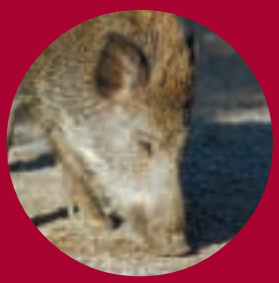
2001

SVARM 2001

Swedish Veterinary Antimicrobial Resistance Monitoring



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Swedish Veterinary Antimicrobial Resistance Monitoring

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Preface

This is the second yearly report from SVARM, the Swedish programme for monitoring of antimicrobial resistance in bacteria isolated from animals. Antimicrobial susceptibility data for intestinal bacteria of healthy animals (indicator bacteria), zoonotic bacteria and animal pathogens are presented. Statistics on use of antimicrobials for animals is also included. Comments on the results in relation to earlier reports are done when appropriate. It has long been recognised that better data on antimicrobial resistance and antimicrobial usage constitute a basis for strategies aiming at containing the emergence and further spread of resistance. The ultimate goal is to preserve the effectiveness of available drugs for the benefit of future generations of animals and people. It is now a well established fact that resistant bacteria or resistance genes can spread between different populations of animals and humans. Hence, the ideal monitoring programme should on a regular basis provide data on resistance and use of antimicrobials in all relevant sectors. Such integrated programmes are running only in a few countries.

The Copenhagen meeting on the Microbial Threat in 1998 identified key areas in which EU Member Countries should take initiatives in order to counter the spread of antibiotic resistance among human and animal bacteria. Surveillance of resistance to antimicrobials and monitoring of the use of antimicrobials were two of the key areas identified. At a follow-up meeting in 2001, the Visby conference, the present situation was reviewed. Data presented there illustrated that antimicrobial resistance remains a major problem in public health, whereas the impact on animal health is less well documented.

The main objectives of monitoring antimicrobial resistance in bacteria of animal origin are to detect (undesired) trends, provide a basis for policy recommendations, measure the effects of interventions and generate exposure data for risk assessments. Working groups within the EU (ARBAO) and the OIE have suggested minimum criteria for monitoring programmes.

In order to give a good overview and to facilitate interpretation of the results, the distributions of the MICs of the antimicrobials tested are presented. Furthermore, the prevalence of resistance patterns or phenotypes of the strains is given.

The occurrence of certain resistance phenotypes is discussed. It must be made clear that the relationship between the amounts used of a certain antimicrobial and development of resistance is complex. Apart from antibiotics, many factors such as population density, hygiene, and movement of animals will influence the level of resistance. However, there is strong scientific evidence that the use of an antimicrobial will eventually result in decreased susceptibility among exposed bacteria.

The Visby conference 2001 identified obstacles for implementing monitoring systems for surveillance of antimicrobial resistance and use of antimicrobials. As for surveillance of antimicrobial resistance an obvious obstacle was lack of financial resources. Another obvious obstacle was a general lack of know-how required for producing quality data on susceptibility testing and hence surveillance is often hampered on local, national and European levels. There is need for increased involvement of personnel trained in medical/veterinary sciences at all levels of microbiology laboratory services.

Further it was pointed out that while waiting for a common European definition of resistance and a common principle for setting breakpoints, surveillance should be based on quantitative data and when possible on the detection of resistance mechanisms or genes. As for monitoring the use of antimicrobials it became apparent that only eight of 13 countries present at the Visby conference were able to collect national data on antimicrobials used as therapeutics in farmed animals and companion animals or as feed additives. An identified obstacle was that the responsibility for collecting data was not clearly defined for all countries present.

Through collaboration with the National Food Administration, results from a limited number of *Campylobacter* isolates from food are included in this report. It is our ambition to expand this collaboration so that more information on resistance in bacteria isolated from food can be included in forthcoming reports. Coordination with human medicine is also under way. Moreover, the statistics on use of antimicrobials will be more useful once it is possible to divide the data per animal species.

Summary

This second report from SVARM confirms that the situation regarding antimicrobial resistance in the bacteria of animal origin studied is favourable. The results concur with last years report (SVARM 2000) and previous Swedish studies in this field indicating that the situation is stable. The favourable situation is probably the result of a tradition of prudent use of antimicrobials in animals and a good animal health status.
The information gathered in programmes like SVARM, monitoring both antimicrobial consumption and occurrence of resistance, should further the understanding of the epidemiology of antimicrobial resistance. From the data gathered in SVARM after two years, certain issues that deserve further study have been identified. One such issue is co-selection of resistance whereby use of one antimicrobial selects for resistance not only to itself but also to other drugs. Thus, co-selection might explain occurrence of resistance to drugs not currently used, or the persistence of resistance for long periods after the use was discontinued.

Consumption of antimicrobials

Antimicrobials for use in animals in Sweden are only available on veterinary prescription and guidelines emphasising judicious use have been issued. Use for growth promotion was banned in 1986. In year 2001, a total of 17.3 tons of antimicrobials were used for animals in Sweden. The figure is roughly equal to the amount used year 2000 (17.1 tons) and represents a decline of about 16% since 1996. The decline cannot be explained by a shift to use of more potent substances. The major part (about 85%) was used for treatment of individual animals. Over the last five years this amount has remained relatively stable whereas the amount used for treatment of groups or flocks of animals has decreased.

To detect changes in usage it is not altogether relevant to compare total amounts used. For example the use of drugs with mastitis as one (of several) authorised indications has decreased over the last 10 years when total amounts of active substance are compared. By contrast, when the figures are expressed in a unit that corrects for dose and population changes (daily doses for cows/1000 cows and days), an increase is apparent. This highlights the overall need for development of defined units of measurement to facilitate temporal analysis and comparisons between regions or countries.

Another obstacle for analysis of changes in usage is that many of the drugs are used in several animal species. For more precise estimates of treatment incidence, data must be broken down at least by animal species. Unfortunately, the possibilities to do so using current systems are limited which hampers the development of new or improved systems. Such systems are needed to analyse trends in use and resistance, to identify possible risk factors and to follow compliance with policy recommendations. Sweden has a long tradition of monitoring use of antimicrobials for animals. However, the responsibility for collecting and analysing such data has never been defined.

Resistance in zoonotic bacteria

The situation regarding antimicrobial resistance in *Salmonella* from animals in Sweden continue to be favourable and stable since monitoring of resistance began in the late 1970s. The resistance observed is largely linked to occurrence of multiresistant isolates of *S.* Typhimurium. These phagetypes (DT104, DT193 and DT120) are rare and thus resistance levels are low. The favourable situation is probably to a large extent due to the Swedish *Salmonella* control programme, through which occurrence of *Salmonella* in Swedish food producing animals is detected and measures taken to counteract its spread. Data on *Salmonella* isolated from imported food and animal feed as well as from human cases of salmonellosis would provide a broader view of antimicrobial resistance in *Salmonella* encountered in Sweden.

Levels of resistance were low also among *Campylobacter* isolated from healthy animals at slaughter. One exception was resistance to nalidixic acid or enrofloxacin, which was surprisingly common (30%, respectively) in *Campylobacter* spp. isolated from pigs. The figures are difficult to explain since no fluoroquinolones are authorised for group treatment of pigs in Sweden. Moreover, the prevalence of this resistance trait was low among *Escherichia coli* in the material from healthy animals as well as among clinical isolates of *E. coli* (see Resistance in indicator bacteria and Resistance in animal pathogens). In this year's SVARM, *Campylobacter* isolated from food and water are included. Overall, the resistance figures were low also among these isolates. Resistance in indicator bacteria

In SVARM, the antimicrobial susceptibility in *Escherichia coli* and *Enterococcus* spp. isolated from healthy animals sampled at slaughter serve as indicator of the selective pressure exerted by antimicrobials used in specific animal populations. Although unlikely to cause disease, these bacteria can constitute a reservoir of transferable resistance genes that can spread to bacteria with potential to cause disease in animals and humans. This year, data on indicator bacteria isolated from pigs and broiler chickens is reported. In addition a material from wild boars is included for comparison to a population not exposed to antimicrobials.

Overall, the figures for 2001 are low in an international perspective and of similar magnitude in isolates from pigs and chickens. Occurrence of resistance is with few exceptions similar to levels for year 2000 and can generally be linked to use of the antimicrobial in the respective animal species. Occasional resistant isolates in samples from wild boars might indicate a transmission of resistance traits between animal species. As there is no selection pressure in the population of wild boars, the traits would not be amplified and, as expected, resistance among isolates from wild boars was rare.

Resistance to some antimicrobials can however not be explained by a selective pressure through therapeutic use. Instead, occurrence of these traits might be a consequence of co-selection of resistance whereby use of one antimicrobial selects for resistance also to other unrelated substances. In the combined data for years 2000 and 2001 there are indications of linked resistance in *E. coli* as well as in enterococci, which implies that co-selection of resistance, might occur.

In agreement with last year's survey no vancomycin resistant enterococci were found on direct culture. This indicates that the prevalence of vancomycin resistance is low from an international perspective. However, after selective culture, 24 vancomycin resistant isolates were found in samples from chickens year 2001 and two isolates year 2000. The results show that the vancomycin resistance gene (*van*A) is present at a low prevalence among enterococci although the drug selecting for vancomycin resistance, avoparcin, has not been used in Swedish animal production since the early 1980s.

Resistance in animal pathogens

Data on antimicrobial susceptibility in animal pathogens was obtained from the database at SVA. The presented data mostly originate from isolates obtained from diagnostic submissions and therefore might be biased towards treatment failures or otherwise problematic cases. Therefore the results might represent a worst-case scenario and conclusions regarding susceptibility in general must be made with caution.

In pigs, resistance in *E. coli* isolated from diagnostic submissions was more prevalent than among isolates of the same bacterial species from healthy pigs (indicator bacteria). Resistance to tetracycline, streptomycin or the combination trimethoprim-sulphonamide were the most prevalent traits and have been dominant in the material over the last ten years. Resistance to some of the antimicrobials tested is surprisingly high, as the substances are used sparingly or not at all used in pig production in Sweden. This might be due to co-selection of resistance by other antimicrobials. Among *Brachyspira hyodysenteriae* no resistance to tiamulin was detected but tylosin resistance was common. As the therapeutic arsenal against this pathogen is limited to a few substances only, it is of vital importance to continuously monitor it's antimicrobial susceptibility.

Among *Pasteurella multocida*, obtained within the framework of a control programme, resistance was rare. Antimicrobial resistance was rare among *Staphylococcus aureus* isolated from cases of chronic or subclinical mastitis in dairy cows. The most prevalent trait was penicillin resistance due to β-lactamase production which occurred in 18% of the isolates.

As shown in last years report, resistance to the combination trimethoprim-sulphonamide in *Streptococcus zooepidemicus* from the respiratory tract of horses has increased markedly over the last ten years. The figure for year 2001 is similar to last years figure and shows that about half of the isolates from diagnostic submissions were resistant to this drug combination. Notably, the susceptibility to penicillin was high in this pathogen. Among *E. coli* from the genital tract of mares, resistance to trimethoprim-sulphonamide, ampicillin or streptomycin was relatively common. However, the increase in levels of resistance to trimethoprim-sulphonamide observed in *S. zooepidemicus* was not paralleled in this bacterial species. Occurrence of acquired resistance in *Rhodococcus equi* and *Actinobacillus* spp. was low although occasional isolates of the latter pathogen were resistant to penicillin.

In dogs, *Staphylococcus intermedius,* isolated from bacteriological samples from skin, were to a large extent β–lactamase producers and consequently resistant to penicillin. Resistance to macrolides, lincosamides or tetracycline was also common emphasising the need for culture and subsequent susceptibility testing for an effective therapeutic choice. The need for susceptibility testing also applies to *E. coli* from the urinary tract of dogs. A relatively large amount (10-20%) of these isolates were resistant to ampicillin, streptomycin, tetracycline or the combination trimethoprim-sulphonamide and multiresistance was not uncommon.

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Sammanfattning

Denna andra rapport från SVARM bekräftar att läget avseende resistens mot antibiotika hos de bakterier från djur som undersökts är gynnsamt. Årets resultat överensstämmer i huvudsak med de i fjolårets rapport (SVARM 2000) och med tidigare svenska studier. Den gynnsamma situationen är troligen en följd av en tradition av omdömesgill användning av antibiotika till djur i kombination med ett gynnsamt sjukdomsläge.

Information som samlas in i program som i likhet med SVARM rapporterar både förbrukning av antibiotika och förekomst av resistens ökar förståelsen av resistensepidemiologi och urskiljer områden som kräver ytterligare studier. Ett sådant område är co-selektion av resistens, vilket innebär att användning av ett antibiotikum selekterar för resistens inte bara mot detta medel utan även mot andra substanser. Co-selektion kan vara orsaken till att resistens påvisas mot antibiotika som inte längre används, eller används endast i liten omfattning, till djur i Sverige.

Användning av antibiotika

I Sverige används antibiotika till djur endast efter förskrivning av veterinär. Riktlinjer för förskrivning, i vilka riskerna för resistensutveckling beaktas, har utarbetats. Användning av antibiotika i tillväxtbefrämjande syfte förbjöds 1986.
Den totala förbrukningen år 2001 var 17.3 ton aktiv substans vilket är ungefär lika mycket som år 2000 (17.1 ton) men innebär en minskning med omkring 16 % sedan 1996. Minskningen kan inte förklaras med en ökad användning av substanser med högre aktivitet per viktsenhet. Merparten (omkring 85 %) användes för behandling av enskilda djur. Mängden antibiotika som används till enskilda djur har varit relativt konstant under de senaste fem åren medan den mängd som används för behandling av djurgrupper genom inblandning i foder eller vatten har minskat.

Det är inte helt invändningsfritt att jämföra totala mängder substans för att upptäcka förändringar i användning av antibiotika. Ett exempel är användningen av antibiotika med juverinflammation som en av flera indikationer. När de totala mängderna aktiv substans jämförs förefaller användningen ha minskat under de senaste tio åren. Om däremot den förbrukade mängden uttrycks i en enhet som tar hänsyn till dos och förändringar i djurpopulationen (dygnsdos för kor/1000 kor och dagar) har förbrukningen ökat påtagligt. Exemplet belyser behovet av utveckling av definierade enheter som ett mått på förbrukningen för att underlätta jämförelser mellan regioner och länder.

En annan svårighet vid analys av förändringar i bruk av antibiotika är att många substanser används till flera olika djurslag. För en bättre uppskattning av behandlingsincidens måste förbrukningsdata kunna delas upp åtminstone per djurslag. Detta är inte möjligt i dagsläget vilket hindrar utvecklingen av nya och förbättrade system nödvändiga för att analysera trender i förbrukning och resistens, för att identifiera riskfaktorer och för att bedöma följsamheten till riktlinjer för användning av antibiotika. Sverige har en lång tradition av övervakning av användning av antibiotika till djur men ännu har ansvaret för insamling och analys av förbrukningsdata inte fastställts.

Resistens hos zoonotiska bakterier

Läget avseende antibiotikaresistens hos *Salmonella enterica* isolerade från djur i Sverige är fortfarande gynnsamt och har varit stabilt sedan övervakning av resistens hos dessa bakterier inleddes 1978. De resistenta isolat som påvisats är i stor utsträckning multiresistenta *S.* Typhimurium av fagtyperna DT104, DT193 eller DT120. Dessa fagtyper är ovanliga hos djur i Sverige varför förekomsten av resistens är låg. Den gynnsamma situationen är förmodligen en följd av det svenska salmonellakontrollprogrammet varigenom salmonellasmitta i djurbesättningar upptäcks och åtgärder vidtas för att förhindra dess spridning. För en mer fullständig bild av resistensläget hos *Salmonella* i Sverige behövs uppgifter om antibiotikakänsligheten även hos isolat från importerade livsmedel och djurfoder liksom från humana fall av salmonellos.

Hos *Campylobacter* isolerade från friska djur var resistens ovanlig liksom bland *Campylobacter* isolerade från livsmedel eller vatten. Ett undantag var resistens mot nalidixinsyra eller enrofloxacin (30 %) bland isolat från friska svin. Den höga förekomsten av resistens bland dessa isolat är svår att förklara eftersom ingen fluorokinolon för gruppbehandling av svin är registrerad i Sverige. Därtill var dessa resistenstyper ovanliga bland *Escherichia coli* isolerade från friska svin liksom bland *E. coli* isolerade från kliniska fall (se Resistance in indicator bacteria and Resistance in animal pathogens).

Resistens hos indikatorbakterier

I SVARM har antibiotikakänsligheten hos *E. coli* och *Enterococcus* spp. isolerade från tarminnehåll från friska djur valts som indikator på det selektionstryck som blir följden av antibiotikaanvändning i en djurpopulation. Dessa bakterier förorsakar sällan sjukdom men kan bära resistensgener som kan överföras till sjukdomsframkallande bakterier. I årets rapport presenteras data för indikatorbakterier från svin och slaktkyckling. Dessutom är isolat från vildsvin inkluderat som en jämförelse med

indikatorbakterier från en djurpopulation som inte exponeras för antibiotika.

Förekomsten av resistens hos indikatorbakterier från svin och kyckling var med få undantag av samma storleksordning som år 2000. Andelen resistenta isolat var liten i jämförelse med vad som rapporterats från liknande övervakningsprogram i andra länder. I huvudsak förkom resistens mot substanser som används till respektive djurslag. Enstaka resistenta isolat påvisades i prov från vildsvin vilket kan tyda på att en överföring av resistens mellan djurslag sker. Eftersom ett selektionstryck saknas i vildsvinspopulationen sker ingen selektion vilket innebär att andelen resistenta isolat blir låg.

Hos isolat från både svin och kyckling förekom resistens mot antibiotika som används i liten omfattning eller inte alls. Detta kan inte förklaras med ett selektionstryck utan är troligen en följd av co-selektion där användning av en antibiotikum selekterar för resistens även mot andra, ej besläktade, substanser. I det kombinerade materialet från år 2000 och 2001 finns indikationer på kopplad resistens hos både *E. coli* och enterokocker vilket innebär att co-selektion av resistens kan förekomma.

I likhet med fjolårets rapport påvisades inget isolat av vancomycinresistenta enterokocker vid direktodling. Detta tyder på att förekomsten av resistens mot vancomycin är låg i ett internationellt perspektiv. Vid selektiv odling påvisades däremot vancomycinresistenta enterokocker i 24 prov från kyckling år 2001 och två prov år 2000. Resultaten visar att resistensgenen (*vanA*) förekommer i låg prevalens bland enterokocker trots att det antibiotikum som selekterar för vancomycinresistens, avoparcin, inte har använts i svensk animalieproduktion sedan 1982.

Resistens hos sjukdomsframkallande bakterier från djur

Uppgifter om sjukdomsframkallande bakteriers antibiotikakänslighet härrör i allmänhet från isolat från diagnostiska prov insända till SVA. Data kan därför vara vinklade mot särskilt problematiska och svårbehandlade fall. Resultaten skall tolkas med detta i åtanke och generella slutsatser avseende antibiotikakänsligheten hos de undersökta bakterierna måste göras med försiktighet.

Hos *E. coli* från svin var resistens vanligare i isolat från diagnostiska prover än hos isolat av samma bakterie från friska grisar (indikatorbakterier). Resistens mot tetracyklin, streptomycin eller trimetoprim/sulfonamid var de mest prevalenta resistenstyperna liksom under de senaste tio åren. Resistens mot några av de testade substanserna är oväntat hög då de används sparsamt eller inte alls i svensk svinuppfödning. Orsaken kan vara co-selektion av resistens som en följd av användning av andra substanser. Hos *Brachyspira hyodysenteriae* påvisades ingen resistens mot tiamulin men resistens mot tylosin var vanlig. Eftersom den terapeutiska arsenalen mot denna infektion är begränsad till ett fåtal antibiotika är det av stor betydelse att kontinuerligt övervaka antibiotikakänsligheten hos denna bakterie. Hos *Pasteurella multocida*, insamlade inom ramen för ett kontrollprogram, var resistens ovanlig.

Resistens var ovanlig hos *Staphylococcus aureus* isolerade från kronisk eller subklinisk juverinflammation hos mjölkkor. Penicillinresistens pga av β-laktamas produktion var den vanligaste resistenstypen och förekom hos 18% av isolaten.

I fjolårets rapport redovisades en markant ökning av resistens mot kombinationen trimetoprim/sulfonamid hos *Streptococcus zooepidemicus* från luftvägarna hos hästar under de senaste tio åren. I likhet med förra årets material var omkring 50 % av de undersökta isolaten år 2001 resistenta mot kombinationen av dessa substanser. Känsligheten för penicillin var däremot genomgående hög. Hos *E. coli* från könsorganen hos sto var resistens mot trimetoprim/sulfonamid, ampicillin eller streptomycin relativt vanlig. Någon ökning av resistens mot trimetoprim/sulfonamid liknande den hos *Streptococcus zooepidemicus* föreligger däremot inte. Förvärvad resistens hos *Rhodococcus equi* och *Actinobacillus* spp. var ovanlig men enstaka isolat av den sistnämnda bakterien var resistenta mot penicillin.

Hos hundar var *Staphylococcus intermedius* isolerade från bakteriologiska prover från hud i stor utsträckning β-laktamas bildare och därmed resistenta mot penicillin. Resistens mot makrolider, linkosamider eller tetracyklin var också vanlig vilket understryker vikten av bakteriologisk odling och känslighetsbestämning i valet av effektiv terapi. Nödvändigheten av känslighetsbestämning gäller även *E. coli* isolerade från urinvägarna på hundar. En relativt stor andel (10-20 %) av dessa isolat var resistenta mot ampicillin, streptomycin, tetracyklin eller kombinationen trimetoprim/sulfonamid och multiresistens var inte ovanlig.

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Use of antimicrobials

Use of antimicrobials

Through an initiative of SVA and Apoteket AB (the National Corporation of Swedish Pharmacies), statistics on total sales of antibiotics for use in animals in Sweden are available since 1980. For a review of the figures from 1980-2000 as well as references to earlier publications, see SVARM 2000.

Use of antimicrobials – the figures for 2001

Material included

In Sweden, antimicrobials for use in animals are only available on veterinary prescription and all pharmaceuticals are dispensed by pharmacies. In 1986, the Feedstuffs Act restricted the use of antibiotics for veterinary medicinal purposes, i.e. their use as growth promoters was banned.

Drug statistics are based on sales figures provided by Apoteket AB and represent total amount of antimicrobials authorised for veterinary use sold from wholesalers to pharmacies calculated to kg active substance. These figures include antimicrobials for all animal species (food producing animals, fish, pets and horses etc) and formulations for systemic, intramammary and obstetric use as well as intestinal anti-infectives. It is assumed that the amount sold is also used during the observation period. Drugs authorised for human use but prescribed for animals are not included. Such drugs are primarily prescribed in small animal medicine and their use is declining as the number of products authorised for veterinary use is increasing.

In addition, a breakdown of the statistics with regard to prescriptions of drugs with mastitis as one of the approved indications is included. To facilitate temporal analysis and comparisons, a defined daily dose for cows (DDDcow) is introduced as a unit of measurement.

Details on animal numbers are found in Appendix 1 and on methodology in Appendix 2.

Overall use

The total usage of antimicrobials is presented in table AC I. The different substances are not equal in their biological activity per weight unit and therefore, each substance group should be evaluated separately. Nonetheless, the total figures indicate trends in the material. During the last part of the 90s, the use decreased steadily. In 2001, it was roughly unchanged compared with year 2000.

Antimicrobials that showed increasing sales figures between 2000 and 2001 are the cephalosporins, macrolides and lincosamides and the fluoroquinolones. For the cephalosporins, this trend has been noted since 1997, i.e. their introduction on the Swedish market. It is likely that this reflects an increased prescription to pets of recently authorised veterinary drugs instead of prescription off-label of drugs of the same class authorised for humans. As drugs authorised for humans are not included in the statistics, the total use of cephalosporins may well be unchanged. For macrolides and lincosamides, and fluoroquinolones, the changes must be interpreted with caution as they diverge from earlier (decreasing) trends.

The use of tetracyclines continued to decrease and is close to half of what it was in the mid-90s. The figures from the two last years include drugs marketed with special licence. In chickens, ionophoric antibiotics are given to control coccidiosis. The sales of these products are discussed under the section on group treatment (see Table AC III).

Use for systemic treatment of indiviual animals

In 2001, 84% of the volume sold was in the form of products formulated for use in individual animals, excluding topical use such as intrauterine or intramammary use (Table AC II). The use of most groups has decreased or been relatively unchanged over the last five years. A large part of the injectables is most likely used for treatment of bovine mastitis.

Table AC I. The total amount of antimicrobial drugs authorised for veterinary use expressed as kg active substance (sales statistics from Apoteket AB).

ATCvet code	Substance class	Year							
		1980	1988	1996	1997	1998	1999	2000	2001
QG01AA, QJ01A	Tetracyclines	9 819	4 691	2 698	2 558	2 897	2 251	1 754[2]	1 453[4]
QJ01B	Chloramphenicol	47	35	–	–	–	–	–	–
QJ01CE, QJ01R, QJ51R	Penicillin G and V[1]	3 222	7 143	8 818	8 781	8 547	8 692	8 254	8 414
QJ01CA, QJ01CR	Aminopenicillins	60	655	835	841	824	809	852	752
QJ01D	Other beta-lactam antimicrobials	9	–	–	53	133	245	315	474
QA07AA, QJ01G, QJ01R, QJ51R	Aminoglycosides	5 274	3 194	1 164	1 077	930	846	797[4]	770[4]
QA07AB, QJ01E	Sulphonamides	6 600	3 072	2 198	2 151	2 345	2 403	2 338	2 485
QJ01E	Trimethoprim and derivatives	134	250	339	352	390	397	390	414
QJ01F	Macrolides and lincosamides	603	1 205	1 649	1 747	1 846	1 467	1 352	1 510
QJ01MA	Fluoroquinolones			173	179	175	155	156	182
QJ01XX92, QJ01XX94	Pleuromutilins		124	1 142	1 094	1 032	847	871	841
QJ01MB	Quinoxalines	6 250	7 164	1 098	534	–	–	–	–
QJ01XX91	Streptogramins	–	1 088	525	288	150	125	–	–
	Other substances[2]	861	1 567	–	–	–	–	–	–
	Antimicrobial feed additives[3]	8 380	–	–	–	–	–	–	–
Total		**41 259**	**30 189**	**20 639**	**19 655**	**19 269**	**18 237**	**17 079**	**17 295**

[1] Calculated as benzyl-penicillin; [2] Mainly nitroimidazoles, QP5 1AA; [3] Substances included are avoparcin, bacitracin, nitrovin, oleandromycin and spiramycin.[4] Drugs marketed with special licence are included.

Therefore, much of the decrease may be explained by a steadily decreasing number of dairy cows. However, sale of trimethoprim in combination with sulphonamides increased, largely due to an increased use of formulations intended for oral use in horses. The increased sale of cephalosporins is related to use in pets and was commented on above.

Use for treatment of groups or flocks

The proportion of drugs authorised for treatment of groups of animals via feed or water has decreased steadily over the years (Table III). Only four classes of antimicrobials of this type remain on the market. All groups show a declining trend over the period. It can be assumed that today, the bulk of the sales of drugs for group treatment is aimed for treatment of enteric and respiratory infections in pigs. The number of pigs slaughtered was stable from 1995 until 1999 but dropped by 14% in 2000. Thus, the decrease in sales from 1996 until 1999 is likely to reflect a true decrease in use of antimicrobials for group treatment.

By contrast, the changes between 1999 and 2000 are fully explained by the drop in numbers of swine. In 2001, an increased use of macrolides was noted compared with figures from 2000. Macrolides are used for treatment of swine dysentery and mycoplasma infections in pigs. The number of pigs slaughtered in 2001 was unchanged compared to 2000. However, as the number of sows increased by 5%, it is possible that part of the increase in use reflects an increased number of piglets that have yet not reached slaughter weight (for demographics see Appendix I).

Coccidiostats of the ionophore group are used to control coccidiosis in the production of chickens for slaughter. Since the late 80s, narasin is by far, the most widely applied substance. The number of chickens has increased by more than 10% since 1995, but the use of anticoccidials has decreased. This decrease is partly explained by extended withdrawal times. Another contributing factor is the fact that up until 2000, lower doses were often used in the latter part of the rearing period. This was changed in 2001 and the volume used increased accordingly.

Monitoring of drugs with mastitis as one of the indications

Antimicrobial treatment of bovine mastitis contributes significantly to the overall use of antimicrobials in Sweden. Comprehensive policies and guidelines on therapy of mastitis have therefore been issued. As a consequence, attention has been drawn to the need for reliable data on the use of drugs for this indication.

Methodological considerations - units of measurement

In Sweden, clinical mastitis is mostly treated by injections of antimicrobial drugs. In figure AC I, the effect of different units of measurement for this subset of wholesalers' data from Sweden is exemplified. Measured as uncorrected weight units, the figures seem to show a reduction in use. However, the number of dairy cows declined by 26% between 1990 and 2000. When the weight units are corrected for number of cows, an obvious increase is noted. Finally, using defined daily doses for cows (DDDcow/1000 cowdays) as unit, the increase is even more pronounced (37%).

The concept of DDDcow was developed in collaboration between Norway and Sweden. Drugs with mastitis as one of the indications were selected, doses were defined and the sales calculated to DDDcow per 1000 cows and day (Grave *et al.*, 1999, see also Appendix 2 for methodology).
Most of the drugs that are included are authorised not only for mastitis, but for other indications, and for other animal species as well. However, estimates based on animal health records indicate that of the injectable drugs, 40-50% of the calculated DDDcow sold was used for treatment of mastitis. Therefore, the data is likely to reflect trends in usage for treatment of mastitis.

Table AC II. The amount of antimicrobial drugs in kg active substance authorised for individual treatment. Intramammaries (QJ51) are not included. The calculation is based on sale statistics from Apoteket AB.

ATCvet code	Substance class	Year							
		1980	1988	1996	1997	1998	1999	2000	2001
QA07A	Intestinal anti-infectives	NA[3]	NA[3]	863	706	649	607	587[5]	614[5]
QJ01A	Tetracyclines	549	514	596	663	656	695	634[5]	623[5]
QJ01B	Chloramphenicol	47	35	–	–	–	–	–	–
QJ01C	Penicillins[1,2]	3 222	7 143	9 560	9 530	9 287	9 424	9 037	9 095
QJ01D	Cephalosporins	–	–	–	53	133	245	315	474
QJ01E	Sulphonamides and trimethoprim	6 734[4]	3 322[4]	2 033	2 107	2 335	2 376	2 336	2 478
QJ01F	Macrolides and lincosamides	295	454	675	652	645	559	531	522
QJ01G	Aminoglycosides[2]	5 274[4]	3 194[4]	650	617	535	528	474	454
QJ01M	Fluoroquinolones	–	–	147	147	150	144	150	169

[1] Calculated as benzyl-penicillin; [2] The amount includes QJ01R, combinations; [3] Separate figures not available for 1980 and 1988, for these years the intestinal anti-infectives are included in the sulphonamides and aminoglycosides; [4] Figures include intestinal anti-infectives (QA07A); [5] Drugs marketed with special licence are included.

Table AC III. The amount of antimicrobials drugs authorised for group treatment and ionophoric anticoccidials in kg active substance. Based on sale statistics from Apoteket AB and from the Board of Agriculture.

ATC vet	Substance class	1980	1988	1996	1997	1998	1999	2000	2001
QJ01A	Tetracyclines	9 270	4 177	2 089	1 881	2 230	1 545	1 111[3]	822[3]
QJ01F	Macrolides and lincosamides	308	751	975	1 096	1 201	908	821	988
QJ01M	Fluoroquinolones	–	–	27	32	25	11	7	13
QJ01X	Pleuromutilins	–	101	1 069	1 029	969	795	815	793
QP51A	Nitroimidazoles	791	1 557	–	–	–	–	–	–
QJ01M	Quinoxalines	6 250	7 164	1 098	534	–	–	–	–
QJ01X	Streptogramins	–	1 088	525	288	150	125	–	–
	Antibacterial feed additives[1]	8 380	700	–	–	–	–	–	–
QP51AH	Ionophoric antibiotics (coccidiostats)	390	6 991	11643	10 805	9 941	9 562[2]	9 368[2]	10 019[2]

[1] Substances included are avoparcin, bacitracin, nitrovin, oleandromycin and spiramycin; [2] From 1999 regulated and classified as feed additives (dir 70/524/EEC). Figures from 1999 and onwards are from the Feed Controll of the board of Agriculture (www.sjv.se).[3] Drugs marketed with special licence are included.

Injectables

The total use of the selected drugs expressed as DDDcow/1000 cows and day increased during the study period (Table AC IV). The increase is probably, at least partly, explained by use of higher doses and longer duration of treatment for each case. The highest figures are recorded for 1994. In that year, the dairies lowered their limits for bulk-milk cell counts and this may have affected the number of treatments.

Among the different drug classes, the use of penicillins increased while the use of combinations of procaine penicillin and dihydrostreptomycin decreased. The relative proportion of penicillins of the total number of DDDcow increased from 60% to 75% between 1990 and 2001.

Among the different penicillins, the use of benzylpenicillin increased sharply in 1994, accompanied by a decrease in use of procaine penicillins. This is likely to be a reflection of increased milk withdrawal times for the products containing procaine penicillin as from 1994. Interestingly, after a couple of years the use of procaine penicillin increased again. Enrofloxacin was introduced in 1989, which may explain that the figures for 1990 and 1991 are lower than the other years. The use of macrolides increased until the mid-90s and has since decreased. This decrease could have been influenced by policy recommendations issued in 1995 (Ekman *et al.*, 1995), by extended milk withdrawal periods in 1996, or both.

Intramammaries

In absolute figures, the number of single-dose applicators for intramammary therapy during lactation has decreased and that for dry cow treatment has increased since 1990 (data not shown). To be noted is that one of the short acting intramammary products is also authorised for other indications than mastitis and for other animal species.

In Table AC V, figures on sales expressed as DDDcow/1000 cows and day is shown. One single-dose applicator was defined as one daily dose. The products have been divided according to their indication, i.e. for therapy of mastitis during lactation or for dry cow treatment. For the former category, the incidence has decreased over the period studied. By contrast, the use of dry-cow treatment doubled from 1990 to 1993 and has since 1995 remained relatively unchanged.

Figure AC I. Sales of injectable veterinary antimicrobials with mastitis in bovines as one indication expressed as tonnes active substance, kg active substance/1000 cows or defined daily doses for cows/1000 cows and day (see Table AC V for doses used).

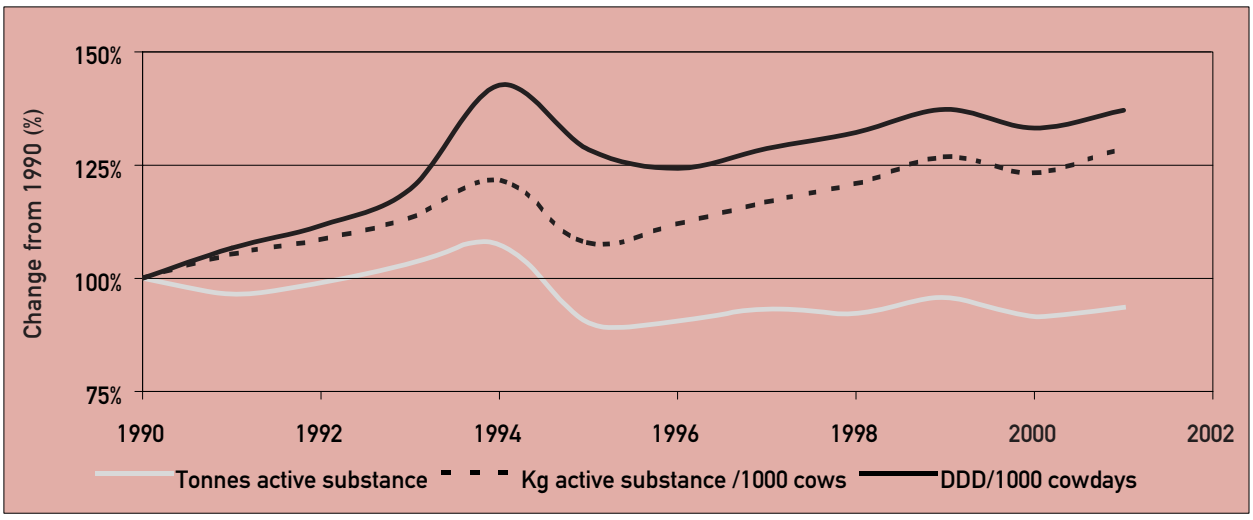

Table AC IV. Antimicrobials for injection with mastitis in bovines as one indication expressed as defined daily doses for cows (DDDcow) per 1000 cows and day (according to Grave *et al.*, 1999). Based on sale statistics from Apoteket AB and animal numbers from Official Statistics Sweden.

ATCvet	Active substance	DDD cow (g)	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001
QJ01A	Oxytetracycline	5	0.5	0.5	0.5	0.5	0.7	0.7	0.6	0.7	0.7	0.8	0.7	0.5
QJ01C	Benzylpenicillin	12.6	0.1	0.1	0.1	0.2	1.9	2.2	1.7	1.5	1.3	1.1	1.0	1.0
QJ01C	Procaine penicillin	15	3.1	3.6	3.6	3.9	2.7	2.0	2.9	3.3	3.6	4.1	4.1	4.5
QJ01C	Penethamte hydroiodide	10	<0.1	–	–	–	–	–	–	–	–	–	–	–
QJ01E	Sulphonamide and trimethoprim	24	0.2	0.2	0.3	0.2	0.3	0.2	0.3	0.3	0.3	0.3	0.2	0.3
QJ01F	Spiramycin	5	0.3	0.3	0.4	0.4	0.8	0.6	0.4	0.3	0.3	0.3	0.2	0.2
QJ01M	Enrofloxacin	1.25	0.3	0.4	0.5	0.6	0.8	0.7	0.5	0.5	0.6	0.5	0.5	0.6
QJ01R	Procaine penicillin +DHS[1]	10	0.9	0.7	0.6	0.5	0.5	0.4	0.3	0.3	0.3	0.3	0.2	0.2
Total			**5.3**	**5.7**	**6.0**	**6.4**	**7.6**	**6.9**	**6.6**	**6.9**	**7.1**	**7.4**	**6.9**	**7.3**

[1] DHS=dihydrostreptomycin

General comments

Overall, no dramatic changes in use of antimicrobials were noted when figures from the years 2000 and 2001 were compared. Data can be split according to types of products. Thereby, information on amounts for medication of individual animals and for groups/flocks of animals (e.g., for mixing in feed or water) can be derived. Over the last five years, the use of antimicrobials intended for treatment of groups or flocks of animals has decreased while the amount of drugs for treatment of individual animals has remained relatively unchanged.

The subset of drugs with mastitis as one (of several) authorised indications has been studied separately. Expressed as kg active substance, the sales of this subset have decreased over the last 10 years. By contrast, when the figures are expressed in a unit that corrects for dose and population changes (daily doses for cows/1000 cows and days), a pronounced increase is apparent. This highlights of the overall need for development of defined units of measurement to facilitate temporal analysis and comparisons between regions or countries.

In the subset of drugs with mastitis as one of the indications discussed above, many of the drugs studied are also used for treatment of other animals, e.g. horses. The incidence of use of antimicrobials for horses is unknown, and no reliable figures on the development of the equine population over time are available. For more precise estimates of treatment incidence, data must be broken down at least by animal species. Unfortunately, the possibilities to do so using current systems are limited. These shortcomings hamper analysis of trends in use and resistance.

Sweden has a long tradition of monitoring use of antimicrobials for animals. Data are followed closely by the stakeholders (e.g. experts, decision makers, practising veterinarians and farmers organisations) and are often subject of debate. However, the responsibility for collecting and analysing the data has never been determined. This situation hampers the development of new or improved systems. Such systems are needed to analyse trend in use and resistance, to identify possible risk factors and to follow compliance with policy recommendations.

Table AC V. Antimicrobials for intramammary use (QJ51) calculated as number of single-dose applicators per 1000 cows and day (DDDcow/1000 cows at risk and day). Based on sale statistics from Apoteket AB.

Indication	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001
For therapy during lactation	1.9	1.9	1.8	1.7	1.8	1.5	1.5	1.5	1.3	1.1	1.1	1.1
For dry cow treatment	0.9	1.1	1.4	2.2	2.4	2.0	2.1	2.0	2.0	1.9	1.8	1.9
Total	**2.9**	**3.0**	**3.1**	**3.9**	**4.2**	**3.5**	**3.5**	**3.5**	**3.3**	**3.0**	**2.9**	**3.0**

Resistance in zoonotic bacteria

Resistance in zoonotic bacteria

The monitoring program encompasses zoonotic bacteria isolated from animals of Swedish origin. This year data on antibacterial susceptibility among *Salmonella enterica* and among *Campylobacter jejuni* and hippurate-negative thermophilic *Campylobacter* spp. are presented. In addition, the National Food Administration has contributed with data on antibacterial susceptibility among *Campylobacter* spp. from food and water and these data are presented here.

Salmonella

Isolates included

Salmonellosis in animals is a notifiable disease in Sweden and confirmation at SVA of at least one isolate from each incident is mandatory. From these isolates, one from each animal species (warm-blooded wild and domesticated) involved in each notified incident were included.
In Sweden, monitoring of antimicrobial susceptibility among *Salmonella* of animal origin has been performed regularly since 1978. Although the antimicrobials included in the test panels have varied, microdilution methods have been used in all these surveys. For comparison, data from previous years are therefore presented together with data for 2001.

Results and comments

A total of 52 isolates were investigated (Table S I). Of these, 31 were *S.* Typhimurium, seven *S.* Dublin, one *S.* Enteritidis and the remaining, 13 isolates, were other serovars. The distributions of MICs of the antimicrobials tested are shown in Table S IIA and S IIB. About half of the isolates (55%) emanated from major food producing animals and the remaining from pets and horses (31%) and wild animals (14%) (Table S I).

Overall, only three isolates (6%) were classified as resistant to any of the antimicrobials tested. These were all *S.* Typhimurium, one isolate each of the phage types 40, 104 and 120.
The DT 40 isolate, from a wild bird, was resistant to nalidixic acid only. The isolates of DT 104 and DT 120 emanated from cats and had similar antibiograms. Both isolates were resistant to seven of the tested antimicrobials (amoxicillin/clavulanic acid, ampicillin, chloramphenicol, florfenicol, streptomycin, sulphamethoxazole and tetracycline).

The occurrence of resistance among *S.* Typhimurium in 2001 and in previous years is shown in Table S III. The proportions of different animal sources vary between the different time periods. The material from the years 1978-88 includes only isolates from cattle. Since then, the proportion of cattle isolates has gradually decreased but isolates from major food producing animals have constituted over 50% of the materials in all years except in 1999 and 2001 (Table S III).

Resistance to most antimicrobials among *S.* Typhimurium has been low and stable over the years. The only apparent trend is a lower prevalence of resistance to streptomycin in isolates from 1999-01 than in isolates from previous years. Since 1997, phage typing (Colindale system) of *S.* Typhimurium is included in the surveys. This has revealed that overall levels of resistance in the material is strongly linked to occurrence of specific multiresistant phage types. In the years 1997-2001, resistance to more than one antimicrobial was found in 18 isolates of *Salmonella enterica* of which 14 were *S.* Typhimurium. Of these latter isolates, nine were DT 104, three DT 193 and one DT 120. The DT 104 isolates, and also the DT 120 isolate, had the typical resistance pattern ampicillin, chloramphenicol, streptomycin, sulphonamides and tetracycline (ACSSuT), some isolates were resistant also to the combination trimethoprim-sulphonamide. The DT 193 isolates had the pattern ampicillin, cephalothin, streptomycin, sulphonamides and tetracycline, some isolates were resistant also to trimethoprim-sulphonamide. Appearance of these phage types, albeit sparse, in the materials greatly influences the incidence of resistance.

Interestingly, of the six DT 120 isolates included in the material since 1997 only one was multiresistant. Three isolates from 2001 (cattle, pig and horse) were susceptible to all antimicrobials tested whereas two isolates from 1997 (dog and horse) were resistant to sulphonamides.

As the material consists of one isolate from each notified incident of *Salmonella* in Sweden, including those detected in food-producing animals in the *Salmonella* control programme, it is thought to be representative for *Salmonella* prevalent in animals in the country. In the light of this, the overall situation of antimicrobial resistance in *Salmonella*, from domesticated as well as from wild animals, is favourable. There is no evident spread of multiresistant clones among domesticated animals within the country, probably a result of the strategies in the Swedish *Salmonella* control programme. Further, of the 19 multiresistant isolates of *Salmonella* enterica found since 1997 only one originated from wild animals.

Table S I. Number of isolates of *Salmonella enterica* tested for antimicrobial susceptibility in 2001 presented by serotype and source of isolate.

Serotype	Phage type	Dog	Horse	Cat	Cattle	Pig	Poultry	Wild birds	Total
S. Typhimurium	1						1	1	**2**
	12						1		**1**
	40			9		5		3	17
	41					1	1	1	**3**
	93							1	**1**
	104			1					**1**
	120		1	1	1	1			**4**
	195							1	**1**
	NT					1			**1**
S. Bovismorbificans		1							**1**
S. Dublin					7				7
S. Enteritidis		1							**1**
S. Livingstone			1	1			4		**6**
S. Mendoza						1			**1**
S. Rissen							1		**1**
S. San-Diego							1		**1**
S. subspecies I					1				**1**
S. species							2		**2**
Total		**2**	**2**	**12**	**9**	**9**	**11**	**7**	**52**
Percent of total		**4%**	**4%**	**23%**	**17%**	**17%**	**21%**	**13%**	

Table S II. Distribution of MICs for *Salmonella enterica* (A) (n=52) and for *Salmonella* Typhimurium (B) (n=31) from animals in 2001.

A *Salmonella enterica*	**Breakpoint resistance** (mg/L)	**% Resistant**	**Distribution (%) of MICs[1]** (mg/L)															
Substance			**≤0.03**	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**	**128**	**256**	**512**	**>512**
Amoxi/Clavulan[2]	>8/4	4						67.3	28.8			3.8						
Ampicillin	>8	4					11.5	55.8	28.8					3.8				
Apramycin	>32	0							1.9	19.2	59.6	19.2						
Ceftiofur	>2	0				9.6	32.7	57.7										
Chloramphenicol	>8	4							15.4	67.3	13.5	3.8						
Enrofloxacin	>0.5	0	1.9	69.2	25.0	3.8												
Florfenicol	>16	4							21.2	63.5	11.5		3.8					
Gentamicin	>8	0					7.7	34.6	50.0	7.7								
Nalidixic acid	>16	2								36.5	50.0	11.5		1.9				
Neomycin	>32	0						17.3	65.4	13.5	1.9	1.9						
Streptomycin	>32	4							1.9	1.9	13.5	48.1	30.8		3.8			
Sulphamethoxazole	>256	4												42.3	40.4	13.5		3.8
Tetracycline	>8	4						21.2	59.6	13.5	1.9			1.9	1.9			
Trimethoprim	>8	0			1.9	17.3	75.0	1.9	1.9	1.9								

B *Salmonella* **Typhimurium**	**Breakpoint resistance** (mg/L)	**% Resistant**	**Distribution (%) of MICs[1]** (mg/L)															
Substance			**≤0.03**	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**	**128**	**256**	**512**	**>512**
Amoxi/Clavulan[2]	>8/4	6						58.1	35.5			6.5						
Ampicillin	>8	6						54.8	38.7					6.5				
Apramycin	>32	0							3.2	6.5	71.0	19.4						
Ceftiofur	>2	0					29.0	71.0										
Chloramphenicol	>8	6							9.7	80.6	3.2	6.5						
Enrofloxacin	>0.5	0		64.5	32.3	3.2												
Florfenicol	>16	6							16.1	77.4			6.5					
Gentamicin	>8	0					3.2	32.3	61.3	3.2								
Nalidixic acid	>16	3								45.2	41.9	9.7		3.2				
Neomycin	>32	0						6.5	83.9	3.2	3.2	3.2						
Streptomycin	>32	6									9.7	58.1	25.8		6.5			
Sulphamethoxazole	>256	6												35.5	35.5	22.6		6.5
Tetracycline	>8	6						12.9	67.7	12.9				3.2	3.2			
Trimethoprim	>8	0			3.2	25.8	64.5	3.2	3.2									

[1] Hatched fields denote range of dilutions tested for each substance. MICs above the range are given as the concentration closest to the range. MICs equal to or lower than the lowest concentration tested are given as the lowest tested concentration; [2]Concentration of amoxicillin given, tested with clavulanic acid in concentration ratio 2/1.

Table S III. Occurrence of resistance to antimicrobials and source of isolates in *Salmonella* Typhimurium from animals 1978 to 2001.

Substance	Breakpoint resistance (mg/L)	Percent resistance							
		1978-86 (n=117)	1987-88[1, 2] (n=8)	1989-92 (n=79)	1993-96 (n=87)	1997-98 (n=50)	1999 (n=101)	2000 (n=46)	2001 (n=31)
Amoxicillin/Clavulanic acid	>8/4	–	–	–	–	–	–	2	6
Ampicillin	>8	2	0	3	8	12	5	2	6
Apramycin	>32	–	–	–	–	–	–	0	0
Ceftiofur	>2	–	–	–	–	–	–	0	0
Cephalothin	>16	–	–	1	0	0	3	–	–
Chloramphenicol	>8	–	4	3	6	12	2	2	6
Enrofloxacin	>0.5	–	–	0	1	0	0	0	0
Florfenicol	>16	–	–	–	–	–	–	2	6
Gentamicin	>16	–	–	0	0	0	0	0	0
Nalidixic acid	>16	–	–	–	–	–	–	4	3
Neomycin	>32	–	0 [3]	0	0	12	0	0	0
Streptomycin	>32	78	78	25	13	20	6	4	6
Tetracycline	>8	14	14	3	7	12	5	2	6
Trimethoprim	>8	–	–	–	–	–	–	0	0
Trimethoprim/Sulphmethoxazole	>0.5/9.5	0	0	1	1	8	3	–	–
Percent of isolates from:									
Cattle, sheep, pigs, poultry		100	100	59	55	56	23	57	39
Horses, cats, dogs		–	–	15	22	16	53	37	38
Wildlife		–	–	26	23	28	24	7	23

[1] Only isolates from cattle; [2] 1988 includes isolates to September, isolates from October-December 1988 given under 1989; [3] Breakpoint for resistance >8 mg/L.

Campylobacter from animals

Infection with *Campylobacter* in animals is not notifiable. The principal reservoirs for *Campylobacter* are birds and mammals, both wild and domesticated. It is difficult to correlate this pathogen to diarrhoeic disease since there is a high carrier rate in clinically healthy animals. In humans in Sweden, *Campylobacter* infection is the major cause of bacterial enteric disease. *Campylobacter jejuni* and *C. coli* are the most important species from a zoonotic point of view (Zoonoses in Sweden, 2001).

Isolates included

Campylobacter were isolated from samples collected at slaughter from healthy animals. In cattle and pigs, intestinal contents (caecum or colon) were sampled and in broiler chickens cloacal swabs. Samples were collected during the years 1999 (pigs), 1999/2000 (cattle) and 2001 (chickens). Antimicrobials included in the test panels and concentration ranges are given in Table Camp II. Breakpoints used are provisional and may be changed during following years. The isolates were identified as *Campylobacter jejuni* and as hippurate-negative thermophilic *Campylobacter*. For details on methodology, including sampling strategy, see Appendix 3.

Results and comments

The material includes 50 isolates from chickens, 67 isolates from cattle and 98 isolates from pigs (Table Camp I). The proportion of isolates of *C. jejuni* and hippurate-negative thermophilic *Campylobacter* spp. varied between the three animal species. *C. jejuni* was the most prevalent species in chickens and cattle and hippurate-negative thermophilic *Campylobacter* in pigs.

All Campylobacter

Levels of antimicrobial resistance among all *Campylobacters* were low with the exception of high levels of resistance to nalidixic acid (28%) and enrofloxacin (28%) among *Campylobacter* isolated from pigs (Table Camp II).

Among cattle isolates, only ampicillin resistance was of appreciable magnitude (6%) and among chicken isolates, nalidixic acid and enrofloxacin resistance, 6 and 4% respectively, were the most prevalent traits.

Cattle

All campylobacter isolates were identified as *C. jejuni* (Table Camp I). The overall resistance in *C. jejuni* recovered from cattle was very low (Table Camp III). Ampicillin resistance was the most prevalent (6%) trait, followed by nalidixic acid (2%) or enrofloxacin (2%).

Chickens

In isolates from chicken, 86% were identified as *C. jejuni* (Table Camp I). Also among these isolates the resistance rates were very low (Table Camp III). The only resistance traits found were nalidixic acid resistance (5%), enrofloxacin resistance (2%) and ampicillin resistance (2%). Seven of 50 isolates were identified as hippurate-negative thermophilic *Campylobacter* and among these, one isolate was resistant to nalidixic acid and enrofloxacin.

Pigs

Seven of 98 isolates from pigs were identified as *C. jejuni*. Among these, one isolate was resistant to erythromycin and one isolate to nalidixic acid. The rest, 91 isolates, were identified as hippurate-negative thermophilic *Campylobacter*, most likely *C. coli.*

Surprisingly, a high proportion of the hippurate-negative thermophilic *Campylobacter* spp. were resistant to nalidixic acid (30%) and enrofloxacin (30%) (Table Camp IV). Resistance rates to other antimicrobial agents were very low. The only resistance traits found were erythromycin resistance (2%) and tetracycline resistance (2%). To exclude the possibility that these resistant strains were *C. lari*, considered to be inherently resistant to nalidixic acid, an additional test with indoxyl acetate was performed. All isolates were indoxyl acetate positive and obviously not *C. lari.*

Table Camp I. Prevalence of campylobacter in samples of intestinal content from cattle, 1999/2000, pigs, 1999 and in cloacal swabs from chicken, 2001.

Animal species	Number tested for antimicrobial resistance	*Campylobacter* species isolated. Number of isolates and percent of total isolates in brackets.	
		C. jejuni	Hippurate-negative *Campylobacter* spp.
Cattle	67	67 (100%)	0 (0%)
Pigs	98	7 (7%)	91 (95%)
Chickens	50	43 (86%)	7 (14%)

Table Camp II. Occurence of recistance (%) among isolates of *Campylobacter* spp. from cattle, 1999/2000, pigs, 1999 and chickens, 2001.

Substance	Range tested (mg/L)	Breakpoint resistance mg/L	Percent resistant		
			Cattle n=67	Pigs n=98	Chickens n=50
Ampicillin	0.5-64	>16	6	0	2
Enrofloxacin	0.03-4	>1	2	28	4
Erythromycin	0.12-16	>16	0	2	0
Gentamicin	0.25-8	>8	0	0	0
Nalidixic acid	1-128	>16	2	28	6
Tetracycline	0.25-32	>8	0	2	0

Table Camp III. Distribution of MICs for *Campylobacter jejuni* from cattle (n=67), 1999/2000 and chickens (n=43), 2001.

Substance	Breakpoint resistance (mg/L)	Animal species	Percent resistant	Distribution (%) of MICs[1] (mg/L)													
				≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Ampicillin	>16	Cattle	6					7.5	4.5	38.8	40.3	3.0		1.5	4.5		
		Chickens	2					2.3	11.6	46.5	30.2	7.0				2.3	
Enrofloxacin	>1	Cattle	2	3.0	22.4	61.2	11.9				1.5						
		Chickens	2		51.2	44.2			2.3			2.3					
Erythromycin	>16	Cattle	0			3.0	7.5	34.3	34.3	19.4	1.5						
		Chickens	0			2.3	14.0	62.8	16.3	4.7							
Gentamicin	>8	Cattle	0				1.5	25.4	70.1	3.0							
		Chickens	0					67.4	27.9	4.7							
Nalidixic acid	>16	Cattle	2						1.5	22.4	52.2	19.4	3.0			1.5	
		Chickens	5							23.3	72.1						4.7
Tetracycline	>8	Cattle	0				94.0	6.0									
		Chickens	0				95.3		2.3	2.3							

[1] Hatched fields denote range of dilutions tested for each substance. MICs above the range are given as the concentration closest to the range. MICs equal to or lower than the lowest concentration tested are given as the lowest tested concentration.

Table Camp IV. Distribution of MICs for hippurate-negative thermophilic *Campylobacter* spp. from pigs (n=91), 1999.

Substance	Breakpoint resistance (mg/L)	Animal species	Percent resistant	Distribution (%) of MICs[1] (mg/L)													
				≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Ampicillin	>16	Pigs	0					1.1	8.8	18.7	45.1	25.3	1.1				
Enrofloxacin	>1	Pigs	30	1.1	40.7	19.8	8.8			5.5	15.4	8.8					
Erythromycin	>16	Pigs	1					5.5	13.2	28.6	38.5	13.2		1.1			
Gentamicin	>8	Pigs	0					1.1	39.6	59.3							
Nalidixic acid	>16	Pigs	30							2.2	27.5	34.1	6.6		7.7	18.7	3.3
Tetracycline	>8	Pigs	2				56.0	20.9	15.4	3.3	2.2		1.1		1.1		

[1] Hatched fields denote range of dilutions tested for each substance. MICs above the range are given as the concentration closest to the range. MICs equal to or lower than the lowest concentration tested are given as the lowest tested concentration.

Campylobacter from food and water

Isolates included

Isolates from food and water originate from a study on the prevalence of *Campylobacter* in meat and raw water by the National Food Administration under the year 2000. Food samples positive for *Campylobacter* emanated from retail sales (70%), restaurant (20%), and meat plants (10%). Water samples positive for *Campylobacter* emanated from raw water (incoming water at a water plant). The isolates were classified to species level by PCR. For details on methodology, see Appendix 3. Antimicrobials included in the test panels and concentration ranges used are given in Table Camp V. Breakpoints used are provisional and may be changed during following years.

Results and comments

The 93 isolates originated from meat from chicken (n=63), duck (n=1), turkey (n=4), pork (n=4), lamb (n=2), and from raw water (n=19). Eleven of the 74 isolates from food originated from imported meat. Of the 74 isolates from meat, 71 were identified as *C. jejuni* and three as *C. coli*. Of the isolates from raw water, nine were *C. jejuni* and ten *C. coli*. The distribution of MICs among *Campylobacter* spp. from food and raw water is shown in Table Camp V.

Food

Overall, 12 isolates (16%) were classified as resistant to at least one of the antimicrobials tested. Five *C. jejuni* and one *C. coli* isolate were resistant to both enrofloxacin and nalidixic acid. Five of these isolates originated from Swedish chicken meat. The sixth isolate (*C. jejuni*), originating from imported chicken meat, was in addition resistant to ampicillin and tetracycline. Besides the multiresistant isolate, one isolate from Swedish chicken meat and two from imported chicken meat were resistant to ampicillin.
One isolate resistant to erythromycin was a *C. coli* from Swedish pork. Two isolates of *C. jejuni* from Swedish chicken meat and pork were exclusively resistant to nalidixic acid.

Water

Only two isolates from raw water mediated any resistance traits, namely nalidixic acid and tetracycline, respectively.

General comments

In wild and domesticated animals, *Campylobacter* is carried in the intestinal tract and can during the slaughter process contaminate food products. The predominant species in chickens and cattle is *C. jejuni* and in pigs *C. coli*. The species most commonly isolated from humans is *C. jejuni*.

In Sweden, the erythromycin resistance figures are very low. Erythromycin resistance was not found in any of the *Campylobacter* isolated from chickens and cattle and in only 2% of the isolates from pigs. These are very low figures in an international perspective [Antimicrobial Feed Additives (SOU 1997:132) also accessible at http://jordbruk.regeringen.se]. Nalidixic acid and enrofloxacin resistance was very low in *Campylobacter* isolates from chickens and cattle, but resistance rates in *Campylobacter* spp. isolated from pigs were surprisingly high.
These figures (30%, respectively) are difficult to explain since no fluoroquinolones are authorised for group treatment of pigs in Sweden. For comparison it can be mentioned that the prevalence of quinolone resistance in indicator *E. coli* and clinical isolates is low (see Resistance in indicator bacteria and Resistance in animal pathogens).

In this year's SVARM, isolates from food and water are included. Overall, the resistance figures are very low. The most prevalent resistance trait found in samples from meat was nalidixic acid resistance (11%) and only 1% was resistant to erythromycin.

Table Camp V. Distribution of MICs for *Campylobacter* spp. from food (n=74) and raw water (n=19), 2000.

Substance	Breakpoint resistance (mg/L)	Animal species	Percent resistant	Distribution (%) of MICs[1] (mg/L)												
				≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Ampicillin	>16	Food	6					6.8	8.1	12.2	47.3	16.2	4.1	1.4	2.7	1.4	
		Raw water	0					26.3	15.8	26.3	31.6						
Enrofloxacin	>1	Food	8		9.5	70.3	10.8		1.4		1.4	6.8					
		Raw water	0		36.8	58.1		5.3									
Erythromycin	>16	Food	1			1.4	9.5	40.5	28.4	20.3				1.4			
		Raw water	0			5.3	10.5	58.1	10.5	15.8							
Gentamicin	>8	Food	0					17.6	73.0	8.1	1.4						
		Raw water	0					36.8	42.1	21.1							
Nalidixic acid	>16	Food	11							5.4	59.5	20.3	4.1			2.7	8.1
		Raw water	5							21.1	68.4	5.3			5.3		
Tetracycline	>8	Food	1				63.5	21.6	6.8	1.4		5.4			1.4		
		Raw water	5				47.4	36.8	10.2					5.3			

[1] Hatched fields denote range of dilutions tested for each substance. MICs above the range are given as the concentration closest to the range. MICs equal to or lower than the lowest concentration tested are given as the lowest tested concentration.

Resistance in indicator bacteria

Resistance in indicator bacteria

The prevalence of acquired resistance to antimicrobials among bacteria of the normal enteric microflora can serve as an indicator of the selective pressure exerted by use of antimicrobial agents in exposed populations. Although these bacteria are unlikely to cause diseases, they form a reservoir of transferable resistance determinants from which resistance genes can spread to bacteria responsible for infections in animals or humans. Thus, surveillance of resistance among indicator bacteria in the normal enteric microbiota can be of great value to detect trends and to follow the effects of interventions.

In SVARM, *Escherichia coli* and *Enterococcus* spp. serve as indicator bacteria. In year 2001, isolates from fattening pigs and from broiler chickens are included in the monitoring programme. In addition, data for isolates from wild boars are presented as a reference to populations of bacteria not exposed to the selective pressure of antimicrobial use.

Of special interest in monitoring antimicrobial susceptibility among indicator bacteria is the occurrence of specific patterns of resistance. Such patterns, or phenotypes, can indicate that resistance genes are located on the same genetic element. The danger of such elements is evident as a single transfer event conveys resistance to several antimicrobials to the recipient bacterium (co-transfer). Thereby, use of one antimicrobial can select for resistance to other unrelated antimicrobials (co-selection). In SVARM 2001, analyses of associations between resistance to different antimicrobials were performed on the combined data for years 2000 and 2001. The Chi-Square test was used for statistical inference regarding linked resistance and for analysis of differences in occurrence of resistance between year 2000 and 2001.

Isolates included

Escherichia coli and *Enterococcus* spp. were isolated from intestinal content (ceacum or colon) from healthy pigs and broiler chickens sampled at slaughter. Each isolate from pigs originates from a unique herd and each isolate from chickens from a unique flock but not nessecarily from a unique herd. Antimicrobials included in the test panels and concentration ranges used are given in Table EC III and ENT II. For details on methodology, including sampling strategy, see Appendix 3.

The same methodology was used to isolate *E. coli* and *Enterococcus* spp. in faeces from wild boars shot in the wild. Faecal samples were collected by hunters in 15 different geographical regions in southern Sweden.

Escherichia coli

Results and comments

The material includes 308 isolates of *E. coli* from pigs, 87 from wild boars and 296 from chickens (Table EC I). Isolates were obtained from about 85% of the samples from pigs and chickens, a similar isolation frequency as in last year's survey (SVARM 2000). In faecal samples from wild boars the isolation frequency was slightly higher.

Pigs

Resistance levels were low and of the same magnitude as in year 2000 (Table EC III). Resistance to sulphonamides, streptomycin, or tetracycline were the most common traits (8-10%). Lower levels, 2-3%, were found for resistance to amoxicillin/clavulanic acid, ampicillin, chloramphenicol or trimethoprim. Only occasional isolates, about 1%, were resistant to enrofloxacin or nalidixic acid. As in year 2000, 10 percent of the isolates were resistant to more than one antimicrobial, with eight substances represented in the patterns (Table EC IV).

The most prevalent resistance phenotype, resistant to three or more antimicrobials, was the combination sulphonamides-ampicillin-chloramphenicol, which was found in six isolates (Table EC IV). Two of these isolates were also resistant to trimethoprim and one isolate to streptomycin. The most prevalent phenotype year 2000, streptomycin-sulphonamides-ampicillin, was found in five isolates in this year's survey.

In the combined data for year 2000 and 2001 there is a statistically significant association between resistance to sulphonamides and streptomycin ($p<0.001$) (Table EC II). This agrees with the common occurrence of linked resistance genes to these two antimicrobials (Sundin and Bender, 1996).

Table EC II. Cross tabulation of succeptibility to sulphonamides and streptomycin in *E. coli* isolated from pigs years 2000 and 2001 (n=568).

		Sulphonamides	
		Resistant	Sensitive
Streptomycin	Resistant	30	33
	Sensitive	18	487

Table EC I. Prevalence of *Escherichia coli* in samples of intestinal content from pigs and chickens and in faecal samples from wild boars, 2001.

Animal species	Number of samples cultured	Percent positive cultures	Number of isolates tested for antimicrobial susceptibility
Pigs	364	85	308
Wild boars	94	93	87
Chickens	354	84	296

Notably, of the 14 isolates resistant to ampicillin in years 2000 and 2001, 13 were also resistant to streptomycin, sulphonamides, tetracycline or trimethoprim. The latter drugs are used as therapeutics in Swedish pig production whereas ampicillin is used to a limited extent only. Thus, the occurrence of ampicillin resistance might be influenced by co-selection. Likewise, resistance to chloramphenicol appears to be associated with sulphonamide resistance as all eight isolates resistant to chloramphenicol were also resistant to sulphonamides.

Wild boars

Occurrence of resistance among isolates from wild boars was rare (Table EC III). Only seven isolates (8%) were resistant to any of the tested antimicrobials. One of these isolates was multiresistant with amoxicillin/clavulanic acid, ampicillin, streptomycin, sulphonamides and trimethoprim included in the resistance pattern.

Chickens

Resistance levels were low and of the same magnitude as in year 2000 (Table EC III). Sulphonamide resistance was the most common trait (12%). Resistance to amoxicillin/clavulanic acid, ampicillin, tetracycline, nalidixic acid or streptomycin was less common (2-4%) and only occasional isolates were resistant to enrofloxacin, gentamicin, neomycin or trimethoprim. Fourteen isolates (5%) were resistant to more than one antimicrobial with seven of the tested substances represented in the patterns (Table EC IV). Prevalence of isolates resistant to more than one antimicrobial was lower than in year 2000 (9%).

Only six isolates (2%) were resistant to three or more of the antimicrobials tested. Three of these isolates were resistant to sulphonamide-trimethoprim-tetracycline, of which two were resistant also to nalidixic acid. The most prevalent resistance phenotype year 2000, streptomycin-sulphonamide-tetracycline, was not found in 2001.

It is notable that eight of the 21 isolates resistant to ampicillin in the combined data for years 2000 and 2001were resistant also to sulphonamides. Sulphonamides are used, albeit sparingly, in chicken production to treat outbreaks of coccidiosis.

General comments

Overall, the figures for 2001 are low in an international perspective and of similar magnitude in isolates from pigs and chickens. There are no significant differences in occurrence of resistance in relation to the results from year 2000. In isolates from both animal species, resistance to sulphonamides is the most common trait. Sulphonamides are used as therapeutics in pigs and most sparingly in chickens. Occurrence of resistance to other antimicrobials can generally also be linked to use of the substance in the respective animal species.

Resistance to chloramphenicol in isolates from pigs and ampicillin resistance in isolates from chickens can however not be linked to therapeutic use. In the combined data for years 2000 and 2001 there are indications of associations between resistance to these substances and resistance to other antimicrobials used therapeutically. This implies that co-selection of resistance might occur.

Occurrence of occasional resistant isolates in samples from wild boars, might indicate a transmission of resistance traits between animal species. As there is no selection pressure in the population of wild boars, the traits are not amplified and, as expected, resistance was rare.

Table EC III. Occurrence of resistance (%) among isolates of *Escherichia coli* from pigs, wild boars and chickens, 2001. Data for 2000 are presented for comparison (SVARM 2000).

Substance	**Range tested** (mg/L)	**Breakpoint** (mg/L)	**Percent resistant** 95% confidence interval inside brackets				
			Pigs		**Wild boars**	**Chickens**	
			2000 n=260	**2001** n = 308	**2001** n = 87	**2000** n=274	**2001** n=296
Amoxicillin/Clavulanic acid[1]	2-16	>8	3 (1.3-6.0)	3 (1.6-5.9)	1 (0.0-6.2)	5 (2.6-8.0)	3 (1.2-5.3)
Ampicillin	0.25-32	>8	3 (1.3-6.0)	3 (1.6-5.9)	1 (0.0-6.2)	5 (2.6-8.0)	3 (1.2-5.3)
Apramycin	0.25-32	>32	0 (0.0-1.4)	0 (0.0-1.2)	0 (0.0-4.2)	0 (0.0-1.3)	0 (0.0-1.2)
Ceftiofur	0.25-2	>2	0 (0.0-1.4)	0 (0.0-1.2)	0 (0.0-4.2)	0 (0.0-1.3)	0 (0.0-1.2)
Chloramphenicol	2-16	>8	<1 (0.0-2.1)	2 (0.9-4.6)	1 (0.0-6.2)	<1 (0.1-2.6)	0 (0.0-1.2)
Enrofloxacin	0.03-4	>0.5	0 (0.0-1.4)	<1 (0.0-1.8)	0 (0.0-4.2)	2 (0.4-3.7)	<1 (0.0-1.9)
Florfenicol	2-16	>16	0 (0.0-1.4)	0 (0.0-1.2)	0 (0.0-4.2)	0 (0.0-1.3)	0 (0.0-1.2)
Gentamicin	0.25-32	>8	<1 (0.0-2.1)	0 (0.0-1.2)	0 (0.0-4.2)	<1 (0.0-2.0)	<1 (0.0-1.9)
Nalidixic acid	1-128	>16	0 (0.0-1.4)	<1 (0.0-1.8)	1 (0.0-6.2)	4 (2.3-7.5)	2 (0.6-3.9)
Neomycin	1-128	>32	1 (0.2-3.3)	0 (0.0-1.2)	1 (0.0-2.6)	<1 (0.1-2.6)	<1 (0.0-1.9)
Streptomycin	2-256	>32	13 (9.2-17.8)	9 (6.4-13.2)	2 (0.3-8.1)	4 (2.3-7.5)	2 (1.0-4.8)
Sulphametoxazole	64-512	>256	7 (4.2-10.7)	10 (6.7-13.6)	2 (0.3-8.1)	12 (8.1-16.0)	12 (8.1-16.1)
Tetracycline	0.5-64	>8	7 (4.2-10.7)	8 (5.6-12.1)	2 (0.3-8.1)	8 (4.8-11.5)	4 (2.7-7.4)
Trimethoprim	0.12-16	>8	5 (2.4-7.9)	2 (0.9-4.6)	1 (0.0-6.2)	<1 (0.1-2.6)	1 (0.2-2.9)

[1] Concentration of amoxicillin given, tested with clavulanic acid in concentration ratio 2/1 (amoxicillin/clavulanic acid).

Table EC IV. Number of isolates of *Escherichia coli* resistant to two or more antimicrobials, presented by animal species and resistance phenotype, 2001. "R" in hatched fields indicates resistance. Data for 2000 are presented for comparison (SVARM 2000).

Pigs		Chickens		Resistance pattern[1]									
2000 n = 260	**2001** n = 308	**2000** n = 274	**2001** n = 296	**Sm**	**Su**	**Am[2]**	**Tr**	**Tc**	**Cm**	**Nm**	**Ef**	**Nal**	**Gm**
1		1		R	R	R	R	R		R			
1	1			R	R	R	R	R					
3	1			R	R	R	R						
1				R	R	R		R		R			
	1	1		R	R	R			R				
	2			R	R	R							
		1		R	R			R	R		R	R	
		1		R	R			R		R		R	
2	1			R	R		R						
1	3	1		R	R			R					
1				R	R				R				
			1	R	R					R		R	
3	8	3	3	R	R								
1				R			R						
1				R			R			R			
7	4	1		R				R					
		1		R				R				R	
	2				R	R	R		R				
	3				R	R			R				
		2	4		R	R							
			1		R		R	R					
			2		R		R	R				R	
1	1	1			R		R						
		1			R			R					R
		1	2		R			R				R	
1	1	6	1		R			R					
	1				R				R				
1						R	R						
		1						R				R	
	1	3									R	R	

Total

25 (10%)	30 (10%)	25 (9%)	14 (5%)

[1] Sm: streptomycin; Su: sulphonamides; Am: ampicillin; Tr: trimethoprim; Tc: tetracycline; Cm: chloramphenicol; Nm: neomycin; Ef: enrofloxacin; Nal: nalidixic acid; Gm: gentamicin; [2] Denote resistance also against amoxicillin/clavulanic acid.

Table EC V. Distribution of MICs for *Escherichia coli* from pigs (n=308), wild boars (n=87) and chickens (n=296), 2001.

Substance	Breakpoint resistance (mg/L)	Animal species	Percent resistant	Distribution (%) of MICs[1] (mg/L)															
				≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	>512
Amoxicillin/ Clavulanic acid[2]	>8	Pig	3							9.4	72.4	14.9		3.2					
		Wild boar	1							8.0	63.2	27.6		1.1					
		Chicken	3							9.5	73.6	14.2	0.3	2.4					
Ampicillin	>8	Pig	3					0.6	6.5	39.9	49.4	0.3			3.2				
		Wild boar	1						5.7	58.6	33.3	1.1			1.1				
		Chicken	3					0.3	5.7	47.6	43.2	0.3			2.7				
Apramycin	>32	Pig	<1								3.2	41.2	44.5	11.0					
		Wild boar	0							1.1	1.1	32.2	55.2	10.3					
		Chicken	0						0.3		0.7	29.7	59.1	10.1					
Ceftiofur	>2	Pig	0				31.5	65.6	2.9										
		Wild boar	0				14.9	78.2	6.9										
		Chicken	0				16.9	72.0	11.1										
Chloramphenic.	>8	Pig	3							2.9	69.5	25.3	0.6						
		Wild boar	1								71.3	27.6	1.1						
		Chicken	0							1.7	64.2	34.1							
Enrofloxacin	>0.5	Pig	<1	36.0	62.3	1.3			0.3										
		Wild boar	0	29.9	67.8	2.3													
		Chickens	<1	33.4	63.5	1.0	1.0	0.7			0.3								
Florfenicol	>16	Pig	<1							1.6	61.7	35.7	1.0						
		Wild boar	0								43.7	52.9	3.4						
		Chicken	0							1.4	49.0	49.0	0.7						
Gentamicin	>8	Pig	0					0.6	17.2	51.6	28.2	2.3							
		Wild boar	0					1.1	47.1	44.8	6.9								
		Chicken	<1					0.3	16.6	50.7	27.7	4.4	0.3						
Nalidixic acid	>16	Pig	<1							7.5	51.3	39.3	1.6				0.3		
		Wild boar	1							8.0	77.0	13.8		1.1					
		Chicken	2							8.4	52.0	36.1	1.7			0.7	1.0		
Neomycin	>32	Pig	0						3.9	53.6	36.7	5.5		0.3					
		Wild boar	1						2.3	66.7	26.4	3.4				1.1			
		Chicken	<1						1.4	51.7	40.9	5.7			0.3				
Streptomycin	>32	Pig	9								6.2	49.0	31.2	4.2	2.3	1.9	2.6	2.6	
		Wild boar	2									48.3	49.4			1.1	1.1		
		Chicken	2								2.0	56.4	35.8	3.4	1.0		0.7	0.7	
Sulphametoxazole	>256	Pig	10												61.0	28.9	0.3		9.7
		Wild boar	2												35.6	62.1			2.3
		Chicken	12												64.2	23.0	1.0		11.8
Tetracycline	>8	Pig	8						23.4	60.7	7.5		0.3	0.6	1.9	5.5			
		Wild boar	2						20.7	69.0	8.0					2.3			
		Chicken	4						22.3	62.8	10.1	0.3	0.3			4.1			
Trimethoprim	>8	Pig	2			2.3	18.2	62.7	13.3	0.3	0.3	0.6		2.3					
		Wild boar	1			1.1	9.2	59.8	26.4	2.3				1.1					
		Chicken	1			1.7	20.6	59.5	15.9	1.0	0.3			1.0					

[1] Hatched fields denote range of dilutions tested for each substance. MICs above the range are given as the concentration closest to the range. MICs equal to or lower than the lowest concentration tested are given as the lowest tested concentration; [2] Concentration of amoxicillin given, tested with clavulanic acid in concentration ratio 2/1 (amoxicillin/clavulanic acid).

Enterococci

Results and comments

The material includes 279 isolates from pigs, 90 from wild boars and 302 from chickens (Table ENT I). Enterococci were more prevalent in samples from chickens and wild boars than from pigs. Isolation frequencies in samples from pigs and chickens were roughly equal to those in year 2000.

The proportion of isolates of *E. faecalis*, *E. faecium* or *E. hirae* varied between the three animal species (Table ENT I). *E. faecium* was predominant in chickens as in year 2000. *E. faecium* was also the most prevalent species isolated in samples from pigs and wild boars but not as dominating as in chickens. In last year's survey, *E. hirae* was the most common species (44%) isolated in samples from pigs.

Other species of enterococci isolated were *E. mundtii* (9%), *E. durans* (5%) and *E. gallinarum* (1%) in pigs and *E. mundtii* (3%) and *E. durans* (2%) in chickens. In wild boars, *E. durans* (19%) and *E. mundtii* (13%) constituted about one third of the isolates. About three percent of the isolates could not be assigned to species of enterococci.

All enterococci

Overall, levels of antimicrobial resistance in enterococci were lower among isolates from pigs than among isolates from chickens and rare in isolates from wild boars (Table ENT II). Levels of resistance in isolates from pigs and chickens are similar to those reported in year 2000.

Resistance to tetracycline (22%) or erythromycin (12%) were the most prevalent traits among isolates from pigs. Also in isolates from wild boars tetracycline resistance was common (22%). In isolates from chickens, resistance to narasin was the most common trait (75%) but levels of resistance to tetracycline, bacitracin or erythromycin were also relatively high (16-31%). It should be observed that flavomycin and virginiamycin are not included in the overall comparison as the inherent susceptibility to these substances differs between species of enterococci.

No isolate obtained from direct culture was resistant to vancomycin. However, all samples were also cultured in enrichment-broth containing vancomycin. From these cultures 24 vancomycin resistant isolates (VRE) were obtained. The isolates were from chickens emanating from 14 different breeders. All isolates were *E. faecium*, had MICs >128 mg/L for vancomycin and carried the *vanA* gene-cluster. The isolates were resistant to narasin and to erythromycin. However, only one isolate had high-level erythromycin resistance (MIC >32 mg/L).

Similar patterns on biochemical typing using the PhenePlate™ system indicate that the isolates belong to a single clone (see Appendix 3 for details). In last year's survey, two isolates of VRE were found using the same sampling and culture procedures. The isolates from year 2000 also emanated from chickens but had different biochemical patterns compared to the isolates from 2001.

Table ENT I. Prevalence of enterococci in samples of intestinal content from pigs and chickens and in faecal samples from wild boars, 2001. Species not identified as *E. faecalis*, *E. faecium* or *E. hirae* are given as "other species".

Animal species	Number of samples cultured	Percent positive cultures	Number of isolates tested for antimicrobial susceptibility	*Enterococcus* species isolated. Number of isolates and percent of total isolates in brackets.			
				E. faecalis	*E. faecium*	*E. hirae*	Other species
Pigs	470	59%	279	52 (19%)	106 (38%)	77 (28%)	44 (16%)
Wild boars	96	94%	90	12 (13%)	35 (39%)	9 (10%)	34 (38%)
Chickens	324	93%	302	49 (16%)	204 (68%)	27 (9 %)	22 (7%)

Table ENT II. Occurrence of resistance (%) among isolates of *Enterococcus* spp. from pigs, wild boars and chickens, 2001. Data for 2000 are presented for comparison (SVARM 2000).

Substance	Range tested (mg/L)	Breakpoint resistance (mg/L)	Percent resistant 95% confidence interval inside brackets							
			Pigs				Wild boars		Chickens	
			2000 n=241		2001 n=308		2001 n=90		2000 n=261		2001 n=302	
Ampicillin	0.25-32	>8	<1	(0.0-2.6)	<1	(0.1-2.6)	0	(0.0-4.0)	0	(0.0-1.4)	<1	(0.0-1.8)
Avilamycin	0.5-32	>8	<1	(0.1-3.0	1	(0.0-2.0)	0	(0.0-4.0)	0	(0.0-1.4)	<1	(0.0-1.8)
Bacitracin[1]	0.5-32	>32	2	(0.5-4.7)	1	(0.2-3.1)	2	(0.3-7.8)	20	(14.9-24.9)	16	(12.3-20.9)
Erythromycin	0.25-32	>4	11	(8.1-17.3)	12	(8.0-15.8)	3	(0.7-9.4)	19	(14.6-24.5)	21	(16.1-25.5)
Flavomycin	2-128	>32	NR[2]		NR[2]		NR[2]		NR[2]		NR[2]	
Gentamicin	0.5-32, 512	>512	0	(0.0-1.7)	1	(0.2-3.1)	0	(0.0-4.0)	0	(0.0-1.4)	0	(0.0-1.2)
Narasin	0.12-16	>2	2	(0.5-4.7)	3	(1.3-5.6)	1	(0.0-6.0)	72	(65.8-77.0)	75	(69.6-79.6)
Neomycin	2-128, 1024	>1024	3	(1.0-6.0)	2	(0.6-4.1)	0	(0.0-4.0)	0	(0.0-1.4)	0	(0.0-1.2)
Streptomycin	2-128, 1024	>1024	4	(2.3-8.4)	7	(3.9-10.0)	0	(0.0-4.0)	2	(0.9-4.9)	<1	(0.1-2.4)
Tetracycline	0.25-32	>82	7	(23.9-36.5)	22	(17.5-27.6)	22	(14.1-32.2)	37	(30.9-43.0)	31	(25.6-36.3)
Vancomycin	1-128	>16	0	(0.0-1.7)	0	(0.0-1.3)	0	(0.0-4.0)	0	(0.0-1.4)	0	(0.0-1.2)
Virginiamycin	0.5-64	>8	NR[2]		NR[2]		NR[2]		NR[2]		NR[2]	

[1] MIC in U/mL; [2] Not relevant as susceptibility in some species of *Enterococcus* is inherently low.

Pigs

Among *E. faecalis,* resistance to tetracycline, erythromycin or streptomycin were the most common traits, 63, 27 and 25% respectively (Table ENT VI). Prevalence of resistance was lower among *E. faecium* and *E. hirae* although tetracycline resistance occurred in 7-10% of the isolates. Erythromycin resistance, the most common trait in E. faecium (11%), was not found among *E. hirae*. Notably, only three of the 12 *E. faecium* isolates resistant to erythromycin had high-level resistance (MICs >32 mg/L). In contrast, all 14 erythromycin resistant *E. faecalis* had high-level resistance (Table ENT X and XI). Although occurrence of resistance to single antimicrobials differs numerically between year 2001 and 2000 no statistically significant differences were found for any of the species of enterococci tested.

Resistance to more than one antimicrobial occurred in 17 *E. faecalis* (33%) and in seven *E. faecium* (7%) isolates (Table ENT VIII and IX). In *E. faecalis* eight and in *E. faecium* seven antimicrobials were represented in the resistance patterns. The most prevalent *E. faecalis* phenotype, with resistance to three or more antimicrobials, was tetracycline-erythromycin-streptomycin, which was found in four isolates. Two of these were also resistant to neomycin and one to narasin. The most prevalent resistance phenotype year 2000, erythromycin-streptomycin-neomycin, was found in two isolates in year 2001. Among *E. faecium* three of the seven isolates were of these two phenotypes.

Table ENT III. Cross tabulation of succeptibility to erythromycin and tetracycline in *E. faecalis* isolated from pigs years 2000 and 2001 (n=108).

		Tetracycline	
		Resistant	Sensitive
Erythromycin	Resistant	29	5
	Sensitive	42	32

Notably, of the 34 isolates of *E. faecalis* resistant to erythromycin in the combined data for year 2000 and 2001, 29 were resistant to tetracycline (Table ENT III). The association is statistically significant (p=0.004) and indicates a linkage of resistance genes and possibilities for co-selection of resistance to these drugs in *E. faecalis* in pigs.

Wild boars

Among *E. faecalis* and *E. hirae*, only resistance to tetracycline was found (Table ENT VI). Nine of the 12 E. faecalis isolates tested were resistant to this antimicrobial. Interestingly eight of these isolates emanated from wild boars shot in the same geographical region. Tetracycline resistance was the most prevalent trait also among *E. faecium* and in addition erythromycin or bacitracin resistance occurred in occasional isolates. Resistance to more than one antimicrobial occurred in only one *E. faecium* isolate resistant to both tetracycline and bacitracin.

Chickens

Resistance to narasin was the most prevalent trait occurring in 80-90% of *E. faecium* and *E. hirae* and in 45% of *E. faecalis* isolates (Table ENT IV). The high levels of resistance probably reflect the use of narasin as a coccidiostat in chicken production. Erythromycin resistance was also frequent in all three species of enterococci (15-41%) and resistance to tetracycline or bacitracin was common among *E. faecium* and *E. faecalis* (15-67%).

Levels of resistance were of similar magnitude as in year 2000 with two exceptions. In year 2001 occurrence of resistance to tetracycline in *E. faecium* was lower (p=0.023), whereas occurrence of resistance to virginiamycin among *E. hirae* was higher (p=0.001) than in year 2000. Conclusions on trends in occurrence of resistance should however be made from observations over a longer period of time. The observed differences might be explained by the general issue of mass-significance and must be interpreted with caution.

Table ENT IV. Cross tabulation of susceptibility to erythromycin versus narasin, erythromycin versus bacitracin and bacitracin versus tetracycline in *E. faecalis* isolated from chickens years 2000 and 2001 (n=96).

		Narasin	
		Resistant	Sensitive
Erythromycin	Resistant	24	10
	Sensitive	18	44

		Bacitracin	
		Resistant	Sensitive
Erythromycin	Resistant	18	16
	Sensitive	8	54

		Bacitracin	
		Resistant	Sensitive
Tetracycline	Resistant	24	37
	Sensitive	2	33

Table ENT V. Cross tabulation of susceptibility to to bacitracin versus narasin, for virginiamycin versus narasin and for virginiamycin versus tetracycline in *E. faecium* isolated from chickens years 2000 and 2001 (n=355).

		Narasin	
		Resistant	Sensitive
Bacitracin	Resistant	55	5
	Sensitive	228	67

		Narasin	
		Resistant	Sensitive
Virginiamycin	Resistant	32	2
	Sensitive	251	70

		Tetracycline	
		Resistant	Sensitive
Virginiamycin	Resistant	18	16
	Sensitive	93	228

Resistance to more than one antimicrobial occurred in 28 isolates of *E. faecalis* (57%) and in 96 *E. faecium* isolates (48%) (Table ENT VII and IX). In the resistance patterns of *E. faecalis* the same six antimicrobials as in year 2000 were represented. The most prevalent resistance phenotype, tetracycline-erythromycin-narasin, was found in 11 isolates. This was also the most common phenotype in *E. faecalis* year 2000. In *E. faecium*, six of the tested substances were represented in the resistance patterns. The most prevalent phenotype, tetracycline-narasin-bacitracin, was found in 10 isolates. This was also the most common phenotype in year 2000.

Notably, of the 34 *E. faecalis* isolates resistant to erythromycin in the combined data for years 2000 and 2001, 32 were resistant also to other antimicrobials. The association between resistance to erythromycin and narasin is statistically significant ($p<0.001$) as is the association between resistance to erythromycin and bacitracin ($p<0.001$) and between tetracycline and bacitracin ($p<0.001$) (Table ENT IV). Notably, all the 19 isolates with high-level resistance for erythromycin (MIC >32 mg/L) were narasin resistant.

There are also statistically significant associations between resistance to different antimicrobials in *E. faecium* in the combined data for years 2000 and 2001 (Table ENT V). Hence, resistance to bacitracin ($p=0.012$) or virginiamycin ($p=0.028$) appears to be associated with narasin resistance. Moreover, resistance to virginiamycin appears to be associated with tetracycline resistance ($p=0.004$).

The results indicate that selection of resistance to substances not used in chicken production (bacitracin and virginiamycin) or used in small amounts only (tetracycline and macrolides) might occur in enterococci in chickens. Possibly the use of narasin as coccidiostat co-selects for resistance to other substances.

General comments

Overall, levels of antimicrobial resistance are low in an international perspective and with few exceptions similar to levels for year 2000. Generally, occurrence of resistance appears to be linked to therapeutic use of an antimicrobial. In pigs, resistance to tetracycline or erythromycin was common, especially among *E. faecalis*, probably reflecting the therapeutic use of these or related substances. Also the widespread resistance to narasin in isolates from chickens concurs with the use of this substance in chicken production.

Selective pressure through therapeutic use cannot explain resistance to some antimicrobials. Hence, resistance to erythromycin, tetracycline, virginiamycin or bacitracin among isolates from chickens cannot directly be linked to use of the respective drugs. Macrolides and tetracyclines are scarcely used in Swedish chicken production whereas virginiamycin and bacitracin have not been used since the 80s. The fact that resistance to these antimicrobials still occurs to some extent can be a remnant of the past use or the result of co-selection. In the combined data from years 2000 and 2001 there are indications of linked resistance genes in enterococci from chickens as well as from pigs suggesting that use of one antimicrobial might select for resistance to others.

Likewise, resistance to vancomycin occured in the population of enterococci although the drug selecting for vancomycin resistance, avoparcin, has not been used in Swedish animal production since the mid 1980s. In the surveys years 2000 and 2001, no isolate obtained from direct cultures was resistant to vancomycin.

This indicates that the prevalence of vancomycin resistance in enterococci from pigs and chickens is low in an international perspective. However, after selective culture, 24 isolates were found in samples from chickens in year 2001 and two isolates year 2000. The results show that vancomycin resistance genes (*vanA*) are present among enterococci inhabiting the gut of Swedish chickens although the prevalence is low.

Another example of resistance in a population of bacteria not exposed to a selective pressure is the data from wild boars. Although overall occurrence of resistance was rare, a surprisingly high level of tetracycline resistance was found illustrating the complex nature of resistance epidemiology.

Table ENT VI. Occurrence of resistance (%) among *E. faecalis, E. faecium* and *E. hirae* presented by source of isolates and bacterial species, 2001. Range of dilutions tested and breakpoints for resistance are given in Table ENT II. Data for 2000 are presented for comparison (SVARM 2000).

Substance	**Pigs**						**Wild boars**			**Chickens**					
	E. faecalis		*E. faecium*		*E. hirae*		*E. faecalis*	*E. faecium*	*E. hirae*	*E. faecalis*		*E. faecium*		*E. hirae*	
	2000	2001	2000	2001	2000	2001	2001	2001	2001	2000	2001	2000	2001	2000	2001
	n=56	n=52	n=48	n=106	n=106	n=77	n=12	n=35	n=9	n=47	n=49	n=151	n=204	n=28	n=27
Ampicillin	0	2	0	1	0	0	0	0	0	0	0	0	<1	0	0
Avilamycin	0	0	2	1	<1	0	0	0	0	0	0	0	0	0	4
Bacitracin	0	0	4	3	0	0	0	6	0	23	31	20	15	7	4
Erythromycin	36	27	2	11	4	0	0	9	0	30	41	12	15	25	22
Flavomycin	2	2	NR[1]	NR[1]	NR[1]	NR[1]	0	NR[1]	NR[1]	11	6	NR[1]	NR[1]	NR[1]	NR[1]
Gentamicin	0	4	0	0	0	1	0	0	0	0	0	0	0	0	0
Narasin	2	4	2	4	2	3	0	0	0	43	45	79	80	89	90
Neomycin	7	6	2	2	<1	0	0	0	0	0	0	0	0	0	0
Streptomycin	13	25	2	4	<1	0	0	0	0	9	4	1	0	4	0
Tetracycline	68	63	10	7	15	10	83	11	11	60	67	38	27	7	4
Vancomycin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Virginiamycin	NR[1]	NR[1]	2	3	0	0	NR[1]	0	0	NR[1]	NR[1]	8	11	11	52

[1]Not relevant as susceptibility in some species of *Enterococcus* is inherently low.

Table ENT VII. Occurrence of resistance (%) among *E. faecalis, E. faecium* and *E. hirae* presented by bacterial species and source of isolates, 2001. Range of dilutions tested and breakpoints for resistance are given in Table ENT II. Data for 2000 are presented for comparison (SVARM 2000).

Substance	***E. faecalis***					***E. faecium***					***E. hirae***				
	Pigs		Wild boars	Chickens		Pigs		Wild boars	Chickens		Pigs		Wild boars	Chickens	
	2000	2001	2001	2000	2001	2000	2001	2001	2000	2001	2000	2001	2001	2000	2001
	n=56	n=52	n=12	n=47	n=49	n=48	n=106	n=35	n=151	n=204	n=106	n=77	n=9	n=28	n=27
Ampicillin	0	2	0	0	0	0	1	0	0	<1	0	0	0	0	0
Avilamycin	0	0	0	0	0	2	1	0	0	0	<1	0	0	0	4
Bacitracin	0	0	0	23	31	4	3	6	20	15	0	0	0	7	4
Erythromycin	36	27	0	30	41	2	11	9	12	15	4	0	0	25	22
Flavomycin	2	2	0	11	6	NR[1]	NR[1]	NR[1]	NR[1]	NR[1]	NR[1]	NR[1]	NR[1]	NR[1]	NR[1]
Gentamicin	0	4	0	0	0	0	0	0	0	0	0	1	0	0	0
Narasin	2	4	0	43	45	2	4	0	79	80	2	3	0	89	90
Neomycin	7	6	0	0	0	2	2	0	0	0	<1	0	0	0	0
Streptomycin	13	25	0	9	4	2	4	0	1	0	<1	0	0	4	0
Tetracycline	68	63	83	60	67	10	7	11	38	27	15	10	11	7	4
Vancomycin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Virginiamycin	NR[1]	NR[1]	NR[1]	NR[1]	NR[1]	2	3	0	8	11	0	0	0	11	52

[1]Not relevant as susceptibility in some species of *Enterococcus* is inherently low.

Table ENT VIII. Number of isolates of *Enterococcus faecalis* resistant to two or more antimicrobials, presented by animal species and resistance phenotype, 2001. "R" in hatched fields indicates resistance. Data for 2000 are presented for comparison (SVARM 2000).

Pigs		Chickens		Resistance pattern[1]								
2000 n = 56	**2001** n = 52	**2000** n = 47	**2001** n = 49	**Tc**	**Em**	**Sm**	**Na**	**Ba**	**Nm**	**Gm**	**Am**	**Fl**
		2		R	R	R	R	R				
	1	1		R	R	R	R					
	1			R	R	R						
2	1			R	R	R			R		R	
	1			R	R	R			R	R		
	1			R	R				R	R		
1		1	3	R	R		R					
		2	7	R	R		R	R				
			1	R	R		R					R
		5		R	R			R				
15	6	1	2	R	R							
			1	R			R	R				
		2	1	R			R					
		1	1	R			R					R
		1	6	R				R				
1				R		R			R		R	
2	3			R		R						
	1			R			R				R	R
		2	1				R					R
			1			R	R					
		1	3		R		R					R
		1	1		R		R	R				
1					R	R			R		R	
	2				R	R						

Total

22 (39%)	17 (33%)	20 (43%)	28 (57%)

[1] Tc: tetracycline; Em: erythromycin; Sm: streptomycin; Na: narasin; Ba: bacitracin; Nm: neomycin; Gm:gentamicin; Am: ampicillin; Fl: flavomycin.

Table ENT IX. Number of isolates of *Enterococcus faecium* resistant to two or more antimicrobials, presented by animal species and resistance phenotype, 2001. "R" in hatched fields indicates resistance. Data for 2000 are presented for comparison (SVARM 2000).

Pigs		Chickens		Resistance pattern[1]							
2000 n = 48	**2001** n =106	**2000** n = 151	**2001** n = 204	**Tc**	**Em**	**Vi**	**Sm**	**Na**	**Ba**	**Nm**	**Am[2]**
		1		R	R	R		R	R		
			1	R	R	R		R			
		1		R	R				R		
	1	2		R	R			R	R		
		5	5	R	R			R			
		2	3	R	R						
	1			R	R		R			R	
	1			R	R		R				
		2	2	R		R		R	R		
		9	5	R				R	R		
		5	7	R		R		R			
		25	23	R				R			
				R		R					
			1	R					R		
			1		R			R	R		
		5	17		R			R			
	1		1		R				R		
		1			R	R	R				
1	1				R		R			R	
	1					R	R				
		3	11			R		R			
	1					R		R	R		
		14	19					R	R		
			1					R			R

Total

1 (1%)	7 (7%)	75 (50%)	96 (48%)

[1] Tc: tetracycline; Em: erythromycin; Vi: virginiamycin; Sm: streptomycin; Na: narasin; Ba: bacitracin; Nm: neomycin; Am: ampicillin. [2] Denotes resistance also against amoxicillin/clavulanic acid.

Table ENT X. Distribution of MICs for *Enterococcus faecalis* from pigs (n=52), wild boars (n=12) and chickens (n=49), 2001.

Substance	Breakpoint resistance (mg/L)	Animal species	Percent resistant	Distribution (%) of MICs[1] (mg/L)														
				≤0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	>1024
Ampicillin	>8	Pig	2			5.8	59.6	30.8		1.9	1.9							
		Wild boar	0				91.7	8.3										
		Chicken	0		4.1	10.2	79.6	6.1										
Avilamycin	>8	Pig	0				3.8	53.8	42.3									
		Wild boar	0					50.0	41.7	8.3								
		Chicken	0			2.0	2.0	57.1	36.7	2.0								
Bacitracin[2]	>32	Pig	0					1.9	3.8	75.0	19.2							
		Wild boar	0					8.3	33.3	58.3								
		Chicken	31				2.0	2.0	8.2	26.5	16.3	14.3	30.6					
Erythromycin	>4	Pig	27		1.9	11.5	28.8	21.2	9.6				26.9					
		Wild boar	0			83.3		8.3	8.3									
		Chicken	41		8.2	28.6	8.2	12.2	2.0	10.2	4.1		26.5					
Flavomycin	>32	Pig	2					5.8	61.5	30.8					1.9			
		Wild boar	0					25.0	66.7	8.3								
		Chicken	6					2.0	67.3	20.4	4.1		2.0		4.1			
Gentamicin	>512	Pig	4							7.7	48.1	38.5				1.9	3.8	
		Wild boar	0							41.7	58.3							
		Chicken	0				2.0	6.1	10.2	49.0	28.6	4.1						
Narasin	>2	Pig	4	1.9	11.5	73.1	9.6		1.9	1.9								
		Wild boar	0		50.0	50.0												
		Chicken	45	12.2	18.4	10.2	4.1	10.2	24.5	14.3	6.1							
Neomycin	>1024	Pig	6								1.9	3.8	15.4	42.3			30.8	5.8
		Wild boar	0								8.3		58.3	33.3				
		Chicken	0						4.1	2.0	18.4	32.7	16.3	18.4			8.2	
Streptomycin	>1024	Pig	25									5.8	21.2	42.3			5.8	25.0
		Wild boar	0									8.3	83.3	8.3				
		Chicken	4								4.1	24.5	53.1	12.2			2.0	4.1
Tetracycline	>8	Pig	63			3.8	5.8	23.1	3.8		5.8	23.1	34.6					
		Wild boar	83			8.3		8.3				66.7	16.7					
		Chicken	67			2.0	22.4	6.1	2.0		22.4	14.3	30.6					
Vancomycin	>16	Pig	0				3.8	71.2	25.0									
		Wild boar	0					83.3	16.7									
		Chicken	0				14.3	73.5	12.2									
Virginiamycin	NR[3]	Pig	–					1.9		3.8	67.3	26.9						
		Wild boar	–						8.3	16.7	75.0							
		Chicken	–			2.0	2.0	8.2	14.3	22.4	42.9	8.2						

[1]Hatched fields denote range of dilutions tested for each substance. MICs above the range are given as the concentration closest to the range. MICs equal to or lower than the lowest concentration tested are given as the lowest tested concentration; [2] MIC in U/mL, see Appendix 3 for details; [3] Not relevant as susceptibility in *E. faecalis* is inherently low.

Table ENT XI. Distribution of MICs for *Enterococcus faecium* from pigs (n=106), wild boars (n=35) and chickens (n=204), 2001.

Substance	Breakpoint resistance (mg/L)	Animal species	Percent resistant	Distribution (%) of MICs[1] (mg/L)														
				≤0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	>1024
Ampicillin	>8	Pig	1		17.0	17.0	32.1	28.3	3.8	0.9	0.9							
		Wild boar	0		5.7	2.9	28.6	60.0	2.9									
		Chicken	<1		15.7	19.6	24.0	25.0	10.8	4.4	0.5							
Avilamycin	>8	Pig	1			0.9	7.5	18.9	59.4	12.3	0.9							
		Wild boar	0				2.9	14.3	80.0	2.9								
		Chicken	0			1.5	4.9	26.0	61.3	6.4								
Bacitracin[2]	>32	Pig	3			10.4	11.3	10.4	2.8	12.3	34.9	15.1	2.8					
		Wild boar	6				5.7	2.9	8.6	14.3	42.9	20.0	5.7					
		Chicken	15			2.0	21.6	2.9	3.9	21.1	21.6	12.3	14.7					
Erythromycin	>4	Pig	11		24.5	16.0	5.7	15.1	27.4	7.5	0.9		2.8					
		Wild boar	9			2.9	20.0	25.7	42.9	8.6								
		Chicken	15		9.3	17.2	33.3	16.7	8.8	2.9	0.5		11.3					
Flavomycin	NR[3]	Pig	-						1.9				1.9	4.7	91.5			
		Wild boar	-										2.9		97.1			
		Chicken	-						2.0	6.4	2.0	4.9	1.5	2.0	81.3			
Gentamicin	>512	Pig	0					6.6	12.3	51.9	25.5	3.8						
		Wild boar	0						8.6	71.4	14.3	5.7						
		Chicken	0			0.5	1.0	6.4	22.1	51.5	17.6	1.0						
Narasin	>2	Pig	4	2.8	12.3	23.6	53.8	3.8	3.8									
		Wild boar	0		2.9	51.4	45.7											
		Chicken	80	0.5	0.5	2.9	8.3	7.8	26.0	48.5	5.4							
Neomycin	>1024	Pig	2						4.7	25.5	34.9	23.6	6.6	2.8				1.9
		Wild boar	0							14.3	45.7	22.9	14.3	2.9				
		Chicken	0					1.5	15.2	30.9	33.3	14.2	4.4	0.5				
Streptomycin	>1024	Pig	4					2.8		0.9	10.4	40.6	38.7	1.9			0.9	3.8
		Wild boar	0							2.9		37.1	57.1	2.9				
		Chicken	0					0.5		0.5	15.2	47.1	34.3	2.5				
Tetracycline	>8	Pig	7		6.6	2.8	63.2	18.9	1.9		0.9	2.8	2.8					
		Wild boar	12				37.1	48.6	2.9			2.9	8.6					
		Chicken	27		2.0	4.4	50.5	13.7	1.0	2.0	3.9	8.3	14.2					
Vancomycin	>16	Pig	0				80.2	16.0	3.8									
		Wild boar	0				57.1	25.7	17.1									
		Chicken	0				78.9	12.7	8.3									
Virginiamycin	>8	Pig	3			17.0	22.6	27.4	21.7	8.5	2.8							
		Wild boar	0			22.9	42.9	20.0	8.6	5.7								
		Chicken	11			11.3	31.9	26.5	8.3	11.3	9.8	1.0						

[1]Hatched fields denote range of dilutions tested for each substance. MICs above the range are given as the concentration closest to the range. MICs equal to or lower than the lowest concentration tested are given as the lowest tested concentration; [2] MIC in U/mL, see Appendix 3 for details; [3] Not relevant as susceptibility in *E. faecium* is inherently low.

Table ENT XII. Distribution of MICs for *Enterococcus hirae* from pigs (n=77), wild boars (n=9) and chickens (n=27), 2001.

Substance	Breakpoint resistance (mg/L)	Animal species	Percent resistant	Distribution (%) of MICs[1] (mg/L)														
				≤0.12	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**	**128**	**256**	**512**	**1024**	**>1024**
Ampicillin	>8	Pig	0		46.8	23.4	18.2	11.7										
		Wild boar	0		11.1	11.1	44.4	33.3										
		Chicken	0		51.9	22.2	14.8	7.4		3.7								
Avilamycin	>8	Pig	0			3.9	18.2	24.7	49.4	3.9								
		Wild boar	0					55.6	44.4									
		Chicken	4					14.8	70.4	11.1	3.7							
Bacitracin[2]	>32	Pig	0			7.8	27.3	54.5	2.6	2.6	5.2							
		Wild boar	0				22.2	44.4	11.1	11.1		11.1						
		Chicken	4				11.1	18.5	11.1	11.1	7.4	37.0	3.7					
Erythromycin	>4	Pig	0		6.5	92.2	1.3											
		Wild boar	0		11.1	88.9												
		Chicken	22		7.4	59.3	11.1			7.4			14.8					
Flavomycin	NR[3]	Pig	-						1.3		1.3		1.3		96.1			
		Wild boar	-								11.1				88.9			
		Chicken	-						11.1	55.6	7.4	3.7			22.2			
Gentamicin	>512	Pig	1						3.9	54.5	33.8	6.5					1.3	
		Wild boar	0					11.1		22.2	44.4	22.2						
		Chicken	0					18.5	59.3	7.4	14.8							
Narasin	>2	Pig	3	14.3	18.2	31.2	33.8		2.6									
		Wild boar	0		22.2	33.3	22.2	22.2										
		Chicken	89		3.7	7.4			18.5	63.0	7.4							
Neomycin	>1024	Pig	0						1.3	2.6	32.5	33.8	24.7	5.2				
		Wild boar	0					11.1	11.1		11.1	22.2	22.2	22.2				
		Chicken	0					3.7	29.6	33.3	18.5	7.4	3.7	3.7				
Streptomycin	>1024	Pig	0								1.3	11.7	68.8	18.2				
		Wild boar	0								11.1	11.1	44.4	33.3				
		Chicken	0								3.7	66.7	18.5	11.1				
Tetracycline	>8	Pig	10			19.5	57.1	11.7	1.3			2.6	7.8					
		Wild boar	11			11.1	77.8				11.1							
		Chicken	4			3.7	25.9	66.7					3.7					
Vancomycin	>16	Pig	0				76.6	22.1	1.3									
		Wild boar	0				66.7	33.3										
		Chicken	0				88.9	11.1										
Virginiamycin	>8	Pig	0			49.4	16.9	24.7	7.8	1.3								
		Wild boar	0			11.1		88.9										
		Chicken	52				3.7	37.0		7.4	33.3	18.5						

[1]Hatched fields denote range of dilutions tested for each substance. MICs above the range are given as the concentration closest to the range. MICs equal to or lower than the lowest concentration tested are given as the lowest tested concentration; [2]MIC in U/mL, see Appendix 3 for details; [3] Not relevant as susceptibility in *E. hirae* is inherently low.

Resistance in animal pathogens

Resistance in animal pathogens

Data emanate, if not otherwise stated, from routine antimicrobial susceptibility testing of isolates from bacteriological examination of clinical submissions or post-mortem examinations at SVA. Samples were cultured by routine methods and isolates tested for antimicrobial susceptibility by a microdilution method (VetMIC™). Various panels of VetMIC™ with different antibacterials and dilutions were used depending on bacterial species. For further details, see Appendix 3. It should be observed that the breakpoint for resistance to trimethoprim-sulphonamide used in this year´s report is set at >4mg/L whereas >8 mg/L was used in SVARM 2000. Susceptibility against the combination was tested at the concentration ratio 1/20 (trimethoprim/sulphamethoxazole). The breakpoints relate to the concentration of trimethoprim. To facilitate comparisons, levels of resistance for previous years presented in SVARM 2001 have been adjusted using the breakpoint >4mg/L.

Pig

Isolates included

Escherichia coli for the years 1992-2001 were isolated from clinical submissions of gastro-intestinal tract samples (gut content, faecal samples or mesenteric lymph nodes). However, the material from years 1989-91 includes all *E. coli* isolated from pigs, irrespective of type of material cultured.

Brachyspira hyodysenteriae isolates emanate from clinical submissions of faecal samples. All isolates of *B. hyodysenteriae* obtained in pure culture were tested for susceptibility using a specially adapted broth dilution method (see Appendix 3 for details).

Isolates of *Pasteurella multocida* were obtained from samples collected within the framework of a control programme for atrophic rhinitis in nucleus and multiplying pig herds, see Appendix 3 for details.
Isolates from all parts of Sweden are included. No information on herds of origin was available but it is probable that most isolates of *Escherichia coli* and *Brachyspira hyodysenteriae* originate from herds with diarrhoeal problems. This implies that the data presented might not be representative of bacterial populations in general. However, these biases are probably inherent throughout the period and assessment of trends for *E. coli*, for which the material is large enough to be divided into three periods, appears relevant.

Results and comments

Escherichia coli
In *E. coli*, resistance to tetracycline, streptomycin or the combination trimethoprim-sulphonamide were the most prevalent traits (Table Pig I). Resistance to these three antimicrobials has been dominant during the observation period and apart from a declining prevalence of streptomycin resistance, no obvious trends can be discerned. The presented results tally with those of previous investigations from Sweden (Melin *et al.*, 1996 and Melin *et al.*, 2000).

Tetracycline, streptomycin or the combination trimethoprim-sulphonamide are used as therapeutics in pig production. However, use of streptomycin is low and limited to injectables (in combination with penicillin) or to oral treatment of diarrhoea. Interestingly, in the survey of indicator bacteria there was a statistically significant association between resistance to streptomycin and sulphonamides in *E. coli* from pigs (see Resistance in indicator bacteria). Therefore, the high frequency of resistance to streptomycin in isolates from clinical submissions might reflect not only use of the substance in pig production but also co-selection of resistance by use of other drugs e.g. sulphonamides.

Levels of resistance to ampicillin or chloramphenicol (around 10%) were surprisingly high throughout the observation period. These antimicrobials are used to a very limited extent (ampicillin) or not at all (chloramphenicol) in pig production in Sweden. In the data for indicator bacteria there are indications that resistance to these substances is associated with resistance to therapeutically used drugs (see Resistance in indicator bacteria). Probably co-selection retain resistance to these drugs as suggested by Bischoff *et al.* (2002) for chloramphenicol resistance in *E. coli* from piglets with neonatal diarrhoea in the United States.

There are also other tentative explanations to the maintenance of those resistance genes in the porcine *E. coli* population in the absence of an antimicrobial selection pressure. Through the vaccination programme for neonatal piglet diarrhoea, a selection pressure is exerted on *E. coli* strains producing heat-labile enterotoxin (LT) and certain adhesins, whereas the selection pressure exerted on strains producing only the heat-stable enterotoxins (ST) is less (Söderlind *et al.*, 1982). Mobile genes encoding for ST often recombine with plasmids carrying antimicrobial resistance genes or otherwise are co-transferred with antimicrobial resistance plasmids (Franklin and Möllby, 1983). Thus, the vaccination programme might indirectly contribute to the maintenance and dissemination of porcine *E.coli* carrying plasmids encoding for both ST and antimicrobial resistance genes even in the absence of an antimicrobial selection pressure.

Resistance in *E. coli* isolated from clinical submissions occurred to the same antimicrobials as in isolates from pigs sampled at slaughter but at considerably higher levels (see Resistance in indicator bacteria). This probably reflects that the former isolates emanate from herds with diarrhoeal problems where antimicrobials are used to treat the infections. In addition, a link between determinants of virulence and resistance traits is likely. As the material from diagnostic submissions probably is biased towards virulent strains of *E. coli*, higher resistance levels than in isolates originating from pigs sampled at slaughter can be expected. Moreover, mostly pigs under the age of four months are represented in the material from diagnostic submissions whereas pigs sampled at slaughter are approximately six

months old. The presented data must be viewed in the light of these differences in sampled populations.

Brachyspira hyodysenteriae

The breakpoints for antimicrobial resistance for *B. hyodysenteriae*, tentatively denoted in Table Pig II, are based on the MIC distribution for the tested isolates. The level of resistance to tylosin was high (83%) and of similar magnitude as in last year's survey. Notably, resistance to tylosin appears to have increased substantially since 1988-90 when a 20 % of the isolates, tested with an agar dilution technique, had MICs >16 mg/L (Gunnarsson *et al*,. 1991). Tylosin resistance in *B. hyodysenteriae* is caused by a single point mutation in the 23S rRNA gene. This mutation also causes lincosamide resistance (Karlsson *et al*., 1999).
No resistance to tiamulin was observed in the isolates from year 2001. However, in year 2000 two isolates had MICs of 1 mg/L and deviated from the susceptible population. This emphasise that special attention should be paid to emergence of isolates with decreased susceptibility, especially as the therapeutic arsenal available to treat infections with *B. hyodysenteriae* is limited to few antimicrobials.

Pasteurella multocida

Antimicrobial resistance was rare in isolates of *P. multocida* (Table Pig II) as it was in *Pasteurella* spp. isolated from Swedish calves (SVARM 2000). The presented data emanate from isolates obtained in samples collected within a control programme for atrophic rhinits in nucleus and multiplying herds. The disease, caused by toxin producing *P. multocida*, is demonstrated in very few herds (<1%) affiliated with the programme and it is therefore unlikely that the material is biased towards herds with respiratory problems. Thus, the situation regarding antimicrobial resistance might be different in *P. multocida* from production herds with respiratory problems. This is illustrated by a material of 38 *P. multocida* isolated from clinical submissions of samples from the respiratory tract from pigs the years 1992-2001 (data not shown). In that material, resistance to trimethoprim-sulphonamide occurred in 47% and streptomycin resistance in 16% of the isolates.

Table Pig I. Occurrence of resistance among *Escherichia coli* in pigs the years 1989-91, 1992-96, 1997-2000 and 2001 and distribution of MICs among the isolates from 2001. All isolates are from the gastro-intestinal tract, isolated in samples for diagnostic submissions or from post mortem investigations.

Substance	Breakpoint resistance (mg/L)	Percent resistant				Distribution (%) of MICs[1] 2001 (mg/L)								
		1989-91 n=248	1992-96 n=301	1997-00 n=399	2001 n=82	≤0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	>8	7	15	13	12				73.2	14.6		12.2		
Ceftiofur	>2	-	-	-	0[6]	50.0	45.5	4.5						
Chloramphenicol	>8	11	7[4]	13	7[7]				15.0	58.3	20.0		6.7	
Enrofloxacin	>0.5	1[3]	4	3	1	97.6	1.2		1.2					
Florfenicol	>16	-	-	-	0[6]				22.7	31.8	40.9	4.5		
Gentamicin	>8	1	0[4]	1[5]	0[8]				61.7	33.3	4.9			
Neomycin	>32	5	6	5	4					75.6	20.7			3.7
Nitrofurantoin	>32	4	4	5	3[7]							81.7	15.0	3.3
Streptomycin	>32	44	40	34	27					3.7	52.4	13.4	3.7	26.8
Tetracycline	>8	28	30	32	35			24.4	15.9	23.2	1.2	35.4		
Trim-Sulpha[2]	>4	17	16	13[5]	20		80.5				19.5			

[1] Hatched fields denote range of dilutions tested for each substance. MICs above the range are given as the concentration closest to the range. MICs equal to or lower than the lowest concentration tested are given as the lowest tested concentration; [2] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphamethoxazole); [3]227 isolates tested; [4] 300 isolates tested; [5] 398 isolates tested; [6]22 isolates tested; [7]60 isolates tested; [8]81isolates tested.

Table Pig II. Occurrence of resistance among *Brachyspira hyodysenteriae* in pigs the years 2000 and 2001 and distribution of MICs among the isolates from 2001. Isolates emanate from diagnostic submissions of faecal samples.

Substance	Breakpoint resistance (mg/L)	Percent resistant		Distribution (%) of MICs[1] 2001 (mg/L)														
		2000 n=50	2001 n=75	≤0.016	0.031	0.063	0.125	0.25	0.5	1	2	4	8	16	32	64	128	>128
Tiamulin	>2	0	0	2.7	13.3	44.0	37.3	1.3	1.3									
Tylosin	>16	72	83								4.0	8.0	5.3					82.7

[1] Hatched fields denote range of dilutions tested for each substance. MICs above the range are given as the concentration closest to the range. MICs equal to or lower than the lowest concentration tested are given as the lowest tested concentration.

Table Pig III. Occurrence of resistance and distribution of MICs among *Pasteurella multocida* in pigs 2000-01. All isolates are from the respiratory tract, isolated from nasal swabs.

Substance	Breakpoint resistance (mg/L)	Percent resistant n=75	Distribution (%) of MICs[1] (mg/L)												
			≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Ampicillin	>16	0		2.7	41.3	56.0									
Cephalothin	>16	0							98.7	1.3					
Chloramphenicol	>8	0						98.7	1.3						
Clindamycin	NR[3]	-							12.0	34.7	53.3				
Enrofloxacin	>2	0			98.7		1.3								
Erythromycin	NR	-						8.0	54.7	37.3					
Gentamicin	NR	-					1.3		65.3	29.3	1.3	2.7			
Neomycin	NR	-						5.3	50.7	38.7	5.3				
Nitrofurantoin	NR	-							53.3	44.0	1.3		1.3		
Penicillin	>8	0	1.3	20.0	64.0	14.7									
Spiramycin	NR	-									2.7	12.0	85.3		
Streptomycin	>32	4							1.3	18.7	41.3	34.7	2.7		1.3
Tetracycline	>8	1				96.0	2.7						1.3		
Trim-Sulpha[2]	>4	0	70.7	22.7	5.3	1.3									

[1] Hatched fields denote range of dilutions tested for each substance. MICs above the range are given as the concentration closest to the range. MICs equal to or lower than the lowest concentration tested are given as the lowest tested concentration; [2] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphamethoxazole); [3]Not relevant as the inherent susceptibility is such that the MIC range is above concentrations that can be obtained during therapy.

Cattle

Isolates included

Staphylococcus aureus emanate from diagnostic submissions and were collected consecutively during March-May 2001. Only the first isolate from an individual herd was included and isolates from cows with acute clinical mastitis were excluded. Therefore the data set comprise isolates from subclinical and from chronic, clinical mastitis.

Results and comments

Occurrence of antimicrobial resistance among *S. aureus* was rare except for resistance to penicillin (Table Cattle I). Eighteen percent of the isolates were β-lactamase producers and therefore resistant to penicillin. Among *S. aureus* isolated from acute clinical mastitis in Sweden, only 6 percent were β-lactamase producers (Nilsson *et al.*, 1997).

The higher level of penicillin resistance presented here might reflect the composition of the data set. Probably several isolates from cows with chronic mastitis are included. It is likely that β-lactamase producing *S. aureus* are more prevalent in this type of mastitis than in acute infection. All isolates were sensitive to oxacillin indicating that methicillin resistance does not occur in *S. aureus* causing mastitis in Sweden. This resistance trait is so far very rare in staphylococci causing mastitis but has recently been found in isolates of *S. aureus* originating from mastitic milk in Korea (Kang *et al.*, 2001). This finding emphasise that testing for methicillin resistance should be included in monitoring of resistance in *S. aureus* causing mastitis.

Table Cattle I. Occurrence of resistance and distribution om MICs among *Staphylococcus aureus* in milk from dairy cows with mastitis (acute mastitis excluded), 2001.

Substance	Breakpoint resistance (mg/L)	Percent resistant n=99	Distribution (%) of MICs[1] (mg/L)												
			≤0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	>256
Cephalothin	>1	0	15.2	64.7	20.2										
Chloramphenicol	>8	3						10.1	86.9	3.0					
Clindamycin	>4	0				100.0									
Enrofloxacin	>0.5	0[4]		91.8	8.2										
Erythromycin	>4	0		1.0	51.5	47.5									
Gentamicin	>16	0		9.1	51.5	33.3	6.1								
Neomycin	>32	0				81.8	11.1	6.1	1.0						
Nitrofurantoin	>32	0						1.0	73.7	24.2	1.0				
Oxacillin	>1	0[4]			98.0	2.0									
Penicillin	-[3]	18													
Spiramycin	>16	6						5.1	17.2	71.7	6.1				
Streptomycin	>32	0					3.0	45.5	37.4	12.1	2.0				
Tetracycline	>8	0			82.8	16.2	1.0								
Trim-Sulpha[2]	>4	0		100.0											

[1] Hatched fields denote range of dilutions tested for each substance. MICs above the range are given as the concentration closest to the range. MICs equal to or lower than the lowest concentration tested are given as the lowest tested concentration; [2] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphamethoxazole); [3]denotes β-lactamase production; [4]98 isolates tested.

Horse

Isolates included

Streptococcus zooepidemicus and *Rhodococcus equi* were isolated from bacteriological samples from the respiratory tract. *Escherichia coli* were isolated from samples from the female genital tract and *Actinobacillus* spp. from synovial fluid or blood culture.

All isolates originate from diagnostic submissions and no selection based on individual animal or stable was possible. The data set is likely to represent the central-east part of Sweden rather than the whole country. Further, the data are probably biased towards treatment failures and recurrent infections. However, as these biases are assumed to be of similar magnitude throughout the period studied, assessment of trends of resistance frequencies appears relevant.

Results and comments

Streptococcus zooepidemicus

Among *S. zooepidemicus*, resistance to the combination trimethoprim-sulphonamide was common (44%) and of similar magnitude as in year 2000 (Table Horse I). The level of resistance to this antimicrobial combination has increased markedly since the beginning of the 90s, probably a consequence of an increased therapeutic use of trimethoprim-sulphonamide formulations for oral use. Resistance to other antimicrobials was rare year 2001 as well as over the whole period studied. In particular the high and uniform susceptibility to penicillin should be emphasised. *S. zooepidemicus* has an inherent low susceptibility to aminoglycosides (gentamicin, neomycin) and therefore, assigning resistance levels is not relevant for these substances.

Rhodococcus equi

The antimicrobial susceptibility of *R. equi* is inherently low to many antimicrobials (Table Horse II). Classification of resistance levels is therefore not relevant for most of the antimicrobials tested. Only for erythromycin and the aminoglycosides (e.g. gentamicin), the susceptibility is such that the MIC ranges are below concentrations that can be obtained during therapy. Erythromycin and lately gentamicin has been used for therapy in combination with rifampin. The frequency of acquired resistance to either of the two first substances is still very low. The level of resistance to chloramphenicol year 2001 was lower than in previous years and the level for spiramycin resistance higher. However, the small number of isolates tested year 2001 makes conclusions regarding trends unwarranted.

Escherichia coli

In *E. coli*, the levels of resistance year 2001 were of similar magnitude as those from years 1997-00 (Table Horse III). The predominant resistance traits were streptomycin and trimethoprim-sulphonamide (18-20%). Resistance to ampicillin or tetracyclines is less common, about 10%. Levels of resistance to ampicillin or streptomycin were lower year 2001 than in the first half of the 90s whereas the level for trimethoprim-sulphonamide resistance was higher. However, the increase in occurrence of the latter resistance trait in *E. coli* does not parallel the striking increase in resistance among *S. zooepidemicus.*

Interestingly, tetracycline resistance was less common in isolates of *E. coli* from horses than from pigs or dogs. The resistance trait was also uncommon in isolates of *S. zooepidemicus* and *Actinobacillus* spp. from horses (see above). This might be a reflection of the historically limited use of tetracyclines in horses. In later years, the substance is however used to some extent in therapy for erlichiosis.

Actinobacillus spp.

The susceptibility *Actinobacillus* spp. to many of the tested substances is inherently low. To assign levels of resistance based on the presented distributions of MICs therefore does not seem valid for all antimicrobials (Table Horse IV). Although the number of isolates tested is limited, occasional isolates appears to have acquired resistance to penicillins or tetracyclines.

The results agree with those from a previous study where 149 Swedish isolates of *Actinobacillus* spp. from horses were tested (Sternberg *et al.*, 1999). Also in that study, acquired resistance to penicillins was observed. The majority of penicillin resistant isolates were β-lactamase producers. In addition, occasional isolates had MICs indicating acquired resistance to trimethoprim-sulphonamide or to streptomycin.

Table Horse I. Occurrence of resistance among *Streptococcus zooepidemicus* from horses the years 1992-93, 1996, 2000 and 2001 and distribution of MICs among the isolates from 2001. All isolates are from diagnostic submissions of samples from the respiratory tract.

Substance	Breakpoint resistance (mg/L)	Percent resistant				Distribution (%) of MICs[1] 2001 (mg/L)										
		1992-93 n = 100	1996 n = 160	2000 n = 301	2001 n=147	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	>16	0	0	0	0		99.3				0.7					
Chloramphenicol	>8	1	<1	<1[5]	<1						36.7	60.5	2.0		0.7	
Clindamycin	>4	2	1	<1[5]	<1					99.3			0.7			
Erythromycin	>4	1	1	<1[5]	<1				98.6	0.7			0.7			
Gentamicin	NR[3]	–	–	–	-					0.7		1.4	10.2	46.9	40.8	
Neomycin	NR	–	–	–	-							0.7		2.7	34.0	62.6
Penicillin	>8	0	<1	0[6]	0[8]	98.6	0.7			0.7						
Spiramycin	>16	1	1	<1[6]	<1							97.3	2.0			0.7
Tetracycline	>8	2	2	4[6]	3					30.6	4.1	60.5	1.4	0.7	2.7	
Trim-Sulpha[2]	>4	2	3[4]	58[7]	50		5.4	0.7	37.4	5.4		0.7	6.1	44.2		

[1] Hatched fields denote range of dilutions tested for each substance; MICs above the range are given as the concentration closest to the range. MICs equal to or lower than the lowest concentration tested are given as the lowest tested concentration; [2] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphamethoxazole) [3] Not relevant as the inherent susceptibility is such that the MIC range is above concentrations that can be obtained during therapy; [4] 159 isolates tested; [5] 300 isolates tested; [6] 299 isolates tested; [7] 298 isolates tested; [8]146 isolates tested.

Table Horse II. Occurrence of resistance among *Rhodococcus equi* from horses the years 1992-96, 1997-2000 and 2001 and distribution of MICs among the isolates from 2001. All isolates are from diagnostic submissions of samples from the respiratory tract.

Substance	Breakpoint resistance (mg/L)	Percent resistant			Distribution (%) of MICs[1] 2001 (mg/L)												
		1992-96 n=46	1997-00 n=73	2001 n=20	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Ampicillin	NR[3]	-	-	-						10.0	45.0	35.0	10.0				
Chloramphenicol	>8	33	25	5								95.0	5.0				
Clindamycin	NR	-	-	-					5.0	30.0	65.0						
Enrofloxacin	NR	-	-	-[7]			10.5	36.8	52.6								
Erythromycin	>4	2	1	0				100.0									
Gentamicin	>16	2	0[5]	0					100.0								
Neomycin	>32	0	0	0						95.0	5.0						
Penicillin	NR	-	-	-[7]					5.3	15.8	47.4	21.1	10.5				
Spiramycin	NR	-	-	-							5.0		5.0	40.0	50.0		
Streptomycin	>32	4[4]	2[6]	0[7]					15.8	63.2	15.8	5.3					
Tetracycline	NR	-	-	-								65.0	25.0	10.0			
Trim-Sulpha[2]	NR	-	-	-					5.0	40.0	20.0	25.0	10.0				

[1] Hatched fields denote range of dilutions tested for each substance. MICs above the range are given as the concentration closest to the range. MICs equal to or lower than the lowest concentration tested are given as the lowest tested concentration; [2] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphamethoxazole) [3] Not relevant as the inherent susceptibility is such that the MIC range is above concentrations that can be obtained during therapy; [4] 45 isolates tested; [5] 72 isolates tested; [6] 65 isolates tested; [7] 19 isolates tested.

Table Horse III. Occurrence of resistance among *Escherichia coli* from horses the years 1992-96, 1997-2000 and 2001 and distribution of MICs among the isolates from 2001. All isolates are from diagnostic submissions of samples from the female genital tract.

Substance	Breakpoint resistance (mg/L)	Percent resistant			Distribution (%) of MICs[1] 2001 (mg/L)									
		1992-96 n=176	1997-00 n=323	2001 n=103	≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	>8	19	11	10					29.1	56.3	4.9		9.7	
Chloramphenicol	>8	5	6	3					1.9	57.3	37.9		2.9	
Enrofloxacin	>0.5	2	1	3[4]		95.1	2.0	2.9						
Gentamicin	>8	3	4	2				16.5		78.6	2.9		1.9	
Neomycin	>32	2	3	2					37.9	5.8	53.4	1.0		1.9
Nitrofurantoin	>32	2	2	2								95.1	2.9	1.9
Streptomycin	>32	31	20	20							39.8	37.9	1.9	20.4
Tetracycline	>8	7	7	8				9.7	18.4	61.2	2.9	1.0	6.8	
Trim-Sulpha[2]	>4	12[3]	16	18	66.0		14.6	1.9			3.9	13.6		

[1] Hatched fields denote range of dilutions tested for each substance. MICs above the range are given as the concentration closest to the range. MICs equal to or lower than the lowest concentration tested are given as the lowest tested concentration; [2] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphamethoxazole); [3]175 isolates tested; [4] 102 isolates tested.

Table Horse IV. Occurrence of resistance among *Actinobacillus* spp. from horses years 1992-2001 and distribution of MICs among the isolates. All isolates are from diagnostic submission of samples of synovial fluid or blood culture.

Substance	Breakpoint resistance (mg/L)	Percent resistant	Distribution (%) of MICs[1] 1992-2001 (mg/L)										
		n = 40	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	>16	5						87.5	5.0		2.5	5.0	
Chloramphenicol	>8	0						97.5	2.5				
Clindamycin	NR[2]	–[4]					5.3	26.3	47.4	21.1			
Enrofloxacin	>2	0			97.5	2.5							
Erythromyci	NR	–[4]					7.9	36.8	42.1	13.2			
Gentamicin	NR	–					12.5		30.0	47.5	10.0		
Neomycin	NR	–						10.0	10.0	10.0	25.0	45.0	
Nitrofurantoin	>32	0							7.5		92.5		
Penicillin	>8	8[4]	21.1	15.8	31.6	10.5	7.9	5.3			7.9		
Spiramycin	NR	–[4]										39.5	60.5
Streptomycin	NR	–								27.5	50.0	17.5	5.0
Tetracyclin	>8	3					82.5	12.5	2.5			2.5	
Trim-Sulpha[2]	>4	0		95.0			2.5	2.5					

[1] Hatched fields denote range of dilutions tested for each substance. MICs above the range are given as the concentration closest to the range. MICs equal to or lower than the lowest concentration tested are given as the lowest tested concentration; [2] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphamethoxazole); [3]Not relevant as the inherent susceptibility is such that the MIC range is above concentrations that can be obtained during therapy; [4]38 isolated tested.

Dog

Isolates included

Antimicrobial susceptibility in *Staphylococcus intermedius*, isolated from bacteriological samples from skin, and in *Escherichia coli* isolated from urine are presented.
All isolates emanate from diagnostic submissions and might include repeat isolates from the same patients. It is probable that isolates from dogs in the central-eastern part of Sweden are over-represented. Further, it is likely that there is a bias towards isolates from dogs with recurrent disease or from therapeutic failures. Nonetheless, assuming that these biases are inherent throughout the study period inferences regarding trends seem relevant.

Results and comments

Staphylococcus intermedius
In isolates of *S. intermedius*, levels of resistance year 2001 did not deviate from figures for year 2000 (Table Dog I). Resistance to penicillin (β-lactamase production) has been high (70-80%) over the period and similar rates were reported already in 1978. Thus, β-lactam antibiotics are not likely to be efficient for treatment of recurrent pyodermas in dogs. However, this group of antimicrobials is widely used for other indications in dogs, which may explain the stable maintenance of this resistance determinant in canine staphylococci.

In addition to the antimicrobials given in Table Dog I, a subset of isolates from year 2001 were tested for susceptibility to the combination amoxicillin-clavulanic acid (data not shown). All 42 isolates tested, including 34 β-lactamase producers, were susceptible to the combination (MICs <8/4 mg/L, amoxicillin/clavulanic acid).

Resistance against macrolides (erythromycin and spiramycin), lincosamides (clindamycin) or tetracycline was high (18–28%) and seems to have increased over the monitored period, at least regarding resistance to erythromycin and clindamycin. The observation concurs with earlier reported findings (Sternberg, 1999). Macrolides and lincosamides are commonly prescribed to dogs (Odensvik *et al.*, 2001) and it is plausible that the observed increase in resistance is related to this use.

In staphylococci, *erm* genes commonly convey resistance to macrolides. Constitutive expression of such genes also conveys resistance to lincosamides. In the present data, 64% of the macrolide-resistant isolates were also resistant to lincosamides indicating a high frequency of constitutively expressed *erm* genes. Further, 53 % of the isolates resistant to macrolides-lincosamides were also resistant to tetracycline. Isolates with this resistance phenotype comprise 8% of the total material. An association between resistance to these antimicrobials in *S. intermedius* from dogs is consistent with earlier observations from similar materials (Hansson *et al.*, 1997).

Escherichia coli
Among *E. coli,* levels of resistance were mostly of similar magnitude year 2001 as in previous years (Table Dog II). The results are consistent with data presented in a study from 1993 (Franklin *et al.*, 1993). No obvious trends in occurrence of resistance can be distinguished except a reduction in the occurrence or chloramphenicol resistance from 17-20% in the first part of the 90s to 4-7% in years 2000 and 2001. The decline might reflect the abandoned use of chloramphenicol in the 1980s.

Resistance against ampicillin, streptomycin, tetracycline or the combination trimethoprim-sulphamethoxazole occurred in 10-20 % of the isolates. With the possible exception of streptomycin, all these antimicrobials are commonly used for pets. Resistance frequencies to substances sparingly used (gentamicin, neomycin and nitrofurantoin) are low (<5%).

The frequency of resistance to fluoroquinolones (enrofloxacin) is surprisingly high throughout the observed period (7-9%). However, it must be observed that the breakpoints chosen for this report are based on microbiological criteria. Thus, using breakpoints based on pharmacokinetics of these drugs (>2mg/L) to define resistance, the frequency is only 3%. Nonetheless, as sales of fluoroquinolones for dogs and cats have increased steadily during the last 10 years (Odensvik *et al.*, 2001), the levels of resistance must be monitored closely.

For the years investigated, between 16.3% and 28.4% of the isolates were resistant to at least two antimicrobials (20.9% of the total material). For this analysis, isolates with decreased susceptibility to enrofloxacin (MIC= 0.5 mg/L) were counted as resistant. As no obvious trend over time could be discerned, in the following, only proportions of resistance phenotypes in the total material (n=565) are discussed. Multiresistance, e.g. resistance to at least three antimicrobials, was seen in 13.6% of the material. Among these, nearly half were resistant to at least five antimicrobials (5.7% of the total material; Table Dog III).

Among isolates resistant to at least two antimicrobials, resistance to at least ampicillin and streptomycin was the most common phenotype. Most of these isolates were also resistant to tetracycline (7.4%) or trimethoprim-sulphonamides (8.1%). Resistance to ampicillin, streptomycin, tetracycline, trimethoprim-sulphonamides and chloramphenicol was found in 4.2% of the isolates. One isolate from 1995 was resistant to all tested substances.

The figures illustrate that while the majority of the isolates showed full susceptibility or were resistant to one antimicrobial only, the remainder were often truly multiresistant. The comparatively high frequency of multiresistance probably reflects a high proportion of treatment failures and recurrent cases among the cases sampled. Resistance to all the drugs most commonly used to treat urinary tract infections, i.e. ampicillin, enrofloxacin and trimethoprim-sulphonamides were found in 3.4% of the isolates. One fourth of these had MICs of enrofloxacin of 0.5 mg/L, meaning that therapy with fluoroquinolones could still be effective. Nonetheless, the data show that in some cases, the choice of antimicrobials for treatment is severely limited. The results emphasise that culture and subsequent testing for antimicrobial susceptibility is imperative for the therapeutic choice in recurrent and non-responding urinary tract infections.

Table Dog I. Occurrence of resistance among *Staphylococcus intermedius* in dogs the years 1992-93, 1995, 2000 and 2001 and distribution of MICs for the isolates from 2001. All isolates are from diagnostic submissions of samples from skin.

Substance	Breakpoint resistance (mg/L)	Percent resistant				Distribution (%) of MICs[1] 2001 (mg/L)								
		1992-93 n=204	1995 n=94	2000 n=145	2001 n=156	≤0.25	0.5	1	2	4	8	16	32	>32
Cephalothin	>16	0	0	0	0					100.0				
Chloramphenicol	>8	3[4]	2	4[6]	4				3.5	61.4	31.6		3.5	
Clindamycin	>4	12	13	22	18			78.2	0.6	3.2	17.9			
Enrofloxacin	>0.5	-	-	-	4[7]	95.7		4.3						
Erythromycin	>4	19	25	30	28		66.7	5.1	0.6		27.6			
Gentamicin	>16	0	0	0[6]	0				99.4	0.6				
Neomycin	>32	<1	1	0	0[8]				74.6		24.6	0.9		
Nitrofurantoin	>32	1	0	<1	<1							99.4		0.6
Oxacillin	>1	1	0	1	<1		98.1	1.3	0.6					
Penicillin	-[3]	77[5]	71	75	79									
Spiramycin	>16	20	25	30	26[8]					11.4	57.9	4.4		26.3
Tetracycline	>8	24	25	33	25[9]			74.2		0.6		25.2		
Trim/Sulpha[2]	>4	1[4]	2	2[6]	3		80.1	16.7			3.2			

[1] Hatched fields denote range of dilutions tested for each substance. MICs above the range are given as the concentration closest to the range. MICs equal to or lower than the lowest concentration tested are given as the lowest tested concentration; [2] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphamethoxazole) [3]denotes β-lactamase production; [4] 203 isolates tested; [5] 200 isolates tested; [6] 143 isolates tested; [7]47 isolates tested; [8]114 isolates tested; [9]155 isolates tested.

Table Dog II. Occurrence of resistance among *Escherichia coli* in dogs the years 1992-93, 1995, 2000 and 2001 and distribution of MICs for the isolates from 2001. All isolates are from diagnostic submissions of urine samples.

Substance	Breakpoint resistance (mg/L)	Percent resistant				Distribution (%) of MICs[1] 2001 (mg/L)								
		1992-93 n = 150	1995 n = 96	2000 n = 185	2001 n=183	≤0.25	0.5	1	2	4	8	16	32	>32
Amoxicillin/Clav.[2]	>8	-	-	-	24[6]						76.1	23.9		
Ampicillin	>8	19	24	20[5]	20				50.8	29.0	1.1	19.1		
Chloramphenicol	>8	17	20	7	4[7]				8.8	45.3	42.3	1.5	2.2	
Enrofloxacin	>0.5	7[4]	5	9	7	90.7	2.2	1.1	6.0					
Gentamicin	>8	1[4]	2	3[5]	4				42.1	50.8	2.7	0.5	3.8	
Neomycin	>32	3	3	5	4[7]				54.0	6.6	35.0			4.4
Nitrofurantoin	>32	2	3	2	2							96.7	1.1	2.2
Streptomycin	>32	16	28	17	16					2.2	49.2	30.1	2.7	15.8
Tetracycline	>8	16[4]	22	13	11[8]			22.1	23.8	43.1	0.6	10.5		
Trim/Sulpha[3]	>4	9	12	12	12		88.0	0.5			11.5			

[1] Hatched fields denote range of dilutions tested for each substance. MICs above the range are given as the concentration closest to the range. MICs equal to or lower than the lowest concentration tested are given as the lowest tested concentration; [2] Concentration of amoxicillin given; tested in concentration ratio 2/1 (amoxicillin/clavulanic acid); [3] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphamethoxazole); [4] 149 isolates tested; [5] 184 isolates tested; [6] 46 isolates tested; [7]137 isolates tested; [8]181 isolates tested.

Table Dog III. Number of isolates of *E. coli* resistant to five or more antimicrobials, presented by animal species and resistance phenotype, 2001. "R" in hatched fields indicates resistance and DS decreased susceptiblity (enrofloxacin, MIC=0.5mg/L).

Year					Resistance pattern[1]								
1992-93 n=149	1995[2] n=95	2000 n=185	2001[3] n=135	Total n=564	Am	Sm	TS	Tc	Cm	Nm	Ef	Gm	Nf
	1			1	R	R	R	R	R	R	R	R	R
2	1			3	R	R	R	R	R	R	R		
			1	1	R	R	R	R	R	R	DS		
			1	1	R	R	R	R	R	R		R	
		1		1	R	R	R	R	R	R			
1				1	R	R	R	R	R		R		R
1	2	5		8	R	R	R	R	R		R		
		1		1	R	R	R	R	R		DS		
2	3	1	1	7	R	R	R	R	R				
			2	2	R	R	R	R		R		R	
1				1	R	R	R		R	R			
		1		1	R	R	R		R		DS		
			1	1	R	R	R			R		R	R
		1		1	R	R		R	R	R			
		1		1	R		R	R	R		R		
	1			1		R	R	R	R				R
7 (4.7%)	8 (8.4%)	11 (5.9%)	6 (4.4%)	32 (5.7%)									

[1] Am: ampicillin; Sm: streptomycin; TS: Trimethoprim-sulphonamides; Tc: tetracycline; Cm: chloramphenicol; Nm: neomycin; Ef; enrofloxacin; Gm:gentamicin; Nf: nitrofurantoin. [2] One isolate that had not been tested for all included antimicrobials was excluded. [3] Forty-six isolates from the fall of 2001 that had not been tested for all included antimicrobials were excluded.

Appendix 1: Demographic data

Statistics on animal numbers and agricultural holdings with animals are provided by Statistics Sweden in collaboration with the Board of Agriculture. Figures are based either on total census or on samples of the populations. The countings are made in June and/or December. Statistics is published annually as a Yearbook of Agricultural Statistics and also on the Internet via the websites for Statistics Sweden (www.scb.se) or the Board of Agriculture (www.sjv.se). Figures on number of animals slaughtered in 2000 and 2001 and number of chickens slaughtered all years has been provided by the National Food Administration.

The number of dairy cows has decreased by 36% since 1980 (Table AP1 I). Most of the decrease took place from 1985 to 1987 and from 1990 to 1991. The number of beef cows has more than doubled since 1980. The increase was most marked in the beginning of the 90s and has since 1999 stabilized around 165 000. The number of dairy herds has decreased by 73% since 1980 (Table AP1 II). The herd size for both beef and dairy cows has more than doubled since 1980. The average size for dairy herds in 2000 was 34 cows.

The total number of pigs slaughtered decreased during the 80s but was rather constant over most of the 90s (Table AP1 III). From 1999 until 2000, the number dropped by 9%, which can be compared with a drop by 1% from 2000 until 2001. The number of holdings with pigs has decreased by about 80% since 1980 (Table AP1 II). The marked reduction in the beginning of the 90s is largely explained by the introduction of sow-pool systems. The average number of sows per herd has tripled and was in 2000 56 sows.

The production of chickens for slaughter has almost doubled from 1980 until 2001 (Table AP1 III).

Table AP1 I. Number of livestock (in thousands) from 1980-2001[1]. The figures represent census figures from counts of all, or samples of the population in the given years.

	1980	1985	1990	1995	1999	2000[4]	2001[4]
Cattle							
Dairy cows	656	646	576	482	449	428	418
Beef cows	71	59	75	157	165	167	166
Other cattle > 1 year	614	570	544	596	600	589	573
Calves < 1 year	595	563	524	542	499	500	494
Total, cattle	**1 935**	**1 837**	**1 718**	**1 777**	**1 713**	**1 685**	**1651**
Swine							
Boars	12	11	9	8	4	4	4
Sows	278	249	221	237	220	202	212
Fattening pigs >20 kg [2]	1 254	1 127	1 025	1 300	1 240	1 146	1090
Piglets <20 kg [3]	1 170	1 113	1 009	769	651	566	586
Total, swine	**2 714**	**2 500**	**2 264**	**2 313**	**2 115**	**1 918**	**1892**
Sheep							
Ewes and rams	161	173	161	195	194	198	208
Lambs	231	252	244	266	244	234	244
Total, sheep	**392**	**425**	**405**	**462**	**437**	**432**	**452**
Laying hens							
Hens	5 937	6 548	6 392	6 100	5 648	5670	5687
Chickens reared for laying	2 636	2 159	2 176	1 812	2 202	1654	1721
Total, hens	**8 573**	**8 708**	**8 568**	**7 912**	**7 850**	**7324**	**7408**

[1] Source: Yearbook of Agricultural Statistics, Sweden 1981, 1986, 1991, 1996, 2000 and 2001 and Statistical Messages, JO 20 SM 0201. For 1980 and 1985 only cattle and sheep at premises with more than 2 ha counted; [2] Before 1995, the figure denotes pigs above 3 months of age; [3] Before 1995, the figure denotes pigs below 3 months of age; [4] The number are based on countings made in June 2000 and 2001.

Table AP1 II. Number of holdings with animals from 1980-2001[1].

	1980	1985	1990	1995	1999	2000	2001
Cattle							
Dairy cows	44 100	30 100	25 900	17 700	14 000	12 700	11 800
Beef cows	12 400	10 300	10 900	17 100	14 300	13 900	13 600
Other cattle >1 year	63 200	52 700	42 700	39 200	32 200	30 500	29 100
Calves <1 year	62 300	52 000	42 000	36 500	29 200	27 700	26 300
Total, cattle	70 500	58 900	47 300	42 000	34 000	32 100	30 500
Sheep, excluding lambs	10 100	10 500	9 700	10 000	8 200	8 000	8 100
Swine	26 100	19 900	14 300	10 800	6 000	4 800	4 500
Laying hens	23 600	17 500	12 900	9 600	6 400	5 700	5 800
Chickens reared for laying	5 100	2 700	1 900	1 400	800	700	1 000
Without cattle, sheep, pigs or hens	32 300	35 400	36 700	33 600	36 800	33 300	NA[2]

[1] Source: Yearbook of Agricultural Statistics, Sweden 1981, 1986, 1991, 1996 and 2000 and Statistical Message, JO 20 SM 0201.[2] NA=not available.

Table AP1 III. Number of animals slaughtered (in thousands) from 1980-2001[1].

	1980	1985	1990	1995	1999	2000	2001
Cattle							
Cattle >1 year	574	584	523	502	482	492	458
Calves < 1 year	130	138	70	46	39	39	33
Total, cattle	704	722	592	548	521	531	491
Pigs	4 153	4 283	3 659	3 763	3 815	3 247	3169
Sheep	302	328	280	145	198	208	194
Chickens (broiler)	40 466	36 410	38 577	60 300	66 145	68 616	73 355

[1] Source: National Food Administration

Appendix 2: Materials and methods, use of antimicrobials

Wholesaler data

Antimicrobial drugs used in veterinary medicine in Sweden are only available on veterinary prescription. Furthermore, antimicrobial drugs have to be dispensed through pharmacies, which in turn are supplied solely by two drug wholesalers. Sales statistics are available from Apoteket AB (The National Corporation of Swedish Pharmacies).

These statistics describe the amount of medicinal products sold from the wholesalers to the pharmacies. As the pharmacies stock a limited number of veterinary drugs, the wholesalers´statistics can be used as an approximation on the actual usage of antimicrobials. Wholesalers´ data have a very high degree of completeness. This is explained by the fact that the wholesalers represent the entire drug distribution network, i.e., there are no other sources of antimicrobials for use or prescription by veterinarians.

Sweden has a long tradition in drug consumption statistics. Apoteket AB, former Apoteksbolaget AB, has since 1976 followed the consumption of drugs for use in humans mainly by using wholesalers´ statistics. However, it has never been determined weather Apoteket AB is responsible or not for producing sales statistics of veterinary medicinal products. Further, no governmental authority has yet been given the responsibility to gather or supervise such data. Notwithstanding, SVA and Apoteket AB have collaborated over the years and data on the total use of antimicrobials for animals in Sweden are available since 1980. For a review of the figures from 1980-2000 as well as references to earlier publications, see SVARM 2000.

Classification of drugs

Veterinary medicinal drugs are classified according to the Anatomical Therapeutic Chemical veterinary classification system (ATCvet) (WHO, Guiedelines for ATCvet classification). The system is based on the same main principles as the ATC classification system for substances used in human medicine. In both the ATC and ATCvet systems, drugs are divided into groups according to their therapeutic use. First, they are divided into 15 anatomical groups, classified as QA-QV in the ATCvet system (without Q in the human system), on basis of their main therapeutic use. Thereafter subdivision is made according to therapeutic main groups, which is followed by a further division in chemical/therapeutic subgroups.

Antimicrobials are classified in the QJ group - general anti-infectives for systemic use. However, antimicrobials can also be found in other groups such as QA (alimentary tract and metabolism), QD (dermatologicals), QG (genito-urinary system) and QS (sensory organs) depending on the therapeutic use.

Inclusion criteria

All veterinary antibacterial drugs authorised for use in animals except dermatologicals, ophtalmologicals and otologicals were included (i.e., ATCvet codes QA, QG and QJ). Veterinary drugs are preparations authorised for use in animals. Human drugs may be authorised not only for humans, but for animals as well. This latter category is not included in the statistics. However, no such drugs are authorised for use in the major food producing animal species, and the volume sold is very limited.

Drugs with antibacterial activity can also be found in other groups, notably among the antiprotozoals (QP51). Of these, the nitroimidazoles were included earlier but no such substances are presently authorised for use in animals. Sulfaclozine is licensed for treament of coccidiosis only and has therefore not been included. The ionophoric antibiotics are presently regulated as feed additives and not sold though pharmacies and are therefore not included in the wholesalers' statistics. However, the Board of agriculture 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 Table AC III.

DDD mastitis

In an earlier publication, the sale of antimicrobials drugs with mastitis as one of the indications in Norway and Sweden from 1990-1997 has been described (Grave et al, 1999). The figures have been updated annually and published in Swedish (Odensvik 1999, 2000, 2001).

Figures on sales of antimicrobial drugs with mastitis as one of the approved indications were selected from the wholesalers' statistics. Most of these drugs are authorised for other indications, and for other animal species. However, as mastitis is by far the single most common indication for their use, the data can be used to evaluate trends.

To facilitate temporal analysis and comparisons, a defined daily dose for cows (DDDcow) was introduced as a unit of measurement.

For injectable drugs, doses were, with some exceptions, defined on basis of dosage recommendations given in Norwegian and Swedish pocket formularies listing pharmaceutical specialities with marketing authorisation. In the study, 500 kg cow weight was chosen to establish the total daily dose. The weight of 500 kg was chosen because it is technically easy to handle although not identical to the average weight of dairy cows in Norway and Sweden. Figures on numbers of dairy cows were obtained from Official Statistics Sweden. Finally, the number of DDDcow/1000 cows at risk/day was calculated using the formula:

$$\frac{\text{Amount of drug sold in one year (mg)}}{\text{DDDcow (mg)} * 365 * \text{no. of cows at risk}} * 1000 \text{ cows at risk} = \text{DDD/1000 cows at risk/day.}$$

For intramammary drugs, one single-dose applicator was chosen as the defined dose. The number of single-dose applicators sold each year was divided by the number of cows at risk (in thousands) and days at risk (365) that year.

Distribution of veterinary medicines in Sweden

Marketing of drugs in Sweden is regulated by the Medicinal Products Act, which applies both to human and veterinary drugs. According to the Act, a medicinal product may not be sold until it has been granted marketing authorisation by the Medical Products Agency (MPA). The MPA has issued provisions concerning authorisation, distribution and prescription of veterinary medicinal products.

The state-owned Apoteket AB has exclusive rights regarding retail sales of medicines in Sweden. Apoteket AB operates according to guidelines set out in an agreement with the State. According to the Act, only pharmacies run by Apoteket AB are permitted to sell drugs. This implies that veterinarians in Sweden are not permitted to sell drugs, although they may for practical reasons hand over medicines for emergency use. Veterinarians are, however, under no conditions permitted to make a profit from dispensing medicines.

Appendix 3: Materials and methods, resistance monitoring

Sampling strategy

Zoonotic bacteria

Salmonella
Isolates of *Salmonella* from warm-blooded animals (wild and domesticated) are included. Salmonellosis in animals is a notifiable disease in Sweden. It is mandatory that at least one isolate from each notified incident, including incidents detected in the Swedish *Salmonella* control programme, is confirmed at SVA. The first isolate from each animal species in each notified incident is included in the material presented in SVARM. Therefore, the material is thought to be representative for *Salmonella* prevalent among animals in Sweden.

Campylobacter from animals
Campylobacter spp. was isolated from samples of intestinal content (caecum or colon) from cattle and pigs sampled at slaughter and from cloacal swabs from healthy broiler chickens. A new *Campylobacter* programme in broilers started in Sweden July 1st, 2001. Of the 489 slaughtergroups included in the programme, 50 groups were randomly selected. One *Campylobacter* isolate from each of the selected slaughtergroups was used in SVARM.

Campylobacter from food and water
Campylobacter isolates from food and water originate from a study on the prevalence of Campylobacter in meat and raw water by the National Food Administration year 2000. The positive food samples were from retails (70%), restaurants (20%) and meat plants (10%), and the water samples from the incoming water at a water plant.

Indicator bacteria

Indicator bacteria, *Escherichia coli* and *Enterococcus* spp., were isolated from samples of intestinal content (caecum or colon) from healthy slaughter pigs and broiler chickens. Samples were collected at slaughter.

To obtain a representative material of randomly selected samples from the two animal species, the number collected at each abattoir was determined in proportion to the number of animals slaughtered at the abattoir each year. Four abattoirs for chickens and five for pigs participated in the collection of samples. The abattoirs represented in the monitoring programme are geographically separated and accounted for 40 and 63 percent, respectively, of the total slaughter in Sweden during 1998-1999.

Sampling was performed weekly, with exceptions for holidays and summer vacations, by meat inspection staff or abattoir personnel. Each sample collected from pigs represents a unique herd whereas each sample from chickens represents a unique flock, but not necessarily a unique herd. By these measures, bacterial isolates included are from healthy individuals randomly selected among Swedish herds/flocks.

In this years SVARM, *E. coli* and *Enterococcus* spp. were isolated also from wild boars. Faecal samples were collected from wild boars shot in the wild. Hunters in 15 different geographical regions in southern Sweden collected the samples.

Animal pathogens

With the exception of *Pasteurella multocida* from pigs, isolates of animal pathogens included emanate from routine bacteriological examinations of clinical submissions or post-mortem examinations at SVA.

Isolates from pigs included are *E. coli* from the gastro-intestinal tract (gut content, faecal samples or mesenteric lymph nodes), *Brachyspira hyodysenteriae* isolated from faecal samples and *Pasteurella multocida* from nasal swabs collected within the framework of a control program for atrophic rhinitis in nucleus and multiplying pig herds. From cattle, *Staphylococcus aureus* from subclinical and from chronic, clinical mastitis are included. Further, from horses *Streptococcus zooepidemicus* and *Rhodococcus equi* from the respiratory tract, *Actinobacillus* spp. from synovial fluid or blood culture and *E. coli* from the genital tract of mares are included. From dogs, *Staphylococcus intermedius* isolated from skin samples and *E. coli* isolated from samples of urine are included.

Isolation and identification of bacteria

Zoonotic bacteria

Salmonella
Salmonella was isolated and tentatively identified at SVA or at regional laboratories according to standard procedures. All samples within official control programmes are cultured according to the procedures laid down by the Nordic Committee in Food Analysis, 1999.
Confirmation and serotyping of isolates was performed at the Department of Bacteriology, SVA following standard procedures according to Kaufmann and White.
Phagetyping of *S.* Typhimurium and *S.* Enteritidis was performed by Swedish Institute for Infectious Disease Control (SMI), Stockholm.

Campylobacter from animals
Campylobacter spp. from animals was isolated and identified at SVA according to standard procedures. Samples were cultured for thermophilic *Campylobacter* spp. using a modified NMKL method (NMKL Nr 119, 1990) using Preston enrichment broth and Preston selective agar (Oxoid). Species identification in all *Campylobacter* was performed with the following biochemical tests: oxidase, catalase and hippurate hydrolysis. In isolates from chickens, a motility test was added. From these tests, *C. jejuni* can be identified whereas other isolates are described as hippurate-negative thermophilic *Campylobacter* spp. In *Campylobacter* isolated from pigs, 95% were hippurate-negative thermophilic *Campylobacter* spp. and presumably the majority of these isolates consist of *C. coli*. Since 30% of the hippurate-negative thermophilic *Campylobacter* spp. was resistant to nalidixic acid, an additional test with indoxyl

acetate hydrolysis was performed to exclude that these isolates were *C. lari*, which is inherently resistant to nalidixic acid. Results were interpreted according to Nachamkin, 1999.

Campylobacter from food and water
Campylobacter spp. from food and water was also isolated and identified according to the NMKL method mentioned above. Species identification was performed by a combination of two PCR methods discriminating *C. jejuni*, *C. coli* and *C. lari* (Fermér and Olsson Engvall, 1999; Linton *et al.*, 1997).

Indicator bacteria

Escherichia coli
Intestinal content (caecum or colon) from cattle, pigs and chickens was diluted (1/10) in phosphate/sodium chloride buffer, spread onto MacConkey agar and incubated overnight at 37°C. One large red colony, typical for *E. coli,* was sub-cultivated on blood agar. *E. coli* was identified by positive reactions for indole and p-nitrophenyl-β-D-glucopyranosiduronic acid (PGUA). Only isolates fulfilling these criteria were included and tested for susceptibility. Isolates were stored at -70°C.

Enterococci
Intestinal content (caecum or colon) from cattle, pigs and chickens was diluted (1/10) in phosphate/sodium chloride buffer and cultured both on solid media without vancomycin and selectively enriched in broth supplemented with vancomycin.
Culture without vancomycin: 0.1 mL of the diluted faecal material was spread onto Slanetz-Bartley (SlaBa) agar and incubated 48 hours at 37°C. One colony, randomly chosen, was sub-cultured on bile-esculin agar and blood agar (37°C, 24-48 hours). In case of dubious results, the isolate was tested with pyrrolidonyl arylamidase (PYR). Only isolates with positive reaction in the PYR-test were included. Bile-esculine positive colonies were tested for antimicrobial susceptibility and identified to species using the following biochemical tests: mannitol, sorbitol, arabinose, saccharose, ribose, methyl-α-D-glucopyranoside and raffinose. Results were interpreted according to Devriese *et al.* (1993).
Enrichment in broth with vancomycin: 5 mL of the diluted faecal material (see above) was inoculated in 5 mL enrichment broth (Enterococcosel) supplemented with 16 mg/L vancomycin (final concentration: 8 mg/L vancomycin) and incubated in 37°C, 24 hours. 0.1 mL was spread onto SlaBa agar supplemented with 8 mg/L vancomycin and incubated in 37°C, 48 hours. One colony, randomly chosen, was sub-cultivated on bile-esculin agar and blood agar (37°C, 24-48 hours). Bile-esculin positive colonies were tested for antimicrobial susceptibility and at the same time species identified as above. Isolates were stored at -70°C.
Isolates resistant to vancomycin were genotyped with PCR for the *vanA* gene. Identification of the genes *vanB*, *vanC-1* and *vanC-2/3* and species *E. faecium* and *E. faecalis* was also possible in the same PCR reaction (Dutka-Malen *et al.*, 1995). In addition, the vancomycin resistant isolates were typed with the PhenePlate™ biochemical fingerprinting system for bacteria, based on measurements of the kinetics of bacterial biochemical reactions (Kühn *et al.*, 1995).

Animal pathogens

Animal pathogens were isolated and identified at the Dept. of Bacteriology, Dept. of Ruminant and Porcine Diseases (*Pasteurella multocida*) and Dept. of Mastitis and Diagnostic Production (*Staphylococcus aureus*), SVA following standard procedures.

Pasteurella multocida
From direct cultures of nasal swabs on blood plates, one colony macroscopically identified as *Pasteurella multocida* was collected for further identification by positive reactions for indole production and oxidase. Isolates fulfilling these criteria were tested for antimicrobial susceptibility.

Susceptibility testing

Antimicrobial susceptibility testing was performed by a microdilution method, VetMIC™, where antimicrobials were dried in serial twofold dilutions in microtitre wells. Various panels were used depending on which bacterial species was tested, see Table AP3 I. VetMIC™ is produced at the Dept. of Antibiotics, SVA.

The tests were performed following the standards for microdilution of the National Committee of Clinical Laboratory Standards (NCCLS, 1999).

For susceptibility testing of *Brachyspira hyodysenteriae*, a specially developed VetMIC™ panel was used. The antimicrobials were dried in serial twofold dilitions in the wells of tissue culture trays. The wells were filled with 0.5 mL of a suspension of bacteria in Brain Heart Infusion broth with 10% fetal calf serum. The trays were incubated in an anaerobic atmosphere for four days on a shaker.

Minimum inhibitory concentration (MIC) is registered as the lowest concentration of the antimicrobial that inhibits bacterial growth. An isolate is regarded as resistant to a specific antimicrobial when the MIC is distinctly higher than those of inherently susceptible strains of the bacterial species in question. In other words, microbiological criteria were used to define resistance. Where appropriate, the breakpoints suggested by NCCLS (1999) for animal pathogens were also taken into consideration. The breakpoints defining resistance are shown in Table AP3 I.

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

Quality assurance system

The Dept. of Antibiotics, Dept. of Bacteriology and laboratories at SVA using VetMIC™ for antimicrobial susceptibility tests are accredited to perform the method according to SS-EN ISO/IEC 45001 by the Swedish Board for Accreditation and Conformity Assessment (SWEDAC).

As quality control for susceptibility tests of zoonotic and indicator bacteria, *Escherichia coli* ATCC 25922, *Enterococcus faecalis* ATCC 29212 and *Campylobacter jejuni* CCUG 11284 (analogue to *Campylobacter jejuni* ATCC 33560) were included at least on a weekly basis. Relevant control strains were also included and evaluated at least once weekly for animal pathogens.

The Dept. of Antibiotics participates in several proficiency tests for antimicrobial susceptibility testing. These are arranged either as national or international studies. Likewise, the Dept. of Bacteriology and the Dept. of Mastitis and Diagnostic Production participate in proficiency tests concerning isolation and identification of *Salmonella* spp. and general clinical veterinary bacteriology and susceptibility tests.

Data handling

Data on isolates of *Salmonella* and animal pathogens are routinely registered in an Oracle database at SVA. Records include source of cultured sample, antimicrobial susceptibility etc. From this database, relevant data for calculations and analysis were extracted to an Access database.

Data on samples for cultivation of indicator bacteria were recorded in an Access database on arrival of samples. Recorded data were animal species, date of sampling, abattoir and herd of origin. For samples from chickens, also flock of origin was recorded. Isolates of *Campylobacter* from animals were registered with the information of animal species. Subsequently, results of laboratory investigations were recorded in the same database.

Calculations and analysis of data were performed using the computer programs Access, Excel and Minitab.

Concerning confidence limits

When the prevalence of antimicrobial resistance is close to zero, e.g. when one out of 120 isolates is resistant, the question arises how to calculate the prevalence of resistance and its confidence intervals. In the example, the prevalence could be estimated to 0.83% while the 95% confidence interval is trickier. The normal approximation to the binomial distribution would give a lower confidence of - 0.8% and an upper confidence limit of 2.5%. The lower limit is nonsensical and indicates the unsuitability of the normal approximation in this case.

There are several ways out of the dilemma; one is to calculate the exact binomial confidence limits, which would be possible in some cases (small number of isolates). Another alternative is to run Monte-Carlo simulations based on the beta-distribution which is possible but quite laborious for a huge set of data since each prevalence estimate has to be simulated 10 000 times.
Finally the relationship between the F-distribution, the beta-distribution and the binomial distribution can be used. This gives the formulae that enables calculations of the confidence intervals (Rao, 1965). Using this approach, the confidence intervals in the example would be 0.021% and 4.6%.

In conclusion, the normal approximation to the binomial distribution might be unsuitable when the prevalence is close to 0% or close to 100% since the approximation might lead to confidence intervals lower than 0% or higher than 100%. Moreover, when the prevalence of resistance is less than 5% using the link between the F-distribution and the binomial distribution yield different confidence intervals compared to those obtained from the normal approximation and should accordingly be preferred.

Table AP3 I. Breakpoints and range of dilutions (mg/L) used for antimicrobial susceptibility testing of bacteria. Isolates with MIC values higher than the given figures are considered resistant.

Antimicrobial agent	Breakpoint	Range	Used in*	Breakpoint	Range	Used in*	Breakpoint	Range	Used in*	Breakpoint	Range	Used in*	Breakpoint	Range	Used in*	Breakpoint	Range	Used in*
Amoxicillin and Clavulanic acid[1]	>8	2-16	AC	>8	8-16	D	>8	1-8	F									
Ampicillin	>8	0.25-32	AEF	>16	2-16	M	>8	2-8	BD	>16	0.5-64	G	>16	0.12-16	IK			
Apramycin	>32	0.25-32	AF															
Avilamycin	>8	0.5-32	E															
Bacitracin[2]	>32	0.5-32	E															
Ceftiofur	>2	0.25-2	ABF															
Cephalothin	>16	4-16	N	>16	4-32	I	>1	0.12-1	J									
Chloramphenicol	>8	2-16	ABCDFIJ KLMN															
Clindamycin	>4	1-8	JK	>4	1-4	N												
Enrofloxacin	>0.5	0.03-4	AF	>0.5	0.25-2	CJ	>0.5	0.25-1	BDN	>2	0.25-2	IM	>1	0.03-4	G			
Erythromycin	>4	0.5-4	KLN	>4	0.25-32	E	>16	0.12-16	G	>4	0.25-2	J						
Flavomycin	>32	2-128	E															
Florfenicol	>16	2-16	ABF															
Gentamicin	>8 (>16)[4]	0.25-32	AF (J)	>8	1, 4-16	C	>8 (>16)[4]	2-16	BD (N)	>16	1,4-16	L	>512	0.5-32, 512	E	>8	0.25-8	G
Nalidixic acid	>16	1-128	AFG															
Narasin	>2	0.12-16	E															
Neomycin	>32	1-128	AFJ	>32	2-32	CDLN	>32	4-32	B	>1024	2-128, 1024	E						
Nitrofurantoin	>32	4-32	BCJM	>32	16-32	DN												
Oxacillin	>1	0.5-1	N	>1	0.5-4	J												
Penicillin	>8	0.06-8	IKM															
Spiramycin	>16	4-32	JKLN															
Streptomycin	>32	2-256	AFJ	>32	2-32	C	>32	4-32	BD	>32	1-128	IL	>1024	2-128, 1024	E			
Sulphamethoxazole	>256	64-512	AF															
Tetracycline	>8	0.5-64	AFIJ	>8	1-16	CKM	>8	1-8	BDN	>8	0.25-32	EG						
Tiamulin	>2	0.016-2	H															
Trimethoprim	>8	0.12-16	AF															
Trimethoprim and sulphamethoxazole[3]	>4	0.12-8	CLM	>4	0.5-4	BDN	>4	0.06-8	I	>4	0.25-8	J						
Tylosin	>16	2-256	H															
Vancomycin	>16	1-128	E															
Virginiamycin	>8	0.5-64	E															

[1] Concentration of amoxicillin given, tested with clavulanic acid in concentration ratio 2/1; [2] MIC in U/mL; [3] Concentration of trimethoprim given, tested with sulphamethoxazole in concentration ratio 1/20.
[4] Breakpoint >16 is used for *S. aureus* and *S. intermedius.*

*

A *E. coli* (indicator)
B *E. coli* (pathogen, pigs)
C *E. coli* (pathogen, horses)
D *E. coli* (pathogen, dogs)
E Enterococci (indicator)
F *Salmonella*
G *Campylobacter*
H *Brachyspira hyodysenteriae*
I *Pasteurella multocida*
J *Staphylococcus aureus*
K *Streptococcus zooepidemicus*
L *Rhodococcus equi*
M *Actinobacillus* spp.
N *Staphylococcus intermedius*

Appendix 4: Antimicrobial agents licensed

Antimicrobial agents licensed for therapy in veterinary medicine in Sweden year 2002 are listed in Table AP4 I.

Only substances licensed for systemic, oral, intrauterine or intramammary use are included (ATCvet codes QJ, QG, QA and QP). Data from FASS VET. 2002. For explanation of ATCvet code, see Appendix 2.

Table AP4 I. Antimicrobial agents authorised for therapeutic use in cattle, pigs, poultry, horses, dogs and cats in Sweden, 2002. Routes of administration are indicated.[1]

Antimicrobial agent	ATCvet code	Animal species					
		Cattle	Pigs	Poultry	Horses	Dogs	Cats
Tetracyclines							
Doxycycline	QJ01A A02					O	O
Oxytetracycline	QJ01A A06, QG51A A01	I O U	I O U	O		O	O
Beta-lactams, penicillins							
Ampicillin	QJ01C A01	O	O		O	O	O
Amoxicillin	QJ01C A04		I			I O	O
Penicillin G	QJ01C E01	I	I		I		
Penicillin G, procaine	QJ01C E09	I	I		I	I	I
Penicillin V	QJ01C E02					O	O
Amoxicillin/Clavulanic acid	QJ01C R02		I			I O	I O
Beta-lactams, cephalosporins							
Cephalexin	QJ01D A01					O	
Cefadroxil	QJ01D A09					O	O
Ceftiofur	QJ01D A90	I					
Sulphonamides + Trimethoprim							
Sulphadiazine/Trimethoprim	QJ01E W10	I	I		I O	O	O
Sulphadoxine/Trimethoprim	QJ01E W13	I	I		I		
Sulphonamides							
Formosulphatiazole	QA07A B90	O	O		O	O	O
Sulphaklozin	QP51A G04			O			
Macrolides							
Spiramycin	QJ01F A02	I					
Tylosin	QJ01F A90	I	I O	O		I	I
Lincosamides							
Clindamycin	QJ01F F01					O	O
Pirlimycin	QJ51F F90	M					
Aminoglycosides							
Gentamicin	QJ01G B03				I U	I	I
Dihydrostreptomycin (DHS)	QA07A A90	O U	O U		O U	O	O
Fluoroquinolones							
Enrofloxacin	QJ01M A90	I	I	O		I O	I O
Danofloxacin	QJ01M A92	I	I				
Marbofloxacin	QJ01M A93					O	O
Orbifloxacin	QJ01M A95					O	
Pleuromutilins							
Tiamulin	QJ01X X92		I O				
Combinations							
Penicillin G, procaine/DHS	QJ01R A01, QJ51R C23	I M	I		I	I	I
Penicillin G, benzatin/DHS	QJ51R C24	M					
Penicillin G, ester/Framycetin	QJ51R C25	M					
Penicillin G, ester/DHS	QJ51R C25	M					

[1] O = oral; I = injection; U = intrauterine; M = intramammary; [2] Authorisation temporarily withdrawn october 2000.

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