenamine			RTI antibiotics			UTI antibiotics			SSTI antibiotics		
	2015	2016	Difference in percent	2015	2016	Difference in percent	2015	2016	Difference in percent	2015	2016	Difference in percent
January-March	106.8	105.9	-0.8%	94.3	94.4	0.1%	3.9	4.0	3.1%	6.1	5.5	-9.8%
April-June	81.7	88.1	7.9%	69.2	75.5	9.0%	3.7	3.6	-2.5%	6.6	7.0	6.2%
July-September	60.5	64.4	6.5%	45.9	50.5	10.2%	4.2	4.2	0.8%	8.6	7.9	-7.1%
October-December	92.0	97.8	6.2%	77.3	82.8	7.0%	4.7	4.6	-0.4%	7.7	8.0	4.4%
January-December	340.9	356.1	4.5%	286.8	303.2	5.7%	16.4	16.5	0.2%	28.9	28.4	-1.6%

FIGURE 1.11. 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 2016.

In the end of 2016, the number of laboratory verified cases of Influenza (Public Health Agency of Sweden, 2017) and the number of reported RSV cases (Public Health Agency of Sweden, 2017) were greater than in 2015. In addition, the influenza and RSV season started earlier in the autumn than the year before. Together this leads to more Influenza and RSV cases in 2016 compared to 2015. This might be one explanation to the increased sales of RTI antibiotics in 2016.

In January 2016, a new national reform regarding free drugs to children under 18 years was implemented in Sweden (Medical Products Agency, 2017). The objective of the reform was to allow health care on equal conditions for children and reduce health inequalities between different socioeconomic groups. The sales of the six most commonly used drug groups to children under six years old have all increased in a great amount in 2016 compared to 2015: Skin protection and moisturizing creams (D02AXÖÖ) have increased by 86%, salbutamol (R03AC02) by 20%, fluticasone (R03BA05) by 15%, mucolytics combinations (R05CB10) by 10%, desloratadin (R06AX27) by 16% and hydrocortisone (D07AA02) by 49%.

In summary, the increased sales of antibiotics seen during the whole year in 2016 and the increased sales of other types of drugs indicates that the national reform also can be a factor that might explain the increase in antibiotic sales to children.

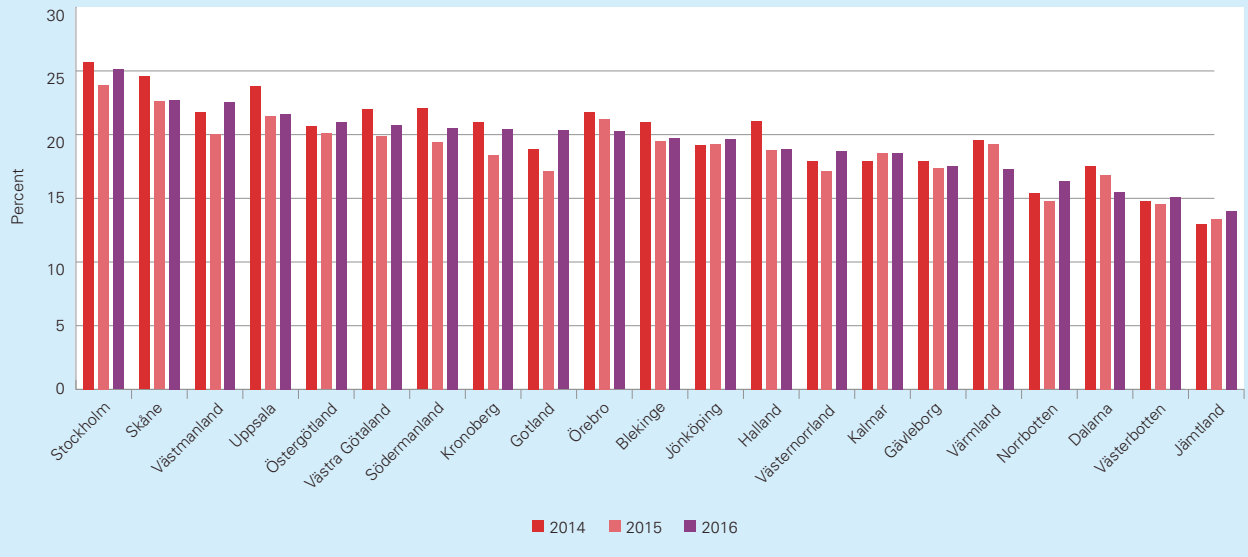
An increase was seen in 15 out of Sweden's 21 counties. There are great national variations in antibiotic sales to children 0-6 years, from 431.8 prescriptions per 1 000 children and year in Stockholm County to 205.1 in Jämtland County, Figure 1.11. The great variation between the counties might suggest antibiotic overuse in some counties.

Different kinds of penicillins are the most commonly prescribed antibiotics in this age group and penicillin V (J01CE02), amoxicillin (J01CA04) and flucloxacillin (J01CF05) represent 59.5%, 12.0% and 6.6% respectively of the total sales in 2016, Table 1.1.

Over the years, the total sales of antibiotics to children aged 0-6 years have decreased by 52.3%, from 746 prescriptions per 1 000 children and year in 2000 to 356 in 2016. The great decrease seen over the years 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 21.3 %, which is more than in 2015, Table 1.1. The proportion increased in 17 out of Sweden's 21 counties during 2016 and it ranges within the country, from 25.1% in Stockholm County to 14.0% in Jämtland County, Figure 1.12.

FIGURE 1.12. The proportion (%) of children 0-6 years treated with at least one course of antibiotics (J01 excl. methenamine) in 2014-2016.



Antibiotic consumption in long-term care facilities

Data in this chapter originates from the annual Swedish point prevalence survey called Swedish-HALT. Swedish HALT aims to support prevention of health care associated infections and improve the use of antibiotics in assisted living facilities.

In 2016, the total prevalence of residents with antibiotic treatment (J01 excluding methenamine) was 3%, which is the same prevalence as in 2015. The greatest prevalence was measured at short-term care units (7.9%). The prevalence varied between different types of units, Figure 1.13. The most common indication for the therapeutic antibiotic prescriptions at long-term care facilities for elderly people was UTI (40%) followed by SSTI (29%), and RTI (16%). Chronic wound infections was the most common diagnosis (35%) out of all antibiotics for any SSTI, followed by acute wound infection (20%). Cystitis was the most common diagnosis (47%) out of all antibiotics for any UTI.

Beta-lactamase resistant penicillins (J01CF) and lincosamides (J01FF) were the two most used antibiotics to treat SSTI in both women and men. Treatment of women and men with cystitis seemed to follow national treatment guidelines. In 2016, more than 80% out of all antibiotic therapies for cystitis in women were first line antibiotics (pivmecillinam J01CA08 and nitrofurantoin J01XE01), Figure 1.14. The use of pivmecillinam and nitrofurantoin were also increasing to men diagnosed with cystitis compared to 2015 (Swedres-Svarm 2015).

FIGURE 1.13. Prevalence of eligible LTCF residents receiving at least one antibiotic treatment (J01 excl. mentenamine), by unit type. n=total number of included residents at respectively unit type.

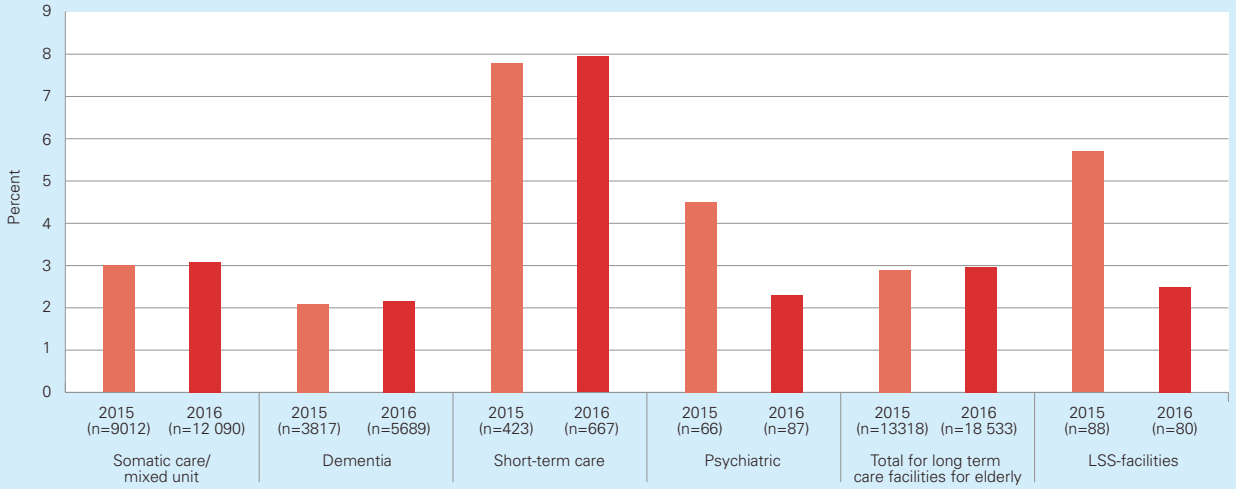
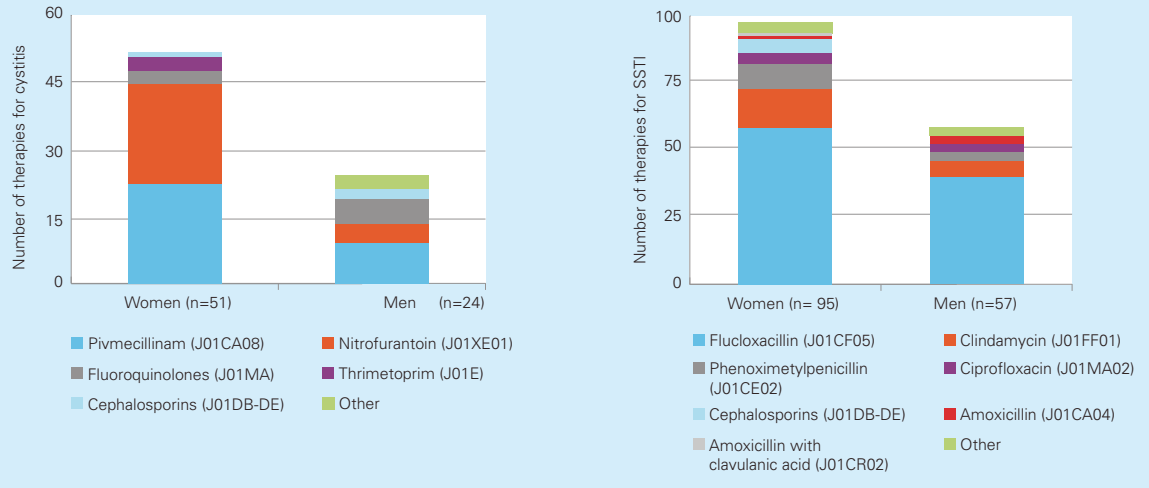


FIGURE 1.14. Distribution of substances for the indications cystitis and SSTI, per gender. n=total number of therapies.



County data

In 2016, 18.5% of the Swedish population was treated with at least one course of antibiotics, which is marginally less than in 2015 when 18.6% were treated, Table 1.1. However, the proportion of people treated with antibiotics varies within Sweden, from 20.2% 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 11 out of Sweden's 21 counties in 2016, Figure 1.15.

In 2016, the average sales of antibiotics in outpatient care measured as prescriptions per 1 000 inhabitants in Sweden was 318. 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 21.4%, Figure 1.16.

In 2016, a reduced number of prescriptions per 1 000 inhabitants was seen in 13 out of Sweden's 21 counties, Figure 1.16.

There are still regional differences between different parts of Sweden and prescriptions per 1 000 inhabitants range from 345 in Stockholm County to 252 in Västerbotten County, Figure 1.16. However, the regional differences within Sweden have decreased over the years, which can be explained by a more appropriate antibiotic use.

The variation between counties is probably not explained by differences in morbidity (Hedin 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).

FIGURE 1.15. The proportion (%) of people treated with at least one course of antibiotics (J01 excl. methenamine) in 2014-2016.

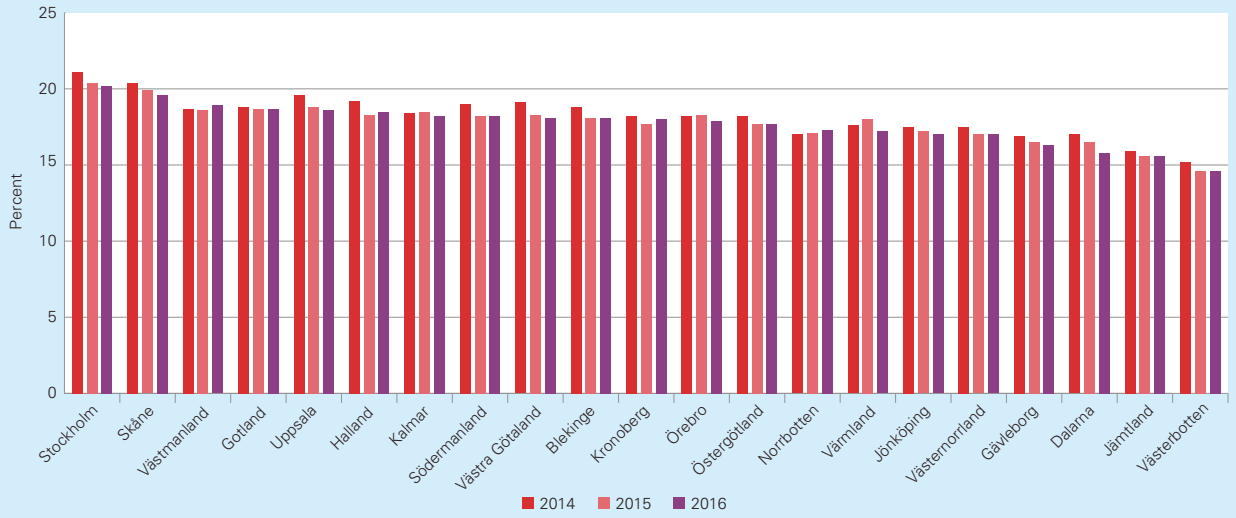
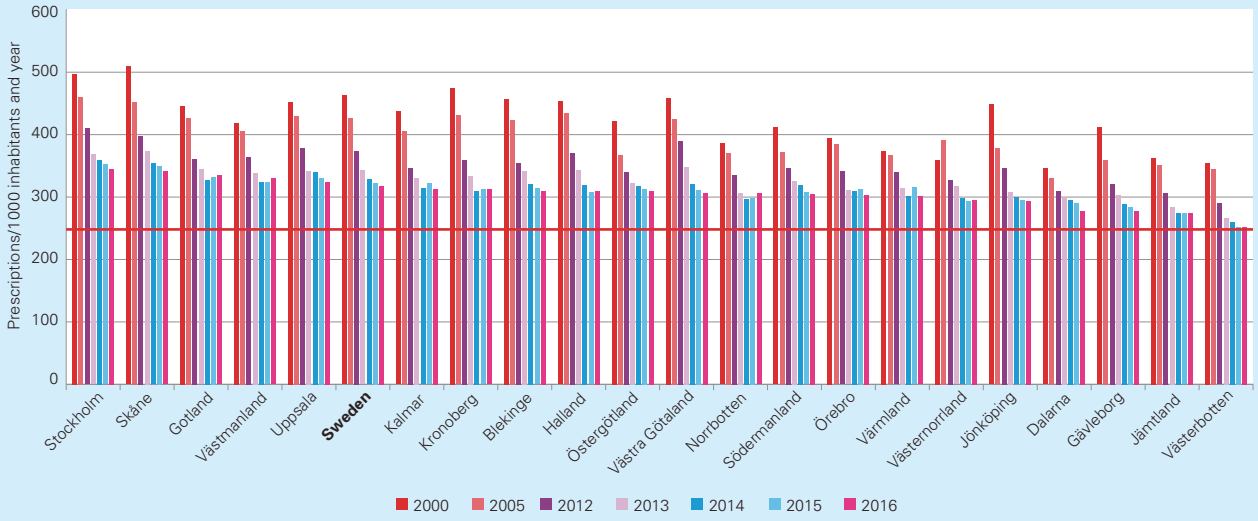


FIGURE 1.16. Sales of antibiotics in outpatient care 2010-2016, prescriptions/1 000 inhabitants and year. The red line indicates the Swedish long term target of 250 prescriptions/1 000 inhabitants and year. The data are sorted according to the sales in 2016.



Earlier studies in Sweden have shown overuse of antibiotics in RTI (Mölstad et al., 2009, Neumark 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 2016 the proportion of penicillin V was 70% on a national level, which is slightly more than in 2015. Värmland County had the greatest proportion, 78%, and Stockholm County the lowest, 67%, Figure 1.17.

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 2016. Kronoberg County had the highest proportion (16%) and Östergötland County the lowest proportion (11%), Figure 1.18.

FIGURE 1.17. Proportion penicillin V of antibiotics commonly used to treat respiratory tract infections in children 0-6 years, per county, 2015-2016. The red line indicates Strama´s goal at minimum 80% penicillin V.

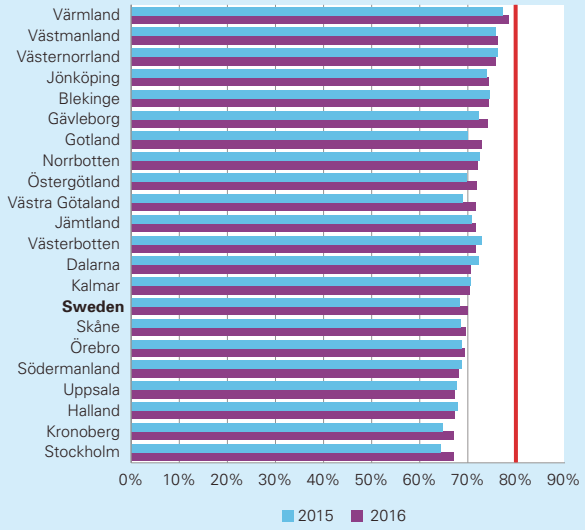
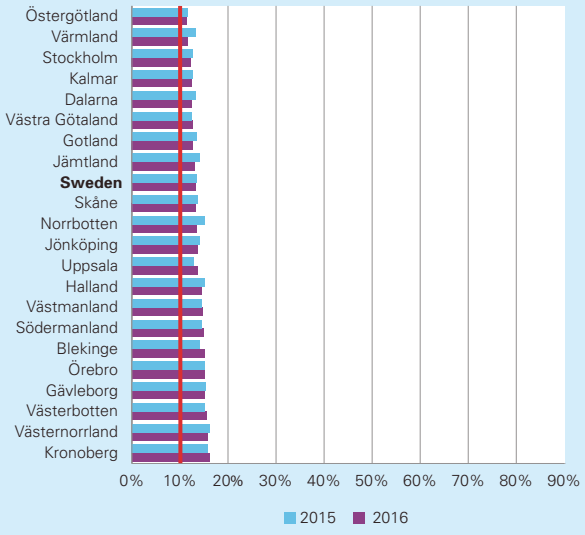


FIGURE 1.18. Proportion of fluoroquinolones of antibiotics commonly used to treat urinary tract infections in women 18-79 years, per county, 2015-2016. The red line indicates Strama´s goal of maximum 10% fluoroquinolones.



Antibiotic consumption and *Clostridium difficile* infection (CDI)

The most important risk factor for CDI is antibiotic exposure; which enables *C. difficile* to proliferate upon gut microbiota depletion. To evaluate the effect of antibiotic exposure on CDI incidence in different age groups and gender, we compared the antibiotic sales in outpatient care to the incidence of CDI. The main antibiotic classes that are considered risk factors for CDI are cephalosporins, fluoroquinolones, lincosamides and macrolides; tetracyclines were also included in the analysis due to their high sales rates in Sweden. CDI incidence is greatest in the age groups 0-4, 65-84 and ≥85 years of age. In the age groups 15-44 and ≥85 years of age we found significant differences in incidence between sexes, women had higher incidence levels in the 15-44 age group while men had higher incidence levels in the age group ≥85 years of age, see Figure 1.19. In the 15-44 age group antibiotic sales of cephalosporins, lincosamides, macrolides and tetracyclines were significantly higher to women, only fluoroquinolones sales were higher for men. While in the age group ≥85 years of age sales of fluoroquinolones, lincosamides and tetracyclines were higher for men, see Figure 1.20. These results correlate with

FIGURE 1.19. Average incidence of new CDI cases/100 000 inhabitants (2012-2016) divided into age groups and by gender. Error bars show standard deviation. One-way ANOVA
*** p-value <0.001, ** p-value <0.01.

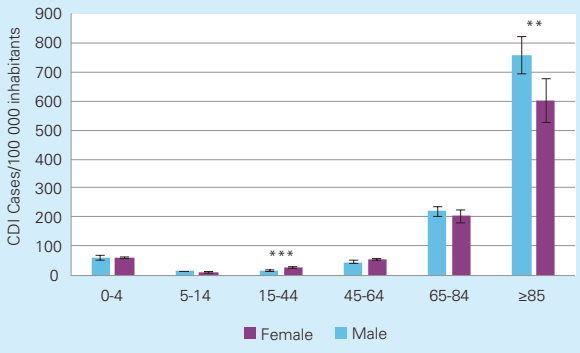


FIGURE 1.20. 2016 sales of cephalosporins, quinolones, lincosamides, macrolides and tetracyclines in outpatient care (DDD/1 000 inhabitants) divided into age groups and by gender. Multi-factor ANOVA ***p-value <0.00001 ** p-value<0.0001, * p-value<0.001.

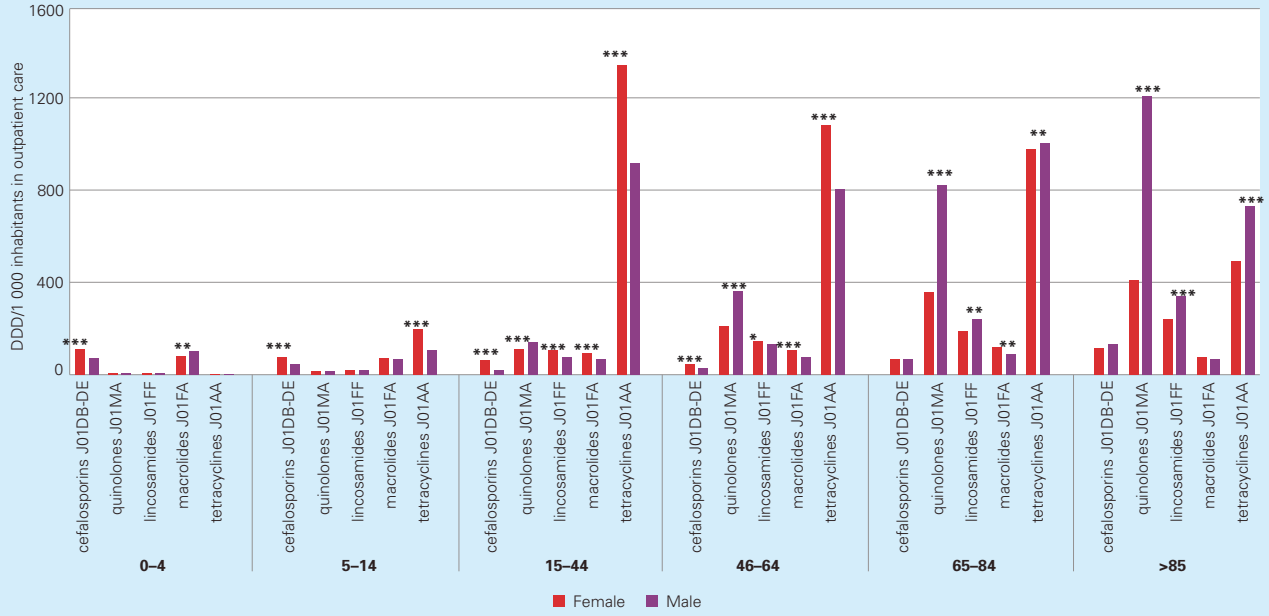
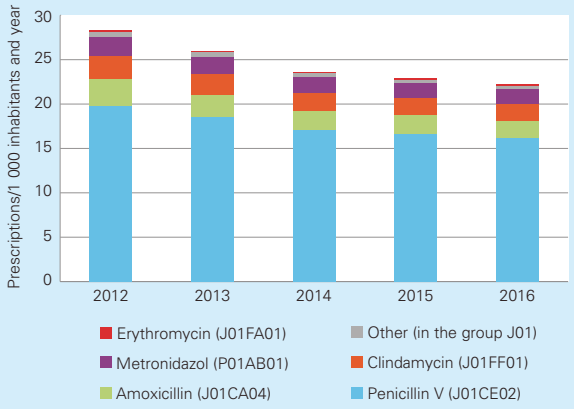


FIGURE 1.21. Sales of antibiotics prescribed by dentists in outpatient care, 2012-2016.

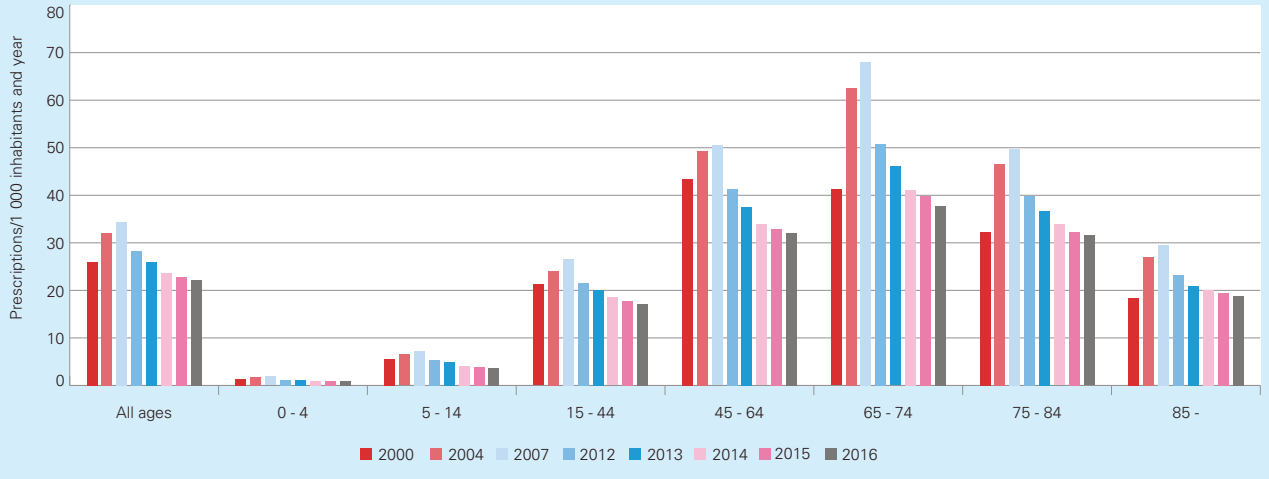


the difference in CDI incidence levels observed between genders. It is also notable that the total sales of antibiotics in all age groups is higher for women (figure 1.5) which stresses the importance of limiting the use of antibiotics that are known risk factors for CDI when possible.

Antibiotics in dentistry

The sales of antibiotic prescribed by dentists decreased by 3% in 2016 compared with 2015, from 22.9 to 22.2 prescriptions per 1 000 inhabitants and year for J01 and metronidazole (P01AB01), see Figure 1.21. Penicillin V (J01CE02) is the most commonly prescribed antibiotic followed by amoxicillin (J01CA04) and clindamycin (J01FF01). These antibiotic substances represent 73%, 9% and 9% respectively of

FIGURE 1.22. Sales of antibiotics (J01 and P01AB01) prescribed by dentists in outpatient care, 2000-2016, different age groups.



all antibiotics prescribed by dentists. However, the greatest decrease in 2016 was seen for erythromycin (15%) and clindamycin (5%), measured as prescriptions per 1 000 inhabitants and year. Amoxicillin has decreased by 36% between 2012 and 2016, this might be cause of the new stricter treatment recommendations for the use of prophylaxis which was implemented in 2012. A big increase was seen for clindamycin between 2001 and 2011. Since 2012, the trend has reversed and the prescribing of clindamycin has decreased each year hereafter.

The age group 65-74 years stands for the highest consumption of antibiotics prescribed by dentists, followed by the age groups 45-64 years and 75-84 years. The antibiotic consumption peaked in 2007 and has thereafter decreased in all age groups (50-35%) see Figure 1.22.

Dentists account for approximately 6% of all antibiotics prescribed in outpatient care in Sweden, see Figure 1.23. The proportion varies between 4% in some counties to 7% in some counties. The total sales of antibiotics (J01 and metronidazole), measured as prescriptions per 1 000 inhabitants and year, decreased in 19 out of 21 counties in 2016 compared with 2015. There are big differences between the counties, Figure 1.24. Even greater differences than for total sales in outpatient care, Figure 1.16. Dentists in Skåne County prescribe the most (28.0 prescriptions/1 000 inhabitants) and more than twice as much as Västerbotten County that prescribe the least (12.3 prescriptions/1 000 inhabitants), see Figure 1.24. There is no known explanation for the differences.

FIGURE 1.23. Sales of antibiotics in outpatient care 2012-2016, prescriptions/1 000 inhabitants and year for different prescribers.

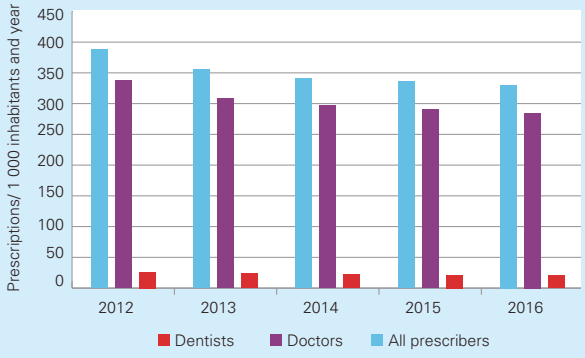
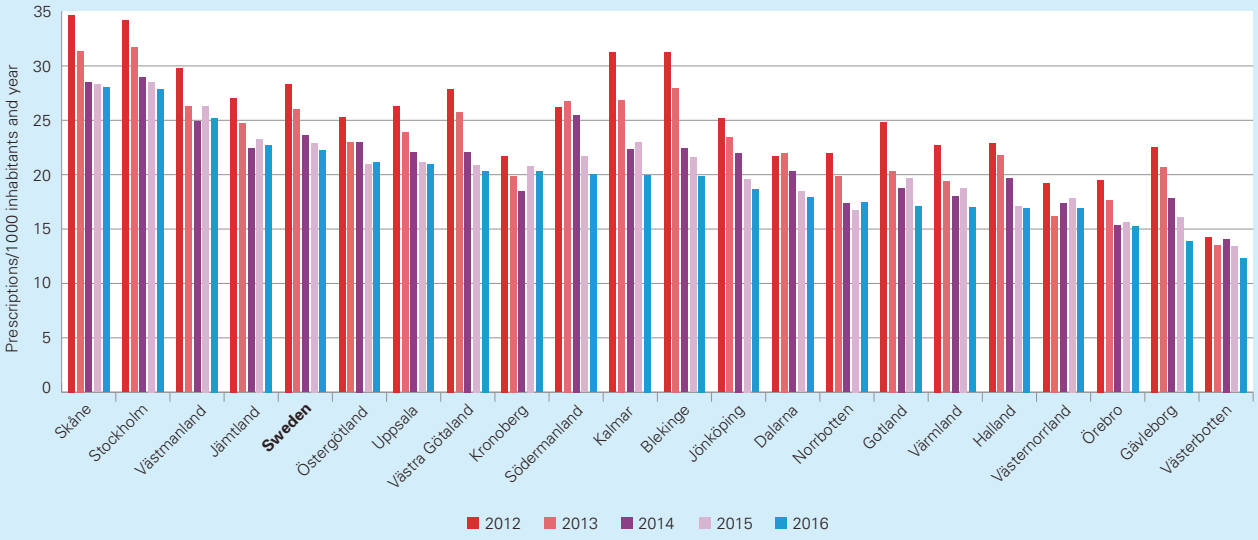


FIGURE 1.24. Sales of antibiotics prescribed by dentists in outpatient care per county, 2012-2016, Antibiotics for systemic use (J01) and metronidazol (P01AB01).



Antibiotics in hospital care

Sales data in this chapter originates from two different sources: 1) antibiotics sold by requisitions to acute care hospitals only, here called Swedish acute care hospitals, this provides a more detailed analysis, and 2) all antibiotics sold by requistions, below mentioned 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 65%.

Antibiotic consumption in Swedish acute care hospitals

When analysing data from acute care hospitals, the consumption was slightly lower in 2016 compared with 2015 measured as DDD/100 patient-days and as DDD/100 admissions, Table 1.3.

Figure 1.25 shows the most frequent groups of antibiotics used in hospital care. The consumption of cephalosporins, and vancomycin did not change during the last year, and stayed at almost the same level as in 2015. Beta-lactamase resistant penicillins, penicillins with enzyme inhibitor and aminoglycisides continues to increase as in previous years, while fluoroquinolones, carbapenems and beta-lactamase sensitive penicillins decreased.

FIGURE 1.25. Antibiotic groups often used within hospital care 2012-2016 DDD/100 patient-days in Swedish acute care hospitals.

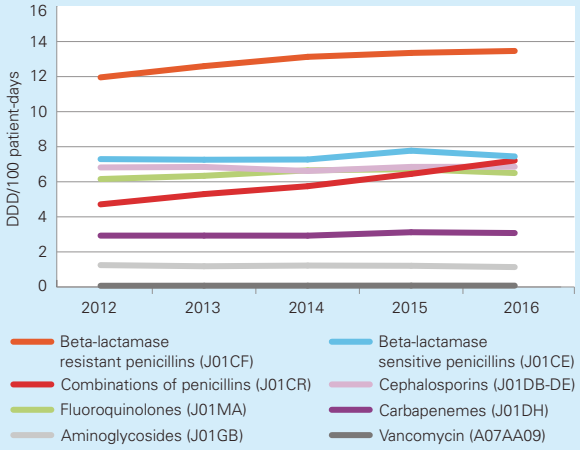


TABLE 1.3. DDD/100 patient-days and DDD/100 admissions in somatic medical care in Swedish acute care hospitals 2012-2016.

	DDD/100 admissions					DDD/100 patient-days				
	2012	2013	2014	2015	2016*	2012	2013	2014	2015	2016*
Tetracyclines (J01AA)	24.2	23.3	23.9	23.9	21.7	5.5	5.2	5.4	5.4	4.9
Penicillins with extended spectrum (J01CA)	30.6	31.8	33.1	33.9	32.8	6.9	7.2	7.4	7.7	7.4
Betalactamase sensitive penicillins (J01CE)	32.3	32.2	32.4	34.3	32.9	7.3	7.3	7.3	7.8	7.4
Betalactamase resistent penicillins (J01CF)	53.0	55.9	58.5	59.0	59.4	12.0	12.6	13.1	13.4	13.5
Combinations of penicillins (J01CR)	20.9	23.5	25.6	28.5	31.8	4.7	5.3	5.7	6.5	7.2
Cephalosporins (J01DB-DE)	30.2	30.4	29.5	30.2	30.3	6.8	6.8	6.6	6.8	6.9
Carbapenems (J01DH)	13.0	13.0	13.1	13.8	13.6	2.9	2.9	2.9	3.1	3.1
Trimethoprim (J01EA)	2.6	2.0	1.8	1.8	1.1	0.6	0.4	0.4	0.4	0.2
Trimethoprim with sulphonamides (J01EE)	10.5	10.6	10.6	10.7	11.2	2.4	2.4	2.4	2.4	2.5
Macrolides (J01FA)	4.3	4.5	4.4	4.9	5.3	1.0	1.0	1.0	1.1	1.2
Lincosamides (J01FF)	8.4	8.8	8.7	8.5	8.4	1.9	2.0	1.9	1.9	1.9
Aminoglycosides (J01GB)	5.5	5.2	5.4	5.3	5.0	1.2	1.2	1.2	1.2	1.1
Fluoroquinolones (J01MA)	27.3	28.1	29.7	29.7	28.7	6.2	6.3	6.7	6.7	6.5
Glycopeptides (J01XA)	4.3	4.3	4.5	4.7	4.6	1.0	1.0	1.0	1.1	1.1
Imidazole derivates (J01XD)	5.9	5.4	4.6	4.4	4.0	1.3	1.2	1.0	1.0	0.9
Nitrofurantoin (J01XE)	2.1	2.3	2.4	2.2	2.2	0.5	0.5	0.5	0.5	0.5
Vancomycin (A07AA09)	0.3	0.3	0.3	0.3	0.3	0.1	0.1	0.1	0.1	0.1
Pivmecillinam (J01CA08)	8.4	8.9	9.5	9.5	8.7	1.9	2.0	2.1	2.1	2.0
Piperacillin and tazobactam (J01CR05)	15.3	17.6	20.8	22.6	25.1	3.5	4.0	4.7	5.1	5.7
Moxifloxacin (J01MA14)	1.7	1.7	1.8	1.7	1.9	0.4	0.4	0.4	0.4	0.4
Methenamine (J01XX05)	2.4	2.4	2.4	2.4	1.9	0.5	0.5	0.5	0.5	0.4
Linezolid (J01XX08)	0.4	0.5	0.6	0.6	0.8	0.1	0.1	0.1	0.1	0.2
All agents (J01)	277.9	284.4	292.5	299.9	297.2	62.7	64.1	65.6	67.9	67.3

*Denominator data from 2015

The use of penicillins with enzyme inhibitor have increased substantially in recent years, while the use of carbapenems for the first time has decreased. 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 2016 penicillins with enzyme inhibitor increased with 12% measured as DDD per 100 patient-days compared to 2015. The corresponding figure for carbapenemes was a decrease by 1.5%. The increase of these substances during recent years is probably a result of an increased number of infections with ESBL. Invasive infections caused by ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* 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, and last year it increased some (0.8%) compared to 2015. 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 (3.3%) in 2016 compared to 2015. One reason to why they are not increasing might be that the resistance is already quite extensive.

According to available data, antibiotic consumption in Swedish acute care hospitals show a wide variation between the counties in the use of narrow-spectrum penicillins, ranging from 6% to 19% of the total hospital consumption measured as DDDs, Figure 1.26. There are, however, great differences in dosages of penicillin G between the counties. DDD is 3.6 g and in Sweden the dosage varies from 1g three times a day to 3g three times a day. Type of hospital and patient composition may also influence the 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.

In acute care hospitals the use of cephalosporins varied between 3.1% and 14.3%, and the corresponding figure for fluoroquinolones were 8.1% to 14.5%, and 6.2% to 14.2% for piperacillin-tazobactam, and 2.4% to 6.9% for carbapenems, Figure 1.27. 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 27.5% in Jönköping County to 36.5% 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 1.26. Percentage of narrow spectrum penicillins (penicillin V and G) of all antibiotics in Swedish acute care hospitals 2016, per county.

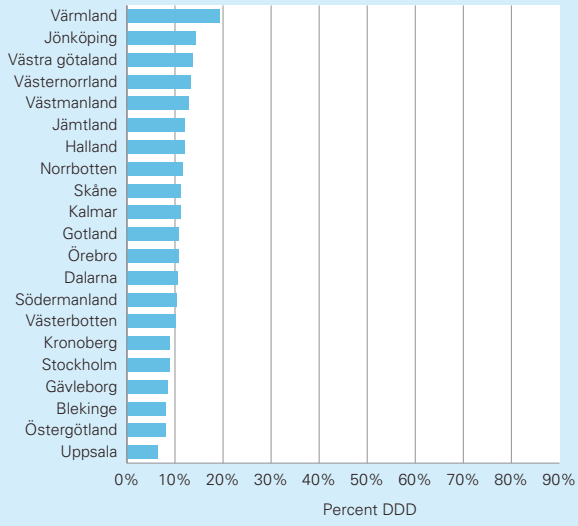
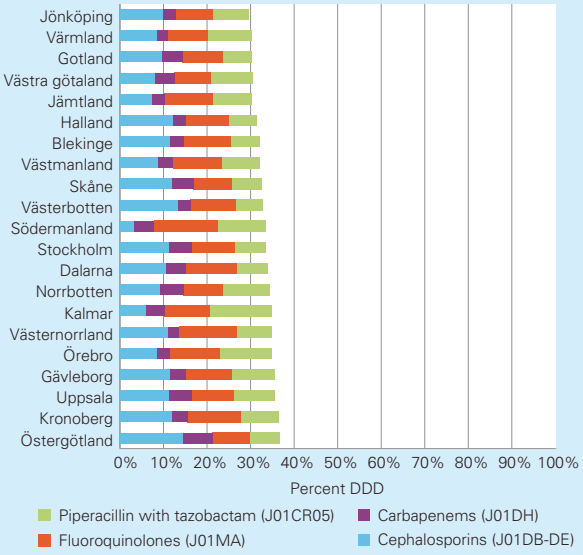


FIGURE 1.27. Percentage of broad spectrum antibiotics (fluoroquinolones, cephalosporins, piperacillin with tazobactam and carbapenems) of all antibiotics in Swedish acute care hospitals 2016, per county.



Antibiotic consumption in hospitals

The total antibiotic sale on requisition has increased in Sweden during 2000-2007 and has since then been on a quite stable level. During the last year the consumption decreased and the levels for 2016 are slightly lower than those in 2015. 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 1.57 DDD/1 000 inhabitants and day, Table 1.4.

Figure 1.28 is the same as Figure 1.25, the only difference is that this one includes all sales on requisition (hospitals, nursing homes and other units order's of antibiotics on requisition). The figure shows the clear shift from high use of broad spectrum antibiotics to narrow spectrum antibiotics.

Antimicrobial stewardship in Stockholm hospitals

The emerging threat of antimicrobial resistance calls for a reduction of inappropriate use of antibiotics. Antimicrobial stewardship (AMS) has proven to combat antimicrobial resistance, improve patient outcomes, and reduce health care costs. AMS programs include a large variety of strategies and outcomes, with the general aim to promote the rational use of antimicrobial agents. This includes the selection of the optimal drug, dosing, duration of therapy, route of administration and de-escalation.

AMS has been successfully implemented in Swedish primary care by Strama, which has resulted in a considerable reduction of antibiotic consumption in the last decades. However, during the last years, we have had an alarming trend with an increasing use of broad-spectrum antibiotics in Stockholm hospitals, and solutions to address it are urgently required. The regional Strama group in Stockholm County, Strama Stockholm, is therefore shifting focus to improve antibiotic use among inpatient facilities.

Recently two important publications on AMS for hospital inpatients have been published: A Cochrane review on interventions to improve antibiotic prescribing practises (1), and evidence-based guidelines for implementation and measurement of AMS interventions provided by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America (2). They conclude that interventions providing advice or feedback from infectious disease (ID) specialists to prescribers are more effective in improving prescribing practices than interventions that do not. Passive educational activities, such as lectures or informational pamphlets, have limited effect, and should be used to complement other stewardship activities.

The Strama group in Stockholm takes a significant part in the training of medical students, interns and residents, integrating fundamental antibiotic stewardship principles into their curricula. In addition, the group provide treatment recommendations and arrange meetings with clinicians in hospital facilities, reconnecting prescription and resistance data. However, historically Strama Stockholm have focused mainly on educational activities, and have experienced the frustrating lack of effect on prescription patterns in spite of perceived positive response. In order to make the activities more interactive, lectures have been replaced with interactive case-discussions. A patient case-based e-learning for clinicians working in hospital facilities has also been developed (3). Given the knowledge that interventions providing advice from ID specialists to other physicians are the most effective, Strama Stockholm are now adding a prescription feedback intervention – so called AMS ward rounds.

AMS ward rounds

Ward rounds where an ID specialist gives advice on antibiotic treatment are standard in Swedish intensive care units, oncology, hemathology and other highly specialized units with patients at risk for complicated infections. In other units, ID consultants are available for consults on request. However, many infections are treated without an ID specialist being involved, resulting in poor adherence to treatment recommendations. By adding ID specialist-run AMS ward rounds, physicians are guided on antibiotic treatment also in less complicated patients, promoting the selection of the optimal antibiotic drug regimen. AMS ward rounds has previously been successfully introduced in Malmö hospital at internal medicine units, and proven efficient in reducing antibiotic use without negative effect on patient outcome or increasing costs (4). This type of intervention is now promoted at a national level by Program Council Strama, and highly recommended for all Swedish hospitals.

Experiences of AMS ward rounds in Stockholm County

There are seven major hospitals in Stockholm County. Of these, five have ID departments, also serving the other hospitals with ID specialist consultants. All hospitals have a local Strama group, led by the chief medical officer in cooperation with local ID specialists and supported by Strama Stockholm. Strama Stockholm strongly encourages the hospitals to introduce AMS ward rounds, and supports the introduction by providing data on consumption and prescription of antibiotics, in order to identify units that could benefit from the intervention. However, the introduction of AMS rounds must be led by experienced ID specialists, with local knowledge about the care conducted by other units and an understanding of the problems that may contribute to overuse and misuse of antibiotics at different wards. It is important that the clinicians have confidence in the ID specialist and a well known and respected colleague is preferable. This can be a great challenge considering their already heavy work load and limited resources.

In Stockholm the consumption of antibiotics is particularly high at internal medicine units, and AMS ward rounds are being introduced step wise at these units, each hospital and ID department according to their own circumstances and resources.

The start up of AMS ward rounds includes identifying wards that could benefit from AMS rounds, motivating them and setting a structure for a trial period. In general, the ID specialist meet the clinician in charge of a specific ward twice a week to discuss all patients that are treated with antibiotics, regardless of whether the cli-

nician has questions or not. The clinician is advised to discontinue or adjust therapy if the available diagnostic tests or clinical course warrant changes. The AMS ward rounds service is advisory and all decisions are made and documented by the clinician.

The amount of time allocated for each ward varies and is a matter of discussion. Evaluation of the intervention is recommended. Strama Stockholm provides comparisons of antibiotic data in terms of total usage, choice of antimicrobial agents and intravenous versus oral administration before and after the introduction of AMS rounds. More detailed evaluations may be done by the ID specialists in charge of the intervention. If the AMS ward rounds are evaluated as successful, they can – if the required resources are available - be expanded to other units and integrated into the daily work of the ID specialists.

AMS rounds have so far been implemented at two Stockholm hospitals, and are being well received. Preliminary data on antibiotic consumption are promising. However, as mentioned, this work requires experienced ID specialists being available to do the work. Although AMS in general and rounds in particular are shown to be cost effective in the larger perspective, they are time consuming for the physicians performing it. With the limited resources in todays' health care it is a great challenge to add AMS rounds to an already heavy work load of the ID specialists and integrate the rounds into the daily work. Economic resources have to be allocated. The goal in Strama Stockholm is to expand the rounds to more wards in both internal medicine and surgery, and to introduce this activity at the remaining hospitals.

With the alarming threat of increasing antimicrobial resistance, reducing the inappropriate use of antibiotics in hospitals is urgent. AMS ward rounds are definitely important tools in this work, and can hopefully be implemented in all Swedish hospitals in a near future.

References:

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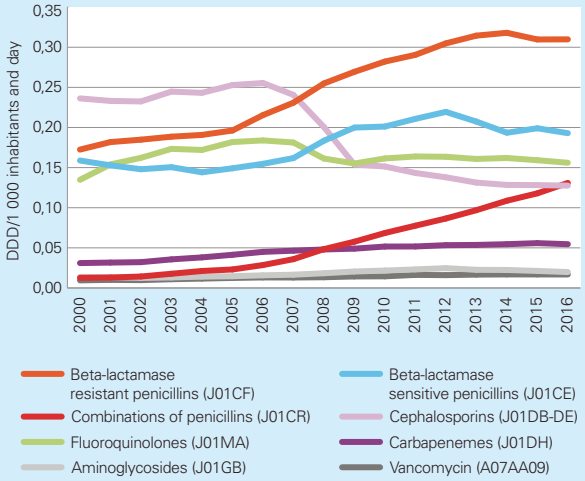
TABLE 1.4. Antibiotic consumption in hospital care 2000-2016, DDD/1 000 inhabitants and day.

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
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	1.57
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	0.01
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	1.58

FIGURE 1.28. Antibiotic groups often used within hospital care 2000-2016, DDD/1 000 inhabitants and day.



The consumption of cephalosporins, fluoroquinolones, aminoglycosides, vancomycin and beta-lactamase resistant penicillins did not change during the last year. Beta-lactamase sensitive penicillins decreased during the last year, and for the first time also carbapenems decreased. Penicillins with enzyme inhibitor continued to increase like in 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 restricded; 4) extended-spectrum cephalosporins and fluoroquinolones should not be used in situations where treatment with a narrow-spectrum penicillin is an alternative (Hanberger H et al., 2014). This can be reflected in the statistic.

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 (MPA). The reports originate from health care professionals and patients. There are 2390 side effects reported due to the use of the antibiotics during the last five years, 2012-2016. The following organ system groups received most reports related to the use of systemic antibiotic drugs (J01): skin- and subcutaneous tissue disorders (n=1175), gastrointestinal disorders (n=508), general disorders (n= 302), neurological reactions (n=263), immune system disorders (n=196), respiratory disorders (n=195) investigations (n=163), musculoskeletal disorders (n=154), hepatobiliary disorders (n=141), renal and urinary disorders (n=89), psychiatric disorders (n=87) and blood and lymphatic system disorders (n=71).

The majority of the reports (60%) 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 1.5.

TABLE 1.5. Most reported adverse drug reactions related to antibiotic agents to the Swedish Medical Products Agency 2012-2016.

Antibiotic	Total number of adverse drug reaction reports 2012 to 2016	Number of 'serious' reports	Number of fatal cases
Phenoxymethyl-penicillin	298	105	0
Flucloxacillin	292	164	12
Ciprofloxacin	261	169	2
Nitrofurantoin	190	100	2
Clindamycin	187	91	2
Amoxicillin	144	52	0
Sulfamethoxazole and trimethoprim	137	59	1
Doxycycline	113	41	0
Piperacillin and enzyme inhibitor	113	73	2
Cefotaxime	85	45	3

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. Since 2005, data represent sales from pharmacies to animal owners (prescriptions dispensed) or to veterinarians. The sales represent an approximation of the use of antibiotics, assuming that the amount sold is also used during the observation period. Only sales of veterinary products are included, except for statistics on number of packages sold for use in dogs. 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 then, 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 from 2015, it is assumed that the sales of this type of products are no less complete than before the reregulation.

Between 2010 and 2015, there has also been a lack of completeness in the sales of products with general marketing authorisation. This is believed to affect injectable products and should be kept in mind when interpreting the data from recent years. For further information on the lack of completeness of data from recent years, see Swedres-Svarm 2015 p. 109. Data for 2016 is likely to be complete.

Trends in animal populations

Changes in the numbers of animals may affect trends in statistics on consumption of antibiotics. Compared to 2007, the number of pigs slaughtered in 2016 has decreased by 16%, while the number of broilers has increased by 36%. The number of dairy cows decreased by 12% during the same period. The number of horses was estimated to 355 500 in 2016. The number of dogs was estimated to 784 000 in 2012 and 729 000 in 2006. Further details on animal numbers and data sources are found in Demographics and denominator data in this report.

Overall sales

The total yearly sales of antibiotics for animals over the last decade are presented in Table 2.1. The potencies of different antibiotics are not equal and therefore, each class should be evaluated separately.

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 2016, the total reported sales from Swedish pharmacies of antibiotics for animals were 10 543 kg, of which 57% was benzylpenicillin. The corresponding figures for 2007 were 17 106 kg and 44%.

To correct for changes in the numbers of animals over time, the population correction unit (PCU) described in a publication from the European Medicines Agency was applied (EMA, 2011). The PCU is a purely technical term representing an approximation of the summed live-weight of the major animal populations, excluding companion animals. In Figure 2.1, the total sales of antimicrobials for animals (including sales

TABLE 2.1. Yearly sales of antimicrobial drugs for veterinary use expressed as kg active substance[a].

ATCvet code	Antimicrobial class	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
QJ01AA, QG01A	Tetracyclines	1 853	1 649	1 174	1 115	1 073	881	935	787	685	515
QJ01BA	Amphenicols						<1	3	7	11	36
QJ01CE, -R, QJ51	Benzylpenicillin[b]	7 582	7 758	7 721	7 546	6 696	6 362	5 954	5 509	5 861	5 997
QJ01CA, QJ01CR	Aminopenicillins	927	938	1 068	907	723	649	645	635	642	677
QJ01D	Cephalosporins	954	820	738	575	498	410	330	299	267	242
QA07AA, QJ01G, -R, QJ51R	Aminoglycosides & polymixins	718	643	609	557	503	483	341	378	414	385
QA07AB, QJ01E	Sulphonamides	2 427	2 303	2 128	1 998	1 867	1 813	1707	1 699	1 634	1 643
QJ01E	Trimethoprim & derivatives	438	416	379	357	338	329	320	314	313	318
QJ01F	Macrolides & lincosamides	1 520	1 096	988	739	648	632	564	484	485	472
QJ01MA	Fluoroquinolones	180	169	164	148	120	106	52	45	34	30
QJ01XX92, - 94	Pleuromutilins	506	572	398	174	140	99	126	114	122	228
Total		**17 106**	**16 364**	**15 368**	**14 117**	**12 606**	**11 763**	**10 975**	**10 270**	**10 468**	**10 543**

[a]Data from 2010-2015 are uncertain because of a lack of completeness mainly affecting injectable products. [b]Also includes small amounts of penicillinase stable penicillins.

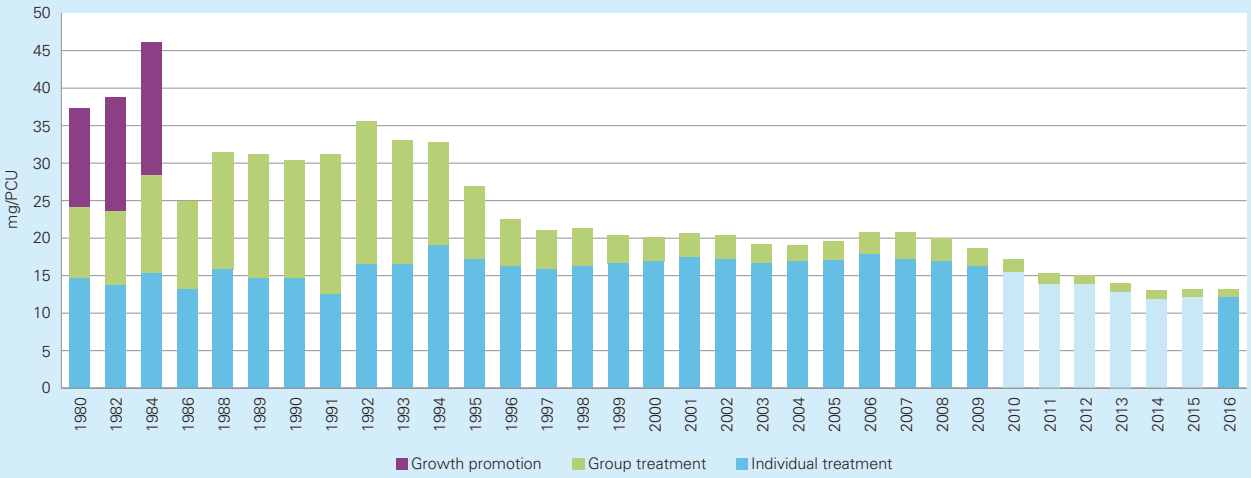
for companion animals) from 1980 are presented as mg active substance per PCU. The overall sales have decreased by around two thirds compared to the average figures for 1980-1984 (i.e. before the Swedish ban on growth promoting antimicrobials in 1986). This is explained first by the removal of growth promoting antimicrobials in 1986, followed by a major gradual decrease from the mid-90s of the sales of veterinary products for medication via feed or water (group medication), followed by a decrease of sales of injectable products in the past decade.

Sales of antibiotics for parenteral use

The sales of antibiotic products formulated for injection are presented in Table 2.2. 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 2016 can probably be explained by a restored completeness.

Sales of injectable fluoroquinolones have decreased by 86% since 2007. 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.

FIGURE 2.1. Sales of antibiotics for animals expressed as mg per population correction unit (PCU)[a]



[a]Data from 2010-2015 are uncertain because of a lack of completeness mainly affecting injectable products. This is indicated by a paler colour for antibiotics for individual treatment. In the present figure, all products (including tablets) are included while in data presented in the European surveillance of veterinary antimicrobial consumption tablets are excluded when calculating mg/PCU.

TABLE 2.2. Yearly sales of antibiotics for parenteral use (injections) expressed as kg active substance[a].

ATCvet code	Antibiotic class	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
QJ01AA	Tetracyclines	588	557	527	492	471	422	424	396	335	255
QJ01BA	Amphenicols						0	3	7	11	36
QJ01CA, QJ01CR	Aminopenicillins	142	143	152	144	146	143	131	145	165	192
QJ01CE, -R, QJ51	Benzylpenicillin	7 505	7 674	7 641	7 492	6 627	6 290	5 901	5 455	5 800	5 871
QJ01DD	Cephalosporins	26	25	21	13	13	8	4	2	4	8
QJ01G, -R,	Aminoglycosides	343	318	301	272	246	210	104	145	144	139
QJ01E	Trimethoprim & sulphonamides	685	691	669	685	667	699	857	849	825	775
QJ01F	Macrolides & lincosamides	216	136	118	101	95	95	95	90	90	98
QJ01MA	Fluoroquinolones	125	118	113	105	83	69	29	25	19	17
QJ01XX92, -94	Pleuromutilins	36	36	28	17	13	14	17	13	10	13
Total		**9 666**	**9 699**	**9 568**	**9 322**	**8 362**	**7 950**	**7 565**	**7 125**	**7 402**	**7 404**

[a]Figures for 2010-2015 are uncertain because of indications of lack of completeness.

The reduction from 2012 to 2016 was 75%, indicating 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 2.3. 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 for oral medication of individual animals have decreased gradually over the past decade (-78% since 2007). A more pronounced decrease is noted after 2012 (- 66% to 2016). This is probably a reflection of the above-mentioned regulation restricting veterinarians' prescribing of fluoroquinolones.

Major downward trends from 2007-2016 are noted for all classes. For further comments see Comments on trends by animal species, Horses and Dogs.

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 2.4. Data for 1984 are given as historical reference. Today, the sales of products for medication of groups of animals are 3% of what they were 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 2007 (Table 2.4). An exception is peni-

TABLE 2.3. Yearly sales of antibiotics for oral medication of individual animals, expressed as kg active substance.

ATCvet code	Antibiotic class	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
QJ01AA	Tetracyclines	44	47	48	46	49	50	47	38	31	23
QJ01CA, QJ01CR	Aminopenicillins	756	681	650	598	514	501	500	460	445	438
QJ01DB	Cephalosporins	924	792	714	562	484	402	325	297	263	234
QA07AA	Aminoglycosides	126	131	118	109	98	102	77	61	100	97
QA07AB, QJ01E	Trimethoprim & sulphonamides	2 179	2 028	1 838	1 670	1 539	1 442	1 169	1 164	1 081	1 184
QJ01FF	Lincosamides	194	216	214	210	192	178	164	159	144	135
QJ01MA	Fluoroquinolones	52	46	46	39	35	32	22	18	14	11
Total		**4 276**	**3 941**	**3 630**	**3 234**	**2 938**	**2 706**	**2 304**	**2 198**	**2 079**	**2 122**

TABLE 2.4. Yearly sales of antibiotics authorised for group treatment and of ionophoric anticoccidials, expressed as kg active substance.

ATCvet code	Antibiotic class	1984	2007	2008	2009	2010	2011[a]	2012	2013	2014	2015	2016
QA07A	Intestinal anti-infectives		158	106	107	119	77	75	76	80	91	73
QJ01A	Tetracyclines	12 300	1 217	1 040	594	575	552	408	463	352	317	237
QJ01C	Penicillins incl. aminopenicillins		28	111	266	164	36	5	13	30	31	117
QJ01EW	Sulphonamides & trimethoprim										42	1
QJ01F	Macrolides & lincosamides	607	1 107	744	657	427	361	359	305	235	251	239
QJ01MA	Fluoroquinolones		3	5	5	4	2	6	1	2	1	1
QJ01MQ	Quinoxalines[b]	9 900										
QJ01XX91	Streptogramins[b]	8 800										
QJ01XX92, -94	Pleuromutilins		471	536	370	157	127	85	109	101	113	215
QP51AA	Nitroimidazoles	1 440										
	Feed additives[c]	700										
Total		**33 747**	**2 984**	**2 543**	**1 999**	**1 447**	**1 154**	**937**	**968**	**800**	**845**	**882**
QP51AH	Ionophoric antibiotics (coccidiostats)[d]	7 900	12 527	13 376	12 471	15 325	14 693	12 860	12 489	14 194	18 204	18 420

[a]For some classes, data on sales of products sold with special licence may be incomplete for 2011. 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).

cillins, where sales have varied over the last decade. Penicillins for group medication are sold with special license, and it is possible that all sales have not been captured all years. The sales of pleuromutilins have decreased since the mid-90s and were 54% lower in 2016 than in 2007. However, sales in 2016 were notably higher than in 2015. 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. The higher figure reported for 2016 is assumed to be due to control efforts in some larger herds. There is a continued drop in sales of tetracyclines for group medication, but sales of macrolides seem to have stagnated (see also Consumption by animal species, Pigs).

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, 2017). 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 (2017), 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 8.9 recorded treatments per 100 completed/interrupted lactations in 2015/2016. Treatment with benzylpenicillin was by far the most common (around 90% of reported treatments). Treatment of mastitis with fluoroquinolones has decreased from 2.5 recorded treatments per 100 completed/interrupted lactations in 2007 to 0.3 in 2015.

Pigs

Almost all sales of antibiotics for pigs are dispensed by pharmacies (on prescription) directly to the animal owner. The pharmacy records the animal species electronically, and data below are based on such records.

In 2007 and 2016 the sales of antibiotics for pigs were 4 719 and 2 967 kg active substance, respectively, or 17.8 and 12.7 mg/kg slaughtered pig. These measures do not take the difference in dosing and length of treatment into account. To account for such factors, sales figures for 2007 and 2016 were calculated to DDDvet (defined daily doses for animals) and DCDvet (defined course doses) using the units published by the European medicines agency (EMA 2016). As a denominator, an estimate of the live pig biomass as for PCU were used. Measured as DDDvet, the consumption has decreased from 4.5 in 2007 to 3.6 DDDvet per 1000 kg pig and day (a decrease by 20%). The change is less pronounced when DCDvet are used; 344 DCDvet per 1000 kg pig were sold in 2007 compared to 326 DCDvet per 1000 kg pig in 2016 (a decrease by 5%). The difference in magnitude of the change over time between the units of measurement is explained by a shift from products with longer treatment duration, i.e. products for group medication, towards products with shorter treatment times i.e. injectables. The proportion of the total number of DCDvet per 1000 kg pig that were products for medication of groups of animals (administered in feed or water) was 34 and 15% for 2007 and 2016, respectively.

Of the total sales in kg active substance during 2016, 77% were products for use in individual animals, and of those 64% were products containing benzylpenicillin. Colistin is used for treatment of weaning diarrhoea in herds with acute problems. In 2016, the sales corresponded to 0.3 mg/kg pig slaughtered. The total sales of fluoroquinolones for pigs were only 1 kg active substance and there were no sales of third generation cephalosporins for pigs.

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 and the Swedish Veterinary Association 2011).

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 ten years, the yearly sales of fluoroquinolones for slaughter chickens and hens have been around or much below 1 kg, mostly below 0.25 kg. Mostly the types of products sold with chickens, hens or turkeys as recorded species are tablets or injectables and quantities very small, indicating that they were not used for treatment of commercially raised chickens. Cephalosporins or colistin are never used.

From 2011, the Swedish poultry meat association requests their members to report all treatments of broilers, parents and grandparents as part of the Poultry health control programme. According to the reports, a total of 14 of 3 300 broiler flocks (0.4%) were treated in 2016. This corresponds to 0.15 mg active substance/kg slaughtered chicken. Nine of the flocks were treated with phenoxymethylpenicillin, four with amoxicillin and one with sulphonamide-trimethoprim. In addition, grandparent and parent flocks (253 flocks in total) were treated on 48 occasions; in 41 of these phenoxymethylpenicillin was used, 6 amoxicillin and 1 sulphonamide-trimethoprim.

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). Since 2007, there has been a 40% decrease in sales of such products, measured as tubes of oral paste and sachets of oral powder (from 307 per 1000 horses to 183 per 1000 horses). In 2013, guidelines for use of antibiotics in horses were published by the Swedish Veterinary Association and in 2015, this guidance was updated by the Medical products agency (Läkemedelsverket 2015). It is possible that the 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.

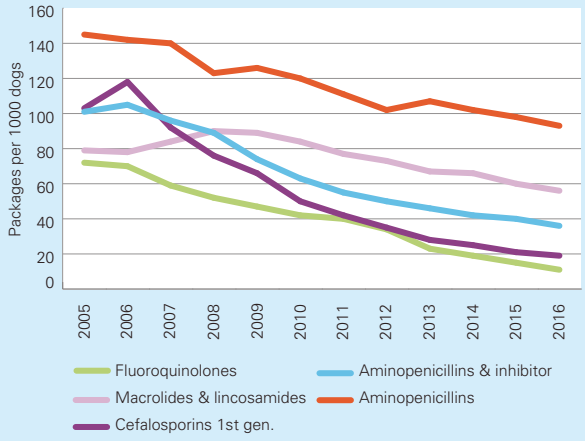
The sales of other antibiotics for horses are difficult to estimate, as such products are frequently sold on requisition and administered by the veterinarian in connection with an examination; in ambulatory practice, in clinics or in hospitals.

Dogs

In 2016, the overall sales of veterinary products for oral medication of dogs were 747 kg compared to 1 879 kg in 2007. Aminopenicillins (without clavulanic acid), first generation cephalosporins and lincosamides were by far the classes with largest consumption in 2016 (290, 224 and 136 kg, respectively).

The figures above refer to sales of veterinary products only. In 2006, the total number of all prescriptions of antibiotics dispensed 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 236 packages per 1000 dogs (-58%). Trends over time for the five largest classes (corresponding to 90% of the total sales) are illustrated in Figure 2.2. The most prominent changes relative to 2006 are noted for cephalosporins (-84%), fluoroquinolones (-84%) and aminopenicillins with clavulanic acid (-66%).

FIGURE 2.2. Sales of the five largest antibiotic classes among antibiotics for oral medication of dogs expressed as packages per 1 000 dogs (2005-2016). Data include antibiotics authorised for veterinary use as well as antibiotics for human use.



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.

Antibiotic resistance in humans

Overview of surveillance systems

The national surveillance systems collect data from two different sources: notifiable diseases and data from clinical samples, which is submitted voluntarily. The clinical samples are mostly from patients with suspected infections, whereas for the notifiable diseases a large proportion of the samples are taken for screening or case finding purposes.

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.

Voluntary surveillance based on clinical samples

Svebar

In 2016, all voluntary data on clinical isolates from humans have been collected though Svebar. This is a system that automatically collects all culture results from participating laboratories. Currently 15 laboratories deliver data to Svebar. It is not possible to deduplicate Svebar data since patient identification is not permitted in the system. Consequently, duplicate findings from blood and other samples will be reported. For unusual resistance types, this can result in differences in proportion of resistance compared to previous years so all resistance trends should be interpreted with caution.

Isolates from blood cultures reported to ECDC/EARS-Net

EARS-Net started in 1998 as EARSS (the European Antimicrobial Resistance Surveillance System) with data from blood cultures on *Staphylococcus aureus*, and *Streptococcus pneumoniae*, and now includes eight species. Sweden participated already the first year. The coordination and validation of results from the participating Swedish laboratories is done by the Public Health Agency of Sweden. Data for EARS-Net 2016 was collected through Svebar for the first time and a total of 14 laboratories were included as they delivered data from the entire year. In general, the proportions of resistance to clinically important antibiotics were low, and this has been the typical situation for Sweden all through the EARSS/EARS-Net history. The resistance trends should be interpreted with caution since patients infected with multi-resistant isolates tend to be sampled more often.

ResNet

One part of the national surveillance programme on antibiotic resistance, ResNet, makes use of zone-diameters reported by the clinical microbiological laboratories participating. Before 2015, the web-based software ResNet was used 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. *Streptococcus pneumoniae* and *Haemophilus influenzae*, commonly causing respiratory tract infections have been included in the programme since 1994. *Escherichia coli* from urine and *Staphylococcus aureus* from skin and soft-tissue infections was included in 2002. In 2005, *Klebsiella pneumoniae* mainly from urine was included.

In 2016, 14 of the 26 laboratories delivered data through Svebar to be included in ResNet. This is the first year for this approach of data collection and the aim is to include data from more laboratories in the future. All resistance data for ResNet were analysed using SIR reported to Svebar during the period 2016-03-01 to 2016-05-31. Data on zone-diameters have been used previous years but due to reporting problems in Svebar only SIR results could be used. The aim is to go back to zone-diameters in 2017.

Microbiological surveillance program

The Public Health Agency of Sweden offers the clinical microbiology laboratories to participate in these programs by sending isolates for verification and characterization. Regarding antibiotic resistance there are currently programs for, *Clostridium difficile*, Enterobacteriaceae with ESBL or $ESBL_{CARBA}$, MRSA, PNSP, and VRE. For *C. difficile* all isolates from one week during the spring and during the fall are ribotyped and tested for antibiotic susceptibility to indicatior antibiotics. For Enterobacteriaceae with ESBL all cefadroxil resistant *E. coli* and *K. pneumoniae* isolates from urine are collected during one month every other year, the isolates are characterized genotypically and phenotypically. All isolates carrying $ESBL_{CARBA}$ are collected and characterized by whole genome sequencing. For MRSA *spa*-type and PVL-status is determined. All PNSP isolates are characterized with serotyping. Isolates from all VRE cases are characterised by whole genome sequencing for epidemiological type and resistance genes.

Overview of sampling and culture results

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 23 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 2016 are given in the section Demographics and denominator data.

In the following figure 3.1 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 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 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 two years.

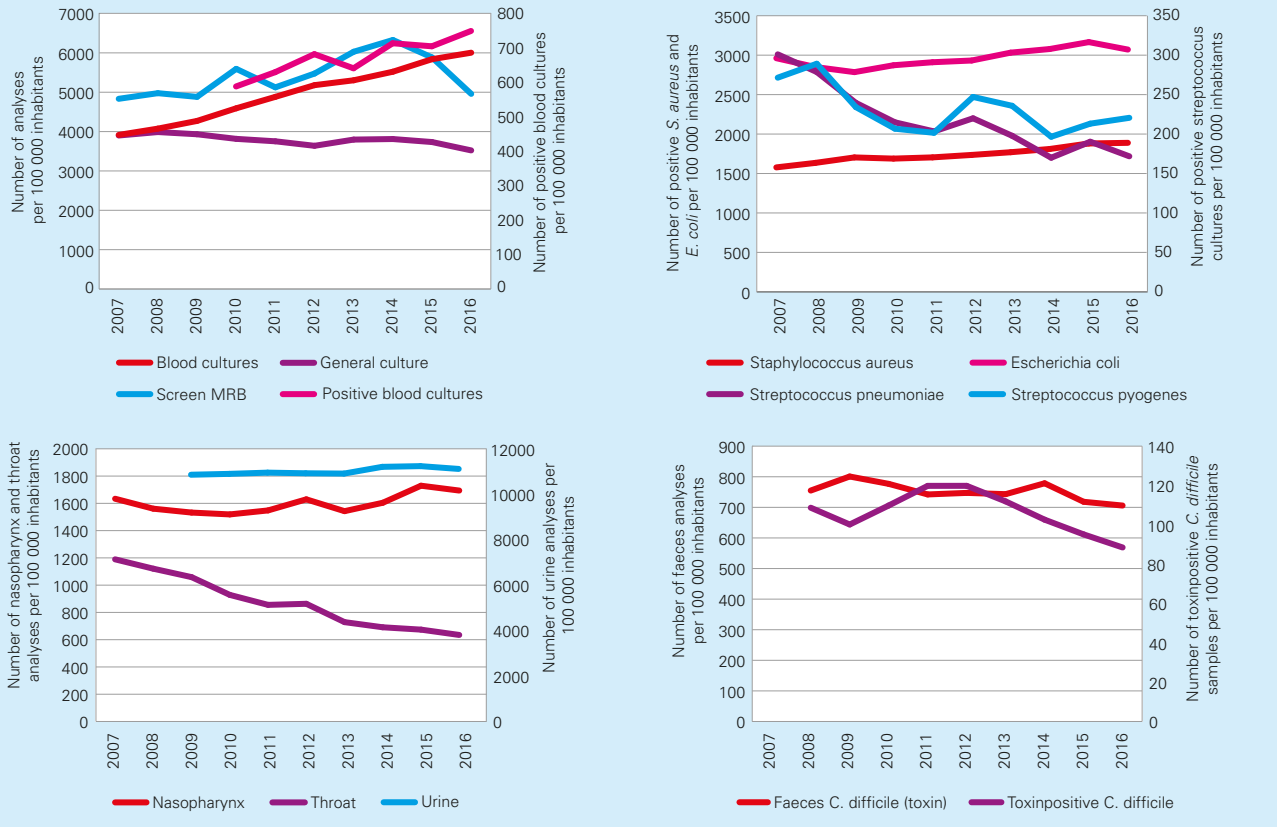
Escherichia coli, Klebsiella pneumoniae, and other Enterobacteriaceae including ESBL and $ESBL_{CARBA}$

Mandatory reporting of ESBL-producing Enterobacteriaceae

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

A total of 10 659 cases were notified in 2016, an increase with 11 percent compared to 2015. Since 2007 the number of cases has increased continuously each year with 8-33 percent. The national incidence was 107 cases per 100 000 inhabitants. An increased incidence was seen in 15 out of 21 Swedish counties, with the highest incidence found in Blekinge county (182 cases per 100 000 inhabitants; Figure 3.2). There was a three-fold difference in incidence between the counties. In part the large variation in incidence between

FIGURE 3.1. Denominator data for humans. Number of requested analyses, and number of positive analyses or isolates. All per 100 000 inhabitants.



counties could be explained by different screening and contact tracing practices.

As in previous years the most commonly reported species was *Escherichia coli* found in 86% of all cases, followed by *Klebsiella pneumoniae* with 9% (Table 3.1).

ESBL-producing bacteria were most often found in urine samples (n=5 870, 55%). The second and third most common sources were fecal and rectal samples with 22% (n=2 378) and 12% (n=1 263) 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 four percent of the cases. In 2016, 609 cases with ESBL-producing bacteria were reported as invasive infections, compared to 578 cases 2015. Among these, 488 were new cases for 2016 and 121 were known carriers of ESBL, notified during previous years.

In 2016, 6 783 cases with ESBL-producing Enterobacteriaceae were reported from women and 3 875 cases from men. The gender distribution has not changed significantly since the surveillance started. The incidence was highest in the age group 80 years and older, followed by the age group 0 year (Figure 3.3). In the other age groups the incidence remained at a lower but slightly increasing level. Among the elderly urinary tract infection is a common bacterial infection which could explain the higher incidence in this group. The high incidence in neonates are probably a result of screening practices at neonatal units and contact tracing for new cases.

TABLE 3.1. Distribution of species among human cases of ESBL-producing Enterobacteriaceae 2016.

Species	Number of cases	Proportion, %
Escherichia coli	9504	86.2
Klebsiella pneumoniae	1011	9.2
Proteus mirabilis	84	0.8
Citrobacter species	32	0.3
Shigella species	25	0.2
Salmonella species	18	0.2
Enterobacteriaceae (not specified or species not reported)	350	3.2
Total number reported	**11024**[a]	

[a]In 330 patients two or more ESBL-producing species were reported resulting in a higher number of isolates than number of cases reported.

FIGURE 3.2. The incidence (cases per 100 000 inhabitants) of ESBL-producing Enterobacteriaceae in Swedish counties 2016, in relation to sample material.

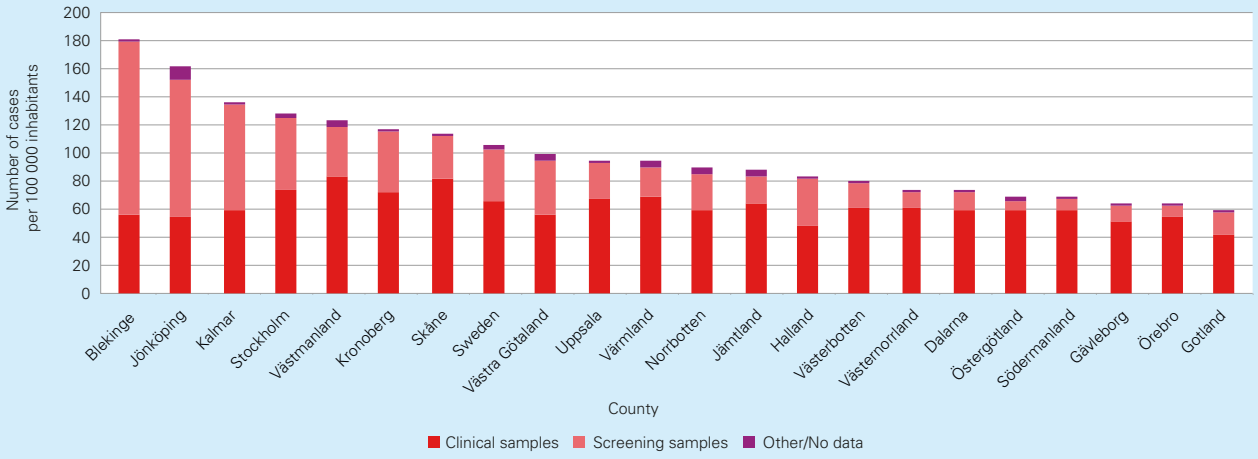


FIGURE 3.3. Incidence per age group of notified human cases of ESBL-producing Enterobacteriaceae 2007-2016.

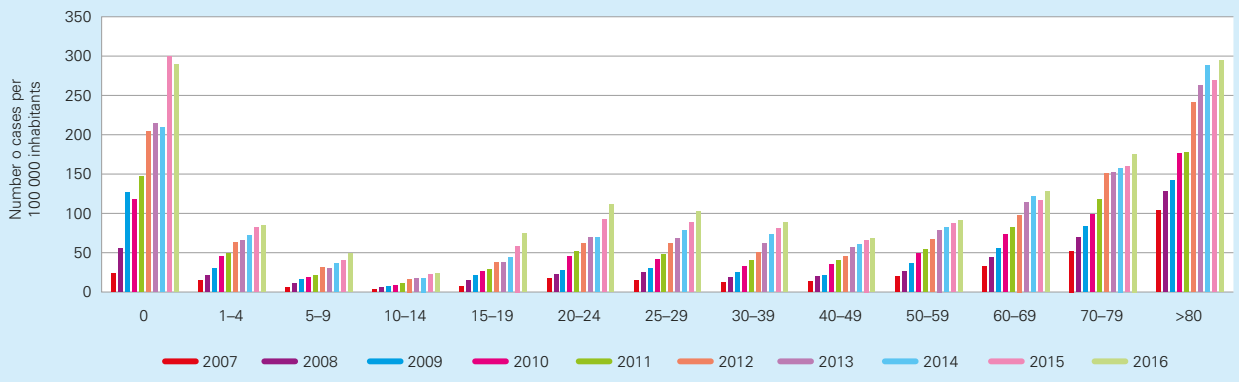
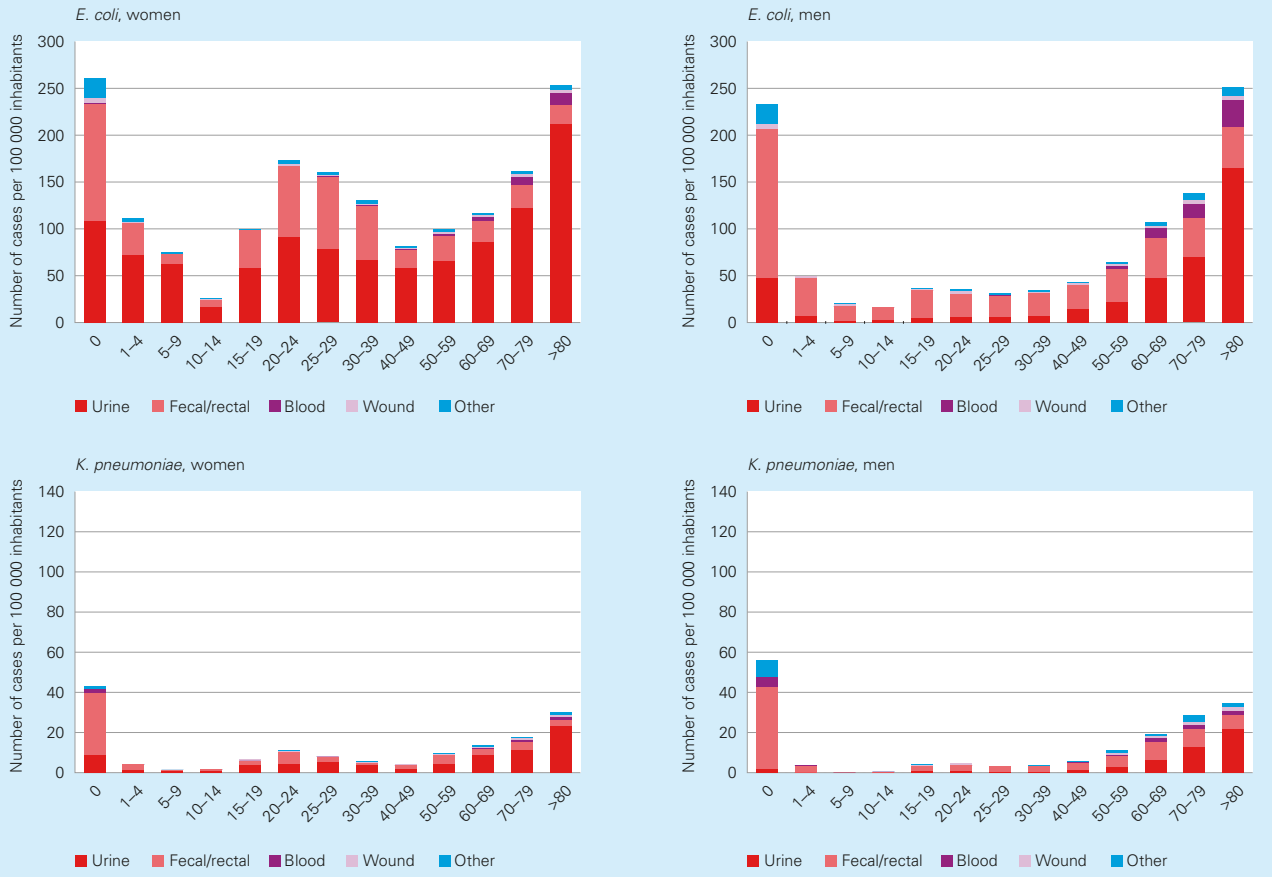


FIGURE 3.4. Age, gender and sample type distribution of human cases of ESBL-producing *E. coli* and *K. pneumoniae* 2016.



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 3.4). ESBL-producing *E. coli* were derived from women in 65% of the cases. They had a median age of 44 years compared to 60 years for men. The *K. pneumoniae* ESBL cases were more equally distributed between sexes, with median ages of 60 years for women and 64 years for men.

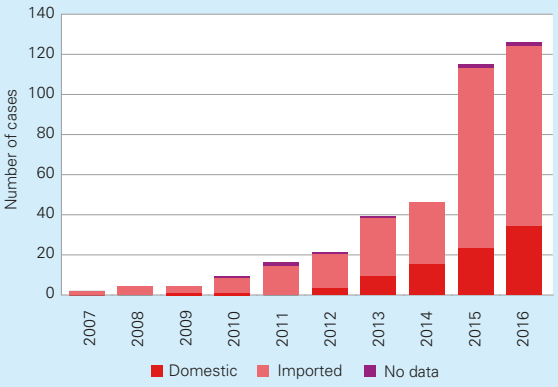
Outbreak investigations

In 2016, one outbreak with ESBL-producing *K. pneumoniae* was reported. The outbreak started at a thoracic clinic in the autumn of 2015 and ended in mid-june 2016. A total of 55 patients were affected. Extensive work on investigation on the underlying causes of the spread of the bacterial strain, tracing and improvement of hygiene in the affected units has been carried out by health care units in cooperation with the infection control team and the County Medical Officers (CMO). Small clusters with both ESBL-producing *K. pneumoniae* and *E. coli* have been noted at neonatal units in different parts of Sweden during 2016.

Mandatory reporting of $ESBL_{CARBA}$-producing Enterobacteriaceae

$ESBL_{CARBA}$ of clinical importance belong to one of three kinds, either KPC (*K. pneumoniae* Carbapenemase)/IMI (imipenem-hydrolyzing ß-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).

FIGURE 3.5. Number of human cases of $ESBL_{CARBA}$ annually notified as domestic and imported in Sweden, 2007-2016.



In 2016, 126 new cases with an $ESBL_{CARBA}$-producing Enterobacteriaceae were reported, compared to 115 new cases in 2015. Cases were reported from nineteen Swedish counties with nearly half of the cases being reported from Stockholm. Of all cases, 27% (n=34) were reported as domestic (Figure 3.5). The five most common countries for imported infections were Turkey (n=9), Iraq (n=8), India (n=7), Lebanon (n=7) and Morocco (n=6).

A majority of the domestic cases in 2016, were identified during investigation of clinical symptoms in contrast to year 2015 when several cases were identified in targeted screening at neonatal units (Figure 3.6). Screening continues to be the leading cause of identification of $ESBL_{CARBA}$-producing Enterobacteriaceae among imported cases. The number of domestic cases with hospital acquired $ESBL_{CARBA}$ decreased from 13 to 6 compared to 2015 but for nearly half of the domestic cases information of acquisition was missing (Figure 3.7). Hospital acquired infection dominated among imported cases but decreased slightly from 64 to 58 compared to 2015 though data on acquisition was missing for 26 cases.

The $ESBL_{CARBA}$-producing Enterobacteriaceae were identified in fecal/rectal samples (n=79), urine (n=26), wound (n=6), respiratory samples (n=1), blood (n=6), and for eight cases sample material was missing. The cases were evenly distributed between gender, and the median ages were 50 and 58 years for women and men, respectively.

In 2016 the most common carbapenemase-producing Enterobacteriaceae was *E. coli* accounting for 56% of all cases, followed by *K. pneumoniae* with 31%. Genes coding for carbapenem resistance have also been detected in several other species of Enterobacteriaceae (Figure 3.8). The dominating enzyme type in 2016 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. Most isolates with $ESBL_{CARBA}$ carry genes that can confer resistance to many antimicrobials, leaving very few options for antibiotic treatment.

FIGURE 3.6. Indications for sampling of domestic (A) and imported (B) cases of $ESBL_{CARBA}$ producing Enterobacteriaceae in humans in Sweden 2012-2016. Number of reported cases each year is shown in brackets.

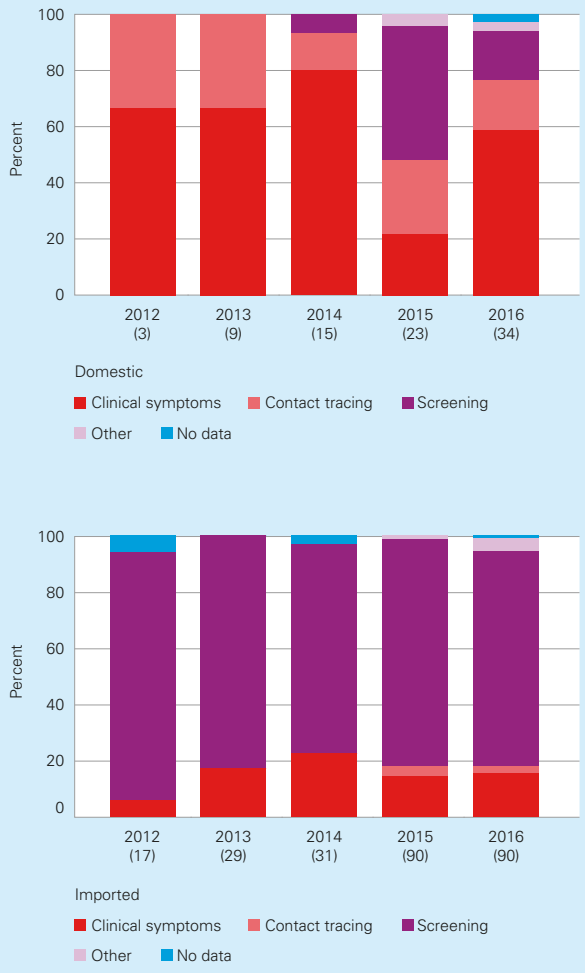
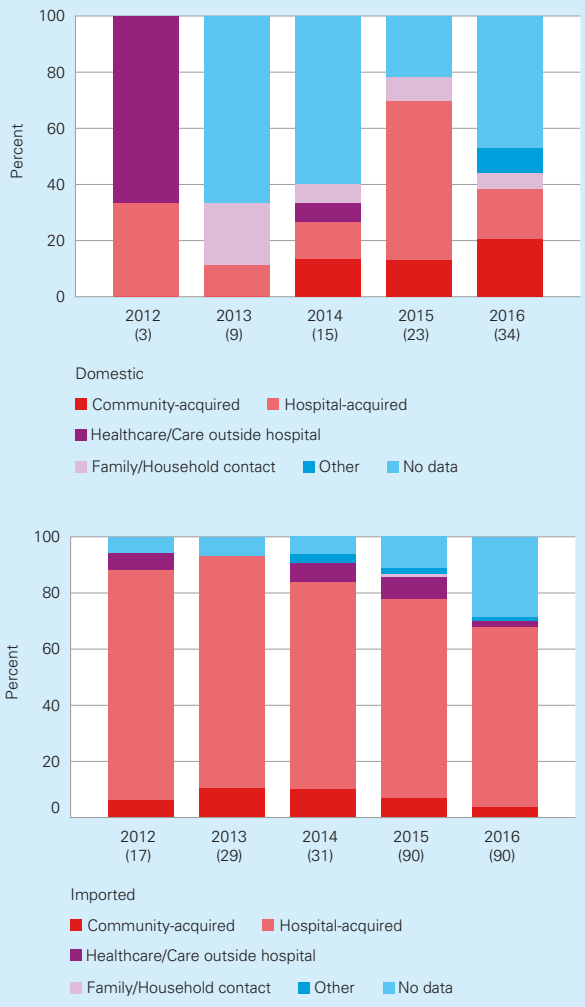


FIGURE 3.7. Epidemiological classification of the acquisition of domestic (A) and imported (B) cases of $ESBL_{CARBA}$ producing Enterobacteriaceae in humans in Sweden 2012-2016. Number of reported cases each year is shown in brackets.



Colistin resistance in Enterobacteriaceae and colistin use in humans and animals

Currently six *mcr*-positive isolates have been identified in humans Sweden, no *mcr*-positive isolates have yet been detected in animals.

Since the initial report of the plasmid-borne *mcr-1* (Mobile Colistin Resistance) gene in November 2015 (Liu Y, Wang YY, et al. 2016), a number of follow up reports have described the prevalence of *mcr* worldwide. So far most of the findings are of the *mcr-1* gene variant but other variants have been described (9, 10). Most findings were livestock associated but human cases increased as well. Reports showed a coexistence of *mcr-1* and carbapenem-resistant Enterobacteriaceae (CPE) with genes such as NDM, KPC, VIM and OXA-48 (Delgado-Blas JF, Ovejero CM, et al. 2016, Yao X, Doi Y, et al. 2016, Du H, Chen L, et al. 2016, Falgenhauer L, Waezsada SE, et al. 2016, Haenni M, Poirel L, et al. 2016, Zhang R, Huang Y, et al. 2016). *Mcr-1* was also detected in the successful *E. coli* clone ST131 (Zheng B, Dong H, et al. 2016). Colistin is one of the last-resort antimicrobial agent for infections caused by MDR bacteria which makes the combination between carbapenemases and MCR of serious clinical concern.

To identify the *mcr*-gene phenotypic screenings with colistin followed by genotypic analysis by PCR or WGS (Whole genome sequencing) for isolates with a colistin MIC >2 mg/L is recommended. Most of the *mcr*-positive isolate have a colistin MIC >2 mg/L but studies have described *mcr*-positive isolates that are sensitive to colistin, i.e. MIC of ≤0.125 mg/L (Liassine N, Assouvie L, et al. 2016).

Recommended Methods for detection

Today the only recommended susceptibility testing method is the reference method broth microdilution (BMD). Other susceptibility testing methods such as gradient tests, disc diffusion and agar dilution are at this moment not reliable (European Centre for Disease Prevention and Control. 2016, The European Committee on Antimicrobial Susceptibility Testing. 2017). European Centers for Disease Control recommends that clinical laboratories should perform colistin susceptibility tests on all MDR Enterobacteriaceae isolates from patients that have been in contact with healthcare facilities abroad, and further test for presence of the *mcr*-gene by using for example PCR or WGS (European Centre for Disease Prevention and Control. 2016).

Human isolates

All Enterobacteriaceae isolates which are sent to the Public Health Agency of Sweden for molecular characterization are analyzed with WGS, and screened for *mcr*-gene variants. Most isolates are sent for verification of carbapenem resistance. As was described in Swedres-Svarm 2015, two *mcr-1* positive isolates were described until 7th of March 2016. One year later, until 21st of March 2017, four more *mcr*-positive human isolates have been identified. Three of these isolates were found in a point prevalence national surveillance program where resistance in cefadroxil resistant *E. coli* and *K. pneumoniae* isolated from urine is characterized. Two *E. coli* and one *K. pneumoniae* were identified. The fourth identified *mcr*-positive isolate was detected in an ESBL-producing *E. coli* from a routine clinical specimen sent for verification. Four of the total six individuals identified with *mcr*-positive isolates had a documented travel history, all of them had been to Asia.

Isolates from veterinary medicine

No *mcr*-gene positive isolates have yet been detected in bacterial isolates from food or animals in Sweden. Within the framework of Svarm, *E. coli* from intestinal contents of healthy farm animals and from meat (Table 6.15), as well isolates from screen-studies for ESBL-producing *E. coli* from these matrices have been phenotypically tested for colistin resistance since 2010. Also, isolates of *Salmonella* from all notified incidents in animals have been tested since 2013 (Table 6.14). In all, 5 isolates of *E. coli* and 9 of *Salmonella* from these matrices were phenotypicaly resistant to colistin but all were negative for *mcr*-genes when tested by PCR. In addition, phenotypically colistin resistant isolates of Enterobacteriaceae from clinical submission to SVA are, when available, tested for *mrc*-genes by PCR. In 2016, 33 isolates from various animal species and matrices were tested and all were negative.

Sales of colistin

The total sales of colistin for systemic use (J01XB01) in Sweden has increased over the last years. However, the consumption in humans is low and in 2016 the sales was 0.006 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 18% since 2000. In 2016, the total sales of topical products with hydrocortisone in combinations with polymyxin B were 39 packages per 1 000 inhabitants and year.

In 2016, the total sales of polymyxins to humans in Sweden measured in mg active substance per kg estimated biomass in human corresponded to 0.000011 (0.000008 colistin and 0.000003 polymyxin B).

In Sweden, colistin is authorised for use in pigs for oral treatment of weaning diarrhea (QA07AA10). In 2016, the overall sales of colistin for animals corre-

sponded to 0.09 mg active substance per population correction unit (PCU, figure for 2015 without farmed fish used as denominator). In 2014, the average reported sales of polymyxins in 29 countries in the EU/EEA was 10.0 mg per PCU (EMA, 2016).

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 2016, a total of 13 859 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 70% of the total sales, and corresponded to around 12 packages per 1 000 dogs and year.

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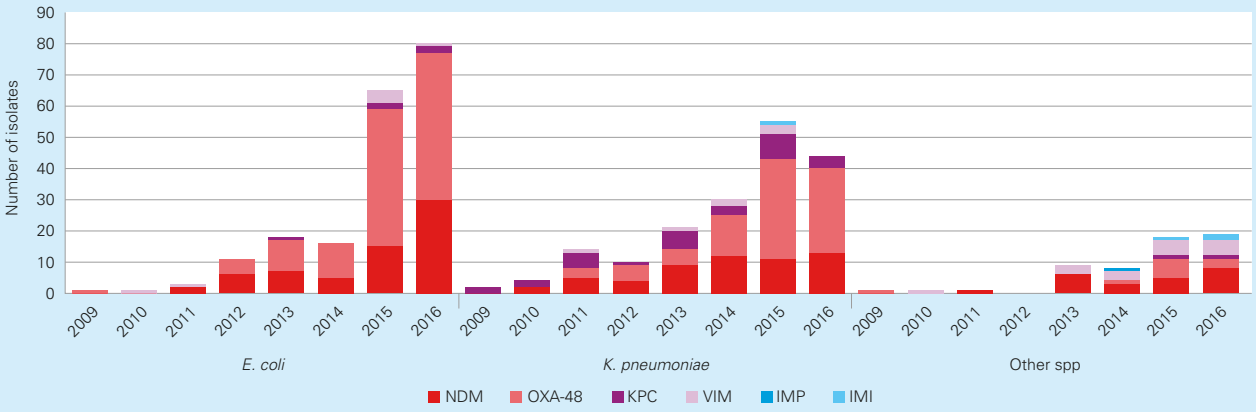
Zheng B, Dong H, et al. 2016, Coexistence of MCR-1 and NDM-1 in Clinical Escherichia coli Isolates. Clin Infect Dis. Aug 9. pii: ciw553. [Epub ahead of print].

FIGURE 3.8. Number of isolates of different species with different ESBL-enzymes among human cases with $ESBL_{CARBA}$ in Enterobacteriaceae in Sweden 2009-2016. In a small number of samples two or more $ESBL_{CARBA}$-producing species were reported resulting in a higher number of isolates than number of cases reported and in some samples two different enzyme types were detected in the same sample.



Outbreak investigations

During 2016 two clusters of $ESBL_{CARBA}$-producing *E. coli* with NDM-5 were identified at the Public Health Agency of Sweden. Clade 1, contained seven isolates with sequence type 167 and the same resistance genes CTX-M, CIT and NDM-5, they were isolated from patients in five different counties in Sweden. Clade 2, contained five isolates with sequence type 405 and the same resistance genes CIT and NDM-5. The isolates were from patients in four different counties in Sweden. These two clades were not genetically related, they had different sequence types and also the plasmids differed. For most of the patients in the both clades no epidemiological links could be found. A majority of cases in both clades were clinical cases.

Escherichia coli, clinical isolates from blood and urine

Escherichia coli reported to EARS-Net

The numbers of isolates of *E. coli* (n=6 985) were much greater than the numbers for the other pathogens reported to EARS-Net. The proportion of resistance for *E. coli* to the antibiotics included in EARS are shown in Figure 3.9. Increasing trends of resistance to third-generation cephalosporins over the past six years are seen, due to an increasing prevalence of ESBL-producing isolates. Resistance to fluoroquinolones is now on a level of 13.6%, with a slight increase over the past three years while the carbapenem resistance remains at a very low level (0.1%).

Escherichia coli from urine (ResNet)

Overall, resistance rates reported in ResNet remained stable. *E. coli* isolates, mainly derived from urinary tract infections, have been included in the national surveillance programme ResNet regularly since 1996 and every year since 2001. Resistance to commonly prescribed oral antibiotics for treatment of urinary tract infections (UTI) caused by *E. coli* has been tested every year. Cefadroxil resistance is used as an indicator for presence of genes coding for ESBLs. Ampicillin was substituted for amoxicillin-clavulanic acid from 2015 but is not shown in the figures since only two years of data is available. It should be noted that

FIGURE 3.9. Antibiotic resistance in *E. coli* isolates from bloodstream infections included in EARS-Net surveillance during the years 2007-2016.

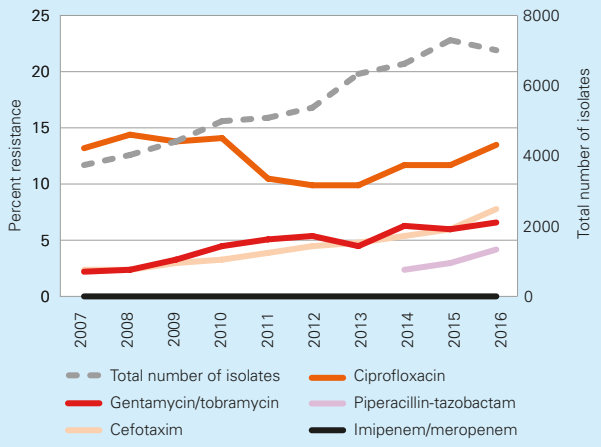
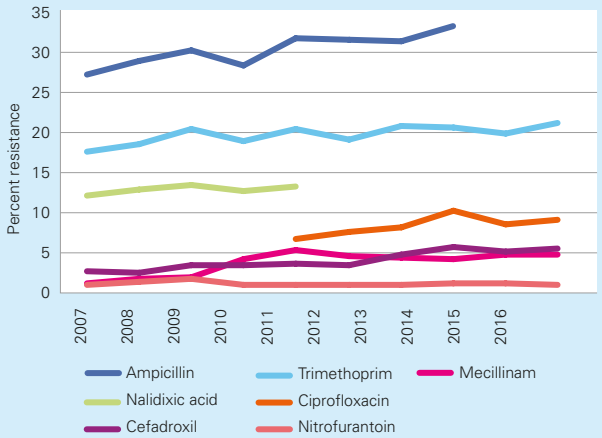


FIGURE 3.10. Resistance rates for antibiotics commonly used to treat urinary tract infections, *Escherichia coli* 2007-2016 (ResNet).



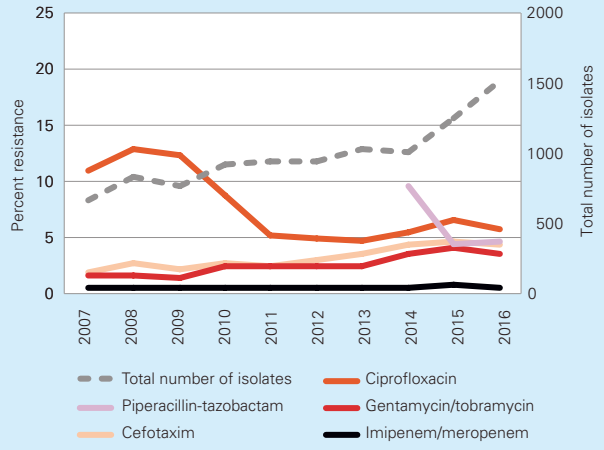
ciprofloxacin 5µg is now the recommended disk for detecting fluoroquinolone resistance, and the resistance rate represents resistance R and not I+R as was the case when nalidixic acid was used (Figure 3.10).

Klebsiella pneumoniae, clinical isolates from blood and urine

Resistance data on *K. pneumoniae* reported to EARS-Net

The proportion of resistance for *K. pneumoniae* to the antibiotic combinations defined by EARS are shown in Figure 3.11. The resistance to third-generation cephalosporins and flouroquinolones are quite stable over time. The carbapenem resistance remains at a very low level (0.1%).

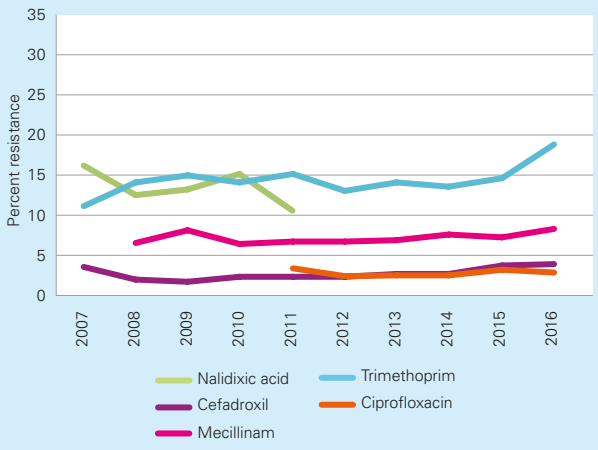
FIGURE 3.11. Antibiotic resistance in *K. pneumoniae* isolates from bloodstream infections included in EARS-Net surveillance during the years 2007-2016.



Resistance data on *K. pneuomoniae* from urine (ResNet)

K. pneumoniae isolates mainly derived from urine samples have been included in the surveillance programme since 2005. In 2016, the resistance levels for all tested antibiotics remained at approximately the same levels as seen in 2015 with exception for trimethoprim (Figure 3.12).

FIGURE 3.12. Resistance rates for antibiotics commonly used to treat urinary tract infections, *Klebsiella pneumoniae* 2007-2016 (ResNet).



Staphylococcus aureus including MRSA

Mandatory reporting of methicillin resistant *Staphylococcus aureus*

Background

MRSA has been notifiable according to the Communicable Disease Act since year 2000. Infection control programmes for MRSA have been developed and implemented locally under supervision of the County Medical Officers (CMO) and infection control teams. The programmes are based on early case-finding through screening of patients with risk factors and, in cases of confirmed MRSA, contact tracing combined with infection control measures such as hospital care of patients with clinical infection caused by MRSA in single rooms and campaigns on basic hygiene precautions.

Notifications of MRSA according to the Communicable Disease Act

In 2016 a total of 4 402 cases of MRSA were notified, an increase by 520 cases (13%), see Figure 3.13. This is a smaller increase than previous year (33%).

The national incidence, based on yearly number of cases, increased from 39 cases per 100 000 inhabitants to 44 cases per 100 000 inhabitants. The last ten years there has been a significant increase ($p<0.001$) of the MRSA incidence with 103% per five years. When analysing the incidence based on number of cases monthly however there is a significant ($p<0.001$) decline in MRSA incidence from December 2015 to December 2016, see figure 3.14. The incidence among domestic cases has doubled the last 10 years from 7 cases/100 000 inhabitants to 16 cases/100 000 inhabitants, however no increase in incidence was seen between 2015 and 2016 (16 cases/100 000 inh).

The highest incidence was seen in the counties of Blekinge (120 cases/100 000 inh), Kalmar (106 cases/100 000 inh) and Jämtland (71 cases/100 000 inh), while the lowest incidence was seen in Södermanland (27 cases/100 000 inh), Västerbotten (28 cases/100 000 inh) and Västra Götaland (29 cases/100 000 inh). Different screening and contact tracing practices and uneven distribution between counties of people seeking political asylum are probable explanations to the large variation in incidence between counties.

In 2016, 37% (n=1 635) of all reported MRSA were domes-

FIGURE 3.13. Number of human cases of MRSA acquired in Sweden and acquired outside of Sweden year 2007-2016.

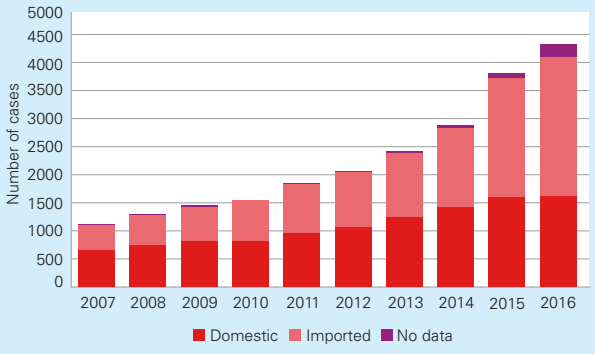
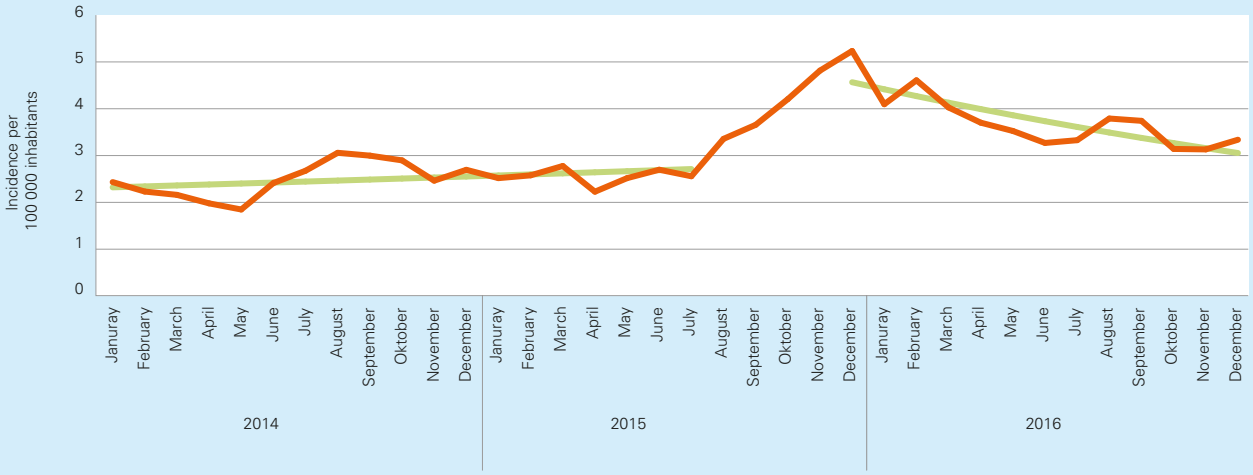


FIGURE 3.14. The MRSA incidence (human cases) from January 2014 to December 2016.



tic cases and 57% (n=2 529) were acquired abroad. When imported, MRSA was most often acquired in Syria (n=777, 18%) followed by Iraq (n=346, 8.2%), Afghanistan (n=204, 4.6%) and the Philippines (n=78, 1.8%). For approximately five percent (n=238) country of infection was missing ("No data"). The most commonly reported indication for sampling among domestic cases were investigation of clinical symptoms (n=809, 49%) and contact tracing (n=618, 38%), see figure 3.15A. Among imported cases screening remains most common (n=1186, 47%) followed by clinical symptoms and contact tracing, see figure 3.15B. Overall, the majority of samples from investigations of clinical symptoms were wound samples (n= 1 014, 67%).

Among samples from screening throat swabs were most common (n=532, 37%). Invasive MRSA infection was reported in 44 cases during 2016 compared to 36 cases during 2015. Out of them were 33 cases newly notified 2016 and 11 cases in patients already known to carry MRSA.
Community acquired infections continue to be most common among domestic and imported cases in 2016, Figure 3.16A and B. A higher proportion of hospital acquired MRSA was noted among imported cases (n=404, 16%), than among domestic cases (n=76, 4.6%). The number of domestic cases with hospital acquired MRSA decreased from 105 cases (6.4%) in 2015 to 76 cases (4.6%) in 2016. The proportion of cases with MRSA acquired in healthcare/care outside hospital were low for both domestic (n=104, 6.4%) and imported (n=133, 5.3%) cases. One out of five (n=491, 19%) imported cases and 11% (n=186) of the domestic cases with MRSA had no information on epidemiological classification. The classification is based on information in the clinical notifications and subsequent investigations by the CMOs.

Among the domestic MRSA cases 2016, the incidence was highest in the age group 0 year olds (218 cases/100 000 inh), followed by the age group ≥80 years (29 cases/100 000 inh), see figure 3.17. The incidence of MRSA among the 0 year old was 13 times higher than the overall incidence

FIGURE 3.15A AND B. Indications for sampling of domestic A) to the left and imported B) to the right, human MRSA cases year 2007-2016. Presented as proportion (%) of all samples.

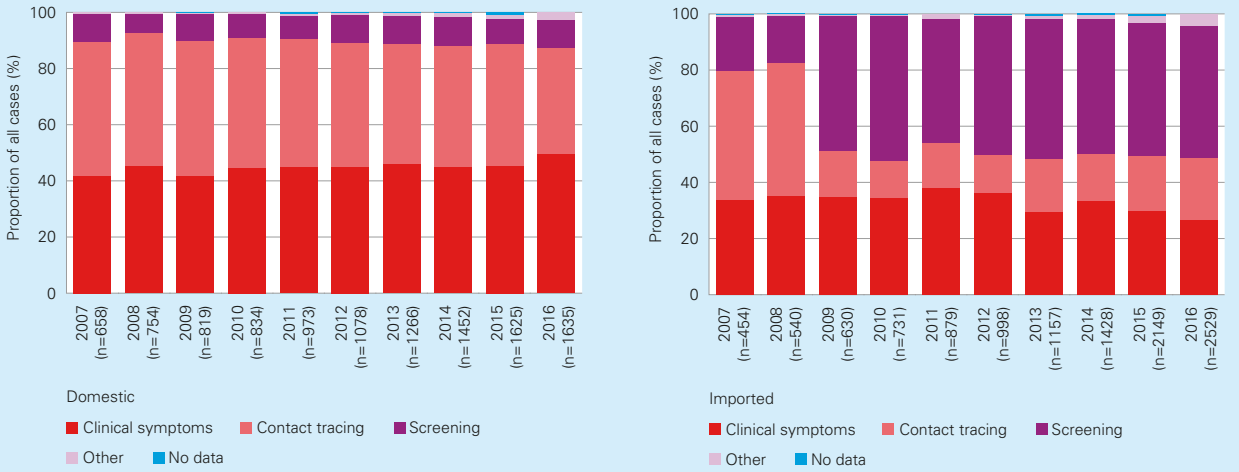
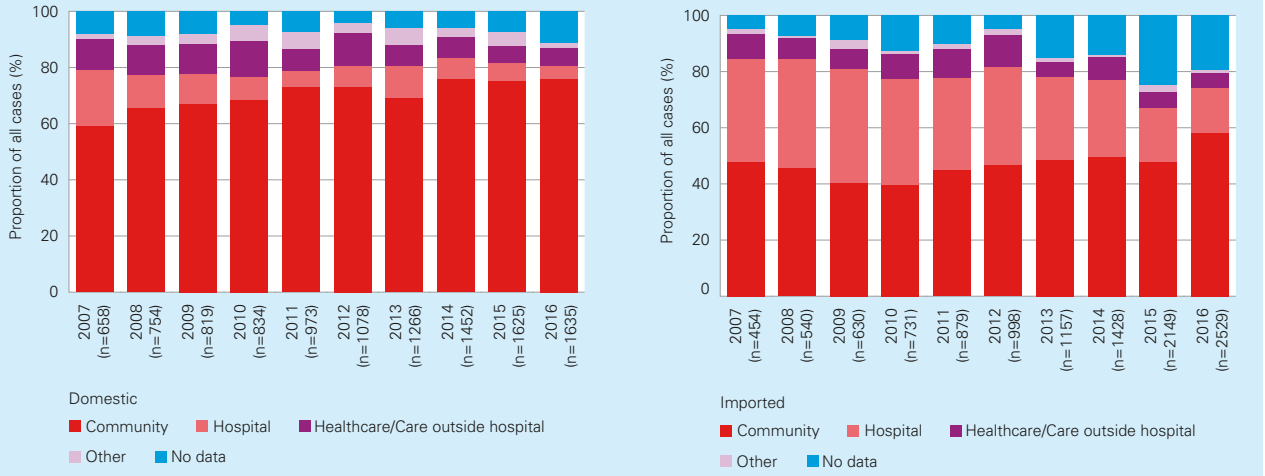


FIGURE 3.16A AND B. Epidemiological classification of domestic A) to the left and imported B) to the right, human MRSA cases year 2007-2016. Presented as proportion (%) of all samples.



for domestic cases (16 cases/100 000 inh). In the other age groups the incidence remained at similar levels as in 2015, with a range from 8.6 to 28 cases per 100 000 inh. Out of the 260 domestic MRSA cases among 0 year olds 149 (57%) was detected through contact tracing, 62 (24%) by screening and 40 (15%) by clinical symptoms. One in ten was healthcare related (n=25, 10%), 7 of these were part of 2 neonatal outbreaks comprising 3 or more cases, 225 cases (87%) were community acquired.

Outbreak investigations

During 2016, thirteen outbreaks (three or more cases/outbreak) were reported in seven different counties. These outbreaks comprised 67 cases, representing 1.5% of all cases of MRSA in 2016. The three most common *spa*-types were t002, t127 and t008. Eight outbreaks were reported from long-term care facilities, three from healthcare outside hospitals whereas two were hospital outbreaks.

Epidemiological typing of MRSA

The 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 2016, *spa*-typing results were available for MRSA isolates from 98% of the notified cases, and all but 31 of the 4 314 isolates were typable. A total of 484 *spa*-types were recorded as compared to 464 in 2015.

The ten most common *spa*-types in 2016 were t304 (n=510), t223 (n=501), t127 (n=251), t044 (n=226), t002 (n=201), t008 (n=171), t386 (n=107), t019 (n=99), t690 (n=96) and t021 (n=78). A total of 52% (n=2 240) of the notified cases had an MRSA with a top ten *spa*-type. Three of these *spa*-types, t304, t223 and t021, were more prevalent in 2016 than in 2015.

FIGURE 3.17. Incidence of domestic MRSA in humans 2007-2016 among different age groups.

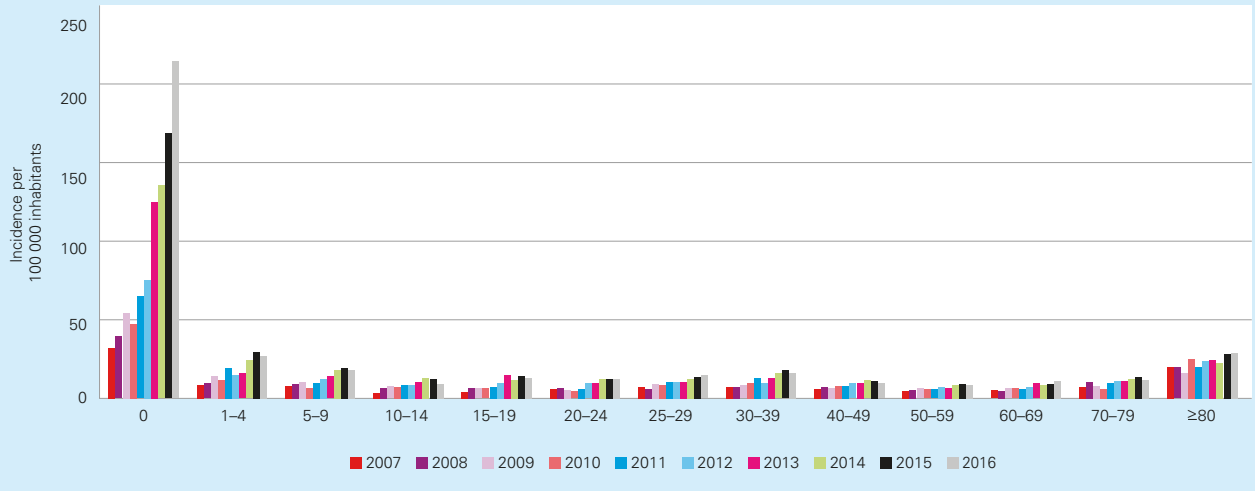


FIGURE 3.18. The ten most common *spa*-types, with PVL-status, in 2016 among human MRSA aquired in Sweden (dom) and outside of Sweden (imp).

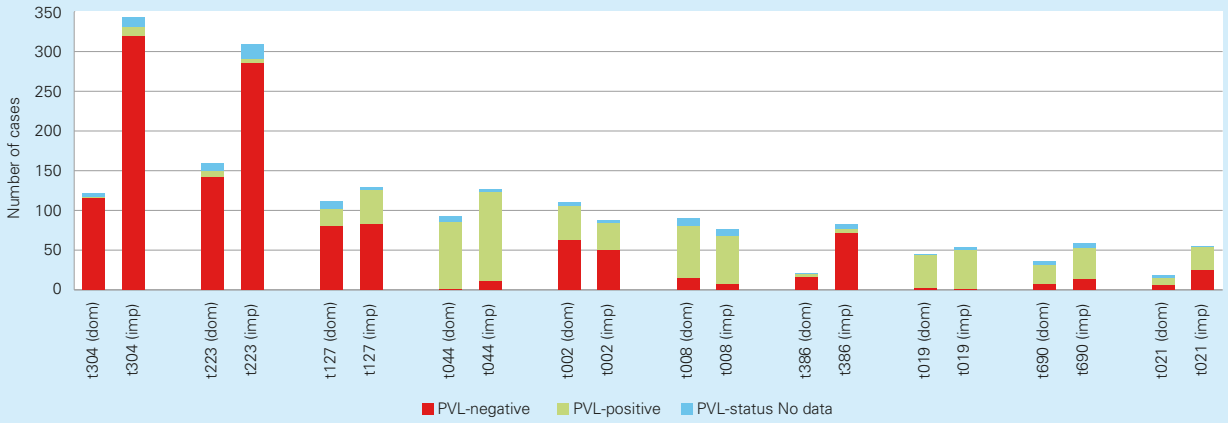
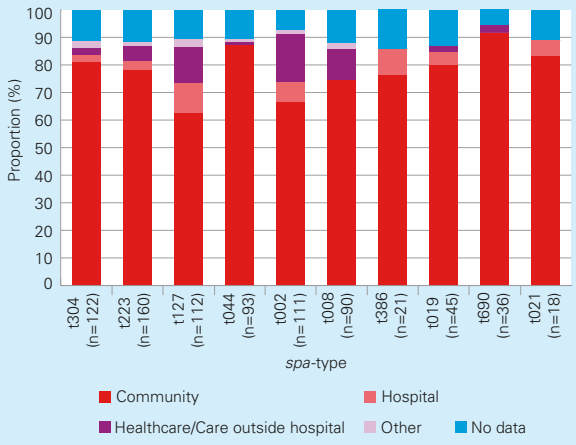


FIGURE 3.19. The ten most common *spa*-types 2016 in relation to epidemiological classification of human MRSA aquired in Sweden. Presented as proportion (%) of the number of cases per *spa*-type (n).

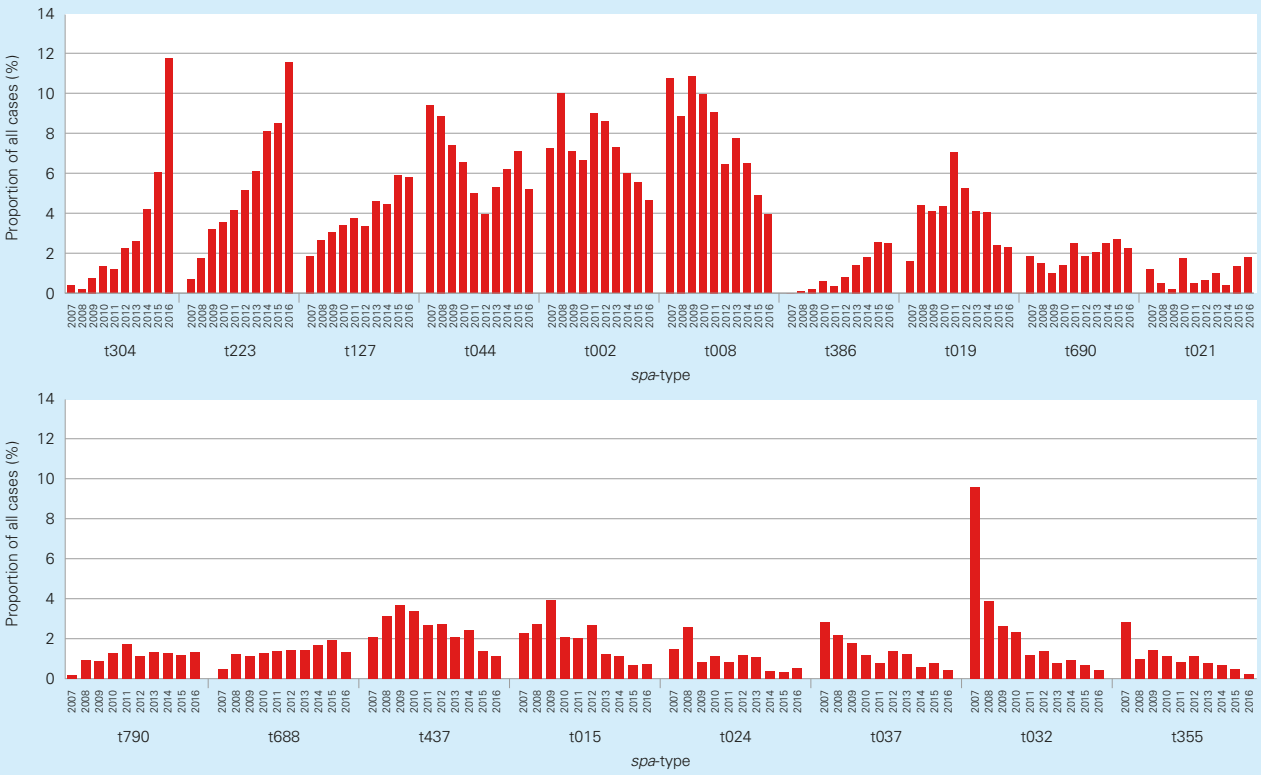


The distribution of the top ten spa-types in 2016, and information on PVL-status, is shown for isolates from cases with domestically acquired MRSA (n=1 608) and MRSA acquired abroad (imported, n=2 472), respectively, in Figure 3.18. All ten *spa*-types were seen among both domestic and imported cases. Information regarding where the MRSA was acquired was missing for 234 cases.

The distribution of the top ten *spa*-types of MRSA aquired in Sweden in relation to epidemiological classification is shown in Figure 3.19. For all ten *spa*-types, acquisition in the community was most common. For three of the *spa*-types, t044, t008 and t690, there were no reported cases with hospital acquired MRSA. Among MRSA acquired in hospital, t127 was the most common *spa*-type, and for MRSA acquired in Healthcare/Care outside hospital, t002 was most commonly seen.

Figure 3.20A and B show the proportions of each of the top ten *spa*-types per year for 2007-2016. In total, 18 *spa*-types have been among the top ten during one or more years. In 2007, t032 was the most common *spa*-type (98 cases) and in 2016, t304 was the most common (510 cases). Four *spa*-types, t044, t002, t127 and t008, have been among the top ten during the whole ten year period.

FIGURE 3.20A AND B. The most common *spa*-types among MRSA in humans year 2007-2016. Presented as proportion of all cases (%).



Staphylococcus aureus, clinical isolates from blood and skin and soft tissue infections

S. aureus from blood (EARS-Net)

The total number of *S. aureus* from blood samples decreased during 2016, most likely a result of that only 14 laboratories reported data to Svebar in 2016 compared to 18-19 earlier years when a different data collection method was used. The rate of MRSA in blood has been steady through the years (indicated by cefoxitin resistance). The increase in cefoxitin resistance seen 2016, to a level of 2.3%, should be interpreted with caution since patients infected with multiresistant isolates tend to be sampled more often. Antibiotic susceptibility to vancomycin was tested for 443 out of 2 238 (20%) *S. aureus* and no resistance was detected (Figure 3.21).

S. aureus from skin and soft tissue infections (ResNet)

S. aureus from skin and soft tissue infections has been included in the annual surveillance programme since 1994. 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 1.8% in 2016. The average resistance proportions for erythromycin and clindamycin indicates an increasing trend over the past three years. Resistance to aminoglycosides was still only 1% (Figure 3.22).

FIGURE 3.21. Antibiotic resistance in *S. aureus* isolates from bloodstream infections included in EARS-Net surveillance during the years 2007-2016.

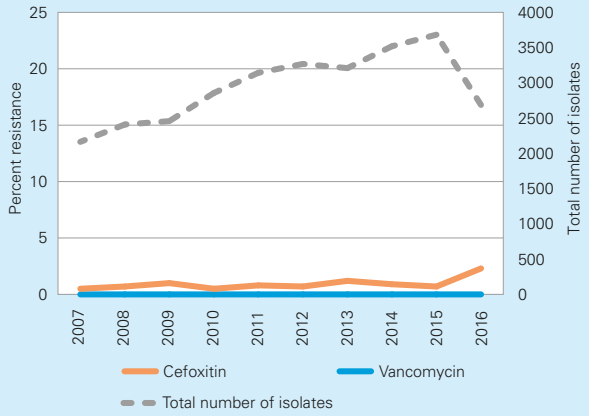
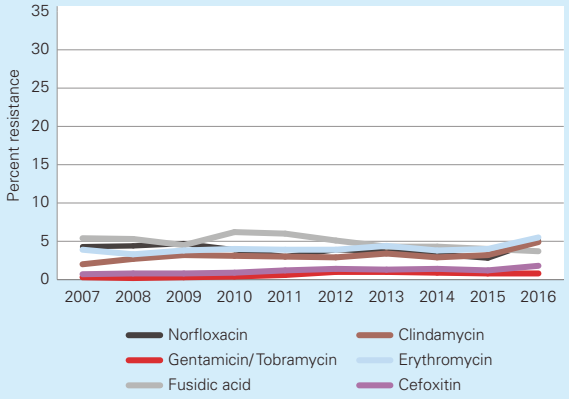


FIGURE 3.22. Resistance rates for *S. aureus* from skin and soft tissue infections 2007-2016 (ResNet).



Antibiotic resistance in MRSA from humans – results from Svebar

In previous Swedres – Svarm reports, antibiotic resistance in MRSA was, with the exception of 2009, reported until 2011. Here the data from previous reports are summarized and results from Svebar for 2013-16 are added.

The previously reported results were based on all MRSA isolates sent for epidemiological typing. This included all isolates except those from two or three laboratories.

Svebar is an automated system, which collect all culture results including susceptibility test results from participating laboratories. Currently fifteen out of twenty-six laboratories deliver data to Svebar. This covers approximately seventy percent of the Swedish population.

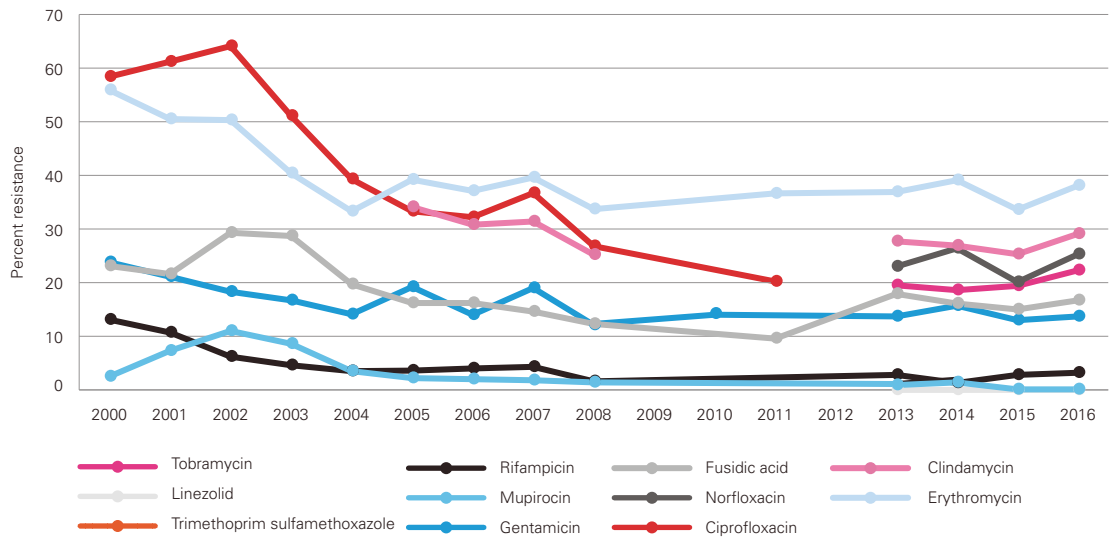
In this compilation of data from Svebar only results from samples obtained for clinical diagnostic purposes were selected, i.e. results from screening and case-finding were excluded. Thus, this compilation differs from the ones previously presented in Swedres-Svarm in two aspects: The previous data was case-based whereas the data from Svebar may contain duplicate results from patients. Secondly, the previous data included all MRSA-cases, irrespective of the indication for culture, whereas the data from Svebar is from cultures taken for diagnostic purposes.

Culture results from Svebar are presented in Table 1. The proportion of resistance among MRSA is shown in Figure 1. It is interesting to note that despite the difference between the periods in how data were obtained, the proportions of resistance among MRSA to other antibiotics remain at similar levels. The decrease between 2000 and 2004 reflects the shift from hospital to community acquired strains.

TABLE 1. Number of *S. aureus* and MRSA from clinical cultures and the proportion of MRSA for 2013 – 2016.

Year	2013	2014	2015	2016
Number of *S.aureus*	72560	95444	100543	105990
Number of MRSA	827	1099	1423	1708
Proportion of MRSA	1,1%	1,2%	1,4%	1,6%

FIGURE 1. Antimicrobial resistance in MRSA.

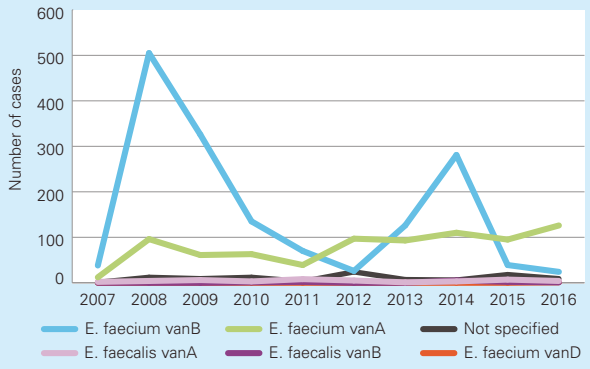


Enterococcus faecalis and *Enterococcus faecium* including VRE

Mandatory reporting of vancomycin resistant enterococci

Vancomycin resistant enterococci (VRE) are important causes of nosocomial infections in many parts of the world, usually involving high-risk populations frequently in contact with health-care 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. From 2000 to 2006 only low numbers (18-35 cases 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 and included 872 cases. 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* 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 (Figure 3.23).

FIGURE 3.23. Number of cases of VRE and their corresponding to species and van-gene.



Notifications of VRE according to the Communicable Disease Act

165 cases were reported in 2016, a slight increase compared to 2015 (n=157). For 2016, 81 cases (49%) were reported as acquired in Sweden and 83 cases (50%) as acquired abroad, data is missing for one case (Figure 3.24). VRE cases were reported from 18 of the 21 Swedish counties with a national incidence of 1.65 per 100 000 inhabitants and year. Eight counties had a higher incidence than the national incidence, Norrbotten (4.8), Uppsala (3.6), Gävleborg (2.8), Stockholm (2.1), Västerbotten (1.9), Skåne (1.7), Gotland (1.7) and Jönköping (1.7). The most common countries reported for VRE acquisition abroad were Greece (n=8), Spain (n=7), Iran (n=5), Serbia (n=5) and Thailand (n=5). Seventy-five (90%) of the cases with acquisition abroad were healthcare related (Figure 3.25A and B). Accordingly a majority of the isolates (n=139, 84%) were from feaces and rectum, and only 16 percent from urine, wound or other clinical samples. The VRE cases were equally distributed between sexes (46% female and 54% male), with median ages of 71 years for women and 68 years for men. In 2016, 151 cases were reported as *E. faecium* and 5 cases as *E. faecalis*. In three cases both *E. faecium vanA* and *E. faecalis vanA* could be isolated (Figure 3.23). One invasive VRE infection was reported in 2016.

FIGURE 3.24. Number of VRE cases and country of acquisition reported during ten years (2007-2016).

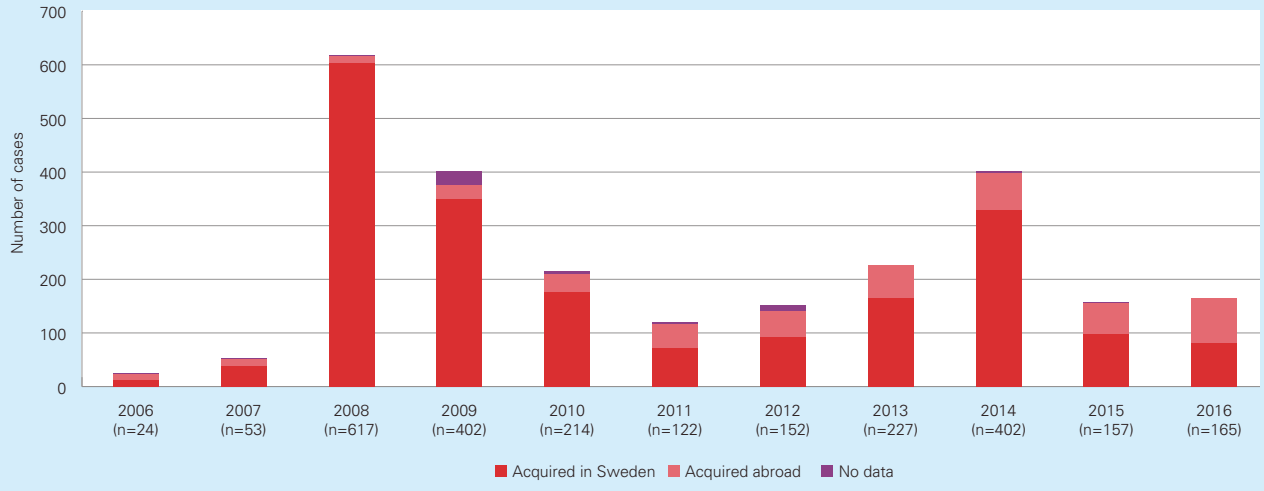
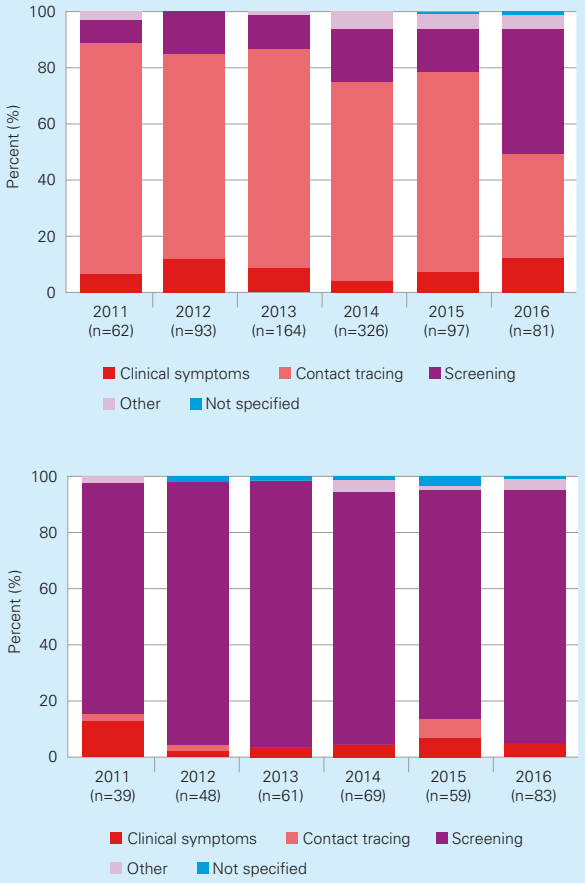


FIGURE 3.25A AND B. Source of VRE acquisition in Sweden (top) and abroad (bottom) 2011-2016.



Epidmiological typing of VRE in outbreaks

Since May 2016 epidemiological typing of VRE has been performed with whole genome sequencing (WGS). The Public Health Agency changed method for epidemiological typing from pulsed field gel electrophoresis (PFGE) for the benefit of whole genome sequencing and "single nucleotide polymorphism" (SNP) based analysis. WGS with SNP analysis is more discriminatory and give higher resolution than PFGE and can be visualized graphically to illustrate how isolate relates to other known cases. This image shows a family tree of submitted isolates based on SNPs. The already established national nomenclature used for VRE based on PFGE patterns have been possible to continue to use for whole genome sequencing. International nomenclature for enterococci with whole genome sequencing based on "expanded MLST" is under development but currently lacking.

The *E. faecium* with *vanB* causing the outbreak 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* have caused more but smaller hospital-related outbreaks while *E. faecium* with *vanB* have caused fewer outbreaks but with more cases. In 2016, fourteen hospital-related outbreaks were reported as well as some additional cases that can be associated to cases found earlier than 2016. The three largest outbreaks were found in Uppsala, Norrbotten, and Västmanland Counties, with 8, 9 and 11 patients respectively *(E. faecium vanA)*. The epidemiological typing of VRE from all new cases makes it possible to identify outbreaks among the relatively large number of isolates with "unique" patterns.

Enterococcus faecalis and *Enterococcus faecium*, clinical isolates from blood

Enterococcus faecalis and *faecium* from blood (EARS-Net)

Enterococci causes considerably fewer bloodstream infections than *E. coli*. All *E. faecalis* isolates were susceptible to vancomycin while the resistance for *E. faecium* was 0.4% (Figures 3.26 and 3.27). The high-level aminoglycoside resistance (HLAR) decreased slightly compared to 2015 for both *E. faecium* and *E. faecalis*.

FIGURE 3.26. Antibiotic resistance in *E. faecalis* isolates from bloodstream infections included in EARS-Net surveillance during the years 2007-2016.

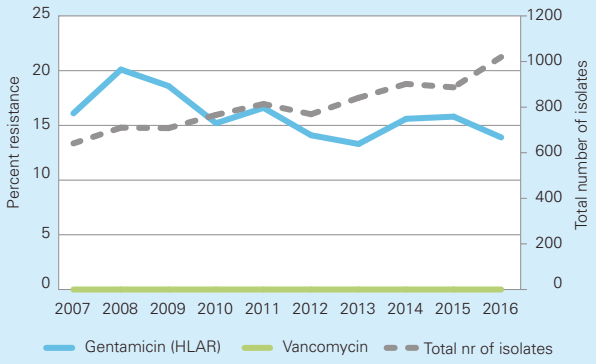
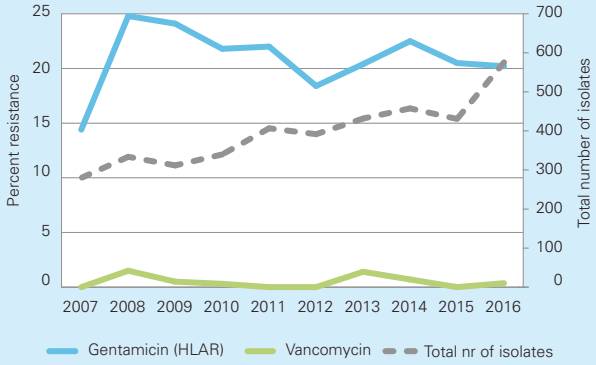


FIGURE 3.27. Antibiotic resistance in *E. faecium* isolates from bloodstream infections included in EARS-Net surveillance during the years 2007-2016.



Streptococcus pneumoniae including PNSP

Mandatory reporting of *Streptococcus pneumoniae* with reduced susceptibility to penicillin (PNSP)

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.

Notifications according to the Communicable Disease Act

In 2016 a total of 67 PNSP (MIC >1mg/L) cases were reported in Sweden including two cases of invasive infections (blood). Forty-eight percent of the cases had been infected in Sweden and forty percent of the cases in a foreign country. For the remaining eight cases no country of acquisition was given. The incidence of PNSP in Sweden 2016 was 0.67 cases per 100 000 inhabitants and year. PNSP was most common in the age-groups 0-4 years (43% in 2016), independent of year observed (Figure 3.28). Of the reported cases in 2016, 63% were male and 37% female. PNSP were reported from 15 of 21 Swedish counties, with Norrbotten (n=14), Skåne (n=8), Stockholm (n=8), Örebro (n=5), Västernorrland (n=5) and Västerbotten (n=5) accounting for 67% of all notifications. The remaining nine counties reported 1-4 cases each. PNSP were most often found in cultures from the nasopharynx. In 40 cases (60%) the detection of PNSP was due to clinical infection, two cases were reported as invasive (blood). Three cases were detected through contact tracing and sixteen cases through targeted screening. In the remaining cases another reason for sampling was stated (n=3) or the information was missing (n=5).

Serotype distribution

In order to follow and evaluate the effect of vaccination against pneumococcal disease and to identify spread of antibiotic resistant clones, the Public Health Agency of Sweden has continued to collect and perform serotyping on PNSP isolates according to the previous definition. In 2016, about 325 samples with an MIC ≥ 0.5 mg/L were collected, which is approximately the same amount as in 2015. The serotype distribution from these 325 isolates were, in descending order: 19F* (21%), non-typable (NT; 15%), 23F* (9%), 35B (9%), 19A* (7%), 9N (5%), 6A* (4%), 6B (4%), 9V* (4%) and 11A (4%). Of the serotyped isolates 54% constituted types included in vaccine used for children in the national programme (marked with asterisk, *).

A total of 48 isolates with MIC > 1 mg/L were sent to the Public Health Agency of Sweden for serotyping during 2016. Of these, 38 isolates belonged to serotypes included in the vaccines. The two invasive cases were caused by PNSP with serotype 23F.

Streptococcus pneumoniae, clinical isolates from blood and respiratory specimens

Streptococcus pneumoniae reported to EARS-Net

The antibiotic susceptibility for PcG and erythromycin in *S. pneumoniae* remained approximately at the same level during 2016 as in 2015 (Figure 3.29). In 2016 the total number of *S. pneumonia* isolates from blood (Svebar data from 15 laboratories), subjected to antimicrobial susceptibility testing increased from 912 (2015) to 1421 which is a result of a different data collection method used where repeated sampling cannot be excluded.

FIGURE 3.28. Incidence per agegroup for PNSP acquisition in Sweden and abroad 2016.

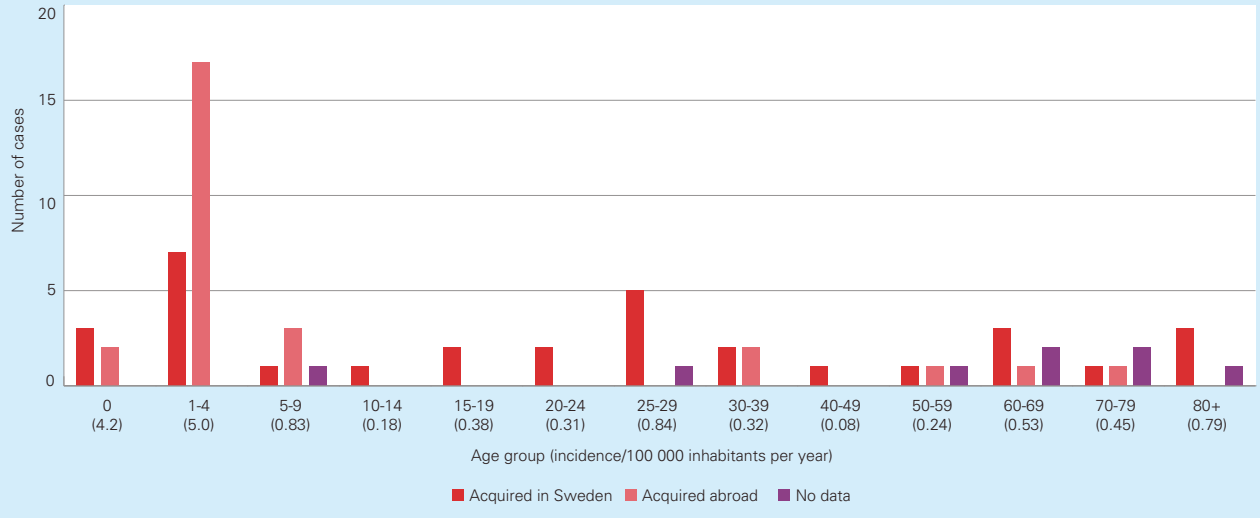
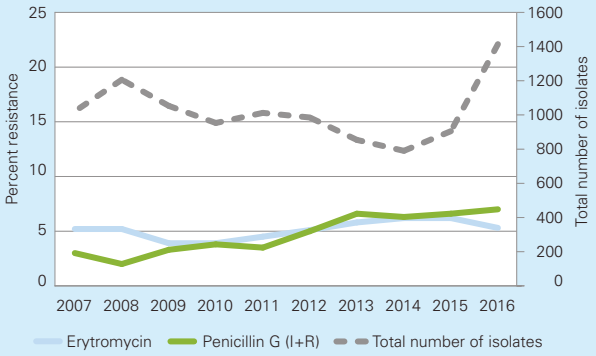


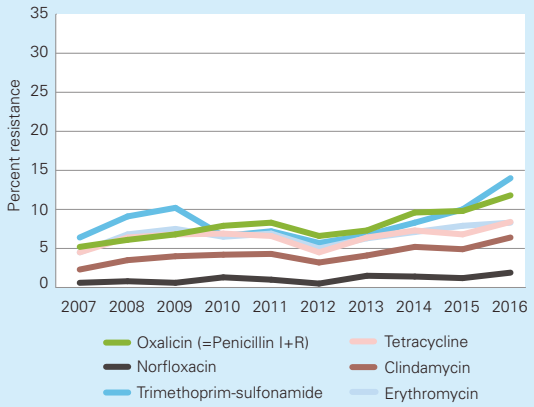
FIGURE 3.29. Antibiotic resistance in *S. pneumoniae* isolates from bloodstream infections included in EARS-Net surveillance during the years 2007-2016.



Streptococcus pneumoniae from nasopharyngeal cultures (ResNet)

Isolates collected and tested in the surveillance programme were from respiratory samples, mainly derived from nasopharyngeal cultures. In 2016, all resistance data for ResNet were analysed using SIR reported to Svebar during the period 2016-03-01 to 2016-05-31. The clinical laboratories have tested isolates for susceptibility to penicillin (by means of oxacillin 1 µg screen disk), erythromycin, clindamycin (since 2004), tetracycline, trimethoprim-sulfonamide, and norfloxacin (since 2005, used as indicator for fluoroquinolone resistance) using the disk diffusion method. Since 2012, there has been a slow increase in the proportions of resistance for all tested antibiotics (Figure 3.30).

FIGURE 3.30. Resistance to antibiotics commonly used to treat respiratory tract infections, *S. pneumoniae* 2007-2016 (ResNet).



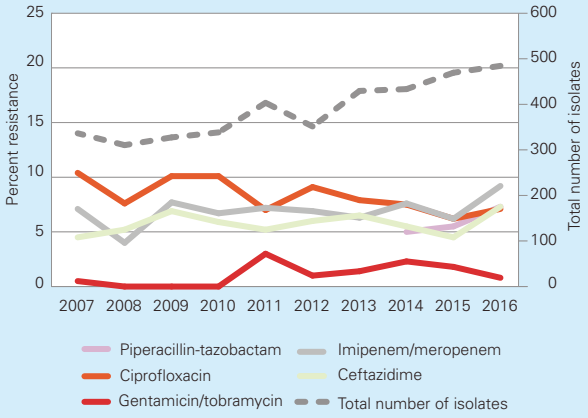
Pseudomonas aeruginosa and *Acinetobacter* spp.

Pseudomonas aeruginosa and *Acinetobacter* spp. reported to EARS-Net

The proportion of resistance for *P. aeruginosa* to the antibiotics reported to EARS are shown in Figure 3.31. The resistance trends for *P. aeruginosa* should be interpreted with caution since patients infected with multi-resistant isolates tend to be sampled more often and deduplication of Svebar data is not possible. The resistance to ceftazidime in *P. aeruginosa* (7.3%) is due to other mechanisms than ESBL production, and the rates are quite stable over time.

During 2016, a total of 86 isolates of *Acinetobacter* spp. from blood was reported in Svebar. The carbapenem-resistance was 1.2% (n=1). In Sweden, it is still rare for *Acinetobacter* to cause sepsis compared to other parts in Europe where multiresistant *Acinetobacter* is a problematic pathogen in hospitals. Since included in EARS-Net, Sweden has reported 59 (2014), 74 (2015) and 86 (2016) isolates of *Acinetobacter* spp.

FIGURE 3.31. Antibiotic resistance in *P. aeruginosa* isolates from bloodstream infections included in EARS-Net surveillance during the years 2007-2016.

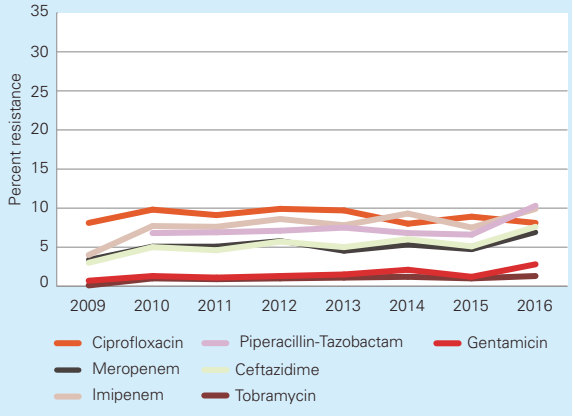


Resistance data on *Pseudomonas aeruginosa* (ResNet)

P. aeruginosa has been included in the surveillance programme on a yearly basis since 2006, with the exception of 2008. All *P. aeruginosa* isolates with the exclusion of respiratory isolates are included.

Four beta-lactam antibiotics are tested; one cephalosporin, one penicillin-inhibitor combination, and two carbapenems. For all of them, the rates of resistance have been more or less stable since 2010. For the carbapenems, resistance to imipenem continues to be higher (9.9%) than to meropenem (6.9%) in 2016 (Figure 3.32).

FIGURE 3.32. Resistance to antibiotics tested against *P. aeruginosa* 2007-2016 (ResNet).



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

Incidence of CDI

In 2016, 6 613 new CDI cases were reported corresponding to an incidence of 66 cases per 100 000 inhabitants Thus, the incidence continued to decrease, compared to 2015 by 8% (Figure 3.33). The mean incidence of new CDI cases per 10 000 patient-days for 2016 was 10 cases/10 000 patient-days

FIGURE 3.33 Incidence of new cases of CDI (cases per 100 000 inhabitants) in Swedish counties 2014-2016, arranged in descending order according to incidence rates for 2016.

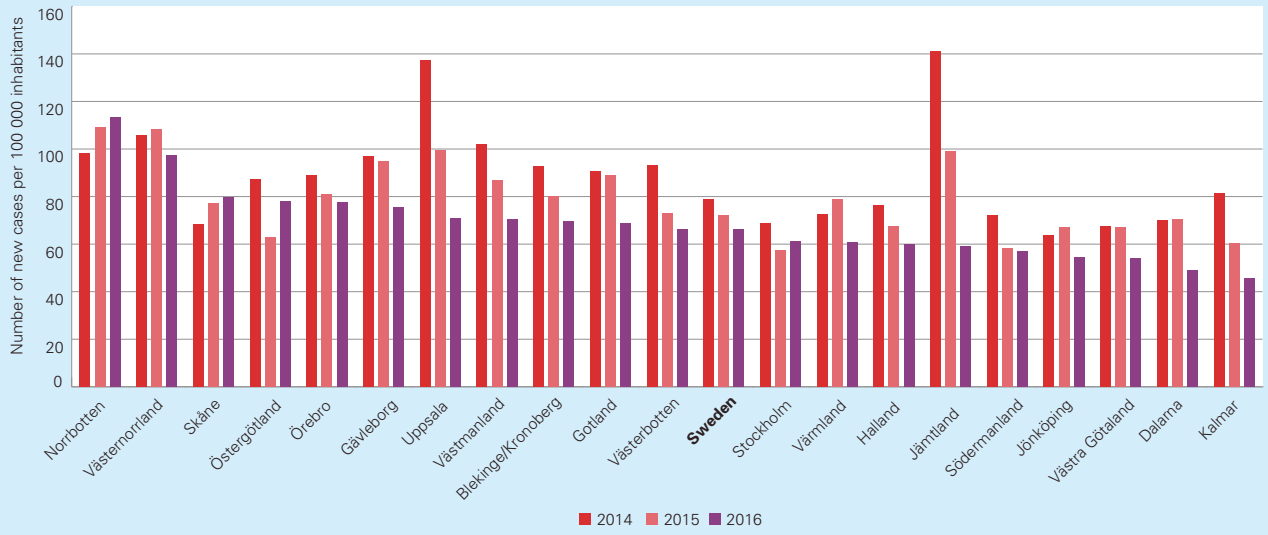
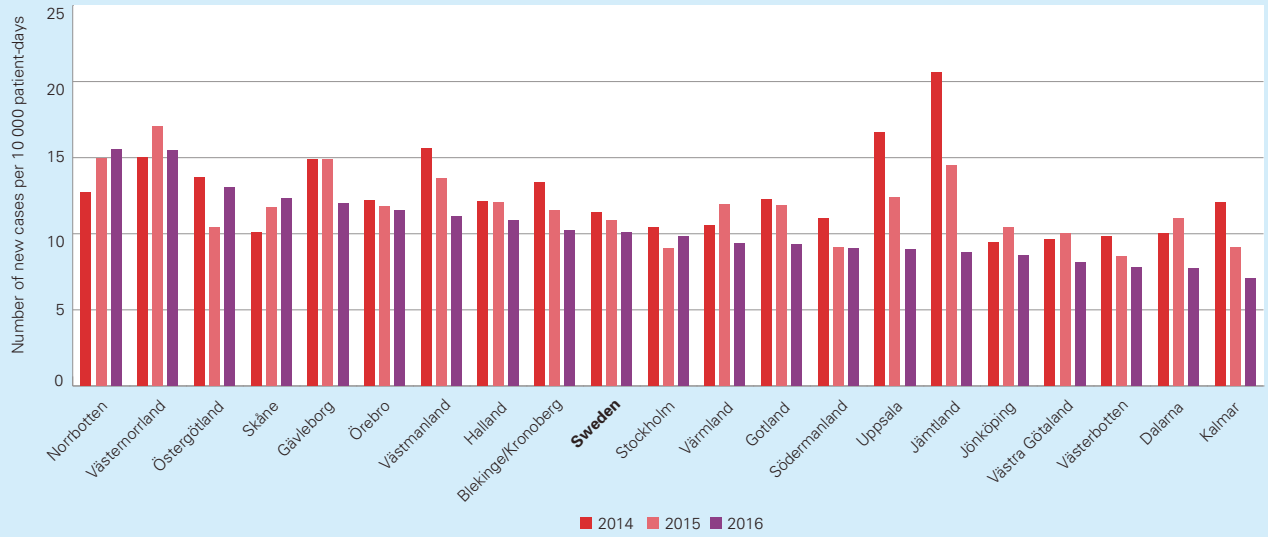


FIGURE 3.34. Incidence of new cases of CDI (cases per 10 000 patient-days) in Swedish counties 2014-2016, arranged in descending order according to incidence rates for 2016. (Incidence of cases for 2016 is calculated using patient-days for 2015).



(patient-days data is from 2015), a reduction of 9% compared to the incidence in 2015 which was 11 cases/10 000 patient-days (Figure 3.34).

Antibiotic resistance in *Clostridium difficile* isolates 2016

In 2016 we observe the largest reduction in isolates resistant to the three indicator antibiotics tested, moxifloxacin, erythromycin and clindamycin. Furthermore only 2.56% of the collected isolates were MDR (resistant to moxifloxacin, clindamycin and erythromycin), a reduction of 58% compared with 2015 (6% MDR) (Figure 3.35). No isolates with reduced susceptibility against the treatment options, metronidazol and vancomycin, were found. The reduction of MDR is mainly associated with a reduction of isolates belonging to PCR ribotypes that have historically shown a high level of resistance against the indicator antibiotics (Figure 3.36). With the exception of PCR ribotype 078/126 we have observed a great reduction in resistance to moxifloxacin in PCR ribotypes 001, 012 and 046, which have been previously associated with MDR.

FIGURE 3.35 Percentage of *C. difficile* isolates 2009-2016 resistant to erythromycin, clindamycin, moxifloxacin or MDR.

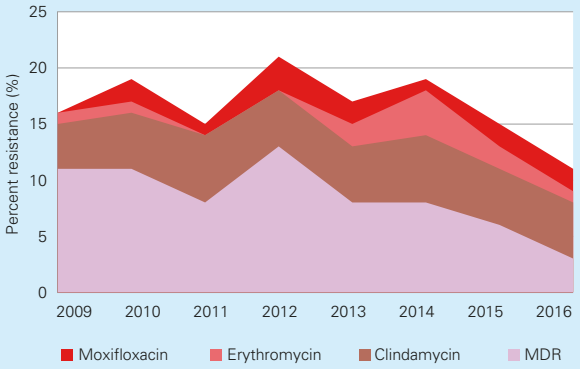
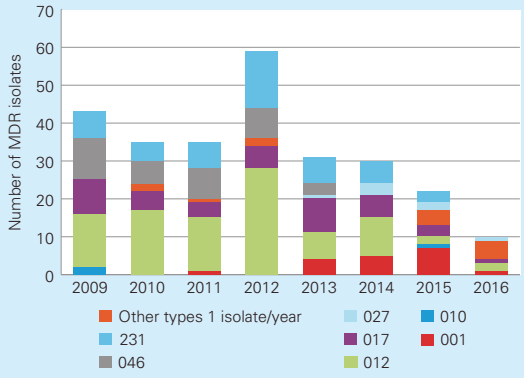


FIGURE 3.36 Number of MDR *C. difficile* isolates per PCR ribotype 2009-2016.



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

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

Svebar data from bloodcultures from fifteen laboratories were used to look at antibiotic susceptibility in other pathogens, not only those specified by EARS-Net, causing invasive infections. Data from previous Swedres-Svarm reports

FIGURE 3.37. Antimicrobial resistance in invasive isolates of *Streptococcus pyogenes* (GAS) during nine years (2008-2016).

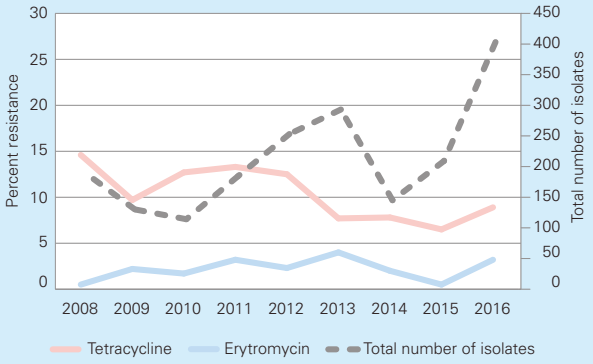


FIGURE 3.38. Antimicrobial resistance in invasive isolates of *Streptococcus agalactiae* (GBS) during nine years (2008-2016).

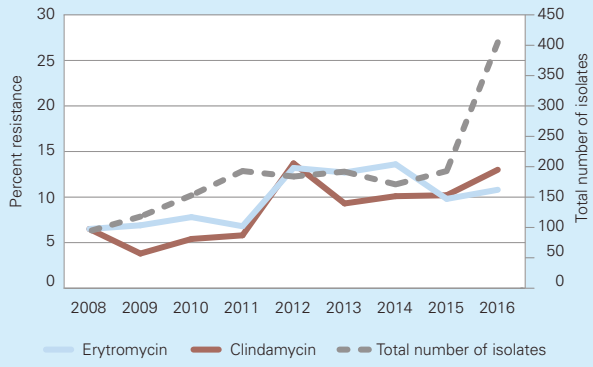
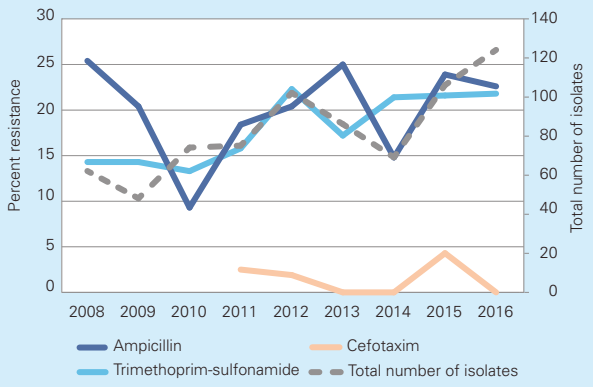


FIGURE 3.39. Antimicrobial resistance in invasive isolates of *Haemophilus influenzae* during nine years (2008-2016).

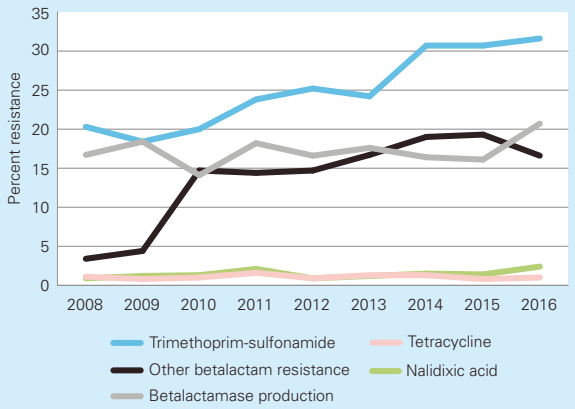


(2008-2015) for *Streptococcus pyogenes* (GAS), *Streptococcus agalactiae* (GBS) and *Haemophilus influenzae* are presented together with the most recent data from 2016 (Figures 3.37 to 3.39). Invasive isolates of *S. pyogenes* (n=626) and *H. influenza* (n=178) are notifiable according to the Communicable Disease Act, but regardless of their antibiotic susceptibility. It is therefore of value to summarise this kind of information in this report. *S. agalactiae* is not included in the Communicable Disease Act, but it is an important pathogen in the context of pregnancy and child birth.

Haemophilus influenzae from nasopharynx (ResNet)

Haemophilus influenzae was re-introduced into the yearly surveillance programme on antibiotic resistance in 2008 after several years with no data collections. In 2016, 14 laboratories delivered data through Svebar (Figure 3.40). The resistance trends should be interpreted with caution since data for 2016 was collected with a different method compared to earlier years. The high increase in resistance to trimethoprim-sulfonamide seen in 2014 remained at a steady level. Tetracycline resistance was still rare (1.0%) as was resistance to fluoroquinolones (2.4%), detected by the nalidixic acid screening disk. During 2016, the resistance correlating to beta-lactamase production increased while the resistance due to beta-lactamase negative ampicillin resistant (BLNAR) decreased. 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 frequency of BLNAR. By doing so the results from 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.

FIGURE 3.40. Resistance rates for *Haemophilus influenzae* during year 2008-2016 (ResNet).



Mycobacterium tuberculosis

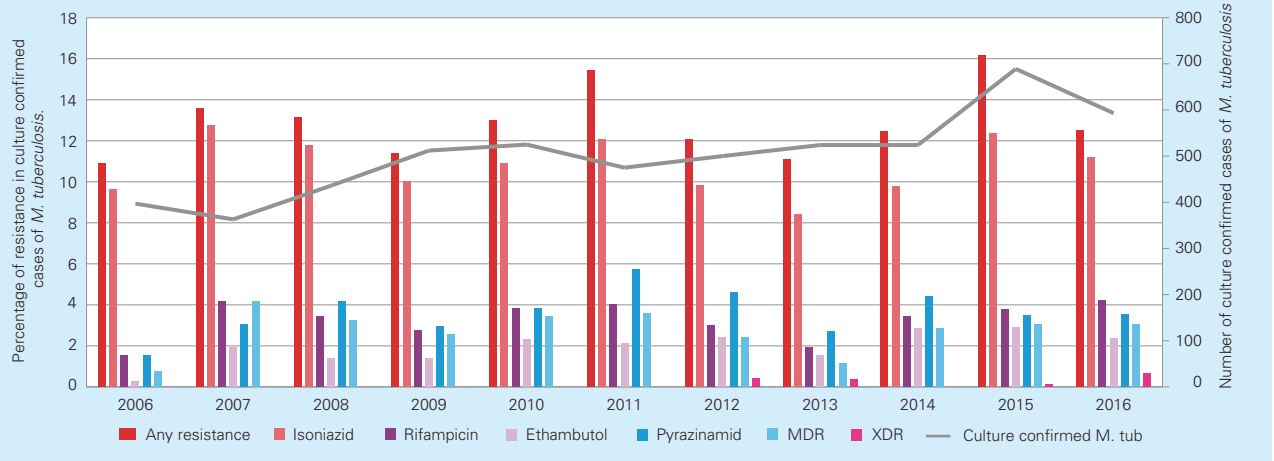
During 2016 in total 734 cases of tuberculosis (TB) were reported compared to 835 cases during 2016 which is a decrease of 12 %. Out of the 734 cases seven was already on TB treatment when arriving in Sweden.

The number and proportion of culture confirmed cases were 598 (82%) compared to 697 (83%) in 2015. *Mycobacterium bovis* was identified in five cases and *Mycobacterium tuberculosis* in 593 cases out of which for two it was not possible to do an analysis of resistance. The proportions of cases diagnosed with MDR-TB increased from 3.2% (22/687) in 2015 to 3.7 % (22/591) in 2016. Four of the MDR-cases were 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 74 patients corresponding to 12.5% of the 591 with culture confirmed *M. tuberculosis*, see Figure 3.41. As always the most common resistance found was against isoniazid.

Among the cases born in Sweden 9.5% (6/63) of those with culture confirmed diagnosis had some kind of resistant

FIGURE 3.41. Drug resistant *M. tuberculosis* in Sweden 2006–2016



TB. Of these six, there were three with MDR-TB and one with XDR-TB. All four of them had been infected outside of Sweden.

Of all the TB cases reported in Sweden 2016, 90% were born in another country. In total 528 in this group had a culture confirmed TB and 68 (13%) had some kind of resistance out of which 15 had MDR-TB and three had XDR-TB.

Genetic typing of TB isolates has been performed in Sweden since the late 1990's. This is done to identify clusters of cases as clustering indicates possible ongoing spread and helps to identify missed opportunities of infection control. Since September 2016 the laboratory at Folkhälsomyndigheten has changed from MIRU-VNTR to whole genome sequencing, a method that has a higher resolution and will reduce the risk of "false" clustering of cases with no connection.

The proportion of patients with *M. tuberculosis* resistant against isoniazid has decreased in 2016 but the proportion of MDR-TB and XDR-TB has increased slightly.

Neisseria gonorrhoeae

Gonorrhoea is a notifiable infection and in 2016, 1778 cases (17.8 cases per 100 000 inhabitants) of gonococcal infections were reported to the Public Health Agency of Sweden. Most of these cases were identified in the three largest counties of Sweden, which comprise the cities Stockholm, Gothenburg, and Malmö, respectively. Clinical isolates are in the present report described from the Swedish Reference Laboratory for Pathogenic Neisseria (an external body of the Public Health Agency of Sweden), Department of Laboratory Medicine, Clinical Microbiology, Örebro University Hospital, Örebro and the Department of Laboratory Medicine, Clinical Microbiology, Skåne University Hospital. Data from Stockholm county are not yet available. In 2016, *N. gonorrhoeae* strains from 601 cases, corresponding to 34% of all reported cases, were fully characterised at these two laboratories.

Antimicrobial susceptibility testing was performed according to standardized and quality assured methodology using Etest for MIC determination of ceftriaxone, cefixime, azithromycin, spectinomycin, and ciprofloxacin. The used SIR criteria have been determined by The European Committee on Antimicrobial Susceptibility Testing (EUCAST).

In Table 3.2, the results for 2016 are compared with those from 2008 to 2015. Briefly, the level of resistance to ciprofloxacin, which previously was used as first-line treatment for gonorrhoea, remains stably high. The level of resistance to azithromycin that has been stably high (9-13%) since 2010, significantly decreased to 3% in 2016. The resistance to cefixime has decreased since 2012 (10%) and in 2016 reached only 1% resistance, which is the lowest level of cefixime resistance since 2008. Furthermore, as in 2015 no resistance to ceftriaxone was identified. This is exceedingly promising because ceftriaxone is the last remaining option for empirical antimicrobial monotherapy of gonorrhoea. Similar decreases in the resistance to these extended-spectrum cephalosporins (ceftriaxone and cefixime) have been reported in several 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 has been effective. No gonococcal isolates resistant to spectinomycin have yet been detected in Sweden. However, the availability of spectinomycin can be limited (in Sweden as in most countries globally), and it is not suitable as monotherapy for pharyngeal gonorrhoea.

Neisseria meningitidis

Invasive meningococcal disease is a notifiable disease, and in 2016 a total of 62 clinical cases (0.6 cases per 100 000 inhabitants) of the disease were reported. In total, 53 clinical invasive isolates from blood, cerebrospinal fluid or puncture (one isolate per patient) were analysed at the Swedish Reference Laboratory for Pathogenic Neisseria (an external body of the Public Health Agency of Sweden), Department of Laboratory Medicine, Clinical Microbiology, Örebro University Hospital.

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

Sixteen (30%) isolates had an intermediate susceptibility to penicillin G (MIC>0.064 mg/L), whereof one isolate was resistant (MIC=0.38 mg/L). One of the isolates with intermediate susceptibility to penicillin G was also the only iso-

TABLE 3.2. Proportions (%) of antibiotic resistance in Swedish *Neisseria gonorrhoeae* strains 2008-2016

	2008 (n=447)	2009 (n=384)	2010 (n=618)	2011 (n=805)	2012 (n=877)	2013 (n=967)	2014 (n=384)	2015 (n=462)	2016 (n=601)
Cefixime	1	5	6	8	10	4	2	2	1
Ceftriaxone	<1	0	2	2	1	<1 (0.3)	<1 (0.3)	0	0
Azithromycin	13	6	12	11	10	13	9	10	3
Ciprofloxacin	63	75	56	55	62	53	60	53	53
Spectinomycin	0	0	0	0	0	0	0	0	0

late resistant to ciprofloxacin (MIC=0.094 mg/L). All isolates (100%) were susceptible to cefotaxime (MIC values of <0.002-0.047 mg/L), meropenem (MICs: 0.004-0.047 mg/L), chloramphenicol (MICs: 0.125-2 mg/L), and rifampicin (MICs: 0.003-0.023 mg/L). None of the isolates obtained in 2016 produced ß-lactamase, and in fact no ß-lactamase-producing meningococcal isolate has ever been identified in Sweden.

Zoonotic pathogens: *Campylobacter* and *Salmonella*

Campylobacter

Data on antibiotic resistance in *Campylobacter* spp. from humans is largely lacking. A total of 76 cases with *Campylobacter* spp. in blood cultures were reported during 2016 from 14 laboratories delivering data to Svebar. The nomenclature for *Campylobacter* presented in Table 3.3 is the result of the local clinical microbiological laboratories species identification routines. There is therefore no separate group for *C. coli*. Resistance to ciprofloxacin was seen in 13% (n=9/69) of the isolates and all of the isolates tested for erythromycin (n=63) were susceptible (Table 3.3).

TABLE 3.3. Number of *Campylobacter* isolates found in blood (Svebar data) and their correspodning susceptibility to ciprofloxacin and erythromycin 2016.

Species	Ciprofloxacin		Erytromycin		Number of cases
	n tested	% R	n tested	% R	
C. jejuni	49	16.3	46	0	51
C. jejuni/coli	6	16.7	6	0	8
C. ureolyticus					2
C. rectus					1
C. upsaliensis	1	0			1
Campylobacter spp.	13	0	11	0	13
Total	**69**	**9**	**63**	**0**	**76**

Salmonella

Salmonella from human clinical specimens

Infection with *Salmonella* in humans is a notifiable disease in Sweden. The focus of epidemiological typing is mainly of domestic cases in order to identify outbreaks. Antibiotic susceptibility testing on isolates has mainly been performed on isolates from blood, the data reported is therefore limited to isolates from blood. Since the majority of *Salmonella* isolated in Sweden comes from persons who were infected while travelling abroad (71%), their resistance patterns reflect the situation at their geographical origin. During 2016, 13 laboratories delivered data on invasive *Salmonella* infections and antibiotic susceptibility through Svebar. A total of 129 isolates of *Salmonella* spp. in blood were found (Table 3.4). This number is a bit higher than the cases with salmonella in blood reported to SmiNet (n=96) since it is not possible to identify duplicates in Svebar-data. The resistance to ciprofloxacin was 31% (n tested=67) and 6.7% for trimethoprim-sulfphonamide (n tested=75).

TABLE 3.4. Number of *Salmonella* isolates found in blood from Svebar data 2016.

Species	Number of isolates
Salmonella enteritidis	5
Salmonella typhimurium	3
Salmonella saintpaul	3
Salmonella anatum	2
Salmonella virchow	2
Salmonella heidelberg	2
Salmonella newport	1
Salmonella agona	1
Salmonella braenderup	1
Salmonella infantis	1
Salmonella javiana	1
Salmonella group O9	17
Salmonella group B	9
Salmonella group O4	8
Salmonella group CO	3
Salmonella typhi	14
Salmonella paratyphi A	10
Salmonella spp.	46
Total	**129**

WHO GLASS – Global Antimicrobial Resistance Surveillance System

TABLE 1. Objectives of GLASS

- Foster national surveillance systems and harmonized global standards
- Estimate the extent and burden of AMR globally by selected indicators
- Analyze and report global data on AMR on a regular basis
- Detect emerging resistance and its international spread
- Inform implementation of targeted prevention and control programmes
- Assess the impact of interventions

TABLE 2. Priority specimens and pathogens for surveillance of AMR. Describes the combinations defined in the GLASS manual (http://www.who.int/antimicrobial-resistance/publications/surveillance-system-manual/en/), where more detailed tables on pathogen/antimicrobial combinations are available.Foster national surveillance systems and harmonized global standards

Specimen	Priority pathogens for surveillance
Blood	E. coli, K. pneumoniae, A. baumanii, S. aureus, S. pneumonia, Salmonella spp.
Urine	E.coli, K. pneumoniae
Faeces	Salmonella spp., Shigella spp.
Urethral and cervical swabs	N. gonorrhoeae

A Global Antimicrobial Resistance Surveillance System launched by WHO

The Global Antimicrobial Resistance Surveillance System (GLASS) was launched by WHO in 2015, and is the first platform on a global level for sharing of standardized information on antimicrobial resistance (AMR). Aggregated national data from countries is being gathered and compiled to inform decision-making and provide the evidence base for advocacy. As of April 2017 forty-three countries from all WHO regions have expressed interest in participating in GLASS. Sweden has fully enrolled and will deliver national resistance data for the first data call.

GLASS aims to combine clinical, laboratory and epidemiological data to form the basis for local, national and regional action and to monitor the effectiveness of interventions. A road map outlines the development of the system and its implementation between the period 2015 and 2019 and the focus of this phase will be on surveillance of resistance in common human bacterial pathogens that pose the greatest threats to health. In a meeting hosted by the Swedish Ministry of Health and Social Affairs, WHO and the Public Health Agency of Sweden in 2014, 30 WHO Member States, from all WHO regions, reaffirmed the need for a global system for AMR surveillance. Participants in the consultation also agreed on the surveillance approach proposed by WHO. In May 2015, the Sixty-eighth World Health Assembly adopted the global action plan on antimicrobial resistance. One of the five strategic objectives of the action plan is to strengthen the evidence base through enhanced global surveillance and research. The need for cross sectoral work on AMR was further emphasized at the highest political level, at the United Nations General Assembly in 2016, strengthening the global efforts on AMR. In April 2017 a second Member States consultation was hosted by the Swedish Ministry of Health and Social Affairs, WHO and the Public Health Agency of Sweden, with focus on strategies to coordinate and further improve global collaboration to meet the needs of Member States in the implementation of AMR surveillance.

In support to WHO of the work of implementation of GLASS in Member States, the WHO Collaborating Centre for antimicrobial resistance containment was established at the Public Health Agency of Sweden in 2016. The initial emphasis will be on strengthening Member States' national capacity for AMR surveillance and contribution to GLASS.

GLASS promotes collection of standardized, comparable and validated data on AMR

The goal of GLASS is to enable collection, analysis and sharing of standardized, comparable and validated data on AMR. The objectives of GLASS, as described in the manual published by WHO, are listed in table 1. GLASS also promotes timely specimen collection to improve patient safety and a guide on Diagnostic stewardship is available on the WHO website. Implementation of diagnostic stewardship can improve surveillance data and is defined by GLASS as:
"coordinated guidance and interventions to improve appropriate use of microbiological diagnostics to guide therapeutic decisions. It should promote appropriate, timely diagnostic testing, including specimen collection, and pathogen identification and accurate, timely reporting of results to guide patient treatment."

Benefits for countries of participating in GLASS

Countries can benefit from participation in GLASS through support for capacity building of national surveillance systems, and also technical support for microbiological laboratories. GLASS will provide access to training and implementation tools, and support in collecting AMR data at local and national levels as well as guidance to Member States in compiling harmonized, standardized AMR surveillance data, and in sharing these data via the IT platform.

A network of WHO Collaborating Centres was established in 2016, aiming to support low and middle income countries in developing national AMR surveillance systems and to build capacity to produce high quality surveillance data that can be reported to GLASS. Sweden supports WHO in coordination of the network in 2017 and 2018.

Countries can join GLASS in a stepwise approach

The official call for country enrolment to participate GLASS is open on the WHO website (http://www.who.int/antimicrobial-resistance/global-action-plan/surveillance/glass-enrolment/en/). The official call for 2016 data is open from 1 April to 1 July 2017. Member States can enroll in GLASS in a stepwise manner; participating countries will be requested to provide information on the national surveillance system. Depending on the availability of data and national priorities and resources, Member States are encouraged to provide data to GLASS on defined priority pathogens, listed in table 2. By submitting their expression of interest the countries confirm commitment to build capacity to collect and share data.

Future perspectives

During the period 2015–2019 GLASS will provide the standards and tools for routine surveillance based on microbiological and clinical information on priority bacterial infections in humans, start country enrolment and produce global reports on GLASS implementation and AMR rates. Further development of GLASS will be based on the lessons learnt during this period. The list of components proposed to be included in the surveillance programme on specimen types, pathogens and types of resistances, will be revised and updated according to needs as the priorities of countries and regions vary. The GLASS data-sharing platform will also allow progressive incorporation of information from other surveillance systems, such as for foodborne AMR, monitoring of antimicrobial use and AMR associated with animals. There is also an aim to further evaluate the application of molecular methods for AMR surveillance and to set up a framework for early detection and information sharing of unusual types of AMR.

Antibiotic resistance in animals

Notifiable diseases

In Sweden, findings of $ESBL_{CARBA}$-producing Enterobacteriaceae and methicillin-resistant coagulase-positive staphylococci in animals are notifiable (SJVFS 2012:24 with amendments). In the monitoring, the attention regarding methicillin-resistant coagulase-positive staphylococci is mainly directed towards methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus pseudintermedius* (MRSP). Furthermore, as also Enterobacteriaceae producing $ESBL_A$ or $ESBL_M$ as well as *Enterococcus faecalis* and *Enterococcus faecium* with resistance to vancomycin (*vanA* or *vanB*, VRE) are notifiable when detected in humans, specific attention is also paid to these bacteria in animals.

ESBL-producing Enterobacteriaceae

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 4.1.

During 2016, samples of intestinal contents from healthy broilers (n=302) and healthy turkeys (n=86) as well as samples of broiler meat (n=269) at retail were screened for *E. coli* resistant to ESCs and carbapenems using selective media. The meat samples comprised of fresh meat originating both from Sweden (n=243) and other countries (n=26). 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 2016, $ESBL_A$ or $ESBL_M$ were detected in 127 (42%) of the samples of intestinal contents from broilers, 1 (1%) of the samples of intestinal contents from turkeys and in 117 (43%) of the samples from broiler meat. Separated by origin, $ESBL_A$ or $ESBL_M$ were detected in 107 (44%) of the samples from broiler meat originating from Sweden and 10 (38%) of the samples from broiler meat originating from other countries. This difference is however not statistically significant ($p=0.3$, X^2). $ESBL_{CARBA}$ was not isolated from any sample.

About three quarters of the isolates (92/129) from broilers carried a gene in the CTX-M-1-group and all the remaining isolates carried a gene in the CIT-group. For fifteen of the isolates the exact gene was determined by sequencing. Ten isolates were confirmed to carry the gene $bla_{CTX\text{-}M\text{-}1}$ ($ESBL_A$) and five to carry the gene $bla_{CMY\text{-}2}$ ($ESBL_M$). In previous years, isolates with $bla_{CMY\text{-}2}$ have dominated among ESBL-producing *E. coli* from broilers even if a shift towards $bla_{CTX\text{-}M\text{-}1}$ could be seen already in 2015. Apart from the 126 isolates with $ESBL_A$ or $ESBL_M$, there were three isolates from broiler meat where no genes conferring transmissible ESBL or AmpC resistance could be detected.

About two thirds of the isolates (72/117) from broiler meat carried a gene in the CTX-M-1-group and all but one of the remaining isolates carried a gene in the CIT-group. The last isolate carried a TEM-gene. The exact gene was determined by sequencing for twelve isolates (six with a gene in the CTX-M-1-group, five with a gene in the CIT-group and the one isolate with a TEM-gene). Five of the isolates with a gene in the CTX-M-1-group were confirmed to carry the gene $bla_{CTX\text{-}M\text{-}1}$ ($ESBL_A$) and the last of them carried the gene $bla_{CTX\text{-}M\text{-}15}$ ($ESBL_A$). The five isolates with a gene in the CIT-group were all confirmed to carry the gene $bla_{CMY\text{-}2}$ ($ESBL_M$). The isolate with a TEM-gene was confirmed to carry the gene $bla_{TEM\text{-}52}$ ($ESBL_A$). Apart from the 117 isolates with $ESBL_A$ or $ESBL_M$, there were two isolates from broiler meat where no genes conferring transmissible ESBL or AmpC resistance could be detected.

Apart from the obvious resistance to beta-lactams, the most common resistance traits among the isolates of ESBL-producing *E. coli* from broilers and broiler meat respectively were resistance to sulphonamides (74% and 65% respectively) and tetracycline (28% and 22% respectively). The different resistant patterns occurring among ESBL-producing *E. coli* from broilers and broiler meat are presented in Table 4.2.

Due to differences in methodology during 2010-2016, changes of the proportion of broiler caecal samples positive for ESC resistant *E. coli* over time cannot be directly assessed. However, the samples from 2014, 2015 and the first half of 2016 were cultured in duplicate with 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 the latter method, ESC resistant *E. coli* were isolated from 41 (26%) of 159 samples in 2016 (Figure 4.1).

FIGURE 4.1. Proportion (%) of samples from broilers positive for $ESBL_A$ or $ESBL_M$ from 2010 to 2016.

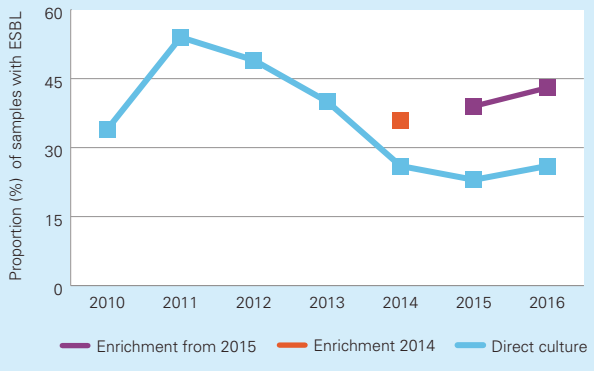


TABLE 4.1. Results of the screening studies for *E. coli* with $ESBL_A$ or $ESBL_M$ in healthy individuals of different animal species and meat of Swedish origin.

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	2016	302	130	127	42	93[a]						34[b]
Broilers	Meat	2016	243	109	107	44	66[a]		1				40[b]
Broilers	Intestine	2015	100	40	39[a]	39[a]	18[c]						22[c]
Broilers	Intestine	2014	200	72	71	36	1						70[d]
Broilers	Intestine	2013	100	45	40	40					2		38[d]
Broilers	Meat	2013	59	31	30	51							30[d]
Broilers	Intestine	2012	200	102	97	49							97[d]
Broilers	Meat	2012	97	41	40	41							40[d]
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
Calves	Intestine	2015	103	5	0	0							
Calves	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	2016	86	1	1	1	1						
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[d]
Horses	Faeces	2010	431	9	6	1						6	

[a] CTX-M-1-group, ten caecal and four meat isolate sequenced and possessed the gene $bla_{CTX\text{-}M\text{-}1}$. [b] CIT-group, five caecal and three meat isolates were sequenced and possessed the gene $bla_{CMY\text{-}2}$ [c] One isolate carried both an $ESBL_A$ and an $ESBL_M$ gene [d] CIT-group, all isolates from broilers or broiler meat with a CIT-group enzyme in other years possessed the gene $bla_{CMY\text{-}2}$.

The isolate from intestinal contents of turkeys carried the gene $bla_{CTX\text{-}M\text{-}1}$ ($ESBL_A$). This is the first time that an isolate with $ESBL_A$ or $ESBL_M$ has been reported from turkeys in Sweden

Companion animals and horses

In Svarm, there are no recurring active screenings for ESBL-producing Enterobacteriaceae in healthy companion animals or horses. However, the results of the screenings for ESC resistant *E. coli* that have been performed are shown in Table 4.1.

However, for a number of years 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. During 2016, 51 submitted isolates of Enterobacteriaceae with phenotypic resistance to ESCs were confirmed to produce $ESBL_A$ or $ESBL_M$ at SVA (Table 4.3). The isolates were from cats (n=2), dogs (n=31) and horses (n=18). This is an increase in the number of ESBL-producing Enterobacteriaceae since 2015. As also the proportion of submitted isolates that were confirmed to produce $ESBL_A$ or $ESBL_M$ increased, this could reflect a true increase in the occurrence of $ESBL_A$ and $ESBL_M$ among dogs and horses in Sweden. However, it could also reflect an increased awareness and knowledge among clinicians.

TABLE 4.2. Different resistant phenotypes occurring among *E. coli* with $ESBL_A$ or $ESBL_M$ from intestinal contents from broilers and from broiler meat, 2016.

Resistance pattern	**Caecal samples** No. (%) of isolates	**Meat samples, Sweden** No. (%) of isolates	**Meat samples, other countries** No. (%) of isolates
Amp, Ctx		1 (1)	
Amp, Ctx, Caz	22 (17)	31 (29)	3 (30)
Amp, Ctx, Sul	3 (2)	3 (3)	
Amp, Ctx, Caz, Sul	57 (45)	41 (38)	
Amp, Ctx, Caz, Tet	1 (1)		
Amp, Ctx, Caz, Cip, Nal	8 (6)	5 (5)	
Amp, Ctx, Caz, Sul, Gen	1 (1)		
Amp, Ctx, Caz, Sul, Tet	24 (19)	13 (12)	2 (20)
Amp, Ctx, Caz, Sul, Tmp		2 (2)	2 (20)
Amp, Ctx, Caz, Cip, Nal, Gen		1 (1)	
Amp, Ctx, Caz, Sul, Cip, Nal		2 (2)	
Amp, Ctx, Caz, Sul, Tet, Chl	7 (6)	2 (2)	
Amp, Ctx, Caz, Sul, Tet, Gen	4 (3)	6 (6)	2 (20)
Amp, Ctx, Caz, Sul, Tet, Tmp			1 (10)

TABLE 4.3 Clinical isolates of different bacterial species of Enterobacteriaceae, producing $ESBL_A$ or $ESBL_M$, from companion animals and horses submitted 2008-2016.

Resistance group	Resistance gene	Bacterial species	Animal species	2008	2009	2010	2011	2012	2013	2014	2015	2016
All	All	Enterobacteriaceae	Cats		1	3	3			1	2	2
All	All	Enterobacteriaceae	Dogs	1	3	4	18	12	14	22	24	31
All	All	Enterobacteriaceae	Horses	2	5	24	16	6	9	8	14	18
CIT	CMY-16	*Escherichia coli*	Cat							1		
	CMY-2	*Escherichia coli*	Cat		1[a]	1						1
		Escherichia coli	Dog			1	9	4	5	5	6	5
		Klebsiella pneumoniae	Dog								1	
		Proteus mirabillis	Dog				1				2	2
CTX-M-1	CTX-M-1	*Enterobacter cloacae*	Dog							4		
		Escherichia coli	Dog			1		1	1	3		
		Enterobacter cloacae	Horse								1	
		Enterobacter spp.	Horse						1			
		Escherichia coli	Horse		2	9	8	3	3	2	3	5
		Klebsiella oxytoca	Horse							1		
		Serratia odorifera	Horse			1						
	CTX-M-3	*Enterobacter* spp.	Dog						1			
		Escherichia coli	Dog						2		1	2
	CTX-M-15	*Enterobacter cloacae*	Cat								1	
		Escherichia coli	Cat			1						1
		Klebsiella pneumoniae	Cat			1	1					
		Enterobacter cloacae	Dog								2	2
		Enterobacter spp.	Dog		1	2	1	2	1	6		
		Escherichia coli	Dog	1			2	3	2		2	7
		Morganella morganii	Dog									1
		Klebsiella pneumoniae	Dog		1						1	2
		Escherichia coli	Horse		1	1						1
		Klebsiella pneumoniae	Horse		1						3	
	CTX-M-55	*Escherichia coli*	Dog								1	1
	CTX-M-57	*Escherichia coli*	Dog								1	
CTX-M-2	CTX-M-2	*Escherichia coli*	Dog				1					
CTX-M-9	CTX-M-9	*Escherichia coli*	Dog				1	2	1	1		
		Escherichia coli	Horse							1		
	CTX-M-14	*Kluyvera* sp.	Cat				1					
		Escherichia coli	Dog								5	5
		Klebsiella pneumoniae	Dog								1	
		Escherichia coli	Horse				1				1	
	CTX-M-27	*Escherichia coli*	Dog				3		1	1	1	1
SHV	SHV-12	*Escherichia coli*	Dog							2		3
		Citrobacter braakii	Horse			1						
		Enterobacter aerogenes	Horse									1
		Enterobacter amnigenus	Horse							1		
		Enterobacter cloace gruppen	Horse									1
		Enterobacter cloacae	Horse							1	2	4
		Enterobacter spp.	Horse		1	3	5	3	3			
		Escherichia coli	Horse	2		2	2					3
		Escherichia hermanii	Horse			1						
		Klebsiella oxytoca	Horse						2		1	1
		Klebsiella pneumoniae	Horse							1		
		Leclercia adecarboxylata	Horse									1
		Pantoea agglomerans	Horse									1
TEM	TEM-52	*Escherichia coli*	Cat								1	
unknown	unknown	*Escherichia coli*	Cat				1					
unknown	unknown	*Escherichia coli*	Dog		1	1						
unknown	unknown	*Enterobacter cloacae*	Horse							1	3	
unknown	unknown	*Escherichia coli*	Horse			1						
unknown	unknown	*Klebsiella pneumoniae*	Horse			5						

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

Quantification of $ESBL_A$ and $ESBL_M$-producing *Escherichia coli* in broilers

For seven years now, the occurrence of $ESBL_A$ and $ESBL_M$-producing *Escherichia coli* in healthy broilers has been investigated in the Svarm-programme using selective methods. These studies have shown that $ESBL_A$- or $ESBL_M$-producing *E. coli* are present in the intestines of a large proportion of the birds. To properly assess the risk for public health by this occurrence it is however also important to consider the proportion of *E. coli* in the gut flora that are in fact $ESBL_A$- or $ESBL_M$-producers. For this reason, broiler caecal samples screened for $ESBL_A$-or $ESBL_M$-producing *E. coli* in Svarm 2016 were also analysed with a quantitative method.

Materials and methods

Quantification was performed on a total of 125 caecal samples from which $ESBL_A$- or $ESBL_M$-producing *E. coli* had been isolated in the selective screening (two positive samples were not available for quantification). From the initial suspensions of 1 g of caecal material in buffered peptone water, tenfold dilutions were made. From each dilution, 10 µL were plated by the running drop method (Herigstad et al, 2001) onto square plates with MacConkey agar (Oxoid) and MacConkey agar supplemented with cefotaxime (1 mg/L). The agar plates were incubated for 24 hours at 44°C. The highest dilution with visible growth on each plate was recorded and the ratio of *E. coli* that were $ESBL_A$- or $ESBL_M$-producers was calculated.

Results and discussion

The results from the quantification of $ESBL_A$- or $ESBL_M$-producing *E. coli* in broiler caecal samples are presented in Table.

In a majority of the samples, the $ESBL_A$- or $ESBL_M$-producing *E. coli* only constitute a small part of all the *E. coli* in the intestinal flora. It is however also clear that in some of the birds, basically all the *E. coli* produces $ESBL_A$ or $ESBL_M$. The reason for this variation is not known. Antibiotics are rarely used for treatment of bacterial diseases in broilers in Sweden. Still, every year some flocks are treated and one possible explanation for the high ratio of $ESBL_A$- or $ESBL_M$-producing *E. coli* in some samples could be antibiotic treatment of these specific flocks.

The results are in accordance with a similar investigation performed within the Norwegian surveillance program NORM-VET in 2014 and also concur with the fact that $ESBL_A$- or $ESBL_M$-producers are rare among randomly selected indicator *E. coli* from broilers in Sweden.

TABLE: Number and proportion (%) of broiler caecal samples in which a certain ratio of *Escherichia coli* is $ESBL_A$/$ESBL_M$-producers.

$ESBL_A$/$ESBL_M$-producing *E. coli* (%)	No. of samples	Proportion (%) of samples
0.0001	2	1.6
0.001	22	17.6
0.01	51	40.8
0.1	28	22.4
1.0	14	11.2
10.0	6	4.8
100.0	2	1.6

References

Herigstad B, Hamilton M, et al. 2001, How to optimize the drop plate method for enumerating bacteria. *J Microbiol Methods*, 2001 44:121-9.

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Methicillin resistant *S. aureus* (MRSA)

In Sweden, MRSA in animals was first verified in 2006 and was made notifiable in 2008. During 2016, four new cases of MRSA in companion animals were detected; two dogs and two cats. In addition, MRSA was detected in one hedgehog and in an outbreak in goats and sheep at a zoo. Up to and including 2016, a total of 114 cases have been confirmed in domesticated animals. In addition, MRSA has been found in 40 hedgehogs. Most cases in domesticated 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 about 1000 isolates have been tested up to and including 2016. 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. The 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.

Companion animals and horses

In dogs, cats and horses, there was no active monitoring of MRSA during 2016. 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 2016, MRSA was detected in clinical samples, mostly from wound infections, from two dogs and two cats.

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 4.5). In isolates from horses, *spa*-type t011, CC398, has dominated. All isolates from both companion animals and horses have been PVL-negative.

Other animals

A screening study in hedgehogs was performed in 2015 and MRSA was isolated from 35 out of 55 sampled animals. MRSA has also been detected in a few samples from hedgehogs before this study and in one sample during 2016. All isolates from hedgehogs have been MRSA with *mecC*.

In 2016 and early 2017 there was an outbreak of MRSA with *mecC* among goats and sheep at a zoo. The goat first sampled had dermatitis around the nostrils. In the contact tracing that followed, MRSA was found in samples from 19 goats and 4 sheep in 2016, both with similar symtoms and without clinical symtoms. There was an epidemiological link through direct or indirect contact between all positive animals.

Methicillin-resistant *Staphylococcus pseudintermedius* (MRSP)

The number of MRSP cases reported in 2016 to the Swedish Board of Agriculture were 55 and except for 2 cases, a cat and a harbor seal (*Phoca vitulina*), all were connected to dogs (Figure 4.2). This number is about the same level as 2015, but slightly higher than 2013-2014. Isolates from 45 of the 55 cases were available for further typing at SVA. The sampling site of these 45 isolates was unknown in 12 of the cases, 14 were from skin (including external ear canal), 15 from wounds (including surgical wounds), and the remaining 4 were isolated from various other sites.

In all, 17 isolates could by typed by sequencing the *spa*-gene, and belonged to *spa*-types t02 (n = 5), t05 (n = 2), t76 (n = 4), t06 (n = 1), t10 (n = 1), t18 (n = 1), t51 (n = 1), t56 (n = 1). One isolate belonged to a new *spa*-type, which was close related to t05 differing in only one nucleotide. The remaining 28 isolates were subjected to MLST, and out of these 4 isolates belonged to ST71, 5 to ST258, 6 to ST551 and 3 to ST730 while the remaining 10 isolates belonged to different singletons. Compared to the previous years the picture of MRSP is more diverse and is no longer completely dominated by the European clone ST71-J-t02-II-III, described by Perreten et al. (2010). However, ST71 is still common in Sweden and accounts for a similar proportion of the cases as in 2015 (Figure 4.2). Although, more interesting is that occurrence of ST258 dropped markedly from 2015 from 20 isolates (34%) to only 5 isolates (11%), which is on the same level as in 2014. Isolates belonging to ST258 have previously been described as an emerging clone in Europe (Duim et al., 2015; Osland et al., 2012; Damborg

FIGURE 4.2. Number of cases with methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) in Sweden notified to the Swedish Board of Agriculture 2008-2016. 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 2013-2016.

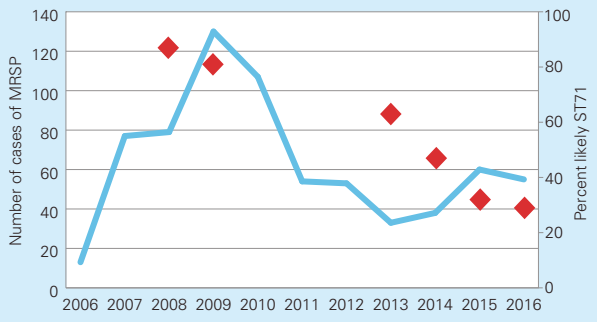


TABLE 4.4. Large animals. Isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) in Swedish horses, pigs, cows, goats and sheep up to and including 2016. All isolates were positive for the *mecA* or *mecC* and *nuc* genes by molecular methods. Shaded areas indicate MIC above EUCAST ECOFF.

Animal species	Year	Clinical background/ Sampling site	Antibiotic, MIC (mg/L)													*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	1	0.25	0.25	≤0.25	≤0.25	≤0.5	0.12	≤0.5	2	0.25	1	8	t843	*mecC*
Goat[b]	2016	dermatitis	4	>16	2	1	≤0.25	≤0.25	≤0.5	0.12	≤0.5	4	1	≤0.5	8	t9268	*mecC*
Sheep[b]	2016	screening	1	16	1	1	≤0.25	≤0.25	≤0.5	0.12	≤0.5	2	0.25	1	8	t9268	*mecC*

[a] tested with 2% NaCl; [b]This animal is included in an outbreak of MRSA in goats and sheep at a zoo.

TABLE 4.5. Companion animals. Isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) in Swedish dogs and cats up to and including 2016. 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, MIC (mg/L)													*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*
Dog	2016	wound	>16	16	>4	2	16	≤0.25	32	0.5	16	>32	>4	>32	64	t034	*mecA*
Dog	2016	wound	4	16	>4	1	≤0.25	>32	8	4	≤0.5	4	0.5	4	8	t044	*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*
Cat	2016	wound	1	16	>4	2	≤0.25	>32	≤0.5	0.5	≤0.5	2	2	2	8	t008	*mecA*
Cat	2016	nasal infection	16	>16	>4	2	≤0.25	≤0.25	≤0.5	≤0.06	≤0.5	2	0.12	≤0.5	4	t304	*mecA*

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

et al., 2013). The MLSTs ST551 and ST730 were described for the first time this year.

All isolates were defined as multi-resistant, but 78% were susceptible to fusidic acid, 53% to gentamicin and 100% to nitrofurantoin. The occurrence of ST71 isolates resistant to tetracycline decreased from 37% in 2015 to just 2% (one isolate) this year, while fusidic acid resistance was on the same level (3%). The 5 isolates belonging to ST258 were all also susceptible to gentamicin and fusidic acid. The 6 isolates belonging to the new ST551 were all resistant to enrofloxacin, erythromycin, clindamycin, gentamicin, tetracycline and trimethoprim/sulfa, and all but one isolate were susceptible to fusidic acid. The 3 isolates belonging to ST730 were susceptible to enrofloxacin and gentamicin, with one isolate also being susceptible to erythromycin and clindamycin.

Zoonotic pathogens

Zoonoses are diseases 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

Findings of *Salmonella* in animals are notifiable in Sweden. In Svarm, antibiotic susceptibility is determined in one isolate from each notified incident in farm animals and horses each year. Isolates from incidents previously notified but still under restrictions are also included. In incidents involving more than one serovar, one isolate of each serovar is tested. From incidents in companion animals and wild animals a selection of isolates 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 2016

Altogether, 77 isolates were tested of which 56 were *S.* Typhimurium (Table 4.6). Distributions of MICs and resistance in all isolates are presented in Table 4.7 and for the subset *S.* Typhimurium in Table 4.8. The majority of isolates (86%) were susceptible to all antibiotics tested, but eleven isolates were resistant to at least one substance and four isolates (5%) were multiresistant (Table 4.9). In the subset of *S.* Typhimurium resistance was overall low but has varied over the years due to occurrence of multiresistant strains in individual years (Figure 4.3).

FIGURE 4.3. Resistance (%) in *Salmonella* Typhimurium from all animals, 2000-2016. The number of isolates each year varies (n=24-85).

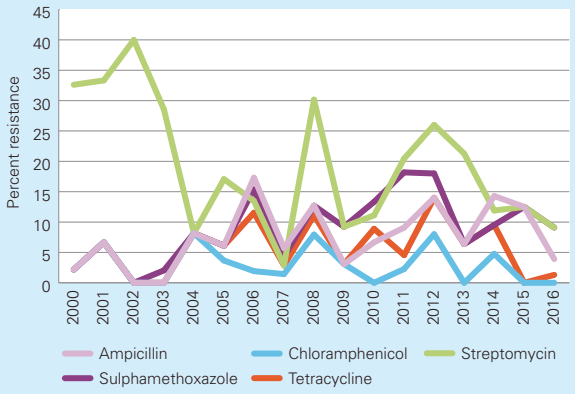


TABLE 4.6 Number of *Salmonella enterica* isolates tested for antibiotic susceptibility, 2016.

Serovar	Cattle	Pigs	Sheep	Poultry	Dogs	Cats	Wild birds	Wild mammals	Total
S. Aarhus	1								**1**
S. Agona					1				**1**
S. Cerro				2					**2**
S. Dublin	4								**4**
S. Duesseldorf	1								**1**
S. enterica subspecies *diarizonae* (IIIb)			3						**3**
S. Enteritidis								1	**1**
S. Fulica								1	**1**
S. Indiana					1				**1**
S. Livingstone				1					**1**
S. Mbandaka				1	1				**2**
S. Newport							1		**1**
S. O4,5:-:1,5							2		**2**
S. Typhimurium	8	5		10	6	12	15		**56**
Total	**14**	**5**	**3**	**14**	**9**	**12**	**18**	**2**	**77**
Percent of total	18	6	4	18	12	16	23	3	

TABLE 4.7. Distribution of MICs and resistance (%) in *Salmonella enterica* (n=77) from all animals, 2016.

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	4								96.1								3.9			
Cefotaxime	0			5.2	27.3	62.3	5.2													
Ceftazidime	0						62.3	35.1	1.3	1.3										
Chloramphenicol	0									23.4	75.3	1.3								
Ciprofloxacin	1			27.3	71.4			1.3												
Colistin	1[a]							5.2	45.5	48.1	1.3									
Florfenicol	0										94.8	5.2								
Gentamicin	0						3.9	68.8	27.3											
Kanamycin	0											100								
Nalidixic acid	1									6.5	84.4	7.8					1.3			
Streptomycin	9									1.3	3.9	18.2	67.5	3.9	1.3	1.3	2.6			
Sulphamethoxazole	9													13.0	62.3	14.3	1.3	1.3		7.8
Tetracycline	1								68.8	29.9					1.3					
Trimethoprim	6					1.3	40.3	46.8	5.2					6.5						

[a] Transmissible resistance genes (*mcr-1* and *mcr-2*) not found.

TABLE 4.8. Distribution of MICs and resistance (%) in *Salmonella* Typhimurium (n=56) from all animals, 2016.

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	5								94.6								5.4			
Cefotaxime	0					28.6	66.1	5.4												
Ceftazidime	0						62.5	35.7	1.8											
Chloramphenicol	0									21.4	78.6									
Ciprofloxacin	2			19.6	78.6			1.8												
Colistin	0							7.1	50.0	42.9										
Florfenicol	0										94.6	5.4								
Gentamicin	0							66.1	33.9											
Kanamycin	0											100								
Nalidixic acid	2									8.9	82.1	7.1					1.8			
Streptomycin	13											12.5	75.0	5.4	1.8	1.8	3.6			
Sulphamethoxazole	13													14.3	60.7	12.5		1.8		10.7
Tetracycline	2								64.3	33.9					1.8					
Trimethoprim	9						33.9	50.0	7.1					8.9						

TABLE 4.9. MICs (mg/L) in the four isolates of *Salmonella enterica* resistant to three or more antibiotics, 2016. Shaded fields indicate resistance.

Source	Serovar	Amp	Ctx	Caz	Cip	Nal	Chl	Flf	Col	Gen	Kan	Str	Sul	Tet	Tmp
Dog	*S.* Typhimurium	≤1	0.12	0.5	0.5	>128	4	8	1	0.5	≤8	64	>1024	≤1	0.25
Dog	*S.* Typhimurium	>128	0.12	≤0.25	0.06	8	4	≤4	1	0.5	≤8	256	>1024	64	0.25
Cattle	*S.* Typhimurium	>128	0.12	≤0.25	0.06	4	4	≤4	2	1	≤8	256	512	≤1	>16
Cattle	*S.* Typhimurium	>128	0.06	≤0.25	0.06	2	4	≤4	1	0.5	≤8	128	>1024	2	>16

One isolate of *S.* Mbandaka from poultry was phenotypically resistant to colistin (MIC 4 mg/L) (Table 4.7) but was negative for the *mcr-1* and *mcr-2* genes on testing with PCR. No isolate was resistant to extended spectrum cephalosporins.

All the four multiresistant isolates were *S.* Typhimurium, of which two were from dogs and two from cattle (Table 4.9). The two isolates from cattle were resistant to ampicillin, streptomycin, sulphonamide and trimethoprim. One of the isolates from dogs was resistant to ampicillin, streptomycin, sulphonamide and tetracycline and the other was resistant to quinolones (ciprofloxacin and nalidixic acid), streptomycin and sulphonamide.

Farm animals 2000-2016

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 2000-2016, isolates from the vast majority of notified incidents in major farm animals were tested in Svarm, in total 684 isolates. About half of the isolates, 336 (49%), were *S.* Typhimurium and of these 37% were from pigs, 32% from cattle, 30% from poultry and 1% from sheep.

TABLE 4.10. Resistance phenotypes of *Salmonella* Typhimurium (n=336) from notified incidents in farm animals, 2000-2016. All isolates were tested for susceptibility to ampicillin, florfenicol, gentamicin, chloramphenicol, ciprofloxacin, nalidixic acid, streptomycin, sulphamethoxazole, tetracycline, trimethoprim and to ceftiofur or cefotaxime.

		Phagetype																						
Phenotype	**Source**	**1**	**7**	**9**	**10**	**12**	**15a**	**39**	**40**	**41**	**99**	**104**	**110b**	**120**	**125**	**126**	**146**	**193**	**195**	**NST**	**NT**	**Monophasic**	**Not typed**	**Sum**
AmpStrSulTetNalChlFlf	**Pigs**											1												1
AmpStrSulTetChlFlfGm	**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
AmpStrSulTm	**Cattle**																						2	2
AmpStrSul	**Cattle**													1								1	1	3
StrSulTet	**Cattle**																			1				1
AmpSul	**Cattle**											2												2
AmpSul	**Pigs**											1												1
StrGm	**Cattle**									1														1
StrGm	**Pigs**								1															1
StrGm	**Poultry**									1														1
StrSul	**Pigs**																					2		2
StrSul	**Poultry**						2																	2
SulTm	**Cattle**																1			1			1	3
SulTm	**Pigs**																						1	1
Amp	**Poultry**																			2				2
Gm	**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	**Sheep**	1																					3	4
Susceptible	**Cattle**	4			2		1	1	1	6		2		5	1	1				27	1	1	14	67
Susceptible	**Pigs**	1	1			2			33	5	1	1		8					1	18	2		19	92
Susceptible	**Poultry**	1		1		1			5	1			1	2				1	1	43	4		26	87
Sum		**7**	**1**	**1**	**2**	**4**	**3**	**1**	**44**	**19**	**1**	**22**	**1**	**20**	**1**	**2**	**1**	**1**	**2**	**104**	**11**	**9**	**79**	**336**

The majority (73%) of *S.* Typhimurium isolates from the incidents in farm animals were susceptible to all antibiotics tested but 37 (11%) were multiresistant (Table 4.10). 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 (*S. enterica* subsp., *enterica* (I), *S.* Duesseldorf, *S.* Yoruba, *S.* Dublin) than Typhimurium were multiresistant. Of these, five isolates were from cattle and one from poultry.

The 37 multiresistant isolates of *S.* Typhimurium in the period 2000-2016 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 2016 none of the notified incidents in farm animals or other animals involved monophasic *S.* Typhimurium I (O 4,5,12:i- /O 4,5:i:- / O 4:i:-). However, previously eight incidents of monophasic *S.* Typhimurium have been confirmed in farm animals in Sweden since this variant was first found in 2006. Three incidents involved only cattle, three only pigs, one only ducks, and one incident involved both cattle and poultry. In six of the incidents the isolates were multiresistant (Table 4.9). Monophasic *S.* Typhimurium has also been isolated from three dogs and a wild bird. Epidemiological links were confirmed between some of the incidents of monophasic *Salmonella*.

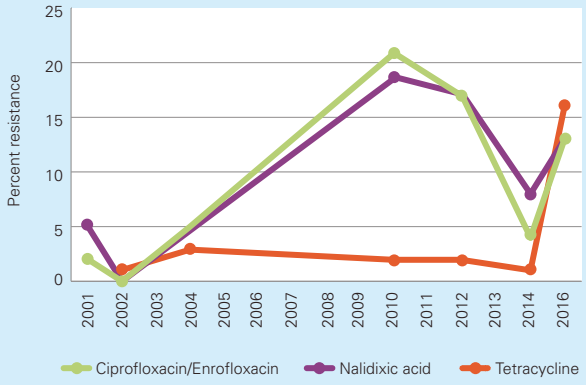
Campylobacter

The isolates of *Campylobacter jejuni* tested are from caecal content of broilers collected at abattoirs and were isolated within the framework of the Swedish Campylobacter control programme 2016. For details on methodology see Materials and methods, resistance in bacteria from animals.

Of the 170 isolates tested, 127 (75%) were susceptible to all six antibiotics. Resistance to tetracycline only was the most common phenotype and this is new for 2016 (Table 4.11). Resistance to fluoroquinolones only (ciprofloxacin and nalidixic acid) was the second most common phenotype. Seven isolates (4%) were resistant to both fluoroquinolones and tetracycline.

In comparison to previous years, quinolone resistance increased notably in 2010 but has declined since then and this year there is a slight increase again (Figure 4.4). The reasons for the quinolone and tetracycline resistance are not known but selection through use of antibiotics is unlikely since these substances seldom are used in broiler production in Sweden.

FIGURE 4.4. Ciprofloxacin, nalidixic acid and tetracycline resistance (%) in *Campylobacter jejuni* from broilers years 2001, 2002, 2004, 2010, 2012, 2014 and 2016. In years 2001-2002 enrofloxacin was tested instead of ciprofloxacin. The number of isolates per year has varied in (n=38-170).



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. It is likely that in some cases there are more than one animal sampled from the same herd.

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.

TABLE 4.11. Distribution of MICs and resistance (%) for *Campylobacter jejuni* from broilers, 2016.

Antibiotic	Resistance (%) n=170	Distribution (%) of MICs (mg/L)											
		≤0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Ciprofloxacin	13	83.5	3.5				8.2	3.5	1.2				
Erythromycin	0				100								
Gentamicin	0		53.5	45.3	1.2								
Nalidixic acid	13					0.6	68.2	17.6	0.6		0.6	12.4	
Streptomycin	1			22.9	60.0	12.4	4.1				0.6		
Tetracycline	16			82.9	1.2		0.6		0.6	14.1	0.6		

Pigs

Escherichia coli

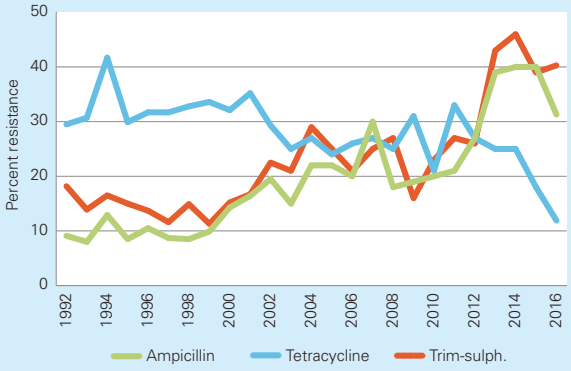
Isolates of *Escherichia coli* are from clinical submissions of faecal samples or samples taken post mortem from the gastro-intestinal tract. During the latest years, the number of samples submitted has decreased and the sampling strategy has probably changed to some extent. This may influence the proportion 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 4.12). Resistance to ampicillin and to trimethoprim-sulphamethoxazole has increased considerably the last years but the increase has levelled off in 2015-2016 (Figure 4.5).

Multiresistance occurred in 25% (17/67) of the isolates in 2016 and has varied over the years (25% in 2015, 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-sulphamethoxazole was the most common trait in multiresistant isolates in 2016, as in previous years. Two isolates were resistant to five antibiotics, six isolates were resistant to four and nine isolates to three antibiotics.

FIGURE 4.5. Resistance (%) in *Escherichia coli* from pigs 1992-2016. Clinical isolates from faecal samples or from samples taken post mortem from the gastro-intestinal tract. The number of isolates each year varies (n=67-482).



Brachyspira hyodysenteriae

Isolates of *Brachyspira hyodysenteriae* are from clinical submissions of faecal samples. Only the first isolate from each herd each year are tested for antibiotic susceptibility. Analysis of antibiotic susceptibility data from isolates of *B. hyodysenteriae* from Sweden 1990-2010 has resulted in a proposal for wild type cut-off values for the antibiotics tested at SVA (Pringle et al., 2012). In Table 4.13 these values are used and historical data have been adjusted. With the wild type cut-off value >0.25 mg/L for tiamulin, some isolates are classified as resistant. With the previously used clinical breakpoint >2 mg/L, three isolates from 2016 are classified as clinically resistant. During 2016, clinical resistance in *B. hyodysenteriae* was detected for the first time in samples from Swedish pigs. For further information see In focus, Tiamulin-resistant *Brachyspira hyodysenteriae*. The cut-off value for tylosin (>16 mg/L) has not been changed compared to previous years. Tylosin resistance has decreased over the years.

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 tiamu-

TABLE 4.12. Distribution of MICs and resistance (%) in *Escherichia coli* from pigs 2016. Clinical isolates from faecal samples or from samples taken post mortem from the gastro-intestinal tract.

Antibiotic	Resistance (%) 2016 n=67	Distribution (%) of MICs (mg/L) ≤0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Ampicillin	31					62.7	6.0			31.3		
Cefotaxime	0		100.0									
Colistin	0				95.5	4.5						
Enrofloxacin	9	91.0	3.0	3.0	3.0							
Gentamicin	1					98.5	1.5					
Neomycin	7						91.0	1.5		1.5	6.0	
Nitrofurantoin	0							46.3	50.7	1.5	1.5	
Streptomycin	33							55.2	11.9	6.0	6.0	20.9
Tetracycline	12					88.1			11.9			
Trim-Sulph.[a]	40			58.2	1.5			40.3				

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

TABLE 4.13. Resistance (%) in *Brachyspira hyodysenteriae* from pigs 2005-2016 and distribution of MICs for isolates from 2009-2016. Clinical isolates from faecal samples.

Antibiotic	Resistance (%)			Distribution (%) of MICs (mg/L)													
	2005-06	2007-08	2009-16														
	n=54[a]	n=38[c]	n=80[e]	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Doxycycline	9	3	3			22.5	66.3	8.8		2.5							
Tiamulin	7	18	9		41.3	36.3	13.8	2.5	2.5				3.8				
Tylosin	81	76	53							6.3	26.3	13.8	1.3			1.3	51.3
Tylvalosin	NA[b]	93[d]	51				1.3	17.5	30.0	2.5	10.0	26.3	10.0		2.5		
Valnemulin	0	18	8	77.5	15.0		1.3	2.5				3.8					

[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, 11 isolates 2016.

TABLE 4.14. Distribution of MICs for *Brachyspira pilosicoli* from pigs 2005-2016, n=313. 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			39.9	48.9	4.2	2.6	4.2	0.3						
Tiamulin		35.1	24.6	12.1	9.3	5.8	1.6	0.6	2.2	8.6				
Tylosin							6.4	19.5	13.7	3.8	4.2	4.5	5.4	42.5
Tylvalosin[a]				0.7	12.7	26.7	27.3	4.0	1.3	3.3	12.0	12.0		
Valnemulin	47.0	18.8	5.4	10.5	7.0	4.2	2.2	1.3	3.5					

[a] 150 isolates tested.

lin of >2 mg/L and for tylosin of >16 mg/L are used at SVA. With these breakpoints, 11% of the isolates are resistant to tiamulin and 57% to tylosin (Table 4.14). If the same wild type 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. For more information on SvarmPat, see In Focus, SvarmPat – monitoring of resistance in pathogens from farm animals. The resistance situation is favourable and almost no resistance is detected (Table 4.15). 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 4.16).

TABLE 4.15 . Distribution of MICs and resistance (%) in *Actinobacillus pleuropneumoniae* from pigs 2011-2016. Clinical isolates from post mortem investigations of lungs. The number of isolates each year varies (n=18-57).

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)															
	2011-2016																
	n=214	≤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									100							
Ciprofloxacin	0	0.5	19.6	34.6	45.3												
Florfenicol	<1										99.5		0.5				
Gentamicin	0									13.6	75.7	10.7					
Nalidixic acid	0								4.2	70.1	25.2	0.5					
Penicillin	0			0.5	1.9	13.1	43.0	41.6									
Streptomycin	NR[a]											0.5	34.6	62.6	2.3		
Tetracycline	0								100								
Trimethoprim	0					26.6	49.5	21.5	1.4	0.9							

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

Tiamulin-resistant *Brachyspira hyodysenteriae*

During year 2016 tiamulin-resistant *Brachyspira hyodysenteriae* was found for the first time in Sweden. Treatment failure with tiamulin was observed in a piglet producing herd (herd A, Table) with swine dysentery and susceptibility tests of *B. hyodysenteriae* isolates from the herd gave tiamulin MICs >8 mg/L (isolate 130:3 and 130:4, Table). There are no internationally accepted clinical breakpoints for *Brachyspira* spp. but the clinical breakpoint for tiamulin resistance used at SVA is >2 mg/L.

Background

The anaerobic spirochete *B. hyodysenteriae* is the causative agent of swine dysentery, a serious diarrhoeal disease of pigs. The drug of choice for eradication of *B. hyodysenteriae* in Swedish pig herds is tiamulin. Another pleuromutilin antibiotic, valnemulin, is also authorized for treatment of swine dysentery but is currently not available on the Swedish market. Both of these pleuromutilins are important in the control of swine dysentery worldwide.

Tiamulin was introduced on the Swedish market in 1988 and in the 1990s the use increased markedly. During those years, the major indication for usage of tiamulin was swine dysentery. A control program against swine dysentery was launched in Sweden by the Swedish Animal Health Service year 2000 and since then the number of *B. hyodysenteriae* positive samples at SVA has been decreasing (Råsbäck et al., 2009; Fellström et al., 2005). This coincides with a decrease in the total use of pleuromutilins in Sweden which currently has returned to the levels of the first years on the Swedish market for tiamulin (for details see Svarm 2010 and Sales of antibiotics for animals).

In the control program, nucleus and multiplying herds are certified as free from swine dysentery by going through a sampling and observation period of six months. If *B. hyodysenteriae* is detected an eradication program is conducted. When a herd is certified as free, two negative samplings per year of pigs susceptible to swine dysentery (20-40 kg body weight) are required to retain the certification (Fellström et al., 2009).

The outbreak and its management

Herd A is a farrow-to-finish herd with 500 sows that was diagnosed with swine dysentery early in 2016. An eradication program including treatments with tiamulin was carried out in the spring of that year, unfortunately without success. Problems with swine dysentery continued and in late summer treatment with tiamulin did no longer give expected effect and faecal swabs were sent to SVA for culture and susceptibility test. The isolates that were obtained in August were pleuromutilin resistant but still macrolide susceptible. Subsequently a new eradication program was initiated using tylvalosin to treat all adult pigs and oxytetracycline to treat growing pigs before they were sold. Tetracycline was used to minimize the risk of selection for point mutations causing macrolide resistance during the program. However, at the same time the eradication program started an isolate (133:4) with high MICs of both macrolides and pleuromutilins was found.

During September and October pleuromutilin resistant isolates of *B. hyodysenteriae* were found in five additional herds with fattening pigs (Table). Three of these herds (B, E and F) had purchased growers from herd A. Herd D had not bought pigs from herd A and most likely contracted the disease via a truck that had not been properly cleaned and disinfected after transporting growers from herd A to another herd. Herd C is a minor farrow-to-finish farm and has, so far, no known connection to the other herds. The shared resistance phenotype of the isolates, preliminary RAPD (Random Amplification of Polymorphic DNA) results and the epidemiologic links between the herds indicate that it is one pleuromutilin resistant clone that has spread.

The second eradication attempt of *B. hyodysenteriae* in herd A was completed in December 2016. A few samples from pigs with loose faeces have been taken at the time of writing this report and all have been negative in culture for *B. hyodysenteriae*.

Conclusion

Despite the favourable situation in Sweden with very few swine dysentery herds and a tendency of increased antibiotic susceptibility among the few *B. hyodysenteriae* isolates obtained each year this resistant clone has emerged. So far, no clinical signs of swine dysentery have been recorded after the second eradication. The main antibiotic treatment this time was tylvalosin. Fortunately, the isolates from herd A were macrolide susceptible, or in the case with 133:4, had an MIC of tylvalosin of 16 mg/L. It is also possible that *B. hyodysenteriae* with the resistance phenotype of isolate 133:4, that was isolated simultaneously with the start of the eradication program, did not cause any problem because it had not yet spread in the entire herd.

The worst-case scenario is that a clone with both pleuromutilin and macrolide resistance is disseminated. To our knowledge there is no experience of eradication of *B. hyodysenteriae* with any other antibiotic. If there would be no treatment option left for an eradication program, the only alternative is depopulation and repopulation of the herd.

TABLE. Resistance phenotypes for *B. hyodysenteriae* isolate from the outbreak. Shaded fields denote MIC above the proposed wild type cut-off values proposed by Pringle et al. (2012).

			Antibiotic. MIC (mg/L)					
Herd	**Isolate**	**Month**	**Tiamulin**	**Valnemulin**	**Doxycycline**	**Lincomycin**	**Tylosin**	**Tylvalosin**
A	128:1	Feb	≤0.063	≤0.031	0.25	≤0.5	≤2	1
A	131:5	June	0.25	0.5	≤0.12	1	4	1
A	130:2	July	0.12	0.5	≤0.12	1	≤2	0.5
A	130:3	Aug	>8	>4	≤0.12	2	≤2	0.5
A	130:4	Aug	>8	>4	0.25	2	≤2	0.5
A	133:4	Oct	4	4	≤0.12	4	>128	16
B	131:1	June	≤0.063	≤0.031	0.25	≤0.5	≤2	1
B	130:5	Sept	>8	>4	≤0.12	2	4	0.5
C	135:2	Sept	>8	>4	0.25	2	4	0.5
D	131:2	Sept	>8	>4	≤0.12	2	4	1
D	131:3	Sept	>8	>4	≤0.12	2	≤2	0.5
E	132:1	Oct	0.12	0.25	≤0.12	≤0.5	≤2	0.5
E	132:4	Oct	8	>4	≤0.12	2	≤2	0.5
F	135:3	Oct	>8	>4	0.25	2	4	1

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Råsbäck T, Johansson K-E, et al. 2009. Laboratory diagnostics of *Brachyspira* species and a new bacteria causing dysentery in pigs. *Svensk Vet Tidn* 61:11-16.

TABLE 4.16. Distribution of MICs and resistance (%) in *Pasteurella* spp. from pigs 2005-2016. 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 (%) 2005-2015 n=267	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	>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]										98.9	1.1					
Gentamicin	1									71.9	22.2	5.2	0.4	0.4			
Nalidixic acid	0[b]								50.5	40.2	8.2		1.0				
Penicillin	0					52.1	43.4	4.5									
Streptomycin	NR[e]										3.0	43.8	34.5	13.1	5.6		
Tetracycline	0								98.5	1.5							
Trim-Sulph	1[f]							96.1	0.7	1.3	0.7	1.3					

[a] 104 isolates tested; [b] 97 isolates tested [c] 170 isolates tested; [d] 263 isolates tested; [e] Not relevant since the genus has inherently low susceptibility to streptomycin; [f] 153 isolates tested, concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphamethoxazole).

Isolates from 2013-2016 (n=129) were identified to species level by MALDI-TOF MS and are *Pasteurella multocida*. Isolates from earlier years were identified with biochemical methods. Most of these isolates are *P. multocida*, but species identification of some isolates is uncertain. Cut-off values as given in Table 6.12 for *P. multocida* are used in Table 4.16 for all isolates.

Cattle

Escherichia coli from faecal samples

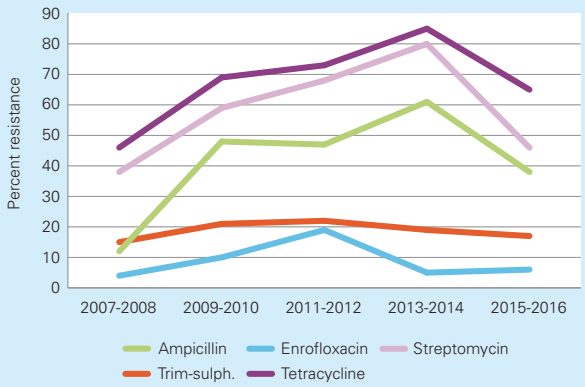
Isolates of *E. coli* are from the gastro-intestinal tract of calves. Most of the isolates are probably from calves no more than a few weeks old, i.e. during a period when resistance in enteric bacteria often is high in cattle. Resistance is high to tetracycline, streptomycin and ampicillin (Table 4.17 and Figure 4.6), as in previous years. Multiresistance occurred in 31% (9/29) of the isolates from 2016, compared to 56% in 2015, 76% in 2014, 70% in 2013 and 50% in 2012.

One isolate from 2016 had an MIC of cefotaxime above the ECOFF and had an AmpC phenotype when tested further, but no genes conferring transferable extended spectrum cephalosporin (ESC) resistance were detected when tested with PCR.

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 were susceptibility tested increased in 2013. The number of susceptibility tested isolates each year is still higher than before the regulation. Although antibiotic treatment may not be indicated for *E. coli* mastitis, fluoroquinolones may be the clinically most effective group of antibiotics if treatment is required.

FIGURE 4.6. Resistance (%) in *Escherichia coli* from cattle 2007-2016. 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).



In the material from 2016, 30% (22/74) 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 4.18). Multiresistance occurred in 24% (18/74) of all isolates. Resistance to ampicillin, streptomycin, tetracycline and trimethoprim-sulphamethoxazole were the most common traits and 14% of all isolates were resistant to all four of these antibiotics.

One isolate had an MIC of cefotaxime above the ECOFF and had an AmpC phenotype when tested further, but no genes conferring transferable extended spectrum cephalosporin (ESC) resistance were detected when tested with PCR.

TABLE 4.17. Distributions of MICs and resistance (%) in *Escherichia coli* from cattle 2016. Clinical isolates from faecal samples or from samples taken post mortem from the gastro-intestinal tract.

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)										
	2016 n=29	≤0.12	0.25	0.5	1	2	4	8	16	32	64	>32
Ampicillin	34					58.6	6.9			34.5		
Cefotaxime	3[b]		96.6	3.4								
Colistin	0				100							
Enrofloxacin	3	96.6	3.4									
Gentamicin	0					100						
Neomycin	21						75.9	3.4	3.4	3.4	13.8	
Nitrofurantoin	0							58.6	41.4			
Streptomycin	34							48.3	17.2	3.4	3.4	27.6
Tetracycline	62					37.9				62.1		
Trim-Sulph.[a]	10			89.7				10.3				

[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 had an AmpC phenotype but no genes conferring transferable ESC resistance were detected with PCR.

TABLE 4.18. Resistance (%) in *Escherichia coli* from dairy cows 2013-2016. Distribution of MICs from 2016. Clinical isolates from milk.

Antibiotic	Resistance (%)				Distribution (%) of MICs (mg/L)										
	2013 n=142	2014 n=95	2015 n=113	2016 n=74	≤0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Ampicillin	14	20	20	27					56.8	16.2			27.0		
Cefotaxime	NA[b]	NA	3[c]	1[e]		98.6		1.4							
Ceftiofur	1	0	NA	NA											
Colistin	NA	NA	<1[d]	0				89.2	10.8						
Enrofloxacin	5	6	2	4	95.9	1.4	2.7								
Gentamicin	0	0	0	1					98.6	1.4					
Neomycin	4	1	<1	0						98.6	1.4				
Nitrofurantoin	NA	NA	0	0							29.7	62.2	4.1	4.1	
Streptomycin	16	25	20	26							66.2	8.1	1.4	2.7	21.6
Tetracycline	9	19	11	16					79.7	2.7	1.4		16.2		
Trim-Sulph.[a]	11	17	12	22			75.7	2.7			21.6				

[a]Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphamethoxazole); [b] Not analysed; [c]The isolates with MICs 1 and 2 were further tested with PCR but genes genes conferring transferable ESC resistance 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 *mcr-1* and *mcr-2* genes; [e] The isolate with MIC 1 mg/L was further tested and had an AmpC phenotype but no genes conferring transferable ESC resistance were detected with PCR.

TABLE 4.19. Resistance (%) in *Klebsiella pneumoniae* from dairy cows 2013-2016 and distributions of MICs 2016. Clinical isolates from milk.

Antibiotic	Resistance (%)				Distribution (%) of MICs (mg/L)										
	2013 n=41	2014 n=39	2015 n=41	2016 n=36	≤0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Ampicillin	NR[b]	NR	NR	NR								8.3	91.7		
Cefotaxime	NA[c]	NA	0	0		100									
Ceftiofur	1	0	NA	NA											
Colistin	NA	NA	0	3[d]				80.6	16.7			2.8			
Enrofloxacin	5	6	2	14	86.1	11.1	2.8								
Gentamicin	0	0	0	0					100						
Neomycin	4	1	0	0						100					
Nitrofurantoin	NA	NA	NR	NR								5.6	38.9	52.8	2.8
Streptomycin	16	25	15	3							97.2		2.8		
Tetracycline	9	19	10	6					94.4				5.6		
Trim-Sulph.[a]	11	17	0	6			94.4				5.6				

[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; [d] The isolate with MIC 16 mg/L was negative for *mcr-1* and *mcr-2* genes with PCR.

Klebsiella pneumoniae from milk samples

Isolates of *Klebsiella pneumoniae* are from clinical submissions of milk samples from dairy cows. Resistance was uncommon and 75% of isolates was susceptible to all tested antibiotics, excluding ampicillin. Multiresistance did not occur in isolates from 2016. One isolate had an MIC of colistin above the ECOFF. The isolate was tested with PCR for detection of *mcr-1* and *mcr-2* genes and these genes were not detected.

Pasteurella spp.

Most isolates of *Pasteurella* spp. are from nasal swabs from calves with respiratory disease or from post mortem investigations of lungs. Fifty-four isolates from 2016 are from a study were both calves with and without respiratory disease were sampled. Isolates from 2013-2016 were identified to species level by MALDI-TOF MS and are *Pasteurella multocida*. Isolates from earlier years were identified with biochemical methods. Most of these isolates are also *P. multocida*, but species identification of some isolates is uncertain. Cut-off values as given in Table 6.11 for *P. multocida* are used in Table 4.20 for all isolates.

Antibiotic resistance was generally rare among isolates of *Pasteurella* spp. (Table 4.20), but in 2016 beta-lactamase producing *P. multocida* was isolated from calves in four herds. In addition, 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. Penicillin is considered the antibiotic of choice for treatment of pneumonia in cattle in Sweden. Sampling and susceptibility testing is of utmost importance for early detection of resistance, especially if therapeutic failure is seen.

TABLE 4.20. Distribution of MICs and resistance (%) in *Pasteurella* spp. from calves 2005-2016. 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	2016 n=104	≤0.06	0.12	0.25	0.5	1	2	4	8	16	>16
Ampicillin	0	13				56.7	29.8		1.9	11.5		
Enrofloxacin	0[b]	0		98.1	1.9							
Florfenicol	0	0						99.0	1.0			
Penicillin	0	13	2.9	53.8	29.8		13.5					
Tetracycline	0	0					100					
Trim-Sulph.[a]	0	0				99.0		1.0				

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

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 2009-2016 are compiled and presented as distributions of MICs in Table 4.21. 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 2009-2016 are compiled and presented as distributions of MICs in Table 4.21. ECOFFs for *F. columnare* are not available.

Flavobacterium psycrophilum

Isolates of *Flavobacterium psycrophilum* are from clinical submissions of farmed fish. Data from 2015-2016 are compiled and presented as distributions of MICs in Table 4.22. Most isolates are from rainbow trout. Recently, Smith et al. (2014) proposed epidemiological cut-offs for florfenicol, oxolinic acid and oxytetracycline for *F. psycrophilum*. These are used in the distributions in Table 4.22. Resistance to oxolinic acid and oxytetracycline was high in this material.

In Figure 4.7. resistance to tetracycline and quinolones (nalidixic acid or oxolinic acid) in *F. psycrophilum* 2005-2016 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 4.7. Resistance (%) in *Flavobacterium psycrophilum* from farmed fish 2005-2016 with a three years moving average. The number of isolates each year varies (n=12-62).

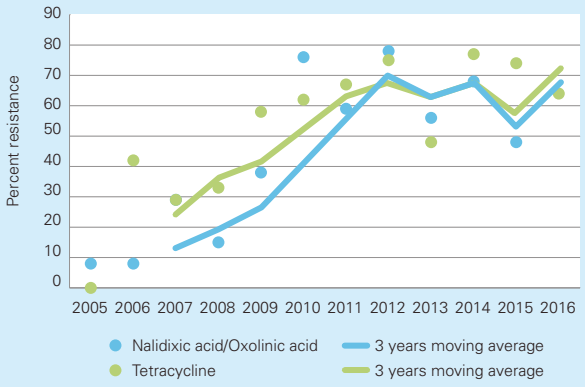


TABLE 4.21. Distribution of MICs for *Aeromonas salmonicida* subsp. *achromogenes* (n=78) and *Flavobacterium columnare* (n=47) from farmed fish 2009–2016.

Bacterial species	Antibiotic	Resistance (%) 2009-2016	Distribution (%) of MICs (mg/L) ≤0.5	1	2	4	8	16	32	64	>64
Aeromonas salmonicida subsp. *achromogenes*	Florfenicol	1			97.4	1.3		1.3			
	Nalidixic acid[a]		81.7	1.7					1.7	6.7	8.3
	Tetracycline	3	94.9	2.6		1.3		1.3			
Flavobacterium columnare	Florfenicol				100						
	Nalidixic acid[b]		77.4	12.9	3.2	3.2				3.2	
	Tetracycline		97.9	2.1							

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

TABLE 4.22. Distributions of MICs and resistance (%) in *Flavobacterium psycrophilum* from farmed fish 2015–2016.

Antibiotic	Resistance (%) 2015-2016 n=47	Distribution (%) of MICs (mg/L) ≤0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8
Florfenicol	0						8.5	42.6	40.4	8.5			
Oxolinic acid	55				2.1	34.0	8.5			55.3			
Oxytetracycline	79				19.1	2.1	2.1		19.1	19.1	34.0	4.3	

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. This is archived by monitoring and documenting antibiotic resistance, by activities that increase knowledge of antibiotic resistance and prudent use of antibiotics, and by communication of knowledge to practitioners and farmers.

Selected studies within SvarmPat in 2016:

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 2010-2016, about 1 000 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, about 500 isolates of *S. aureus* without beta-lactamase production was tested in 2013, but MRSA was not detected.
- 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. The most commonly found bacterial species are *S. aureus*, *Streptococcus dysgalactiae*, *Escherichia coli* followed by *Streptococcus uberis*. Penicillin resistance in *S. aureus* from cows with clinical mastitis in this monitoring is very uncommon.

Respiratory tract samples from pigs, cattle and sheep

- The important respiratory pathogens *Actinobacillus pleuropneumoniae* and *Pasteurella multocida* from pigs, *P. multocida* and *Mannheimia haemolytica* from cattle and *M. haemolytica* and *Bibersteinia trehalosi* from sheep are continuously susceptibility tested within SvarmPat. Resistance to penicillin in these bacteria is 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.
- During 2016, a study of different variants of sampling swabs for detection of relevant bacterial pathogens like *P. multocida* and *M. haemolytica* in the nasal cavity of calves was conducted. Sampling was done in 10 beef calf herds and altogether 100 calves were sampled. The short swab commonly used in routine sampling gave a significantly lower isolation frequency than E-swab and two longer sampling swabs. Penicillin resistant *P. multocida* was detected in three of the herds.
- During 2016, a study on pneumonia in sheep was conducted. Lungs with pneumonic lesions were collected from two slaughterhouses. A total of 44 lungs were examined macroscopically and histologically and with bacteriological culturing and PCR for *Mycoplasma* spp. *Mycoplasma ovipneumoniae* was correlated to a specific gross appearance of the lungs but could not be correlated with any specific histological findings. Penicillin resistance in *M. haemolytica* was not found in this study.

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, but resistance to tiamulin in *B. hyodysenteriae* was detected for the first time in 2016 (see In focus: Tiamulin-resistant *Brachyspira hyodysenteriae*). Within SvarmPat, isolates from all identified herds with these diseases in Sweden are susceptibility tested. For resistance results see Clinical isolates from animals.
- Resistance to ampicillin and trimethoprim-sulphamethoxazole in *Escherichia coli* from pigs with diarrhoea has been increasing over the years. The increase may be due to sampling bias towards herds with therapeutic failure. To collect a set of more representative isolates, a study with randomized sampling from pigs with neonatal diarrhoea and post weaning diarrhoea was started in 2016. The results will be compiled and analysed during 2017.

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.

Horses

Escherichia coli

Isolates of *Escherichia coli* are from clinical submissions of the genital tract of mares. As in previous years, the proportion of resistance to trimethoprim-sulphamethoxazole and streptomycin was most common in 2016 (Table 4.23 and Figure 4.8). The general decline in figures seen between 2004 and 2014 has reversed into an increase for ampicillin, streptomycin and trimethoprim-sulphamethoxazole, while the figure for gentamicin continue to decline (Figure 4.8). However, the proportion of resistance in the tested isolates has differed somewhat over the years and trends are difficult to estimate.

Multiresistance was detected in 10% (31/324) of the isolates, which is higher than in 2012-2015 (4-6%), but comparable to 11% in 2011 (see previous Swedres-Svarm reports). Seventeen of the multiresistant isolates were resistant to three antibiotics; nine to four; three to five and two isolates were resistant to six antibiotics. The most common phenotype was resistance to ampicillin, streptomycin and trimethoprim-sulphamethoxazole, representing 81% (25/31) of the multiresistant isolates. The two isolates resistant to six antibiotics had the common phenotype and were in addition resistant to cefotaxime, gentamicin and tetracycline.

Three of the *E. coli* isolates were resistant to cefotaxime (MIC >0.25 mg/L). Genes conferring transferable ESC resistance were detected in two of the isolates. For more information, see Notifiable diseases, ESBL-producing Enterobacteriaceae.

Nineteen isolates were resistant to colistin (MIC >2 mg/L). Four of the isolates were available for PCR detection of the *mcr-1* and *mcr-2* genes, and all four were negative.

Streptococcus equi subsp. *zooepidemicus*

Isolates of *Streptococcus equi* subsp. *zooepidemicus* are from clinical submissions, and mainly from the respiratory tract. Resistance to antibiotics was rare in 2016 (Table 4.24). Isolates of *S. zooepidemicus* have remained susceptible to penicillin over the years studied but in 2016 two isolates had penicillin MICs 0.12 and 0.25 mg/L, respectively. Such results indicate methodological errors and warrants retesting of the isolates (CLSI 2013). However, the isolates were not available for confirmatory analyses of the high penicillin MICs and they were therefore excluded from the dataset.

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

FIGURE 4.8. Resistance (%) in clinical isolates of *Escherichia coli* from horses 2004-2016. Isolates are from clinical sampling of the genital tract of mares. The number of isolates each year varies (n=124-324).

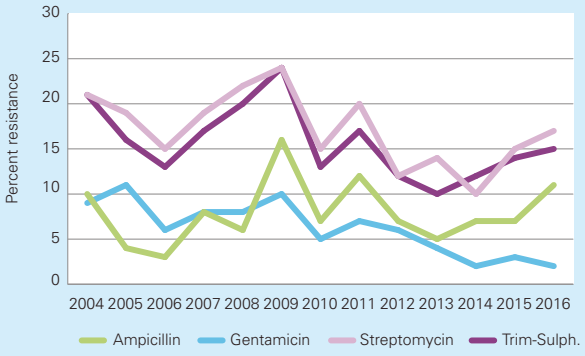


FIGURE 4.9. Resistance (%) in clinical isolates of *Staphylococcus aureus* from skin of horses 2008-2016. The number of isolates each year varies (n=75-145).

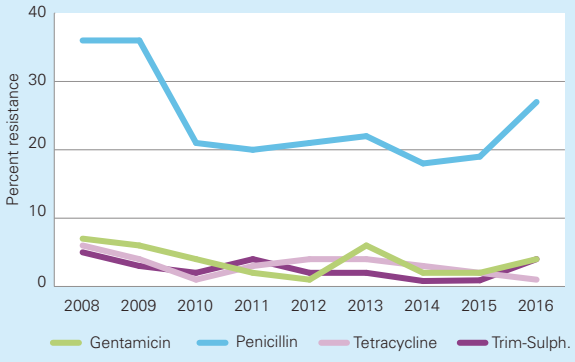


TABLE 4.23. Distributions of MICs and resistance (%) in *Escherichia coli* from horses in 2016. Clinical isolates from the genital tract of mares.

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)										
	2016 n=324	≤0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Ampicillin	10					80.3	9.0	0.3		10.5		
Cefotaxime	1		99.1				0.9					
Colistin	6				72.2	21.9	4.3	0.9	0.6			
Enrofloxacin	2	97.5	0.3	1.9	0.3							
Gentamicin	2					97.8	0.3			1.9		
Neomycin	1						98.8			0.3	0.9	
Nitrofurantoin	<1							59.3	38.0	1.5	0.9	0.3
Streptomycin	17							80.3	2.8	1.2	4.0	11.7
Tetracycline	5					95.1	0.3			4.6		
Trim-Sulph.a	15			83.3	1.2		0.3	15.1				

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

TABLE 4.24. Distribution of MICs and resistance (%) in *Streptococcus zooepidemicus* isolated from horses in 2016. Clinical isolates mainly from the respiratory tract.

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)								
	2016 n=114[c]	≤0.03	0.06	0.12	0.25	0.5	1	2	4	>8
Cephalotin	0						98.2	2		
Clindamycin	6					93.9	6.1			
Erythromycin	0					100				
Gentamicin	NR[b]							0.9	13.2	86.0
Penicillin	0	98.2	1.8							
Tetracycline	NR				0.9		10.5	71.1	15.8	1.8
Trim-Sulph.[a]	5				75.4	19.3	2.6			2.6

[a] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim-sulphamethoxazole); [b] NR= Not relevant as the inherent susceptibility is above concentrations that can be obtained during therapy. [c] Data was available for 116 isolates, but two of these isolates had penicillin MICs 0.12 and 0.25 mg/L. These two isolates were not available for confirmatory analyses of the high penicillin MICs and they were therefore excluded from the dataset.

TABLE 4.25. Distribution of MICs and resistance (%) in *Staphylococcus aureus* isolated from horses 2016. Clinical isolates from the skin.

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)										
	2016 n=75[c]	≤0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Cefoxitin	0			2.7	2.7	56.0	38.7					
Cephalotin	3				97.3	2.7						
Clindamycin	3			97.3	2.7							
Enrofloxacin	3			97.1	2.9							
Erythromycin	0			89.3	10.7							
Fusidic acid	21			78.7	16.0		5.3					
Gentamicin	4				94.7	1.3	4.0					
Nitrofurantoin	0								100			
Oxacillin	0		53.3	13.3	21.3							
Penicillin[a]	27											
Tetracycline	1		74.7	24		1.3						
Trim-Sulph.[b]	4		90.7	5.3	2.7	1.3						

[a] Denotes beta-lactamase production; [b] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim-sulphamethoxazole); [c] n=75 for all antibiotics, except enrofloxacin with 35 tested isolates.

Staphylococcus aureus

Isolates of *Staphylococcus aureus* are from clinical submissions of samples from skin lesions, excluding wounds and abscesses. Table 4.25 presents the distribution of MICs and resistance of isolates in 2016. The proportions of resistance to gentamicin, penicillin, tetracycline and trimethoprim-sulphamethoxazole over the last nine years are shown in Figure 4.9. Resistance to penicillin dominates. In 2008-2009, 36% of the tested isolates were resistant to penicillin. The figures declined in 2010 and stabilised to around 20% for six years (2010-2015), but increased to 27% in 2016.

Multiresistance was detected in 4% (3/75) of the isolates. The three isolates were resistant to three antibiotics, but no common phenotype was seen.

None of the isolates was resistant to oxacillin (MIC >1) or cefoxitin (MIC >4). For more information on MRSA isolated from horses, see Notifiable diseases, MRSA in animals.

Dogs

Escherichia coli

Isolates of *Escherichia coli* are from clinical submissions of urine, submitted either as urine or cultures from dip-slides or other agar plates. As in previous years, resistance to ampicillin was most common in 2016 (Table 4.26 and Figure 4.10). Since 2005 to 2016 the proportion of resistance in the tested isolates has differed somewhat between the years and trends are difficult to estimate (Figure 4.10).

Multiresistance was detected in 9% (99/1162) of the isolates, a somewhat higher figure compared to 2015 (7%). Sixty-nine percent (68/99) of the multiresistant isolates were resistant to three antibiotics; 19% (18/99) to four; 10% (10/99) to five; 2% (2/99) to six and 1% (1/99) to seven antibiotics. The most common phenotype, resistance to ampicillin, streptomycin and trimethoprim-sulphamethoxazole, was detected in

69% (68/99) of the isolates in 2016 in comparison to 40% in 2015. Isolates resistant to four or more antibiotics, and of the common phenotype (n=22), were commonly also resistant to tetracycline (15/22).

Twenty-seven of the isolates were resistant to cefotaxime (MIC >0.25 mg/L). Genes conferring transferable ESC resistance were detected in 16 of the isolates. For more information, see Notifiable diseases, ESBL-producing Enterobacteriaceae.

Fifty-three isolates were resistant to colistin (MIC >2 mg/L). Three isolates were available for PCR detection of the *mcr-1* and *mcr-2* genes, and all three were negative.

FIGURE 4.10. Resistance (%) in clinical isolates of *Escherichia coli* from dog urine 2005-2016. The number of isolates each year varies (n=304-1162).

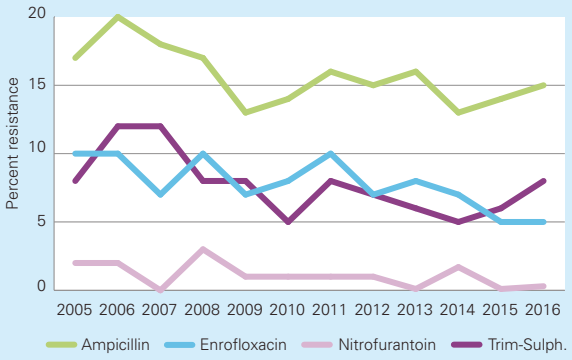


TABLE 4.26 . Distribution of MICs and resistance (%) in *Escherichia coli* from dogs 2016. Clinical isolates from urine.

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)										
	2016 n=1162	≤0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Ampicillin	15					69.2	15.7	0.3	0.4	14.4		
Cefotaxime	2		97.7	0.4	0.3	0.3	1.3					
Colistin	5				81.6	13.9	3.7	0.3	0.5			
Enrofloxacin	5	94.3	1.8	2.6	0.6			0.7				
Gentamicin	1					99.5	0.5					
Neomycin	1						99.0	0.5	0.1	0.1	0.3	
Nitrofurantoin	<1							55.2	43.4	1.0	0.3	0.3
Streptomycin	9							85.7	4.8	1.5	2.8	5.2
Tetracycline	5					94.3	0.8	0.1	0.2	4.7		
Trim-Sulph.[a]	8			91.6	0.7	0.9	0.2	6.7				

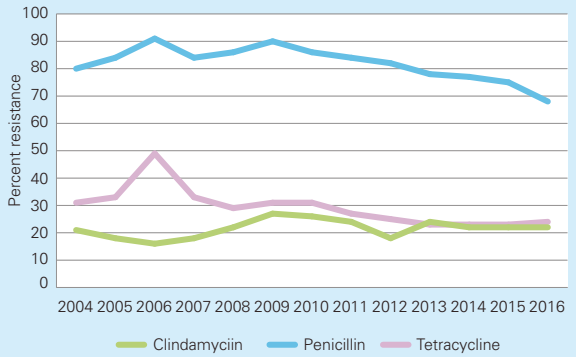
[a]Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim-sulphamethoxazole).

TABLE 4.27. Distribution of MICs and resistance (%) in *Staphylococcus pseudintermedius* isolated from clinical submissions of skin samples in dogs 2016.

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)										
	2016 n=376[c]	≤0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Cephalothin	1				98.9	0.8	0.3					
Cefoxitin[d]	-		81.1	17.6	0.5	0.8						
Clindamycin	23			77.1	1.3	0.3	21.3					
Enrofloxacin	4		93.3	3.1	2.5	1.2						
Erythromycin	26			74.2	3.5		22.3					
Fusidic acid	20			68.4	11.7	1.6	18.4					
Gentamicin	3				94.7	2.4	1.1	1.9				
Nitrofurantoin	<1								98.4	1.3	0.3	
Oxacillin	1		96.8	2.1	0.3	0.8						
Penicillin[a]	68											
Tetracycline	24		74.5	1.6		0.3	0.3	23.4				
Trim-Sulph.[b]	20		52.1	27.4	14.9	2.1	0.3	3.2				

[a] Denotes beta-lactamase production; [b] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphamethoxazole: [c] n=376 for all substances, except enrofloxacin with 163 tested isolates; [d] No breakpoint available for *S. pseudintermedius*.

FIGURE 4.11. Resistance (%) in clinical isolates of *Staphylococcus pseudintermedius* from skin of dogs 2004-2016. The number of isolates each year varies (n=89-566).



Staphylococcus pseudintermedius

Isolates of *Staphylococcus pseudintermedius* are from clinical submissions of samples from skin lesions, excluding wounds and abscesses.

Resistance to penicillin due to penicillinase-production dominates, but the proportion has declined from 90% in 2009 to 68% in 2016 (Table 4.27 and Figure 4.11). Resistance to erythromycin and tetracycline fluctuates slightly over the years, but remains at approximately same levels (Figure 4.11).

Multiresistance is common in *S. pseudintermedius*. Between 2009 and 2015 the figures on multiresistance reported in Svarm for the included isolates have varied from 26 to 36% (see previous Swedres-Svarm reports). In 2016 the corresponding figure was 28% (106/376). This is high compared to the proportion of multiresistance in isolates of

TABLE 4.28. Distribution of MICs and resistance (%) in *Staphylococcus schleiferi* isolated from various locations in dogs 2016.

Antibiotic	Resistance (%) 2016 n=163[c]	Distribution (%) of MICs (mg/L) ≤0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Cephalothin	1				99.4	0.6						
Cefoxitin[d]			40.5	57.1	2.5							
Clindamycin	7			92.6	3.7		3.7					
Enrofloxacin	20		76.4	3.6	20.0							
Erythromycin	6			94.5	1.8		3.7					
Fusidic acid	14			71.8	14.1	8.6	5.5					
Gentamicin	1				97.5	1.8	0.6					
Nitrofurantoin	0								98.2	1.8		
Oxacillin	0		98.8	1.2								
Penicillin[a]	2											
Tetracycline	4		87.7	6.7	1.8			3.7				
Trim-Sulph.[b]	2		87.1	10.4	2.5							

[a] Denotes beta-lactamase production; [b] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphamethoxazole); [c] n=163 for substances, except enrofloxacin with 55 tested isolates; [d] No breakpoint available for *S. schleiferi*.

TABLE 4.29. Distribution of MICs and resistance (%) in *Pseudomonas aeruginosa* from dogs 2016. Clinical isolates from the external ear canal.

Antibiotic	Resistance (%) 2016 n=349	Distribution (%) of MICs (mg/L) ≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Enrofloxacin	13	0.9	2.3	12.6	43.6	28.1	4.9	7.7			
Colistin[a]	1				77.7	17.5	4.3	0.3	0.3		
Gentamicin	2					92.3	5.4	0.6	0.9	0.9	

[a]Colistin MICs are valid for Polymyxin B.

TABLE 4.30. Distribution of MICs and resistance (%) in *Pasteurella canis*. Clinical isolates from dogs 2016.

Antibiotic	Resistance (%) 2016 n=253	Distribution (%) of MICs (mg/L) ≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	0				100.0						
Enrofloxacin	2	97.6	0.4	0.4	0.8	0.4		0.4			
Gentamicin	<1					98.8	0.8		0.4		
Penicillin	0	99.2	0.8								
Tetracycline	0				100.0						
Trim-Sulph.[a]	0			99.6		0.4					

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

S. schleiferi from dogs (3%), *S. aureus* from horses (4%) and *S. felis* from cats (5%).

One third (34% or 36/106) of the multiresistant isolates and 10% (36/376) of all isolates were resistant to five or more antibiotics. Seventy-three percent (77/106) of the multiresistant isolates were resistant to penicillin, clindamycin and erythromycin. In the isolates, resistant to four or more antibiotics, this phenotype was present in 88% (59/67) and most common combined with resistance to tetracycline 64% (43/106), fusidic acid 49% (33/106) and/or trimethoprim/sulphamethoxazole 42% (28/106). The same phenotype (resistance to penicillin, clindamycin and erythromycin) dominated also in isolates of *S. felis*.

Four isolates with oxacillin MIC >0.5 mg/L were analysed with PCR. Two isolates were found to be MRSP and two were negative. For more information on MRSP isolated from dogs in Sweden, see Notifiable diseases and MRSP in animals.

Staphylococcus schleiferi

Isolates of *Staphylococcus schleiferi* are from clinical submissions of samples of various locations, but mainly external ear canal, skin or wound.

The proportion of resistance in isolates of *S. schleiferi* (Table 4.28) is lower than in isolates of *S. pseudintermedius* (Table 4.27) from dogs, except for enrofloxacin (20%). The corresponding figure for enrofloxacin in *S. pseudintermedius* was 4%. For *S. aureus* isolated from horses and for *S. felis* from cats the resistance to enrofloxacin was even lower, 1% and 0% respectively. As the data of enrofloxacin was based on few isolates (n=55) the proportion of resistance in *S. schleiferi* may be uncertain. In contrast, the penicillinase production of the tested isolates was only 3% in *S. schleiferi* and 68% in *S. pseudintermedius* (Table 4.27). Furthermore, multiresistance was detected in 3% (5/163) of *S. schleiferi* isolates compared to 28% in *S. pseudintermedius*. Of the five multiresistant *S. schleiferi* isolates, two were resistant to three antibiotics and three to four antibiotics.

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).

The isolates of *P. aeruginosa* were earlier tested with Polymyxin B but this was replaced by colistin in 2014 (as a test substance also for Polymyxin B). All tested isolates have been sensitive to Polymyxin B throughout the years. Between 2014 and 2016, 1% of the tested isolates have been resistant to colistin.

The proportion of resistance to enrofloxacin declined from 25% in 2009 to 10% in 2015 (see previous Swedres-Svarm reports). In 2016, 13% of the isolates were resistant to enrofloxacin, while the figures for gentamicin have stabilized to about 1-2% over the recent years. (Table 4.29). None of the isolates were resistant to all three antibiotics. Two of the isolates were resistant to both enrofloxacin and gentamicin and 14% (48/349) were resistant to one of the tested antibiotics.

Pasteurella canis

Isolates of *Pasteurella* spp. are from clinical submissions of samples from various locations, but mainly the external ear canal, skin lesions, wounds, abscesses and the respiratory tract. *Pasteurella canis* was the most commonly detected *Pasteurella* spp. in the material (n=253). *Pasteurella dagmatis* (n=29), *P. multocida* (n=23) and *P. stomatis* (n=22) were less common. As shown in Table 4.30 the proportion of resistance in the *P. canis* isolates was low to the tested antibiotics. All isolates of the other *Pasteurella* spp. mentioned above were susceptible to all the tested antibiotics (data not shown). The same cut-off values were used for all *Pasteurella* spp. tested.

Cats

Escherichia coli

Isolates are from clinical sampling of urine, submitted either as urine or cultures from dip-slides or other agar plates. Resistance to ampicillin was the most common phenotype in 2016 (Table 4.31). The proportions of resistance have fluctuated somewhat over the years studied, but are overall stable (Figure 4.12).

Of the *E. coli* isolates tested in 2016, 3% (16/537) were multiresistant which is comparable to figures in 2010-2015 (2-5%). Eleven of the 16 isolates were resistant to three antibiotics; two to four and three to six antibiotics. The most common phenotype (8/16), was resistance to ampicillin, streptomycin and trimethoprim-sulphamethoxazole.

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

Twenty-three isolates were resistant to colistin (MIC >2 mg/L). Two of the isolates were available for PCR detection of the *mcr-1* and *mcr-2* genes, and both were negative.

Staphylococcus felis

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

FIGURE 4.12. Resistance (%) in clinical isolates of *Escherichia coli* from urine of cats, 2007-2014. The number of isolates each year varies (n=131-461).

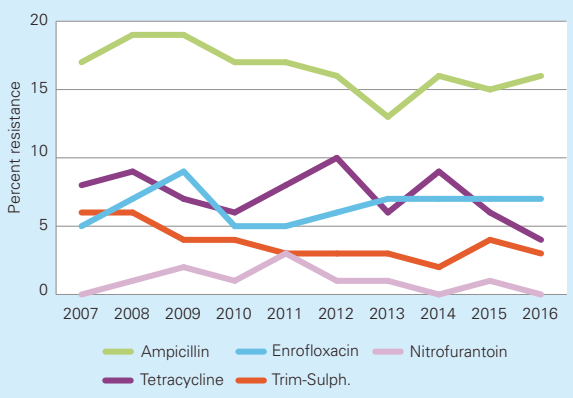


TABLE 4.31. Distribution of MICs and resistance (%) in *Escherichia coli* isolated from cats 2016. Clinical isolates from urine.

Antibiotic	Resistance (%) 2016 n=537	Distribution (%) of MICs (mg/L) ≤0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Ampicillin	16					73.9	9.3	0.6		16.2		
Cefotaxime	1		98.7	0.7	0.2		0.4					
Colistin	4				80.3	15.5	3.5	0.2	0.6			
Enrofloxacin	7	92.6	1.9	4.1	0.9	0.4		0.2				
Gentamicin	1					99.1	0.4	0.4	0.2			
Neomycin	1						99.1	0.4	0.2		0.4	
Nitrofurantoin	0							57.7	41.0	1.1	0.2	
Streptomycin	5							89.2	6.0	0.2	1.1	3.5
Tetracycline	4					95.2	0.4	0.2	0.4	3.9		
Trim-Sulph.[a]	3			97.0	0.4	0.2	0.2	2.2				

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

TABLE 4.32 Distribution of MICs and resistance (%) in *Staphylococcus felis* isolated from various locations in cats 2016.

Antibiotic	Resistance (%) 2016 n=277[c]	Distribution (%) of MICs (mg/L) ≤0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Cephalothin	1				99.3	0.7						
Cefoxitin[d]			97.5	1.4		1.1						
Clindamycin	7			93.1	0.4		6.5					
Enrofloxacin	0		97.9	2.1								
Erythromycin	17			83.4	8.7		7.9					
Fusidic acid	1			90.6	8.3	0.7						
Gentamicin	1				97.8	1.4	0.4	0.4				
Nitrofurantoin	0								98.9	1.1		
Oxacillin	0		98.9	1.1								
Penicillin[a]	14											
Tetracycline	1		94.9	4.0	0.4			0.7				
Trim-Sulph.[b]	0		97.8	2.2								

[a] Denotes beta-lactamase production; [b] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphamethoxazole); [c] n=277 for substances, except enrofloxacin with 97 tested isolates; [d] No breakpoint available for *S. felis*.

TABLE 4.33. Distribution of MICs and resistance (%) in *Pasteurella multocida*. Clinical isolates from cats 2016.

Antibiotic	Resistance (%) 2016 n=349	Distribution (%) of MICs (mg/L) ≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	0				100.0						
Enrofloxacin	1	98.0	0.6	0.9	0.6						
Gentamicin	<1					41.3	52.2	6.3		0.3	
Penicillin	0	84.2	14.9	0.9							
Tetracycline	1				98.6	0.9			0.6		
Trim-Sulph.[a]	3			94.6	1.4	0.6		3.4			

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

The proportion of resistance to the tested antibiotics in isolates of *S. felis* (Table 4.32) are less compared to *S. pseudintermedius* in dogs (Table 4.27). For example, resistance to penicillin due to penicillinase production was 14% in *S. felis*, but 68% in *S. pseudintermedius*.

Multiresistance was detected in 5% (15/277) of the isolates and comparable to the figures in 2015 (4%), as well as figures of *S. aureus* from horses (4%) and *S. schleiferi* from dogs (3%), but less than *S. pseudintermedius* (28%). Fourteen of the fifteen multiresistant isolates were resistant to three antibiotics and one to four antibiotics. All the multiresistant isolates (15/15) were resistant to penicillin, clindamycin and erythromycin, with gentamicin added for the isolate resistant to four antibiotics.

Pasteurella multocida

Isolates of *Pasteurella* spp. are from clinical submissions of samples from various locations, but mainly from wound or skin lesions, abscesses, external ear canal and the respiratory tract.

Pasteurella multocida was the most common *Pasteurella* spp. (n=349) found in cats. The proportion of resistance to antibiotics used in pets was low in the tested *P. multocida* isolates (Table 4.33), although somewhat higher compared to *P. canis* in dogs (Table 4.30). *Pasteurella stomatis* (n=20), *P. dagmatis* (n=19) and *P. canis* (n=1) were also detected in the studied material. Except for one isolate (*P. stomatis* resistant to gentamicin) those isolates were susceptible to all the tested antibiotics (data not shown). The same cut-off values were used for all *Pasteurella* spp. tested.

Indicator bacteria from animals

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

In 2016, indicator bacteria from broilers and turkeys were studied. Samples of intestinal contents were collected at slaughter and cultured for *E. coli* and samples from turkeys were also cultured for enterococci. In addition, samples were 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.

TABLE 4.34. Resistance (%) and multiresistance (%) in indicator *Escherichia coli* from broilers and turkeys, 2016. Data on indicator *Escherichia coli* from previous Svarm-reports are given for comparison.

		Resistance (%)									
Antibiotic	**ECOFF (mg/L)**	**Broilers**	**Turkeys**	**Broiler meat**	**Cattle**	**Pigs**	**Laying hens**	**Pig meat**	**Sheep**	**Horses**	**Dogs**
		2016 n=175	**2016** n=85	**2012** n=92	**2015** n=101	**2015** n=200	**2012** n=61	**2011** n=20	**2006-09** n=115	**2010-11** n=274	**2012** n=74
Ampicillin	>8	13	8	18	1	21	3	30	2	2	9
Azithromycin	16	0	0	-	1	<1	-	-	-	-	-
Cefotaxime	>0.25	3	0	0	0	1	2	0	0	0	1
Ceftazidime	>0.5	3	0	-	0	0	-	-	-	-	-
Chloramphenicol	>16	0	0	0	0	3	0	0	0	<1	0
Ciprofloxacin	>0.06	6	1	4	0	3	5	10	<1	<1	3
Colistin	>2	0	0	1	1	0	0	0	-	<1	0
Gentamicin	>2	1	0	3	0	<1	2	0	3	<1	0
Meropenem	>0.12	0	0	-	0	0	-	-	-	-	-
Nalidixic acid	>16	6	1	4	0	2	5	0	0	<1	0
Sulphamethoxazole	>64	13	6	16	2	25	8	10	7	15	4
Tetracycline	>8	11	16	14	1	10	13	0	<1	2	8
Tigecycline	>1	0	0	-	0	0	-	-	-	-	-
Trimethoprim	>2	7	4	7	0	20	5	10	2	16	1
Multiresistance[a]											
Susceptible to all above		71	71	66	96	68	80	70	89	83	84
Resistant to 1		17	24	18	2	9	7	10	9	2	8
Resistant to 2		5	6	7	2	4	7	5	2	12	7
Resistant to 3		4		3		14	7	15	<1	2	
Resistant to >3		4		5		6				<1	<1

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

Escherichia coli

Broilers

Escherichia coli was isolated from 175 (84%) of 208 samples cultured. The majority of the isolates (71%) was susceptible to all antibiotics tested (Table 4.34). Resistance to sulphonamides (13%), ampicillin (13%) and tetracycline (11%) were the most common traits. Fourteen isolates (8%) were multiresistant and all of these had resistance to sulphonamides and ampicillin in their phenotype. Twelve of these isolates were resistant also to trimethoprim.

Since the start of the monitoring in year 2000, resistance to each specific antibiotic tested has been below 15%. This favourable situation is likely due to the limited use of antibiotics in broiler production in Sweden (see Sales of antibiotics for animals). Resistance to sulphonamides, tetracycline, ampicillin and trimethoprim has, however, gradually increased in recent years whereas resistance to quinolones has decreased again after an increase in previous years (Fig 4.13). The reasons for these changes are not known.

Three isolates were resistant to cefotaxime and ceftazidime and all carried a $bla_{\text{CTX-M-1}}$ gene. Using selective culture,

FIGURE 4.13. Percent resistance in *Escherichia coli* from intestinal content from broilers 2000-2016. The number of isolates each year varies (n=175-307).

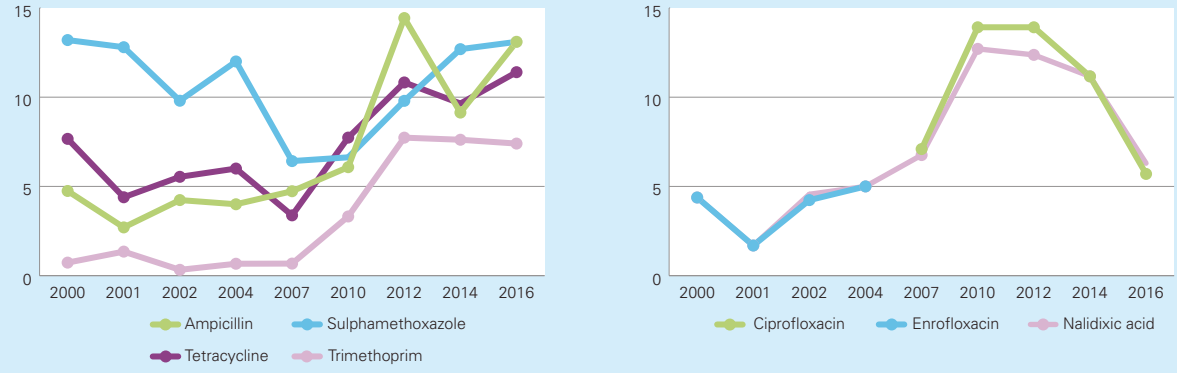


TABLE 4.35. Distribution of MICs and resistance (%) in *Escherichia coli* from intestinal content from broilers (n=175) and turkeys (n=85), 2016.

Antibiotic	Source	Resistance %	Distribution (%) of MICs (mg/L)																	
			≤0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	>1024
Ampicillin	Broilers	13							6.3	46.3	33.7	0.6				13.1				
	Turkeys	8							7.1	54.1	30.6					8.2				
Azithromycin	Broilers	0								1.1	48.0	49.7	1.1							
	Turkeys	0								3.5	57.6	36.5	2.4							
Cefotaxime	Broilers	2					98.3					1.7								
	Turkeys	0					100		1.7											
Ceftazidime	Broilers	2						98.3	1.1	0.6										
	Turkeys	0						100												
Chloramphenicol	Broilers	0										99.4	0.6							
	Turkeys	0										100								
Ciprofloxacin	Broilers	6	84.0	9.7	0.6	2.9	2.9													
	Turkeys	1	95.3	3.5			1.2													
Colistin	Broilers	0							100											
	Turkeys	0							100											
Gentamicin	Broilers	1						75.4	20.0	4.0										
	Turkeys	0						71.8	27.1	1.2										
Meropenem	Broilers	0		100																
	Turkeys	0		100																
Nalidixic acid	Broilers	6									93.1	0.6		1.7	2.3	1.7	0.6			
	Turkeys	1									97.6	1.2				1.2				
Sulphamethoxazole	Broilers	13										13.7	50.9	18.9	3.4		0.6			12.6
	Turkeys	6										12.9	41.2	35.3	4.7				1.2	4.7
Tetracycline	Broilers	11								88.6					4.0	7.4				
	Turkeys	16								83.5				1.2	8.2	7.1				
Tigecycline	Broilers	0					100													
	Turkeys	0					100													
Trimethoprim	Broilers	7					44.0	45.7	2.3	0.6					7.4					
	Turkeys	4					50.6	43.5	2.4						3.5					
			≤0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	>1024

ESC resistant *E. coli* was isolated from 130 (43%) of 302 samples of intestinal content from broilers. Ninety-three isolates had resistance genes of the CTX-M-1 group and 34 isolates genes of the CIT-group. In the remaining three isolates, no transferrable genes were detected. For details and comments see Notifiable diseases, ESBL-producing Enterobacteriaceae.

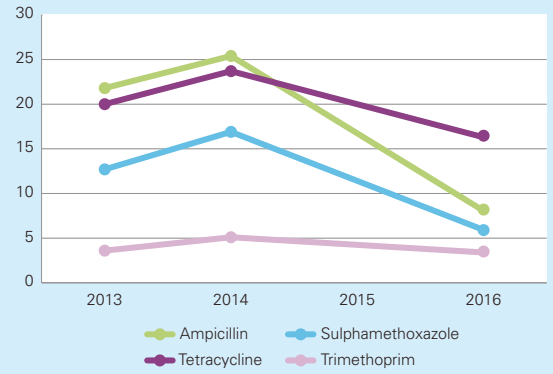
Turkeys

Escherichia coli was isolated from 85 (99%) of 86 samples cultured. The majority of the isolates (71%) was susceptible to all antibiotics tested (Table 4.34). Resistance to tetracycline (16%), ampicillin (8%) and sulphonamides (6%) were the most common traits. Multiresistance was not detected in any of the isolates.

Resistance has for most substances been stable for the three years since 2013 that *E. coli* from turkeys have been studied in Svarm. For ampicillin, sulphonamides and, to some extent, tetracycline there has however been a substantial decrease in the proportion of resistant isolates (Fig 4.14). The total number of isolates tested is small and the results should therefore be interpreted with caution. Resistance in *E. coli* from turkeys is about as prevalent as among isolates from broilers and involves the same antibiotics (Table 4.34).

Using selective culture, ESC resistant *E. coli* was isolated from 1 (1%) of the 86 samples cultured. That isolate carried a $bla_{\text{CTX-M-1}}$ gene. For details and comments see Notifiable diseases, ESBL-producing Enterobacteriaceae.

FIGURE 4.14. Percent resistance in *Escherichia coli* from intestinal content from turkeys 2000-2016. The number of isolates each year varies (n=55-85).



Enterococcus

Turkeys

For the first time, enterococci from turkeys in Sweden were investigated in Svarm 2016. From 86 samples cultured, a total of 41 isolates of *Enterococcus faecalis* and 70 isolates of *Enterococcus faecium* were obtained.

In *E. faecalis* the majority of isolates (93%) was resistant to at least one antibiotic and nineteen (46%) isolates were multiresistant (Table 4.36). Resistance to tetracycline

TABLE 4.36. Resistance (%) and multiresistance (%) in *Enterococcus faecalis* from intestinal content from turkeys, 2016. Data on indicator *Enterococcus faecalis* from previous Svarm-reports are given for comparison.

Antibiotic	ECOFF (mg/L)	Resistance (%)									
		Turkeys	Broilers	Calves	Broiler meat	Laying hens	Pigs	Pig meat	Horses	Sheep	Dogs
		2016 n=41	2014 n=27	2013 n=11	2012 n=78	2012 n=20	2011 n=22	2011 n=29	2010-11 n=34	2006-09 n=24	2006 n=135
Ampicillin	>4	0	0	0	0	0	0	0	0	0	<1
Bacitracin[a]	>32[a]	17	7	0	23	10	0	0	0	0	1
Chloramphenicol	>32	7	0	0	5	0	0	0	18	0	7
Erythromycin	>4	49	7	0	13	10	43	0	21	0	14
Gentamicin	>32	0	4	0	1	0	4	0	21	0	<1
Kanamycin	>1024	0	0	0	0	0	4	0	21	0	4
Linezolid	>4	0	0	0	1	0	0	0	0	0	0
Narasin	>2	61	41	0	37	0	0	0	0	0	1
Streptomycin	>512	2	0	0	5	0	17	3	9	4	9
Tetracycline	>4	80	37	0	36	45	74	7	44	8	32
Vancomycin	>4	0	0	0	0	0	0	0	0	0	0
Virginiamycin	>32	0	0	0	0	0	0	0	0	0	0
Multiresistance (%)											
Susceptible to all above		7	30	100	27	45	17	90	56	92	25
Resistant to 1		20	44		37	45	35	10	24	4	38
Resistant to 2		27	26		29	10	43			4	27
Resistant to 3		41			1						2
Resistant to >3		5			5		4		21		7

[a] MIC in U/ml

TABLE 4.37. Resistance (%) and multiresistance (%) in *Enterococcus faecium* from intestinal content from turkeys, 2016. Data on indicator *Enterococcus faecium* from previous Svarm-reports are given for comparison.

Antibiotic	ECOFF (mg/L)	Resistance (%)									
		Turkeys	Broilers	Calves	Broiler meat	Laying hens	Pigs	Pig meat	Horses	Sheep	Dogs
		2016 n=70	2014 n=187	2013 n=42	2012 n=10	2012 n=36	2011 n=22	2011 n=1	2010-11 n=27	2006-09 n=15	2006 n=29
Ampicillin	>4	7	2	0	0	0	0	0	15	0	0
Bacitracin	>32[a]	9	10	5	40	3	9	0	0	0	3
Chloramphenicol	>32	0	0	0	0	0	0	0	0	0	0
Erythromycin	>4	33	8	10	0	6	9	0	0	0	28
Gentamicin	>32	0	0	2	0	0	0	0	0	0	0
Kanamycin	>1024	0	0	2	0	0	9	0	0	0	0
Linezolid	>4	0	0	0	0	0	0	0	0	0	0
Narasin	>2	79	77	0	80	0	0	0	0	0	7
Streptomycin	>128	3	0	0	0	0	13	0	7	7	0
Tetracycline	>4	29	4	2	30	11	13	0	4	7	17
Vancomycin	>4	0	<1	0	0	0	0	0	0	0	0
Virginiamycin	>4	4	<1	0	10	8	4	100	4	0	0
Multiresistance (%)											
Susceptible to all above		7	15	15	83	78	74		74	87	62
Resistant to 1		46	71	63	12	17	13	100	22	13	30
Resistant to 2		40	11	21	5	6	4		4		6
Resistant to 3		4	2	1							
Resistant to >3		3	1				9				2

[a]MIC in U/ml

TABLE 4.38. Distribution of MICs and resistance (%) in *Enterococcus faecalis* (n=41) and *Enterococcus faecium* (n=70) from intestinal content from turkeys, 2016.

Antibiotic	Bacterial species	Resistance %	Distribution (%) of MICs (mg/L)															
			≤0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	2048	>2048
Ampicillin	*E. faecalis*	0		2.4	22.0	73.2		2.4										
	E. faecium	7		14.3	22.9	15.7	22.9	17.4	7.1									
Bacitracin[a]	*E. faecalis*	17						2.4	19.5	58.5	2.4		7.3	9.8				
	E. faecium	9				14.3	7.1	7.1	30.0	27.1	5.7	5.7		2.9				
Chloramphenicol	*E. faecalis*	7						34.1	56.1	2.4		7.3						
	E. faecium	0					2.9	57.1	40.0									
Erythromycin	*E. faecalis*	49			22.0	2.4	9.8	17.1	4.9				43.9					
	E. faecium	33			8.6	41.4	11.4	5.7	20.0	2.9			10.0					
Gentamicin	*E. faecalis*	0							31.7	68.3								
	E. faecium	0					1.4	24.3	67.1	7.1								
Kanamycin	*E. faecalis*	0									17.1	75.6	7.3					
	E. faecium	0									4.3	42.9	40.0	10.0	2.9			
Linezolid	*E. faecalis*	0			7.3	61.0	31.7											
	E. faecium	0			1.4	15.7	81.4	1.4										
Narasin	*E. faecalis*	61		14.6	22.0			41.5	19.5									
	E. faecium	79			14.3		7.1	62.9	15.7									
Streptomycin	*E. faecalis*	2										9.8	82.9	4.9			2.4	
	E. faecium	3									8.6	81.4	7.1		1.4	1.4		
Tetracycline	*E. faecalis*	80			2.4	17.1					31.7	48.8						
	E. faecium	29			52.9	18.6			1.4		11.4	15.7						
Vancomycin	*E. faecalis*	0				85.4	14.6											
	E. faecium	0				97.1	2.9											
Virginiamycin	*E. faecalis*	0					2.4		12.2	78.0	7.3							
	E. faecium	4			24.3	17.1	51.4	2.9		4.3								
			≤0.12	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**	**128**	**256**	**512**	**1024**	**2048**	**>2048**

[a]MIC in U/ml

(80%), narasin (61%), erythromycin (49%) and bacitracin (17%) were the most common traits. No resistance to vancomycin was detected. The number of isolates tested is small and conclusions on occurrence of resistance must be made with caution.

In *E. faecium* the majority of isolates (93%) was resistant to at least one antibiotic and five isolates (7%) were multiresistant (Table 4.37). Resistance to narasin (79%), erythromycin (33%) and tetracycline (24%) were the most common traits. No resistance to vancomycin was detected. The number of isolates tested is small and conclusions on occurrence of resistance must be made with caution.

The high occurrence of resistance to narasin in both *E. faecalis* and *E. faecium* is interesting as narasin is not used as coccidiostat for turkeys. The ionophore monensin is however used and cross resistance between the two substances could be an explanation. Notably resistance to narasin in enterococci from other animals, where narasin is not used, is rarely found in Sweden (Table 4.36 and 4.37).

Comparative analysis

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 QA07AA, 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 2016, a total of 62.1 and 10.4 tonnes of antibiotics in included ATC classes were consumed in human and veterinary medicine, respectively. It should be noted that there is a lack of completeness of the sales of antibiotics for animals (See Completeness of data in Sales of antibiotics for animals). Figure 5.1 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 (J01C and QJ01C) represent most of the amount in kg active substance of antibiotics for both humans and animals; 70 and 66%, respectively. The substances shown in Figure 5.2 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 2016 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.

Comparison of consumption expressed as mg per kg estimated biomass

In 2016, the consumption was 93.8 and 13.4 mg active substance per kg estimated biomass in human and veterinary medicine, respectively. In Figure 5.3 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 5.3 the largest differences are noted for betalactamase resistant penicillins where consumption by animals is negligible, and for the fluoroquinolones where consumption by humans is 115 times higher than in animals.

FIGURE 5.1. Consumption of beta-lactam antibiotics in human and veterinary medicine, kg active substance, 2016. Please note the difference in indexation of the x-axis between Figures 5.1 and 5.2.

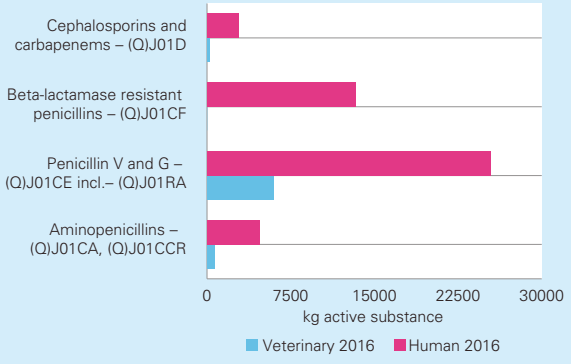


FIGURE 5.2. Consumption of fluoroquinolones, macrolides, lincosamides, trimethoprim and sulphonamides, and tetracyclines in human and veterinary medicine, kg active substance, 2016. Please note the difference in indexation of the x-axis between Figure 5.1 and 5.2.

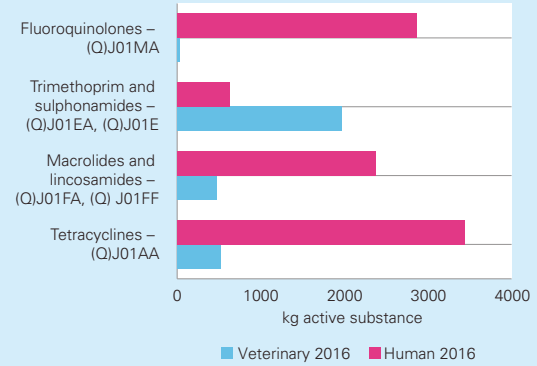


FIGURE 5.3. Consumption of antibiotics in humans and animals expressed as mg active substance per estimated kg biomass in 2016. Only classes where the total consumption exceeded 1 000 kg active substance are shown.

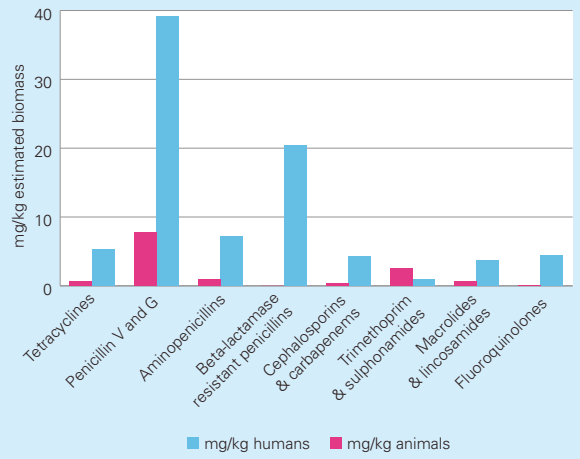
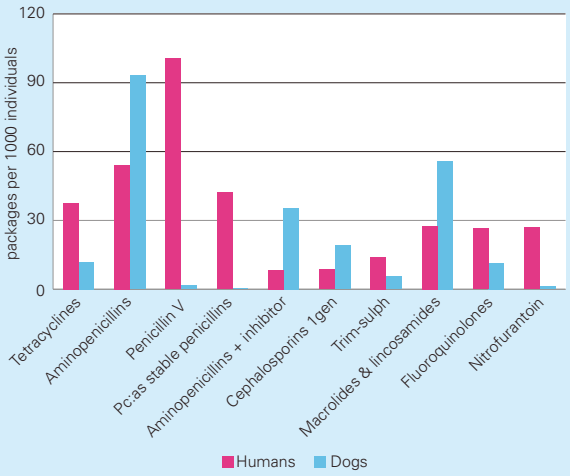


FIGURE 5.4. Outpatient consumption of antibiotics by humans and dogs expressed as packages per 1000 individuals, 2016.



Comparison of outpatient consumption for humans and dogs

One of the indicators of community consumption (outpatient consumption) used by ESAC-Net (Network for European surveillance of antimicrobial consumption in human medicine) is number of packages per 1000 inhabitants (ECDC 2014). This unit is regarded as a proxy for the number of treatments, although more than one package is sometimes used for one course. On average, there was 1.1 package of antibiotics per prescription for humans (2016) and 1.3 package per prescription for dogs (2012, unpublished data).

To compare the consumption for humans and dogs, the number of packages of antibiotics dispensed for use in humans and dogs in 2016 was retrieved and calculated to packages per 1 000 individuals. For dogs, both products authorised for animals and for humans were included.

In total, 362 and 236 packages per 1 000 individuals were consumed by humans and dogs, respectively. In Figure 5.4, consumption of ten classes and subclasses by humans and dogs are shown. Consumption not shown was below 1 package per 1 000 individuals, except "Other antimicrobials" (J01XX) and third generation cephalosporins (J01DD) for humans. Consumption of fenoximethylpenicillin (J01CE) and penicillinase stable penicillins (J01CF) dominates in human medicine but is very limited in canine medicine. Examples of other classes where consumption by humans is larger than by dogs are tetracyclines (J01AA and QJ01AA) and fluoroquinolones (J01MA and QJ0MA). Examples of classes where consumption by dogs was larger than by humans are aminopenicillins (J01CA and QJ01CA), aminopenicillins with inhibitors (J01CR and QJ01CR) and macrolides and lincosamides (J01F and QJ01F).

The pattern of antibiotic consumption of different classes by humans and dogs clearly differ. This may in part be related to availability of suitable products on the market, for example there is currently no product with fenoximethylpenicillin authorised for dogs in Sweden, nor any penicillinase stable penicillins. Differences in main indications for treatment of humans and dogs with antibiotics probably has a larger influence, and possibly also occurrence of antibiotic resistance in the bacteria causing those infections.

Notifiable diseases

Zoonotic aspects on ESBL-producing Enterobacteriaceae

It has been concluded that transmission of Enterobacteriaceae with $ESBL_A$ or $ESBL_M$, and their corresponding genes, between farm animals and humans, can occur (EFSA, 2011, de Been, 2014). The possibility for direct transfer to people handling animals should also be kept in mind.

The available data show that ESBL-producing bacteria are rare in animals in Sweden except for broilers where *E. coli* with $ESBL_A$ or $ESBL_M$ resistance are found in a large proportion of birds. However, in a majority of the samples, the $ESBL_A$- or $ESBL_M$-producing *E. coli* only constitute a small part of all the *E. coli* in the intestinal flora. Previously, it has been clear that the majority of isolates from humans in Sweden is not of the same types of $ESBL_A$ or $ESBL_M$ as in broilers. Due to the shift from bla_{CMY-2} to $bla_{CTX-M-1}$ as the most prevalent gene among *E. coli* from broilers this difference is now less clear. Still, there are no indications that the previous conclusion that food on the Swedish market is a limited source for ESBLs for humans needs to be revised (Börjesson et al., 2016). Nevertheless, continued vigilance towards development of reservoirs of ESBL-producing Enterobacteriaceae clinically associated to humans in animals is warranted.

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.

LA-MRSA

During more than 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. LA-MRSA 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 LA-MRSA in pigs, the pig population constitutes a reservoir with continuous transmission to people in close contact with pigs. The latest screening of pigs in Sweden was in nucleus and multiplying pig herds in 2014. No MRSA was detected, indicating a favourable situation.

MRSA CC398 also occurs among horses and *spa*-type t011, belonging to CC398, is by far the most common type among Swedish horses.

In humans, domestically acquired MRSA CC398 has been detected in 67 cases 2006-2016. The number of cases each year has varied between two and twelve and was eight in 2016. The low number of 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 8 isolates from human cases in 2016 were of *spa*-types t011, t034 and t1451. The epidemiological information on human cases is scarce, and possible animal contact is not known

MRSA with *mecC*

Isolates of MRSA with *mecC* were first reported internationally from dairy cows and humans in 2011 (García-Álvarez et al., 2011, Shore et al., 2011, Ito et al., 2012).

In companion animals, MRSA with *mecC* has been isolated from two dogs (*spa*-types t373 and t843) and three cats (*spa*-types t978 and t843).

Since 2010 and onwards, MRSA with *mecC* has occasionally been isolated from milk samples from dairy cows (*spa*-types t524, t9111 and t843). All isolates were from samples with anonymized origin and therefore the source of MRSA cannot be investigated.

MRSA with *mecC* has been isolated from 40 Swedish hedgehogs. Most of the hedgehogs were sampled in a screening study in 2015 and the isolates belonged to several *spa*-types, of which t843 was most common.

Late in 2016, MRSA with *mecC* was detected in an outbreak in goats and sheep (*spa*-type t9268) at a zoo. There was an epidemiological link between all MRSA-positive animals through direct or indirect contact.

In humans, domestically acquired MRSA with *mecC* has been isolated from 82 cases 2011-2016, of which 10 cases were from 2016. In total, 17 *spa*-types were seen among the human isolates. The two most common *spa*-types were t843 (26 cases) and t373 (20 cases). Some of the *spa*-types in humans have also been found in animals: t843 (dog, cat, dairy cow, hedgehog), t373 (dog), t3391 (hedgehog), t9111 (dairy cow, hedgehog), t978 (cat, hedgehog), t5771 (hedgehog), t9268 (goat, sheep) and t10893 (hedgehog).

MRSA-types typically associated with humans

MRSA isolated from dogs and cats often belong to *spa*-types seen in MRSA from humans. This supports the view that humans often is the source of MRSA in companion animals (EFSA 2009, CVMP, 2009). After transmission to a companion animal, the animal may serve as vector for 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 2016 it was only found in 18 cases. During recent years, isolates with other *spa*-types have been more often detected in dogs, some of these types being common in humans.

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 MRSA-cases in humans in Sweden, it is likely that transmission has occurred from the farmer to cows. In 2014, MRSA of *spa*-type t127 was detected in a milk sample with anonymized origin. Because also this *spa*-type is common among human MRSA-cases, transmission from human to cow can be suspected. There is, however, no epidemiological information available about this case.

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.

For more information on MRSA in Sweden, see Antibiotic resistance in humans and Antibiotic resistance in animals.

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.

VRE

The only occurrence of VRE of significance among animals in Sweden has been in broilers. This occurrence has however decreased in recent years. Moreover, even if the dominating variant of VRE in broilers and, nowadays also in humans, is *E. faecium* with the *vanA* gene, isolates from broilers and humans are not genotypically related. Hence, there are no indications that the presence of VRE in broilers in Sweden has affected the situation in Swedish healthcare.

Zoonotic pathogens

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 extended spectrum cephalosporin resistance has never been found and resistance to fluoroquinolones (e.g. ciprofloxacin) is rare. Thus, the overall situation is favourable which 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. Also, most human infections are acquired abroad. It is therefore not possible to comprehensively relate the situation regarding antibiotic resistance in *Salmonella* from Swedish animals to the situation in humans.

However, the most common serovars from human invasive infections in 2016 (Table 3.4), such as *S.* Typhi and *S.* Paratyphi A, are not associated with animals. Also, several other serovars from human invasive infections are rare in animals in Sweden. Moreover, a large proportion (31%) of the human isolates are resistant to ciprofloxacin. This high rate contrasts with 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

Data for 55 isolates of *Campylobacter* from humans were available 2016 and of these approximately 20% were resistant to fluoroquinolones and none was resistant to erythromycin. From broilers 170 isolates of *C. jejuni* were tested and the resistance percentages were comparable to the figures from isolates from humans, fluoroquinolones (13%), tetracycline (16%) and erythromycin (0%). In contrast data for 2002-2011 (Swedres 2011) higher resistance percentages were reported for human isolates of *Campylobacter* spp. for fluoroquinolones (69%), tetracycline (37%) and erythromycin (7%) than for isolates of *C. jejuni* from broilers 2016. Notably, resistance to erythromycin, the drug of choice for treatment of human campylobacteriosis, has only been found in two isolates from Swedish broiler meat (Svarm 2013) and never in isolates coming directly from animals in Sweden.

Comparisons between data for *Campylobacter* from animals and humans are hampered because the human isolates are not separated by infections acquired in Sweden or abroad. *Campylobacter* spp. isolates acquired within the country are expected to have a lower level of resistance.

Background data, material, methods and references

Demographics and denominator data

Human beings

TABLE 6.1. 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	175 706	279 954	1 347 122	266 788	85 575	2 231 439
Uppsala	25 282	43 026	208 284	49 762	15 578	354 164
Södermanland	19 695	36 229	154 742	47 662	15 567	283 712
Östergötland	31 377	53 671	254 500	66 628	24 003	445 661
Jönköping	25 187	44 286	193 929	51 994	19 926	347 837
Kronoberg	13 528	23 940	106 750	29 106	11 384	191 369
Kalmar	15 027	27 111	129 847	42 703	15 268	237 679
Gotland	3 440	6 253	31 771	10 586	3 455	57 391
Blekinge	10 194	18 797	85 578	26 902	9 640	156 253
Skåne	96 668	157 569	750 676	187 710	66 405	1 303 627
Halland	22 079	40 290	173 928	49 861	17 477	314 784
Västra Götaland	118 230	198 710	957 702	233 808	83 684	1 648 682
Värmland	17 442	31 188	153 516	46 965	17 631	275 904
Örebro	20 487	35 372	163 138	46 122	15 541	291 012
Västmanland	18 167	32 088	147 579	42 591	14 861	264 276
Dalarna	18 212	33 496	153 100	49 508	17 398	281 028
Gävleborg	17 995	33 425	155 153	49 175	16 708	281 815
Västernorrland	15 346	29 285	133 769	42 666	14 805	243 897
Jämtland	8 272	14 880	70 673	21 645	7 721	127 376
Västerbotten	17 719	30 424	151 711	40 225	14 294	263 378
Norrbotten	14 977	28 114	140 707	43 170	14 729	249 733
Sweden	**705 030**	**1 198 108**	**5 664 175**	**1 445 577**	**501 650**	**9 851 017**

TABLE 6.2. Population in Sweden 2000-2016. Numbers represent the population by December 31st 2015.

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Population	8 861 426	8 882 792	8 909 128	8 940 788	8 975 670	9 011 392	9 047 752	9 113 257	9 182 927	9 256 347	9 340 682	9 415 570	9 482 855	9 555 893	9 644 864	9 747 355	9 851 017

TABLE 6.3. Number of admissions and patient-days in somatic medical care in Sweden, 2012-2015. Data represent production by acute care hospitals in the counties

Year	Admissions	Patient-days
2012	1 460 583	6 468 774
2013	1 432 175	6 355 463
2014	1 411 121	6 293 096
2015	1 378 806	6 087 579

TABLE 6.4. Number of admissions and patient-days in somatic medical care 2015. Data represent production by acute care hospitals in the counties.

County	Admissions	Patient-days
Blekinge	23 540	117 425
Dalarna	43 455	178 499
Gotland	10 201	43 016
Gävleborg	36 580	159 615
Halland	39 283	159 261
Jämtland	18 009	85 005
Jönköping	54 851	224 027
Kalmar	41 703	156 615
Kronoberg	26 684	123 859
Norrbotten	36 098	172 854
Skåne	180 729	837 790
Stockholm	276 161	1 075 305
Södermanland	35 405	174 061
Uppsala	55 509	280 346
Värmland	40 989	181 780
Västerbotten	47 351	223 031
Västernorrland	34 977	154 560
Västmanland	36 793	168 992
Västra götaland	234 263	1 107 168
Örebro	42 351	198 695
Östergötland	63 874	265 675
Sweden	**1 378 806**	**6 087 579**

TABLE 6.5. Denominator data from the microbiological laboratories 2016.

Laboratory	Number of analyses 2016									Number of positive samples 2016	Number of positive cultures 2016				
	Blood (pair of bottles)	Cerebro-spinal fluid (CFS)	Nasopharynx	Throat	General culture	Screen MRB	Urine	Faeces SSYC	Faeces *Clostridium difficile* (toxin test)	Blood (pair of bottles)	*Staphylococcus aureus*	*Streptococcus pneumoniae*	*Streptococcus pyogenes*	*Escherichia coli*	*Clostridium difficile* (toxin positive isolates)
Aleris Medilab	1 254	0	8 394	2 797	9 824	18 975	41 089	6 180	1 266	229	4 572	467	761	10 159	194
Borås[b]	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)	15 313	272	6 904	2 486	8 187	6 895	30 607	5 460	1 788	1 864	5 497	696	710	8 508	233
Falun	20 103	182	5 484	1 391	10 423	2 646	33 569	3 870	2 093	1 511	5 170	529	657	8 967	255
Gävle	16 048	194	3 624	928	10 733	3 784	26 969	3 097	1 892	2 198	5 114	407	464	9 394	328
Göteborg	45 631	1 297	2 128	2 621	15 119	25 408	61 347	8 886	3 934	5 594	10 356	646	1 098	14 456	555
Halmstad	15 110	146	3 161	2 136	6 590	14 664	29 193	4 365	1 939	1 820	5 392	568	702	8 600	225
Jönköping	24 062	298	7 744	3 131	18 012	22 488	40 126	7 295	2 822	3 151	9 485	814	1 004	12 812	347
Kalmar	15 198	155	3 982	1 706	7 314	4 271	30 099	4 515	1 456	1 984	5 220	529	734	9 745	160
Karlskrona/ Växjö	23 182	168	7 263	2 418	10 827	13 970	38 918	5 924	3 934	2 680	5 794	716	724	10 166	360
Karlstad	23 917[a]	448	5 572	2 479	14 253	9 772	40 754	4 198	2 400	4 218[a]	7 131	550	814	10 829	325
Karolinska Stockholm	99 650	2 574	30 756	8 186	78 757	187 404	151 203	20 578	11 906	12 642	32 886	2 554	3 207	43 050	1 133
Linköping	27 298	939	7 720	2 502	21 250	10 854	49 877	6 650	3 075	4 296	10 104	772	1 058	14 446	441
Lund/Malmö	78 124	1 638	20 489	11 138	30 607	48 658	168 937	24 391	9 937	9 736	22 783	1 831	3 224	44 387	1 471
Skövde (Unilabs)	15 697	269	3 611	2 687	10 487	10 067	60 398	8 301	2 680	1 536	7 231	174	814	14 918	308
S:t Göran (Unilabs)	18 974	140	7 108	1 974	9 842	36 040	47 244	6 895	1 257	1 700	6 477	639	727	11 848	264
Sunderby Luleå	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sundsvall	15 343	149	2 137	1 365	6 571	7 120	29 321	3 570	NP	2 280	3 999	536	500	8 849	NP
NÄL Trollhättan	19 653	232	2 482	1 166	7 808	14 057	27 666	3 477	1 932	2 419	4 468	268	334	7 959	278
Umeå	17 616	504	4 369	2 036	9 763	9 216	32 441	4 373	1 650	1 774	5 710	642	818	10 096	252
Uppsala	24 781	763	7 985	1 839	14 960	12 428	35 547	4 939	3 233	2 992	6 709	610	673	9 174	389
Visby	4 742	1	2 067	401	3 035	NP	7 039	850	422	461	1 491	235	124	2 103	35
Västerås	16 432	180	3 628	1 878	10 184	7 126	28 451	4 005	2 008	2 242	4 443	443	600	9 042	265
Örebro	18 843	292	11 203	1 960	17 784	7 989	34 797	5 161	2 820	2 232	7 015	1 323	681	8 692	340
Östersund	7 884	166	2 445	920	4 236	3 270	18 685	2 427	1 232	1 038	3 653	402	473	6 351	163
Total	**585 245**	**11 189**	**165 317**	**61 954**	**342 885**	**480 004**	**1 087 533**	**153 935**	**67 376**	**73 004**	**185 272**	**16 652**	**21 415**	**301 643**	**8 454**

[a]not pair; NA, data not available; NP, not performed [b]2015 years data

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 6.6 & 6.7 and on numbers and volumes of animals slaughtered in Table 6.8. & 6.9. In table 6.10, the average herd size 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 6.6. Number of livestock and horses (in thousands) 1980-2016. From the Statistical message JO 20 SM 1701, J0 23 SM 1701 and JO 24 SM 1101.

Animal Species	1980[a]	1985[a]	1990	1995	2000	2005	2010	2014	2015	2016
Cattle										
Dairy cows	656	646	576	482	428	393	348	344	338	331
Beef cows	71	59	75	157	167	177	197	186	184	194
Other cattle >1 year	614	570	544	596	589	527	513	490	487	489
Calves <1 year	595	563	524	542	500	509	479	472	466	476
Total, cattle	1 935	1 837	1 718	1 777	1 684	1 605	1 537	1 492	1 475	1 490
Sheep										
Ewes and rams	161	173	162	195	198	222	273	287	289	281
Lambs	231	252	244	266	234	249	292	301	306	297
Total, sheep	392	425	406	462	432	471	565	588	595	578
Pigs										
Boars & sows	290	260	230	245	206	188	156	145	142	140
Fattening pigs >20 kg[b]	1 254	1 127	1 025	1 300	1 146	1 085	937	857	830	835
Piglets <20kg[c]	1 170	1 113	1 009	769	566	539	427	376	384	378
Total, pigs	2 714	2 500	2 264	2 313	1 918	1 811	1 520	1 378	1 356	1 354
Laying hens										
Hens	5 937	6 548	6 392	6 100	5 670	5 065	6 061	6 549	7 571	8 174
Chickens reared for laying	2 636	2 159	2 176	1 812	1 654	1 697	1 647	1 713	1 842	1 575
Total, hens	8 573	8 708	8 568	7 912	7 324	6 762	7 707	8 262	9 413	9 750
Turkeys										
Total, turkeys						122	130			
Horses										
Total, horses						283[d]	363			356

[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 6.7. Number of holdings with animals of different types, 1980-2016. From the statistical database of the Board of Agriculture

Animal species	1980	1985	1990	1995	2000	2005	2010	2014	2015	2016
Cattle										
Dairy cows	44 143	35 063	25 921	17 743	12 676	8 548	5 619	4 394	4 161	3 900
Beef cows	12 436	10 310	10 883	17 069	13 861	12 821	12 190	10 663	10 405	10 300
Other cattle >1 year	63 179	52 652	42 696	39 160	30 457	24 808	20 295	17 094	16 432	16 100
Calves <1 year	62 314	52 001	41 986	36 542	27 733	22 888	18 494	15 706	15 186	14 800
Total holdings with cattle	70 503	58 872	47 292	41 990	32 063	26 179	21 586	18 210	17 466	17 000
Sheep	10 238	10 595	9 749	10 037	8 089	7 653	8 657	8 912	9 110	8 700
Pigs	26 122	19 937	14 301	10 753	4 809	2 794	1 695	1 282	1 228	1 300
Laying hens	23 603	17 531	12 900	9 593	5 678	4 916	3 703	3 878	2 927	2 900
Chickens reared for laying	5 093	2 714	1 875	1 405	715	634	487	760	730	400

TABLE 6.8. Number of animals slaughtered (in thousands) at slaughterhouses, 1980-2016. From the statistical database of the Board of Agriculture.

Animal Species	1980	1985	1990	1995	2000	2005	2010	2014	2015	2016
Cattle										
Cattle >1 year	574	584	523	502	490	433	425	405	406	395
Calves < 1 year	130	152	70	30	39	33	27	26	22	16
Total, cattle	704	736	593	532	529	466	453	431	428	411
Sheep	302	328	280	189	202	206	255	258	256	251
Pigs	4 153	4 283	3 653	3 743	3 251	3 160	2 936	2 553	2 560	2 526
Broilers	40 466[a]	36 410[a]	38 577[a]	61 313	68 617	73 458	78 507	89 681	95 974	101 322
Turkeys							495	420	475	527

[a] Data supplied by the National Food Administration.

TABLE 6.9. Quantity of livestock slaughtered (in 1000 tonnes) at slaughterhouses, 1990-2016. From the statistical database of the Board of Agriculture.

Animal Species	1990	1995	2000	2005	2010	2014	2015	2016
Cattle								
Cattle >1 year	139.5	140.1	145.4	131.4	133.5	127.5	129.7	128.6
Calves < 1 year	6.8	3.2	4.4	4.5	4.3	4.1	3.5	2.7
Total, cattle	146.3	143.3	149.8	135.9	137.8	131.5	133.1	131.2
Sheep	5.0	3.5	3.9	4.1	5.0	4.1	4.2	5.0
Pigs	293.1	308.8	277.0	275.1	263.5	235.3	233.5	232.8
Broilers	44.0[a]	73.6[a]	89.9	96.2	112.0	128.7	137.7	147.4
Turkeys					3.2	3.3	3.8	4.2

a Data supplied by the National Food Administration.

TABLE 6.10. Average number of animals per holding 1995-2016. From statistical messages JO 20 SM 1401 and JO SM 1502.

Animal Species	1995	2000	2005	2010[a]	2014[a, b]	2015[a, b]	2016[a]
Cattle							
Dairy cows	27.2	33.7	46	61.9	78.4	81,5	85,4
Beef cows	9.2	12.0	13.8	16.2	17.5	17.7	18,7
Sheep	19.5	24.8	29.2	31.7	32.2	31.8	32,5
Boars and sows	31	63	156	156	186	186	182
Fattening pigs	157	294	471	664	791	845	820
Laying hens	640	995	471	1 638	1 689	2 587	2 822

[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 medical 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 (individually packed doses of drugs often dispensed to elderly) 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 antimicrobials in feed if they are controlled and authorised by the Swedish Board of Agriculture (SBA). The feed mills normally acquire the antibiotic products from a pharmacy. All quantities of antibiotic products used by feed mills are reported yearly to the SBA as part of the feed control. Mixing of antibiotics in feed may also take place on farms; provided that the SBA has inspected and authorised the establishment for the purpose. In such cases, the premix is sold by a pharmacy following prescriptions from a veterinarian.

The ATC classification system and defined daily doses (DDD)

Since 1988, the Anatomical Therapeutic Chemical (ATC) and ATCvet classification system recommended by the WHO is used in Sweden for national drug statistics. For drugs sold for use in humans, to facilitate drug utilisation studies from a medical point of view, the concept of defined daily dose (DDD) is used as a unit of comparison in drug statistics. The DDD for a drug is established on the basis of the assumed average dose per day for the drug given to adults for its main indication. If possible, the DDD is given as the amount of active substance. The DDDs are usually equal for all dosage forms of a preparation. The statistical data systems of the Swedish eHealth Agency are upgraded yearly according to the recommendations made by the WHO Collaborating Centre for Drug Statistics methodology in Oslo, Norway. The DDDs used in this report are shown in Table 6.11. 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 produces sales statistics on drugs, for the country as a whole and for individual counties. The sales are registered as number of DDDs, cash value and number of packages. Out-patient care data includes information on the sales of drugs dispensed on prescription by all Swedish pharmacies by the prescription survey, running since 1974. The statistical material was until 1995 built of samples of dispensed prescriptions. From 1996 all prescriptions dispensed by pharmacies are included. From 1999, ApoDos (individually packed doses of drugs often dispensed to elderly) is also included in the survey. Recorded data are trade name, quantity, patient fee, total cost, sex and year of birth of the patient. Data can be expressed as DDD/1000 inhabitants and day or number of prescriptions/1000 inhabitants.

Hospital care data includes drugs delivered by all hospital pharmacies to the hospital departments (se bellow chapter Completeness of data). The sales are expressed as cash value, number of packages and number of defined daily doses.

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

The Swedish eHealth Agency (eHälsomyndigheten) aims to contribute to improved health care 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 Authority. 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.

Therefore, no national database with complete sales statistic is available at this time. Efforts have been made to com-

TABLE 6.11. DDD for all antibiotic substances (J01) sold in Sweden in 2016. Substances are sorted according to ATC-code

	DDD (g)		DDD (g)
J01AA02 – doxycycline	0.1	J01EE01 - sulfamethoxazol and trimethoprim	1.92
J01AA04 – lymecycline	0.6	J01FA01 - erythromycin	1
J01AA06 - oxitetracycline	1	J01FA01- erythromycin erythylsuccinat tablets	2
J01AA07 - tetracycline	1	J01FA06 - roxithromycin	0.3
J01AA12 - tigecycline	0.1	J01FA09 - clarithromycin - oral	0.5
J01BA01 - chloramphenicol	3	J01FA10 - azithromycin - parenteral	0.5
J01CA01 - ampicillin	2	J01FA10 - azithromycin - oral	0.3
J01CA04 - amoxicillin	1	J01FA15 - telithromycin	0.8
J01CA08 - pivmecillinam	0.6	J01FF01 - clindamycin - parenteral	1.8
J01CE01 - benzylpenicillin	3.6	J01FF01 - clindamycin - oral	1.2
J01CE02 - fenoximethylpenicillin	2	J01GB01 - tobramycin - parenteral	0.24
J01CF02 - cloxacillin	2	J01GB01 - tobramycin - oral inhalation solution	0.3
J01CF05 - flucloxacillin	2	J01GB01 - tobramycin - oral inhalation powder	0.112
J01CR02 - amoxicillin and enzyme inhibitor-oral	1	J01GB03 - gentamicin	0.24
J01CR05 - piperacillin and enzyme inhibitor	14	J01GB06 - amikacin	1
J01DB01 - cefalexin	2	J01GB07 - netilmicin	0.35
J01DB03 - cefalotin	4	J01MA01 - ofloxacin	0.4
J01DB05 - cefadroxil	2	J01MA02 - ciprofloxacin - parenteral	0.5
J01DC02 - cefuroxime- parenteral	3	J01MA02 - ciprofloxacin - oral	1
J01DC02 - cefuroxime - oral	0.5	J01MA06 - norfloxacin	0.8
J01DC08 - loracarbef	0.6	J01MA12 - levofloxacin	0.5
J01DD01 - cefotaxime	4	J01MA14 - moxifloxacin	0.4
J01DD02 - ceftazidime	4	J01XA01 - vancomycin	2
J01DD04 - ceftriaxon	2	J01XA02 - teicoplanin	0.4
J01DD08 - cefixime	0.4	J01XB01 - colistin	3 MU
J01DD14 - ceftibuten	0.4	J01XB02 - polymyxin B	0.15
J01DE01 - cefepime	2	J01XC01 - fusidic acid	1.5
J01DF01 - aztreonam - parenteral	4	J01XD01 - metronidazole	1.5
J01DF01 - aztreonam - inhalation	0.225	J01XE01 - nitrofurantoin	0.2
J01DH02 - meropenem	2	J01XX01 - fosfomycin - parenteral	8
J01DH03 - ertapenem	1	J01XX01 - fosfomycin - oral	3
J01DH51 - imipenem and enzyme inhibitor	2	J01XX04 - spectinomycin	3
J01EA01 - trimethoprim	0.4	J01XX05 - methenamine - hippurate	2
J01EC02 - sulfadiazin	0.6	J01XX05 - methenamine - mandelate	3
		J01XX08 - linezolide	1.2

plement 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 1000 inhabitants and day (DDD/1000 inhabitants and day) and prescriptions per 1000 inhabitants. Every purchase of a medicine prescribed in outpatient care is also recorded in the Prescribed Drug Register, held by the Swedish National Board of Health and Welfare. This register provides the opportunity to link each prescription to an individual, which makes it possible to investigate the actual number of individuals or the fraction of the population treated with a specific medicine.

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

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

The Swedish Prescribed Drug Register

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

Number of admissions and patient-days

Each of the 21 county councils in Sweden deliver once a year data to the National Patient Register kept by The National Board of Health and Welfare. Administrative data within hospital care include, among others, date of admission, date of discharge and length of stay. Data for 2016 are not available until the end of 2017, denominator data from 2015 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) 2012-2015 is shown in Table 6.3. The National Board of Health and Welfare keeps a searchable database at the web, http://www.socialstyrelsen.se/statistik.

The point prevalence survey Swedish HALT

All assisted living facilities in all 290 municipalities in Sweden were invited to participate in the Swedish HALT 2014, 2015 and 2016. 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).

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 community consumption (outpatient 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 2.4.

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 clini-

cal 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 were 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.

In 2002, the web-based software (ResNet) was introduced. It received 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 could view their own data and link information to websites of their own local health care system.

Starting 2016 data for ResNet have been collected through Svebar, an automated system to which laboratories deliver all their culture results. Due to technical issues S/IR data were used 2016 instead of zone diameter data.

Surveillance of blood culture results

Starting 2016 all surveillance of blood culture results is using data collected through Svebar, an automated system to which laboratories deliver all their culture results. Deduplication of isolates can not be done with data from Svebar, since personal identities are not allowed in the system. This is mainly expected to influence results for unusual resistance types, where repeated sampling is common.

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

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*.

Starting 2016 these data were collected through Svebar in the same way as described for EARS-Net data.

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 broilers and turkeys, as well as on samples of broiler meat.

Samples from broilers were collected at slaughter within the Swedish Campylobacter programme in which whole caeca are collected from each batch of broilers slaughtered. From these samples, 150 were selected in January-June and 150 in August-November. Each sample was from a unique flock but not always from a unique production site. Samples cultured were collected at eight abattoirs that in 2016 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.

Samples collected from turkey consists of caecal content of healthy turkeys sampled at slaughter. Sampling was performed at two abattoirs in Sweden, from January to December. Each sample is from a unique flock but not always from a unique production site.

Samples from broiler meat were collected throughout the year by municipal environmental departments in twelve different cities in Sweden. In each city, a proportional number of samples in relation to the human population was collected.

MRSA and MRSP

Clinical isolates from cats, dogs, horses, goats and sheep 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.

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 and wildlife from which a subset of isolates is selected by convenience. Isolates from incidents previously notified and still under restrictions are included in the yearly statistics. Also included are isolates obtained in the salmonella surveillance programme from samples collected at slaughter (carcass swabs, neck skins and lymph nodes).

Campylobacter

Campylobacter jejuni were isolated from caecal content from healthy broilers sampled at slaughter within the Swedish Campylobacter programme in which whole caeca are collected from each batch of broilers slaughtered. In 2016, 724 flocks were positive for *C. jejuni*. From these, 170 isolates of *C. jejuni*, each representing one flock was randomly selected for susceptibility testing. The isolates were stored in -70°C until tested.

Clinical isolates from animals

Clinical isolates included are from routine bacteriological examinations of clinical submissions or post-mortem examinations. Part of the isolates of *Actinobacillus pleuropneumoniae* from pigs and part of the isolates of *Pasteurella* spp. from calves are, however, isolated from samples collected in surveys initiated within the SvarmPat programme.

In pigs, isolates of *E. coli* are from the gastro-intestinal tract and isolates of *Brachyspira* spp. from faecal samples. Isolates of *Pasteurella* spp. from pigs are isolated from nasal swabs collected within a control programme for atrophic rhinitis in nucleus and multiplying herds or from tissue samples from lungs taken post mortem. Isolates of *A. pleuropneumoniae* in pigs emanate from tissue samples from lungs sampled post mortem.

In cattle, isolates of *E. coli* are from samples from the gastro-intestinal tract or from milk samples. Isolates of *Klebsiella pneumoniae* are from milk samples. Isolates of *Pasteurella* spp. are from the respiratory tract.

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

In horses, isolates of *E. coli* are from the genital tract of mares, *Streptococcus equi* subsp. *zooepidemicus* mainly 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 various location (mainly external ear canal, skin or wound), *Pseudomonas aeruginosa* from the external ear canal and *Pasteurella* spp. from various locations (mainly external ear canal wound, skin, abscesses 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, abscesses, wound or urine) and *Pasteurella* spp. from various locations (mainly wound, skin, abscesses, external ear canal or the respiratory tract).

Indicator bacteria

The samples from intestinal content from healthy broilers and turkeys that were screened for $ESBL_A$, $ESBL_M$ and $ESBL_{CARBA}$-producing *E. coli* were also used to isolate indicator *E. coli*. However, only 176 of the samples from broilers were cultured for indicator *E. coli* and these samples were

evenly distributed over the year. From turkey, all collected samples were cultured for indicator *E. coli*, *Enterococcus faecalis* and *Enterococcus faecium*.

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 (chrom agar).

Additionally, from broiler samples during January-August, 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* 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 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 chrom agar.

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 and further tested for ESBL detection.

Clinical isolates

Clinical isolates from cats, dogs, and horses were submitted to the Dept. of Animal Health and Antimicrobial Strategies, SVA as bacterial strains. Isolates were species identified by MALDI-TOF MS.

MRSA and MRSP

Isolates were species identified by MALDI-TOF MS and tested for presence of *mecA* and *mecC* with PCR (see below). Isolates were susceptibility tested using microdilution (see below).

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).

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 jejuni from broilers were isolated and identified at the Dept. of Microbiology, SVA. Samples were cultured according to ISO/FDIS-1:2016 for detection of thermophilic *C. jejuni* by direct cultivation on mCCDA and incubation at 42°C for 48 h in a microaerophilic environment. Identification was based on colony morphology, microscopic appearance including motility. All isolates were species identified by MALDI-TOF MS.

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.

Enterococci

Caecum content from turkey was diluted as described for ESBL (see above) and 0.1 mL was spread on Slanetz-Bartley (SlaBa) agar and incubated at 37°C for 48 h. Two colonies, randomly chosen, were sub-cultured on blood agar (37°C, 24 h). Colonies with morphology consistent with enterococci were identified to species level by MALDI-TOF MS. If available, one isolate of *E. faecium* and one isolate of *E. faecalis* from each sample were tested for antibiotic susceptibility.

Susceptibility testing

Microdilution

At SVA, fast growing aerobic bacteria, *Campylobacter* and bacteria from fish 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 jejuni* was tested according to the CLSI standard M45-3rd ed. 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 6.12).

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 the EZseq™ service by Macrogen 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), *A. pleuropneumoniae* ATCC 27090 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, when testing, 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 6.12. Cut-off values (mg/L) for resistance. Values in red are current (March 2017) 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.

Antibiotic	*Actinobacillus pleuropneumoniae*	*Aeromonas salmonicida*	*Brachyspira hyodysenteriae*	*Campylobacter jejuni*	*Campylobacter coli*	*Enterococcus faecalis*	*Enterococcus faecium*	*Escherichia coli* (indicator)	*Escherichia coli* (pathogen)	*Flavobacterium psychrophilum*	*Klebsiella pneumoniae*	*Pasteurella multocida*	*Pseudomonas aeruginosa*	*Salmonella enterica*	*Staphylococcus pseudintermedius, S. felis, S. schleiferi*	*Staphylococcus aureus*	*Streptococcus zooepidemicus*
Ampicillin	>1			>8	>8	>4	>4	>8	>8			>1		>8			
Azithromycin								>16									
Bacitracin[a]						>32	>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	>32	>16	>16			>2		>16			
Ciprofloxacin	>0.06			>0.5	>0.5			>0.06				>0.06		>0.06			
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		>0.5	>0.5	
Ertapenem								>0.06									
Erythromycin				>4	>8	>4	>4								>0.5	>1	>0.5
Florfenicol	>4	>4							>16	>2		>4		>16			
Fusidic acid															>1	>0.5	
Gentamicin	>8			>2	>2	>32	>32	>2	>2		>2	>8	>8	>2	>2	>2	
Imipenem								0.5									
Kanamycin						>1024	>1024							>16			
Linezolid						>4	>4										
Meropenem								>0.12									
Nalidixic acid	>16			>16	>16			>16				>16		>16			
Narasin						>2	>2										
Neomycin									>8		>8			>4			
Nitrofurantoin									>64						>32 (UVI)		
Oxacillin															>0.5	>1[d]	
Oxolinic acid										>0.25							
Penicillin	>0.5											>0.5			[c]	[c]	>0.06
Streptomycin				>4	>4	>512	>128		>16		>16			>16			
Sulphametoxa-zole								>64						>256			
Temocillin								>32									
Tetracycline	>1	>1		>1	>2	>4	>4	>8	>8	>0.12	>8	>2		>8	>1	>1	
Tiamulin			>0.25														
Tigecycline								>0.5									
Trimethoprim	>4							>2						>2			
Trim & sulpha[b]									>1		>1	>4			>0.5	>0.5	>0.5
Tylosin			>16														
Tylvalosin			>1														
Valnemulin			>0.12														
Vancomycin						>4	>4										
Virginiamycin						>32	>4										

[a] MIC in U/mL; [b] Concentration of trimethoprim given, tested with sulphamethoxazole in concentration ratio 1/20; [c] beta-lactamase production; [d] EUCAST ECOFFs are used for MRSA (clindamycin >0.25 mg/L and oxacillin >2 mg/L).

Svarm 2000–2016

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

TABLE 6.13. *Salmonella enterica*, number of isolates 2000-2016.

Source	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Warm-blooded animals	67	52	49	101	68	105	101	112	122	117	82	71	71	86	77	54	77
Cold-blooded animals										17							

TABLE 6.14. *Campylobacter* spp., number of isolates 2000-2016.

Source	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Cattle		67					68							109		23	
Pigs		98		105		100	46		97			83				108	
Broilers		50	100		100				38		100		100		102		170
Broiler meat														111			
Meat (different sources)		74															
Water		19															

TABLE 6.15. Indicator *Escherichia coli*, number of isolates 2000-2016

Source	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
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		175
Broiler meat											77		92				
Laying hens													61				
Turkeys														55	59		85
Horses											274						
Dogs							257						74				
Willow grouse						19											
Wild boars		87															
Sheep									115								

TABLE 6.16. Indicator *Enterococcus faecalis* and *E. faecium*, number of isolates 2000-2016 *E. faecalis*/*E. faecium*).

Source	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
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				
Turkeys																	41/70
Horses											34/27						
Dogs							135/29										
Wild boars		12/35															
Sheep									24/15								

TABLE 6.17. Clinical isolates from animals, number of isolates 2000-2016.

Animal species & bacterial species	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Cattle																	
Escherichia coli (enteric)			220		87	39	24			40	15	15	58	30	29	36	29
Escherichia coli (uterine)														60			
Escherichia coli (udder)				169										142	95	113	74
Klebsiella spp. (udder)				44			24							41	39	41	36
Pasteurella spp.	254			100				27	32	14	27	80	37	39	39	46	104
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	16	57	33	36	37	33	18
Brachyspira hyodysenteriae	50	75	109	100		31	26	23	15	24	9	7	7	8	7	7	11
Brachyspira pilosicoli				93		57	72	44	31	24	13	16	17	12	13	7	17
Escherichia coli (enteric)	399	82	340	340	386	325	298	93	83	102	94	91	74	142	118	84	67
Pasteurella spp.		75						38	25	24	10	17	24	95	19	7	8
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	8
Flavobacterium columnare								30	16	10	5	8	3	5	9	4	3
Flavobacterium psychrophilum								42	27	24	21	27	31	23	61	31	16
Horses																	
Actinobacillus spp.		40															
Escherichia coli (genital)	323	103	166	188	188	161	124	273	174	210	236	174	196	140	229	188	324
Rhodococcus equi	73	20			187												
Streptococcus zooepidemicus	301	174	163	150	185	175	174	180	159	152	43	131	140	123	129	82	114
Staphylococcus aureus										308	131	135	145	139	132	116	75
Dogs																	
Escherichia coli (urinary)	185	183	204	234	247	304	366	425	503	599	803	661	407	840	943	1 112	1 162
Pasteurella canis															207	194	253
Pasteurella multocida					231										29	46	23
Pseudomonas aeruginosa				234						261	313	353	178	309	389	355	349
Staphylococcus pseudintermedius	145	156	133	102	159	126	89	220	258	381	444	388	229	566	513	393	376
Staphylococcus schleiferi															297	201	163
Cats																	
Escherichia coli (urinary)			46	52	55	74	95	131	170	245	236	274	310	404	461	455	537
Beta-hemolytic streptococci												184					
Pasteurella dagmatis															20	22	19
Pasteurella multocida															244	340	349
Staphylococcus felis															244	227	277

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SWEDRES|SVARM 2016

This annual report describes antibiotic resistance and antibiotic usage in human and veterinary medicine in Sweden in 2016.

The situation in Sweden regarding antibiotic resistance in bacteria from humans and animals is favourable when seen in an international perspective, and this confirms that Sweden's strategies to promote responsible use of antibiotics and to contain antibiotic resistance are effective. With that said, it is important to stress that this is a never-ending task and that society must keep a long-term perspective on policies and efforts in this area.

The total sales of antibiotics in humans have continued to decrease, and positive trends regarding choices of antibiotics have also continued in 2016, with one exception: the sales of antibiotics to children have increased. The data show that antibiotics normally used for respiratory tract infections constitutes the largest part of this increase. Sales of antibiotics for animals are also decreasing.

While the sales of antibiotics indicate positive progress, the trends concerning antibiotic resistance are more worrisome. Especially alarming is the upward trend of findings of $ESBL_{CARBA}$ in humans.

This highlights once again that efforts to optimize antibiotic use, prevent infections, and minimize dissemination of antibiotic resistance must be ongoing and must be continually improved based on effective monitoring and best available knowledge.

Focus areas in the 2016 report:
- Antimicrobial stewardship in Stockholm hospitals
- Colistin resistance in Enterobacteriaceae and colistin use in humans and animals
- Antibiotic resistance in MRSA from humans – results from Svebar
- WHO GLASS – Global Antimicrobial Resistance Surveillance System
- Quantification of $ESBL_A$ and $ESBL_M$-producing *Escherichia coli* in broilers
- SvarmPat – monitoring of resistance in pathogens from farm animals
- Tiamulin-resistant *Brachyspira hyodysenteriae*

The Public Health Agency of Sweden has a national responsibility for public health issues. The Agency promotes good public health by generating knowledge and disseminating it 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.