

Bacterial Resistance to Antimicrobial Agents in Finland FINRES 1999

MINISTRY OF AGRICULTURE AND FORESTRY

MINISTRY OF SOCIAL AFFAIRS AND HEALTH



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**MINISTRY OF AGRICULTURE AND FORESTRY
Veterinary and Food Department
Department of Agriculture**

MINISTRY OF SOCIAL AFFAIRS AND HEALTH

NATIONAL AGENCY FOR MEDICINES

NATIONAL PUBLIC HEALTH INSTITUTE

NATIONAL VETERINARY AND FOOD RESEARCH INSTITUTE

PLANT PRODUCTION INSPECTION CENTRE

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Printing house: Sävypaino, Helsinki 1999

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1. Preface

Bacterial resistance to antimicrobial agents is character of microbes, mainly bacteria, which makes them resistant to antimicrobial agents. During the 1990s the increase in bacterial resistance to antimicrobial agents has emerged, throughout the world, as one of the major threats both in human and veterinary medicine. This development was predicted but the faster than expected spread of resistant bacteria has taken even the experts by surprise. Even a small increase in the prevalence of resistance in the most significant pathogenic bacteria may lead to a large increase in morbidity and mortality.

Experts from the European Union assembled in September 1998 to deliberate upon which measures should be taken to prevent the spread of resistant bacteria. A document entitled The Copenhagen Recommendation, drawn up during the assembly, emphasised the importance of mapping out the spread of antimicrobial resistance in bacteria in order to evaluate the extent of the problem in each European Union country.

Wherever antimicrobial agents are used, resistant bacteria are present. The main sector of resistance-increasing medicine usage, in regard to human health, lies within the health care sector. The antimicrobial agents used in animal care are also significant, not only in increasing the resistance in animal pathogens, but also in bacteria transmitted from animals to humans.

Bacterial resistance is a popular topic of discussion but, with a few exceptions, no comprehensive follow-up studies have been published. This report presents integrated data on the resistance status in Finland of the most clinically significant bacteria, both in human and veterinary medicine, and of the so-called indicator bacteria isolated from animals. It is intended that this will create the framework for publish-

ing a regular report on resistance and its development.

The results in this report originate from recently collected data submitted by organisations and experts who monitor bacterial antimicrobial resistance. To provide a perspective of some years' duration to the current trends, the data for some bacteria originate from previously published studies.

When evaluating the importance of antimicrobial resistance figures, many factors must be taken into consideration, the most important ones being the selection of study material and the study methods. Evidently more bacterial samples are taken from sick humans and sick animals. Therefore the published resistance figures represent the status of organisms which cause more complicated infections. However, considerable work has been put into standardising the study methods during the last few years, producing reliable results.

The production of this report was made possible by the close cooperation between the different disciplines. The publishers of this report would like to thank all experts who, with their work, have contributed to the contents of this report. We hope that this report will play its part in contributing to the work done in controlling bacterial resistance in health care, veterinary medicine and animal husbandry.



Tuula Honkanen-Buzalski



Pentti Huovinen

2. Summary

After the work of decades

Bacterial susceptibility testing has been carried out in Finland for decades. The findings of susceptibility testing have, however, been significant only for clinical practice at a local level. It was not until the 1990s that the first comprehensive studies, covering the whole of Finland, on antimicrobial resistance among the most significant bacteria were published. The main reason for this late date was the difference in the methods used contributing to results that were not truly comparable.

In 1991 a network named the Finnish Study Group for Antimicrobial Resistance (FiRe), dedicated to research into the prevalence of resistance in bacteria isolated from humans, was founded in Finland. At present FiRe has 26 participating clinical microbiology laboratories throughout Finland. During the first few years the main task for FiRe was to study the antimicrobial resistance by sampling the clinically most significant bacteria. Bacterial collection was centralised and the susceptibility tests were carried out applying the same methods for all the bacteria. Because sampling studies are labour intensive, the next step was the standardisation of all bacterial susceptibility testing methods employed by the clinical microbiology laboratories. This led to the publication of the FiRe Standard in 1996. The Standard is updated continually in accordance with FiRe's own quality control measures and with foreign research. 1997 was the first year when all the methods were standardised to a level allowing the comparison of susceptibility results.

Even though as many as 200 000 clinical patient samples are tested annually in participat-

ing FiRe laboratories, samples are submitted only from a small proportion of patients with infections. Doctors working in primary health care see 5 million patients annually. This is coupled with the number of hospitalised patients with infections, which mounts up to hundreds of thousands. Bacterial samples from patients with infections are usually taken only in the most serious cases, excepting urinary and throat cultures. This explains why the majority data on drug resistance represents bacteria which cause complicated, prolonged or otherwise therapeutically challenging infections.

The pattern of antimicrobial agents selected for the bacterial susceptibility testing are in accordance with the FiRe Standard protocol, which has been drawn up in collaboration with physicians specialising in infectious diseases.

The resistance among bacteria isolated from animals has been tested largely for clinical purposes, as in human medicine. The prevalence of resistance among salmonella isolated from animals has been monitored since the 1980s. In 1996 the Ministry of Agriculture and Forestry issued a report on the use of antibiotics in veterinary medicine, which stated that the development of antibiotic resistance among bacteria isolated from animals and from foodstuffs of animal origin, should be systematically monitored. The resistance among the most significant pathogenic animal bacteria should also be monitored. The resistance among the so-called indicator bacteria must also be monitored to evaluate the resistance due to the consumption of antibiotic feed additives by animals.

The resistance among animal pathogenic bacteria has mainly been tested to antibiotics used in veterinary medicine. The resistance among zoonotic bacteria has been tested to important antibiotics used in human medicine.

The resistance among the so-called indicator bacteria has been tested to both antibiotics used in veterinary medicine and to antibiotic feed additives.

The methods of testing for antimicrobial resistance also vary in veterinary medicine, because standards have not yet been applied to all the bacteria tested.

The interpretation of the resistance findings

The number of laboratories submitting susceptibility data varies for each bacterium studied; this may be explained, for example, by some laboratories only testing bacteria submitted by primary health care professionals.

In general the antimicrobial susceptibilities among isolates of a particular type are tested to several antibiotics. The number of isolates given in the report refers to the maximum amount of isolates tested.

Results

Some aspects of the susceptibility status of certain bacteria, isolated as pathogens from primary care, show worrying developments.

Even though the susceptibility status of *Streptococcus pneumoniae*, the most common causative agent of otitis media and pneumonia, has remained favourable to penicillin its resistance to macrolides is on the increase. Should this trend continue, serious problems could materialise in the future especially in the treatment of pneumonia as macrolides are, together with penicillin, the first line treatment of pneumonia. The resistance of *Streptococcus pyogenes*, which causes tonsillitis and skin infections, to macrolides is once again on the increase. The increased resistance among both bacteria may at least partially be explained by increased macrolide consumption, which calls for an adjustment in the antimicrobial policy employed.

The susceptibility status among *Salmonella*

and *Campylobacter*, which cause intestinal infections, to fluoroquinolones is on the decrease, at least in infections acquired abroad. Therefore a microbiological diagnosis before treating intestinal infections is paramount to ensure optimal therapeutic results.

There is also cause for optimism. The susceptibility status of hospital isolates has remained reasonably favourable. The prevalence of methicillin resistant *Staphylococcus aureus* (MRSA) has remained low throughout Finland, and MRSA epidemics have been eradicated or well controlled. The multiresistant *Mycobacterium tuberculosis* is also rare in Finland.

In general the resistance status among bacteria isolated in health care is favourable and its monitoring is adequate. However, it remains necessary to develop further surveillance programmes to ensure that the detection of any changes in the bacterial resistance status is more prompt than at present.

Even though the resistance figures presented here are not statistically fully comparable, it can be noted that the antibiotic resistance status of some pathogenic bacteria, both in humans and in animals, show worrying trends.

In animals, for example, *Brachyspira*, which causes diarrhoea in pigs, and *Staphylococcus*, which causes bovine mastitis, are highly resistant to those antibiotics which are most often used therapeutically. However, there is a very low level of resistance among many bacteria isolated from animals (e.g. broilers). This can be explained by the infrequent therapeutic use of antibiotics, for example in broiler production, which prevents the build-up of antimicrobial resistance. This report presents resistance figures among bacteria isolated from foodstuffs which originate from Finnish animals. The prevalence of resistance remains very low and therefore does not contribute towards problems with antibiotic therapy when treating human infections caused by zoonotic bacteria.

3. Antimicrobial susceptibility in medically significant bacteria

3.1. Pathogens in primary care

Streptococcus pneumoniae

In contrast to South and Central Europe and the USA the antimicrobial susceptibility among pneumococci (*Streptococcus pneumoniae*) has remained highly favourable in Finland. The susceptibility among pneumococci to penicillin, tetracycline and clindamycin show little change. However, a clear upward trend can be detected in the resistance to macrolides (erythromycin) and to sulphatrimethoprim. Strains resistant to macrolides were rare at the beginning of the decade, but during 1997 and 1998 there was a clear increase in resistance. It is noteworthy that among pneumococci which were either resistant to penicillin or had a reduced susceptibility to it, the erythromycin resistance was 19 % in 1995 but as high as 42 % in 1998.

The increase in resistance to sulphatrimethoprim must be viewed with caution as differ-

ences in figures for years 1988-90/1995 and 1997/1998 may be explained, at least to some degree, with differences in susceptibility testing methods.

Material, methods and references

1988-90: Samples of middle-ear fluid of children under six years old collected from six different regions. (n=639)

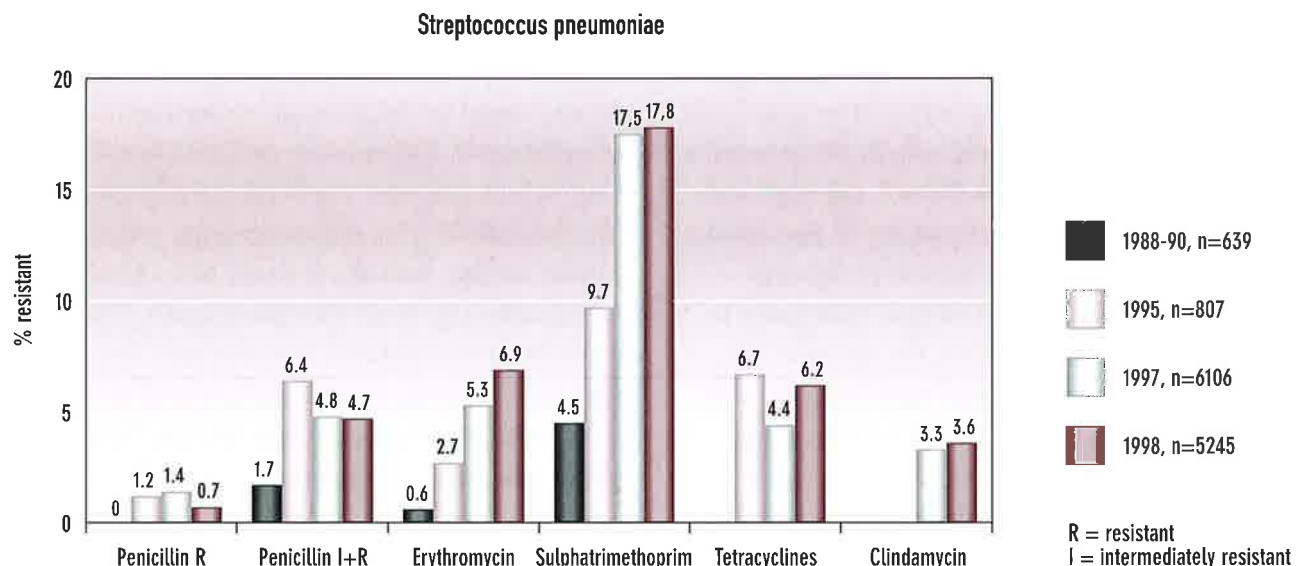
MIC plate dilution method

Nissinen A, Leinonen M, Huovinen P, Herva E, Katila M-L, Kontiainen S, Liimatainen O, Oinonen S, Takala AK, Mäkelä PH. Antimicrobial resistance of *Streptococcus pneumoniae* in Finland, 1987-90. Clin. Infect. Dis. 1995, 20:1275-80.

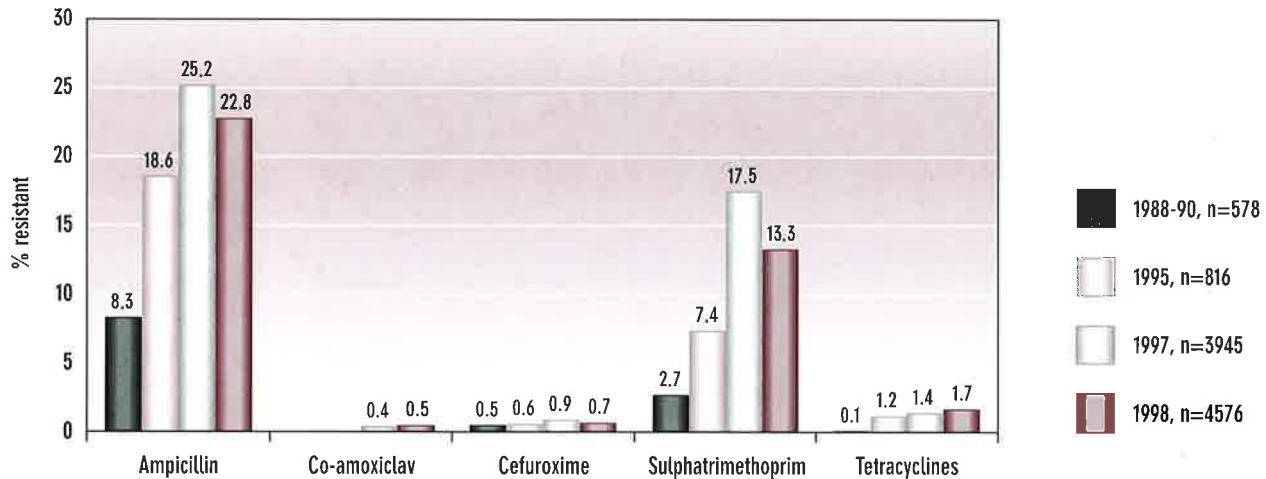
1995: Fifty consecutive isolates, from January to June, submitted by 21 FiRe participating laboratories (n=807)

MIC plate dilution method

Manninen R, Huovinen P, Nissinen A and the



Haemophilus influenzae



Finnish Study Group for Antimicrobial Resistance (FiRe). Increasing antimicrobial resistance in *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* in Finland. *J. Antimicrob. Chemother.* 1997, 40:387-392.

1997: Isolates tested throughout the year by 22 participating FiRe laboratories (n=6106)
Disc sensitivity method in accordance with the FiRe Standard

1998: Isolates tested throughout the year by 20 participating FiRe laboratories (n=5245)
Disc sensitivity method in accordance with the FiRe Standard

Haemophilus influenzae

The level of ampicillin resistance in *Haemophilus* has remained, despite some fluctuation, at approximately 20-25 %. The majority of these isolates produce beta-lactamase which explains the efficacy of co-amoxiclav and cefuroxime therapy. Sulphatrimethoprim resistance is approximately 15 %. The current status of tetracycline resistance is highly favourable.

Material, methods and references

1988-90: Samples of middle-ear fluid of children under six years old collected from six

different regions. (n=578)

MIC plate dilution method

Nissinen A, Herva E, Katila M-L, Kontiainen S, Liimatainen O, Oinonen S, Takala AK, Huovinen P. Antimicrobial resistance in *Haemophilus influenzae* isolated from blood, cerebrospinal fluid, middle-ear fluid and throat samples of children. A nationwide study in Finland in 1988-1990. *Scand. J. Infect. Dis.* 1995, 27:57-61.

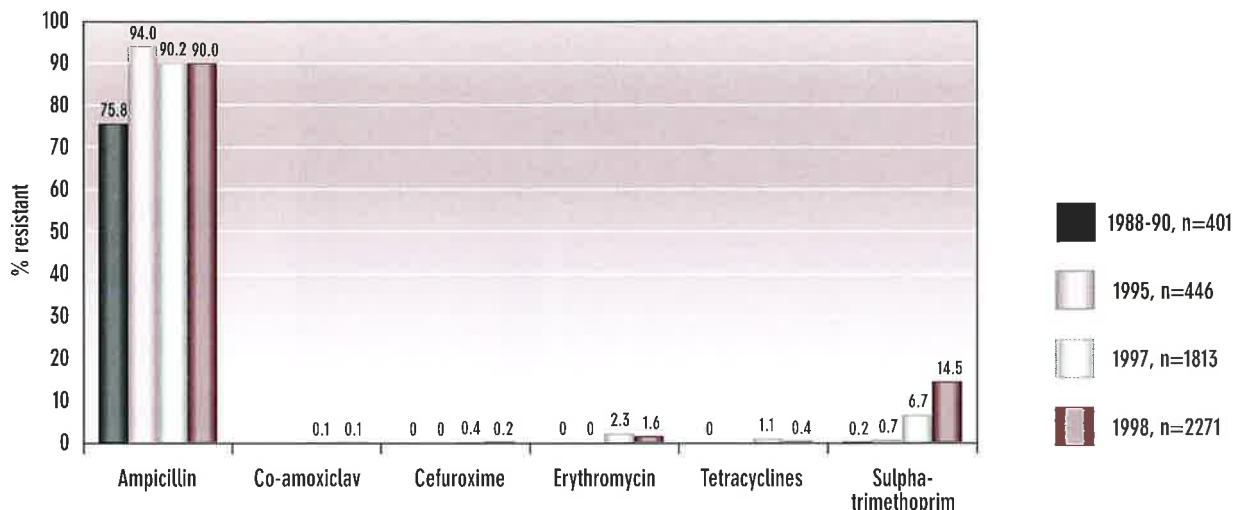
1995: Fifty consecutive *H.influenzae* isolates, from January to June, submitted by 21 participating FiRe laboratories (n=816)

MIC plate dilution method

Manninen R, Huovinen P, Nissinen A and the Finnish Study Group for Antimicrobial Resistance (FiRe). Increasing antimicrobial resistance in *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* in Finland. *J. Antimicrob. Chemother.* 1997, 40:387-392.

1997: Isolates tested throughout the year by 15 participating FiRe laboratories (n=3945)
Disc sensitivity method in accordance with the FiRe Standard

1998: Isolates tested throughout the year by 17 participating FiRe laboratories (n=4576)
Disc sensitivity method in accordance with the FiRe Standard

Moraxella catarrhalis*Moraxella catarrhalis*

The resistance to ampicillin among *Moraxella catarrhalis* has remained at about 90 % for some years. The resistance is beta-lactamase mediated which explains the efficacy of co-amoxiclav and cefuroxime therapy. Macrolide and tetracycline resistance show no change, but there is a clear increase in the occurrence of strains resistant to sulphatrimethoprim.

Material, methods and references

1988-90: Samples of middle-ear fluid of children under six years old collected from six different regions (n=401)

MIC plate dilution method

Nissinen A, Grönroos P, Huovinen P, Herva E, Katila M-L, Klaukka T, Kontiainen S, Liimatainen S, Oinonen S, Mäkelä PH. Development of beta-lactamase-mediated resistance to penicillin in pediatric middle-ear isolates of *Moraxella catarrhalis* in Finland, 1978-1993. Clin. Infect. Dis. 1995, 21:1193- 1196.

1995: Twenty-five consecutive isolates of *M. catarrhalis*, from January to June 1995, submitted by 21 participating FiRe laboratories (n=446) MIC plate dilution method

Manninen R, Huovinen P, Nissinen A and the Finnish Study Group for Antimicrobial Resistance (FiRe). Increasing antimicrobial resistance

in *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* in Finland. J. Antimicrob. Chemother. 1997, 40:387-392.

1997: Isolates tested throughout the year by 20 participating FiRe laboratories (n=1813) Disc sensitivity method in accordance with the FiRe Standard

1998: Isolates tested throughout the year by 15 participating FiRe laboratories (n=2271) Disc sensitivity method in accordance with the FiRe Standard

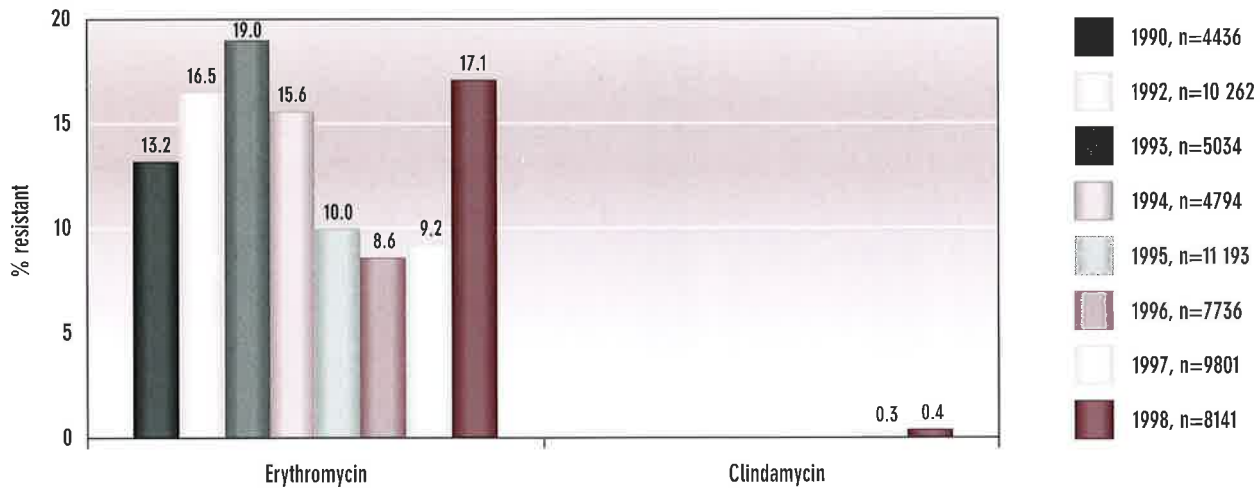
Streptococcus pyogenes

The prevalence of macrolide resistance increased from 1990 to 1993 but showed a decline from 1994 to 1997. This is likely to be due to a decreased consumption of macrolide antibiotics especially in the treatment of group A streptococci infections. The increase in resistance in 1998 has been most pronounced in the region of Helsinki. During 1997 and 1998 the consumption of macrolide antibiotics was once again on the increase.

Material, methods and references

1990: Isolates from six different regions in Finland (n=4436)

Streptococcus pyogenes



MIC plate dilution method

Seppälä H, Nissinen A, Järvinen H, Huovinen S, Henriksson T, Herva E, Jähkölä M, Katilä M-L, Klaukka T, Kontiainen S, Liimatainen O, Oinonen S, Passi-Metsomaa L, and Huovinen P. Emergence of erythromycin resistance in group A streptococci. *N. Engl. J. Med.* 1992, 326:292-297.

1992-1996: Isolates tested throughout the year by participating FiRe laboratories. (n=4794-11 193)

Standardised disc sensitivity method (Nissinen et al. *Scand. J. Infect. Dis.* 1995, 27:52-56)
Seppälä H, Klaukka T, Vuopio-Varkila J, Muotiala A, Helenius H, Lager K, Huovinen P and the Finnish Study Group for Antimicrobial Resistance. The effects of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. *New Engl. J. Med.* 1997, 337:441-446.

1997: Isolates tested throughout the year by 18 participating FiRe laboratories (n=9801)
Disc sensitivity method in accordance with the FiRe Standard

1998: Isolates tested throughout the year by 15 participating FiRe laboratories (n=8141)
Disk sensitivity method in accordance with the FiRe Standard

Neisseria gonorrhoeae

The proportion of ciprofloxacin resistant strains has remained at the same level in 1997 and 1998. The prevalence of penicillin and tetracycline resistant gonococcus is very high and therefore these agents are no longer used to treat gonorrhoea.

Material, methods and references

1986: Isolates collected in the regions of Helsinki, Tampere and Turku (n=1535)

MIC plate dilution method

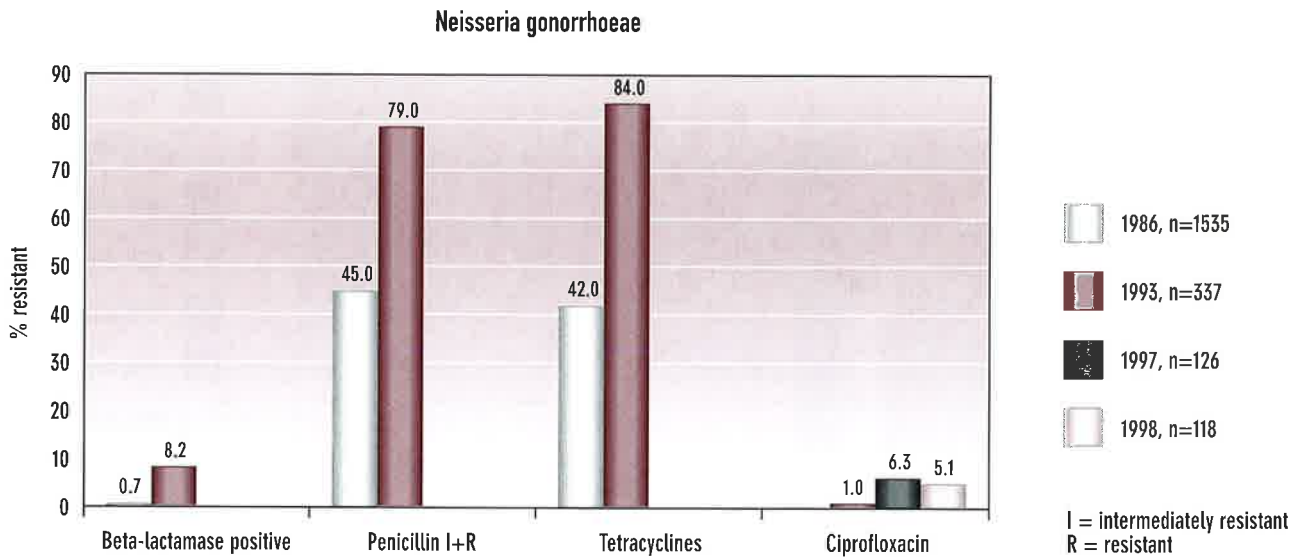
Nissinen A, Järvinen H, Liimatainen O, Jähkölä M, Huovinen P and the Finnish Study Group for Antimicrobial Resistance (FiRe). Antimicrobial resistance in *Neisseria gonorrhoeae* in Finland, 1976 to 1995. *Sex. Transm. Dis.* 1997, 24:576-581.

1993: Isolates collected throughout Finland (n=337)

MIC plate dilution method (Reference as above)

1997: Isolates tested throughout the year by 14 participating FiRe laboratories (n=126)

Disc sensitivity method in accordance with the FiRe Standard; ciprofloxacin susceptibility of the majority of the isolates was tested by the E-test (MIC determination method)



1998: Isolates tested throughout the year by 9 participating FiRe laboratories (n=118)
Disc sensitivity method in accordance with the FiRe Standard; ciprofloxacin susceptibility of the majority of the isolates was tested by the E-test (MIC determination method)

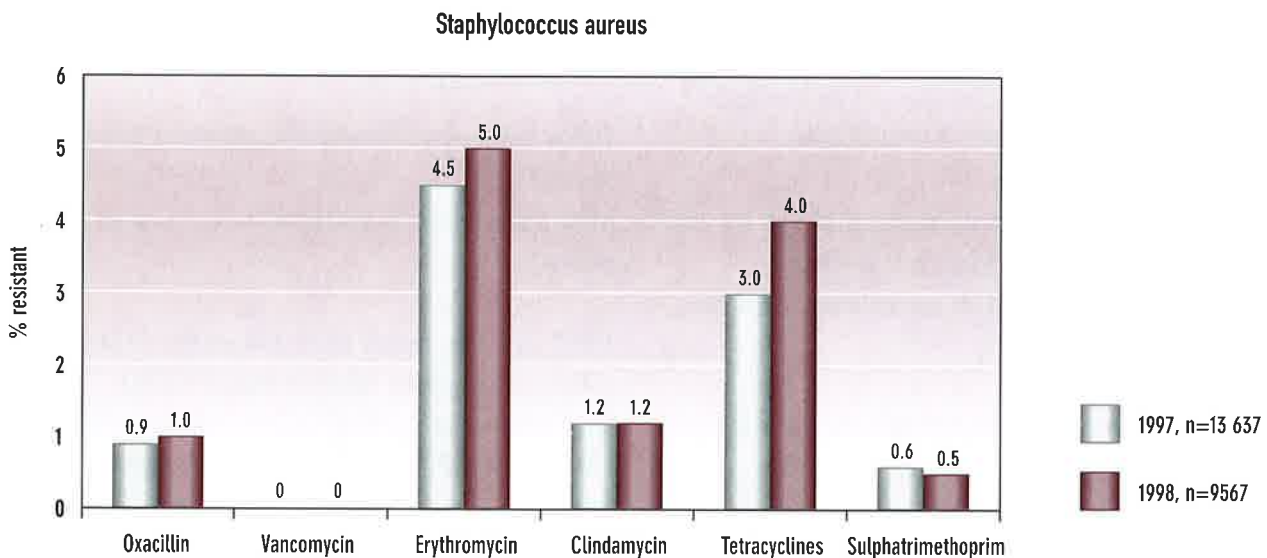
tam antibiotics is only about 1 % of all isolates. The resistance to other antibiotics is also below 5 %.

1997: Isolates tested throughout the year by 15 participating FiRe laboratories (n=13 637)
Disc sensitivity method in accordance with the FiRe Standard

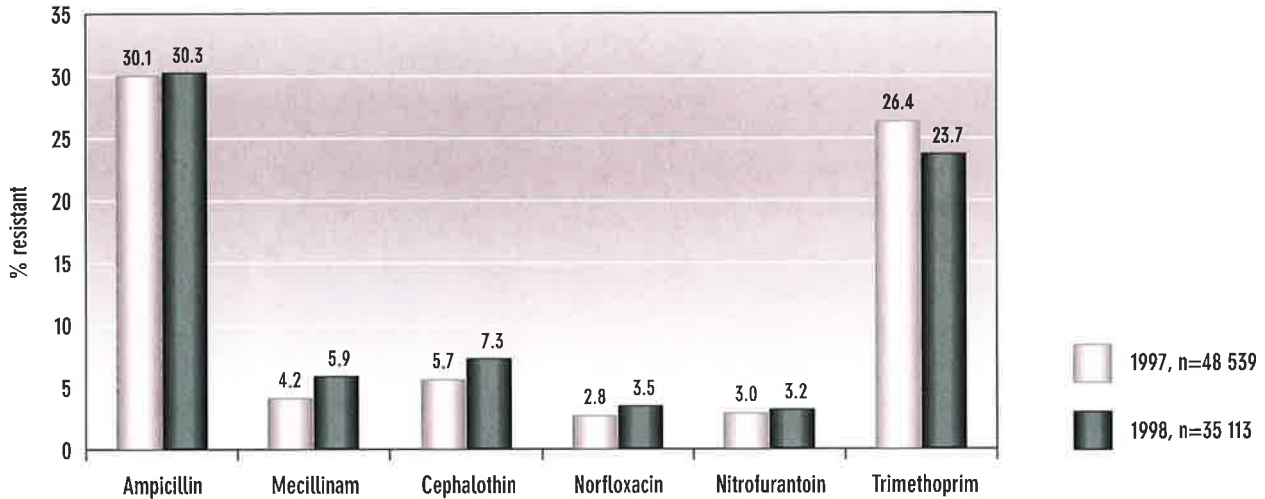
Staphylococcus aureus

The status of susceptibility to *Staphylococcus aureus* strains isolated in primary care is highly favourable. The prevalence of strains resistant to oxacillin and at the same time to all beta-lac-

1998: Isolates tested throughout the year by 12 participating FiRe laboratories (n=9567)
Disc sensitivity method in accordance with the FiRe Standard



Urinary Escherichia coli



Urinary Escherichia coli

E. coli isolated from primary care urine samples are highly susceptible to all antibiotics except ampicillin and trimethoprim. Resistance to norfloxacin, which is a fluoroquinolone, and to nitrofurantoin is below 5%. The prevalence of resistance to mecillinam and cephalothin (a first generation cephalosporin) is somewhat higher.

Material, methods and references

1997: Isolates tested throughout the year by 14 participating FiRe laboratories. (n=48 539)
Disc sensitivity method in accordance with the FiRe Standard

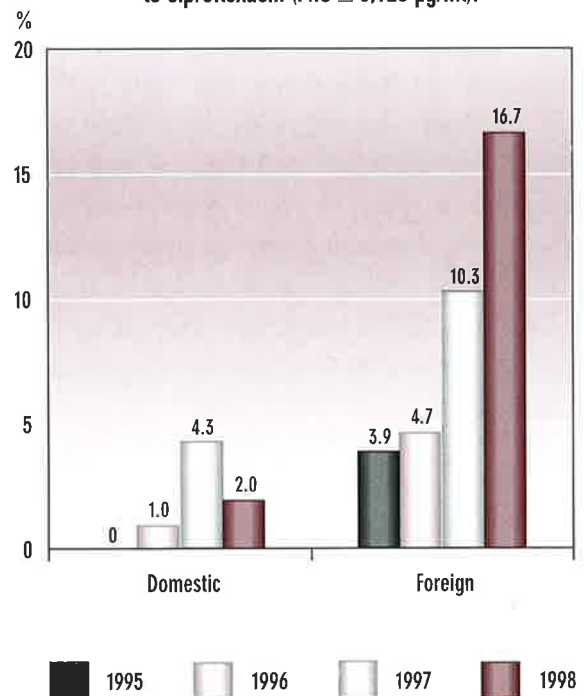
1998: Isolates tested throughout the year by 13 participating FiRe laboratories (n=35 113)
Disc sensitivity method in accordance with the FiRe Standard

Salmonella

Salmonella infections are usually treated with fluoroquinolones as other antimicrobials are not clinically effective and contribute to a prolonged carrier status. According to susceptibility test standards all Salmonella isolated in Finland are susceptible to ciprofloxacin, which represents

fluoroquinolones in the susceptibility tests. Even though the strains do not exhibit true resistance according to guidelines (MIC $\geq 2 \mu\text{g/ml}$), several cases of treatment failure have been described in medical literature. The causative agents in these treatment failures have been strains with MIC from 0.125 to 2 $\mu\text{g/ml}$. To address this concern the Antimicrobial Research Laboratory and the Laboratory of Enteric Pathogens at the National

Salmonella isolates with reduced susceptibility to ciprofloxacin (MIC $\geq 0,125 \mu\text{g/ml}$).



Public Health Institute have introduced more intensive monitoring on the susceptibility status of salmonella of this type in Finland. The material consists of isolates collected annually from one hundred sequential salmonella isolates both of domestic and foreign origin (in 1996 two hundred isolates of each category), which have been susceptibility tested using MIC plate dilution method. The susceptibility status of isolates of domestic origin has remained favourable, whereas the susceptibility status of isolates of foreign origin show worrying downward trends. The genome of all tested strains with lowered susceptibility to ciprofloxacin have been shown to carry a mutation, which is likely to explain the lowered sensitivity.

References

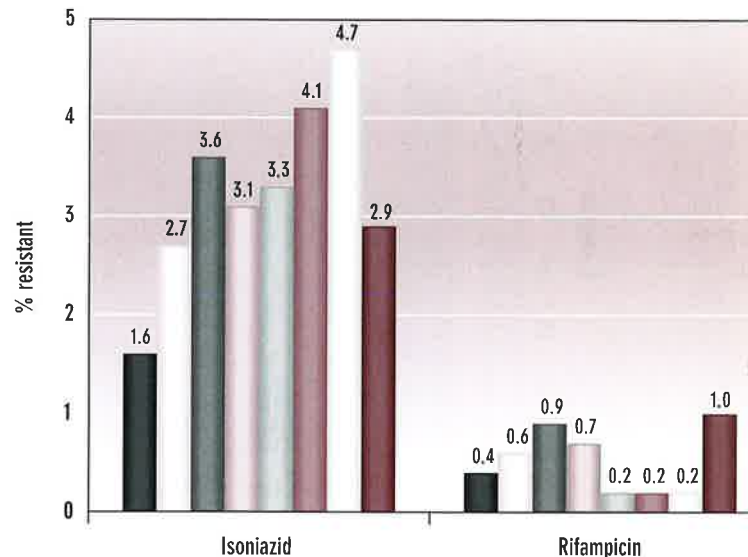
Hakanen A, Siitonen A, Kotilainen P, Huovinen P. Increasing fluoroquinolone resistance in Salmonella serotypes in Finland during 1995-1997. *J. Antimicrob. Chemother.* 1999, 43:145-148.
 Hakanen A, Kotilainen P, Jalava J, Siitonen A, Huovinen P. Detection of decreased fluoroquinolone susceptibility in salmonellas and validation of nalidixic acid screening test. *J. Clin. Microbiol.* 1999 (in press).

Campylobacter

The HUCH (Helsinki University Central Hospital) Diagnostics has organised intensified monitoring of antimicrobial resistance among campylobacter. In 1996-98 ciprofloxacin resistance among campylobacter has fluctuated between 32 and 37 %. Ciprofloxacin resistance is rare in cases acquired domestically. The number of erythromycin resistant strains has remained at around 1-2 %.

Helicobacter pylori

In the data from the HUCH Diagnostics, metronidazole resistance among Helicobacter has fluctuated between 48 and 56 % during the



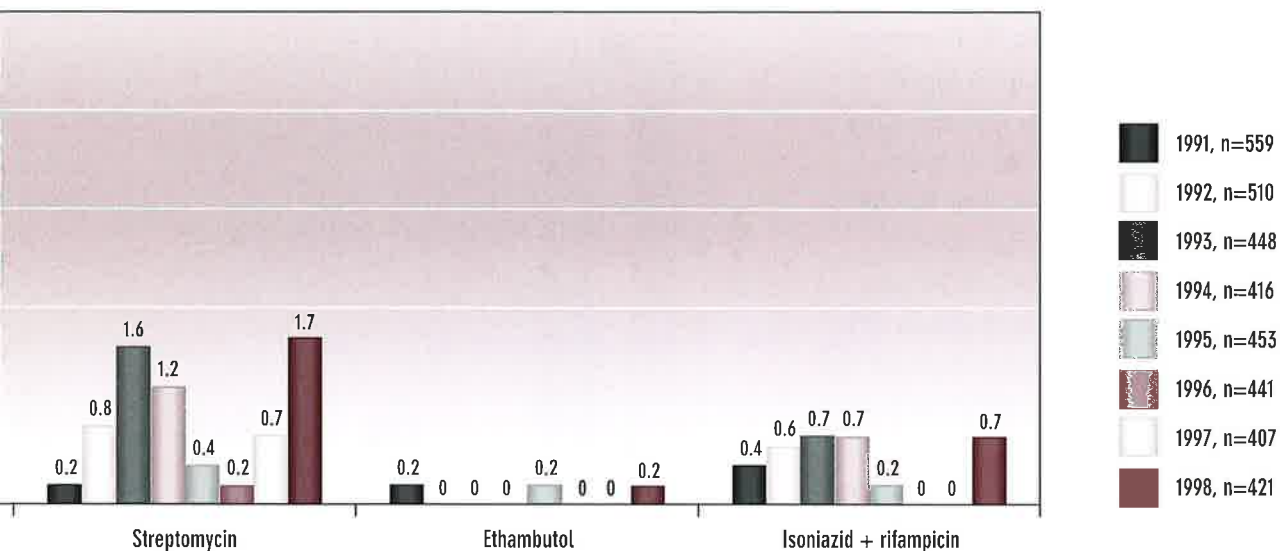
last few years. The occurrence of clarithromycin resistance has remained below 10 %. These findings are based on samples collected during routine diagnostic measures and are irrespective of the patient having received previous Helicobacter eradication therapy.

Mycobacterium tuberculosis

The prevalence of antimicrobial resistance in *Mycobacterium tuberculosis*, isolated in Finland, is among the lowest in the world, and the resistance status has shown little change in the last few years. Isoniazid and rifampicin are the most important agents used in the treatment of tuberculosis. In Finland only a few isolates resistant to rifampicin are identified annually, and isoniazid resistance is 1.5-4.5 %. A combination resistance to both isoniazid and rifampicin, which is the most difficult resistance to treat, is very rare with no cases reported for some years. So far the unfavourable resistance status in Russia and the Baltic Countries has not been reflected in Finland.

Material, methods and references

All *M. tuberculosis* bacteria isolated in Finland and submitted to the Mycobacteria Reference



Laboratory at the National Public Health Institute are tested annually. The method used has been the specialised disc sensitivity method designed for the susceptibility testing of tuberculosis bacteria. Wayne LG, Krasnow I. Preparation of tuberculosis susceptibility testing mediums by impregnated discs. Am. J. Pathol. 1966, 45:769-771.

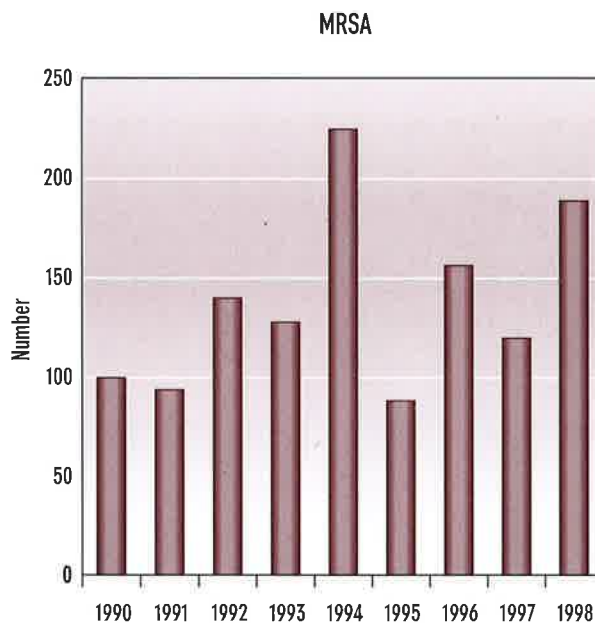
lates submitted to the Laboratory for Hospital Infections at the National Public Health Institute. Figures from 1995 onwards are the number of MRSA positive cases entered into the National Public Health Institute's Register of Infectious Diseases. The actual figure for 1995 is a little higher than the one presented; the discrepancy being due to the National Public Health Institute's Register of Infectious Diseases being established in 1995 and it is possible that not all MRSA isolates were registered.

3.2. Pathogens in hospitals

MRSA

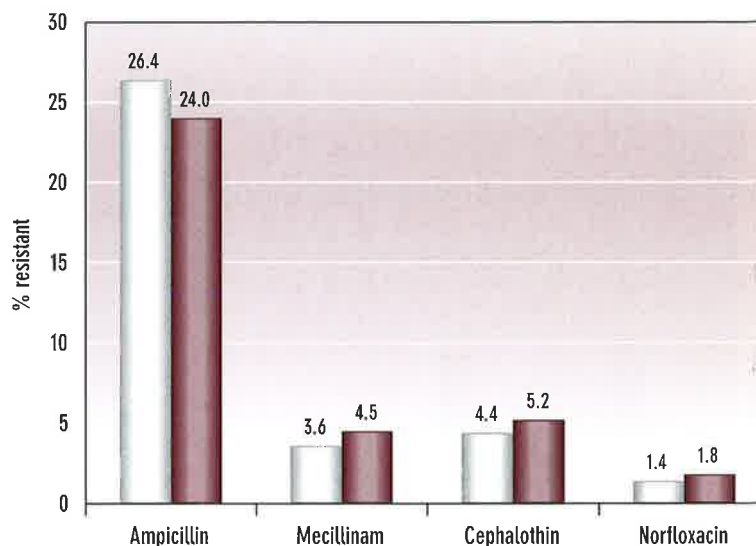
The prevalence of methicillin (oxacillin) resistant Staphylococcus aureus (MRSA) isolates has varied from year to year depending on the epidemiological situation. In 1998 of the 717 cases of Staphylococcus aureus isolated from blood cultures 0.7 % were MRSA positive (5 isolates). The corresponding figure for 1997 was 0.5 % (4/746). No conclusions about a general trend can be drawn from these figures as the number of MRSA positive isolates remains very low.

The figures for 1990 and 1991 were submitted by Orion Diagnostica from their reports. The figures for 1992-94 comprise MRSA iso-



Staphylococcus aureus

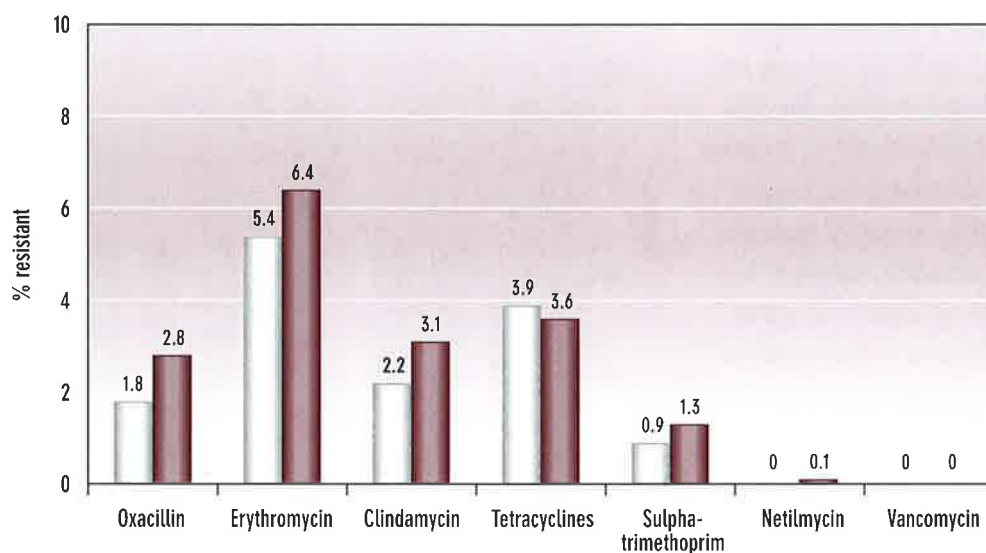
The status of susceptibility to *Staphylococcus aureus* strains isolated in hospitals is highly favourable. The prevalence of strains resistant to oxacillin (MRSA), and at the same time to all beta-lactam antibiotics, is low. The MRSA figures reported by laboratories are clearly higher than the actual number of MRSA isolates would suggest. This could be explained by a proportion of the samples being submitted for screening purposes and several MRSA isolates representing a single patient. The proportion of MRSA in 1998 was 0.7 % (189 MRSA strains among the total of 26 677 *S. aureus* isolates from both hospitals and primary care); the corresponding figure for 1997 was 0.4 % (120 MRSA strains among 32 529 *S. aureus* isolates). These figures compare well with the proportion of MRSA isolates among blood cultures from the same years (0.7 % and 0.5 %, respectively; see number of MRSA isolates). The higher figures for oxacillin resistance are presented here because the prevalence of resistance of other antimicrobials has been calculated in accordance with this oxacillin resistance figure. Erythromycin resistance is just above 5 %, but otherwise the prevalence of resistance is below that. To date no vancomycin resistant strains have emerged.



1997: Isolates tested throughout the year by 18 participating FiRe laboratories (n=18 892)
Disc sensitivity method in accordance with the FiRe Standard

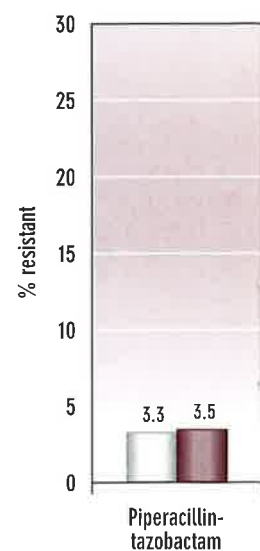
1998: Isolates tested throughout the year by 16 participating FiRe laboratories (n=17 110)
Disc sensitivity method in accordance with the FiRe Standard

Staphylococcus aureus

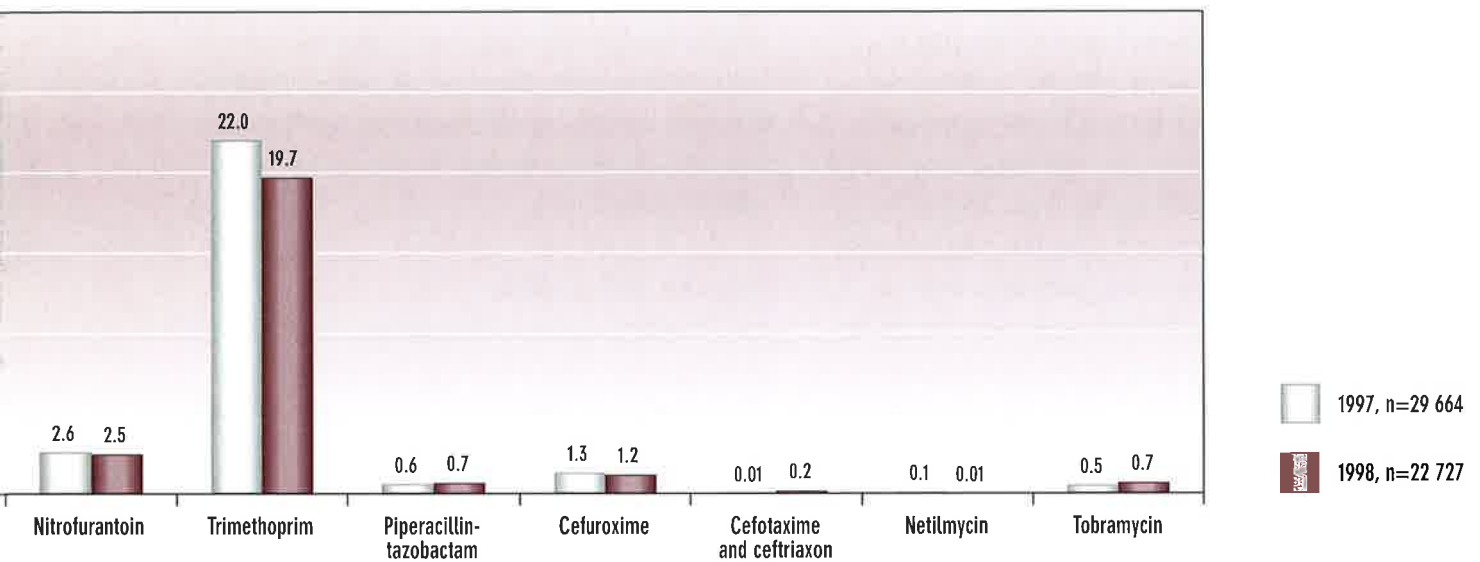


1997,
n=18 892

1998,
n=17 110



Escherichia coli



Escherichia coli

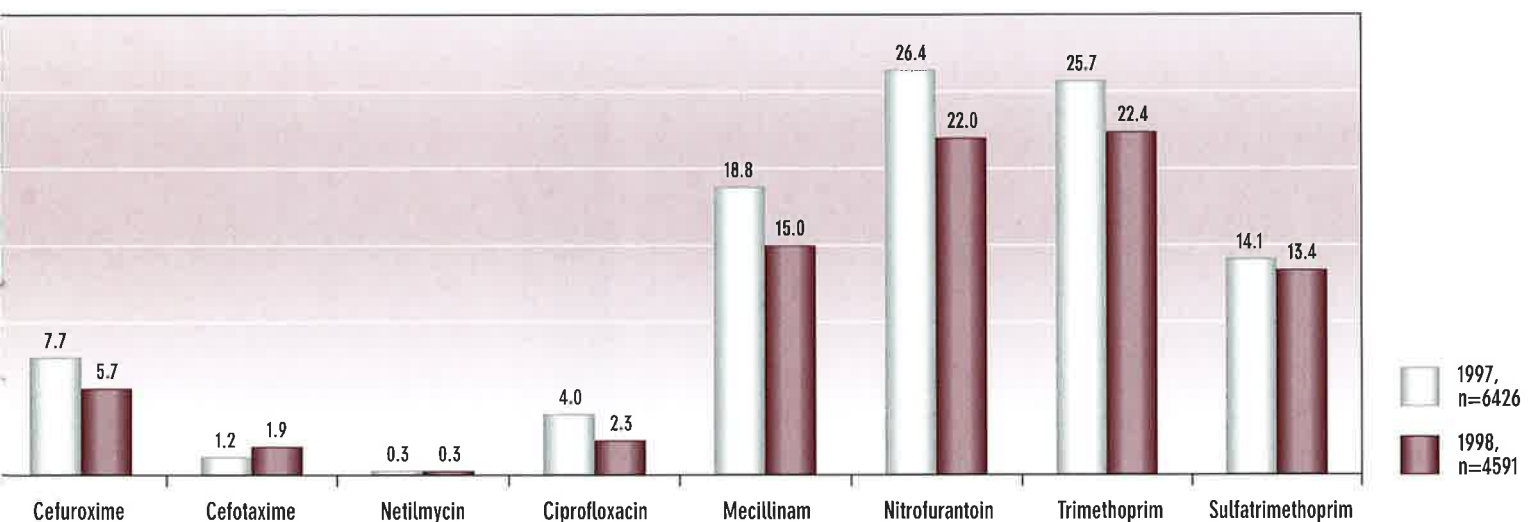
E. coli collected in hospitals are mainly isolated from urine samples. The level of resistance of these isolates is very similar to that of *E. coli* collected from urine samples from the primary health care sector. The efficacy of medication administered intravenously in hospitals is excellent.

Material and methods

1997: Isolates tested throughout the year by 19 participating FiRe laboratories (n=29 664)
Disc sensitivity method in accordance with the FiRe Standard

1998: Isolates tested throughout the year by 16 participating FiRe laboratories (n=22 727)
Disc sensitivity method in accordance with the FiRe Standard

Klebsiella spp.



Klebsiella spp.

Klebsiella isolated from hospital samples is highly susceptible to cefuroxime, cefotaxime (a third generation cephalosporin), piperacillin-tazobactam, netilmicin (an aminoglycoside) and ciprofloxacin (a fluoroquinolone). However, high levels of resistance to antimicrobial agents used to treat urinary tract infections have emerged during the follow-up period; an exception being sulphatrimethoprim, its resistance levels being about half of those of trimethoprim and nitrofurantoin.

Material and methods

1997: Isolates tested throughout the year by 19 participating FiRe laboratories (n=6426)
Disc sensitivity method in accordance with the FiRe Standard

1998: Isolates tested throughout the year by 15 participating FiRe laboratories (n=4591)
Disc sensitivity method in accordance with the FiRe Standard

Pseudomonas aeruginosa

Pseudomonas aeruginosa hospital isolates are highly susceptible to ceftazidime, imipenem and

tobramycin. The prevalence of resistance to ciprofloxacin and piperacillin-tazobactam is slightly higher in relation to other antimicrobials. When comparing the resistance figures the large inter-hospital variation, which is dependant on the epidemic situation, must be taken into account.

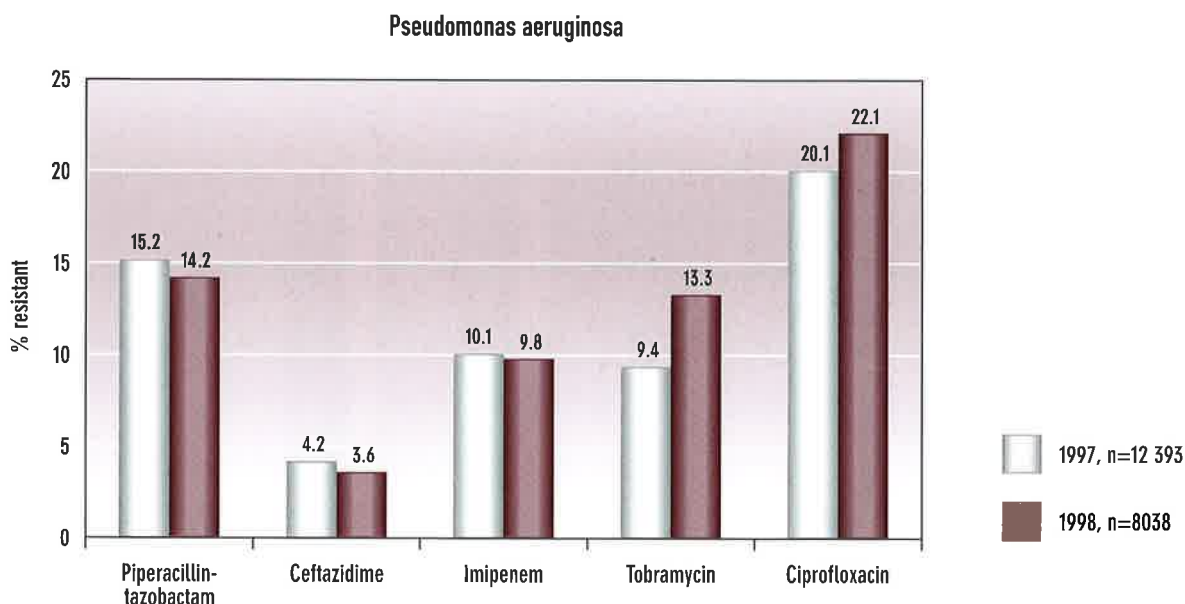
Material and methods

1997: Isolates tested throughout the year by 19 participating FiRe laboratories (n=12 393)
Disc sensitivity method in accordance with the FiRe Standard

1998: Isolates tested throughout the year by 19 participating FiRe laboratories (n=8038)
Disc sensitivity method in accordance with the FiRe Standard

Enterococcus faecalis

The majority of *Enterococcus faecalis* hospital isolates are susceptible to the antimicrobials tested. The seven vancomycin resistant isolates (0.07 %) reported in 1997 submitted by five different laboratories constitute a rare exception; however, there is a possibility of a methodological error in either typing or susceptibility testing.



Material and methods

1997: Isolates tested throughout the year by 16 participating FiRe laboratories (n=11 257)
 Disc sensitivity method in accordance with the FiRe Standard

1998: Isolates tested throughout the year by 16 participating FiRe laboratories (n=10 378)
 Disc sensitivity method in accordance with the FiRe Standard

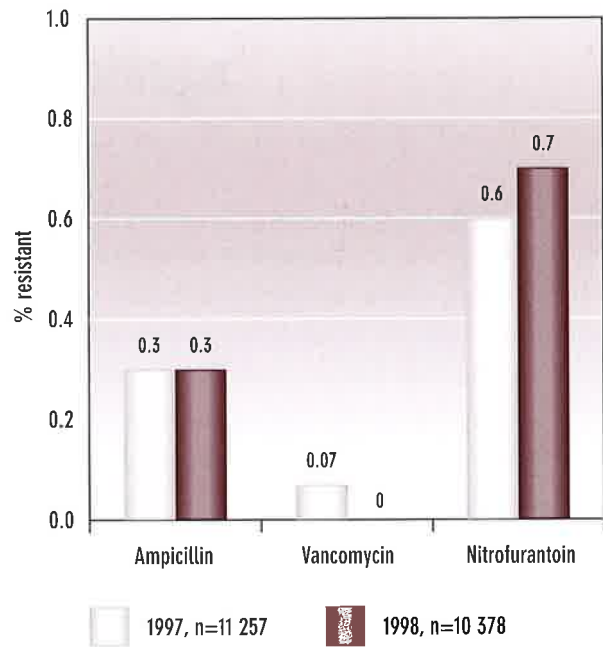
Enterococcus faecium

The majority of *Enterococcus faecium* hospital isolates are resistant to ampicillin. In the data for 1997 the prevalence of vancomycin resistance is high because the material includes a large number of samples submitted for screening purposes especially by Helsinki University Central Hospital (HUCH). Two different figures are presented here, one without the HUCH figures. The figures for other hospitals with lower incidence of resistance also contain some screening samples. Nitrofurantoin resistance has remained below 3 %.

Material and methods

1997: Isolates tested throughout the year by 15 participating FiRe laboratories (n=2147)

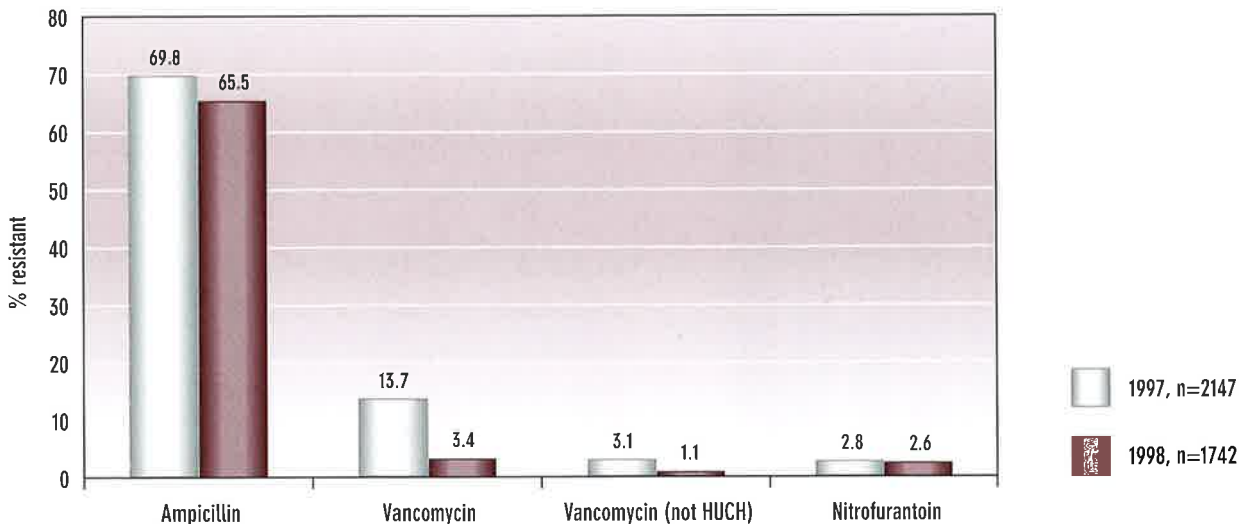
Enterococcus faecalis



Disc sensitivity method in accordance with the FiRe Standard

1998: Isolates tested throughout the year by 14 participating FiRe laboratories (n=1742)
 Disc sensitivity method in accordance with the FiRe Standard

Enterococcus faecium



4. Consumption of antimicrobial agents in health care

The figures for the consumption of antimicrobial agents have been published annually as The Finnish Statistics on Medicines for over twenty years. The Finnish Statistics on Medicines is published jointly by the National Agency for Medicines (Lääkelaitos) and the Social Insurance Institution of Finland (KELA). The level of consumption of systemic antibacterial drugs (ATC Code J01) showed no change from 1990 to 1995 with DDD (defined daily dose) /1000 inhabitants/day fluctuating from 19.4 to 21.3. However, since 1996 a downward trend has been evident, and the decade's lowest consumption level of 18.9 DDD/1000 inhabitants/day was reached in 1998. The hospital share of the total consumption has for a long time been over ten per cent and in 1998 it was 14 %.

The most used antibacterial drugs in Finland in 1998 were penicillins, including amoxicillin (6.02 DDD/1000 inhabitants/day), tetracyclines

(4.90 DDD/1000 inhabitants /day), cephalosporins (2.60 DDD/1000 inhabitants/day; 2.10 DDD/1000 inhabitants/day of first generation cephalosporins), sulphonamides and trimethoprim (2.36 DDD/1000 inhabitants/day) and macrolides (2.08 DDD/1000 inhabitants/day). More detailed information about the usage of antibacterial drugs has been published in The Finnish Statistics on Medicines.

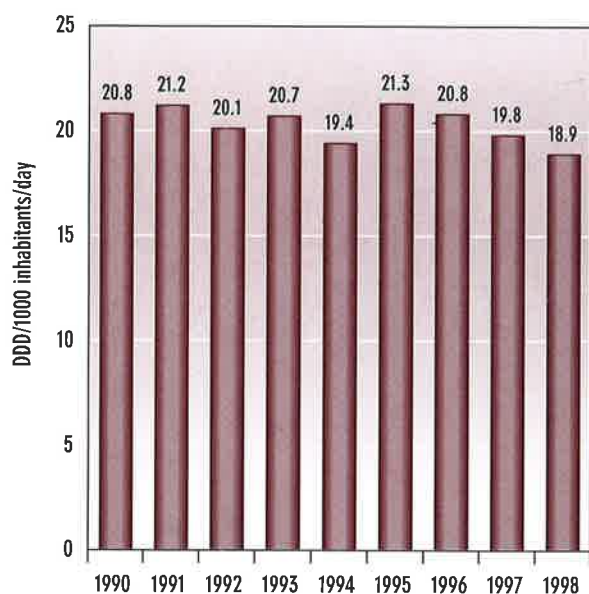
The main reason for the decline in the consumption of macrolides is likely to be the ongoing reassessment, throughout the health care system, of the principles of antimicrobial therapy. The increased importance of bacterial resistance has emphasised the need for implementing a prudent antibiotic policy. The MIKSTRA programme (Antimicrobial Treatment Strategies) was introduced in 1998, which is designed to develop the diagnostics and optimise the treatment of the most common infections encountered in primary care (MIKSTRA work group, 1999). The MIKSTRA programme includes, as well as drug consumption surveillance, the drawing up of treatment guidelines for new primary care infections in conjunction with the current care guidelines supplied by the Finnish Medical Society Duodecim.

References

National Agency for Medicines (Lääkelaitos) and the Social Insurance Institution (KELA). The Finnish Statistics on Medicines 1990-1998.

MIKSTRA-work group. Antibiootteja määrätään entistä harkitummin. MIKSTRA-ohjelman ensimmäisiä tuloksia. (More discretion exercised in antibiotic prescription than before. First results from the MIKSTRA programme) Suom. Lääkäril. (Finn. Med. J.) 1999, 54:3513-3518. (In Finnish)

Consumption of antibacterial agents in Finland.



5. Antimicrobial resistance among bacteria isolated from animals and foodstuffs originating from animals

5.1. Resistance in indicator bacteria

Antimicrobials are used in animal husbandry both therapeutically and as feed additives. In Finland the main consumption of antimicrobial feed additives has been among the pig and poultry industry. The effect of antimicrobial feed additives is based mainly on their prophylactic effect on certain pathogenic bacteria. The consumption of antimicrobials as feed additives has been restricted in recent years, as it has been shown that their consumption will increase the resistance not only among the pathogenic bacteria but also among the bacteria of normal flora. An example is a former poultry feed additive, avoparcin, which has been shown to contribute towards a so-called cross resistance to a highly important human antimicrobial of the same group, vancomycin. The resistance of normal flora bacteria is in general studied using *Escherichia coli* and enterococci (usually *Enterococcus faecalis* and *E. faecium*) as indicator bacteria. Systematic research aimed at indicator bacteria is relatively new. In 1996 the first widespread study on antimicrobial resistance in indicator bacteria from broilers and pigs was carried out in Finland.

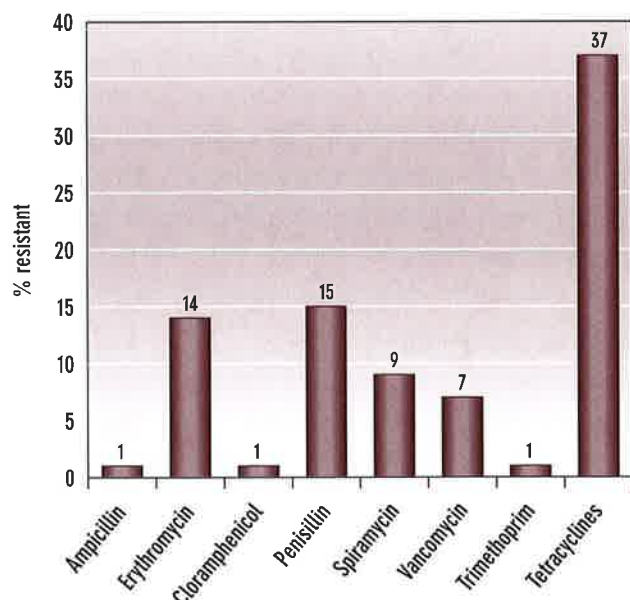
Enterococci and Escherichia coli in broilers

Isolates from the faeces and neck skin samples of healthy broilers included both *Enterococcus* and *E. coli*, which are considered appropriate to demonstrate the resistance among non-pathogenic bacteria, namely indicator bacteria. The resistance among *Enterococcus* to eight anti-

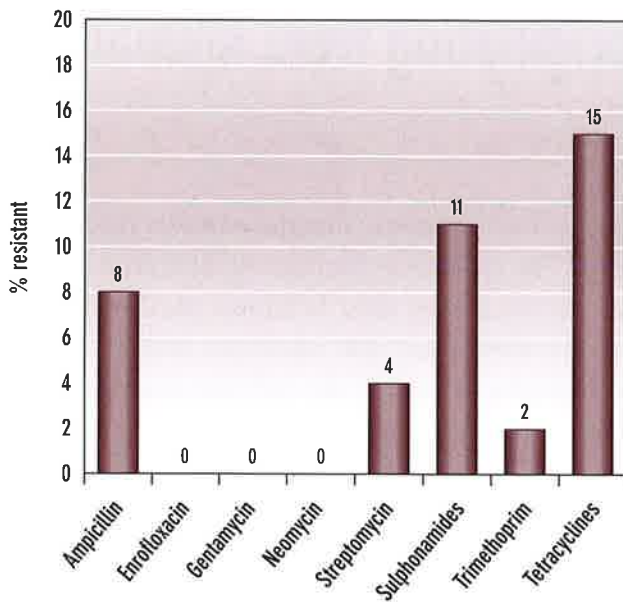
microbials used in animal therapeutics was determined. The resistance among enterobacteria to vancomycin, a drug used in human medicine, was also determined. The resistance among *Enterococcus faecalis* to six antimicrobial feed additives was determined.

Enterococci were highly susceptible to antimicrobials used in animal therapeutics. Only the resistance to tetracycline (37 %) was higher than that of the others; poultry infections are treated with tetracycline more often than with the other antimicrobials tested. The tylosin resistance among *Enterococcus* was 9 %. Four per cent of *Enterococcus* exhibited resistance to three or more antimicrobials. Among feed additives there was resistance to avoparcin (11 %), bacitracin (19 %) and virginiamycin (17 %). The use of virginiamycin was discontinued in

Prevalence of antimicrobial resistance among *Enterococcus* (n=533) isolated from broilers in 1996.



Prevalence of antimicrobial resistance among *E. coli* (n=341) isolated from broilers in 1996.



1990, the use of zinc bacitracin in 1993 and the use of avoparcin in 1996. Because no resistance figures exist from the time period when the beforementioned feed additives were used, no comment may be made about the change in resistance figures. Monensin and salinomycin continue to be used as feed additives, no occurrence of resistance to them was detected and they are not known to contribute towards cross resistance with therapeutic antimicrobials. Avilamycin has not been used in Finland.

The resistance among *E. coli* to ampicillin, streptomycin and trimethoprim was below 10 %. The figure for sulphonamides and tetracycline was somewhat higher. Fourteen percent of *E. coli* isolates were multiresistant strains.

The susceptibility of indicator bacteria from broilers to therapeutic antimicrobials reflects the low consumption of antimicrobials in broiler production.

Material and methods

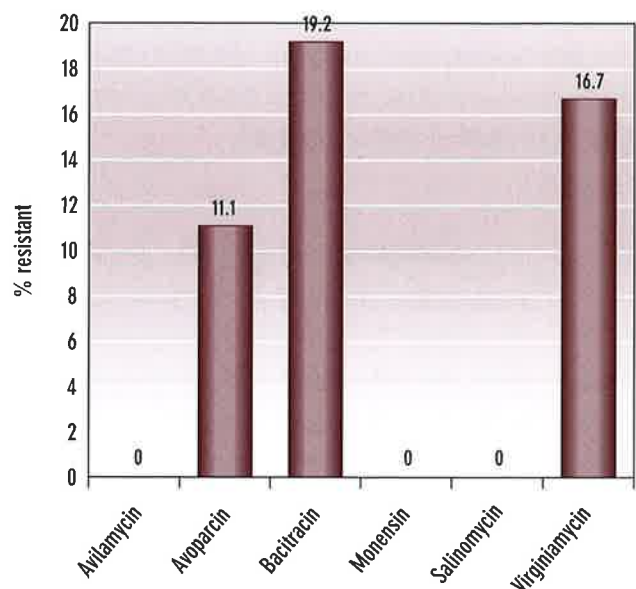
At slaughter the total of 541 *Enterococcus* isolates and 342 *E. coli* isolates were identified from the faeces (n=86) and neck skin samples (n=85) from broilers. The samples originated from 79 farms, which represented over one third of all broiler producers. The antimicrobial

resistance to ampicillin, erythromycin, chloramphenicol, spiramycin, trimethoprim and vancomycin was determined in accordance with a NCCLS (vol. 34, no 20, 1994) standard. The resistance to tylosin was tested by determining MIC. The resistance among *Enterococcus faecium* (n=52) to carbadox, olaquinox, avilamycin, avoparcin, zinc bacitracin, monensin, salinomycin, tylosin and virginiamycin was tested by determining MIC. Isolates were considered resistant to carbadox and olaquinox if they had a MIC \geq 64 μ g/ml. The corresponding breakpoint for avilamycin, avoparcin, monensin, salinomycin and tylosin was 16 μ g/ml, for zinc bacitracin 128 μ g/ml and for virginiamycin 4 μ g/ml.

References

Tylosin and spiramycin as feed additives, Publications of Ministry of Agriculture and Forestry 5/1997, Authors: Tast E, Honkanen-Buzalski T and Mannerkorpi P.
Associations between the use of antimicrobial agents for growth promotion and the occurrence or resistance among *Enterococcus faecium* from broilers and pigs in Denmark, Finland and Norway. Aarestrup F. M. et al. (manuscript)

Prevalence of resistance to antimicrobial feed additives among *Enterococcus faecium* isolated from broilers in 1996.



Enterococci and Escherichia coli in pigs

Both enterococci and *E. coli* were isolated from faecal samples collected from fattening pigs at slaughter. The antimicrobial resistance of these indicator bacteria was determined. The resistance in enterococci was determined to nine antimicrobials, of these neither chloramphenicol nor vancomycin is used in animal therapeutics. The resistance in *E. coli* was determined to eight antimicrobials used in animal therapeutics and to two antimicrobial feed additives, carbadox and olaquinox. The resistance in *Enterococcus faecium* was determined to six antimicrobial feed additives.

The prevalence of resistance among enterococci isolated from pigs was over 50 % to tetracycline, over 10 % to erythromycin and spiramycin and 15 % to tylosin. These are all used in animal therapeutics. The resistance percentages are higher than the corresponding figures obtained from broilers (Page 24). The prevalence of resistance to antimicrobial feed additives was as follows: avoparcin 4.4 %, zinc

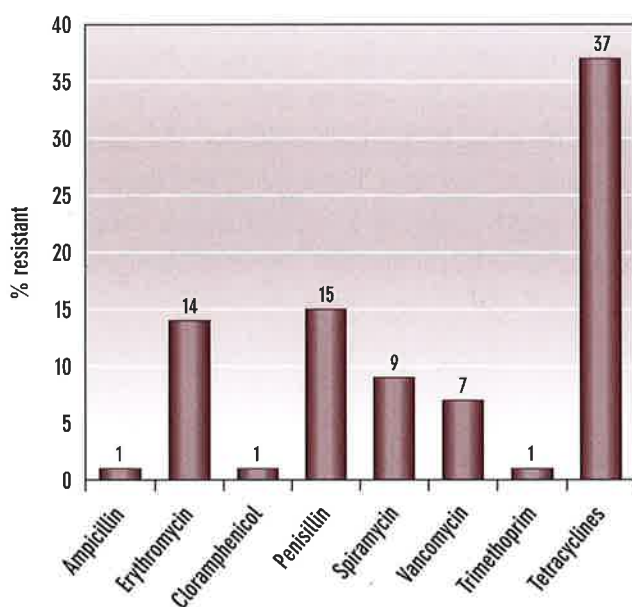
bacitracin 9.3 % and virginiamycin 2.3 %. The use of avoparcin was discontinued in Finland in 1995. Zinc bacitracin has not been used since 1993 and virginiamycin has not been used since 1990. (Page 40).

The prevalence of resistance among *E. coli* was highest to tetracycline, sulphonamides and streptomycin. When the resistance figures of indicator bacteria and pathogenic *E. coli* are compared (Page 31) it is noted that the pathogenic bacteria were always more resistant, but the resistance profile is similar. The resistance to antimicrobial feed additives, carbadox and olaquinox, was 11 % and 24 %, respectively. Carbadox and olaquinox have been regularly added to commercial piglet feed and to some fattening pig feed meal throughout the 1990s (Page 40). In September 1999 the use of carbadox and olaquinox as feed additives in pigs were banned in European Union.

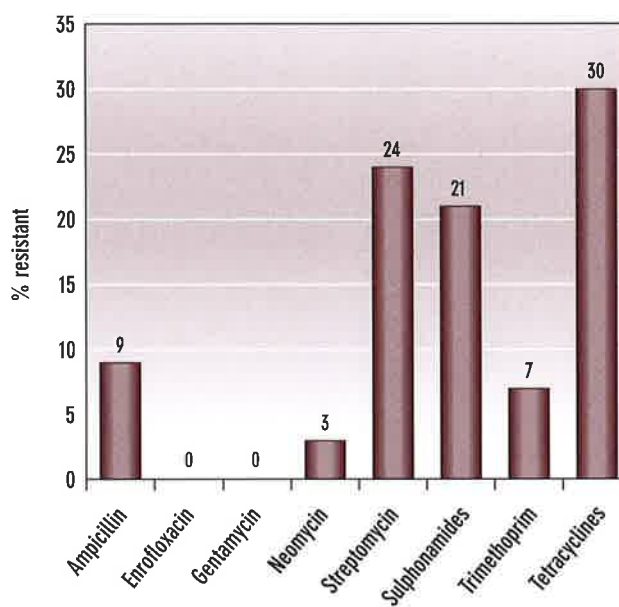
Material and methods

The enterococci and *E. coli* were isolated at three abattoirs; the pigs originated from 180 different farms. The resistance among enterococci (n=204 resistance tested) was tested ac-

Prevalence of antimicrobial resistance among *Enterococcus* (n=204) isolated from the faeces of fattening pigs in 1996.



Prevalence of antimicrobial resistance among *Escherichia coli* (n= 357) isolated from the faeces of fattening pigs in 1996.



cording to a NCCLS standard (vol. 34, no 20, 1994) to ampicillin, erythromycin, chloramphenicol, penicillin, spiramycin, tetracycline, trimethoprim and vancomycin. Tylosin resistance was tested by determining MIC, and isolates with MIC ≥ 16 $\mu\text{g/ml}$ were considered resistant. The resistance among *E. coli* (n=357) was determined to ampicillin, enrofloxacin, gentamicin, neomycin, streptomycin, sulfonamides, sulphatrimethoprim and tetracyclines. The resistance among *E. coli* to carbadox and olaquinox was also determined.

The resistance among *Enterococcus faecium* (n=43) to carbadox, olaquinox, avilamycin, avoparcin, zinc bacitracin, monensin, salinomycin, tylosin and virginiamycin was tested by determining MIC. Isolates with MIC ≥ 64 $\mu\text{g/ml}$ were considered resistant to carbadox and olaquinox. The corresponding breakpoints for avilamycin, avoparcin, monensin, salinomycin and tylosin were 16 $\mu\text{g/ml}$, zinc bacitracin 128 $\mu\text{g/ml}$ and virginiamycin 4 $\mu\text{g/ml}$.

References

Tylosin and spiramycin as feed additives, Publi-

Prevalence of antimicrobial resistance to antimicrobial feed additives, carbadox and olaquinox, among *Escherichia coli* (n=357) isolated from the faeces of fattening pigs.

	MIC ($\mu\text{g/ml}$), number of strains								
	0	2	4	8	16	32	64	128	256
Carbadox	7	23	48	86	91	61	27	14	
Olaquinox	0	0	1	10	78	181	71	16	

Carbadox resistance,
when the limit for susceptible is ≥ 64 11.48 %

Olaquinox resistance,
when the limit for susceptible is ≥ 64 24.37 %

cations of Ministry of Agriculture and Forestry 5/1997, authors Tast, E., Honkanen-Buzalski, T. and Mannerkorpi, P.

Associations between the use of antimicrobial agents for growth promotion and the occurrence or resistance among *Enterococcus faecium* from broilers and pigs in Denmark, Finland and Norway. Aarestrup F. M. et al. (manuscript)

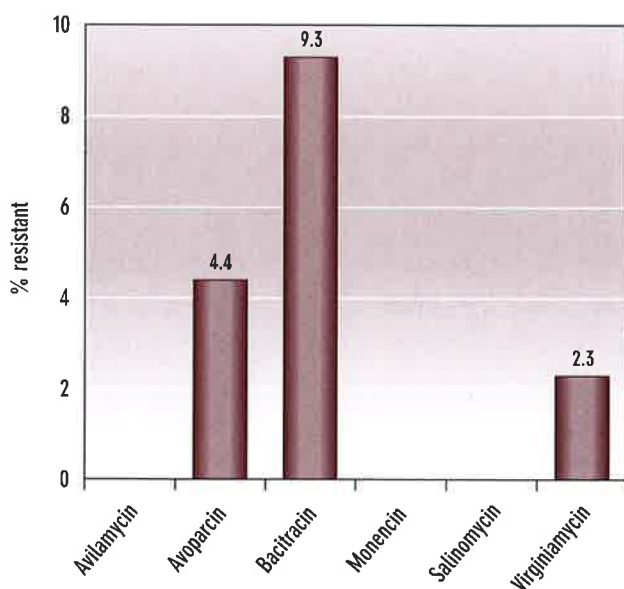
5.2. Resistance in zoonotic bacteria

Among the zoonotic bacteria, only antimicrobial resistance in *Salmonella* has been under surveillance since 1983. The following material on other zoonotic bacteria is relatively limited and the resistance has mainly been tested to antimicrobials used in human medicine. The resistance study on zoonotic bacteria shows that zoonotic bacteria isolated in Finland are, overall, susceptible to therapeutic antimicrobials.

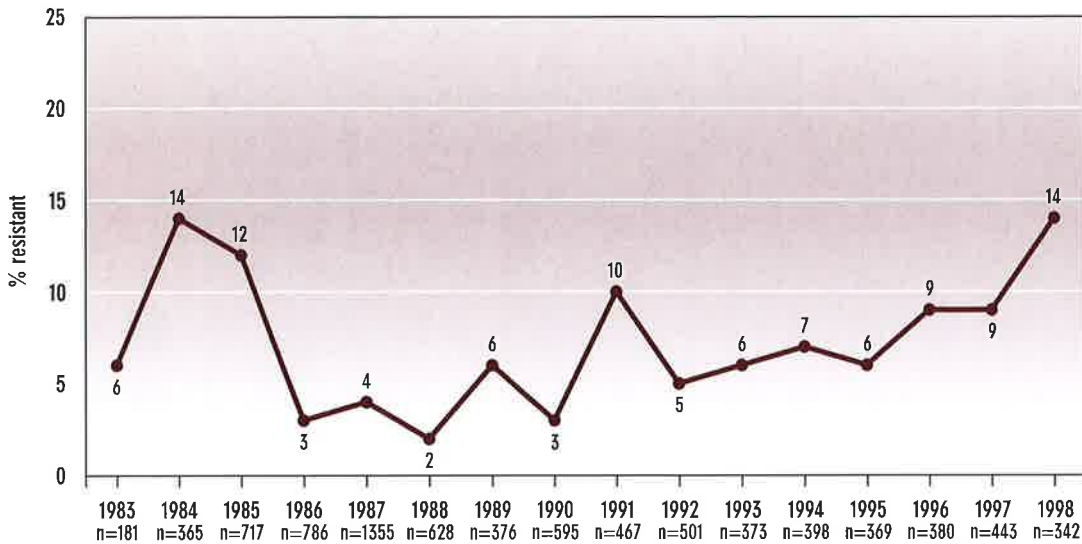
Salmonella

Salmonella cause intestinal infections in animals, but animals may also remain as symptom-free carriers. The presence of *Salmonella* in production animals imposes a significant food

Prevalence of antimicrobial resistance to antimicrobial feed additives among *Enterococcus faecium* (n=43) isolated from the faeces of fattening pigs.

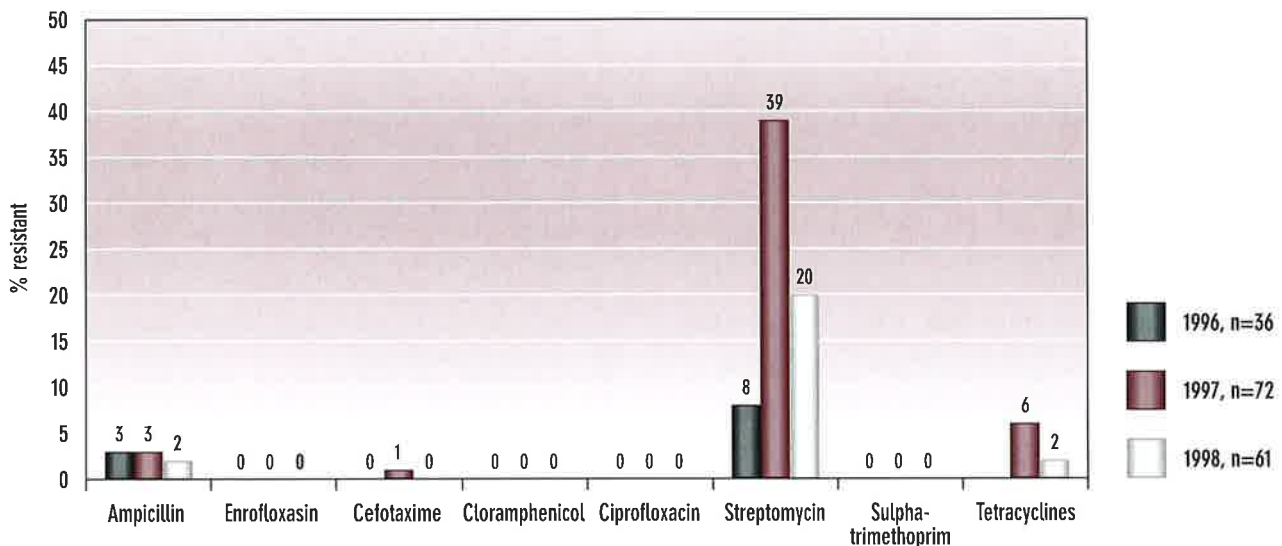


Prevalence of antimicrobial resistance among Salmonella in 1983-1998.



* The figures include only isolates classified as "resistant" and not those classified as "intermediate".

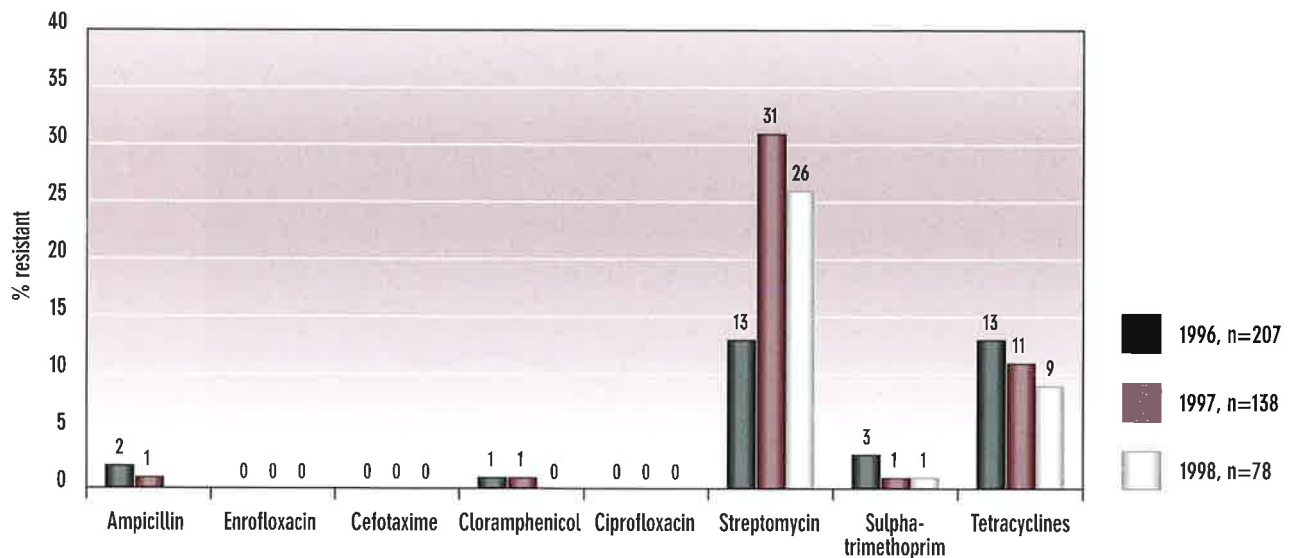
Prevalence of antimicrobial resistance among Salmonella isolated from poultry and poultry processing plants.



hygiene risk. The prevalence of resistance among Salmonella isolated from zoonotic animal bacteria has been under regular surveillance since 1983. The data from 1996 onwards covers the whole of Finland. Salmonella infections in production animals are not treated with antimicrobials in Finland, which explains the low resistance figures.

The most common salmonellosis among poultry is caused by *S. Infantis*. Among the

antimicrobials used for animal medication, resistance occurs mainly to streptomycin only. Among the Salmonella isolated from cattle, resistance occurs mainly to streptomycin and tetracycline. The first multiresistant *S. Typhimurium* strain was isolated in 1995. Since 1995 only few isolations of multiresistant DT104 strains have been identified annually from cattle. Some multiresistant strains have also been identified from cats and dogs.

Prevalence of antimicrobial resistance among *Salmonella* isolated from cattle and abattoirs.

Material and methods

Salmonella isolates in Finland are submitted to the National Veterinary and Food Research Institute (EELA) for serotyping and resistance testing. Since 1995 the resistance to antimicrobials has been tested according to a NCCLS standard (vol. 10, no 7, 1990). Before this the limit values were in accordance with the disc manufacturer's (Rosco) recommendations. The culture media used have been DST, Müller Hinton and Isosensitest agars. When interpreting the results, one strain/ year with different antimicrobial susceptibility has been included from each animal production unit. The antimicrobial resistance to ampicillin, chloramphenicol, streptomycin and tetracycline was determined throughout the follow-up period. Resistance testing has been done to neomycin from 1983 to 1986, to sulphonamide until 1994 and to sulphatrimethoprim since 1995.

Listeria monocytogenes

Listeria monocytogenes is commonly found in the environment. It can be isolated from the gut of warm-blooded animals, from the soil, water, animal feed and foodstuffs. Foodstuffs are con-

sidered to be the most significant source of human infection. Some twenty or thirty serious human listeria infections are identified annually in Finland. *L. monocytogenes* infections rarely cause disease in animals.

The prevalence of resistance among *Listeria monocytogenes* isolated from both foodstuffs and their production environment was determined to six antimicrobials used in human therapeutics. All bacteria tested were susceptible to all six antimicrobials.

Material and methods

Listeria monocytogenes bacteria have been isolated at the National Veterinary and Food Research Institute (EELA) in 1995-1998 from broilers, fish and their production environment. The antimicrobial resistance was tested according to a NCCLS standard (vol. 10, no 7, 1990) by determining MIC for ampicillin, penicillin, erythromycin, rifampicin, tetracycline and vancomycin.

Prevalence of antimicrobial resistance among *L. monocytogenes* isolated from fish products and broilers in 1995-1998.

Number and source of <i>L. monocytogenes</i> strains	Antimicrobials	Range	MIC ($\mu\text{g/ml}$)		Resistance (%)
			50%	90%	
Broiler (26)	Ampicillin	0.12 - 0.25	0.12	0.25	0
	Erythromycin	0.25	0.25	0.25	0
	Penicillin	0.06 - 0.25	0.25	0.25	0
	Rifampicin	0.015 - 0.25	0.06	0.25	0
	Tetracyclines	0.5	0.5	0.5	0
	Vancomycin	1	1	1	0
Environm. samples (5), broiler	Ampicillin	0.12 - 0.25	0.12	0.25	0
	Erythromycin	0.25	0.25	0.25	0
	Penicillin	0.25	0.25	0.25	0
	Rifampicin	0.03 - 0.12	0.06	0.12	0
	Tetracyclines	0.5	0.5	0.5	0
	Vancomycin	1	1	1	0
Fish (20)	Ampicillin	0.12 - 0.25	0.25	0.25	0
	Erythromycin	0.25	0.25	0.25	0
	Penicillin	0.12 - 0.25	0.25	0.25	0
	Rifampicin	0.015 - 0.12	0.06	0.12	0
	Tetracyclines	0.25 - 0.5	0.5	0.5	0
	Vancomycin	0.5 - 1	1	1	0
Environm. samples (2), fish	Ampicillin	0.12 - 0.5	0.12	0.5	0
	Erythromycin	0.25	0.25	0.25	0
	Penicillin	0.25	0.25	0.25	0
	Rifampicin	0.015 - 0.12	0.015	0.12	0
	Tetracyclines	0.5	0.5	0.5	0
	Vancomycin	0.5 - 1	0.5	1	0
Others (15)	Ampicillin	0.12 - 0.5	0.25	0.5	0
	Erythromycin	0.25 - 0.5	0.25	0.5	0
	Penicillin	0.12 - 0.5	0.25	0.5	0
	Rifampicin	0.015 - 0.12	0.06	0.12	0
	Tetracyclines	0.25 - 1	0.5	1	0
	Vancomycin	0.5 - 1	1	1	0

Prevalence of antimicrobial resistance among *L. monocytogenes* isolated from foodstuffs and their production environment in 1999.

Number and source of <i>L. monocytogenes</i> strains	Antimicrobials	Range	MIC ($\mu\text{g/ml}$)		Resistance (%)
			50%	90%	
Butter (4)	Ampicillin	0.5	0.5	0.5	0
	Erythromycin	0.5	0.5	0.5	0
	Penicillin	0.25 - 0.5	0.5	0.5	0
	Rifampicin	0.015 - 0.06	0.015	0.06	0
	Tetracyclines	1 - 2	1	2	0
	Vancomycin	1	1	1	0
Environm. samples (4)	Ampicillin	0.5	0.5	0.5	0
	Erythromycin	0.5	0.5	0.5	0
	Penicillin	0.25 - 0.5	0.25	0.5	0
	Rifampicin	0.015 - 0.06	0.015	0.06	0
	Tetracyclines	1	1	1	0
	Vancomycin	1	1	1	0
Others (4)	Ampicillin	0.12 - 0.5	0.12	0.5	0
	Erythromycin	0.25 - 0.5	0.25	0.5	0
	Penicillin	0.12 - 0.25	0.12	0.25	0
	Rifampicin	0.015 - 0.06	0.06	0.06	0
	Tetracyclines	0.5 - 1	0.5	1	0
	Vancomycin	1	1	1	0

The resistance among *Campylobacter jejuni* (n= 56) isolated from broiler meat and faeces in 1998.

Antimicrobials	Resistance (%)
Ampicillin 25 µg	4
Erythromycin 15 µg	0
Nalidixic acid 30 µg	0
Oxytetracycline 30 µg	0

Campylobacter jejuni

Campylobacter cause food poisoning. Contaminated drinking water or poultry meat is the most common source of infection. *Campylobacter* do not usually cause symptoms in animals. The majority of *Campylobacter* infections isolated in Finland are of foreign origin. *Campylobacter jejuni* isolated from Finnish broiler meat and faeces exhibited very low levels of resistance. Four antimicrobials used in human therapeutics were tested. Of the samples only four percent were resistant to ampicillin. In Finland neither human nor animal therapeutic antimicrobials are used in broiler production, which explains the low level of resistance. The consumption of coccidiostats has had no effect on the resistance to the antimicrobials tested.

Material and methods

The resistance of *Campylobacter jejuni* isolated from broiler faeces and broilers sold in the shops was determined to ampicillin, erythromycin, nalidixic acid and oxytetracycline. The resistance was tested according to a NCCLS standard (M2-A4, vol. 10, no 7, 1990).

Enterohaemorrhagic Escherichia coli (EHEC)

The prevalence of infections caused by enterohaemorrhagic *E. coli*, i.e. the EHEC strain, has increased in the 1990s in almost all industrialised countries. In Finland they are also isolated tens of times every year. The most significant serotype for the strain is O157:H7. In 1998 the

antimicrobial susceptibility of 166 cases of O157-serotypes collected by the National Veterinary and Food Research Institute (EELA) from animal isolates and by the National Public Health Institute (KTL) from human isolates was determined by MIC plate dilution method in the Antimicrobial Research Laboratory of the KTL.

In the studies the bacteria exhibited a high susceptibility to the antimicrobials tested. There was no occurrence of resistance or lowered susceptibility to ampicillin (MIC \geq 8 µg/ml), first and second generation cephalosporins (MIC \geq 8 µg/ml), cefotaxime (MIC \geq 0.064 µg/ml), gentamicin (MIC \geq 4 µg/ml), ciprofloxacin (MIC \geq 0.064 µg/ml) or trimethoprim (MIC \geq 1.0 µg/ml). Of the isolates tested 6,6 % were resistant or had a lowered level of susceptibility to sulphonamides (MIC \geq 256 µg/ml), 3.0 % to tetracycline (MIC \geq 8 µg/ml) and 2.4 % to chloramphenicol (MIC \geq 8 µg/ml).

It is noteworthy that antimicrobials are not administered to treat EHEC infections. The aim of the antimicrobial susceptibility testing was to determine the selective pressure on EHEC by antimicrobials other than those used therapeutically. According to these findings, in comparison to other pathogenic *E. coli* strains, EHEC is highly susceptible to antimicrobials.

5.3. Resistance in bacteria isolated from animal infections

Antimicrobial resistance testing on bacteria isolated from animal infections has been carried out for a few decades. The aim of the testing has been to ensure that the correct therapeutic antimicrobial is used. For practical reasons, only samples of some bacterial infections have been cultured and submitted to antimicrobial resistance testing. A laboratory test has often been requested only after a failed treatment with a "blindly" chosen antimicrobial. It follows that the bacterial samples in the laboratory consist of strains which reflect higher inci-

dence of resistance than the actual situation warrants. The following is an account of the prevalence of resistance to antimicrobials, mainly to those used in animal therapeutics, among bacteria isolated from animal infections. Standardised methods are not always available for resistance testing, for example for bacteria causing fish diseases. In these cases the results are for guidance only and they may only be compared with tests performed using the same methods.

It is evident from the resistance tests that resistance is most prevalent to those antimicrobials which are most often used therapeutically. The resistance status of some bacteria to certain antimicrobials is unfavourable.

Pathogenic Escherichia coli in pigs

Escherichia coli in pigs usually cause infections in the gastrointestinal tract of piglets and other diseases like mastitis in the sows. Antimicrobials are usually used to treat *E. coli* infections. Some resistance to all antimicrobials used therapeutically was identified. The resistance to streptomycin and tetracycline was approximately 50 % and to sulphatrimethoprim approximately 30 % and to neomycin approximately

Prevalence of resistance to antimicrobial feed additives, carbadox and olaquinox, among pathogenic *Escherichia coli* isolated from pigs.

	MIC ($\mu\text{g/ml}$), number of strains						
	4	8	16	32	64	128	≥ 128
Carbadox		12	56	56	45	38	4
Olaquinox		2	34	110	58	6	1

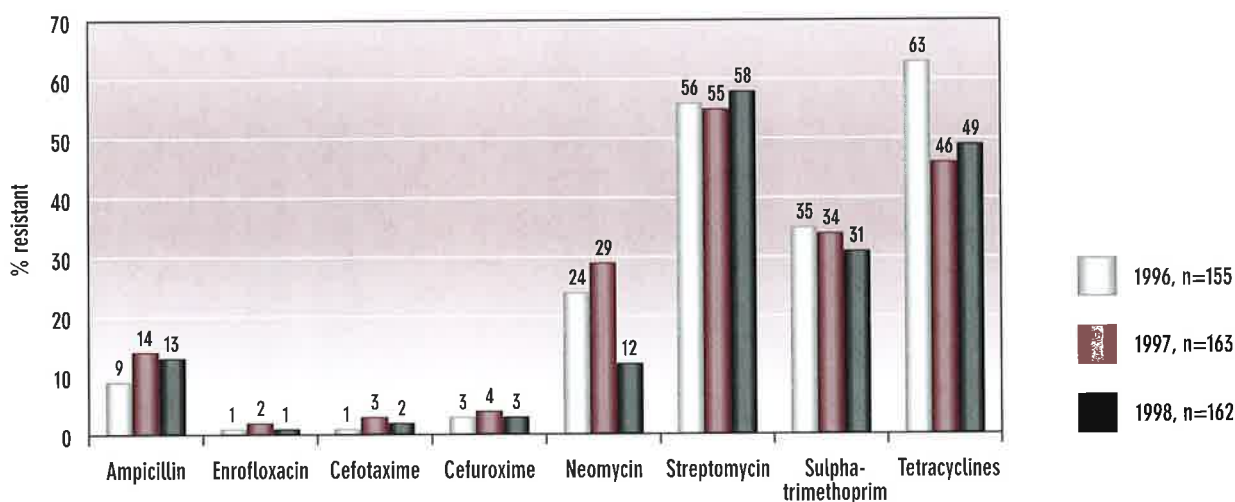
Carbadox resistance,
when the limit for susceptible is ≥ 64 19.91 %

Olaquinox resistance,
when the limit for susceptible is ≥ 64 3.31 %

20 %. These antimicrobials have been used therapeutically in pigs for almost thirty years. First generation cephalosporins and ampicillin have been used since the 1980s and enrofloxacin since the 1990s.

The most common antimicrobial feed additives consumed by piglets and fattening pigs in the 1990s have been carbadox and olaquinox. Approximately 20 % of pathogenic *E. coli* isolates identified in 1994-1999 were resistant to carbadox and 3 % to olaquinox. The consumption of olaquinox in 1990-1994 was very small compared to that of carbadox (Page 40). Since 1994 the consumption of carbadox has declined considerably and the consumption of olaquinox has increased respectively.

Prevalence of antimicrobial resistance among pathogenic *Escherichia coli* isolated from pigs in 1996-1998.



Material and methods

Pathogenic *E. coli* (1996 n=155, 1997 n=179 and 1998 n=162) have been isolated at the National Public Health Institute (EELA) from diagnostic submission from pigs, mainly from enteric infections. All pathogenic *E. coli* are submitted for resistance testing and one distinct resistance profile per pig farm was included in the results. The antimicrobial resistance was determined according to a NCCLS standard (M31-P, vol. 14, no 20, 1994, proposal) to ampicillin, enrofloxacin, tetracycline and sulphatrimethoprim and according to M2-A5, vol. 13, no 24, 1993 to cefuroxime, cefotaxime and streptomycin; the value limits for neomycin were $R \leq 12$, $I = 13 - 16$ and $S \geq 17$. The resistance to carbadox and olaquinox was tested by determining the MIC for 211 *E. coli* isolates identified in 1994-1999. An isolate was considered resistant to carbadox and olaquinox if the MIC $\geq 64 \mu\text{g/ml}$.

Brachyspira in pigs

Brachyspira cause intestinal infections in weaned piglets and young fattening pigs. Pathogenic *Brachyspira* strains are *Brachyspira hyodysenteriae* and *B. pilosicoli*. The pathogenicity of *B. intermedia* is unclear. Bacteria of *Brachy-*

spira sp. Group III are not pathogenic. Antimicrobial therapy, coupled with general sanitation measures, is employed in the preventative work towards diarrhoea caused by *Brachyspira*. Tylosin and lincomycin have been used in pigs since the 1980s to treat diarrhoea caused by *Brachyspira* spp.

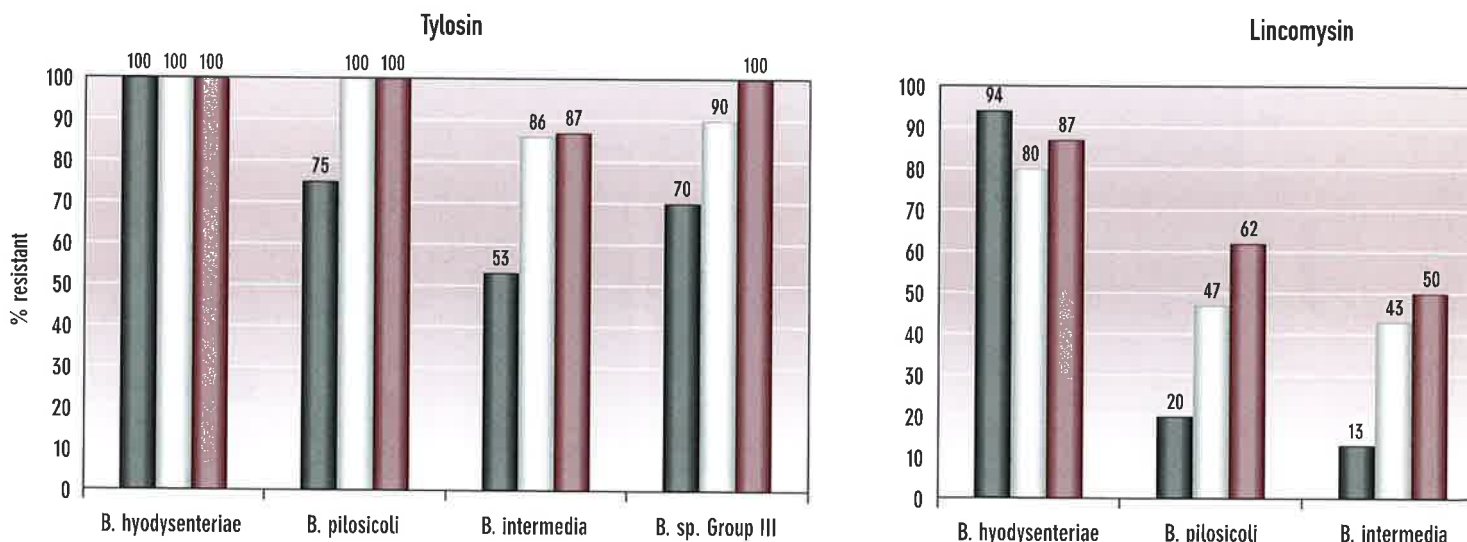
All *Brachyspira* spp. were highly resistant to tylosin and lincomycin but the resistance among the non-pathogenic strains was slightly less. Thiamulin resistance, however, was identified only in a few isolates. The use of thiamulin for the treatment of diarrhoea caused by *Brachyspira* spp. was not widely used until the 1990s.

Material and methods

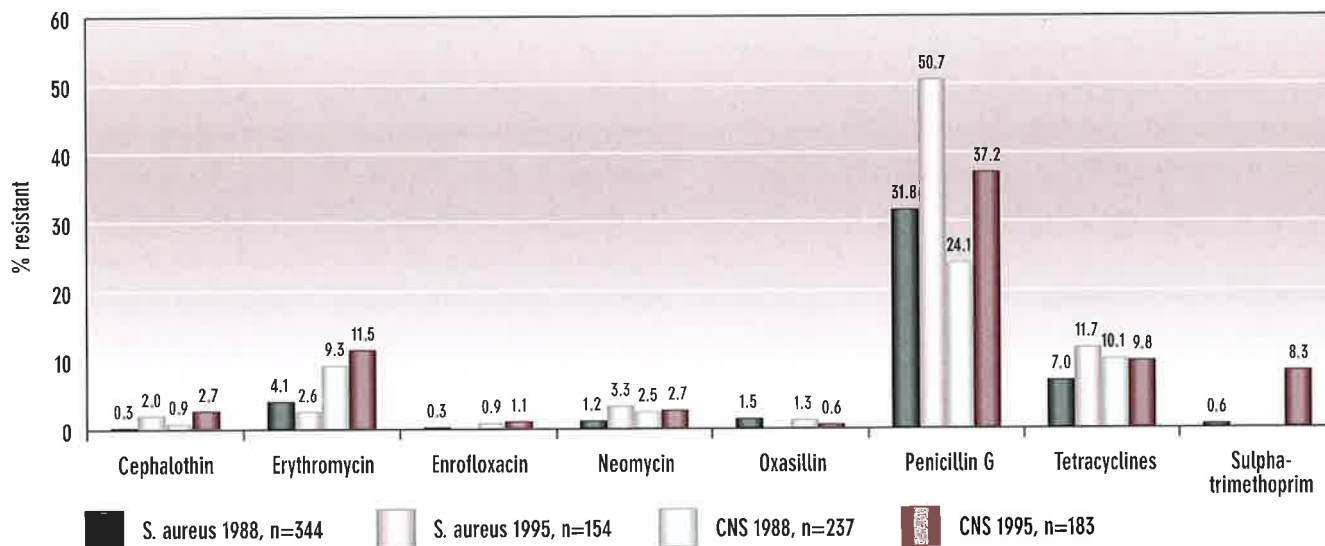
The antimicrobial susceptibility among *B. hyodysenteriae* and *B. pilosicoli*, which are pathogenic in pig, and *B. intermedia*, the pathogenicity of which is unclear, was tested to the following antimicrobials: lincomycin, tylosin and thiamulin. In addition the isolates from the non-pathogenic *Brachyspira* sp. Group III were susceptibility tested to the same antimicrobials. The bacteria were isolated from faecal samples from pigs or samples collected at autopsy, and were examined at the National Veterinary and Food Research Institute (EELA).

The susceptibility testing was done by agar dilution method. The culture media used was

Prevalence of resistance to tylosin, lincomycin and thiamulin among *Brachyspira* spp. isolated from pigs in 1996-1998.



Prevalence of antimicrobial resistance among Staphylococci isolated from mastitis in cows in 1988 and 1995.



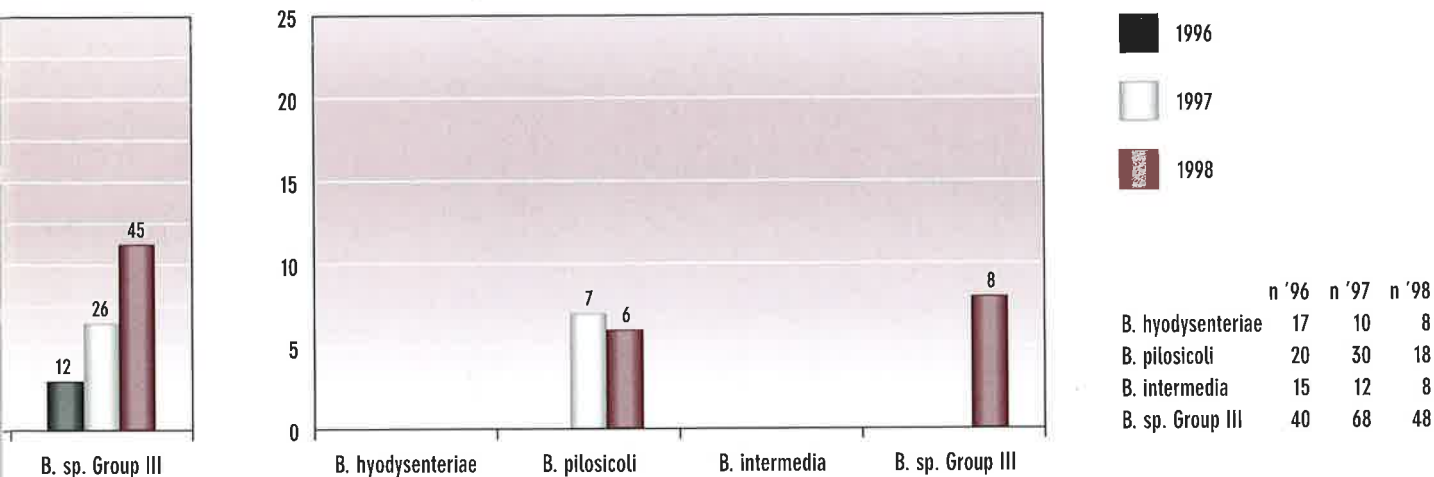
trypticase soy agar with the addition of 5 % sheep blood. Plates were incubated at 42° C for six days. The limit values for tylosin and thiamulin were 4 µg/ml and 1.0 µg/ml, and for lincomycin 32.0 µg/ml and 4.0 µg/ml.

Staphylococci isolated from mastitis in cows

Staphylococci are the most common causative agents of bovine mastitis. Both narrow and broad spectrum antimicrobials are used in the

treatment of mastitis either as intramammary tubes or as injectables. From 1988 to 1995 a survey was carried out in Finland to map out the prevalence of mastitis. The occurrence of resistance among Staphylococcus aureus and coagulase-negative staphylococci (CNS) isolated from milk samples was determined to eight antimicrobials used therapeutically in cows. The resistance levels were highest to penicillin, tetracycline and erythromycin. Both the resistance to penicillin and to coagulase-negative staphylococci (CNS) increased significantly during the survey period. Mastitis caused by staphylococci

Thiamulin



is usually treated by beta-lactam antimicrobials. The treatment of penicillin resistant staphylococci has included, amongst others, cloxacilin, first generation cephalosporin, tetracycline, erythromycin and enrofloxacin. The administration of enrofloxacin for the treatment of mastitis is no longer recommended.

Material and methods

In 1988 milk samples from 17111 cows from 493 dairy farms and in 1995 samples from 10 410 cows from 238 dairy farms were taken. The milk samples were analyzed for bacteria which cause mastitis. The resistance among *S. aureus* (1988 n=344, 1995 n=154) and coagulase-negative staphylococci (1988 n=237, 1995 n=183) to cephalothin, erythromycin, enrofloxacin, neomycin, oxacillin, penicillin, tetracycline and sulphatrimethoprim was tested according to a NCCLS standard (vol. 14, no 20, 1994) using Rosco discs with Müller Hinton agar in 1988 and Oxoid discs with Isosensitest agar in 1995.

References

Myllys, V. et al.: Bovine mastitis in Finland in 1988 and 1995 – Changes in prevalence and antimicrobial resistance. *Acta Vet. Scand.* 39, 119-126.

Aeromonas salmonicida spp. *salmonicida* in fish

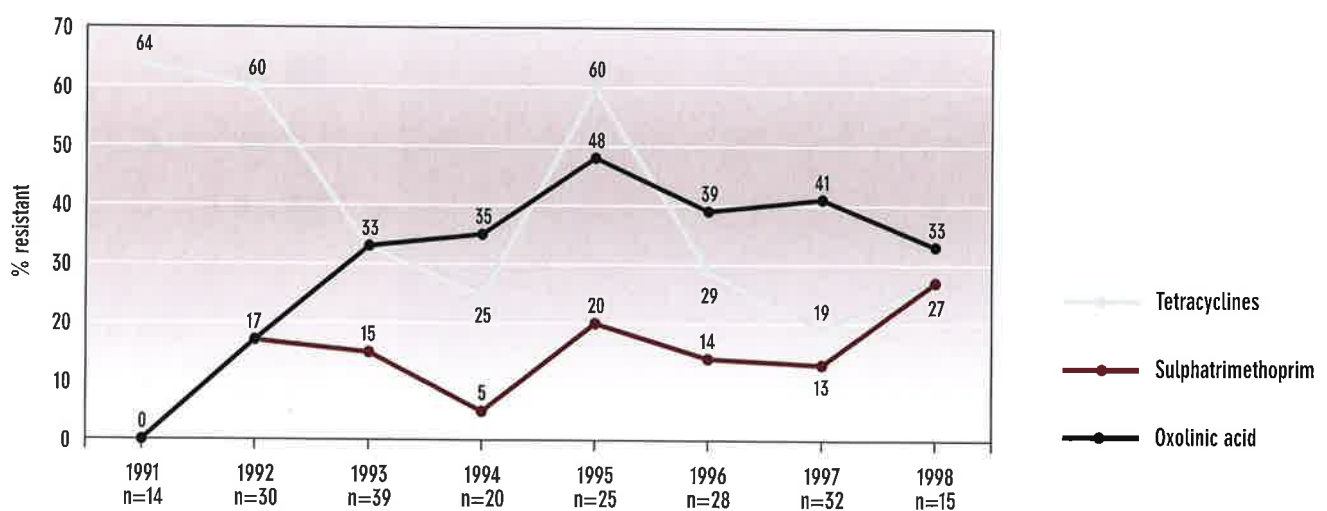
Aeromonas salmonicida ssp. *salmonicida* causes furunculosis in salmonids. Fish of all age are susceptible to furunculosis during the warm water season and the fry also during the cold water season. Furunculosis is treated with antimicrobials, which are usually mixed with feed. The recommended antimicrobial of choice is tetracycline, followed by oxolinic acid. Sulphonamides have the least effect.

During the resistance follow-up period from 1991 to 1998 the resistance to tetracycline has fluctuated between 64 % and 19 %. Soon after the introduction of oxolinic acid the resistance to it increased to 30-40 %. The resistance to sulphatrimethoprim has remained at around 20 %. Improvements in fish farming conditions and the use of vaccines are essential to keep the consumption of antimicrobials as low as possible.

Material and methods

Aeromonas salmonicida ssp. *salmonicida* have been isolated by the National Veterinary and Food Research Institute (EELA) between 1991 and 1995 from diagnostic submissions from fish farms situated on the south coast of Fin-

Prevalence of antimicrobial resistance among *Aeromonas salmonicida* ssp. *salmonicida* isolated from fish in 1991-1998.



land and inland water areas. From 1996 bacterial isolates for this data have been collected nationwide. The number of isolates tested has remained relatively low, fluctuating from 14 to 39. The submission from a fish farm to this data contains only one isolate with different antimicrobial susceptibility / fish species / year.

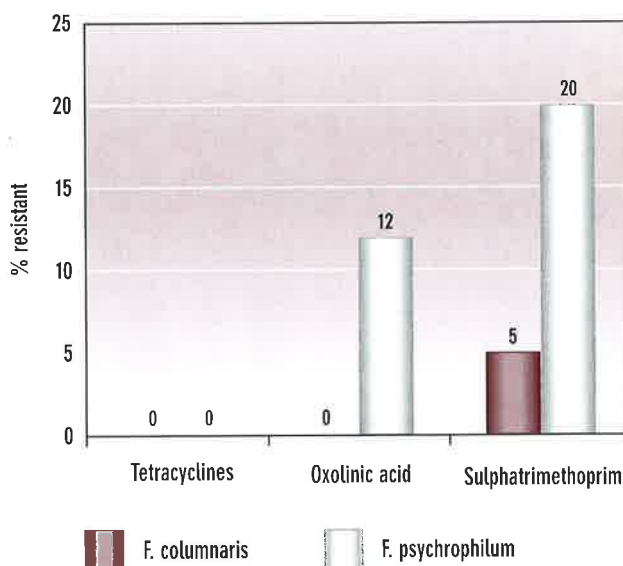
The resistance of the bacteria to tetracycline, sulphatrimethoprim and oxolinic acid has been determined by agar diffusion method at incubation temperature of 22° C with Müller Hinton agar as the culture medium. From 1991 to 1993 Rosco discs were used and limit values supplied by the manufacturer were employed. The following limit values were used when testing oxolinic acid R ≤ 28 mm, I = 29-32 mm and S ≥ 33 mm. From 1994 Oxoid discs were used with a NCCLS standard (vol. 34, no 20, 1994) limit values for tetracycline and sulphatrimethoprim. The limit values for oxolinic acid were R ≤ 19 mm, I = 20-25 mm and S ≥ 26 mm.

Flavobacterium in fish

Flavobacterium psychrophilum and F. columnaris cause ulcerating skin inflammations and systemic infections in fish under breeding conditions. Fry under one year old have the worst mortality rate, but older fish may also be vulnerable to infection. It was not until the early 1990s that the first cases were identified on fish farms in Finland. Tetracycline, and sometimes sulphatrimethoprim, is usually used as the therapeutic agent.

Flavobacterium are cultured on special culture media; it is not known whether these affect the susceptibility testing. Because it is also difficult to standardise the intensity of growth, lowered susceptibility may only be roughly estimated. Both F. psychrophilum and F. columnaris exhibited resistance to sulphatrimethoprim, but only F. psychrophilum exhibited resistance to oxolinic acid. To date no resistance to tetracycline has emerged.

Prevalence of antimicrobial resistance among *Flavobacterium psychrophilum* (n=25) and *Flavobacterium columnaris* (n=19) isolated from fish in 1993-1999.

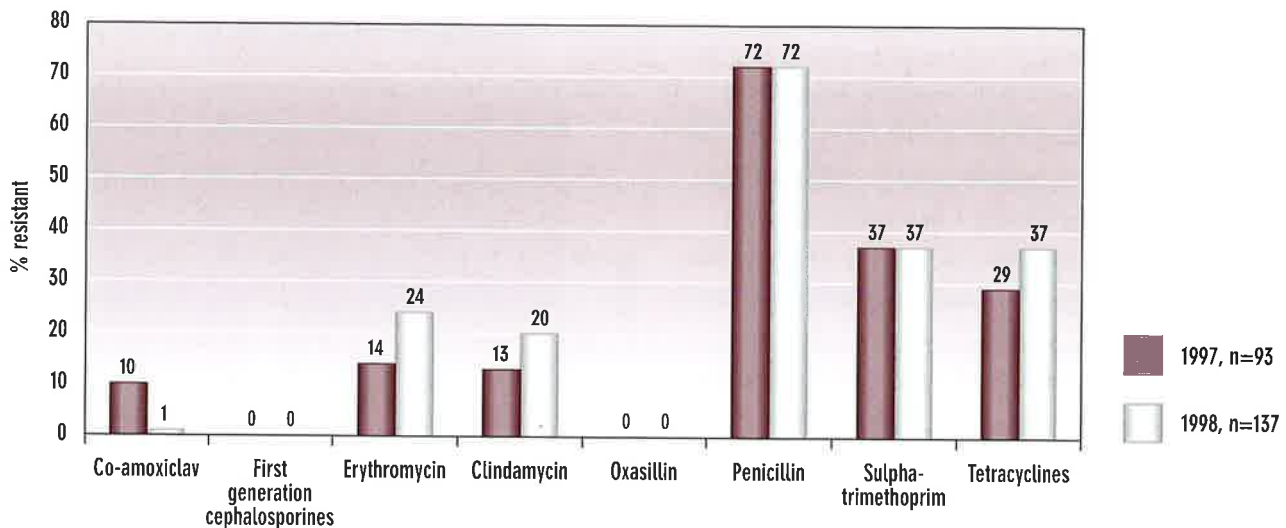


Material and methods

Flavobacterium isolates have been identified at the National Veterinary and Food Research Institute (EELA) mainly from diagnostic submissions from fish farms in North Finland from 1993 to 1999. Anacker-Ordal culture media was used in the susceptibility testing, incubation temperature was 15° C for F. psychrophilum and 20° C for F. columnaris, incubation time varied from two to four days. Isolates were considered to have lowered susceptibility if the zone of inhibition was ≤ 19 mm for tetracycline, ≤ 16 mm for sulphatrimethoprim and ≤ 19 mm for oxolinic acid.

Staphylococci in dogs

Staphylococci in dogs cause mainly skin, ear and urinary tract infections. The causative agent of skin infections is usually S. intermedius. These infections are repeatedly treated with antimicrobials. When the resistance of staphylococci isolates was tested to eight antimicrobials, it was observed that over 70 % were penicillin resistant; resistance to tetracycline was also

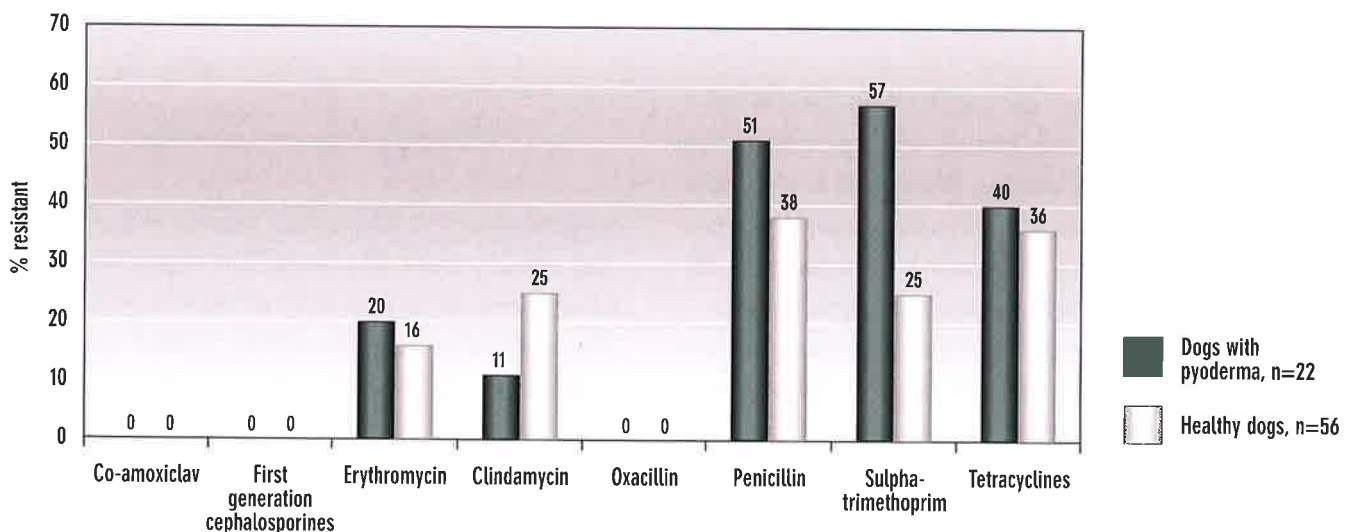
Prevalence of antimicrobial resistance among *Staphylococcus* isolated from dogs.

common. No bacteria resistant to therapeutically used antimicrobials co-amoxiclav and first generation cephalosporins were identified. Oxacillin is not usually used in veterinary therapy and no resistance occurred.

The comparison between *S. intermedius* isolated from chronic skin infections and the skin of healthy dogs was made. Resistance to penicillin, tetracycline and sulphatrimethoprim was present in 40-50 % of the isolates. Resistance to erythromycin and clindamycin was about 20 %. *S. intermedius* isolated from the healthy dogs was somewhat more susceptible to all the antimicrobials, except for clindamycin.

Material and methods

The data shows the resistance in staphylococci (1997 n=93 and 1998 n=137) isolated at the National Veterinary and Food Research Institute (EELA) to co-amoxiclav, erythromycin, cephalosporin (cephalexin or cephalothin), clindamycin, oxacillin, penicillin, sulphatrimethoprim and tetracycline. The resistance was tested according to a NCCLS standard (vol. 14, no 20, 1994). *S. intermedius* isolated from skin infections are also included in the above data. Fifty-six *S. intermedius* isolates were identified from the healthy dogs and their resistance to the same antimicrobials was tested.

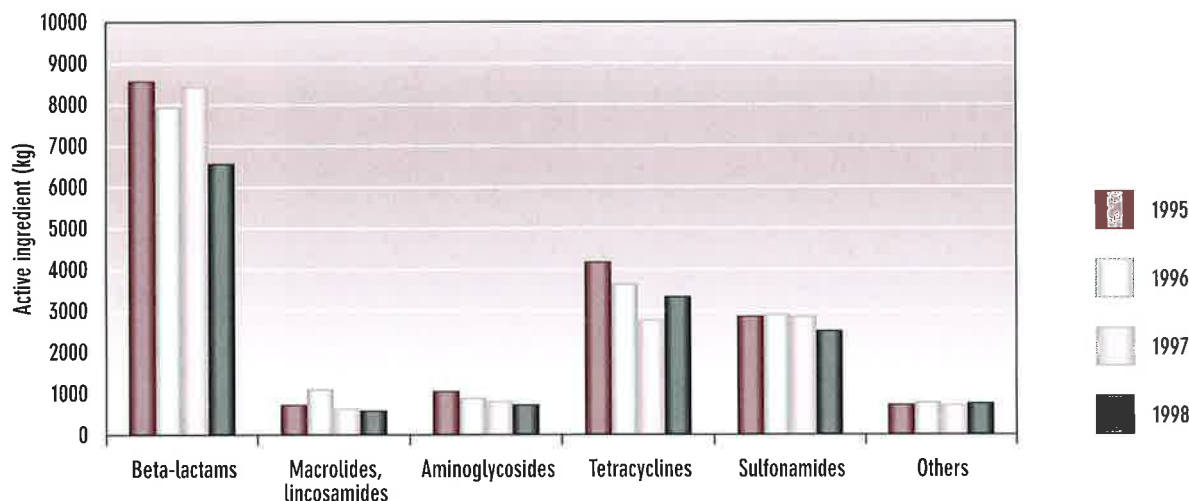
Prevalence of antimicrobial resistance among *Staphylococcus intermedius* isolated from dogs with chronic skin disease and clinically healthy dogs in 1998.

6. Consumption of antimicrobial agents in animals and number of domestic farm animals in Finland

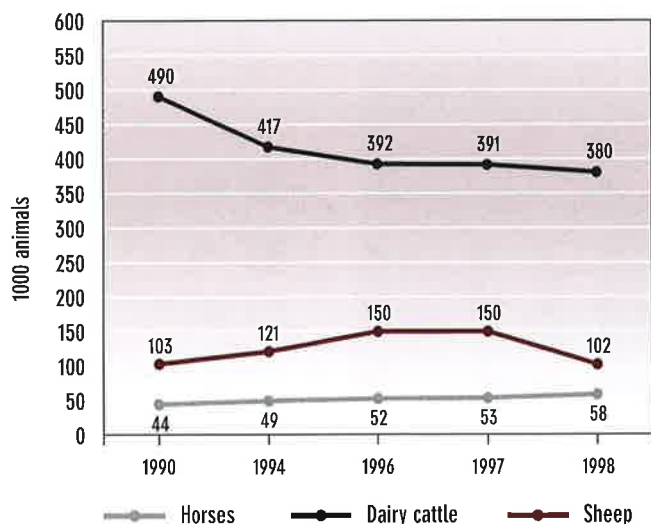
In order to establish the 1998 sales figures for medications used in animal care the Social Insurance Institution of Finland (KELA) and small drug wholesale companies were asked to submit sales figures for medications used in animal care. The sale of the active ingredient by

weight was used as a reference. Drugs which are licensed in human medicine and both sold and used as animal medication are not included. Therefore the figure, especially for oral antimicrobial medication, is a considerable amount lower than the real figure.

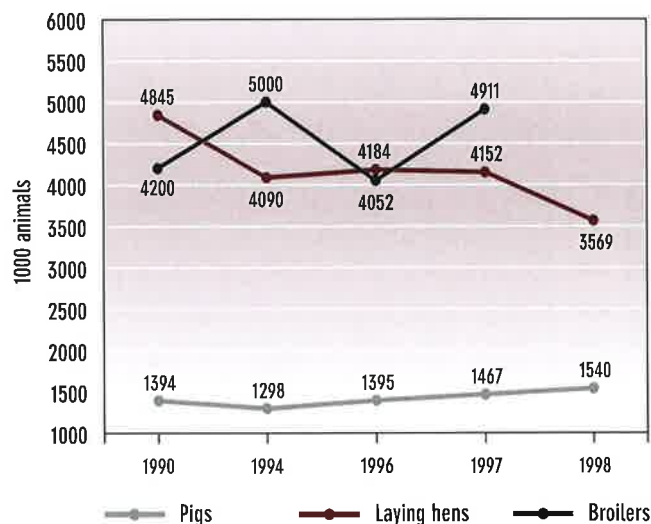
Consumption of antimicrobials.



Number of horses, dairy cattle and sheep in Finland in 1990-1998.



Number of pigs, laying hens and broilers in Finland in 1990-1998.

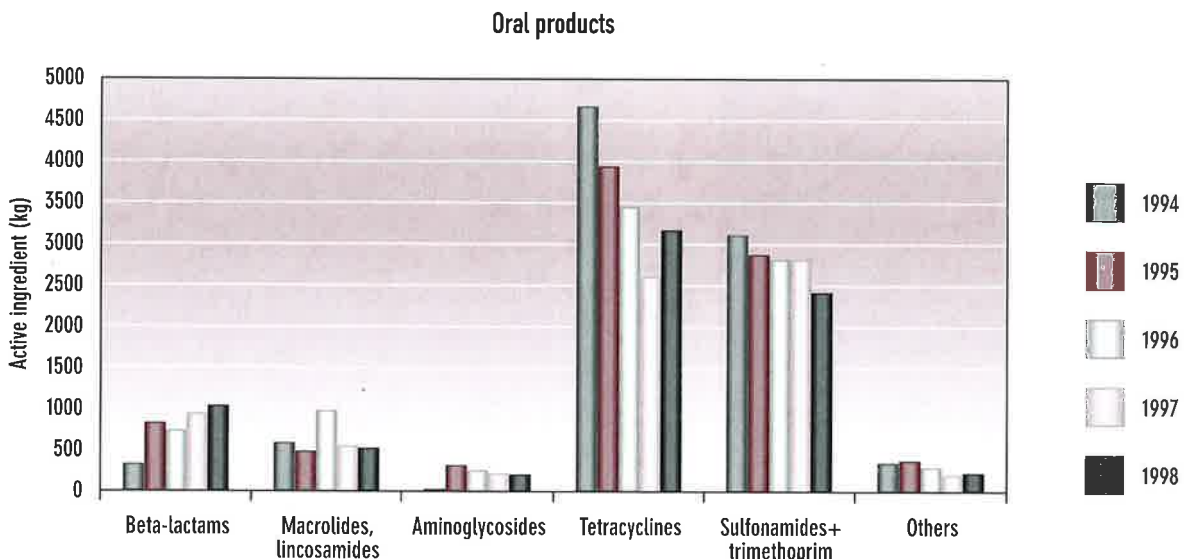
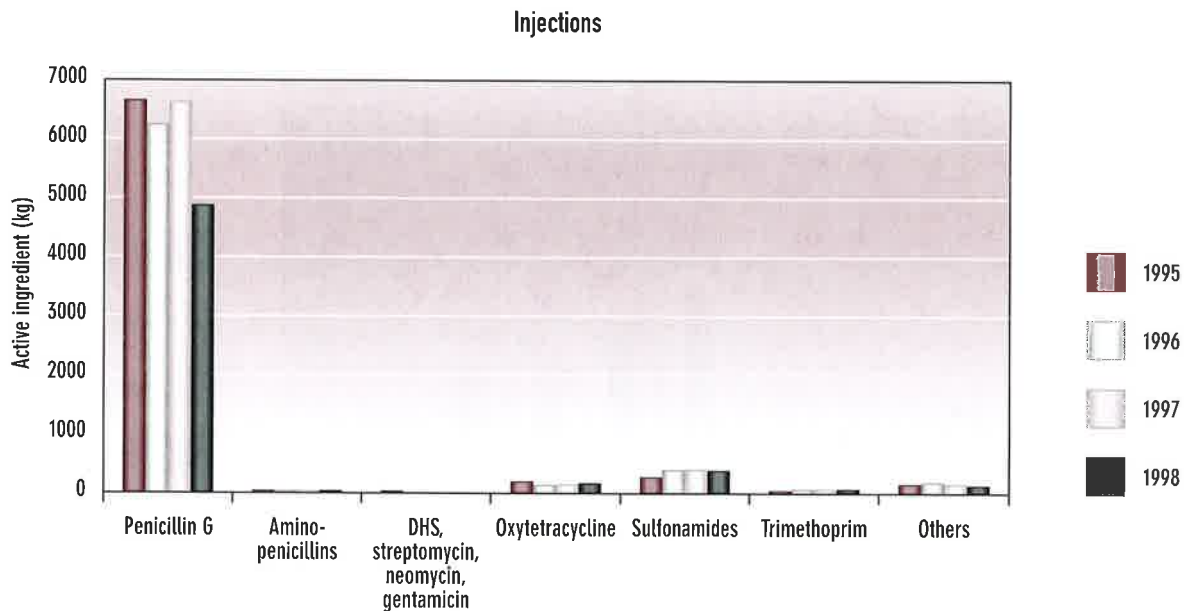


The total consumption of antimicrobials has decreased from 18 197 kg in 1995 to 14 534 kg last year. Because the number of animals shows very little change (the number of cattle is a little lower whereas the number of pigs has been on the increase during the last few years), it may be concluded that the consumption of antimicrobials shows a slight downward trend. As far as resistance prevention is concerned, this on its own is no proof of prudent use of antimicrobials for animal therapeutics, but the trend must be viewed as favourable. It is also note-

worthy that beta-lactam antimicrobials have always been noticeably the most prescribed antimicrobial, but their consumption decreased last year more than that of the other groups. Compared with the previous year the consumption of tetracycline has increased.

Among injectables the consumption of penicillin G has particularly decreased. The other groups of injectables show little change.

Among oral medication both beta-lactam antimicrobials and tetracyclines show an upward trend, whereas the other groups show a



downward trend.

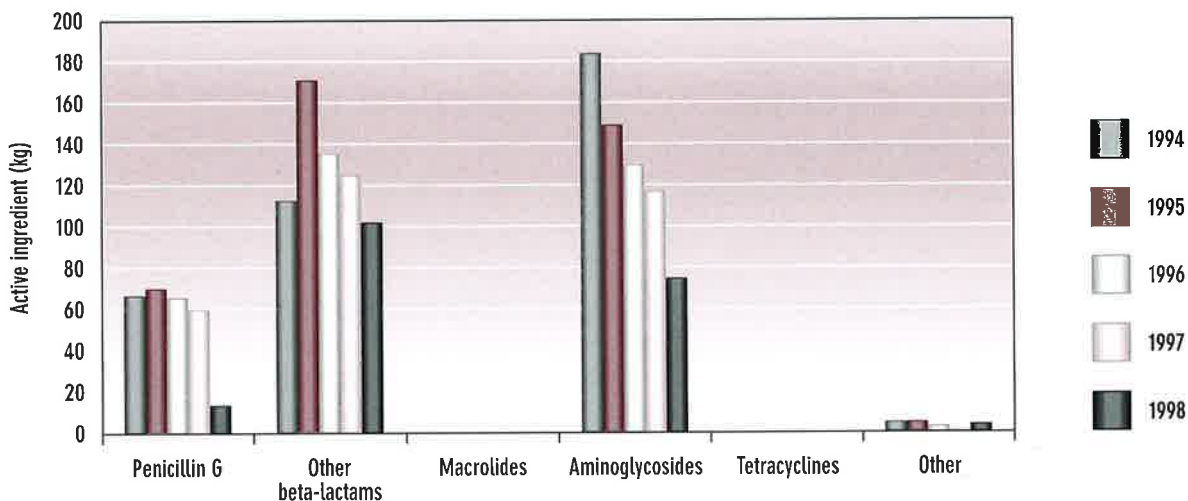
Overall, the use of udder tubes shows the largest decrease. This is partly due to the decrease in the number of milking cows, but other factors such as a transition to injectables or culling may also play a part.

The use of intramammary tubes in lactating cows shows a clear decrease, beta-lactams being an exception. The huge decrease in the consumption of penicillin G may at least partly be explained by new clinical guidelines heralded by the emergence of resistant staphylococcal infec-

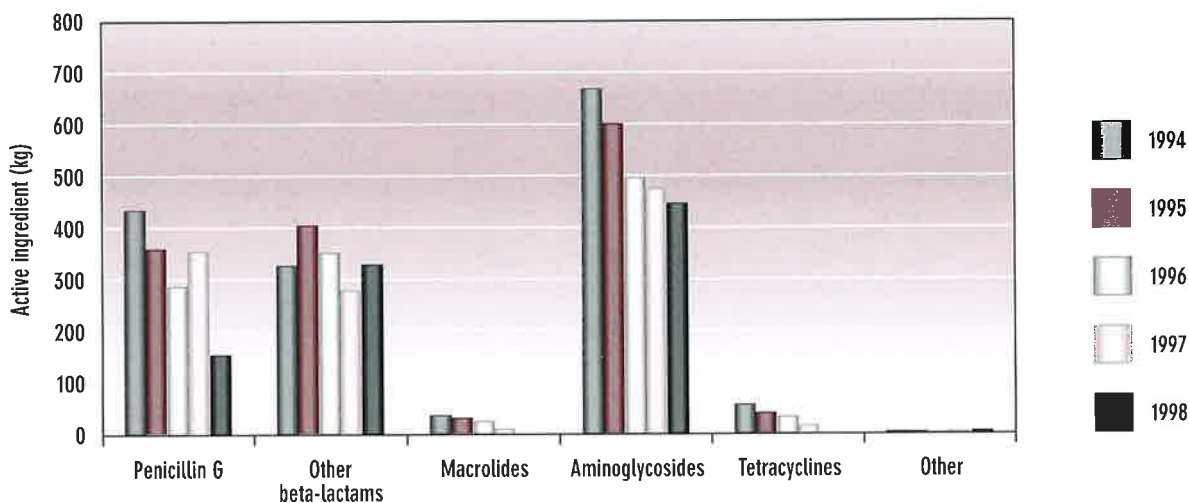
tions. The consumption of macrolides and tetracyclines has totally stopped since 1997. The consumption of dry-cow tubes has decreased even more than the consumption of milking-cow tubes for mastitis; a slight increase is noted only in the antimicrobial group "Others".

The present consumption figures reflect only the total amount consumed by domestic animals. In future it would be necessary to be able to study the consumption figures by different species.

Dry cow preparates



Intramammarys for lactating cows



7. Consumption of antimicrobial feed additives in animals

The Plant Production Inspection Centre monitors the consumption of antimicrobial feed additives annually by collecting data from feed manufacturers. All three main groups of feed additives are included: antimicrobials, growth promoters and coccidiostats, and other medicinal agents.

The consumption of antimicrobial feed additives has been on the decline throughout the 1990s. The consumption of antimicrobials was discontinued in 1996. The total consumption of feed additives in 1990 was 20 493 kg, whereas in 1998 it was 12 900 kg, out of which the growth promoters carbadox and olaquinox constituted 4 006 kg. At present the only

growth promoters consumed are certain piglet feed mixtures produced by a few manufacturers. The consumption has been justified with the prevention of piglet diarrhoea at weaning. A common agreement between the feed and slaughter industry and the farm producers plans to discontinue even this consumption.

The consumption of coccidiostats as necessary prophylactic anti-parasitic agents has followed the trend in broiler and turkey production, which has shown an increase during the last few years. The average consumption has been around 7 920 kg, the distribution being from 4 266 kg to 10 155 kg.

The use of antimicrobial feed additives in Finland in 1990-1998 (kg active ingredient/year).

Feed additives	1990	1991	1992	1993	1994	1995	1996	1997	1998
Antimicrobial growth promoters	12881	9268.1	10513	7822.6	7766.6	5544	4776.9	4006	4016
Avoparcin	2555.9	2137.3	3734.6	3105.8	3389	1294	46.7	0	0
Bacitracin zinc	104	458	554	0	0	0	0	0	0
Flavomycin	3019.6	2244.8	1345.6	249.6	241	60	7.2	0	0
Virginiamycin	256.4	0	0	0	0	0	0	0	0
Carbadox	6745	4328	4799.7	4464.7	4122	2614	1840.9	1123	730
Olaquinox	200	100	79.5	2.5	14.6	1576	2882.1	2883	3286
Coccidiostats and other medicinal substances*	7611.7	9294.5	7783.8	4265.7	7153.4	8136	7976.1	10155	8884
Dimetridazole	0	27	1.8	214	228	231	203.8	63	42
Lasalocid sodium	0	0	0	0	0	0	0	0	3024
Maduramycinammonium	0	0	22.3	144.2	103	0	0	0	0
Monensin sodium	6735.2	8220.7	6441.3	3291.8	5735.7	5754	3652.8	4375	632
Narasin	0	0	0	0	450	1935	2232.4	1959	2866
Salinomycin	0	280.8	462.6	511.6	472.2	216	1704.6	3657	2320
Production of compound feed, mio kg	1188.18	1109.39	1058.84	1008.87	1078.55	1172.50	1161.08	1156.49	1226.77

*Only substances with antimicrobial activity.

Others in use from time to time: amprolium/ethopate, nifursol and dinitolmide.

Data collected by Plant Production Inspection Centre.

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