GERMAP 2012

Antimicrobial Resistance and Consumption

Report on the consumption of antimicrobials and the spread of antimicrobial resistance in human and veterinary medicine in Germany

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Preface

GERMAP 2012 is the third issue of a report that provides a summary of data on the consumption of antimicrobials and the extent of resistances against antimicrobials in human and veterinary medicine. While we had hoped to be able to publish the report earlier, the considerable efforts in the preparation of the report delayed publication once again. Information in this report mostly dates from the period 2009–2011, only rarely from the year 2012.

Many trends already described in GERMAP 2010 continue unbroken. In human medicine, broad spectrum antimicrobials, especially cephalosporins and fluoroquinolones, still have a large share of the overall consumption of antimicrobials. This applies for ambulatory as well as in-patient treatments. As it is known, both antibiotic classes select for multi-drug resistant bacteria more than most other classes. As the PEG resistance study shows, the percentage of multi-resistant isolates of the type 3MRGN (according to the definition of KRINKO, 2012)[1] of all *Escherichia coli* isolates increased from < 1% in 1995 to 14% in 2010. Isolates of the type 4MRGN, which are resistant against carbapenems, were not yet found in this study; however their percentage was 2% of *Klebsiella pneumoniae* isolates and 7% of *Pseudomonas aeruginosa* isolates.

In our opinion, these trends will continue as long as adequate measures like, for example, the appropriate use of antibiotics are implemented only in an insufficient manner. A reduced use of cephalosporins and fluoroquinolones for therapy in both sectors therefore must be a goal with high priority. Furthermore the use of antimicrobials can be reduced in prophylaxis, especially when peri-operative prophylaxis continues too long after surgery. In the ambulatory sector the use of antimicrobials against acute respiratory diseases must be reduced. The attitude to switch from parenteral to oral medication as soon as possible has to be questioned critically, since due to insufficient absorption the selection pressure can be higher after oral application than after parenteral application.[2]

In the veterinary sector reliable data on the sales of antimicrobials in 2011 were available for the first time. The sales data, which were provided by pharmaceutical companies and wholesalers, do not allow conclusions about the actual use of the different antimicrobial classes in various animal species. The development of resistances in bacteria pathogenic for animals is characterized by increasing rates of ESBL-producing bacteria and MRSA. The recent isolation of carbapenemase-producing bacteria from animals[3,4] is proof that a transfer of resistant bacteria or resistance genes between humans and animals is possible in both directions.

The appropriate use of antimicrobials is more essential than ever, as in the near future the development of few (human medicine) or no (veterinary medicine) new antimicrobial compounds or even classes can be expected. This makes the preservation of the effectiveness of current antimicrobials even more important. Appropriate and intelligent use of antimicrobials means to be able to decide in a given situation if, and if yes, which antimicrobial should be given in which dose and by which route of application. In this context the low therapeutic costs of antimicrobials in general and especially of cephalosporins and fluoroquinolones are not helping an appropriate use.

Increasing globalisation, which is caused by more long distance travels and more international business, also means increasing globalisation of the bacterial ecosystem. This has major consequences like extensive interactions between ambulatory medicine and hospitals as well as between humans and animals.

Measures to fight the spread of resistant bacteria cannot solely be limited to more restrictive use of antimicrobials. Good management, profound pre- and post gradual education of all those who are involved as well as efficient hygiene are just as necessary for success. In the veterinary sector strategies for breeding and keeping food producing animals must be questioned critically. In this context the aims set forward in the German Antimicrobial Resistance Strategy (Deutsche Antibiotika-Resistenzstrategie, DART) were not fully accomplished and further efforts are necessary. GERMAP wants to continue to contribute to these efforts in the future.

Again many colleagues from human and veterinary medicine participated in the preparation of the present report. We want to thank all who were involved for their great work, especially those colleagues who followed our invitation to highlight selected specific aspects of the use of antibiotics and resistance. You will find those contributions in this edition under the heading „GERMAP *spezial*".

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On behalf of the editors:

Michael Kresken Jürgen Wallmann Winfried Kern

Vorwort

Mit GERMAP 2012 steht nunmehr zum dritten Mal eine Zusammenfassung von Daten über den Antibiotikaverbrauch und die Verbreitung von Antibiotikaresistenzen in der Human- und Veterinärmedizin in Deutschland zur Verfügung. Wir hatten gehofft, den Bericht bereits früher veröffentlichen zu können, aber die umfangreichen Arbeiten im Zusammenhang mit der Erstellung des vorliegenden Berichtes haben die Veröffentlichung auch dieses Mal verzögert. Die Angaben in diesem Bericht beziehen sich zumeist auf den Zeitraum 2009–2011 und vereinzelt auch auf das Jahr 2012.

Viele der bereits in GERMAP 2010 beschriebenen Trends haben sich fortgesetzt. In der Humanmedizin ist der Anteil der Antibiotika mit einem weiten Wirkungsspektrum am Gesamtverbrauch – mit den Cephalosporinen und Fluorchinolonen an der Spitze – nach wie vor sehr hoch. Dies gilt sowohl für den Antibiotikaeinsatz im ambulanten als auch im stationären Versorgungsbereich. Cephalosporine und Fluorchinolone üben bekanntlich einen besonders hohen Druck zugunsten der Selektion multiresistenter Erreger aus. So hat sich nach den Angaben der PEG-Resistenzstudie der Anteil multiresistenter Stämme vom Typ 3MRGN (gemäß Definition der KRINKO von 2012)[1] an allen *Escherichia-coli*-Isolaten von < 1% im Jahr 1995 auf 14% im Jahr 2010 erhöht. Stämme vom Typ 4MRGN, die eine Resistenz gegen Carbapeneme zeigen, fanden sich in dieser Studie bisher nicht. Unter den *Klebsiella-pneumoniae*-Isolaten betrug der Anteil jedoch bereits 2%, unter den *Pseudomonas-aeruginosa*-Isolaten 7%.

Diese Trends werden sich nach unserer Meinung weiter fortsetzen, wenn geeignete Gegenmaßnahmen wie z.B. die Forderung nach einem sachgerechten Einsatz von Antibiotika nur unzureichend umgesetzt werden. Ein Ziel muss daher sein, den Anteil von Cephalosporinen und Fluorchinolonen für die Therapie von Infektionskrankheiten in beiden Versorgungsbereichen zu senken. Zudem können Antibiotika in der prophylaktischen Anwendung, vor allem in Bezug auf die zu lange postoperative Fortführung der perioperativen Prophylaxe, eingespart werden. In der ambulanten Versorgung muss es außerdem gelingen, den Antibiotikaeinsatz bei akuten Atemwegsinfektionen zu reduzieren. Die Ansicht, möglichst rasch von der parenteralen auf eine orale Applikationsform zu wechseln, ist dagegen aus resistenzepidemiologischer Sicht eher kritisch zu hinterfragen, weil nach oraler Gabe bei unzureichender Resorption des Antibiotikums der Selektionsdruck höher sein kann als nach parenteraler Anwendung.[2]

Für den Bereich der Veterinärmedizin wurden für das Jahr 2011 erstmals verlässliche Daten über die Gesamtmengenabgabe von Antibiotika zur Verfügung gestellt. Die von den pharmazeutischen Unternehmern mitgeteilten Abgabemengen lassen jedoch keinen Rückschluss auf den tatsächlichen Einsatz der verschiedenen Antibiotikagruppen bei den unterschiedlichen Tierarten zu. Die Resistenzentwicklung bei tierpathogenen Bakterien wird vor allem von steigenden ESBL- und MRSA-Raten gekennzeichnet. Die kürzlich gemachte Beobachtung, dass Carbapenemase-bildende Bakterien auch bei Tieren isoliert wurden[3,4], ist ein Beleg dafür, dass der Transfer von antibiotikaresistenten Bakterien oder Resistenzgenen zwischen Menschen und Tieren wechselseitig möglich ist.

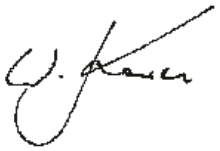
Der sachgerechte Gebrauch von Antibiotika ist mehr denn je erforderlich, da in naher Zukunft nur mit wenigen (Humanmedizin) bzw. nicht (Veterinärmedizin) mit neuen Wirkstoffen oder gar Wirkstoffklassen zu rechnen ist. Umso wichtiger ist der Erhalt der Wirksamkeit der derzeitig eingesetzten Wirkstoffe. Sachgerechter und intelligenter Gebrauch von Antibiotika bedeutet, in der konkreten Situation entscheiden zu können, ob - und wenn ja – welches Antibiotikum in welcher Dosierung und mit welcher Applikationsform verwendet werden soll. In diesem Zusammenhang sind die zum Teil sehr niedrigen Tagestherapiekosten von Antibiotika, hier sind durchaus auch Cephalosporine und Fluorchinolone zu nennen, nicht eben förderlich für den sachgerechten Gebrauch.

Mit der zunehmenden Globalisierung, die z.B. durch stetig zunehmende Fernreisen oder länderübergreifende Geschäftsverbindungen verursacht wird, ist auch eine ansteigende Globalisierung des bakteriellen Ökosystems verbunden. Hieraus ergeben sich weitreichende Konsequenzen, wie z.B. umfangreiche Interaktionen zwischen ambulanter Medizin und Krankenhaus sowie zwischen Menschen und Tieren.

Die Maßnahmen zur Bekämpfung der Ausbreitung resistenter Bakterien können sich nicht auf einen rein restriktiven Einsatz von Antibiotika beschränken. Gutes Management, fundierte Aus-, Weiter- und Fortbildung aller Beteiligten sowie wirkungsvolle Hygienemaßnahmen sind ebenso unabdingbar für den Erfolg. Im Bereich der Veterinärmedizin müssen zudem die Zucht- und Haltungsstrategien von Lebensmittel liefernden Tieren kritisch hinterfragt werden. In diesem Sinn wurden die in der Deutschen Antibiotika-Resistenzstrategie (DART) formulierten Ziele zur Vermeidung der Ausbreitung von Antibiotikaresistenzen bisher nur teilweise erreicht. Weitere Anstrengungen sind somit erforderlich. GERMAP will auch zukünftig seinen Beitrag hierzu leisten.

An der Erstellung des vorliegenden Berichtes waren erneut zahlreiche Kolleginnen und Kollegen aus der Human- und Veterinärmedizin beteiligt. Für die geleistete Arbeit danken wir allen Beteiligten sehr herzlich, insbesondere denjenigen Kolleginnen und Kollegen, die unserer Einladung gefolgt sind, ausgewählte spezifische Aspekte im Umfeld von Antibiotikaverbrauch und Resistenz näher zu beleuchten. Diese Beiträge finden sich in der vorliegenden Ausgabe unter der Bezeichnung „GERMAP *spezial*".

Für die Herausgeber:



Michael Kresken | Jürgen Wallmann | Winfried Kern

1 Summary

Human Medicine

According to 2011 data of the Statutory Health Insurance Research Institute (WIdO) there were almost 38 mil. antibiotic prescriptions in the ambulatory care setting, accounting for 358 mil. DDD ("*defined daily doses*") and expenditures of 684 mil. €. The antibiotic use density was 14.1 DDD per 1,000 subjects covered by statutory health insurance and day. The volume of prescriptions, expenditures and use density in 2011 were slightly lower than in 2008. However, the proportion of second-line drugs has continued to increase - most prominent here are the oral cephalosporins and the fluoroquinolones, and there is no clear reason for this increase. As before significant regional differences in antibiotic use persist, and use density levels are higher in the western than in the eastern federal states except for children. Based on DDD amoxicillin remains the most frequently prescribed drug. We observed an increasing use of fluoroquinolones with age. The estimated total "tonnage" of antibiotics used in the outpatient setting in Germany during the last years is in the range of 500–600 t per year, and this corresponds to approximately 85% of antibiotic use in human medicine.

The most important data source for hospital antibiotic use has become the so-called ADKA-if-RKI surveillance system which has evolved out of the former MABUSE project. Based on ADKA-if-RKI surveillance system data, hospital antibiotic use levels depend on hospital size. In regional and county hospitals, levels have recently been < 60 DDD per 100 patient whereas higher levels were observed in university hospitals. Cephalosporins and fluoroquinolones were the most extensively prescribed antibiotics in the hospital setting. Intensive care units showed twice as extensive antibiotic use overall as normal wards.

Sources for resistance data have been primarily the systematic studies of the Paul-Ehrlich-Society for Chemotherapy (Paul-Ehrlich-Gesellschaft für Chemotherapie, PEG) and, second, routine data out of the resistance surveillance systems ARS (including data from outpatient settings), SARI and EARS-Net. Furthermore, some of the resistance data were obtained from the national reference loboratories.

Taking into account the data published in GERMAP 2008 there have been clear trends over the past years: macrolide resistance among pneumococci was relatively high in 2005 (18% and 33% for isolates from adults versus children, respectively). Thereafter, there was a declining macrolide resistance rate among invasive pneumococci (10% in the year 2011). There was some increase in the number of penicillin-resistant pneumococci in particular among meningitis isolates from children (3% in 2011). In general, however, and compared with the situation in other countries, penicillin resistance in pneumococci remained rare in Germany.

Reduced susceptibility to penicillin was also observed in meningococci. Rates among isolates from the period 2002–2011 were ~14% overall, but only 0.7% were fully resistant. In the year 2012 rates for reduced susceptibility to penicillin and for full resistance were higher (25% and 2%, respectively), possibly in association with changes in the distribution of specific clonal lineages. For example, 23% of meningococci belonging to the ST11-complex, but only 5% of meningococci belonging to ST-41/44-complex show reduced susceptibility to penicillin.

Reduced susceptibility to penicillin was also observed in gonococci (80%) according to a landmark study in 2010/11 in Germany. Many of the isolates (70% or more) were also non-susceptible to ciprofloxacin and to tetracyclines. If empiric therapy of gonorrhea is to yield a ≥ 95% success (as recommended by WHO), third-generation cephalosporins and spectinomycin can be regarded as the only options in this country for a sufficiently effective empirical treatment of gonorrhoea.

No major changes in resistance rates were observed for *Mycobacterium tuberculosis*. The rate of MDR-*M.-tuberculosis* strains remained stable (2%).

Regarding antibacterial resistance in *Salmonella* one needs to look at different serovars. Most serovar-Typhimurium strains have now become MDR strains including emerging strains with ciprofloxacin resistance whereas most serovar-Enteritidis strains remain susceptible to commonly used antibiotics. Fluoroquinolone resistance is frequently observed among serovar-Kentucky strains, and there have been descriptions of strains belonging to serovar Kentucky and serovar Paratyphi B/Java that showed MDR phenotypes including resistance to fluoroquinolones and third-generation cephalosporins.

There has been a trend of somewhat declining rates of resistance to oxacillin among *S. aureus*. In the year 2011 the MRSA rate among bacteremia isolates was 16%. Resistance among MRSA to non-β-lactam drug classes was also declining. This can be explained by the (re-)emergence of new variants such as clonal lineage ST22 [„Barnim Epidemic Strain"] and ST225 [„Rhein-Hessen Epidemic Strain"]) strains. So-called hospital-acquired MRSA remain the most prominent of the isolates in hospitals (~90%) as well as in the community (~75%), and it will be important to closely monitor the epidemiologic evolution and distribution of so-called community-acquired and livestock-associated MRSA in the different healthcare settings. It is known that the zoonotic reservoir is also highly relevant for the emergence of new mec variants (e.g. *mecC*) and new resistance genes (e.g. *cfr*) among MRSA in human medicine. Of note is the recent demonstration of *cfr*-associated resistance to linezolid among *Staphylococcus epidermidis* in German hospitals which has the potential of spread to *S. aureus*.

Human *Escherichia coli* isolates have continued to show increased rates of resistance to many drugs commonly used for empirical therapy of infections (i.e. piperacillin-tazobactam, cephalosporins, and fluoroquinolones). According to data from the PEG studies the rate of extended-spectrum-β-lactamase (ESBL)-positive isolates increased to 17% in 2010. Predominant ESBL enyzmes are those of the CTX-M-15 type that is associated with the pandemic *E. coli* O25b-ST131 clonal group, and of the CTX-M-1 type that is frequently found among veterinary and food *E. coli* isolates. Fluoroquinolone resistance among human *E. coli* isolates remains very high (~30%), and this drug class can no longer be recommended as empirical therapy in severe infections suspected to be due to *E. coli*. The rates of resistance to carbapenems and to tigecycline among *E. coli* continue to be very low (< 1%). Looking at the outpatient setting it is obvious that resistance rates are lower than in hospital settings. Resistance to third-generation cephalosporins, however, and resistance to fluoroquinolones are also prevalent among community isolates of *E. coli*, but detailed systematic data in this setting is not available. Available data for healthy subjects show that the rate of faecal carriage of ESBL-producing bacteria is up to 7%.

ESBL-related resistance to third-generation cephalosporins is also prevalent among *Klebsiella pneumoniae*, and this trend has been associated with increased resistance to piperacillin-tazobactam, fluoroquinolones and gentamicin as well. Although the activity of carbapenems in *K. pneumoniae* is still high, there already have been outbreaks of carbapenem-resistant *K. pneumoniae* in German hospitals which indicates an extreme danger for the hospital system in Germany with its limitations in relevant infrastructure and single-room isolation capacity and its shortness of personnel trained in infectious diseases and infection control.

Regarding *Pseudomonas aeruginosa* there are relevant and significant differences in resistance rates between isolates from intensive versus normal ward care. While the rate of resistance to fluoroquinolones has remained rather stable, resistance to piperacillin (± tazobactam) and the carbapenems seems to increase. Carbapenems are still active against most *Acinetobacter-baumannii*-complex isolates (10%), with higher rates among *A. baumannii* compared with *Acinetobacter pittii*.

The fight against antibiotic resistance is now a top priority task for health personnel and policy makers. Prudent use of antibiotics and implementation of infection control measures are the most important ways to go in this fight. The analysis of the European point prevalence survey of antibiotic use and hospital infection shows that Germany is still in an acceptable range. An important observation was that surgical prophylaxis was given postoperatively (which does not correspond to standard recommendations) in too many instances which can be regarded as a relevant quality gap offering great opportunities to reduce selection pressure and resistance development/spread in hospitals. A second important observation was the frequency of *Clostridium difficile* infection in German hospitals which is likely to be associated with the predominant use of cephalosporins and fluoroquinolones. Rational and prudent antibiotic use through more efforts in the field of training, personnel and infrastructure in *Antibiotic Stewardship* [ABS] will be key, and there is a need to make more use of indicators to identify quality gaps and to measure improvements in processes and outcomes in this area.

Veterinary Medicine

The present data on resistances in bacteria that are pathogenic for animals are based on the results of GE*RM*-Vet, the national resistance monitoring of bacteria that are pathogenic for animals by the Federal Office of Consumer Protection and Food Safety (BVL) and on some regional studies. Since 2001 the GE*RM*-Vet monitoring program has been investigating annually the resistance of bacteria isolated from food producing animals as well as from companion animals. Only data on isolates from diseased animals are included in this report.

The veterinary results show clearly, how important it is to present the data differentiating between host species, type of production, bacterial species and organ systems.

Staphylococcus aureus isolated from dairy cows were susceptible against most tested antimicrobials; as in previous years the percentage of MRSA in *S. aureus* isolates from dairy cows was at about 3%. *S. aureus* isolated from poultry and companion animals showed higher resistance rates (more than 70%) against penicillins, tetracycline and erythromycin compared to previous years. The percentage of MRSA increased and was 15% in poultry and 35% in companion animals. Further, the percentage of methicillin (oxacillin)-resistant *Staphylococcus pseudintermedius* (MRSP) in *S. pseudintermedius* isolates showed an increase from 5% to 10%.

Bovine *Streptococcus* spp. isolated from mastitis cases showed a good susceptibility against most antimicrobials. Exceptions were reduced susceptibilities against tetracycline, erythromycin and pirlimycin.

Bordetella bronchiseptica isolated from respiratory diseases of pigs showed resistance against most β-lactams except amoxicillin/clavulanic acid. Compared to isolates from dogs and cats resistance rates in pigs were slightly higher.

Regardless of their host species the most important bacterial causative agents of respiratory infections, namely *Pasteurella multocida*, *Mannheimia haemolytica* and *Actinobacillus pleuropneumoniae*, showed good susceptibilities also against newer antimicrobials. However, few *P. multocida* isolates from cattle and pigs were resistant against florfenicole. This has been reported repeatedly since 2006/2007.

Pseudomonas aeruginosa isolated from companion animals showed consistently high resistance rates against most tested antimicrobials; based on the *in-vitro* results only very few antimicrobials can be regarded as therapeutically effective.

Escherichia coli isolated from dogs and cats with the indication „enteritis" as well as „disease of the urogenital tract" had lower rates of resistance than isolates from food producing animals. Isolates from pigs and poultry had high resistance rates against tetracycline, ampicillin and doxycycline; the rates of resistance differed between indications. An increase of resistant isolates against the combination of amoxicillin/clavulanic acid was observed in cattle (indication "enteritis") as well as in poultry (indication "sepsis"). As in recent years the highest resistance rates of *E. coli* against a high number of antimicrobials were consistently found in calves.

Most resistances found in *Salmonella enterica* ssp. *enterica* were against ampicillin and tetracycline. Isolates from cattle as well as from pigs increasingly showed intermediate resistance against the combination amoxicilllin/clavulanic acid.

Nationwide data about the delivery of antimicrobials to veterinarians is registered since 2011. Since then pharmaceutical business and distributors are required to report the amount of dispensed antimicrobials each year according to the law on pharmaceutical products (AMG)[1] and the DIMDI regulation on pharmaceutical products.[2] In the following year the amount itemized according to regions is published. In 2011 1,706 t antimicrobials (pure substance) were dispensed. Antimicrobials with the highest amount is tetracyclines (564 t), aminopenicillins (528 t), sulfonamides (185 t) and macrolides (173 t)[3]. A first analysis of preliminary data for 2012 showed,

that approx. 1,619 t antimicrobials (pure substance) were delivered to veterinarians. The largest share had tetracyclines (566 t), penicillins (498 t), sulfonamides (162 t) and macrolides (145 t).[4] Only inclusion of the data of the following years will allow an evaluation of the amounts of dispensed antimicrobials. In spite of the regionalized data a correlation to the resistance situation cannot be established.

A pilot study[5] "VetCAb" was done by the University of Veterinary Medicine Hannover (TiHo) to register the amount of antimicrobials given to food producing animals in Germany. The „VetCAb-Pilot" study showed by conversion into single doses that polypeptides, β-lactams and potentiated sulfonamides were the most used antimicrobials in poultry, β-lactams, polypeptides and tetracycline in pigs and β-lactams and tetracyline and potentiated sulfonamides in cattle. Furthermore a project in the private sector[6] by QS GmbH, Bonn, registers the amount of antimicrobials used in affiliated farms.

The preservation of the efficacy of antimicrobials available for veterinary medicine is one of our most important challenges and will continue to be so in the future. This can only be achieved by a responsible and intelligent use of the antimicrobials according to the current guidelines on the use of antimicrobials.[7]

Before choosing an antimicrobial for therapy, especially when choosing a compound against which the occurrence of resistance is known, an *in vitro* test of suitable antimicrobials is essential.

Better husbandry conditions, good management and optimized hygiene measures are the most important instruments to implement a restrictive use of antimicrobials. Only calling for a reduced amount of used antimicrobials is not adequate for this complex problem.

1. Arzneimittelgesetz in der Fassung der Bekanntmachung vom 12. Dezember 2005 (BGBI. I S. 3394), das durch Artikel 2 G v. der Verordnung vom 19. Oktober 2012 geändert worden ist (BGBl. I S. 2192).
2. Verordnung über das datenbankgestützte Informationssystem über Arzneimittel des Deutschen Instituts für Medizinische Dokumentation und Information (DIMDI-Arzneimittelverordnung – DIMDI-AMV) vom 19. November 2010, eBAnz AT122 2010 B1, 22.11.2010.
3. Wallmann J, Reimer I, Römer A, Bender A, et al. Abgabemengenerfassung antimikrobiell wirksamer Stoffe in Deutschland. Dtsch Tierärtzebl 2013;9:1230-4.
4. Wallmann J, Reimer I, Bender A, Römer A, et al. Abgabemengenerfassung antimikrobiell wirksamer Stoffe in Deutschland 2012. Dtsch Tierärtzebl 2014;2:184-6.
5. van Rennings L, von Münchhausen C, Honscha W, Ottilie H, et al. Kurzbericht über die Ergebnisse der Studie „VetCAb-Pilot". Dtsch Tierärtzebl 2013;8:1080-3.
6. QS Qualität und Sicherheit GmbH, http://www.q-s.de/monitoringprogramme_antibiotikamonitoring.html.
7. Anonymous. Leitlinien für den sorgfältigen Umgang mit antimikrobiell wirksamen Tierarzneimitteln. Dtsch Tierärztebl, Beilage Okt. 2010.

2 Antimicrobial consumption in human medicine

2.1 Outpatient antimicrobial consumption

As was the case in previous years, antimicrobials were among the top-selling active substance classes prescribed in outpatient care under statutory health insurance in 2011. In terms of prescribing rate by number of packages prescribed, they have been taking a leading position among the first five most frequently prescribed active substance classes for many years. Since infectious diseases are usually acute conditions, their treatment takes comparatively little time, and the prescription volume (in defined daily doses, DDD, according to the WHO's ATC index and the official German classification updated by the WIdO – Research Institute of the AOK) is far lower than that of other groups of medicinal substances, such as cardiovascular, antidiabetic and psychotropic drugs.[1]

The development of prescription volume in recent years is shown in Fig. 2.1.1. Over the past few years, the DDD and the number of prescriptions have remained largely constant, whereas the sales generated by SHI with proprietary antimicrobials have dropped over the last few years. In 2011, 38 million prescriptions, accounting for 358 million DDD and a sales volume of € 648 million (Fig. 2.1.1) were counted. These figures, shown in Tab. 2.1.1, refer to antimicrobial classes that are predominantly used in outpatient care.

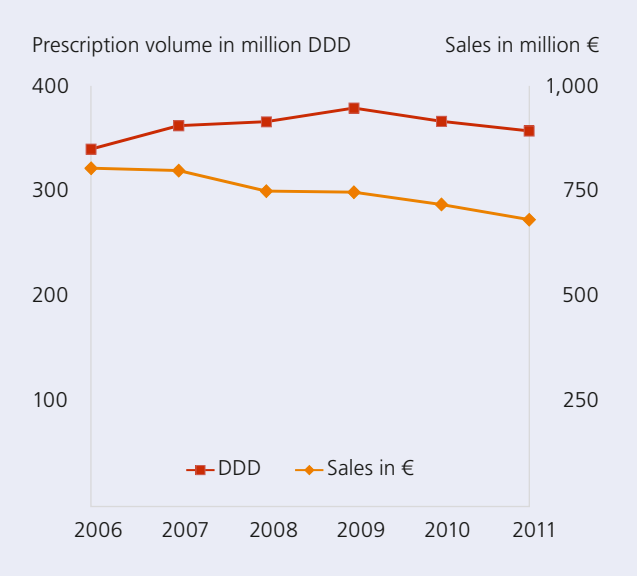


Fig. 2.1.1: Development of prescription volume (in DDD) and antibiotic sales (in €) over the last six years (Source: WIdO, SHI Drug Index)

Penicillin derivatives take first place, followed by tetracyclines and macrolides. Tab. 2.1.1 shows the figures for 2011. Accounting for 72.6 million DDD, amoxicillin (without the therapeutic combinations for Helicobacter eradication) was the antimicrobial agent with the highest prescription volume in 2011, followed by doxycycline ranking second (55 million DDD) and cefuroxime axetil holding third place (41.4 million DDD). When translated into tonnes and taking account of the additional consumption in the non-SHI area, these figures yield a total antimicrobial consumption of approximately 500–600 tonnes per year in outpatient human medicine.

Tab. 2.1.1: Antimicrobials prescribed (by daily dose) in 2011 under statutory health insurance (Source: WIdO, SHI Drug Index)

	Prescribed daily doses (million DDD)	Average DDD costs in €
Basic penicillins (oral penicillins and/or aminopenicillins)	90.6	1.09
Oral cephalosporins, aminopenicillin with β-lactamase inhibitor, flucloxacillin	77.5	2.74
Tetracyclines	66.3	0.72
Newer macrolides/ketolides/azalides	46.6	2.25
Quinolones	37.5	3.34
Folic acid antagonists	15.5	1.81
Nitrofurantoin and other* special urinary tract antimicrobials	11.6	1.80
Lincosamides/streptogramins/fusidic acid	6.6	2.70
Erythromycin and other older macrolides	5.9	2.15
Parenteral β-lactams	0.3	59.16
Imidazoles	< 0.1	21.45

*Nitroxoline and fosfomycin-trometamol

Tetracyclines have been declining in significance for many years. The share of tetracyclines in the total antimicrobial prescription volume dropped from 38% in 1991 to 24% in 2006 and 18% in 2011, respectively. The share of second-line antimicrobials has been increasing slowly but steadily for many years, and has continued to do so in recent years as well (Tab. 2.1.2). The increase in the prescription volume of oral cephalosporins, the combination of aminopenicillin and β-lactamase inhibitor as well as flucloxacillin by 95%, nitrofurantoin and other special urinary tract antimicrobials by 35% and quinolones by 17% between 2006 and 2011 is particularly high. The prescription volume of basic penicillins (aminopenicillins and penicillin V) and tetracyclines dropped over the same period.

The figures relating to outpatient antimicrobial consumption can be best described as DDD per 1,000 inhabitants (or insured) per day (DDD/1,000), referred to as use density. These figures are available for the approximately 70 million insured covered by SHI (85% of the population living in Germany), which allows for regional and international comparisons (see below).

There are significant differences within the various antimicrobial classes, some of which are also observed at regional level (regional prescribing preferences). Among fluoroquinolones, especially the consumption of ciprofloxacin (where the daily treatment costs in the generics market have quickly dropped)

Tab. 2.1.2: Changes in the outpatient prescription volume (by daily dose) of certain antibiotic classes between 2006 and 2011 (Source: WIdO, SHI Drug Index)

	Change
Basic penicillins (oral penicillins and/or aminopenicillins)	-8.6%
Oral cephalosporins, aminopenicillin with β-lactamase inhibitor, flucloxacillin	+95%
Tetracyclines	-20.0%
Newer macrolides/ketolides/azalides	+9.7%
Quinolones	+16.9%
Folic acid antagonists	-27.2%
Nitrofurantoin and other special urinary tract antimicrobials	+34.8%
Lincosamides/streptogramins/fusidic acid	+11.4%
Erythromycin and other older macrolides	-32.0%
Parenteral β-lactams	-4.2%
All antimicrobials	+5.1%

has increased in all KV [Regional Association of Panel Physicians] regions. The more affordable generic drug norfloxacin, however, is subject to an entirely different trend, showing declining rates. The increase in levofloxacin consumption varies greatly between regions, whereas moxifloxacin is showing variations, following a peak in 2005 and another increase in 2007 (Fig. 2.1.2).

The development of outpatient antimicrobial use density in Germany is shown in Fig. 2.1.3. In terms of insured covered by SHI, about 14.1 DDD per 1,000 insured and day were prescribed in 2011 (Fig. 2.1.3). Compared to previous publications, it should be noted that these figures may be based on

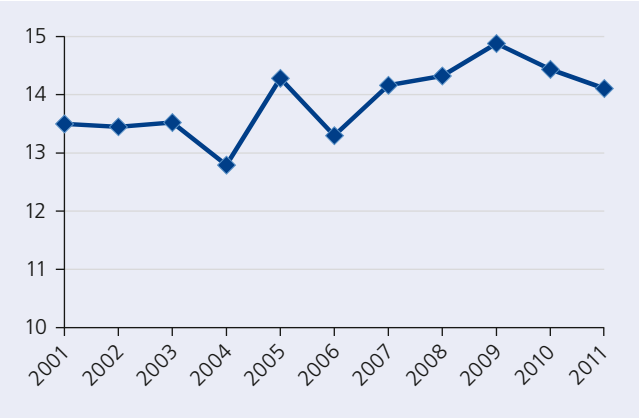


Fig. 2.1.3: Outpatient use density (in DDD per 1,000 insured and day) in Germany since 2001 (Source: WIdO, SHI Drug Index)

previous DDD definitions that no longer apply today. When applying the currently applicable dose definitions retrospectively (Fig. 2.1.3), a slight increase over the last ten years becomes apparent.

When extrapolating the number of inpatient prescriptions to the population and comparing the results with the outpatient use density, it becomes evident that antimicrobial prescriptions in the hospital only account for about 15% of the total prescription volume. In Germany, however, sufficiently reliable extrapolations are only available for Baden-Württemberg from 2002.[2] A 80–90% share of outpatient antimicrobial prescriptions in the total prescription volume has, however, been observed in many countries.[3] The total "tonnage" of antimicrobials used in human medicine ranges between 700 and 800 tonnes per year, thus ranking below the amounts used in veterinary medicine (approx. 1,700 tonnes).

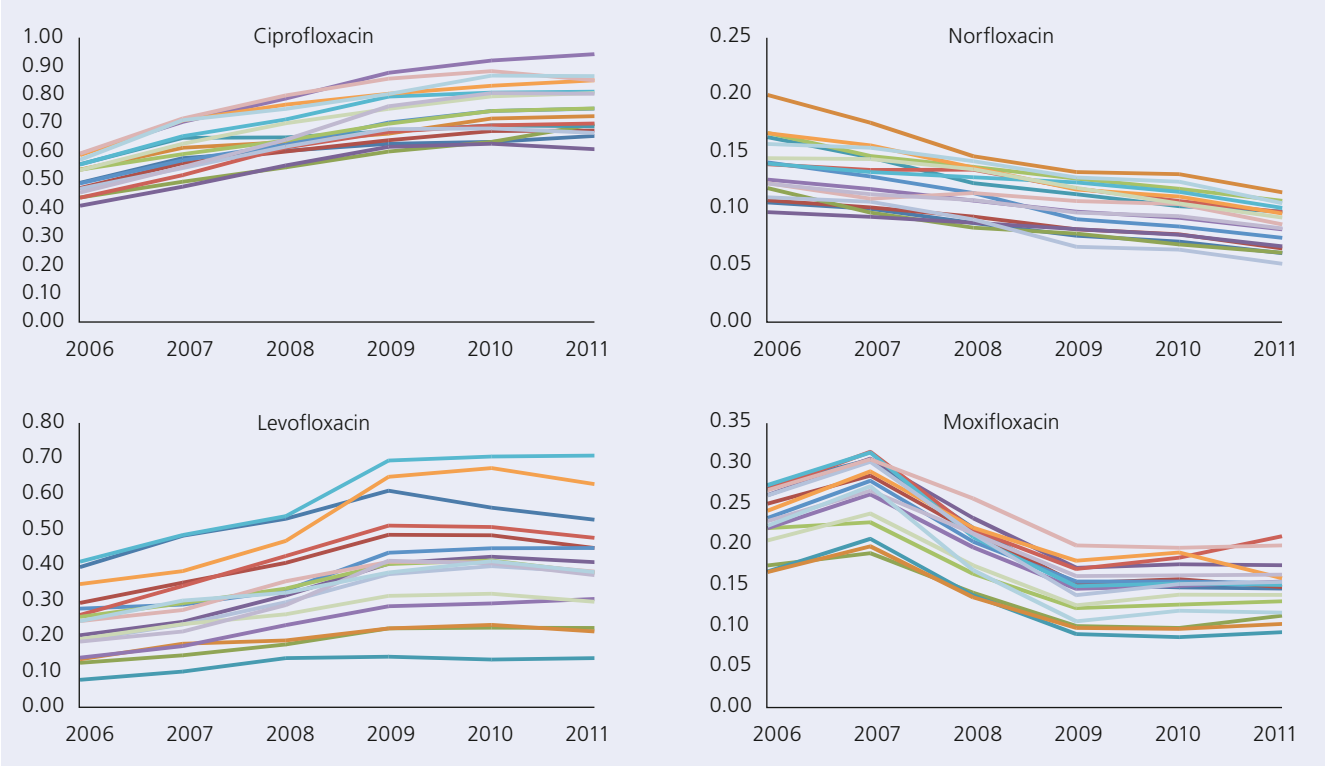


Fig. 2.1.2: Development of the prescription volume of selected fluoroquinolones (in DDD per 1,000 insured and day) in various regions of Germany (every line stands for the data reported by a Regional Association of Panel Physicians (Source: WIdO, SHI Drug Index)

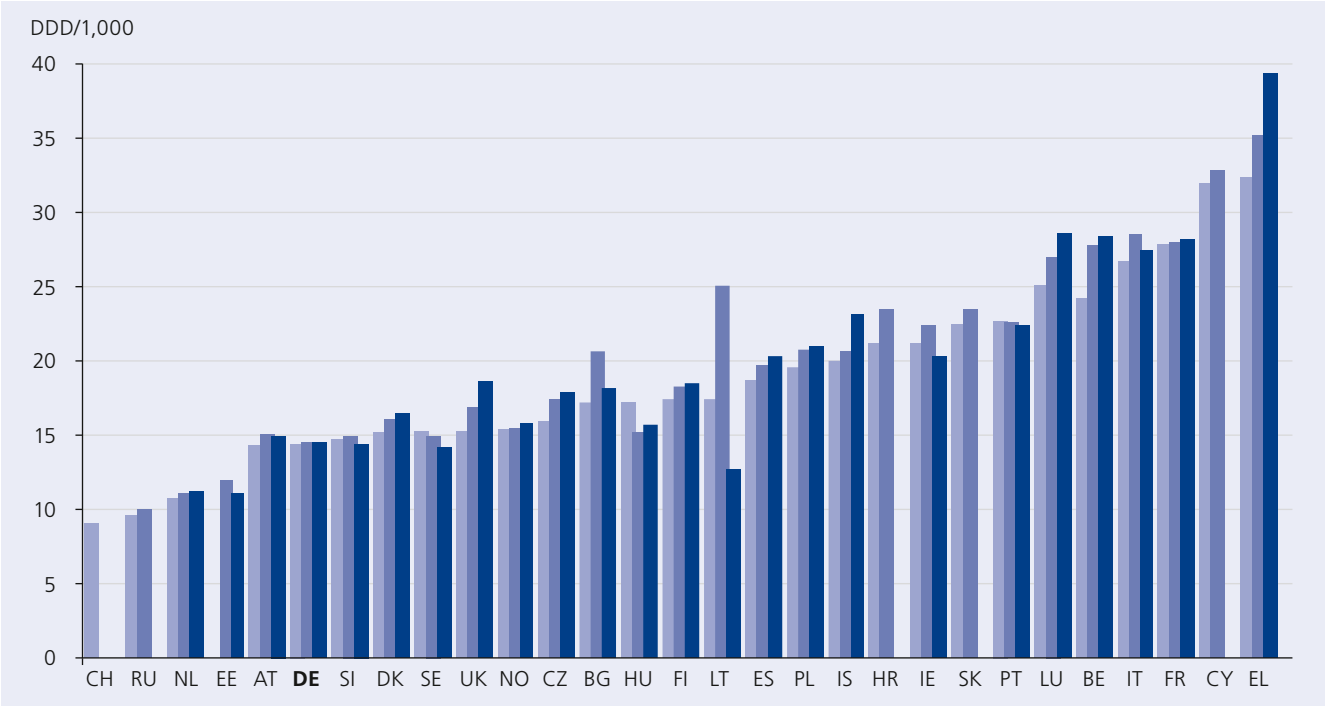


Fig. 2.1.4: Outpatient antibiotic use density in Germany (DE) compared to other European countries at population level, expressed as DDD per 1,000 inhabitants (or insured) and day (Source: WIdO as well as ESAC/ESAC-Net, 2006, 2008 and 2010 data)

Outpatient prescriptions in European comparison

Compared to other European countries, Germany is still ranking in the lower third with an outpatient use density of < 15 DDD/1,000 – along with the Netherlands, Austria, Scandinavia, Slovenia, Russia and Switzerland (Fig. 2.1.4). Greece and Cyprus as well as France, Italy, Belgium and Luxembourg were among the European top users in 2006, 2008 as well as in 2010.[4] In some cases, physicians in these countries prescribed more than twice as many antimicrobials than German ones. The orders of magnitude have only seen minor changes during the last few years (Fig. 2.1.4). Many countries for which more recent data for 2010 is available report an increase in use density, for example Denmark (2008–2010: 16–16.5), Finland (2008–2010: 18–18.5), Great Britain (2008–2010: 16.9–18.6) and Belgium (2008–2010: 27.7–28.4). However, when comparing individual countries including Germany, the general ratios have remained very similar.

The figures for the Netherlands and Switzerland (approx. 10–11 DDD/1,000) show the "lower" end of the use density in modern societies without any recognisable detrimental effect on quality, pointing to potential room for optimisation in the German healthcare system. Similar use densities are observed in the Baltic States and Russia. Numerous studies (also from Germany) demonstrate that the immediate prescription of antimicrobials for respiratory tract infections can and should be reconsidered in many cases: In 90% of these cases, an antimicrobial therapy, whether with doxycycline, amoxicillin or moxifloxacin, is not indicated. According to one of these studies, antimicrobial prescriptions for bronchitis by general practitioners in North Rhine-Westphalia could be reduced by 40–60% – merely by improving the communication between patients and physicians – without using biomarkers such as C-reactive protein or procalcitonin.[5] A recent study has shown that in elderly patients suffering from cough for several days without suspected pneumonia amoxicillin is not more effective than a placebo.[6]

Use density by region

Significant regional differences in antimicrobial consumption within Germany were evaluated specifically and described in greater detail for the first time in 2001.[7] Especially in western regions (old Länder), physicians prescribed significantly more antimicrobials than in the five new Länder. These regional differences have since then seen no substantial change.[8-12] In 2005, for example, the use density in the old Länder ranged between 13.9 DDD/1,000 (Baden-Württemberg) and 18.3 DDD/1,000 (Saarland), thus significantly exceeding that in the new Länder (9.8 to 11.7 DDD/1,000). The 2011 figures show a fluctuation range from 10.6 DDD/1,000 in Saxony to 17.3 DDD/1,000 in North Rhine-Westphalia (Fig. 2.1.5 and 2.1.6), which has superseded Saarland at the top of the list.

Notably, β-lactam consumption (basic penicillins and oral cephalosporins) continues to be higher in western regions and penicillin consumption, in particular, is very low in the new Länder, while the consumption of tetracyclines, fluoroquinolones and newer macrolides is at a similar level (Tab. 2.1.3) – a trend that has already been observed previously in a similar fashion. A certain regional prescribing preference within the antimicrobial classes is also apparent. As briefly addressed above (Fig. 2.1.2), there are distinct differences in the preference for certain antimicrobials, e.g. fluoroquinolones, between the KV-regions: For example, the three major high-consumption regions of moxifloxacin in 2011 were the Eastern German Länder of Mecklenburg-Western Pomerania, Brandenburg and Saxony-Anhalt, with Saarland, Rhineland-Palatinate and Baden-Württemberg being the leaders in levofloxacin consumption (Fig. 2.1.2).

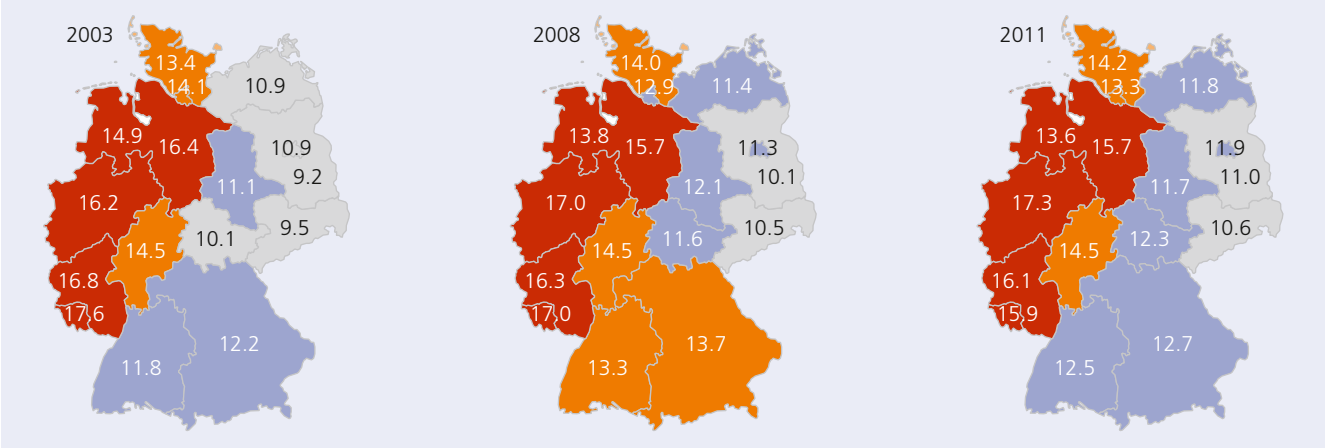


Fig. 2.1.5: Regional antibiotic use density in 2003, 2008 and 2011 (in DDD/1,000) (Source: WIdO, SHI Drug Index)

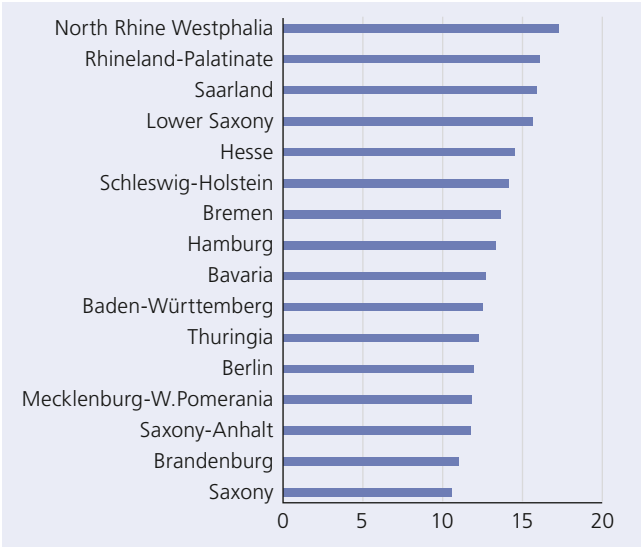


Fig. 2.1.6: Antibiotic use density (in DDD per 1,000 insured and day) in 2011 by KV regions (Source: WIdO, SHI Drug Index)

Tab. 2.1.3: Regional differences in the prescribing of certain antibiotic classes in 2011 in DDD/1,000 insured and day (Source: WIdO)

	East	South	West
Basic penicillins	1.95	3.00	4.55
Tetracyclines	2.52	2.26	2.85
Oral cephalosporins, aminopenicillin with β-lactamase inhibitor, flucloxacillin	2.53	2.99	3.32
Newer macrolides/ketolides/azalides	1.72	1.66	1.99
Quinolones	1.37	1.45	1.54
Folic acid antagonists	0.49	0.56	0.69
Nitrofurantoin and other* special urinary tract antimicrobials	0.40	0.37	0.53
Erythromycin and other older macrolides	0.24	0.15	0.27
Lincosamides/streptogramins/ fusidic acid	0.26	0.20	0.29

East: new Länder and Berlin; South: Baden-Württemberg and Bavaria; West: all other old Länder

Use density by specialist group

Prescriptions by general practitioners in Germany accounted for approx. 53% of all antimicrobial prescriptions (in DDD) in 2011 (compared to 58% in 2003, 57% in 2005 and 54% in 2008; Fig 2.1.7). They were responsible for 53% of the total β-lactam consumption, 63% of all macrolide prescriptions and 54% of all quinolone prescriptions.

They were followed by internists working as general practitioners, paediatricians and ENT specialists ranking second, third and fourth, respectively.

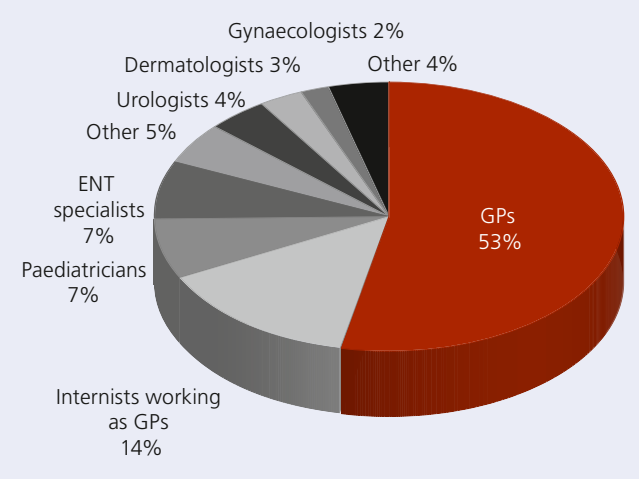


Fig. 2.1.7: Share of individual specialist groups in total antimicrobial consumption in Germany in 2011 (Source: WIdO, SHI Drug Index)

The various specialist groups set different priorities in selecting antimicrobials: Basic penicillins and tetracyclines accounted for 44% of all daily doses prescribed by general practitioners. ENT specialists also preferred β-lactams and tetracyclines, accounting for 81% of the prescribed daily doses of antimicrobials. By contrast, the prescribing behaviour of urologists was entirely different: Folic acid antagonists (incl. co-trimoxazole) and tetracyclines accounted for 24% of the prescribed DDD of antimicrobials, quinolones for 29% and other urinary tract antimicrobials for 31%. Paediatricians preferably prescribed β-lactams and macrolides, with 37% accounting for basic penicillins and 38% for oral cephalosporins and antistaphylococcal penicillins. The prescribing rate of newer macrolides and older macrolides was similar (9–10% each).

The highest antimicrobial prescription volume (by daily dose) per physician was demonstrated by ENT specialists and urologists, followed by general practitioners, paediatricians,

internists working as general practitioners and dermatologists (Tab. 2.1.4).

Tab. 2.1.4: Antibiotic prescription volume per physician of certain specialist groups in 2011 (Source: WIdO, SHI Drug Index)

Specialist group	DDD of antimicrobials prescribed per specialist
ENT specialists	5,538
Urologists	5,211
GPs	4,579
Paediatricians	3,764
Internists working as GPs	3,656
Dermatologists	2,766

Use density by age group

In childhood (< 10 years), between the age of 16 and 19 and in old age (≥ 90 years), antimicrobials in outpatient care are prescribed more often than in other age groups (Fig. 2.1.8). It should be considered that the frequency of hospitalisation increases with age and a relatively large number of antimicrobial prescriptions in this age group are likely to occur as part of inpatient care.

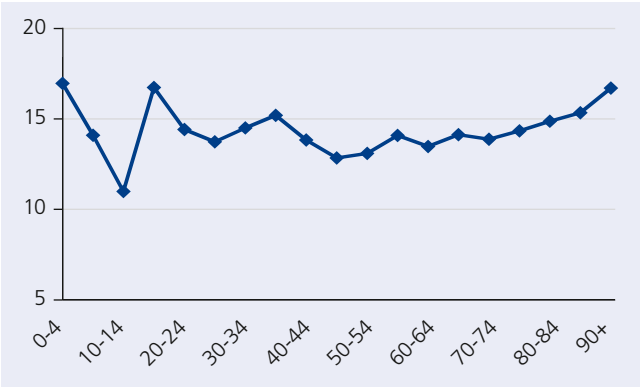


Fig. 2.1.8: Antibiotic use density (in DDD per 1,000 insured and day) in dependence on age (age groups in years) in 2011 (Source: WIdO, SHI Drug Index)

The prescribing rate (in %) in childhood is considerable: In the course of 2010, antimicrobials were prescribed to nearly 70% of all children aged below 5 years (Fig. 2.1.9)[15]. This rate is approximately twice as high as in other age groups. By contrast, the number of days of antimicrobial therapy increases until adulthood, and only declines slightly when retirement age is reached – in this respect, however, the simultaneous rise in the number of inpatient treatments with age should be taken into account.

Antimicrobials prescribed preferably in childhood include basic penicillins and oral cephalosporins. Above the age of 5, the consumption of oral cephalosporins drops significantly in favour of newer macrolides. The prescribing rate of tetracyclines increases with age, representing the most commonly prescribed antimicrobial class above the age of 45, followed by basic penicillins, oral cephalosporins and newer macrolides. On reaching the age of 60, fluoroquinolones are prescribed more often than newer macrolides, taking fourth place behind tetracyclines, oral cephalosporins and pencillins. In old age, fluoroquinolones increasingly gain significance, representing the second most frequently prescribed antimicrobial class behind oral cephalosporins above the age of 80. The prescription volume of urinary tract antimicrobials also increases significantly above the age of 70.

Unlike in adults and total consumption, the regional prescription prevalence rates in children show no gradient from east to west. This has already been observed in a previous study.[13] According to a recent study among GEK members, the highest prescription prevalence in children and adolescents in 2009 was observed in Saxony-Anhalt, Saarland/Rhineland-Palatinate, Thuringia and Mecklenburg-Western Pomerania and the lowest prevalence in Schleswig-Holstein/Hamburg/Bremen and Baden-Württemberg.[11]

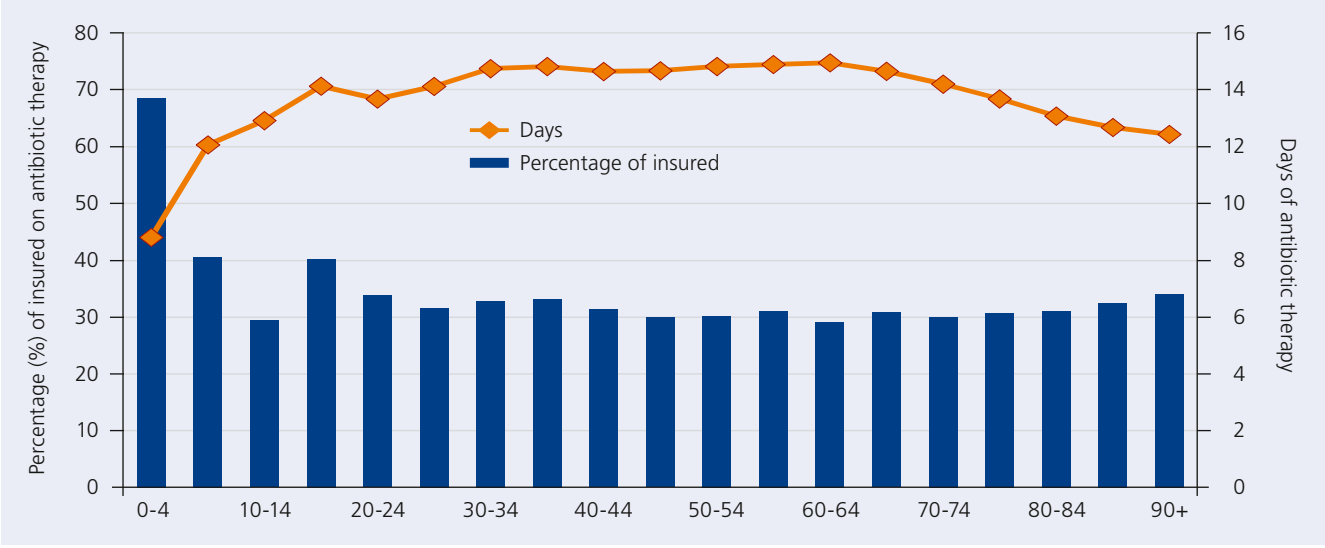


Fig. 2.1.9: Percentage of insured on antibiotic therapy (bars) and days of antibiotic therapy (line) in dependence on age (age groups in years) in 2010 (Source: WIdO, database: AOK prescribing data, 2010)

Seasonal prescription patterns

Due to the clustering of respiratory tract infections during the winter months, the antimicrobial use density during these months is much higher than in summer. These variations can be taken as a basis to identify antimicrobials that are used – appropriately or inappropriately – for the treatment of respiratory tract infections.

National data collected over the period 2007–2011 shows that not only β-lactams and macrolides but also fluoroquinolones are being increasingly used for treatment during the winter months. As expected, amoxicillin and macrolides, but also doxycycline and minocycline, are used much more commonly during the cold season than norfloxacin and ofloxacin (urinary tract infections) (Fig. 2.1.10). The use of newer fluoroquinolones, such as levofloxacin and moxifloxacin as well as cefuroxime axetil and amoxicillin/clavulanic acid, is also subject to strong seasonal variations, with the indications of respiratory tract infection and pneumonia also playing a significant role in this regard. Among fluoroquinolones, ciprofloxacin – in addition to moxifloxacin and levofloxacin – is also subject to seasonal variations; this might be an indication of this substance being used inappropriately for the treatment of respiratory tract infections (Fig. 2.1.10).

The significant increase in the consumption of cefuroxime axetil in dependence on the season is particularly remarkable (Fig. 2.1.10). This increase is assumed to be only partly attributable to the application of cefuroxime in a higher dosage (2 x 500 mg instead of 2 x 250 mg per day) in recent years. The time of this increased consumption is unusual: Unlike the first edition (2005), the second edition (2009) of the S3 guideline on community-acquired pneumonia/deep respiratory tract infections no longer recommended oral cephalosporins as a therapeutic alternative.[14]

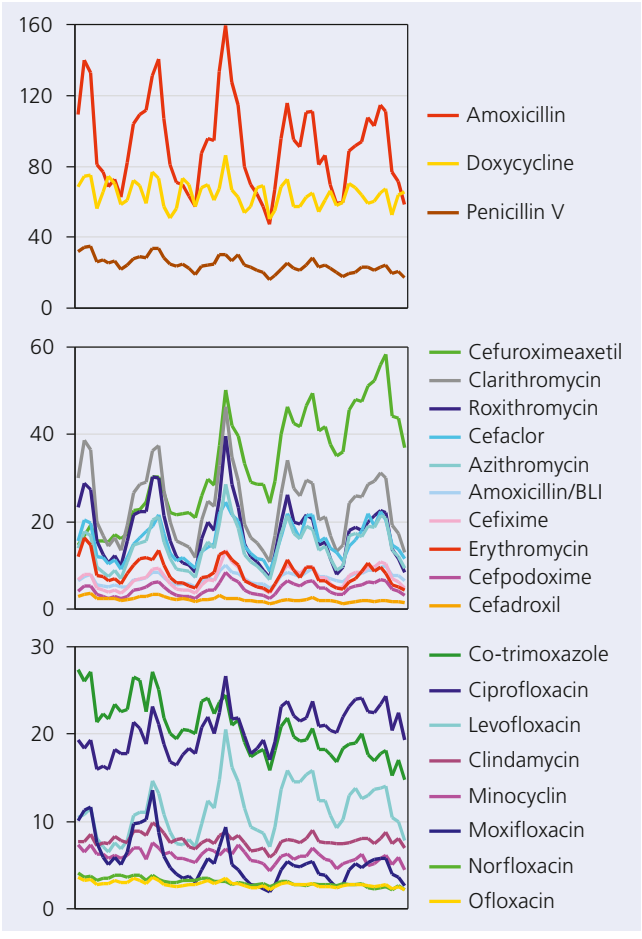


Fig. 2.1.10: Seasonal use of certain antimicrobials in DDD per 1,000 insured and month (Source: WIdO, SHI Drug Index, 1/2007–6/2011 data)

Conclusion

Showing an outpatient antimicrobial consumption of 14 DDD/1,000 insured and day, Germany remains in the lower third compared to other European countries – on a similar level with the neighbouring countries Switzerland, Austria, the Netherlands and Denmark. Western regions, predominantly those bordering on France, Luxembourg and Belgium, remain the high-consumption regions within Germany; however, Saarland has lost its leading position to North Rhine-Westphalia for the first time. The eastern part of the country continues to be the low-consumption region; however, this does not apply in this form to the prescription prevalence in children and adolescents. General practitioners are responsible for most prescriptions. The total antimicrobial consumption has shown a slight upward trend for many years, whereas the share of second-line antimicrobials has increased considerably. This particularly applies to fluoroquinolones and oral cephalosporins used without a confirmed rational background. Amoxicillin is still by far the most frequently prescribed substance. The use of fluoroquinolones increases with age. The age structure of the population and region-specific factors, including presumably socio-cultural variables on part of physicians and patients, seem to be crucial for use density and prescription profile in Germany.

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Antimicrobial prescribing in the outpatient setting – what quality indicators are suitable?

There is plenty of data available on outpatient antimicrobial prescribing in Germany. The Drug Prescription Report has been published annually on behalf of the health insurance funds for many years (www.wido.de/arzneiverordnungs-rep.html). The national data presented therein by the Research Institute of the AOK (WIdO) has become the basis for reporting to European authorities (European Centre for Disease Control and Prevention, ECDC).

In addition to the nationwide analysis of prescriptions, regionally differentiated analyses are increasingly gaining significance. Special analyses of antimicrobial prescribing in the SHI area including regional differentiation of data have already been issued earlier[1,2] by the WIdO – in cooperation with the University Hospital Freiburg – and have become the data basis for the GERMAP series. The Central Research Institute of Ambulatory Health Care in Germany (ZI, i.e. an institute of medical self-administration in statutory health insurance) has recently established a special service for the regional care situation (www.versorgungsatlas.de), which has most recently also offered interesting analyses in the field of influenza vaccination and antimicrobials.[3] The Pharmaceutical Atlas (www.arzneimittel-atlas.de), issued by the IGES Institute in Berlin on behalf of the Association of Research-Based Pharmaceutical Companies, also offers regionalised analyses. In addition, regional analyses of antimicrobial prescribing by Barmer-GEK[4,5] and AOK Hessen[6] are worth mentioning.

In view of this fairly good data availability, it is interesting to see that more than 80% of clinicians – both registered physicians in private practices and hospital-based physicians, in both Eastern and Western Germany – would like to have more information and advice on this subject – according to a survey among about 3,000 physicians conducted in 2007 (EVA study conducted by RKI/BMG [Federal Ministry of Health]).[7] Does this indicate that the "right" or "appropriate" and relevant information has not yet reached the physicians and/or that a fact-based interpretation of the corresponding data has not taken place? Quality indicators could be helpful in this respect. What quality indicators for antimicrobial prescribing are available in private practices? What influence will the application of such indicators have on the situation in Germany?

What indicators have been available so far?

There are extensive lists of indicators for panel physicians in Germany, namely the more than 130 so-called "QISA indicators" (created by the AQUA Institute on behalf of the Federal Association of the AOK, www.qisa.de) and the so-called "AQUIK indicators" (created on behalf of the Federal Association of Panel Physicians, KBV, www.aquik.de). These do not include any quality indicators that are relevant to outpatient antimicrobial use. There are AQUIK indicators in place for HIV/AIDS, hepatitis C and vaccinations. In addition, the AQUA Institute applies what are referred to as practice-specific prescription analyses with a peer review group in their quality circles (on the subject of "pharmacotherapy", amongst others) – however, this data is not generally accessible and its selection and preparation cannot be assessed, which is why it is not suitable for the purpose of external quality assessment.

Following extensive preliminary work as well as a scoring of originally 22 potential indicators for various relevance areas and discussion rounds with international experts, the ESAC study group, which had been funded by the EU from 2001 to 2011, thereafter by the ECDC, has developed a list of 12 potential quality indicators that are based on indication-independent consumption data. The evaluation of these indicators, including consumption data from European countries between 2004 and 2009, has been completed. This allows for identifying potential "areas of concern" in outpatient antimicrobial prescribing quality in certain countries.[8] Tab. 1 compiles the scores of the originally 22 indicators given after a number of Delphi rounds as well as the results for the selected indicators for Germany. Tab. 2 shows the distribution of the figures across Europe. As shown in Tab. 1, figures within the 75–100 percent range are highlighted in red, marking strong outliers that can be interpreted to mean an "area of concern in urgent need of optimisation". Figures within the 50–75 percent range are highlighted in yellow ("some optimisation required").[8,9] For Germany, this would yield the following primary need for optimisation:

- Reduction of cephalosporin consumption, in particular broad-spectrum cephalosporins
- Reduction of antimicrobial, in particular quinolone, consumption for the indication of respiratory tract infections

Proposal of a pilot project for regional indication-specific indicators.

In an effort to advance the above-mentioned efforts, colleagues have attempted to define indication-specific indicators at European level that allow for planning more specific and targeted interventions to improve the quality of outpatient antimicrobial prescribing. Initially, two expert groups joined forces and developed a list of indicators, classified them according to diagnoses (according to the index of the

Tab. 1: Indication-independent quality indicators for outpatient antibiotic prescribing quality that have been selected by the ESAC group as useful after several Delphi rounds[8,9]

Label/ Abbreviation	Indicator description	Scores (1–9) regarding relevance to				Ultimate selection	Figures for Germany in	
		Resistance develop-ment	Benefit for patients (clinical rel.)	Cost effec-tiveness	Health policy		2004	2009
J01_DID	**Total consumption***	8	6.5	7	8	✓	**13.01**	**14.90**
J01A_DID	Tetracycline consumption	6	5	5	5	no		
J01C_DID	**Penicillin consumption**	7	6	6	7	✓	**4.01**	**4.27**
J01D_DID	**Cephalosporin consumption**	7	6	6	6.5	✓	**1.25**	**2.39**
J01E_DID	Sulphonamide/ Trimethoprim consumption	6.5	5	6	5.5	no		
J01F_DID	**Macrolide consumption**	7.5	6	6	7	✓	**2.12**	**2.51**
J01M_DID	**Quinolone consumption**	8	6	7	7.5	✓	**1.15**	**1.48**
J01A_%	Share of tetracyclines in total consumption	5.5	5	5	6	no		
J01C_%	Share of penicillins in total consumption	5.5	5.5	5	6.5	no		
J01D_%	Share of cephalosporins in total consumption	6	5.5	6	6.5	no		
J01E_%	Share of sulphonamides/ trimethoprims in total consumption	5	5	5	6	no		
J01F_%	Share of macrolides in total consumption	7	6	6	6	no		
J01M_%	Share of quinolones in total consumption	7	6.5	7	7	no		
J01CE_%	**Share of basic penicillins in total consumption**	8	7	8	8	✓	**9**	**5.7**
J01CR_%	**Share of penicillin combination drugs (incl. those with β-lactamase inhibitor) in total consumption**	7	7	7	7	✓	**1.5**	**2**
J01DD+DE_%	**Share of third-/ fourth-generation cephalosporins in total consumption**	7	7	8	7.5	✓	**2.8**	**3.42**
J01MA_%	**Share of fluoroquinolones in total consumption**	7	7	7	7.5	✓	**8.8**	**9.9**
J01_B/N	**Ratio between drugs of the groups CR+DC+DD+(F minus FA01) and the groups CE+DB+FA01 ("broad-spectrum" vs. "narrow-spectrum")**	7	7	7	7	✓	**1.96**	**3.98**
J01_SV	**Seasonal variations in total consumption (winter months vs. summer months)**	7	7	7	7.5	✓	**37.7**	**46.1**
J01M_SV	**Seasonal variations in quinolone consumption (winter months vs. summer months)**	7	7	7	7	✓	**26.4**	**31.5**
J01M_SVDID	Seasonal variations in quinolone consumption (winter months vs. summer months) multiplied by quinolone consumption	6.5	6	7	7	no		
J01_TT	Trend in total consumption over time	6	6	7	7	no		

Figures printed in bold refer to the 12 ultimately selected indicators for which data from European countries and its distribution have been ascertained; figures for Germany are provided in the last two columns – figures within the 75-100 percent range are highlighted in red; figures within the 50-75 percent range are highlighted in yellow. See Tab. 2 for the distribution of figures in other European countries. *All antibiotic consumption data is provided in DDD per 1,000 inhabitants (or insured) and day

Tab. 2: Results of a selection of indication-independent quality indicators for outpatient antibiotic prescribing quality in European comparison

2004 Country	[J01_ DID]	[J01C_ DID]	[J01D_ DID]	[J01F_ DID]	[J01M_ DID]	[J01CE_ %]	[J01CR_ %]	[J01DD +DE_%]	[J01MA_ %]	[J01_ B/N]	[J01_ SV]	[J01M_ SV]
Portugal	23.8	11.2	3.2	3.7	3	0.4	30.7	2.1	12.8	13.5	31.8	12.9
Italy	24.8	12.1	3.1	4.8	3	< 0.1	23.8	7.4	10.9	55.4	25.1	17.1
Luxembourg	24.9	10.8	4.7	2.8	2.5	0.7	26.2	< 0.1	10	15	32.5	17.8
France	27	12.8	3.1	4.3	2.1	0.6	19.2	5.7	7.2	20.5	-	-
Belgium	22.7	10.5	3.1	2.3	2.5	0.6	28.4	< 0.1	10.8	27.7	30.9	13.1
Spain	18.5	10.8	1.8	2.4	2.2	0.5	35.1	2.6	11.6	42.1	29.2	12.6
Greece	33	10.4	7.2	9.7	1.9	0.8	15.6	0.7	5.7	24.3	20.4	-32
Hungary	18.2	8.4	2.2	3.1	1.7	6	24.8	2.4	9.1	7.4	37.9	5.5
Croatia	23	11.8	3.4	2.2	1.5	7.4	21.7	1.7	6.3	2.4	29.7	16.1
Austria	12.5	5.1	1.6	3	1.5	8.4	24.3	6.1	11.9	5.2	27.6	16.9
Slovakia	22.5	12.5	2.2	3.3	1.3	20.4	15.2	0.4	5.9	1.7	36.4	4.2
Germany	13	4	1.3	2.1	1.2	9	1.5	2.8	8.8	2	37.7	26.4
Slovenia	16.7	9.9	0.7	3.2	1.1	14.9	24.1	0.4	6.5	3	29.5	8.8
Israel	19.6	11.6	3.5	1.5	1.1	8.2	17.2	0.1	5.5	2.8	16.1	-5.8
Estonia	10.4	4.1	0.7	1.4	0.7	3	6.6	< 0.1	6.7	2.4	43.1	13.7
Russia	9.3	2.2	0.2	1	1.3	1.8	2.7	0.6	13.2	2.1	-	-
Iceland	21.4	11.1	0.4	1.7	0.7	13.6	12.8	0.3	3	1	17.8	8.6
Ireland	20.2	9.8	1.9	2.9	0.8	4.1	23	0.7	3.6	4.6	9.6	3.3
Poland	19.1	7.2	2.5	3	1	1.5	3.2	< 0.1	5.2	8.1	-	-
Czech Rep.	15.9	6.8	1	2.7	1.3	12.1	16.4	< 0.1	8	2.9	25.1	2.9
Bulgaria	16.4	7.7	1.7	1	1.6	5.2	8.5	0.9	9.8	1.4	-	-
Latvia	11.8	5.4	0.3	0.9	0.9	1.6	10.1	0.1	7.1	3	-	-
Netherlands	9.8	3.8	0.1	1.4	0.8	4.3	14.1	0.1	8.4	5.1	15.3	1.1
UK	15	6.8	0.8	2.2	0.5	4.7	6.5	< 0.1	3.2	0.8	16	8
Finland	17.2	5.1	2.1	1.9	0.8	9.1	4.8	< 0.1	4.8	0.8	12	4.3
Denmark	14.1	8.8	< 0.1	2.2	0.3	37	0.4	< 0.1	2	0.2	17.3	8
Norway	15.7	6.5	0.3	1.8	0.4	24.8	< 0.1	< 0.1	2.8	0.2	-	-
Sweden	14.5	6.5	0.4	0.8	1	26.8	1.3	0.1	6.8	0.2	9.6	5.4
2009 Country	**[J01_ DID]**	**[J01C_ DID]**	**[J01D_ DID]**	**[J01F_ DID]**	**[J01M_ DID]**	**[J01CE_ %]**	**[J01CR_ %]**	**[J01DD +DE_%]**	**[J01MA_ %]**	**[J01_ B/N]**	**[J01_ SV]**	**[J01M_ SV]**
Italy	28.7	15.2	2.8	5.3	3.6	0.1	34.3	7.2	12.1	99.3	27.3	20.1
Cyprus	34.4	16.0	6.5	4	4.1	0.3	29.3	1.7	12	26.9	-	-
Luxembourg	28.2	1.5	4.3	3.9	2.8	0.3	29.9	< 0.1	10	33.8	41.9	25.3
Belgium	27.5	15.1	1.8	3	2.6	0.4	32.3	< 0.1	9.5	43.5	33.6	18.2
France	29.6	16.1	2.9	4.2	2	0.5	22	6.4	6.5	42.8	-	-
Spain	19.7	12.3	1.6	1.9	2.4	0.5	38.7	2.8	12	56.9	25.7	17.3
Malta	21.6	9.1	5.5	3.9	1.7	0.1	36.4	0.8	7.7	149.5	-	-
Greece	38.6	12.9	8.7	11.5	2.6	1.9	13.7	0.8	6.8	31.7	32.6	3.3
Slovakia	23.8	9.6	4.1	6.1	2.1	7.8	22.7	2.3	8.6	7.4	35.1	10.3
Portugal	22.9	12	2	3.8	3	0.1	39.2	1.7	13.3	23.2	27.5	7.4
Hungary	16	7.1	2	3	1.8	4.2	28.8	2.4	11	13	57.4	25.1
Poland	23.6	10.7	2.9	3.9	1.3	0.6	20.9	< 0.1	5.3	36.3	-	-
Austria	15.9	7.1	1.8	3.9	1.3	6.2	28.2	5	8.3	7.4	37.5	16.8
Germany	14.9	4.3	2.4	2.5	1.5	5.7	2	3.4	9.9	4	46.1	31.5
Croatia	21.2	9.7	3.7	3.2	1.3	5	23.9	3.9	6.3	4.6	21.1	-4.1
Israel	22.4	11.8	4	1.9	1.4	0.4	20.7	0.1	6.4	9.6	15.4	-6.9
Bulgaria	18.6	8.4	2.3	3.2	2	2	14.4	0.9	10.6	6.2	-	-
Romania	10.2	4.3	2.5	1.8	1.3	1.6	23.6	1	12.3	6.1	-	-
Russia	12.2	4.2	0.5	1.7	2	0.5	7.8	2	15.7	7.4	18.5	8.6
Latvia	10.5	4.8	0.4	0.9	0.9	1.5	12.5	0.5	7.7	6.2	33.4	19.5
Ireland	20.8	10.7	1.3	3.8	0.9	4.1	26.5	0.5	4.5	5.4	18.9	4.1
Slovenia	14.4	9.5	0.4	2.3	1.1	13.5	28.2	0.8	7.5	3.5	26	9.9
Estonia	11.1	4.4	0.8	2.1	0.8	2.2	10.8	< 0.1	7.1	7.9	31.2	4.4
Czech Rep.	18.4	7.7	1.6	3.7	1.3	11.2	21.1	0.4	6.9	4.1	19.1	9.1
Lithuania	19.7	10.1	1.3	1.9	1.2	4.7	8.7	0.4	5.7	2.5	21.1	4.5
Iceland	19.4	10.4	0.3	1.2	0.6	12.1	18.3	< 0.1	2.9	1.7	13.5	5.4
Netherlands	11.4	4.5	< 0.01	1.5	0.9	3.4	16	< 0.1	7.7	6.4	18	2.5
Denmark	16	10	< 0.01	2.3	0.5	32.2	2.6	< 0.1	3.3	0.4	17.9	6.6
Finland	18	6.1	2.3	1.5	0.9	8.1	6.9	< 0.1	4.9	0.7	12.3	6.6
UK	17.3	8	0.6	2.5	0.5	4.3	6.4	< 0.1	2.8	0.8	17.1	7.6
Sweden	14	7	0.2	0.6	0.8	27.8	1.7	0.2	5.7	0.2	11.7	1.2
Norway	15.2	6.6	0.1	1.7	0.5	23.9	< 0.1	< 0.1	3.3	0.2	-	-

Figures for 2004 and 2009; figures within the 75-100 percent range (particularly critical areas) are highlighted in red; figures within the 50-75 percent range (critical areas) are highlighted in yellow[9]. See Tab. 1 for a description of indicators

Tab. 3: Indication-specific quality indicators for outpatient antibiotic prescribing quality that have been selected by the ESAC group and others as useful after several Delphi rounds10,11 as well as proposals regarding selection and adaptations and/or additions for application (pilot project) in Germany

Indication	Label/ Abbreviation	Indicator description	Target range (%)	Notes/Changed proposals regarding application in Germany
U71 – Cystitis	U71_J01_%	Percentage of female patients (> 18 years) with acute cystitis prescribed antimicrobials (J01)	> 80	
	U71_RECOM_%	Percentage of female patients (> 18 years) with acute cystitis prescribed antimicrobials receiving the recommended antimicrobials (J01XE or J01EA or J01XX)	> 80	
	U71_J01M_%	Percentage of women (> 18 years) with acute cystitis receiving quinolones (J01M)	< 5	✓ < 10% for women > 16 years
R76 – Tonsillitis	R76_J01_%	Percentage of patients (> 1 year) with acute tonsillitis prescribed antimicrobials (J01)	< 20	✓ for GPs, internists working as GPs, paediatricians
	R76_RECOM_%	Percentage of patients (> 1 year) with acute tonsillitis prescribed antimicrobials receiving the recommended antimicrobials (J01CE)	> 80	
	R76_J01M_%	Percentage of patients (> 1 year) with acute tonsillitis receiving quinolones (J01M)	< 5	
R78 – Acute bronchitis	R78_J01_%	Percentage of patients (18–75 years) with acute bronchitis prescribed antimicrobials (J01)	< 30	✓ for GPs, internists working as GPs
	R78_RECOM_%	Percentage of patients (18–75 years) with acute bronchitis prescribed antimicrobials receiving the recommended antimicrobials (J01CA or J01AA)	> 80	
	R78_J01M_%	Percentage of patients (18–75 years) with acute bronchitis receiving quinolones (J01M)	< 5	
R74 – Upper respiratory tract infection	R74_J01_%	Percentage of patients (> 1 year) with acute respiratory tract infection prescribed antimicrobials (J01)	< 20	
	R74_RECOM_%	Percentage of patients (> 1 year) with acute respiratory tract infection prescribed antimicrobials receiving the recommended antimicrobials (J01CE)	> 80	
	R74_J01M_%	Percentage of patients (> 1 year) with acute respiratory tract infection receiving quinolones (J01M)	< 5	
R75 – Sinusitis	R75_J01_%	Percentage of patients (> 18 years) with sinusitis prescribed antimicrobials (J01)	< 20	✓ for GPs, internists working as GPs
	75_RECOM_%	Percentage of patients (> 18 years) with sinusitis prescribed antimicrobials receiving the recommended antimicrobials (J01CE)	> 80	
	R75_J01M_%	Percentage of patients (> 18 years) with sinusitis receiving quinolones (J01M)	< 5	
H71 – Otitis media	H71_J01_%	Percentage of patients (> 2 years) with otitis media prescribed antimicrobials (J01)	< 20	
	H71_RECOM_%	Percentage of patients (> 2 years) with otitis media prescribed antimicrobials receiving the recommended antimicrobials (J01CA or J01CE)	> 80	
	H71_J01M_%	Percentage of patients (> 2 years) with otitis media receiving quinolones (J01M)	< 5	
R81 – Pneumonia	R81_J01_%	Percentage of patients (18–65 years) with pneumonia prescribed antimicrobials (J01)	> 90	
	R81_RECOM_%	Percentage of patients (18–65 years) with pneumonia prescribed antimicrobials receiving the recommended antimicrobials (J01CA or J01AA)	> 80	
	R81_J01M_%	Percentage of patients (18–65 years) with pneumonia receiving quinolones (J01M)	< 5	✓ < 20% for patients > 16 years (GPs, internists working as GPs)
NEW:				
R81	R81_J01D_%	Percentage of patients (18–65 years) with pneumonia prescribed cephalosporins (J01D)		< 20% for patients > 16 years (GPs, internists working as GPs)
R81	R81_J01F_%	Percentage of patients (18–65 years) with pneumonia prescribed macrolides (J01F)		< 20% for patients > 16 years (GPs, internists working as GPs)
HNO	HNO_J01C_%	Percentage of patients with prescribed antimicrobials receiving penicillins (J01C)		> 50% (ENT specialists and dentists)

International Classification of Primary Care, ICPC-2-R) and listed 3 indicators for each of the 7 selected diagnoses (Tab. 3).[9-11] This list provides an excellent basis for adding and selecting indicators specifically for Germany – our proposed additions and comments are also listed in Tab. 3. Antimicrobial prescriptions by ENT specialists in private practices are assumed to be "indication-specific" (upper respiratory tract infections/infections in the ENT area).

We take the view that a pilot project including regional calculation of these indicators in the German outpatient setting would be very useful. Areas that are assumed to have inappropriately high prescribing rates of quinolones and cephalosporins could be identified more clearly and other relevant region-specific factors of antimicrobial use in Germany could be delimited more accurately. This would allow for a much "more informed" discussion as to whether and in what areas there is a need for monitoring compliance with guidelines and controlling antimicrobial use (both substance selection and quantity control) and how urgent this need is. This could provide the basis for the further development and adaptation of such indicators, e.g. the separate analysis of selected groups of specialists (such as paediatricians and general practitioners).

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Reviewer: R. Berner

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2.2 Hospital antimicrobial consumption

Of the slightly more than 2,000 German hospitals in 2011, approximately 1,800 were general hospitals with about 450,000 installed beds, nearly 18 million admissions (cases) and > 100 million days of care (patient days). The number of hospitals and hospital beds has been declining for several years, whereas the number of inpatient admissions has increased, i.e. the average length of stay has decreased considerably (Fig. 2.2.1). These changes, which have also been observed in recent years, must be taken into account while interpreting changes in antimicrobial use density. They are likely to be responsible for a considerable part of the increase in antimicrobial use density over the past years – merely due to the fact that the number of cases has increased while the length of stay has decreased.

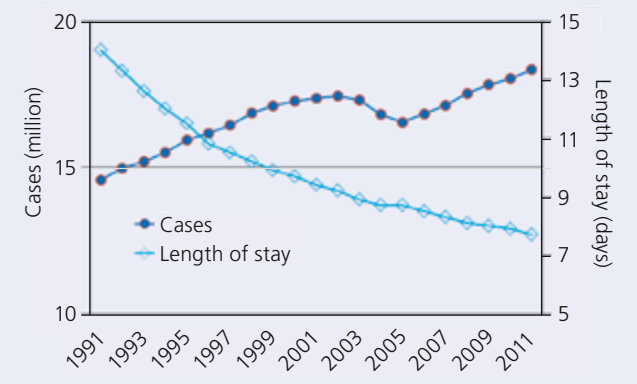

Fig. 2.2.1: Development of number of cases (inpatient admissions) and average length of stay at all German hospitals (incl. specialist hospitals) between 1991 and 2011 (Source: Federal Statistical Office)

Inpatient antimicrobial use density can be best calculated as defined (defined daily doses according to ATC-WHO, DDD) or recommended (recommended daily doses, RDD) daily doses per 100 patient days (DDD/100 or RDD/100) or per hospital case. However, DDD also involve problems, since they often do not correspond to the daily doses commonly used at hospitals – especially as regards the frequently used β-lactams.[1,2] The currently applicable DDD definitions of the WHO as well as the RDD definitions used herein are provided in chapter 7.3.

The data sources used to describe hospital antimicrobial consumption include the data collected within the ADKA-if-RKI surveillance project (www.antiinfektiva-surveillance.de), which evolved out of the MABUSE network (see also Chapter 7.3). The number of participants in the ADKA-if-RKI surveillance project has increased considerably since 2011 – as a result of the accelerated, quarterly data evaluation thanks to the RKI's support as well as the greater willingness to participate in the surveillance project since the amendment of the Infection Protection Act in 2011 (Fig. 2.2.2).

The 2011 data (comprehensive data for 2011 available for 75 acute-care hospitals) can be compared with the 2004 data (survey conducted by the MABUSE network using IMS data on 184 acute-care hospitals). While comparing the data, however, it should be considered that the 2004 and 2011 hospital cohorts are not congruent. The regional analysis (east-west-south) is also limited because the number of cases at the reporting hospitals is still too small.

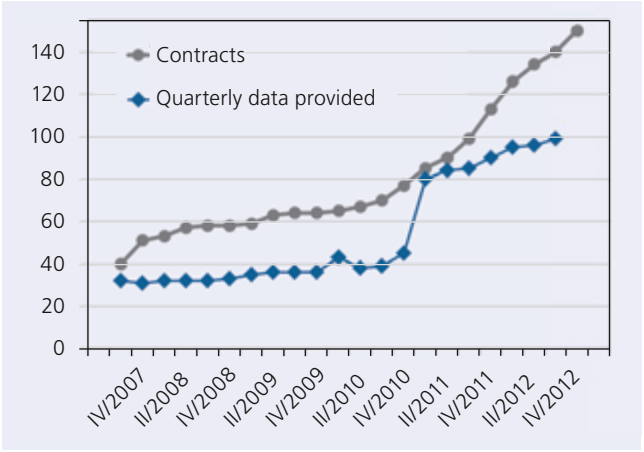

Fig. 2.2.2: Participating hospitals (contracts) and data provided (comprehensive quarterly data) within the ADKA-if-RKI project (Source: Infectiology Freiburg)

According to recent data for 2011, the median antimicrobial use density at German acute-care hospitals amounted to 57 DDD/100 patient days and the weighted average was also 57 DDD/100 patient days. Expressed as number of hospital cases (instead of 100 patient days), the consumption in 2011 was 3 DDD/case (median); the (weighted) average amounted to 3.12 DDD/case. Expressed in RDD, the corresponding figures were 2.1 RDD/100 patient days and 2.15 RDD/case (median and weighted average, respectively).

A comparison with the 2004 data reveals an increase from 50 to 57 DDD/100 patient days. A comparison with corresponding evaluations from other countries demonstrates that Germany is most likely to rank in the midrange in terms of inpatient antimicrobial use density (Tab. 2.2.1). An increase in use density in the hospital sector is also widely observed in other countries, which can be at least partly explained by the increase in the number of cases. However, the sample size at German hospitals is still relatively small – for example, compared to France. Reliable statements require a sample size of > 10% of all acute-care hospitals – differentiated by size (number of beds), region (east-west-south) and level of care (primary, secondary or tertiary care) – including continuous data reporting by all specialities (equivalent to approx. 200

Tab. 2.2.1: European studies on antibiotic use density at hospitals (data provided in DDD/100 days of care) and comparison with the US

	DDD/100 days of care	Source
Europe 2004 (n=139)	50	MacKenzie, et al [3]
Sweden 2006–2001 (n=80)	53–59	SWEDRES* [4]
Denmark 2006–2011 (n=66)	64–91	DANMAP* [5]
Netherlands 2004–2009 (n=86)	54–71	NETHMAP* [6]
Germany 2004 (n=184)–2001 (n=75)	50–57	GERMAP* [7]
France 2007 (n=360[a)])	38–59[b)]	Dumartin, et al [8]
France 2000–2010	42–43[c)]	Cavalié [9]
France 2010 (n=1,115)	37[c)]	Dumartin, et al [10]
USA 2002–2003 (n=130)	79	Polk, et al [11]

* The samples in the various periods were not identical

[a)] Excl. rehabilitation centres and psychiatric clinics

[b)] The higher use density (59 DDD/100) was observed at teaching hospitals (incl. university hospitals)

[c)] The 2010 data also includes psychiatric clinics and inpatient rehabilitation centres

hospitals in Germany). The now consolidated ADKA-if-RKI project is likely to make this happen, while also allowing for the definition of reference figures and benchmarking.

Hospital antimicrobial consumption at population level

Hospital antimicrobial consumption can be extrapolated to the population and can thus be compared with and added to outpatient antimicrobial consumption to obtain the total use density at population level. Such data has been presented within the ESAC project and continues to be estimated as part of the ESAC-Net project. However, only a few, predominantly small, countries are able to provide comprehensive data for the hospital sector.

Based on 2002 hospital consumption data for Baden-Württemberg (already presented in the 2008 GERMAP report), a previous analysis estimated the hospital antimicrobial consumption at ~ 2 DDD per 1,000 inhabitants and day – compared to an outpatient use density of ~ 14 DDD/1,000 insured patients and day at that time. This is equivalent to an estimated share of about 14% in total antimicrobial consumption for the hospital sector. The share varied between antimicrobial classes and amounted to 21% for fluoroquinolones, 7% for co-trimoxazole, 5% for macrolides/clindamycin and 1% for tetracyclines.

More recent data is not available for Germany. Recent data reported from some other European countries demonstrates an 85–90% share in total antimicrobial consumption for the outpatient sector, which has remained relatively constant over the years.

Use density by hospital size

A hospital's average antimicrobial use density depends on the hospital's level of care and size (number of beds and university hospital vs. non-university hospital) as well as on the type of speciality or ward (intensive care unit vs. general ward).

According to the results of the surveys conducted in 2004 and 2011, antimicrobial consumption at university hospitals is, as expected, significantly higher than at non-university hospitals. The increase in use density with hospital size (number of beds) at non-university hospitals observed in 2004 was not that pronounced in 2011 (Fig. 2.2.3). In 2011, the antimicrobial use density at hospitals with < 400 beds was 57 DDD/100 patient days (equivalent to 40 RDD/100), at hospitals with 400–800 beds also 57 DDD/100 patient days (36 RDD/100) and at hospitals with > 800 beds (excl. university hospitals) 52 DDD/100 patient days (36 RDD/100). By contrast, the use density at university hospitals was significantly higher, amounting to 66 DDD/100 patient days (47 RDD/100) (Fig. 2.2.3).

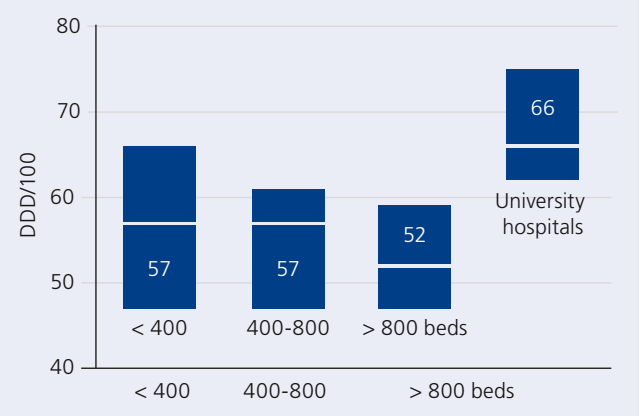

Fig. 2.2.3: Total antibiotic use density in 2011 in dependence on hospital size (number of beds) (medians and interquartile ranges) (Source: ADKA-if-RKI surveillance)

Use density by type of speciality/ward

When comparing use densities by type of ward, a significantly higher use density in intensive care units (Tab. 2.2.2) is observed in 2011 (as in 2004). Amounting to 106 DDD/100 patient days (79 RDD/100) in 2011, the use density in intensive care units was approximately twice as high as on general wards (53 and 59 DDD/100 patient days on general surgical and general non-surgical wards, respectively). These figures are slightly below those reported within the SARI project for 2011 (http://sari.eu-burden.info/auswertung/pages/alle.php).

Despite this extremely high use density, the share of antimicrobials prescribed in intensive care units in all antimicrobial prescriptions is only about 9–13% during the various survey periods (in line with the significantly smaller number of beds and patient days in intensive care units compared to general wards) (Tab. 2.2.3). The above-reported increase in total consumption in 2011 compared to 2004 is thus most likely attributable to increased consumption on general wards.

When also taking into account the type of speciality and the special status of university hospitals, a significantly higher consumption is observed in intensive care units and haematology/oncology departments of university hospitals. The use density in haematology/oncology departments of university hospitals is on a similar level with that in intensive care units. An increased use density is also found in the same specialities

Tab. 2.2.2: Antibiotic use density by type of ward. The figures provided include the median and (in brackets) interquartile ranges in DDD as well as RDD per 100 days of care (Source: MABUSE network, 2004 [IMS Health] and 2011 [ADKA-if-RKI surveillance] data)

Type of ward	2004			2011		
	n	DDD	RDD	n	DDD	RDD
General surgical ward	340	40 (33–49)	27 (22–33)	338	53 (35–72)	35 (22–51)
General non-surgical ward	285	45 (36–56)	32 (26–39)	221	59 (39–81)	39 (29–56)
Intensive care unit	218	110 (87–141)	76 (58–98)	146	106 (83–142)	79 (62–104)

Tab. 2.2.3: Share of DDD (RDD) prescribed per type of ward/specialist department in all DDD (RDD) at hospitals (Source: MABUSE network, 2004 and 2008 data; ADKA-if-RKI Surveillance, 2011 data)

	2004	2008	2011
General surgical ward	48% (46%)	46% (45%)	48% (46%)
General non-surgical ward	42% (43%)	41% (43%)	40% (41%)
Intensive care unit	10% (9%)	13% (12%)	12% (13%)

of non-university hospitals; however, it does not reach the prescription volume of internal, surgical or interdisciplinary intensive care units (Tab. 2.2.4 and 2.2.5).

The type of the intensive care unit also seems to have an influence on antimicrobial use density. Surgical intensive care units of non-university hospitals prescribed more antimicrobials than internal and other non-surgical intensive care units (Tab. 2.2.5). This difference was not observed at university hospitals in 2011, where the highest use densities were found on internal medicine and other non-surgical wards (predominantly in neurological intensive care units).

Tab. 2.2.4: Antibiotic use density on general wards by medical speciality at university and non-university hospitals. The figures provided include the median and (in brackets) interquartile ranges in DDD as well as RDD per 100 days of care (Source: MABUSE network, 2004 [IMS Health] and 2011 [ADKA-if-RKI surveillance] data)

	2004			2011		
Type of ward	**n**	**DDD**	**RDD**	**n**	**DDD**	**RDD**
General surgical ward	**340**			**338**		
– University hospitals						
Surgery		46 (40–62)	34 (27–42)		56 (52–81)	38 (36–58)
Other surgical specialities		63 (52–76)	42 (33–45)		82 (41–129)	57 (26–75)
– Other hospitals						
Surgery		40 (32–49)	27 (21–32)		53 (39–69)	36 (27–47)
Other surgical specialities		41 (28–58)	27 (17–36)		47 (31–70)	29 (19–48)
General non-surgical ward	**285**			**221**		
– University hospitals						
Haematology/Oncology		114 (86–149)	96 (66–128)		128 (115–152)	111 (97–120)
General internal medicine		54 (47–62)	39 (34–46)		71 (49–105)	56 (36–77)
Other non-surgical specialities		40 (37–46)	25 (24–28)		52 (31–79)	30 (23–49)
– Other hospitals						
Haematology/Oncology		54 (39–75)	38 (29–58)		81 (70–90)	64 (45–68)
General internal medicine		45 (36–55)	31 (25–38)		61 (45–75)	41 (32–53)
Other non-surgical specialities		27 (19–40)	21 (13–26)		34 (25–42)	22 (17–30)

Tab. 2.2.5: Antibiotic use density in intensive care units at university and non-university hospitals. The figures provided include the median and (in brackets) interquartile ranges in DDD as well as RDD per 100 days of care (Source: MABUSE network, 2004 [IMS Health] and 2011 [ADKA-if-RKI surveillance] data)

Type of ward	2004			2011		
	n	**DDD**	**RDD**	**n**	**DDD**	**RDD**
Intensive care unit	**218**			**146**		
– University hospitals						
Internal medicine		108 (66–116)	80 (52–91)		169 (162–192)	139 (127–157)
Other non-surgical		104 (80–133)	83 (55–94)		148 (98–156)	105 (72–112)
Surgical/Anaesthesiological		143 (104–181)	104 (71–143)		120 (95–142)	87 (75–100)
Other surgical/interdisciplinary		140 (100–185)	103 (64–120)		125 (69–134)	81 (43–94)
– Other hospitals						
Internal medicine		102 (79–122)	70 (54–90)		101 (82–137)	72 (59–101)
Other non-surgical		69 (15–117)	52 (12–84)		38 (15–45)	27 (8–37)
Surgical/Anaesthesiological		122 (95–182)	82 (61–91)		106 (87–137)	77 (65–107)
Other surgical/interdisciplinary		112 (86–135)	72 (58–95)		114 (95–137)	86 (70–105)

Use density by region

The 2004 data (presented in the 2008 GERMAP report) only revealed minor regional differences – hospitals in Eastern Germany typically had a lower use density. The 2011 data confirms this tendency (Tab. 2.2.6). In both 2004 and 2011, the use density in Eastern Germany was lower than in Western and Southern Germany.

Tab. 2.2.6: Use density (medians) by region in 2011 in DDD as well as RDD (in brackets) per 100 days of care and 2004 reference figures (Source: ADKA-if-RKI surveillance, 2011 data; MABUSE network, 2004 data)

	East	West	South
2011	51 (35)	57 (39)	60 (41)
2004	48 (33)	58 (39)	54 (38)

Antimicrobial classes

In 2011, β-lactams (35 DDD/100 patient days) and fluoroquinolones (7 DDD/100 patient days) were again used most commonly for the treatment of infectious diseases. All other antimicrobial classes only accounted for a smaller portion (< 50%).

This use pattern was already apparent in 2004 and 2007/2008, and the use densities of the two antimicrobial classes have not changed. The largest share within the group of β-lactams was, and still is, held by intermediate-spectrum β-lactams (with cefuroxime as well as combinations of ampicillin/amoxicillin and β-lactamase-inhibitors taking first place), followed by broad-spectrum β-lactams, with their share in intensive care units mostly being higher than on general wards (Tab. 2.2.7). However, the ratio of the shares of intermediate-spectrum and broad-spectrum β-lactams in the total consumption can vary greatly between wards.

Cephalosporins number 1 at hospitals

Overall, the group of cephalosporins had, and still has in 2011, the largest share (28%) in the RDD of antimicrobials (Fig. 2.2.4); they are prescribed somewhat more often than penicillins (25% share in all RDD of antimicrobials). Compared to penicillins, the share of cephalosporins on general surgical wards was, and still is, particularly high (2008, median 35% vs. 19%; 2011, median 37% vs. 16%).

The median ratio of cephalosporins and penicillins (in RDD) was 22% to 26% (2008: 23% to 28%) on general non-surgical wards and 24% to 22% (2008: 26% to 23%) in intensive care units. In 2011, ceftriaxone was again (as in 2007/2008/2009) the most frequently prescribed antimicrobial across all hospitals and specialities, followed by cefuroxime, which headed the TOP-15 list of parenteral antimicrobials in 2004 (Tab. 2.2.8). Among oral antimicrobials, the list of the TOP-15 antimicrobials is also led by a cephalosporin (cefuroxime axetil), as was already the case in 2004 and 2008 (Tab. 2.2.8).

Tab. 2.2.7: Use density of selected groups of antimicrobials in DDD as well as RDD (in brackets) per 100 days of care in 2011 (median figures; source: ADKA-if-RKI surveillance)

Type of ward	Fluoroquinolones	Broad-spectrum β-lactams	Intermediate-spectrum β-lactams	Narrow-spectrum β-lactams	Macrolides + Clindamycin	Glycopeptides
General surgical ward	5.1 (3.9)	3.8 (3.8)	23.7 (13.1)	2.4 (1)	2.4 (1.7)	0.3 (0.3)
General non-surgical ward	7.6 (6.2)	9.9 (10)	16.7 (8.6)	3.9 (1.5)	7.2 (4.9)	0.5 (0.5)
Intensive care unit	13.3 (10.1)	32.3 (31.1)	26.1 (11.3)	4.7 (1.3)	8.8 (6.2)	2.2 (2.2)

Tab. 2.2.8: The TOP-15 antimicrobials (by RDD) prescribed at hospitals and their respective shares in total consumption (in % of RDD) in 2011 (Source: ADKA-if-RKI surveillance) as well as their rankings in previous years (2008 and 2004 reference figures provided by the MABUSE network)

Parenteral antimicrobials					Oral antimicrobials				
2011	2008	2004		%	2011	2008	2004		%
1th	1th	2th	Ceftriaxone	10.1	1th	1th	1th	Cefuroxime axetil	6.8
2th	2th	1th	Cefuroxime	6.0	2th	3th	3th	Ciprofloxacin	5.4
3th	7th	6th	Piperacillin/Tazobactam	5.9	3th	2th	5th	Levofloxacin	4.3
4th	3th	3th	Metronidazole	4.4	4th	9th	7th	Amoxicillin/Clavulanic acid	3.7
5th	4th	5th	Ampicillin/Sulbactam	3.6	5th	4th	2th	Co-trimoxazole	3.6
6th	6th	–	Meropenem	2.5	6th	7th	10th	Clarithromycin	3.2
7th	10th	4th	Cefazolin	2.5	7th	8th	–	Metronidazole	3.0
8th	11th	11th	Ciprofloxacin	2.1	8th	5th	6th	Sultamicillin	2.8
9th	12th	10th	Imipenem	2.0	9th	10th	4th	Amoxicillin	2.6
10th	8th	7th	Vancomycin	1.9	10th	12th	9th	Clindamycin	2.1
11th	9th	8th	Clindamycin	1.7	11th	11th	11th	Roxithromycin	1.7
12th	–	–	Amoxicillin/Clavulanic acid	1.3	12th	6th	12th	Moxifloxacin	1.6
13th	5th	13th	Piperacillin ± Sulbactam	1.1	13th	13th	-	Cefpodoxime proxetil	1.6
14th	14th	–	Levofloxacin	1.1	14th	14th	15th	Doxycycline	1.1
15th	13th	–	Penicillin G	0.8	15th	–	–	Cefaclor	0.5

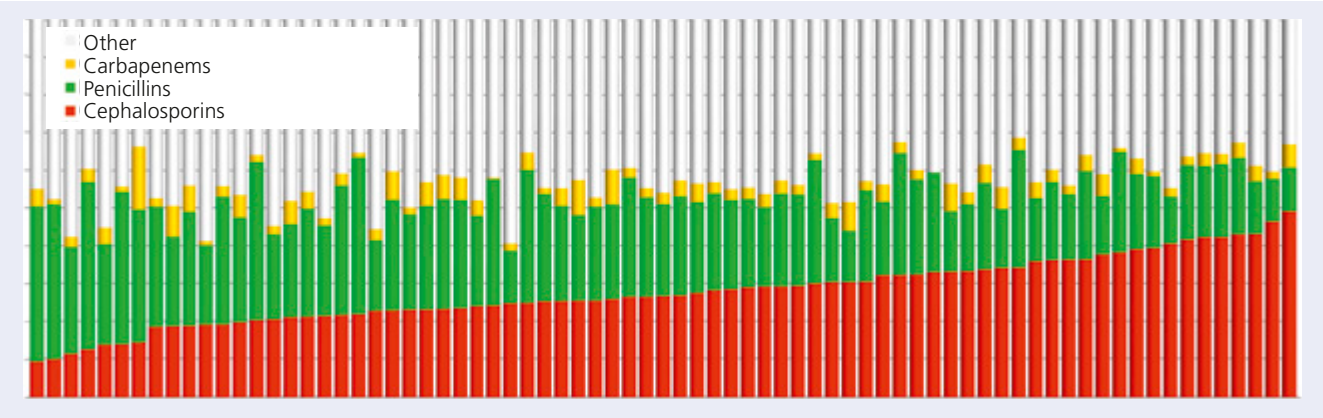

Fig. 2.2.4: Share of β-lactams (cephalosporins, penicillins and carbapenems) in total consumption (in % of RDD) in 2011 (Source: ADKA-if-RKI project)

Fluoroquinolones number 2 behind β-lactams
In 2011, fluoroquinolones represented the second most commonly prescribed antimicrobial class. By now, they take second (ciprofloxacin) and third (levofloxacin) place among orally available antimicrobials. Moxifloxacin (both oral and parenteral) is used far less commonly. The share of oral dosage forms of ciprofloxacin and levofloxacin was 70–80%.

Low glycopeptide and aminoglycoside consumption
As in 2004, the average use density of aminoglycosides and glycopeptides in 2011 was < 0.5 DDD/100 patient days on general surgical wards, < 2 DDD/100 patient days on general non-surgical wards and < 5 DDD/100 patient days in intensive care units (Tab. 2.2.7). Measured by total consumption (in RDD), the shares of these two antimicrobial classes were very small (glycopeptides < 2%, aminoglycosides < 1%).

Conclusion

Inpatient antimicrobial use density seems to have further increased over the past years. In 2011, non-university hospitals showed a use density of < 60 DDD/100 patient days, compared to a use density of > 60 DDD/100 patient days at university hospitals. In 2011, the most frequently prescribed antimicrobials in the hospital sector were again intermediate-spectrum β-lactams (mainly cefuroxime), broad-spectrum β-lactams (mainly ceftriaxone) and fluoroquinolones (predominantly in oral dosage forms). Cephalosporins predominate over penicillins, especially on surgical wards. In line with expectations, the antimicrobial use density in intensive care units is approximately twice as high as on general wards. However, the consumption in intensive care units only accounts for about 10–12% of the total hospital antimicrobial consumption. When extrapolated to the population and taking previous data from Southwestern Germany as a basis, inpatient antimicrobial consumption accounts for < 15% of the total consumption in human medicine. The participation of a greater number of hospitals, including all specialities, in continuous surveillance would be very useful and desirable for further analyses.

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Quality indicators and antimicrobial prescribing at acute-care hospitals

Tab. 1: Selected structure indicators for hospital antimicrobial stewardship with median scores (1–9 Likert scale) after a survey among 75 physicians and pharmacists. Suboptimal scores in grey. ABS=*Antimicrobial Stewardship*

Thematic area/scope	Indicator description
ABS structural prerequisistes: personnel, mandate, objectives, support	Multidisciplinary ABS team is appointed and authorized by the hospital management and is headed by an infectious disease physician (or physician trained in ABS) plus pharmacist
	ABS team is represented in the pharmacy & therapeutics committee
	At least 2 official and minuted ABS team meetings per year
	ABS strategic report includes quantitative objectives with selected indicators
	In-house preanalytical requirements for microbiologic samples, including rejection criteria, have been defined
ABS structural prerequisistes: antimicrobial drug use surveillance	Antimicrobial drug use data (in the form of defined daily doses per occupied bed days or per admission) available at least once per year for several clinical services
	Rate of oral versus parenteral dispensed or prescribed daily doses of the most important and relevant drugs or drug classes available at least once per year for several clinical services
ABS structural prerequisistes: pathogen and antimicrobial drug resistance surveillance	Selected resistance rates and corresponding incidence figures (for clinical isolates) available at least once per year for at least one clinical service
	Incidence figures for *C. difficile*-associated diarrhea available at least once per year for several clinical services and/or for general wards vs. intensive care units
ABS core activities: drug formulary and practice guidelines	In-house list of antiinfectives is available and up to date (not older than 2 years)
	Prescription of restricted/alert antiinfectives from a defined list is individualized (specific patients) and must be approved
	Written, locally consented practice guidelines for empiric therapy, detailing the most important indications and infectious diseases are available and up to date (not older than 2 years)
	Written, locally consented practice guidelines for surgical prophylaxis are available and up to date (not older than 2 years)
	Written, locally consented practice guidelines for parenteral-to-oral switch antimicrobial therapy are available and up to date (not older than 2 years)
ABS core activities: audits	Regular ward rounds by ABS-team members with attending physicians in at least 3 clinical services, at least 3 times each per year
ABS core activities: education	Educational sessions about local practice guidelines (tailored to clinical services needs and/or ward type) organized by ABS team members or ABS representatives from clinical services at least every other year
	In-house and/or extramural ABS-relevant continuing professional education offered for at least 10% of medical staff who are not ABS representatives with at least 4 ABS-relevant CME credits per year
	ABS-relevant continuing professional education offered for ABS team members and ABS representatives from clinical services with at least 8 ABS-relevant CME credits per year
ABS supportive activities	Use of selected antibiograms (communication of reduced findings, adapted according to local guidelines)
	Electronically available guidance and/or assisted decision analysis (adapted to or representing locally consented practice guidelines) via personal computer, PDA or smartphone

* After discussion, classified/consented as suitable despite a score of 5

	Relevance			Practicability					
	Clinical/health benefit and patient outcomes	Ecological/resistance	Economical/cost	Effort to collect data	Barriers to implemenation	Clarity of definition/ understandability	Data verifiability/ reliability	Suitability for external quality assessments	Indicator expression can be influenced by providers/quality gap
	9	8	7	3	5	9	9	9	8
	8	7	7	1	3	9	9	8	8
	8	7	6	2	4	9	9	8	8
	7	7	6	5	5	8	8	7.5	7.5
	9	7	8	3	5	8	8	8	7
	8	8	8	6	4.5	9	9	8	7
	7	6	8	6	5	9	8	8	7
	7	8	6	5	4	8	7	7	5*
	8	7	7	5	4	9	7	8	6
	8	7	7	5	4	9	7	8	7
	9	8	8	3	4	9	8	8	7
	8	8	8	3	5	9	8	7	7
	9	8	8	4	6	9	8	8	8
	9	8	7	3	5	9	8	8	7
	8	7	8	3	5	9	8	8	8
	8	7.5	7	6	6	8	7	7	7
	7	7	6	4	4	8	7	7	7
	8	7	7	5	6	8	7	7	7
	8	7	7	4	5	8.5	8	7	7
	8	8	7	3.5	6	8	7	7	7
	7.5	7	7	4	5	8	8	7	7

Quality measurements are the prerequisite for continuously improving the quality of medical care. For the German hospital system, reasonable and practicable quality measurements and indicators in the field infection medicine and Antimicrobial Stewardship (ABS) have so far not been discussed and defined to a sufficient extent. Lists of quality indicators do exist, for example for the Helios Group (Initiative of Quality Medicine), the hospital groups Rhön, Sana and Asklepios (Quality Clinics) or for mandatory external quality assessment, the development and implementation of which was entrusted to BQS and, since 2009, to the AQUA Institute by the Federal Joint Committee (G-BA). However, these lists only define few indicators for antimicrobial prescribing (for community-acquired pneumonia, antimicrobial prophylaxis for obstetric and gynaecological indications, antimicrobial prophylaxis for surgery of femoral fractures as well as hip and knee replacement surgeries), some of which are already within the target range. Only few more or less plausible and consented lists of structure indicators are available from other countries.[1-3] Lists of process indicators (primarily for pneumonia and surgical prophylaxis) are available from a number of countries (see e.g. www.qualitymeasures.ahrq.gov, www.jointcommission.org or www.ic.nhs.uk).

The lack of consented quality indicators for antimicrobial prescribing at German acute-care hospitals constitutes a problem. In the absence of evidence-based indicators that are derived from guidelines and backed by formal consensus-finding processes, a wide-scale quality campaign with documented optimisation of antimicrobial prescribing quality seems hardly feasible. In collaboration with the ABS expert network (www.antimicrobial-stewardship.de) and the University Hospital Freiburg, the German-Austrian set of guidelines "Strategies to assure rational antimicrobial prescribing at hospitals" (in short "Hospital Antimicrobial Stewardship", HABS) has therefore set itself the goal of creating a list of quality indicators using a multi-stage process including a Delphi survey, to be referred to in the guideline.

Methodology

To this end, a preliminary list of potentially suitable structure and process indicators was initially created in line with the so-called QUALIFY method[4,5] – based on the draft guideline itself and recent literature[6-25], incl. the documents and experiences of the former ESAC group (www.esac.ua.ac.be)[26] and the former ABS International group (www.abs-international.eu)[27,28]. Subsequently, the validity and wording of the contents were discussed as part of a workshop (15 participants) at the ABS expert network meeting in 11/2011, followed by a questionnaire-based scoring (Delphi method, n=75 ABS experts and/or participants of the ABS advanced further training with different professional backgrounds incl. pharmacy and microbiology) of 99 selected indicators regarding their relevance (three categories: clinical, ecological/"resistance", economic) and practicability (six categories: barriers to implementation, effort to collect data, clarity of definition, verifiability, suitability for external quality assessment as well as the ability to influence indicator expression/optimisation potential ["quality gap"]), with due regard to the individual situation (e.g. hospital). The scores were given using a 9-point Likert scale (1= low// not applicable, 9= high/fully applicable) and the results were evaluated according to the recommendations of the "RAND/UCLA appropriateness method"[29] (the original list incl. scores can be found at www.antimicrobial-stewardship.de).

Only indicators where the median clinical relevance score ranged between 7 and 9 and where no more than one of the two relevance categories "ecological" or "economic" had been given a score of 6 were processed further. Those of the remaining indicators that had been given a very high score regarding barriers to implementation or effort to collect data (7–9) were sorted out. Those of the remaining indicators that had been given very high scores in the other four practicability categories (7–9) were preliminarily classified as suitable. Those that had been given a score of 6 (instead of 7–9) in one or two of the four practicability categories were classified as uncertain and requiring further discussion.

As part of another ABS expert workshop in 11/2012, the remaining 67 uncertain and potentially suitable indicators were discussed a new including their definitions and scores and were checked for overlapping contents, while uncertain indicators were reviewed regarding consensus.

Results and conclusions

Based on the results of the Delphi survey, 67 of the 99 initially presented potential quality indicators were subjected to another discussion round, in which 21 structure and 21 process indicators were ultimately selected. Tab. 1 and 2 show these indicators including their relevance and practicability scores. It is interesting to see that only 10 of the original 99 indicators were sorted out on account of their relevance score. It is also remarkable that the participants of the Delphi survey estimated (as expected) that all process indicators involve greater effort to collect data and barriers to implementation than structure indicators. The scores regarding the ability to influence indicator expression/optimisation potential ("quality gap") were rather moderate.

This is the first time that experts who are or will be involved in programmes aimed at improving antimicrobial prescribing quality at hospitals created a list of indicators classified as relevant and practicable, which can now be tested as part of a pilot project – especially regarding their actual (rather than supposed) practicability and optimisation potential on site.

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Tab. 2: Selected process of care indicators for hospital antimicrobial stewardship with median scores (1–9 Likert scale) after a survey among 75 physicians and pharmacists. Suboptimal scores in grey. ABS=*Antimicrobial Stewardship*

		Relevance			Practicability					
Thematic area/scope	**Indicator description**	**Clinical/health benefit and patient outcomes**	**Ecological/resistance**	**Economical/cost**	**Effort to collect data**	**Barriers to implemenation**	**Clarity of definition/ understandability**	**Data verifiability/reliability**	**Suitability for external quality assessments**	**Indicator expression can be influenced by providers/quality gap**
Community-acquired pneumonia	Initial therapy (drugs and dosing) according to practice guideline	9	8	8	6	4	9	7	8	6
	Two sets of blood cultures obtained on the day of therapy initiation	9	7.5	7	5	5	9	7	8	7
	Combination therapy not longer than three days (patients on normal wards only)	7	7	7	5	5	9	7	6	6
	Therapy duration not longer than seven days (patients on normal wards only)	8	8	8	6	6	9	7	7	7
Hospital-acquired pneumonia	Initial therapy (drugs and dosing) according to practice guideline	9	8	7	6.5	5	9	7	7	6
	Two sets of blood cultures obtained on the day of therapy initiation	9	8	7	6	4	9	8	8	7
	Therapy duration not longer than ten days	8	8.5	8	6	5	9	7.5	7	7
Bloodstream infection	Heart ultrasound (TEE) within ten days after first blood culture positivity (bloodstream infection due to *Staphylococcus aureus*, streptococci, non-nosocomial enterococci, HACEK organisms)	9	7	7	5	5	9	7	8	7
	Follow-up blood cultures four to seven days after initial blood culture positivity (bloodstream infection due to *Staphylococcus aureus* and fungi)	8	7	7	6	5	8.5	7	7	7
Urinary tract infection	Documented significant single-organism bacteriuria	9	8	7	5.5	5	8	7	7	6
	Initial therapy (drugs and dosing) according to practice guideline	8	8	7	6	5	9	7	7	7
	Therapy duration not longer than ten days (pyelonephritis, patients on normal wards only)	8	9	8	6	5	9	7	7	6
	Oral antimicrobial drugs initiated not later than day five (pyelonephritis, patients on normal wards only)	8	7	8	6	5	9	7	7	7
	No antimicrobials for asymptomatic catheter-associated bacteriuria	8	9	9	5.5	5	8.5	7	7	7
Parenteral-to-oral switch therapy	Oral administration of antimicrobial drugs with excellent oral bioavailability (fluoroquinolones, clindamycin, cotrimoxazole, doxycycline/minocycline, linezolid, metronidazole, rifampicin, fluconazole, voriconazole)	8	6	9	5.5	5	9	7	7	7
Empiric therapy for indications other than pneumonia and urinary tract infection	Initial therapy (drugs and dosing) according to practice guideline	9	8	8	6	5	9	7	7	7
Dosing	Dose adaptation according to renal function within 2 days	9	5.5*	7	6	5	8	7	7	7
Surgical prophylaxis (colorectal surgery, cardiac surgery, hysterectomy, knee and hip joint prosthesis implant surgery)	Prophylaxis (drugs and dosing) according to practice guideline	9	8	8	5	5	9	7	8	7
	Timing: prophylaxis initiation within one hour before incision	9	8	7	5	4	9	7	8	7
	Timing: prophylaxis discontinued within one day	9	8	8	6	6	9	8	8	7
Management of multidrug resistant organisms (MDRO)	MDRO infection and/or colonization explicitly listed in discharge summary	8	8	7	5	4	9	7	7	6

* After discussion, classified/consented as suitable despite a score of 5.5

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German results of the first European prevalence study on the prevalence of nosocomial infections and antimicrobial use

Introduction and methodology

The ECDC has now also published the EU-wide data for 947 included hospitals from 33 countries: (http://www.ecdc.europa.eu/en/publications/Publications/healthcare-associated-infections-antimicrobial-use-PPS.pdf). The results indicate that Germany performs slightly better in terms of nosocomial infections than most other European countries (prevalence 5.1% vs. 5.7%), with its antimicrobial consumption being comparatively low (prevalence 24.2% vs. 35.0%).

The ECDC defined a standardised methodology on how to conduct the survey.

A standardised European PPS protocol was developed (http://www.ecdc.europa.eu/en/activities/surveillance/HAI/about_HAI-Net/Pages/PPS.aspx). A German translation of the PPS protocol can be found on the NRZ website (www.nrz-hygiene.de).

The ECDC asked the various European countries to analyse a representative random sample of patients. In Germany, 46 hospitals selected according to representative size were to be included. A corresponding random sample was ascertained and the selected hospitals were asked to participate. Additionally, other interested acute-care hospitals were invited to participate in the study. Patients were only included in the study if they were present on the ward at 8 a.m. on the PPS day. Outpatients were excluded.

The PPS had three major endpoints to be determined:

Total NI prevalence: All NIs were counted, regardless of whether they occurred at the surveyed hospital or were already present in the patient at the time of admission. This was done with the aim to record the overall NI prevalence within one country.

Current NI prevalence: The NI prevalence in relation to the hospital stay at the time of the PPS was also determined. This information is relevant for a comparison between hospitals or hospital groups.

Prevalence of antimicrobial treatments: Patients receiving antimicrobials on the day of the survey in relation to all patients.

The NIs were diagnosed using the European definitions (where available) as well as those of the Centers for Disease Control and Prevention (CDC). In short, infections were considered to be nosocomial if the corresponding symptoms were present on the PPS day or if the patient was still receiving antimicrobials for the infection. Only those survey results that were available on the day of the prevalence survey were taken into account in the study. The antimicrobial treatments were documented using the WHO's Anatomical Therapeutic Chemical (ATC) Classification System[4], including the following ATC groups:

- ATC2: J01 – Antimicrobials for systemic use, J02 – Antimycotics for systemic use
- ATC4: A07AA – Antimicrobials, P01AB – Nitroimidazole derivatives, D01BA – Antifungals for systemic use
- ATC5: J04AB02 – Rifampicin (except for treatment of mycobacterial infections)

Antiviral and antitubercular drugs were not included.

The data was collected over the period from September to October 2011 by previously trained staff members of the participating hospitals. The hygiene team or other trained hospital staff members successively visited the hospital's individual wards (at least one entire ward per day), collecting the required data by viewing files and, where necessary, querying ward staff members. Machine-readable questionnaires were created according to the ECDC's guidelines to collect the data. Starting in November 2009, the original documents were sent to the NRZ to be scanned, validated and analysed. The confidence intervals (CI95) were calculated, taking account of the cluster effect of the hospitals by including a factor for overdispersion into the calculation.

Results compared to the first national prevalence study in 1994

Altogether, 132 hospitals with a total of 41,539 included patients participated in this survey. The representative random sample requested by the ECDC comprised 46 hospitals with 9,626 patients. A total of 2,248 NIs were detected in 2,109 infected patients, i.e. 1.07 NIs per patient with a nosocomial infection. In the course of the current hospital stay, 1,666 NIs occurred in 1,560 patients. The number of patients who received antimicrobials on the day of the survey was 10,607. Since the definitions and methods of the first German na-

tional prevalence study in 1994 differ only slightly from those of the first European prevalence study in 2011, all results of both surveys are shown below (Tab. 1) in comparison.

The data of all participating hospitals was presented for the additional analyses. Moreover, the data of the additional analyses includes all NIs, since the national prevalence study was not so much about the situation at individual hospitals as it was about the general problem of NIs in Germany.

Surgical site infections (24.3%), urinary tract infections (23.2%) and lower respiratory tract infections (21.7%) were the most common NIs, followed by *Clostridium difficile* infections (5.7%) and primary bloodstream infections (6.4%). The most common pathogens that caused NIs were *E. coli* (18.0%), enterococci (*Enterococcus faecalis* and *Enterococcus faecium*; 13.2%) and *Staphylococcus aureus* (13.1%) (Tab. 2).

In each case of antimicrobial treatment, it was necessary to determine the specific indication (Tab. 3). Most patients received antimicrobials for existing infections (44.6%), followed by prophylactic administration (30.8%) and NIs (18.4%).

For those patients where no infections were present on the day of the prevalence survey and prophylaxis was listed as the indication, the reasons for the prophylaxis were also recorded. Non-surgical indications accounted for 30.9% of antimicrobial treatments. Among the surgical indications (surgical prophylaxis), the very high percentage of surgical prophylaxes beyond the day of surgery is noteworthy (13.1% of all antimicrobial treatments).

For a relatively large number of antimicrobial treatments (28.2%), the reason for the application was not documented in the patient files.

Tab. 1: Comparison of NI prevalence and prevalence of antibiotic treatments in the NIDEP 1 study and the present study

Parameter	All participants 2011	Representative hospitals 2011	NIDEP 1 1994
Hospitals	132	46	72
Median number of beds	359	216	< 400
Patients	41,539	9,626	14,966
NI prevalence in % (CI95)	5.08 (4.72–5.44)	5.07 (4.51–5.67)	–
NI prevalence during the current hospital stay in % (CI95)	3.76 (3.50–4.02)	3.37 (2.95–3.82)	3.46 (3.1–3.9)
Prevalence of antibiotic treatments in % (CI95)	26.06 (24.49–26.60)	24.17 (21.25–25.48)	17.7

* Initial findings of the prevalence study were published in the Epidemiological Bulletin as early as July 2012.[5] In the further course of the data evaluation for the final report, data from two hospitals turned out to be invalid, which is why the data from these hospitals was not taken into account while creating the final report, resulting in slight deviations.

Tab. 2: Most common pathogens in patients with NI

Pathogen	Number	Percentage (%)
All Nis	2,248	100.0
NIs with pathogen detected on the day of survey	1,236	55.0
All pathogens	1,562	100.0
- All gram-positive	792	50.7
- All gram-negative	673	43.1
- Fungi	89	5.7
- Other	8	0.5
The most common species		
Escherichia coli	281	18.0
Staphylococcus aureus	204	13.1
Clostridium difficile	126	8.1
Enterococcus faecalis	112	7.2
Enterococcus faecium	93	6.0
Pseudomonas aeruginosa	87	5.6
Staphylococcus epidermis	82	5.2
Klebsiella pneumoniae	55	3.5
Candida albicans	50	3.2
Enterobacter cloacae	45	2.9

Tab. 3: Comparison of indications of antibiotic treatments in the present study and the NIDEP 1 study

Reason for antibiotic treatment	Current prevalence survey 2011 Percentage (%)	NIDEP 1 study 1994 Percentage (%)
Community-acquired infection	48.3	47.9
NI	19.0	16.9
Prophylaxis	28.5	35.2
Other	4.2	

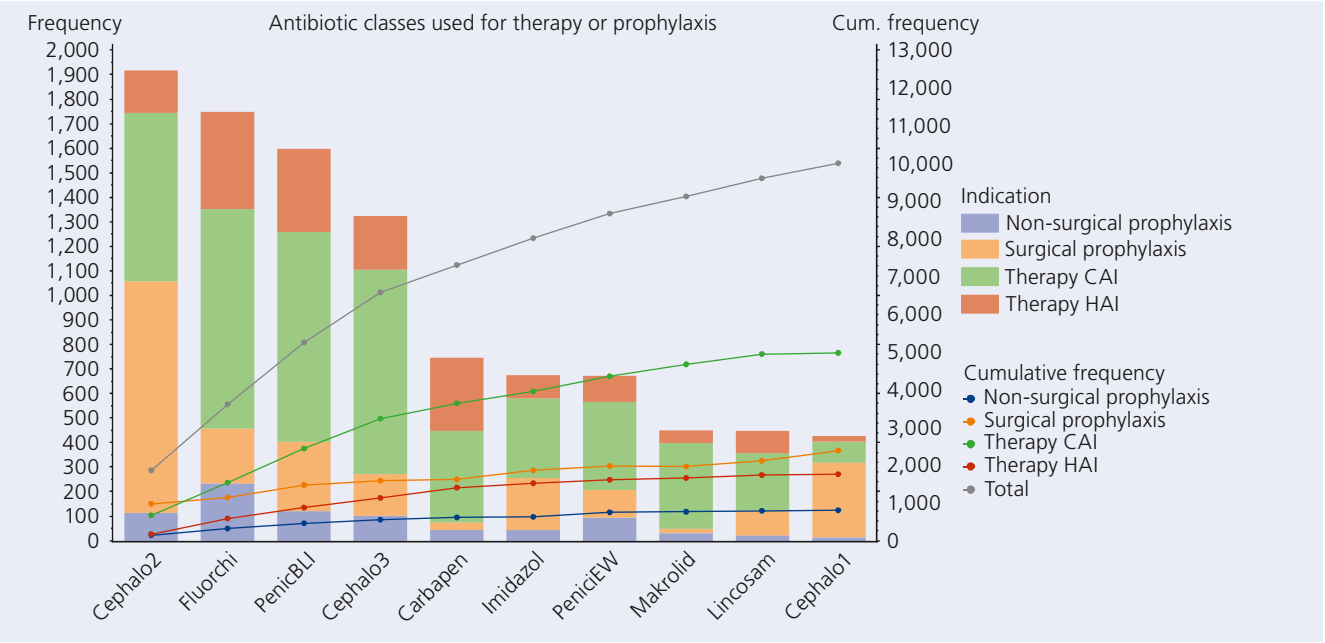

Fig. 1: Cumulative use of the most common antibiotic classes for therapy and prophylaxis (CAI=community-acquired infection, HAI=hospital-acquired infection, Cephalo2=second-generation cephalosporins, PenicBLI=combination of penicillin and β-lactamase-inhibitor, Fluorchi=fluoroquinolones, Cephalo3=third-generation cephalosporins, Carbapen=carbapenems, PeniciEW=extended-spectrum penicillins, Cephalo1=first-generation cephalosporins, SulfoTri=sulphamethoxazole/trimethoprim, Lincosam=lincosamides)

Fig. 1 shows the distribution of the most commonly used antimicrobial classes by therapy and prophylaxis. Second-generation cephalosporins were used most frequently (14.1%), followed by fluoroquinolones (13.5%), combinations of penicillin and β-lactamase inhibitor (12.2%), third-generation cephalosporins (10.3%) and carbapenems (5.7%).

Conclusion

The available data from Germany cannot yet be compared with the data of other European countries because the ECDC has not yet completed the final analysis. A preliminary ECDC pilot study with 66 participating hospitals from 23 countries found a 7.1% overall NI prevalence; 34.6% of patients received at least one antimicrobial on the day of the prevalence survey.[3] However, the hospitals surveyed in this study were not selected to be representative. (Editor's note: The final analysis has now been published: http://www.ecdc.europa.eu/en/publications/Publications/healthcare-associated-infections-antimicrobial-use-PPS.pdf)

It is particularly interesting to compare the current results with the results of the previous, national prevalence study from 1994.[1,2] However, it should be noted that, due to the European guidelines, the methods employed in the two studies are not identical. Moreover, in the present prevalence study, the infections were documented by staff members of the respective hospitals, whereas in the 1994 study the data was collected directly at the hospitals by specifically trained physicians.

It can be assumed that the risk factors for NIs in patients increased over the period 1994–2011; the average patient age alone has gone up, according to the data reported by the Federal Statistical Office – for example, the basic key figures of inpatient hospital care in Germany indicate an increase from 51.8 to 53.2 years over the period 2001–2008 alone.[6]

At the same time, there has been a significant reduction in the patients' average length of stay (from 11.9 days in 1994 to 7.9 days in 2010).

The 1994 national prevalence study found a 17.7% prevalence of antimicrobial treatments.[7] This shows that there has been a rise in the prevalence of antimicrobial treatments, which could be explained by the fact that the average length of stay has decreased considerably, as shown above, and that today's patients are discharged earlier after completing antimicrobial treatment. The percentage of indications for antimicrobial treatment has barely changed since 1994. In terms of prophylactic antimicrobial use, the very high percentage of antimicrobial treatments in connection with prolonged surgical prophylaxis beyond the day of surgery is particularly notable. If this type of use, which is not recommended by medical associations and is not based on evidence, were eliminated entirely, a large portion of Germany's antimicrobial treatments could be avoided straightaway.

The distribution of NIs has also changed little in terms of their prevalence. Remarkably, there is a high percentage of CDI, which hardly played a role in the 1994 survey. This infection and its prevention clearly need to be given greater attention in the future. There have also been only minor changes regarding the causative agents of NIs in comparison with the 1994 prevalence study.

Of course, this prevalence study faces the limitations that generally result from the design of prevalence studies: Patients with risk factors for NIs usually stay longer at the hospital, making it more likely for NIs occurring in these patients to be detected in a PPS (which is why the prevalence of multidrug resistant organisms is not presented at this point). Moreover, there is a higher probability of detecting those NIs which are more often associated with longer hospital stays, such as surgical site infections.

A second limitation is the collection of data by a large number of different data collectors. All data collectors received training in an introductory course and had the opportunity to consult with the study centre in difficult cases. Nevertheless, it can be assumed that the data collectors varied in their sensitivity and specificity.

A third limitation is posed by the differences in the microbiological testing methods in relation to the indication. It should be noted that the scope of microbiological tests performed in respect of many infections is rather limited in Germany compared to neighbouring countries.[8] Since identifying the pathogen is an important criterion for the diagnosis of many NIs, it can be assumed that some of the actually existing NIs were not detected, making the calculated prevalence somewhat of an underestimation.

The following primary conclusions should be drawn from the national prevalence study:

1. The relatively constant NI prevalence indicates that there has been no general increase in the risk of nosocomial infections for patients in Germany over the past 17 years. Nevertheless, nosocomial infections continue to be a major concern in the healthcare sector, and preventive measures should continue to have high priority.

2. The predominant use of broad-spectrum antimicrobials, especially fluoroquinolones and third-generation cephalosporins (24% of all antimicrobial treatments), indicates the need to step up efforts to improve antimicrobial stewardship.

3. The great interest in participation presents the opportunity to regularly offer such studies every few years on a national scale, because they raise interest in and awareness of the problem at local level, contribute to identifying local issues and make it possible to monitor the situation nationwide.

➤ P. Gastmeier, B. Piening
Reviewer: W.V. Kern

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2.3. Antifungal consumption

Outpatient prescriptions

Among systemic antifungals prescribed in outpatient care, terbinafine has been the most commonly prescribed drug for many years (11.5, 13.1 and 16.5 million DDD in 2009, 2010 and 2011, respectively). In 2011, itraconazole was used to a similar extent (2.2 million DDD) as fluconazole (2.2 million DDD).[1,2] A European comparative study (2007 data) found that terbinafine was again the most frequently prescribed systemic antifungal; there were only a few countries where the list was topped by itraconazole (Luxembourg, Croatia, Italy) or ketoconazole (Bulgaria).[3] Conversion into defined daily doses (DDD) per 1,000 inhabitants (or insured) and day yields a use density of 0.665 for terbinafine, 0.09 for itraconazole and fluconazole and < 0.01 for voriconazole and posaconazole (Fig. 2.3.1).

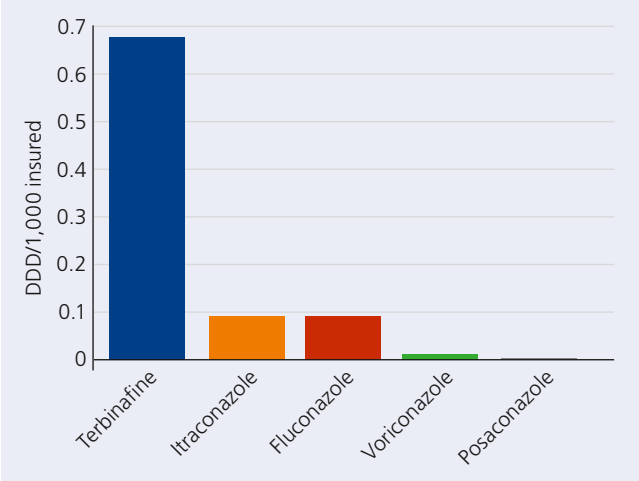

Fig. 2.3.1: Consumption of systemic antifungals in outpatient care (in DDD per 1,000 insured and day) in 2011 (Source: WIdO, SHI Drug Index)

Oral, non-absorbable (nystatin, natamycin and amphotericin B) or inadequately absorbed antifungals (miconazole) as well as topical antifungals (ciclopirox, clotrimazole, econazole) in the form of lozenges, suspensions for oral use, ointments, skin creams, vaginal tablets or vaginal creams were prescribed much more frequently. The most commonly prescribed substance for the treatment and prevention of oral candidiasis and other mucosal fungal infections appears to be amphotericin B (2.1 million DDD in 2011).[1,2] However, reliable consumption data is not available for these groups, since a whole range of these drugs are sold over-the-counter and are not reimbursable, which is why they are not listed in the statistics of drugs prescribed under statutory health insurance.

Inpatient use densities

Surveys conducted at German university hospitals between 2000 and 2003 found average antifungal use densities of ~25 DDD/100 in intensive care units, > 50 DDD/100 in haematology/oncology departments and < 5 DDD/100 on general wards.[4] Subsequent surveys in 2004 showed that the highest consumption rates in non-university hospitals were also observed in haematology/oncology departments, followed by intensive care units.[5] At that time, the median rates were 43 DDD/100 (university hospitals) and 6 DDD/100 (non-university acute-care hospitals) for haematology/oncology departments as well as 20 DDD/100 (university hospitals) and 5 DDD/100 (non-university acute-care hospitals) for intensive care units. A survey among 13 SARI intensive care units (2004–2005) with an average use density of 9 DDD/100 across a broad range from 2 to 23 DDD/100 confirmed this magnitude.[6] Intensive care units with transplant patients showed higher use densities (15 vs. 5 DDD/100).

2004 surveys (in 843 surgical, non-surgical and intensive care units at 184 acute-care hospitals) showed a hospital-wide systemic antifungal use density of < 1/100 DDD/100 at hospitals with up to 800 beds, and a use density of ~3/100 at larger hospitals (incl. university hospitals).[6] More recent data for 2009 on 44 hospitals within the ADKA-if-RKI project shows median total use densities of 1 DDD/100 (interquartile range, 1–2 DDD/100) and < 1 RDD/100 – again indicating lower rates for smaller hospitals and higher rates for hospitals with > 800 beds. The current figures for 2011 based on the data reported by a total of 66 hospitals (Tab. 2.3.1) are within the same magnitude.

A detailed analysis for 2011 based on current surveys within the ADKA-if-RKI surveillance project is now available (Tab. 2.3.1). Again, a noticeably increased antifungal consumption is seen in intensive care units and on haematology/oncology wards.

Tab. 2.3.1: Total antifungal consumption (DDD/100) in intensive care units and on general wards at 66 German acute-care hospitals in 2011 (Source: ADKA-if-RKI surveillance)

Speciality (n)	Median DDD/100 (interquartile range)	
Total	0.9	(0.5–1.5)
Intensive care units		
Surgical (incl. interdisciplinary) (86)	6.1	(2.6–14.9)
Non-surgical (40)	4.5	(2.1–8.3)
General wards*		
Surgery (117)	< 0.5	
Other surgical specialities (127)	< 0.5	
General internal medicine (122)	0.6	
Haematology/Oncology (20)	5.8	(3–20)
Other non-surgical specialities (40)	< 0.5	

* Excl. paediatric and psychiatric wards

Antifungal classes at hospitals

Fluconazole number 1 at hospitals

Azoles were by far most commonly used in all hospital departments both in 2004 and between 2007 and 2011. A detailed evaluation of 2009 and 2011 data of all hospital departments lists fluconazole as the most common antifungal (2011: 0.62 DDD/100) and voriconazole as the second most common antifungal (Tab. 2.3.2). Compared to 2004, itraconazole was prescribed far less frequently in 2009 and 2011. Posaconazole and micafungin were newly added. In the 2008 and 2009 ESAC point prevalence surveys, fluconazole

was again identified as most frequently prescribed systemic antifungal at hospitals.[7]

Tab. 2.3.2: Relative prescribing rate of various antifungals (in % of all DDD and RDD of antifungals) at German acute-care hospitals (general wards and intensive care units) in 2009 and 2011 (Source: ADKA-if-RKI surveillance)

Substance*	Percentage of DDD (RDD)	
	2009	2011
Fluconazole	70 (62)	66 (50)
Voriconazole	13 (22)	15 (22)
Caspofungin	4 (7)	8 (12)
Itraconazole	4 (3)	2 (1)
Posaconazole	3 (6)	5 (7)
L-AmB	3 (5)	2 (4)
Anidulafungin	2 (4)	2 (2)
Micafungin	–	1 (1)
cAmB	1 (2)	1 (1)

* Flucytosine, ketoconazole, micafungin and terbinafine each accounted for < 1%

Other antifungals

Other systemic antifungals were prescribed far less commonly at hospitals (Tab. 2.3.2). The consumption of parenteral amphotericin B (incl. liposomal amphotericin B) at all hospitals which reported data for 2011 was < 1 DDD/100, accounting for only 2–4% (liposomal amphotericin B) and 1% (conventional amphotericin B) of all daily doses. Echinocandins were prescribed far more often. Caspofungin was again the third most frequently used antifungal at hospitals in 2011.

Intensive care units as high-consumption areas

The antifungal use density in intensive care units was much higher than on general wards (Tab. 2.3.1). This disparity was also observed in a similar magnitude in 2004. In individual cases, quarterly use densities of > 40 DDD/100 were observed. It should be noted that these figures represent the amounts dispensed by pharmacies, converted into daily doses, i.e. they do not represent prescriptions at patient level. Surgical and non-surgical intensive care units differ in the range of administered substances (Tab. 2.3.3). Fluconazole was used more commonly on surgical wards.

Tab. 2.3.3: Relative prescribing rate of fluconazole, caspofungin and anidulafungin (in % of all DDD and RDD of antifungals) in intensive care units in 2009 and 2011 (Source: ADKA-if-RKI surveillance)

Substance	Percentage of DDD (RDD) 2009/2011	
	Surgical intensive care units	Non-surgical intensive care units
Fluconazole	82/72	54/49
Caspofungin	5/14	10/16
Anidulafungin	4/4	8/3

Haematology/oncology as high-consumption areas

On haematology/oncology wards, antifungals are also used more often than on other internal medicine wards (Tab, 2.3.1). The median in 2009 was 8 DDD/100 (equivalent to 6 RDD/100). In 2011, the median was 5.8 DDD/100 (equivalent to 4.2 RDD/100). The use pattern also appears to have changed slightly in this case: Voriconazole, and most notably posaconazole, have been used far more frequently in recent years, while both itraconazole and conventional amphotericin B have largely been superseded by other substances.

Conclusion

While antifungal consumption data is available for both outpatient and inpatient care, the figures for the outpatient sector are limited by the great number of over-the-counter topical substances, and the figures for the inpatient sector are based on the data reported by only 66 hospitals with 20 haematology/oncology departments. Overall, there is currently no evidence to suggest any significant increase in consumption in recent years.

Terbinafine has continued to be by far the most commonly prescribed drug in outpatient care in recent times, with fluconazole being most common in inpatient care, as was the case in 2004. Intensive care units and haematology/oncology departments remain the core area of prescriptions, but the use pattern and ratio of the applied substances differ or have changed, while the use density has remained constant.

➤ W.V. Kern
Reviewer: A.J. Ullmann

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3 Veterinary antimicrobial sales

Surveillance of antimicrobial sales

Resistance occurs in both human and veterinary medicine. However, there is no clear dividing line between these two sectors because resistance can be transferred both ways between humans and animals through direct contact as well as via foods of animal origin. Moreover, the rapid transport of humans, animals and foods between countries and continents can lead to a rapid spread of resistance.

There is no simple answer to the question of the relation between antimicrobial consumption and resistance development because the link is probably not linear. In order to better understand any possible correlations and to take effective measures in combating resistance, evidence-based data on antimicrobial consumption is needed in addition to the data on the resistance of the various bacteria.

As part of the Copenhagen Recommendations[1], the EU has passed a recommendation for the Europe-wide collection of regionalised data to assess the current resistance situation as well as the sale and use of antimicrobials.

The type and amount of antimicrobial agents sold to veterinarians by pharmaceutical companies and wholesalers is to be recorded in accordance with the regulation on the database-supported information system for medicinal products of the German Institute of Medical Documentation and Information (DIMDI Regulation on Medicinal Products – DIMDI AMV) of 24 February 2010. The recording of data is designed to help understand the extent of the flow of goods in the general or regional sale of veterinary medicinal products as well as any changes in this flow of goods in the interest of "preventive consumer health protection". When reporting sales data, the first two digits of the recipient's postcode are also recorded with the aim to enable a geographical classification of antimicrobial sales. It is important to note that the development of this Veterinary Drug Index (TAR) should be coordinated with the development of central indices for the monitoring of antimicrobial resistance in veterinary drug use.

The total amount of antimicrobials sold is calculated based on the data reported by the pharmaceutical companies and wholesalers as well as on the data available in the Drug Information System (AMIS). The data recorded and aggregated this way by the DIMDI is forwarded to the Federal Office of Consumer Protection and Food Safety (BVL) and to the Länder for further evaluation. The BVL calculates the sales data for the various antimicrobial classes and for the individual antimicrobial agents, while for those available in the form of "salt" it was initially only necessary to determine the "pure" concentration of the antimicrobial agent.

In addition to the national recording and evaluation of antimicrobial sales data, the BVL also transfers the data into the template of the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project. Antimicrobial sales data for 25 EU member states for 2011 has been published for the first time within the ESVAC project.[2]

Results of surveillance of antimicrobial sales in 2011 and 2012 (TAR)

Antimicrobials classified as "critically important" by the World Health Organization (WHO) and the World Organisation for Animal Health (OIE), such as fluoroquinolones and third- and fourth-generation cephalosporins, were sold in smaller amounts than expected. Sales of veterinary antimicrobials are clearly focused on older antimicrobials, as evidenced by the evaluation of the data, which was first collected and made available to the BVL by the German Institute of Medical Information and Documentation in 2011.

The total amount of primary antimicrobial agents (excluding medicated premixes approved for the production of medicated feed) sold to German-based veterinarians dispensing veterinary drugs was 1,706 tonnes in 2011 and 1,619 tonnes in 2012. Among the 788 veterinary medicinal products approved and subject to reporting in Germany, sales data was reported for 520 (65%) drugs in 2011. The 268 drugs for which no sales data was reported were approved in Germany but apparently not sold in 2011. Similar figures were reported for 2012 as follows: Of the 806 veterinary medicinal products approved and subject to reporting in Germany, sales data was reported for 553 (68.6%) drugs. The 253 drugs for which no sales data was reported were approved in Germany but apparently not sold in the year under review.

Antimicrobial agents and classes

In both years under review (2011, 2012), the largest portion of antimicrobial agents was made up of tetracyclines with approximately 565 tonnes each and penicillins with approximately 527 tonnes and 498 tonnes, respectively, distantly followed by sulphonamides (2011 185 t; 2012 162 t), macrolides (2011 173 t; 2012 145 t) and polypeptide antimicrobials (2011 127 t; 2012 124 t). Further sales included 47 tonnes (2011) and 40 tonnes (2012) of aminoglycosides, 30 tonnes (2011) and 26 tonnes (2012) of trimethoprim, 17 tonnes (2011) and 15 tonnes (2012) of lincosamides, 14 tonnes (2011) and 18 tonnes (2012) of pleuromutilins, 8 tonnes (2011) and 10 tonnes (2012) of fluoroquinolones as well as 6 tonnes of fenicols in both years. For 2011, 5.5 tonnes of cephalosporins were reported, 3.5 tonnes of which were third- and fourth-generation cephalosporins. For 2012, 9 tonnes of cephalosporins were reported, 3.7 tonnes of which were third- and fourth-generation cephalosporins. Nitroimidazoles, nitrofurans und fusidic acid were sold in amounts of less than

Tab. 3.1: Amount of primary antimicrobial agents per antimicrobial class [t] sold to Germany-based dispensing veterinarians, 2011 and 2012

Antimicrobial class	Amount sold [t] in 2011	Amount sold [t] in 2012	Difference [t]
Tetracyclines	564	566	+2
Penicillins	527.5	498	-29.5
Sulphonamides	185	162	-23
Macrolides	173	145	-28
Polypeptide antimicrobials	127	124	-3
Aminoglycosides	47	40	-7
Trimethoprim	30	26	-4
Lincosamides	17	15	-2
Pleuromutilins	14	18	+4
Fluoroquinolones	8	10	+2
Fenicols	6	6	0
Cephalosporins, 1st+2nd generation	2	5	+3
Cephalosporins, 3rd generation	2	2.5	+0.5
Cephalosporins, 4th generation	1.5	1.5	0
Fusidic acid	< 1	< 1	0
Nitrofurans	< 1	< 1	0
Nitroimidazoles	< 1	< 1	0
Total	1.706	1.619	-87

1 tonne. A detailed overview of the reported antimicrobials is provided in Tab. 3.1. The differences in sales between 2011 and 2012 are also shown to allow a comparison.

Classification of antimicrobial sales according to animal species

A clear classification of the reported veterinary drugs according to individual animal species is not possible since the majority of these drugs are approved for use in several animal species.

A distinction between drugs approved for use in food-producing animals (FPA) and those approved for use in non-food-producing animals (N-FPA) shows that drugs approved for use in FPA accounted for 1,698 tonnes (99.5%) and 1,611 tonnes (99,5%) of the total sales of primary antimicrobial agents in 2011 and 2012, respectively. It must be noted that a veterinary drug is classified as approved for use in FPA if at least one of the animal species for which it is approved is a food-producing animal species. Veterinary drugs approved exclusively for use in N-FPA accounted for approximately 8 tonnes in both years.

The number of approved drugs per animal species reported as part of the surveillance of antimicrobial sales is listed in Tab. 3.2. The listing shown should not be understood to mean that the indicated drugs are exclusively approved for and used in the respective animal species. This list provides an overview of how many different drugs were each available for one animal species in 2011 and 2012 for the treatment of the individual animal species.

Regionalised sales data

The DIMDI Regulation on Medicinal Products stipulates that the first two digits of the postcode where the supplied veterinarians are registered must be reported. This makes it possible to classify the amounts sold according to postcode zones (first digit: 0–9) and postcode areas (first two digits: 01–99 [except for 05, 11, 43, 62 – since these do not exist]). However, it does not allow a clear classification according to Länder because there are several overlapping postcode areas. Almost half of the total of antimicrobial agents was supplied to veterinarians in the postcode areas 48 (northern North Rhine-Westphalia) and 49 (western Lower Saxony). A regionalisation of sales data according to the two-digit postcodes is provided in Tab. 3.1. Since there were no significant differences between the two years under review regarding the

Tab. 3.2: Number of drugs per target animal species reported within the surveillance of antimicrobial consumption in 2011 and 2012 (multiple answers possible according to the marketing authorisation)

Animal species	Number of drugs reported in 2011	Number of drugs reported in 2012
Carrier pigeon	10	11
Duck	1	1
Pheasant	2	2
Fish	1	1
Goose	2	2
Poultry	1	2
Chicken	76	79
Dog	174	185
Rabbit	6	7
Cat	89	93
Guinea pig	4	4
Horse	49	48
Turkey	31	34
Cattle	280	296
Sheep	47	48
Pig	262	274
Pigeon	3	14
Goat	15	14

Tab. 3.3: Comparison of sales of antimicrobial agents [t] used in food-producing animals in 25 European member states and percentage of antimicrobial agents in mg per population correction unit (mg/PCU) for 2011 (ESVAC)*

Member state	Total amount sold [t]	PCU [in 1,000 t]	mg/PCU
Austria	53	977	55
Belgium	299	1,695	175
Bulgaria	42	399	104
Cyprus	52	127	408
Czech Republic	61	732	83
Denmark	107	2,479	43
Estonia	8	114	66
Finland	14	520	24
France	913	7,643	117
Germany	1,826	8,600	212
Hungary	148	767	192
Iceland	0,7	114	6
Ireland	89	1,770	49
Italy	1,672	4,497	370
Latvia	6	171	35
Lithuania	14	337	42
Netherlands	364	3,186	114
Norway	7	1,680	4
Poland	473	3,929	120
Portugal	164	1,016	161
Slovakia	11	247	44
Slovenia	8	182	43
Spain	1,781	7,135	249
Sweden	13	835	14
United Kingdom	357	6,724	51
Total	8,481	55,872	

* © European Surveillance of Veterinary Antimicrobial Consumption, 2013. Sales of veterinary antimicrobial agents in 25 EU/EEA countries in 2011 (EMA/236501/2013)

classification of amounts according to postcode areas, only the 2012 data is shown.

ESVAC data

For the first time, the European Surveillance of Veterinary Antimicrobial Consumption project (ESVAC) has published data for 25 EU member states for 2011. The absolute sales data states an amount of 1,826 tonnes for Germany, 1,780 tonnes for Spain and 1,672 tonnes for Italy. All remaining EU member states reported amounts of less than 1,000 tonnes. Regarding these reported amounts, it should be noted that, where possible, the absolute amounts have not been reduced by the respective salt portion of an antimicrobial agent. This is why the absolute amount of 1,826 tonnes stated for Germany in the ESVAC report differs from the amount stated for 2011 in the DIMDI Regulation on Medicinal Products (1,706 tonnes).

When calculating the amount of antimicrobial agent (mg) in correlation with the defined population correction unit (PCU) (number of FPAs multiplied by their estimated weight at the time of treatment), Germany has a factor of 212 mg/PCU, while higher figures were calculated for Cyprus with 408 mg/PCU, Italy with 370 mg/PCU and Spain with 249 mg/PCU. Very low figures were calculated for Norway (4 mg/PCU) and Sweden (14 mg/PCU), amongst others. The 2011 figures calculated for France, the Netherlands and Denmark are 117 mg/PCU, 114 mg/PCU and 43 mg/PCU, respectively.

Conclusion

The sales data shows that the vast majority of sales account for what are called "old" agents, whereas fluoroquinolones as well as third- and fourth-generation cephalosporins play a rather subordinate role in veterinary medicine. More than 95% of antimicrobial agents were sold for oral administration; only fluoroquinolones and third- and fourth-generation cephalosporins as well as fenicols were sold mainly or exclusively for parenteral administration.

The drop in sales by 5.1% when comparing 2011 to 2012 should not be interpreted as an indication of a recent change in antimicrobial use patterns, but rather as a result of economic fluctuations in the pharmaceutical industry.

The main benefit of the surveillance of antimicrobial sales is that it provides the first valid and reliable figures on the amount of antimicrobials sold in Germany to veterinarians dispensing veterinary drugs since the beginning of 2011, while also providing information on the distribution and significance of individual antimicrobial classes in veterinary medicine.

However, this data cannot be correlated with the regional resistance situation, since a region where antimicrobials are sold is not necessarily the region where these are used.

The data and information available to date do not indicate any plans to set a reduction goal and/or abolish the veterinary

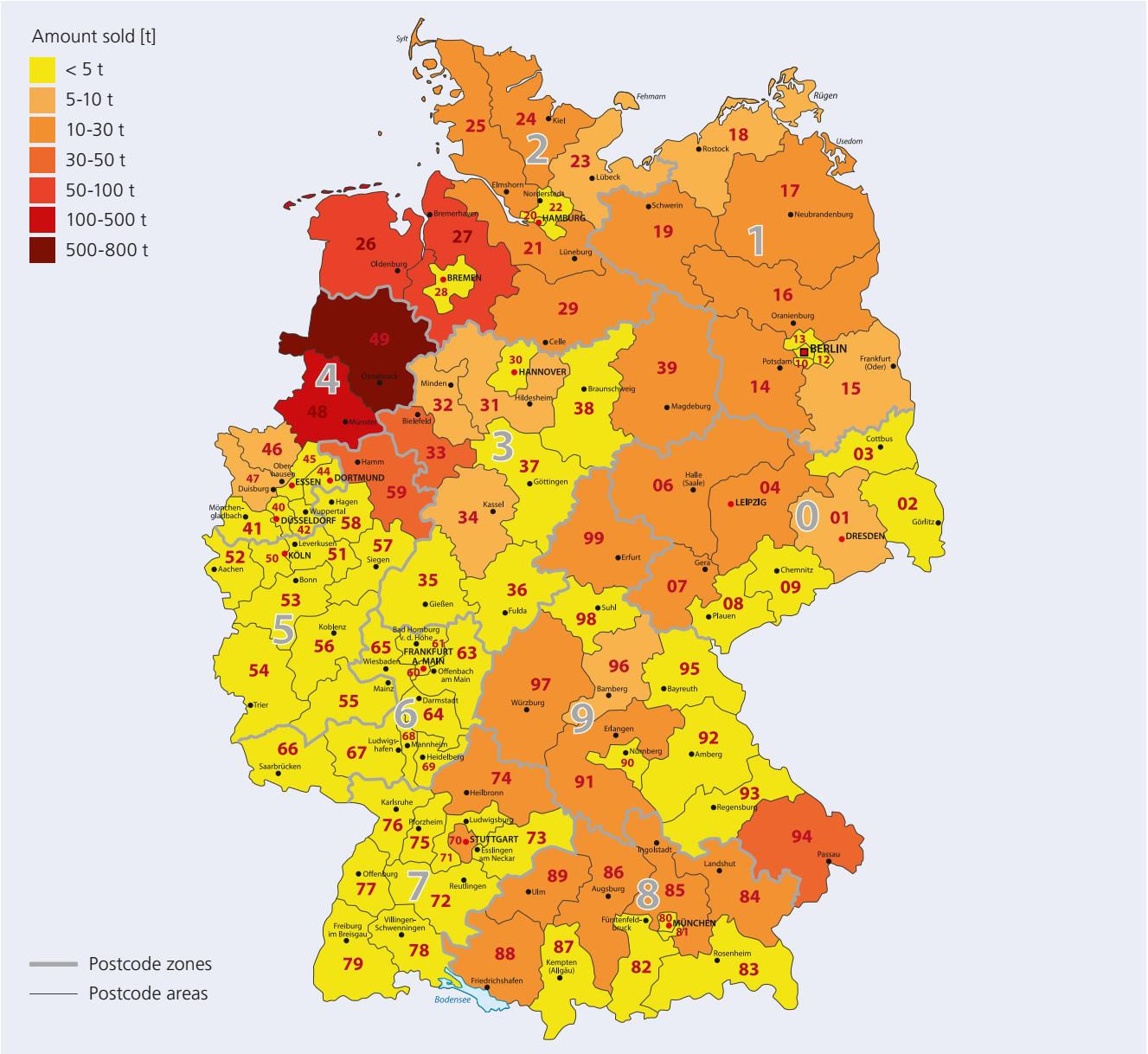

Fig. 3.1: Amount of primary antimicrobial agents (in t) per postcode area sold to Germany-based veterinarians, 2012

dispensing right. Valid data and thorough scientific analysis are required to identify all causes of bacterial resistance to antimicrobials and its impact on humans, animals and ecosystems.

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Reviewers: I. Reimer, A. Bender

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4 Antimicrobial resistance in human medicine

4.1 Extraintestinal infections

4.1.1 *Streptococcus* spp.

4.1.1.1 *Streptococcus pyogenes*

Streptococcus pyogenes is one of the most common causative agents of infectious disease, especially in childhood. The natural reservoir of the pathogen is limited to humans, spanning a wide range of possible diseases. Besides infections of the respiratory tract (tonsillopharyngitis, scarlet fever) and the skin (impetigo contagiosa, erysipelas), it is particularly associated with infections of deeper tissues (phlegmons, necrotising fasciitis, myonecrosis), bloodstream infections and streptococcal toxic shock syndrome. Non-purulent secondary disease caused by *S. pyogenes* infection (acute rheumatic fever, Sydenham's chorea and post-streptococcal glomerular nephritis) has become rare in western industrialised countries.

This report is based on the data reported by the National Reference Centre for Streptococci at the Institute of Medical Microbiology of the University Hospital RWTH Aachen.

Trends in resistance development

The susceptibility of *S. pyogenes* isolates to penicillin G, macrolides and clindamycin was analysed during the period from 1999 through December 2011 (Tab. 4.1.1.1.1). Until 2003, the isolates were almost exclusively obtained from non-invasive infections; subsequently, they came predominantly from invasive infections. The minimum inhibitory concentrations (MIC) were measured using the microdilution method based on the criteria and breakpoints defined by the Clinical and Laboratory Standards Institute (CLSI). The results may differ slightly from those obtained based on the guidelines of the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

The percentage of penicillin-G-susceptible strains was 100% throughout the entire period. To date, no penicillin-resistant *S. pyogenes* isolates have been reported anywhere in the world. The prevalence of macrolide resistance was determined using the data of clarithromycin or erythromycin. The rate of macrolide resistance ranged between 2.4% and 13.6% throughout the entire period. The percentage of isolates that showed intermediate susceptibility to macrolides was comparatively low. Fortunately, the slight drop in the resistance rate observed in recent years stabilised in 2011. The clindamycin resistance rate was very low throughout the entire period.

Conclusion

All *S. pyogenes* strains detected between 1999 and 2011 were susceptible to penicillin G. The rate of macrolide resistance during the study period ranged between 2.4% and 13.6%; the slight drop in the resistance rate observed in recent years has stabilised. The rate of resistance to clindamycin was even lower than to macrolides.

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Tab. 4.1.1.1.1: Resistance rates of *Streptococcus pyogenes* (%)

Year	Isolates (n)	Penicillin G			Macrolide			Clindamycin		
		Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant
1999	380	100	0	0	85.8	1.3	12.9	99.2	0.0	0.8
2000	240	100	0	0	92.9	0.4	6.7	98.3	0.0	1.7
2001	137	100	0	0	90.5	0.0	9.5	100.0	0.0	0.0
2002	243	100	0	0	86.4	0.0	13.6	99.6	0.0	0.4
2003	310	100	0	0	92.6	0.0	7.4	98.7	0.6	0.6
2004	358	100	0	0	93.9	0.0	6.1	98.0	0.0	2.0
2005	196	100	0	0	89.8	1.0	9.2	96.9	0.5	2.6
2006	140	100	0	0	92.9	0.0	7.1	97.1	0.0	2.9
2007	156	100	0	0	95.5	0.0	4.5	98.7	0.6	0.6
2008	146	100	0	0	96.6	0.7	2.7	99.3	0.0	0.7
2009	246	100	0	0	97.6	0.0	2.4	99.6	0.0	0.4
2010	262	100	0	0	95.4	0.0	4.6	98.5	0.0	1.5
2011	226	100	0	0	96.5	0.0	3.5	99.6	0.0	0.4

4.1.1.2 *Streptococcus agalactiae*

Streptococcus agalactiae infections (group B streptococci, GBS) can generally be subdivided into neonatal infections and infections beyond the newborn period. In Germany and virtually all other industrialised countries, GBS is the most common pathogen causing neonatal bloodstream infections. According to the preliminary results of the most recent ESPED survey (Surveillance Unit for Rare Paediatric Diseases in Germany) from 2008 to 2010, the incidence of blood or cerebrospinal fluid culture-positive GBS infections appears to be in decline, accounting for about 0.3 per 1,000 live births. About half of all invasive GBS infections manifest themselves as early-onset bloodstream infections (early-onset disease, EOD) within the first 24 to 48 hours of life, in some cases with a fulminant progression. Infections occurring between the 7th and 90th day of life are referred to as late-onset disease (LOD). In the majority of cases, LOD is associated with the occurrence of meningitis. The manifestation of LOD is often non-specific and insidious. In EOD, the pathogens are acquired by the mother during childbirth; this can be effectively prevented by intrapartum antimicrobial prophylaxis (IAP). National and international guidelines recommend a rectovaginal swab in the 35–37th week of pregnancy to diagnose GBS colonisation, and IAP in the event of a positive diagnosis. However, IAP is not capable of preventing LOD infections, since such pathogens are not acquired before the postpartum period. The decrease in the incidence of invasive GBS infections in Germany is therefore mainly attributable to a decline in EOD cases, while the prevalence of LOD has remained largely unchanged. At least 14% of all newborns in Germany who are affected by an invasive GBS infection show residual impairment at the time of discharge, with up to 5% of cases being fatal.[1] According to most recent US data, neonatal GBS meningitis is associated with long-term effects in more than 40% of affected patients.[2]

However, a German nationwide study, which was conducted from 2008 to 2010 in collaboration with the Robert Koch Institute (RKI) and included all microbiology laboratories in Germany, found that invasive infections are much more common in patients beyond the newborn period. Newborns and infants aged up to 90 days accounted for less than one quarter of the 1,805 invasive isolates submitted to the central study laboratory. The majority of isolates were obtained from adult and, predominantly, older patients: Nearly 90% of the patients were aged 50 years or older, 55% were aged 70 years or older and 25% were at least 80 years old. Most of the isolates were obtained from blood cultures; joint aspirates or joint-associated intraoperative isolates were in second place, accounting for nearly 10%.

Trends in resistance development

The first nationwide study, which was conducted from 2001 to 2003 in collaboration with the RKI, collected close to 300 invasive GBS isolates (exclusively from newborns) and performed antimicrobial susceptibility tests.[3] All tested isolates were highly susceptible to penicillin, ampicillin und cefotaxime. About 10% of the isolates were resistant to erythromycin and nearly 6% were resistant to clindamycin. Given that these medicines are used as alternatives for IAP in pregnant women who are allergic to penicillin, this observation is not insignificant in terms of clinical relevance. Analyses of the findings of several smaller studies conducted in and across various regions in Germany at that time yielded very similar results. The nationwide study conducted from 2008 to 2010, which investigated pathogens causing invasive infections in all age groups, additionally showed full susceptibility of all isolates to penicillin, ampicillin und cefotaxime, indicating MIC values in line with those found in the study conducted from 2001 to 2003 (see Tab. 4.1.1.2.1). However, an increase in macrolide and lincosamide resistance was observed: 22% of the isolates were now resistant to erythromycin and nearly 15% were resistant to clindamycin; this is largely consistent with the erythromycin resistance rate (22.6%) found in other 2006 studies in hospitalised patients in Germany.[4] The results of a 2010 resistance study on outpatient isolates conducted by the Paul Ehrlich Society were even higher, indicating nearly 30% macrolide-resistant strains.[5]

Interestingly, only 16% of the neonatal isolates in the nationwide study (2008–2010) vs. 23% of the adult isolates in the RKI study were resistant to erythromycin. This could be attributable to an association between erythromycin resistance and certain serotypes. Whereas the majority (70%) of neonatal isolates belonged to the serotype III, this rate was only 26% in adult isolates. In contrast, only about 6% of the neonatal isolates belonged to the serotype V, as opposed to 31% in the adult isolates. Since erythromycin resistance is strongly associated with serotype V, this would be a plausible explanation for the different levels of antimicrobial resistance. Conversely, the serotype V in adults could, of course, have also been selected as a result of macrolide therapies they have undergone in the course of their lives.

Tab. 4.1.1.2.1: Antibiotic susceptibility of 976 invasive GBS isolates (2008-2010)

		MIC (mg/l)			
	Resistant (%)	Range	MIC_{50}	MIC_{90}	Breakpoint
Cefotaxime	0	0.016–0.25	0.032	0.047	≤0.5
Clindamycin*	13.8				
Erythromycin*	21.9				
Gentamicin	100	1.5–128	16	32	<1
Linezolid*	0				
Penicillin	0	0.008–0.25	0.032	0.064	≤0.25
Vancomycin*	0				

* These antimicrobials were tested for susceptibility by means of the agar diffusion method and the MIC value was only determined to confirm the resistance of non-susceptible isolates.

Fortunately, no GBS isolates with reduced susceptibility to penicillin have been reported in Germany to date. In the US and Asia, such strains have been observed and confirmed by respective reference laboratories as showing "reduced susceptibility" to penicillin.

Conclusion

Since GBS are still very susceptible to penicillin and/or ampicillin in German clinical practice, these antimicrobials continue to be used for the first-line treatment and prevention of GBS infections. The increase in macrolide and lincosamide resistance is alarming and has practical relevance not so much for treatment as for prevention of neonatal GBS infections in patients with a penicillin allergy; the high rate of resistance to erythromycin and clindamycin in adults must be addressed, including development of therapeutic strategies (e.g. for GBS infections of the skin and soft tissues), if necessary.

➤ R. Berner, F. Lander, B. Spellerberg
Reviewer: N. Schnitzler

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4.1.1.3 *Streptococcus pneumoniae*

Streptococcus pneumoniae is an inhabitant of the mucous membranes of the upper respiratory tract. The carrier rate in healthy adults ranges up to 10%. Young children can be asymptomatic carriers in up to 50% of cases, depending on their age. A major virulence factor of *S. pneumoniae* is its polysaccharide capsule, with significant differences in virulence being caused by the various possible capsular types (also known as serotypes). Non-encapsulated strains are not virulent. Some pneumococcal infections are associated with a clustering of specific serotypes. In children, for example, about 10–15 serotypes are responsible for 80–90% of invasive infections. *S. pneumoniae* infections are usually endogenous. Pneumococcal disease is subdivided into invasive infections (detectable in blood cultures, cerebrospinal fluid and other "sterile" specimens, i.e. meningitis and primary bacteraemia) and non-invasive infections (acute otitis media, sinusitis, non-bacteraemic pneumonia). Community-acquired (pneumococcal) pneumonia, which is invasive (involving the presence of bacteria in the blood) in 10–15% of cases, causes the greatest burden of disease, defined as the product of incidence and mortality. Pneumococci primarily infect people who have a weakened immune system. Besides the conventional forms of immunosuppression, this particularly includes young children (immature immune system) and the elderly (immunosenescence). Further risk factors for severe progression include splenectomy, young age (infants and young children) and old age, underlying cardiopulmonary disease and alcohol abuse.

The pneumococcal conjugate vaccine for children was added to the General Vaccination Recommendations of the German Standing Committee on Vaccination (STIKO) in 2006. The pneumococcal conjugate vaccines provide protection against 7, 10 and 13 serotypes, respectively (7v PnC, 10v PnC, 13v PnC). This report is based on the data reported by the National Reference Centre for Streptococci at the Institute of Medical Microbiology of the University Hospital RWTH Aachen.

Trends in resistance development

S. pneumoniae isolates obtained from children and adults with invasive infections were analysed for susceptibility to penicillin G and macrolides; the prevalence of macrolide resistance was determined using the data of clarithromycin or erythromycin based on the breakpoints defined by the Clinical and Laboratory Standards Institute (CLSI).

Adults

The available data on adults covers the period from 1992 through December 2011. The rate of resistance to penicillin G ranged between 0% and 2.5%, with a trend towards higher resistance rates becoming apparent in recent years, as evidenced by the high rate in 2007. The rate of penicillin G-intermediate *S. pneumoniae* strains ranged between 3.4% and 7.8% from 1992 to 2007, with no comparable tendency being observed in this case. The introduction of new CLSI guidelines in 2008 changed that picture. Since penicillin concentrations in cerebrospinal fluid are lower than in blood, these guidelines specify different breakpoints for meningitis and non-meningitis cases. The use of different breakpoints produced a significant drop in the average resistance rate (Tab. 4.1.1.3.1, Fig. 4.1.1.3.1). As shown in Tab. 4.1.1.3.2,

Tab. 4.1.1.3.1: Resistance rates of *S. pneumoniae* in adults (%)

Year	Isolates (n)	Penicillin G			Macrolide		
		Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant
1992	551	96.4	3.4	0.2	96.4	0.2	3.4
1993	468	95.1	4.9	0.0	94.7	0.2	5.1
1994	350	95.4	4.0	0.6	95.1	0.0	5.7
1995	338	95.6	4.4	0.0	90.2	0.3	9.5
1996	293	92.2	7.8	0.0	90.1	0.3	9.6
1997	167	93.4	6.6	0.0	88.0	0.6	11.4
1998	208	92.8	6.7	0.5	84.6	1.0	14.4
1999	226	93.8	5.8	0.4	82.7	0.0	17.3
2000	216	92.1	7.4	0.5	83.8	0.0	16.2
2001	458	93.9	5.9	0.2	84.9	0.0	15.1
2002	447	96.4	3.4	0.2	86.1	0.2	13.6
2003	566	93.5	6.0	0.5	83.7	0.2	16.1
2004	395	93.9	4.8	1.3	81.8	1.0	17.2
2005	612	94.1	3.9	2.0	81.7	0.0	18.3
2006	635	93.5	5.0	1.4	82.2	0.0	17.8
2007	1,676	93.6	3.9	2.5	83.0	0.8	16.2
2008	1,803	98.9	0.4	0.6	86.9	0.1	13.0
2009	1,948	99.3	0.3	0.4	88.9	0.2	10.9
2010	2,157	98.6	0.6	0.7	91.3	0.1	8.5
2011	2,330	99.2	0.4	0.4	90.4	0.2	9.4

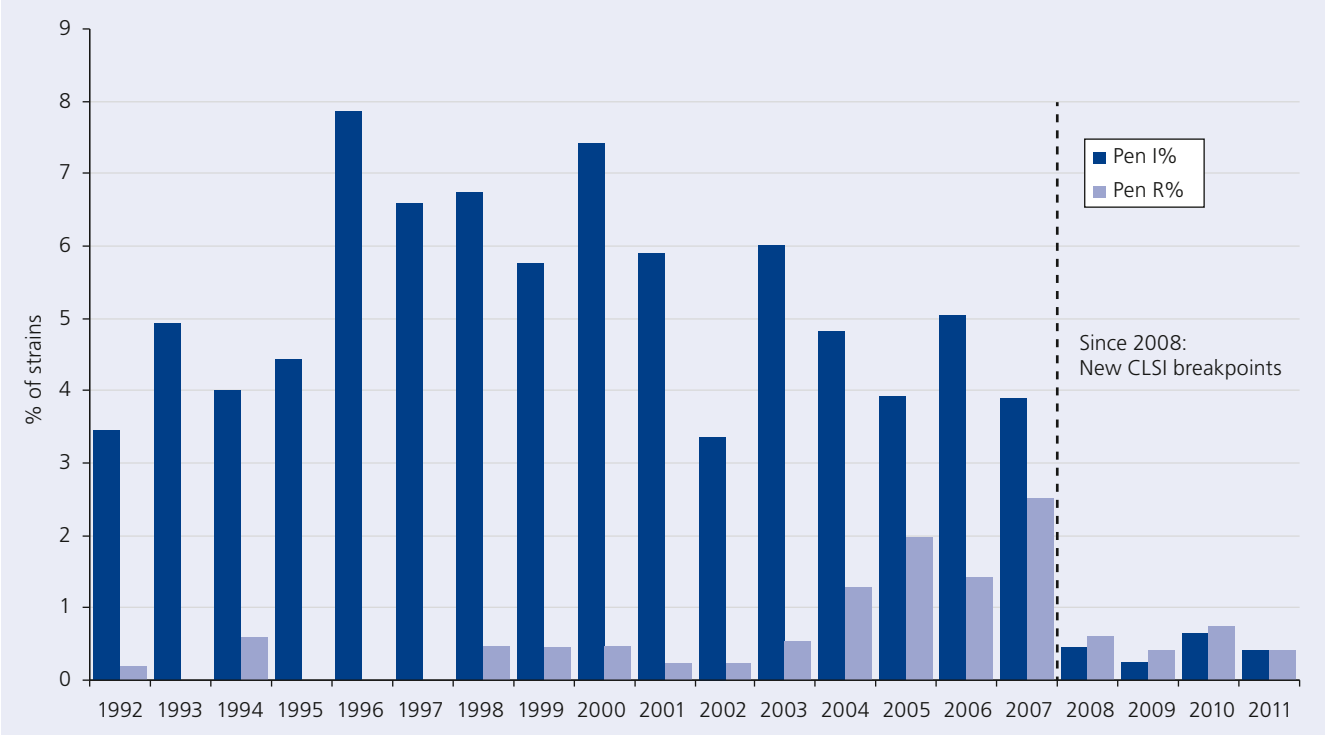

Fig. 4.1.1.3.1: Isolates from adults with reduced susceptibility to penicillin
Pen I%, % of penicillin-intermediate isolates; Pen R%, % of penicillin-resistant isolates

Tab. 4.1.1.3.2: Resistance rates of *S. pneumoniae* in adults (%), differentiated by meningitis and non-meningitis cases

Year	Isolates (n)	Meningitis – Penicillin G			Isolate (n)	Non-meningitis – Penicillin G		
		Susceptible	Intermediate	Resistant		Susceptible	Intermediate	Resistant
2008	178	93.8	0.0	6.2	1.625	99.5	0.5	0.0
2009	174	95.4	0.0	4.6	1.774	99.7	0.3	0.0
2010	176	90.9	0.0	9.1	1.981	99.3	0.7	0.0
2011	153	93.5	0.0	6.5	2.177	99.6	0.4	0.0

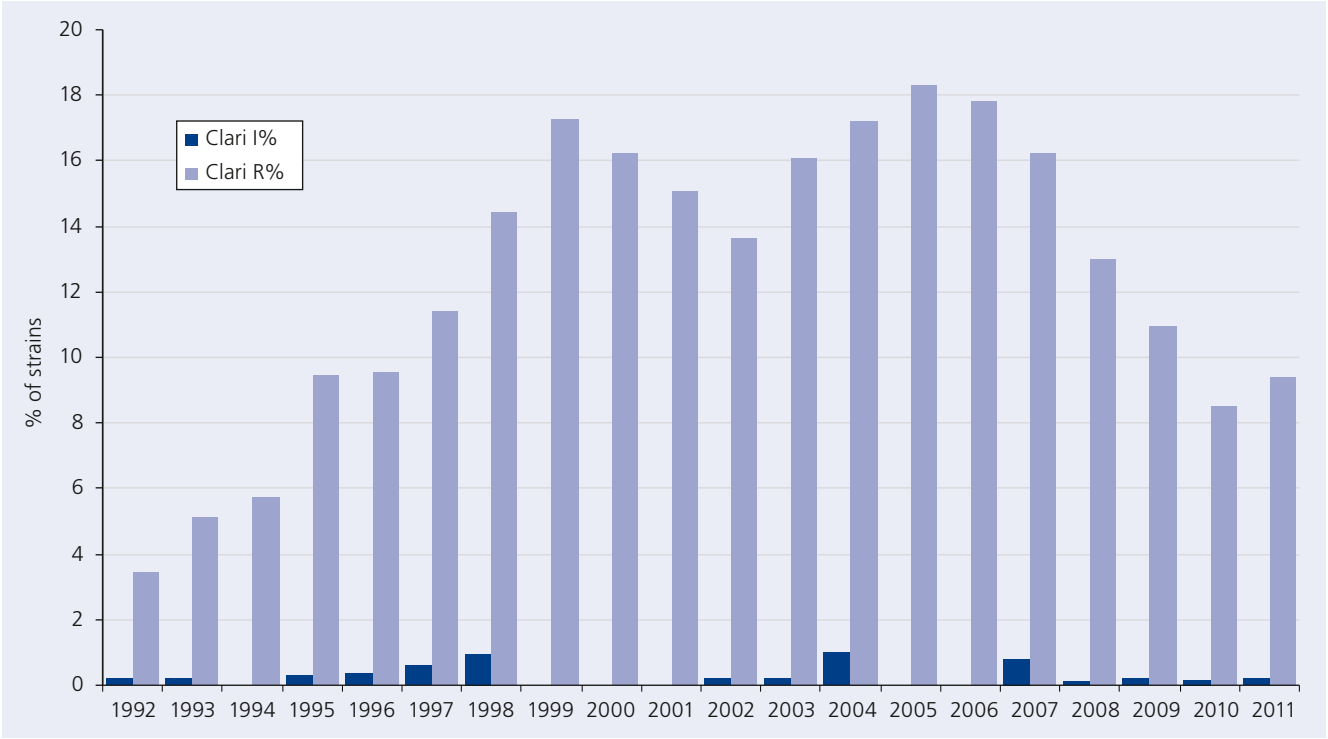

Fig. 4.1.1.3.2: Isolates from adults with reduced susceptibility to macrolides
Clari I%, % of clarithromycin-intermediate isolates; Clari R%, % of clarithromycin-resistant isolates

during the period 2008–2011, 4.6–9.1% of meningitis cases were penicillin G-resistant, while in non-meningitis cases only intermediate isolates were found (0.3–0.7%).

In terms of macrolide resistance, a continuous increase in the resistance rate was observed over the period 1992–1999. Since 2005, the resistance rate has been in decline, most recently accounting for 9.4% resistant isolates in 2011 (Tab. 4.1.1.3.1, Fig. 4.1.1.3.2).

Children

The evaluated data on children was collected from 1997 through December 2011. The rate of resistance to penicillin G during that period ranged between 0% and 3.5%, slightly exceeding that of adults. Again, there appears to have been a trend in recent years towards an increase in resistant strains; however, the number of penicillin-intermediate isolates hardly differs from that in adults. Unlike in adults, the introduction of the new CLSI guidelines in 2008 with a classification into meningitis and non-meningitis cases including the use of different breakpoints did not have a noticeable impact on the average resistance rate (Tab. 4.1.1.3.3, Fig. 4.1.1.3.3). During the period 2008–2011, 3.3–9.6% of meningitis cases in children were penicillin G-resistant, whereas among non-meningitis cases only intermediate resistance was found (0.0 - 2.2%), with the exception of one single resistant isolate which was detected in 2011 (0.7%) (Tab. 4.1.1.3.4).

The prevalence of macrolide resistance in children increased significantly between 1997 (10.6%) and 2005 (33.4%), but

Tab. 4.1.1.3.3: Resistance rates of *S. pneumoniae* in children (%)

Year	Isolates (n)	Penicillin G			Macrolide		
		Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant
1997	160	98.8	1.3	0.0	89.4	0.0	10.6
1998	163	95.7	4.3	0.0	87.7	0.0	12.3
1999	189	95.8	3.2	1.1	77.8	0.0	22.2
2000	212	88.7	10.4	0.9	72.2	0.5	27.4
2001	250	92.0	7.2	0.8	72.8	0.0	27.2
2002	275	93.5	5.8	0.7	71.8	0.4	27.8
2003	246	94.7	4.1	1.2	68.3	0.0	31.7
2004	256	88.7	7.8	3.5	70.3	0.4	29.3
2005	320	94.1	4.7	1.3	66.3	0.3	33.4
2006	294	91.2	5.4	3.4	70.2	0.0	29.8
2007	284	92.6	5.6	1.8	78.9	0.4	20.8
2008	224	97.3	1.3	1.3	84.8	0.0	15.2
2009	262	97.3	1.1	1.5	87.0	0.0	13.0
2010	247	96.0	1.2	2.8	90.7	0.0	9.3
2011	203	96.6	0.0	3.4	89.7	0.0	10.3

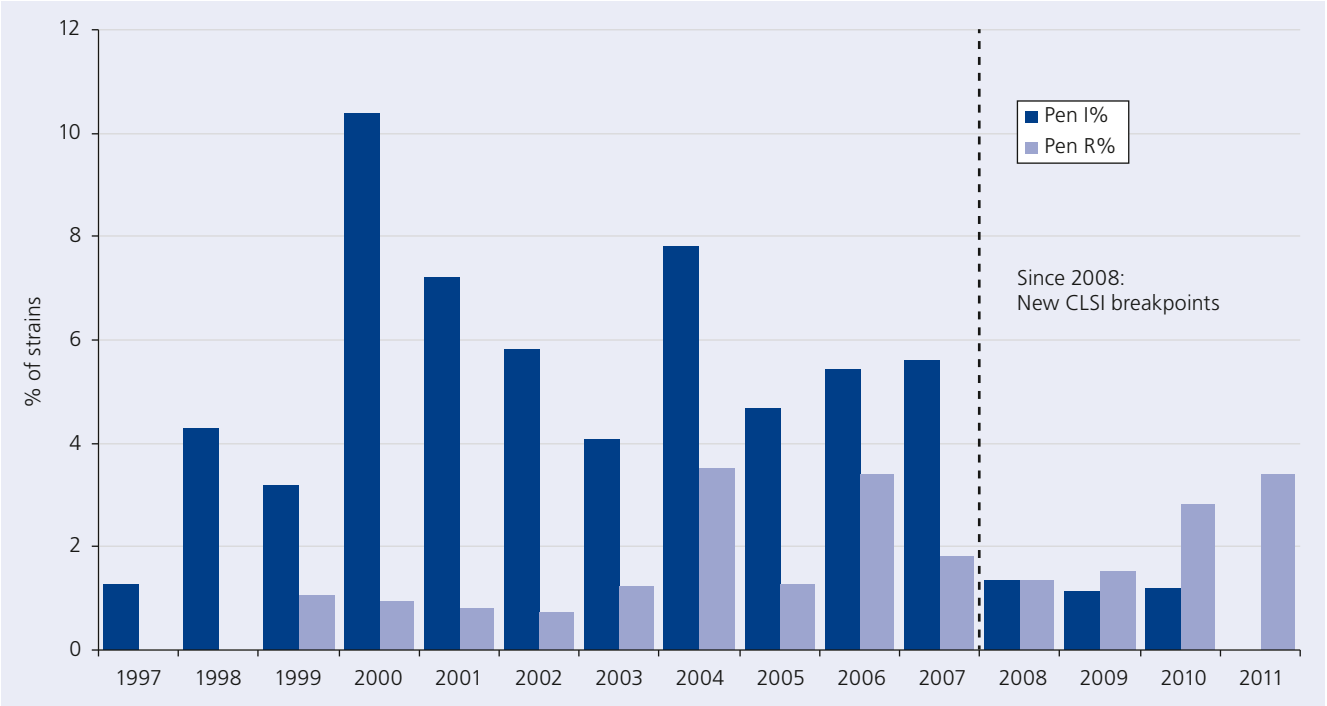

Fig. 4.1.1.3.3: Isolates from children with reduced susceptibility to penicillin
Pen I%, % of penicillin-intermediate isolates; Pen R%, % of penicillin-resistant isolates

Tab. 4.1.1.3.4: Resistance rates of *S. pneumoniae* in children (%), differentiated by meningitis and non-meningitis cases

Year	Isolates (n)	Meningitis – Penicillin G			Isolate (n)	Non-meningitis – Penicillin G		
		Susceptible	Intermediate	Resistant		Susceptible	Intermediate	Resistant
2008	90	96.7	0.0	3.3	134	97.8	2.2	0.0
2009	77	94.8	0.0	5.2	185	98.4	1.6	0.0
2010	73	90.4	0.0	9.6	174	98.3	1.7	0.0
2011	63	90.5	0.0	9.5	140	99.3	0.0	0.7

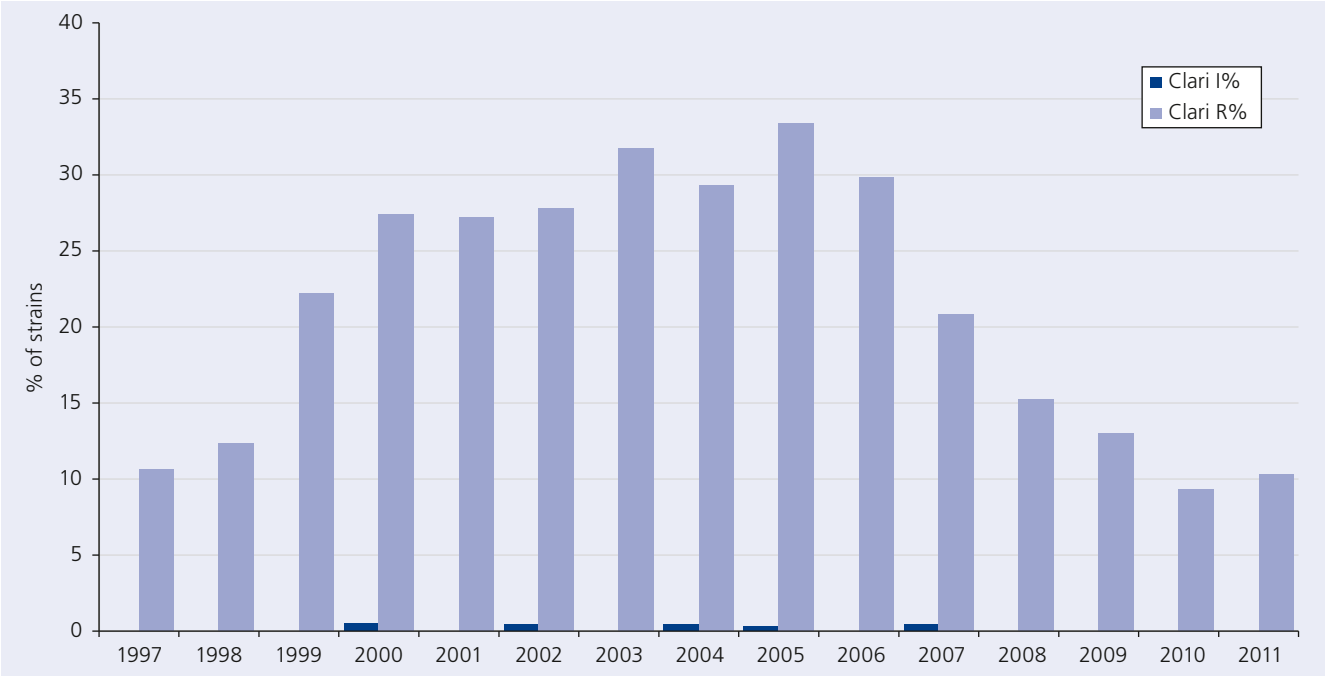

Fig. 4.1.1.3.4: Isolates from children with reduced susceptibility to macrolides
Clari I%, % of clarithromycin-intermediate isolates; Clari R%, % of clarithromycin-resistant isolates

fortunately it gradually decreased again between 2006 (29.8%) and 2010 (9.3%). In 2011, the resistance rate was 10.3%, slightly exceeding that of 2010. The number of macrolide-intermediate isolates was almost negligible, accounting for ≤ 0.5% (Tab. 4.1.1.3.3, Fig. 4.1.1.3.4).

Tab. 4.1.1.3.5: Serotype distribution in children in 2008 and 2011

Sero-type	In PnC vaccine	2008		2011	
		Isolates (n)	%	Isolates (n)	%
4	7v, 10v, 13v	1	0.4	0	0.0
6B	7v, 10v, 13v	10	4.5	3	1.5
9V	7v, 10v, 13v	3	1.3	1	0.5
14	7v, 10v, 13v	12	5.4	2	1.0
18C	7v, 10v, 13v	14	6.3	3	1.5
19F	7v, 10v, 13v	8	3.6	8	3.9
23F	7v, 10v, 13v	5	2.2	0	0.0
Total	7v, 10v, 13v	53	23.7	17	8.4
1	10v, 13v	29	12.9	30	14.8
5	10v, 13v	2	0.9	0	0.0
7F	10v, 13v	32	14.3	23	11.3
Total	10v, 13v	116	51.8	70	34.5
3	13v	12	5.4	14	6.9
6A	13v	12	5.4	2	1.0
19A	13v	10	4.5	21	10.3
Total	13V	150	67.0	107	52.7
6C	no	1	0.4	1	0.5
8	no	1	0.4	-	-
9N	no	4	1.8	2	1.0
10A	no	7	3.1	12	5.9
11A	no	2	0.9	4	2.0
12F	no	4	1.8	4	2.0
15A	no	1	0.4	3	1.5
15B	no	5	2.2	4	2.0
15C	no	5	2.2	7	3.4
16F	no	2	0.9	1	0.5
17F	no	2	0.9	-	-
18A	no	2	0.9	1	0.5
21	no	1	0.4	-	-
22F	no	3	1.3	9	4.4
23A	no	3	1.3	2	1.0
23B	no	1	0.4	12	5.9
24F	no	5	2.2	17	8.4
28A	no	1	0.4	-	-
28F	no	1	0.4	-	-
31	no	1	0.4	-	-
33A	no	1	0.4	-	-
33F	no	3	1.3	4	2.0
35A	no	1	0.4	-	-
35B	no	1	0.4	4	2.0
35F	no	3	1.3	-	-
37	no	-	-	3	1.5
38	no	9	4.0	4	2.0
39	no	1	0.4	-	-
NT	no	3	1.3	2	1.0
Total		224		203	100,0

Tab. 4.1.1.3.6: Penicillin resistance of 7v, 10v and 13v PnC serotypes and other serotypes in 2008 and 2011

Category	2008		2011	
	Isolates (n)	%	Isolates (n)	%
7v PnC serotypes				
Susceptible	50	94.3	15	88.2
Intermediate	2	3.8	0	0.0
Resistant	1	1.9	2	11.8
10v PnC serotypes				
Susceptible	113	97.4	68	97.1
Intermediate	2	1.7	0	0.0
Resistant	1	0.9	2	2.9
13v PnC serotypes				
Susceptible	144	96.0	103	96.3
Intermediate	3	2.0	0	0.0
Resistant	3	2.0	4	3.7
Other serotypes				
Susceptible	74	100.0	93	96.9
Intermediate	0	0.0	0	0.0
Resistant	0	0.0	3	3.1
Total number				
Susceptible	218	97.3	196	96.6
Intermediate	3	1.3	0	0.0
Resistant	3	1.3	7	3.4

Tab. 4.1.1.3.7: Macrolide resistance of 7v, 10v and 13v PnC serotypes and other serotypes in 2008 and 2011

Category	2008		2011	
	Isolates (n)	%	Isolates (n)	%
7v PnC serotypes				
Susceptible	34	64.2	9	52.9
Intermediate	0	0.0	0	0.0
Resistant	19	35.8	8	47.1
10v PnC serotypes				
Susceptible	90	77.6	62	88.6
Intermediate	0	0.0	0	0.0
Resistant	26	22.4	8	11.4
13v PnC serotypes				
Susceptible	122	81.3	92	86.0
Intermediate	0	0.0	0	0.0
Resistant	28	18.7	15	14.0
Other serotypes				
Susceptible	68	91.9	90	93.8
Intermediate	0	0.0	0	0.0
Resistant	6	8.1	6	6.3
Total number				
Susceptible	190	84.8	182	89.7
Intermediate	0	0.0	0	0.0
Resistant	34	15.2	21	10.3

The serotype distribution in children, shown based on the 2008 and 2011 data respectively, confirms that almost two and almost five years after the recommendation for vaccination only 23.7% and 8.4% of isolates, respectively, are covered by the 7-valent conjugate vaccine (7v PnC). These percentages increase to 51.8% and 34.5%, respectively, for the 10-valent conjugate (10v PnC) and to 67.0% and 52.7%, respectively, for the 13-valent conjugate vaccine (13v PnC).

The most common serotypes were serotype 7F (14.3% and 11.3%, respectively) and serotype 1 (12.9% and 14.8%) (Tab. 4.1.1.3.5).

When the pneumococcal conjugate vaccine was introduced, most of the penicillin-resistant and macrolide-resistant strains had serotypes that were included in the 7v vaccine. The reduced prevalence of serotypes included in the pneumococcal

conjugate vaccines (7-valent serotypes in particular) led to a noticeable decrease in macrolide resistance (Tab. 4.1.1.3.7). In terms of penicillin resistance, this effect is not as noticeable, not least due to the increased prevalence of serotype 19A (Tab. 4.1.1.3.6), which is, however, included in the 13-valent conjugate vaccine that has been available since December 2009.

Conclusion

A decrease in the rate of resistance to penicillin G has been observed, especially in adults, as a result of the use of the new CLSI breakpoints since 2008. The overall rates within Europe are comparatively low. The rapid increase in macrolide resistance has been halted in recent years. The resistance rates in both children and adults decreased gradually between 2006 and 2010, accounting for approximately 10% in both age groups in 2011.

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4.1.2 *Staphylococcus* spp.

Staphylococcus aureus

Staphylococcus aureus is considered one of the most important infectious agents in human medicine. Methicillin-resistant *Staphylococcus aureus* (MRSA), which are often also resistant to other antimicrobial classes, pose a great challenge in hospital-associated infections (referred to as HA-MRSA). As a result of shorter hospital stays, hospital-acquired MRSA may often not become apparent as inhabitants or infectious agents until after discharge; these are then termed *hospital-associated community onset* MRSA (HCA-MRSA). Additionally, a distinction is made between MRSA occurring in the population outside and independently from inpatient care facilities (*community-associated* MRSA, CA-MRSA) and those that have their original reservoir in livestock farming (*livestock-associated* MRSA, LA-MRSA).[1,2]

Trends in resistance development

Resistance study conducted by the Paul Ehrlich Society (PEG)

Every three years, the "Susceptibility Testing and Resistance" working group of the Paul Ehrlich Society collects data on the prevalence of resistance in important pathogens isolated from hospital-associated infections, including *S. aureus* isolates. A slight drop in the MRSA rate was recorded in 2010 compared to 2007 (Fig. 4.1.2.1a). Regarding the prevalence of co-resistance in MRSA during the period 1995–2010 (Fig. 4.1.2.1b), a clear downward trend in the prevalence of resistance to several other antimicrobial classes is observed in some cases. The decrease in extensively drug-resistant clones reflects the dynamic spread of certain epidemic MRSA clones.

The variants that have increasingly emerged in recent years (isolates of the clonal lineage ST22 ["Barnim Epidemic Strain"]

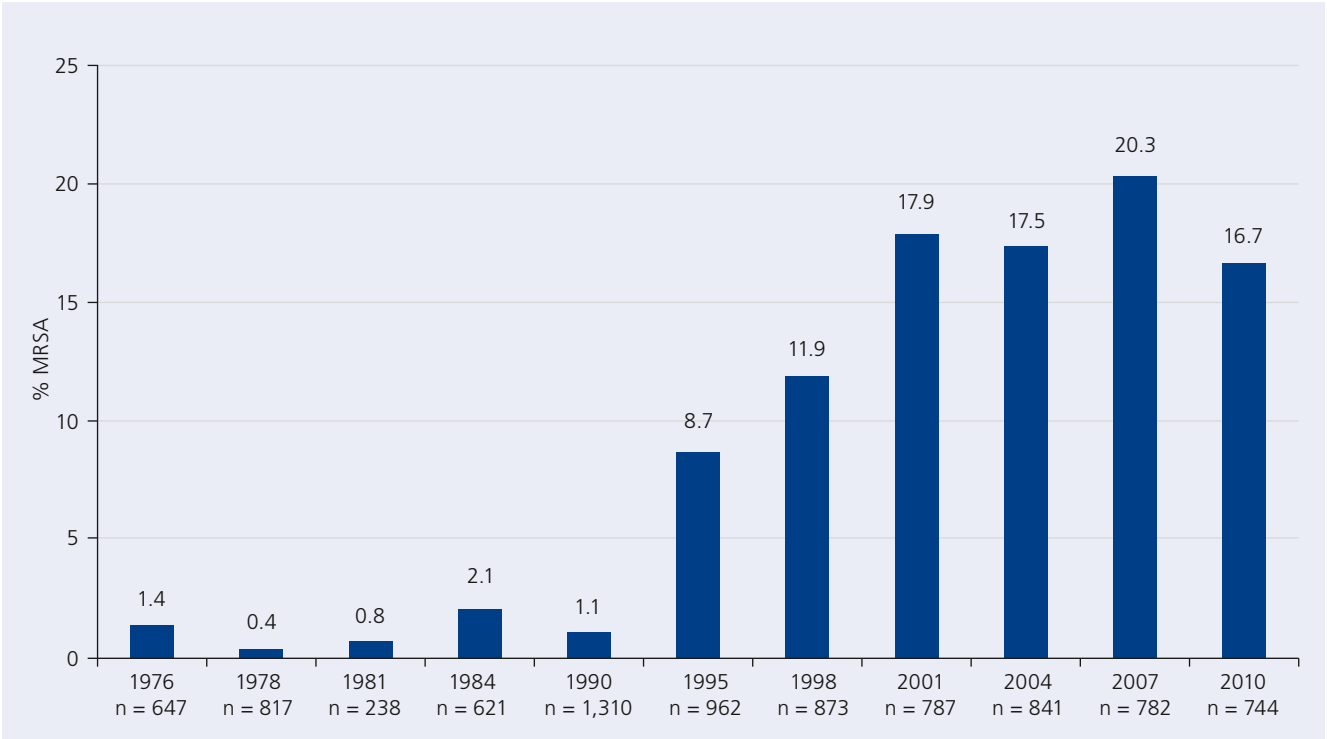

Fig. 4.1.2.1a: Percentage of MRSA in all tested *S. aureus*; data obtained from the resistance studies by the Paul Ehrlich Society

and ST225 ["Rhine-Hesse Epidemic Strain"]) have a considerably narrower resistance spectrum than previous epidemic MRSA. Molecular characterisation of MRSA isolates as part of the PEG 2010 resistance study at the National Reference Centre for Staphylococci produced the following results: Nearly 90% of MRSA isolates from the hospital sector (subproject H) were classified as HA-MRSA using *spa* typing. 30.6% had the *spa* type t032 (clonal lineage ST22) and 26.6% the *spa* type t003 (clonal lineage ST225). Three (2.4%) MRSA isolates were microbiologically confirmed to be CA-MRSA based on the *spa* type and a *luk*-PV-positive PCR (Panton-Valentine leukocidin). In five (4%) cases, the infection was caused by MRSA of the clonal lineage ST398 (t034, t011; LA-MRSA).[3] The vast majority of strains (approximately 75%) from private practices (subproject N) were also HA-MRSA, which are referred to as HCA-MRSA in this case. Again, t003 and t032 were the predominant *spa* types, accounting for 30.8% and 23.1%, respectively. Two isolates each (5.1%) were recognised as CA-MRSA and LA-MRSA, respectively. The percentage of MRSA in the strains from private practices was 10.5%.[4]

Antimicrobial Resistance Surveillance System (ARS)

ARS is a laboratory-based surveillance system that continuously collects resistance data from medical routine (currently 24 inpatient and outpatient care laboratories) on clinically relevant bacteria.[5] The ARS data on MRSA prevalence (2008: 23.7%; 2009: 26.0%; 2010: 26.1%, 2011: 23.4% for inpatient care facilities) indicates a slight downward trend for 2011.

Hospital Infection Surveillance System (KISS)

KISS collects data on the prevalence of nosocomial infections and their causative agents, with a focus on special high-risk areas at hospitals.[6] As part of the ITS-KISS module (infection surveillance in intensive care units), data was collected in 586 intensive care units from January 2005 to December 2009. MRSA are most prevalent in intensive care patients carrying multidrug resistant organisms (MDRO). For example, the MRSA rate in nosocomial infections is 7.2% for ventilator-associated infections of the lower respiratory tract and 5.8% for central venous catheter-associated bloodstream infection. The 2009 data shows an overall prevalence of 1.38 MRSA per 100 patients. The percentage of patients with MRSA has remained constant over the past few years, whereas the rate of other MDRO in intensive care patients has increased (see Fig. 4.1.2.3).[7]

European Antimicrobial Resistance Surveillance Network (EARS-Net)

The data collected within the EARS-Net comprises blood culture isolates (2010: n=1,561; 2011: n=2,388) from up to 25 German laboratories. During the period 1999–2005, a continuous increase in MRSA rates (from 8.3% to 21.4%) was observed; since 2006, these rates have been declining slightly. The rate of methicillin-resistant *S. aureus* was 20.8% in 2010 and 16.1% in 2011. Fig. 4.1.2.2 summarises the data collected from 2008 to 2010 for Germany and other European countries. Most states saw declining or stagnating MRSA rates, except for four countries where MRSA rates increased. However, in eight of the 28 European countries, particularly in Southern and Eastern Europe, MRSA prevalence is still higher than 25%.[8]

Data reported by the National Reference Centre for Staphylococci on the emergence and spread of MRSA

Emergence of epidemic MRSA at German hospitals spread across different regions

Hospital-acquired MRSA (HA-MRSA) occur as epidemic MRSA and belong to clonal lineages with a specific molecular biology. These epidemic strains were initially named in Central Europe after the geographical region where they first occurred. As has been observed for more than a decade, there is a dynamic development of epidemic HA strains.[9,10] In most hospitals, isolates of the clonal lineages ST 22 ("Barnim Epidemic Strain") and ST225 ("Rhine-Hesse Epidemic Strain") are currently most prevalent.[11,12] Both ST22 and ST225 occur throughout Germany. Isolates of the clonal lineages ST8, ST45 ("Berlin Epidemic Strain"), ST228 ("Southern German Epidemic Strain") and ST239 ("Vienna Epidemic Strain") were reported less commonly. MRSA ST239 exhibit a broad resistance phenotype and are found worldwide.[13] Some of the MRSA ST239 detected by the NRZ were found in severely injured patients from abroad. Several HA-MRSA that commonly occur in other European countries, namely t067-ST125 (Spain), t024-ST8 (Denmark) and t041-ST228 (Italy, Croatia), were found only sporadically in Germany.[14]

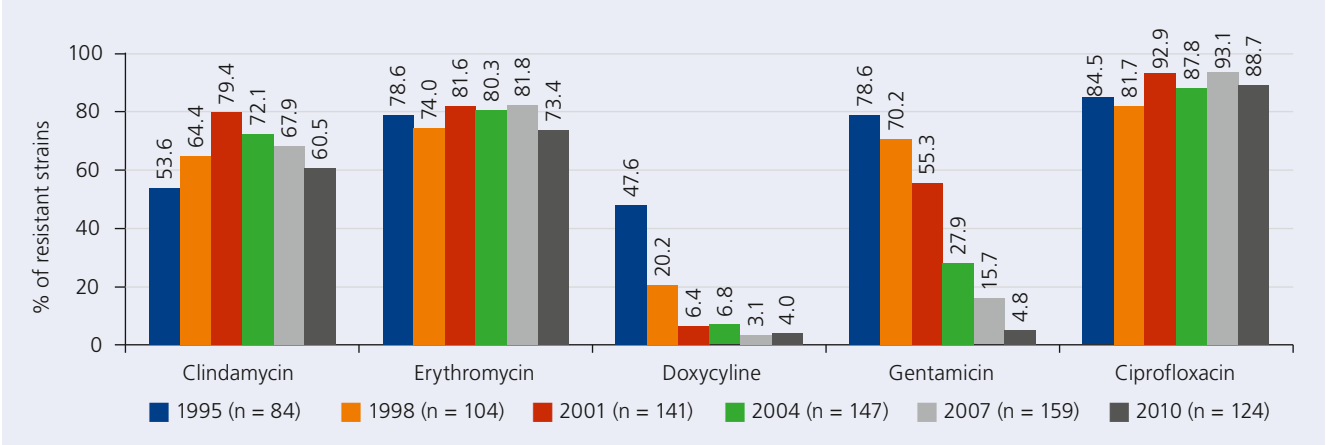

Fig. 4.1.2.1b: Co-resistance to important antimicrobials in MRSA; data obtained from the resistance studies by the Paul Ehrlich Society

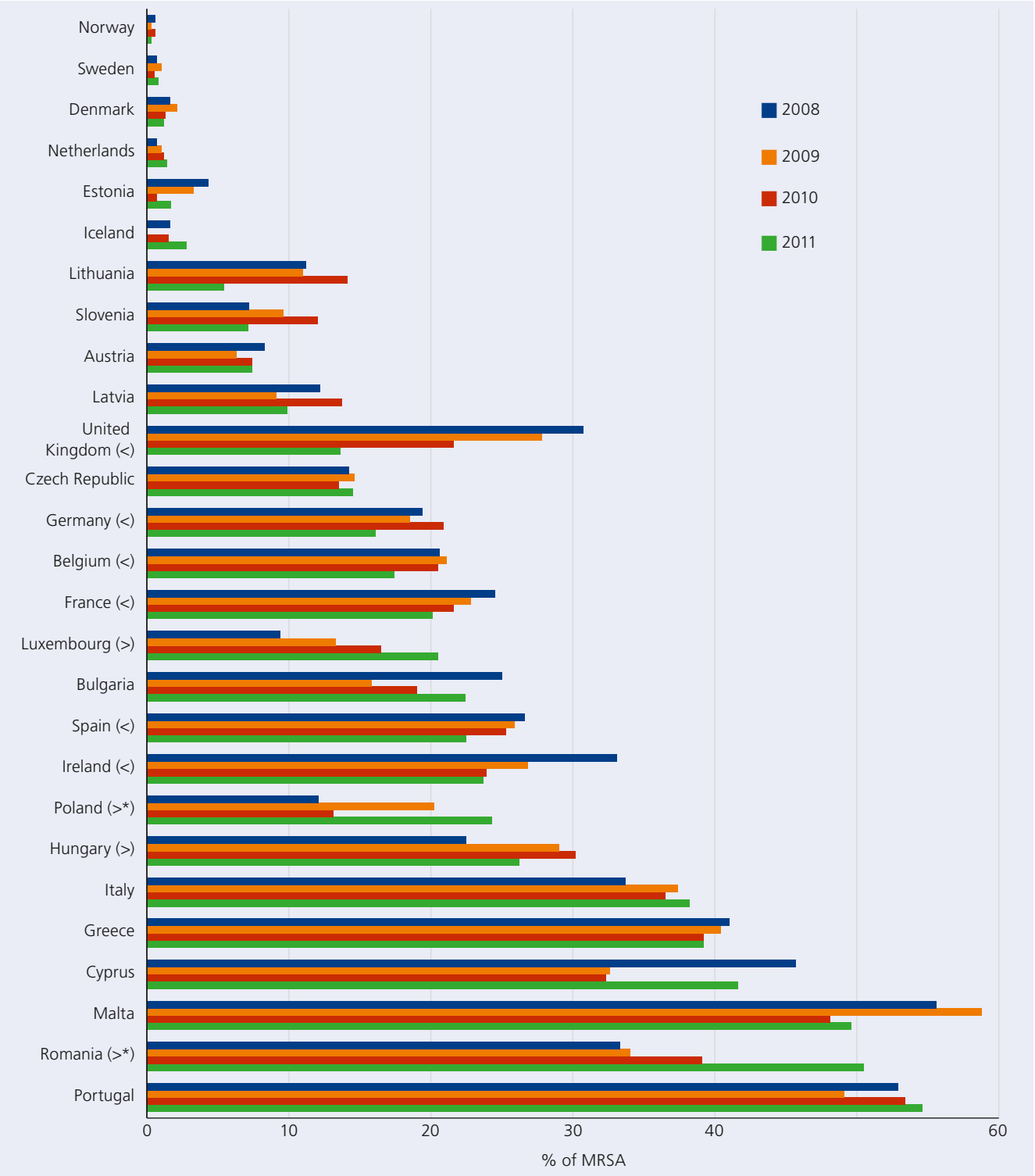

Fig. 4.1.2.2: Percentage of MRSA in *S. aureus* isolates from blood cultures in various European countries (2008–2011)[6]
The < and > symbols indicate a significant increase or decrease in resistance. The >* symbol indicates a significant trend when taking the data from all laboratories into account. However, the trend was not significant when only data was taken into account from laboratories that participated in the study every four years.

MRSA infections in various clinical disciplines of inpatient care facilities

As in previous years, most infections occurred in internal medicine departments, intensive care units and on surgical wards. While surgical site infections were most common on surgical wards, the majority of cases in internal medicine and ICUs were septicaemias and ventilator-associated pneumonias, but also included surgical site infections. The trend of increased submissions of MRSA isolated from urinary tract infections in urology departments remains unchanged.

Resistance to other antimicrobial classes in MRSA from German hospitals

The prevalence of resistance to indicator substances of antimicrobial classes other than β-lactam antimicrobials is summarised in Tab. 4.1.2.1. The trend observed in previous years continues: 93% of MRSA from hospital-associated infections are resistant to ciprofloxacin, with 91% also being resistant to moxifloxacin. For a number of antimicrobials, the rates are well below 10%, such as 1.7% for the important antimicrobial agent rifampicin; low resistance rates were also found

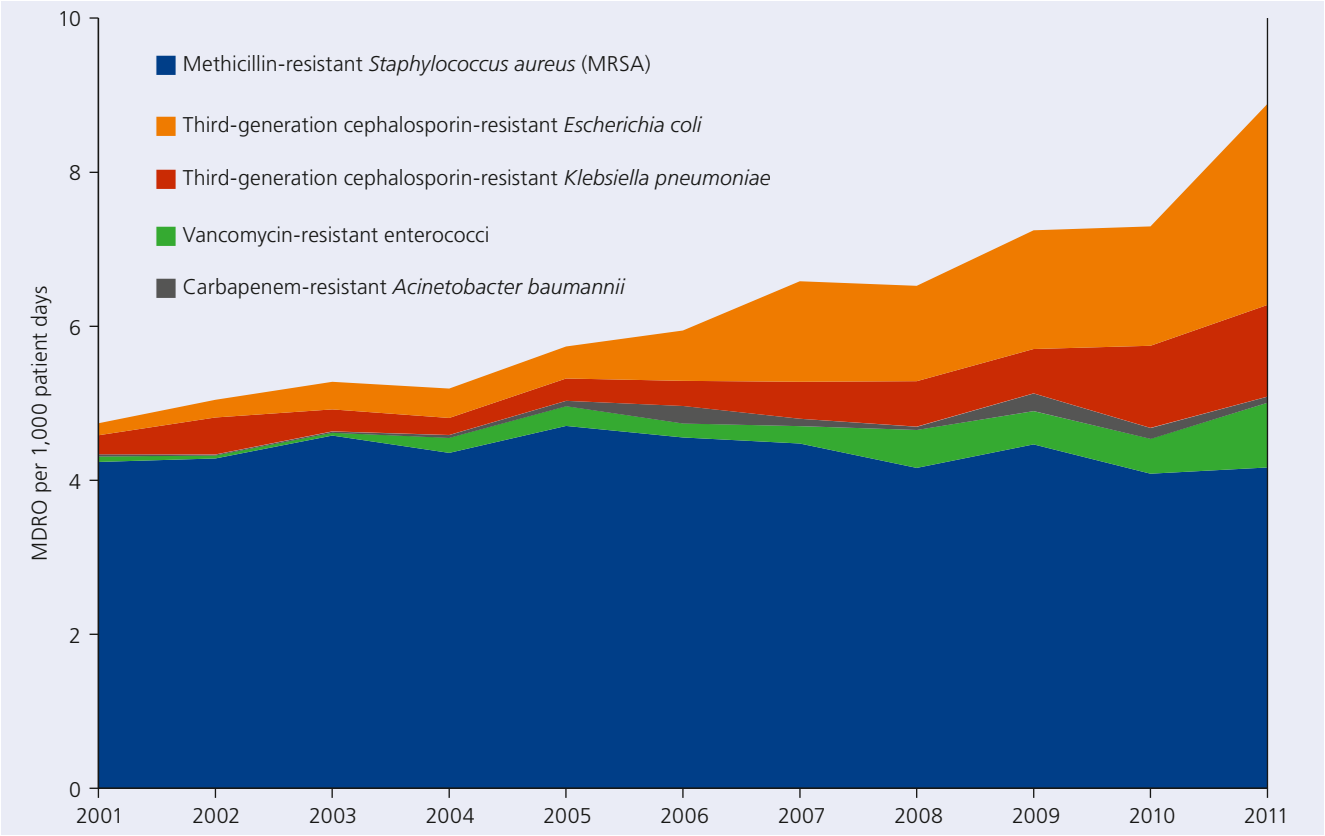

Fig. 4.1.2.3: Prevalence of multi-drug-resistant organisms in German intensive care units (E. Meyer, unpublished 2012 KISS data)

Tab. 4.1.2.1: Resistance to other antimicrobials (in addition to resistance to β-lactam antimicrobials) in HA-MRSA, 2006–2011

Antibiotic	2006 (%)	2007 (%)	2008 (%)	2009 (%)	2010 (%)	2011 (%)
Ciprofloxacin	93.8	95.8	91	90	86	93
Moxifloxacin	–	94.4	89.6	87	86	91.3
Erythromycin	72.5	75	80.7	67	65	64.3
Clindamycin	65.4	72	73.4	60	59	59.9
Gentamicin	13.3	9.8	10.5	9.5	5.3	4.4
Tetracycline	7.4	6.8	7.3	8	6	4.6
Rifampicin	2.5	1.07	0.4	1.6	0.8	1.7
Co-trimoxazole	3.1	2	10.8	5.3	0.8	0.7
Fusidic acid-sodium	6.4	3.8	2	5.2	4	2.7
Fosfomycin	3.3	0.56	1.1	0.15	0.6	0.4
Linezolid	0.04	0.11	0.1	0.1	0.08	0
Tigecycline	0	0	0	0	0.12	0
Daptomycin	0	0	0.65	1.3	1.6	2.1
Mupirocin	2.6	3.3	5.3	4	4.6	6.9
Vancomycin	0	0	0	0	0.08	0
Teicoplanin	0	0	0	0	0.2	0.1

for potential combination drugs (co-trimoxazole, fusidic acid, fosfomycin).

Resistance to mupirocin rose to nearly 7% in 2011. This may be the result of increased mupirocin use within more and more frequent MRSA screenings and decolonisation treatments. Similar assumptions in connection with growing mupirocin resistance in MRSA have already been reported in Asia and, to a lesser extent, in Europe.[15,16]

Daptomycin-resistant MRSA isolates were often multidrug resistant and predominantly belonged to the currently most widespread clonal lineages of HA-MRSA (ST22 and ST225).

As was the case in 2010, one MRSA isolate was found in 2012 that exhibited resistance to glycopeptides (*van*A- and *van*B-negative) as well as to daptomycin. Several studies that performed genome analyses of consecutive isolates obtained in the course of antimicrobial treatment found that the mutations occurring during treatment may cause resistance to both glycopeptides and daptomycin.[17,18] However, the molecular mechanism that gives rise to this resistance phenotype is still the subject of current research.

In 2011 and 2012 (data as of 30 October 2012), there was no evidence of linezolid-resistant *S. aureus*. Among the isolates reported in 2010, the linezolid resistance of one MRSA

ST225 resulted from a mutation in the 23S rRNA, while one LA-MRSA ST398 exhibited *cfr* gene-mediated resistance. The cfr gene was originally found in coagulase-negative staphylococci from animals and later in a porcine MRSA ST398.[19] In Spain, a Madrid hospital reported an outbreak of HA-MRSA infections with *cfr*-mediated linezolid resistance that resulted in the deaths of five people.[20] The emergence of such isolates requires special attention. New types of antimicrobial resistance that can be transferred between bacteria and originate from zoonotic reservoirs can also spread to humans through staphylococci with low host specificity.

Emergence and spread of community-associated MRSA (CA-MRSA) in Germany

The first cases of CA-MRSA were reported in the early 1990s in national minorities in Australia and the US. Today, there are worldwide reports of MRSA occurring outside hospitals independently from HA-MRSA-associated risk factors.[21] The clinical symptoms of these infections usually include localised skin and soft tissue infections, often in the form of recurrent abscesses or furunculosis. Life-threatening clinical manifestations such as necrotising pneumonia or necrotising fasciitis occur very rarely, but are associated with a high mortality rate if they do occur. The NRZ receives CA-MRSA from various testing facilities of registered physicians in private practices and hospitals as well as from laboratories of the Public Health Service (ÖGD).

In 2011 and 2012, as in previous years, most strains were isolated from deep skin and soft tissue infections (abscesses, furuncles, carbuncles, surgical site infections), primarily including isolates of the clonal lineages ST8 (CA-MRSA "USA300"; *arc*A-positive, PVL-positive), ST30 ("Oceanic Clone"; PVL-positive) and ST80 ("European Clone"; *etd*-positive, PVL-positive). Occasionally, clusters of CA-MRSA infections have an increased incidence within families. The global increase in the spread of the Oceanic Clone ST30 can also be seen in the present data, continuing the trend that was already observed in 2010. There were only a few patients where the available data suggested an association between a CA-MRSA ST30 infection and travelling in Southeast Asia.

In some cases, the occurrence of CA-MRSA ST8 ("USA300") was associated with MSM (men-who-have-sex-with-men) staying in the US and/or with US citizens. The detection of PVL-positive, *arc*A-negative CA-MRSA ST8 raised the question of whether these strains were a subpopulation of the "USA300" strain that had lost the ACME gene cluster, or whether they had developed convergently. Further molecular biological studies, including genome-wide SNP analyses, indicate that *arc*A-negative isolates can also be closely related to "USA300" reference strains. It is likely that elements of the accessory genome (incl. *arc*A, PVL, SCC*mec*) can be both acquired and lost at various locations in the phylogenetic tree (Strommenger et al., unpublished).

CA-MRSA ST772 ("Bengal Bay Clone"), which occur predominantly on the Indian subcontinent and have a multidrug resistant phenotype, were first isolated in 2011 and 2012. In most cases, the affected patients had a connection to India, Bangladesh or the UK (large community of Indian origin) [22,23], which we were able to confirm based on the isolates we processed.

Other clonal lineages of CA-MRSA can also be assumed to have been imported from other countries where these MLST types are common, such as ST5 (Southeast Europe), ST152 (Balkan States), ST1 (Canada, US) and ST59 (Asia-Pacific region).

Submissions of LA-MRSA ST398 as the causative agent of community-acquired MRSA infections have been increasing in recent years and now account for a substantial percentage (11% in 2011; mostly deep skin and soft tissue infections, rarely bloodstream infections). Most cases were associated with occupational exposure in conventional livestock farming. On an international scale, cases of human-to-human transmission have also been rather rare, but are known to occur. There was one noteworthy case of infection in a neonate at a Saxon hospital in 2011 that is likely to have resulted from transmission in the domestic environment (father works as veterinarian, but did not undergo microbiological examination).

Tab. 4.1.2.2 shows the prevalence of resistance to antimicrobials other than oxacillin in CA-MRSA. CA-MRSA ST30 exhibit a narrow resistance spectrum; CA-MRSA ST8 ("USA300") are always also resistant to erythromycin, with approximately 60% of the strains also exhibiting resistance to ciprofloxacin und moxifloxacin. In some cases, there is additional resistance to gentamicin, tetracycline and/or fusidic acid. The vast majority of CA-MRSA ST80 are also resistant to tetracycline and fusidic acid, while the newly emerged ST772 are resistant to erythromycin, gentamicin, ciprofloxacin und moxifloxacin. LA-MRSA are always also tetracycline-resistant. Regarding antimicrobials that are preferably used for the treatment of systemic CA-MRSA infections because of their favourable concentration levels in skin and soft tissue, such as rifampicin,

Tab. 4.1.2.2: Prevalence of resistance to other antimicrobials in CA-MRSA

Antibiotic	Prevalence in isolates in 2011 (%)	Clonal lineage predominantly affected by resistance
Oxacillin	100	
Clindamycin	9.6	
Erythromycin	38.4	ST8, ST59, ST772
Gentamicin	13.6	ST152, ST772
Tetracycline	34.4	ST80, ST398
Ciprofloxacin	21.6	ST8, ST772
Moxifloxacin	17.6	ST8, ST772
Fusidic acid-sodium	13.6	ST80
Co-trimoxazole	0	
Rifampicin	0.8	

co-trimoxazole and linezolid, the resistance situation is still good.

Emergence of "new" MRSA tested negative for *mecA* and PBP2a

To date, common MRSA have shown phenotypic resistance to all β-lactam antimicrobials including oxacillin/sulbactam due to the production of the additional penicillin-binding protein PBP2a, which is encoded by the *mecA* gene. The use of PCR detection for the *mecA* gene and the detection of PBP2a by means of an agglutination test have so far been the gold standard for the molecular detection of MRSA.[24] The recently reported emergence of MRSA with negative results for both tests requires special attention. These MRSA were first reported in England and later also in Denmark as well as Germany; with a few exceptions, they belong to the clonal lineages ST130 and ST425.[25,26] In England, they have also been reported in association with mastitis in dairy cattle,[27] which suggests a zoonotic origin.

The β-lactam resistance of these isolates is associated with a penicillin-binding protein that is encoded by the *mecC* gene (known from *S. aureus* LGA251, the genome of which was sequenced) and exhibits ~70% homology with *mecA*.[26] The resistance gene *mecC* (original name: $mecA_{LGA251}$) is associated with an SCC*mec* type-XI element that is assumed to have originated in coagulase-negative staphylococci (CNS). CNS are generally considered to be a reservoir for "new" SCCmec elements. PCR detection is possible using both specific primers and primers that recognise both *mecA* and $mecA_{LGA251}$.[25,28] The isolates of *mecC*-positive MRSA found in Germany exhibit a relatively low cefoxitin MIC, which is why their detection using chromogenic selective media containing cefoxitin may be problematic. MRSA of this sequence type are usually only resistant to β-lactam antimicrobials and occasionally to ciprofloxacin; in Germany, their detection has so far been comparatively rare.[25,28]

Among the 2,329 MRSA isolates processed by the National Reference Centre for Staphylococci in 2011, 44 isolates were *mecA*-negative but showed phenotypic resistance to oxacillin and oxacillin/sulbactam (1.9%), 14 of which were tested positive for *mecC* (0.6%) in further PCR analyses; similar results were found in 2012. So far, these isolates have been found separately in both humans and animals, as has recently been reported in other European countries.[29,30] However, data from Denmark shows that *mecC*-positive MRSA can also be transmitted from cattle and sheep to humans.[31]

Livestock-associated MRSA (LA-MRSA) and their significance for the population

LA-MRSA may cause deep skin and soft tissue infections that require surgical intervention. So far, this has primarily affected people with direct occupational exposure, sometimes including their family members. Overall, these infections are rare.

Nosocomial infections may also occur as a result of nasal colonisation, including infections following hip replacement surgery, pneumonia in mechanically ventilated patients or bloodstream infections.[32] Unlike hospital-acquired MRSA, however, LA-MRSA have so far rarely spread at hospitals. A clustering of infections/colonisations at a Dutch hospital (four patients treated for colonisation in whom an infected venous ulcer was detected simultaneously) nevertheless shows that such a spread is possible.[33] A random sample of blood culture isolates from across Germany indicated that LA-MRSA accounted for 1.7% of MRSA in 2011 (sample of 467 MRSA from blood cultures of all MRSA isolates submitted to the NRZ for Staphylococci in 2011). A testing of clinical specimen isolates from rural districts in northwestern North-Rhine Westphalia with a high density of pig farming showed an average LA-MRSA rate of 9.5% for the period 2008–2011, with 10.3% being isolated from bloodstream infections (data provided by EUREGIO Netzwerk Münsterland/Twente; see also[34]). A point prevalence study at 16 acute-care hospitals and in two rehabilitation centres in the district of Osnabrück found that LA-MRSA accounted for 23.4% of all MRSA isolates.[35]

However, current LA-MRSA still differ from HA-MRSA in terms of their "epidemic potential", i.e. their ability to spread from human to human. Nevertheless, special attention needs to be given to new types of antimicrobial resistance that can reach humans via MRSA with low host specificity originating from animal staphylococci.

Other *Staphylococcus* spp.

Apart from *S. aureus*, the *staphylococcus* species with the highest clinical relevance, there are coagulase-negative, potentially human pathogenic staphylococci, most of which are natural inhabitants of the human skin flora, colonising both the outer skin and mucous membranes. The two most common CNS causing infections in humans are *S. epidermidis* and *S. haemolyticus*.

Trends in resistance development

Resistance study conducted by the Paul Ehrlich Society (PEG)

The PEG resistance studies also regularly collect data on the prevalence of resistance in CNS.[3,4,36]

A slight increase in oxacillin (methicillin)-resistant *S. epidermidis* was observed when comparing 2007 to 2010 (73.8% vs. 76.7%). The data of *S. haemolyticus* shows similar results (2007: 89.0%, 2010: 93.8%). The steady increase in ciprofloxacin-resistant isolates continued in 2010 in both *S. epidermidis* (2007: 66.7%, 2010: 70.5%) and *S. haemolyticus* (2007: 85.4%, 2010: 90.1%). The resistance rates of both species to clindamycin and erythromycin were at a similar level in 2010 as they were in 2007. Gentamicin resistance increased again during the last 3-year period (*S. epidermidis* 2007: 44.7%, 2010: 49.7%; *S. haemolyticus* 2007: 79.3%, 2010: 85.2%). While 17.5% of *S. epidermidis* isolates were found to be teicoplanin-resistant in 2007, that rate was 10.8% in 2010. Among the *S. haemolyticus* isolates, 46.3% (2007) and 24% (2010) were found to be teicoplanin-resistant. No vancomycin- or linezolid-resistant isolates were detected in these two studies.

Data reported by the National Reference Centre for Staphylococci

In 2012, there was a notable number of submissions of linezolid-resistant *S. epidermidis* (24 isolates from 6 different

hospitals; outbreaks were suspected in 3 cases). The majority of these isolates exhibited a multidrug resistant phenotype; in some cases, linezolid MIC values of >256 mg/l were observed. PFGE typing of the strains confirmed the suspicion of an epidemiological connection at two hospitals. The plasmid-mediated resistance determinant *cfr* was detected in 6 isolates. Mutations in the 23S rRNA binding site and in the 50S ribosomal proteins of the peptide translocation centre may also cause resistance to linezolid.[37] Initial analyses of the respective genes indicated various previously published and new mutations in the present isolates.

The emergence of *cfr*-mediated linezolid resistance in *S. epidermidis* at German hospitals requires special attention, given that the resistance plasmid may be transferred to HA-MRSA or others via horizontal transfer (plasmid hospitalism).

Conclusion

The MRSA rate in *S. aureus* infections suggests a downward trend in Germany. However, this decline is counterbalanced by a substantial increase in the rates of multi-resistant gram-negative bacteria (3MRGN, 4MRGN) and VRE. The dynamic emergence and spread of CA-MRSA clones requires further attention, especially the import of rare variants (e.g. ST772) and the tendencies in the prevalence of LA-MRSA. The zoonotic reservoir continues to play a significant role in the introduction of new mec variants (*mecC*) and resistance genes such as *cfr*. The large-scale use of second-line antimicrobials requires timely detection and characterisation of still-rare types of resistance to linezolid, tigecycline and daptomycin.

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Livestock-associated MRSA in Germany: State of research and risk of zoonotic infections

As causative agents of healthcare-associated human infections (hospital-acquired MRSA, HA-MRSA), methicillin-resistant *Staphylococcus aureus* (MRSA) have been representing a continuing challenge in diagnostics, therapy and hospital hygiene for many decades. Additionally, infections in the general population caused by so-called community-associated MRSA (CA-MRSA), which are very often characterised by the capability of producing Panton-Valentine leukocidine (PVL), have emerged in Germany, although they continue to be rare. In Germany, the average MRSA prevalence is approx. 1.5–2.5% in patients on admission to inpatient care, 3–5% in point prevalence surveys at hospitals and 0.5–2% in the general population.[1]

The first MRSA infections in livestock, e.g. dairy cattle (mastitis), were reported as early as the 1970s. Since about 2004, the MRSA detection rate in livestock has, however, increased significantly, entailing the coinage of the term "livestock-associated MRSA" (LA-MRSA). Today we know that approx. 50–70% of all German pig farms grow animals colonized by LA-MRSA. Furthermore, LA-MRSA in Germany have been isolated in primary production from flocks of laying hens (1.4%), broilers (0.7%) and dairy cattle (4.1%) in primary production as well as from veal calves (35.1%) in abattoirs (based on the data reported by the Federal Institute for Risk Assessment, 2009).

Molecular genetic studies have shown that the majority of LA-MRSA (> 90%) belong to the clonal group of the sequence type ST398 (defined by multilocus sequence typing). Typical and rare genotypic characteristics of the clonal complex (CC) CC398 are presented in Tab. 1. MRSA of the clonal complexes CC9 (*S. aureus* protein A [*spa*] type t1430), CC97 (t3992) or CC5 (t002) are found far less commonly in livestock (based on 2009 DARLink data and 2008 data reported by the European Food Safety Authority).

LA-MRSA prevalence in humans

In Germany, 77–86% of farmers having contact with pigs carry LA-MRSA CC398 and approx. 45% of veterinarians treating livestock are nasally colonised. In family members of farmers who are not exposed directly to the corresponding animals, the MRSA colonisation rate is 4–5%.[2,3] A 0.5–1% MRSA CC398 prevalence was found in the general population in rural regions (Lower Saxony and Münsterland) with no direct livestock contact.[4]

Human LA-MRSA infections

Apparently, LA-MRSA CC398 exhibit a broad host range, which is also the reason why they are capable of colonising not only various animal species but also humans.[5] Regarding the pathogenicity of LA-MRSA CC398 for humans, there are numerous case reports demonstrating that this pathogen is capable to cause a similar range of infections as is known for conventional HA-MRSA. Amongst other infections, cases of surgical site infection, osteomyelitis, pneumonia, otomastoiditis, bacteraemia and endocarditis have been documented in humans.[1] Differences to HA-MRSA may exist in respect of (rare) toxin-mediated diseases (Tab. 1).

In the absence of sufficient data, it has so far not been possible to estimate the epidemiological extent of outpatient LA-MRSA infections (e.g. cutaneous abscesses), especially in exposed groups (occupational infections in farmers and veteri-

Tab. 1: Genotypic and phenotypic characteristics of LA-MRSA ST398

Characteristic	Findings
Multilocus sequence typing (MLST)	ST398 (CC398)
S. aureus protein A (*spa*) types	t011, t034, t108, t567, t571, t1451, t2011, t2510; less commonly: t571, t1250, t1255, t1344, t1456, t1580, t2330, t2346, t2576, t2970
Typical *Staphylococcus* cassette chromosome *mec (SCCmec)* elements	IV, V
Typical accessory gene regulator gene (agr) and capsule types	*agr* type I, capsular type 5
Typical antibiotic resistance phenotype (percentage of isolates tested resistant)	Tetracycline (99%), trimethoprim (40–50%), gentamicin (35–45%), macrolides/lincosamides (25–30%), quinolones (less commonly)
Genes of typical adhesion factors (microbial surface components recognising adhesive matrix molecules of the host, MSCRAMM)	*bbp, clfA, clfB, cna, ebh, ebpS, eno, fib, fnbA, fnbB, map, sdrC, sdrD, vwb*
Special, rarely detected virulence factor genes	Genes encoding the Panton-Valentine leukocidin (PVL, *lukF-PV* and *lukS-PV*), enterotoxin and enterotoxin-like genes (*seb, sek, seq*)

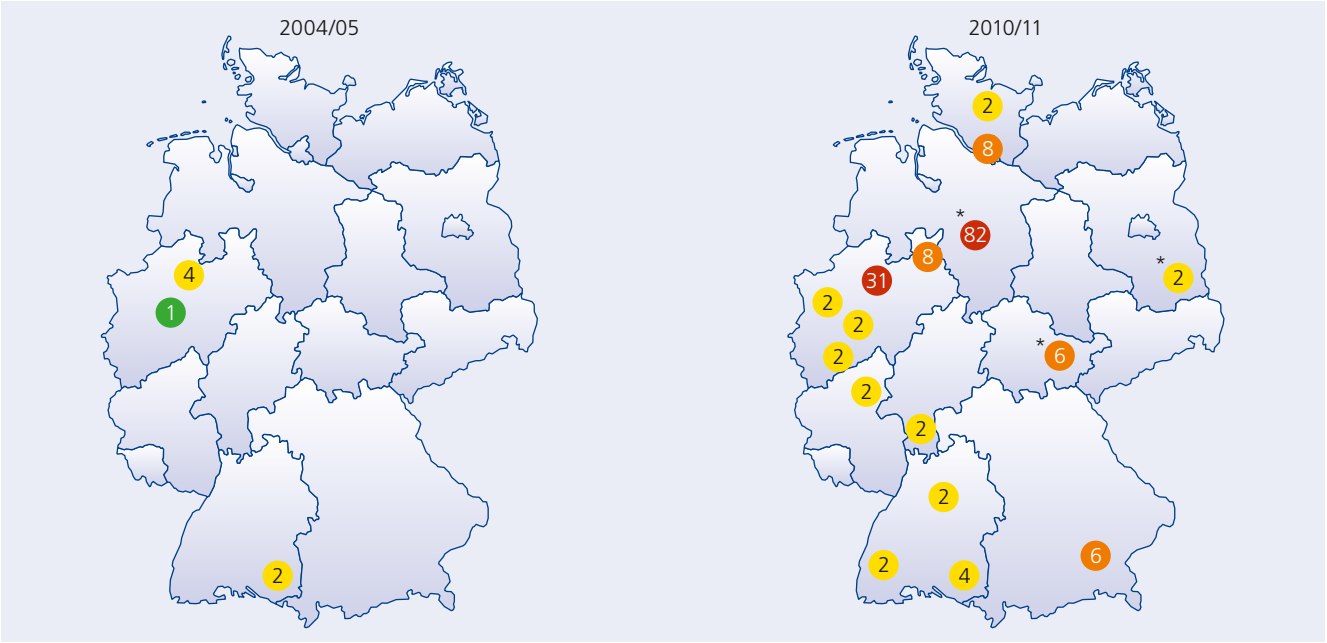

Fig. 1: Distribution and spread of LA-MRSA in Germany in comparison between 2004/05 and 2010/11. The figures indicate the prevalence (%) at the corresponding study centres (green, 1%; yellow, 2–5%; orange, 6–10% and red, > 10%); the asterisks mark Länder in which only one study centre was included and which are thus not necessarily representative[7] [Copyright© American Society for Microbiology. Journal of Clinical Microbiology 2012; 50:3186-92]

narians) in Germany. A random sample of 314 staphylococcal isolates from the period 2007–2011 at the National Reference Centre for Staphylococci revealed an approx. 17% LA-MRSA rate in deep skin and soft tissue infections.[6]

Specific figures on the prevalence of LA-MRSA infections in Germany are currently available mainly for hospital-associated infections. A multicentre study investigating the dynamics of the clonal composition of MRSA has shown that the percentage of LA-MRSA in all MRSA from hospitals increased significantly from 0.3% in 2004 to 5.4% in 2011 (OR = 22.67, 95% CI = 8.51–85.49, $p < 0.0005$), with rural regions in Northwestern Germany with a high density of pig, cattle and poultry farming being predominantly affected (Fig. 1).[7] Between 2008 and 2012, for example, the average percentage of LA-MRSA CC398 in all MRSA from screening tests at 40 hospitals within the EurSafety Health-net project (www.eursafety.eu), based in a livestock-dense region of North Rhine-Westphalia, was 23% (n=9,414). During the same study period, MRSA CC398 at these hospitals also represented 8% of all MRSA from blood cultures (n=194), 11% of all MRSA from deep wound swabs (n=331) and 14% of all MRSA from respiratory secretions (n=346).[8] This data suggests that LA-MRSA CC398 predominate mainly in regions with a high density of livestock farming.

Transmissibility at care facilities

Regarding the nosocomial transmissibility of MRSA CC398 (human-to-human), a Dutch study investigating the transmission rates of LA-MRSA compared to conventional HA-MRSA has found that the transmissibility of MRSA CC398 at hospitals is 5.9 times lower.[9] The reasons for this are unknown, but might be associated with bacterial or host-specific factors. The latter is suggested by data showing that patients admitted with LA-MRSA stay shorter at the hospital and less frequently require intensive care and invasive interventions; factors, which may have an influence on the probability of transmission.[10]

On the other hand, however, there have already been reports of MRSA CC398 outbreaks at hospitals and nursing homes in the Netherlands and other countries. As part of a Dutch survey, MRSA CC398 were detected in 1/853 (0.1%) of the hospital staff, 4.4% of whom had direct contact with pigs or calves.[11] A case-control study in North Rhine-Westphalia has shown that 31% of all patients who were admitted to a university hospital with MRSA CC398 are not exposed to any risk factors to suggest that they have been infected in agriculture.[12] The evaluation of data reported by a Dutch national surveillance system has also demonstrated that the number of MRSA CC398 detections that cannot be explained by livestock contact is increasing. These findings suggest that MRSA CC398 can also spread between humans in the general population, at care facilities or via other indirect routes of transmission.

Transmission via meat and/or dust from animal stables

As evidenced by German data, MRSA can be found in 16% of pork samples, 13% of veal samples and 42% of turkey samples obtained from retailers (based on the 2009 data reported by the Federal Institute for Risk Assessment). In the thawing water of broiler poultry, MRSA were detected in 30% of the samples. Given the above-mentioned low prevalence of enterotoxin-producing LA-MRSA, however, the risk of food poisoning can be classified as low. The risk of transmission to consumers (contact with uncooked meat) is more difficult to estimate. Given the low bacterial count of the pathogen in the meat products, German and European food safety authorities assume a low risk of transmission.

However, pertinent final analysis and risk assessment are not available yet.

Regarding the transmissibility of LA-MRSA via dust from animal stables, it has been documented that in samples obtained at ground level the pathogen can be detected up to a distance of 300 m in exhaust air and up to a distance of 150 m from stables (in a concentration of 2–14 CFU/m³).[13] However, a study from Lower Saxony has demonstrated that living or working at a distance of less than 500 m from an animal stable is not associated with an increased risk of LA-MRSA colonisation. Among persons who are not exposed to animals themselves, significant risk factors for the transmission of MRSA CC398 included family members with livestock contact (OR 3.8) and private visits to animal farms (OR 3.2).[4] In this respect, there is currently no direct evidence to suggest that the amount of MRSA escaping from the exhaust air of animal stables is sufficient to be transmit LA-MRSA to humans or animals. The significance of MRSA dust sedimentation in areas near stables, has, however, not yet been clarified.

Animal LA-MRSA infections

Despite the high colonisation rates of livestock with LA-MRSA ST398, infections occur only rarely; however, cases of mastitis in cattle as well as surgical site infections have been reported. In recent years, MRSA CC398 have nevertheless been increasingly detected as part of outbreaks of nosocomial infections (surgical site infections) at equine hospitals. During an outbreak of surgical site infections, for example, CC398-associated *spa* types were isolated from all seven horses at a Dutch veterinary teaching facility.[14] In most of these outbreak situations, the staff were also found to carry MRSA CC398. The zoonotic routes of transmission of MRSA CC398 between livestock and horses on the one hand and horse owners and veterinary staff on the other are (often) not clear.

Research

There is particular need for research regarding the role of LA-MRSA in outpatient infections in persons with and without exposure to livestock. In addition, many questions concerning prevention strategies have not been clarified (e.g. prevention of spread in the livestock reservoir, e.g. through vaccinations, prevention of infections in animals and humans; possibly prevention of spread in the general population without animal contact; prevention of occupational infections in farmers).

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Regional differences in the resistance of *Staphylococcus aureus* to methicillin (MRSA) within Lower Saxony

Introduction

Studies have shown that the antimicrobial prescribing behaviour differs between the Länder and even between rural districts.[1-3] These variations in prescribing behaviour and demographic structures (e.g. population density, age distribution) in the catchment area of inpatient and outpatient care facilities as well as regional living conditions may have an influence on the antimicrobial resistance situation. The data reported by EARS-Net already reveals significant differences between the participating German hospitals.[2] Moreover, Kohlenberg et al. demonstrate differences in the incidence of infections with multidrug resistant organisms for five regions of Germany.[4]

It is therefore important to know both the national and regional resistance situation. In addition, regional data collection can raise awareness of direct involvement, prompting a faster local response.

Regional data for Lower Saxony is provided by the Antimicrobial Resistance Monitoring in Lower Saxony (ARMIN). The recording of the 2-digit postcode area of the reporting hospitals and private practices makes it possible to investigate the resistance situation at regional level while ensuring the anonymity of the reporting facilities.

The first regional evaluation was aimed at investigating the differences in the resistance of *Staphylococcus (S.) aureus* to methicillin (MRSA). Besides the MRSA prevalence in the individual postcode areas, it was investigated whether livestock-associated MRSA (LA-MRSA) have a higher prevalence in regions of Lower Saxony with a higher livestock density compared to regions with a lower livestock density.

Methodology

Twelve participating laboratories transmit the results of their susceptibility tests for 14 selected infectious agents once a year in anonymised form to the Governmental Institute of Public Health in Lower Saxony (NLGA). The age and sex of the patients as well as information about the reporting facility (nursing ward, intensive care unit, private practice) and its 2-digit postcode are recorded for each identified pathogen. Nursing wards and intensive care units are consolidated to determine the resistance levels in inpatient care.

The MRSA prevalence, i.e. the percentage of methicillin-resistant *S. aureus* in all *S. aureus*, is determined by calculating the resistance to oxacillin. Pathogens detected in screening specimens and swabs from the upper respiratory tract are excluded, and only one detected pathogen per patient within 365 days is included in the analysis.

MRSA of the clonal lineage ST398 are considered to be LA-MRSA. However, the data collected within ARMIN does not contain any information on clonal typing. Unlike HA(hospital acquired)-MRSA, in which tetracycline resistance is currently rather rare, LA-MRSA strains are usually resistant to tetracycline, which is why the resistance of all MRSA to tetracycline was selected as an indicator for the identification of LA-MRSA. All methicillin-susceptible *Staphylococcus aureus* (MSSA) were also tested for susceptibility to tetracycline.

Unless stated otherwise, the term MRSA in the following sections is understood to be the entirety of all MRSA (without distinguishing between HA- and LA-MRSA).

The regional evaluation refers to pathogens detected in 2011.

Results

In inpatient care (approx. 11,200 *S. aureus* tests/year available in ARMIN), the percentage of MRSA in all *S. aureus* increased from 21.0% in 2006 to 23.4% in 2009 (Fig. 1). In 2010, the percentage of MRSA was 24.0% and dropped for the first time in 2011 (21.5%). The evaluation of data from intensive care units (approx. 1,700 tests/year) shows a decline between 2009 and 2011 (from 31.0% to 28.1%). Since 2006, the percentage of MRSA in blood cultures (approx. 1,400 tests/year) declined clearly from 28.8% in 2006 to 23.2% in 2011. In outpatient care (approx. 10,600 tests/year), the MRSA rate has increased slightly over the course of the years (from 9.2% in 2006 to 11% in 2010).

The regional analysis reveals significant differences (Fig. 2). Accounting for more than 25%, the highest MRSA rate in inpatient care is observed in the postcode areas 30 and 37, followed by the postcode areas 31 and 38, i.e. central and southern Lower Saxony. The postcode area 49 (southern Weser-Ems region) also exhibits an MRSA rate of more than 20%. The high MRSA prevalence in central and southern Lower Saxony coincides with regions with a high population density and a high proportion of older inhabitants. This does not apply to the postcode area 49. This predominantly rural region has significantly fewer and rather younger inhabitants. The western part of Lower Saxony is characterised by intensive livestock farming (cf. GERMAP 2008, p. 26). Pig farming is practiced most intensively in the southern Weser-Ems region (Fig. 3). In the postcode area 49, 22.6% of the MRSA isolates are additionally resistant to tetracycline; these

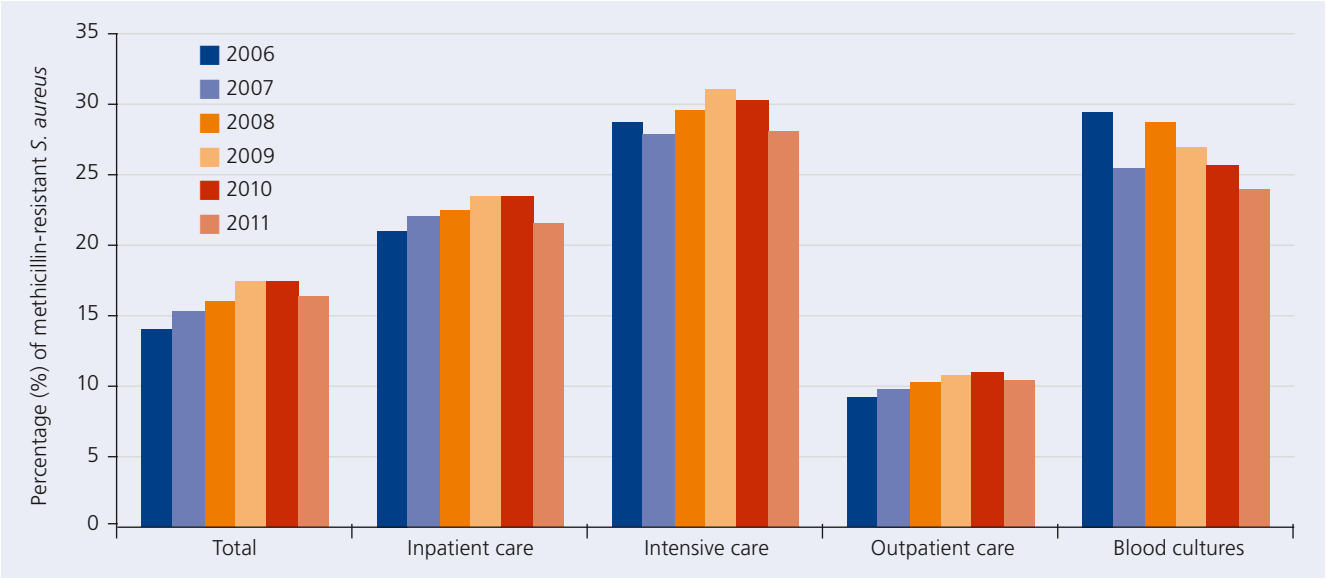

Fig. 1: Development of the percentage of methicillin-resistant *S. aureus* in all *S. aureus* for various submitter groups as well as blood cultures (inpatient care = nursing wards & intensive care units)

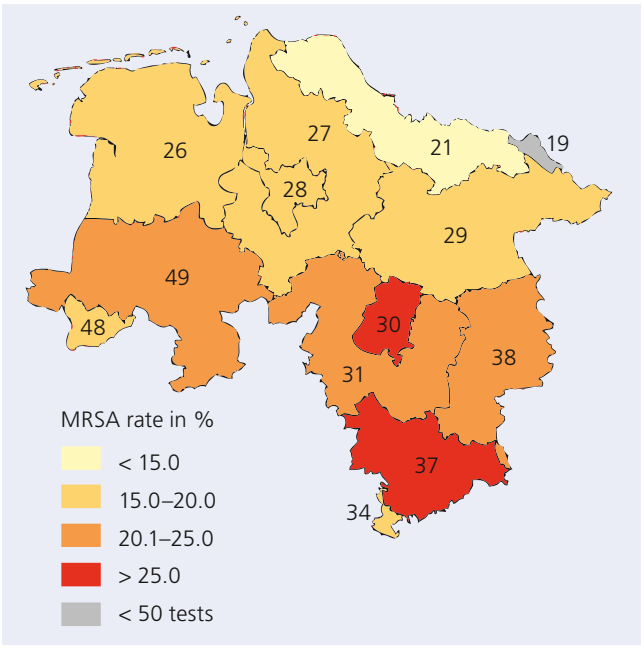

Fig. 2: Percentage of methicillin-resistant *S. aureus* in all *S. aureus* (MRSA rate) in the postcode areas of Lower Saxony, nursing wards & intensive care units, ARMIN 2011)

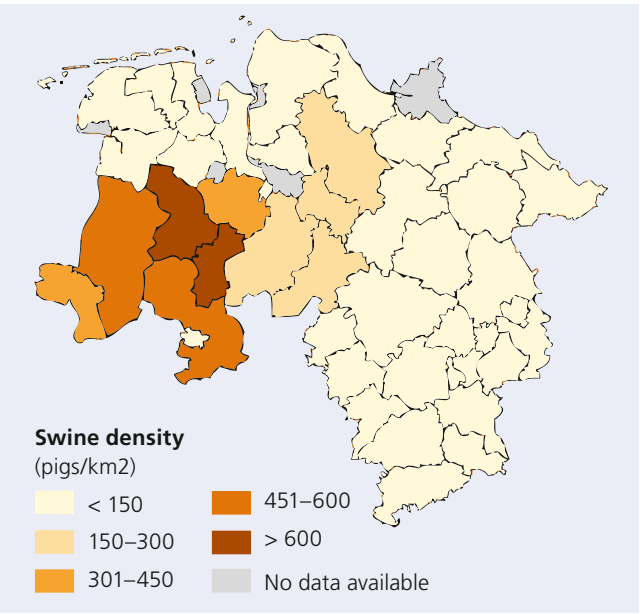

Fig. 3: Swine density (pigs/km^2) in the districts and independent cities of Lower Saxony, Bremen and Hamburg. Data source: Federal and State Statistical Offices: Agricultural Census – Main Survey (01/03/2010)

isolates are most likely to be LA-MRSA (type ST398). In contrast, all other postcode areas with a high MRSA prevalence show tetracycline resistance rates of less than 10% (Fig. 4). By comparison, there are no noteworthy regional differences in the percentage of tetracycline-resistant MSSA in all MSSA: It ranges between 1.9% in the postcode area 21 and 4.9% in the postcode areas 48 and 27.

Discussion

The laboratories participating in ARMIN serve more than 70% of all hospitals in Lower Saxony; in the single postcode areas, this rate varies between 40% and 100%. When taking MRSA isolated from invasive specimens reported by Lower Saxony in accordance with the Infection Protection Act (IfSG) as reference parameters, it becomes apparent that the 2011 data available in ARMIN represents nearly 70% of all MRSA isolated from blood cultures and cerebrospinal fluid and reported in accordance with the IfSG. The data collected within ARMIN can thus be considered representative of Lower Saxony.

Regional evaluations involve the problem of observer bias. For example, the laboratories participating in ARMIN take different breakpoints as a basis and use devices of different manufacturers for susceptibility testing. The submitted data contains no MIC values, only the interpreted result of the susceptibility test (susceptible, intermediate, resistant), as communicated by the laboratories to the facilities in their report. By means of a differentiated data analysis, however, it was largely excluded that these factors have an influence on the regional differences. None of the postcode areas is covered by only one laboratory, and the analysis of individual laboratories demonstrated similar regional differences as the overall data

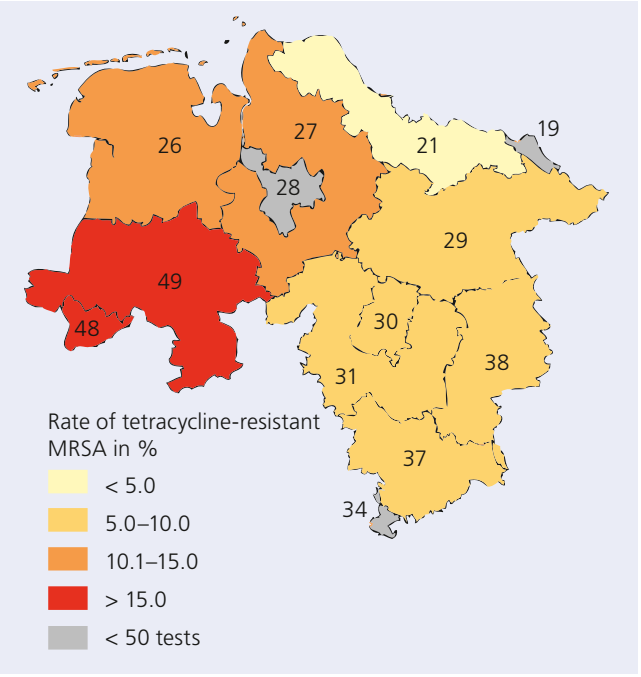

Fig. 4: Percentage of MRSA with additional resistance to tetracycline in the postcode areas of Lower Saxony, nursing wards & intensive care units, ARMIN 2011)

analysis. With the exception of the tetracycline tests of MRSA in the postcode areas 34 and 28, more than 50 pathogen isolates were available in all postcode areas.

LA-MRSA can only be identified on the basis of the ARMIN data by using tetracycline resistance as an indicator. Consequently, the rare cases where HA-MRSA also show resistance to tetracycline are classified incorrectly. However, this error appears to be negligible for the evaluation of regional differences regarding LA-MRSA and for monitoring the development over the years.

The results are consistent with studies that indicate an association between LA-MRSA and pig farming.[5-7] As part of an MRSA point prevalence study in the Osnabrück area, 3,266 hospital patients nasally colonised with MRSA were examined and an MRSA prevalence of 3% was ascertained.[8] By means of subsequent typing, 23% of these isolates were classified as ST398. The ARMIN data for the postcode area 49 presented here (22.6%) is within the same magnitude; however, it does not include screening specimens. Köck et al.[9] also found a 23% prevalence in screening specimens for the period 2008–2012.

Based on these initial results, the analysis of the regional resistance situation appears very useful, and data from ARMIN can be used to analyse the regional resistance situation in Lower Saxony. The geographical proximity between the laboratories participating in ARMIN offers the additional advantage of enabling communication and networking between the laboratories, thereby permitting effective quality management.

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4.1.3. *Enterococcus* spp.

As inhabitants of the intestinal tract, the gram-positive, catalase-negative enterococci are part of the natural intestinal flora of animals and humans, but can also cause a number of infections of varying severity: urinary tract infections, surgical site infections (especially in the abdominal area; often polymicrobial), and even bloodstream infections and endocarditis. Occasionally, enterococci are also found in the vaginal flora and the biliary tract, but only rarely in the oropharynx. Infections predominantly affect premature infants and newborns, elderly patients as well as patients with an underlying disease and/or immunosuppression. Especially in highly developed countries, where people are becoming older through medical progress (often patients with multiple diseases) while new invasive therapeutic options are being established, this leads to a rising number of patients exposed to a high risk of developing enterococcal infections. However, (enteric) colonisations with these bacteria occur more commonly than infections, the approximate ratio being 9:1.

Enterococci are usually characterised by incomplete haemolysis (α-haemolysis) and are also capable of multiplying in extreme environmental conditions: within a broad pH range (pH 4.6 to 9.9), at temperatures between 5°C and 50°C (optimum: 42.7°C; but they also survive for 30 minutes at 60°C) and at a 6.5% sodium chloride concentration or a 40% bile salt concentration.[1,2] Furthermore, these bacteria are resistant to desiccation and can survive on abiotic surfaces, which is relevant for preventive hygiene measures at hospitals.

Enterococci are the second to third most common causative agents of hospital-associated bacterial infections (nosocomial infections). Among the currently known 37 enterococcal species, *Enterococcus (E.) faecalis* and *E. faecium* have the highest clinical relevance: *E. faecalis* is responsible for 60–95%, *E. faecium* for 5–40% of all enterococcal infections (and colonisations). The proportion of *E. faecium* compared to *E. faecalis* has been increasing steadily over the last years. As part of five antimicrobial resistance studies, the Paul-Ehrlich-Gesellschaft für Chemotherapie e.V. (PEG) also found that the proportion of *E. faecium* isolates (in relation to all tested enterococcal strains) has increased as follows: 9.3% (1998) → 15.7% (2001) → 24.4% (2004) → 33.9% (2007) → 41.4% (2010).[3]

The prevalence of these two major enterococcal species at hospitals can be influenced by the following factors: a) type of the respective hospital and its departments, b) pool of patients at the respective hospital (rising number of older and/or immunosuppressed patients who are primarily affected), c) antimicrobial selection pressure prevailing at the hospital and/or in the respective department, d) inadequate implementation of hygiene measures on emergence of multidrug resistant bacterial strains, e.g. vancomycin-resistant enterococci (VRE), which mostly belong to the species *E. faecium*.

Further risk factors for infections or colonisations of patients with enterococci (in particular with the two species mentioned above, including VRE) include previous treatment with antimicrobials that exhibit an "enterococcal gap" (drugs to which enterococci are intrinsically resistant, e.g. all cephalosporins, see below). In addition, longer hospital stays involving varied antimicrobial chemotherapies, severe underlying diseases as well as intraabdominal or cardiac/thoracic surgical procedures can be named as risk factors for enterococcal/VRE infections. Staying in specific hospital units (surgical departments with and without an intensive care unit, internal medicine, haematology/oncology, urology/nephrology, neonatology, transplantation units) is also associated with a high risk of enterococcal/VRE colonisations or infections. The emergence and spread of these pathogens is also facilitated by inadequate standard hygiene, medical staff (including physicians) as potential carriers and contact of patients with other patients colonised or infected with enterococci/VRE as well as with medical devices or surfaces in the patient environment contaminated with these microorganisms (as a consequence of the high environmental persistence of enterococci).

Trends in resistance development

Enterococci exhibit both natural (intrinsic) and acquired resistance to a great number of antimicrobials.

Natural resistance in enterococci affects all cephalosporins, semi-synthetic penicillins (e.g. oxacillin), monobactams, aminoglycosides (low-level resistance type), lincosamides (most of them), polymyxins, streptogramins (e.g. quinupristin/dalfopristin in *E. faecalis*, but not in *E. faecium*) and in individual species vancomycin (low-level resistance of *E. gallinarum, E. casseliflavus*).

Acquired resistance in enterococci can additionally affect the following antimicrobials: ampicillin (especially in *E. faecium*), macrolides, tetracyclines, aminoglycosides (high-level resistance type), chloramphenicol, fluoroquinolones, glycopeptides (especially *E. faecium*: most notably type VanA, in recent years increasingly type VanB), streptogramins (e.g. quinupristin/dalfopristin in *E. faecium*), oxazolidinones (linezolid) and glycylcyclines (tigecycline). However, enterococci resistant to the latter antimicrobials of last resort have so far occurred rarely or extremely rarely until now.[4,5] The in-vivo activity of daptomycin as a therapeutic agent is subject to some controversy or there is sometimes a lack of clinical experience with this antimicrobial. EUCAST (European Committee on Antimicrobial Susceptibility Testing) also does not define any clinical MIC breakpoints, only a wild-type epidemiological cut-off (ECOFF) value of ≤ 4 mg/l. Based on this ECOFF value, out of the more than 3,550 enterococcal isolates tested for susceptibility to daptomycin, only one *E. faecium* isolate (0.03%) with a daptomycin MIC of 8 mg/l (as measured by means of the broth microdilution test and the E-test) was found in the enterococci database of the National Reference Centre for Staphylococci and Enterococci located at the Robert Koch Institute Wernigerode. This collection of 3,550 isolates was made up of 10% *E. faecalis* and 89% *E. faecium*, with 87% of the latter species consisting of VRE.

Since the middle of 2003/the beginning of 2004, an increased prevalence of VRE has been observed at many hospitals in various European countries and the occurrence of outbreaks of infections (and colonisations) with these multidrug resistant organisms continues to be of great interest. *E. faecium* is

considered to be the primary reservoir of *vanA*- and *vanB*-mediated glycopeptide resistance. Genotyping of VRE strains from German hospitals by means of SmaI macrorestriction analysis (MRA) has demonstrated an increased prevalence of ampicillin/vancomycin-resistant *vanA*- or *vanB*-positive *E. faecium* strains. Outbreaks of infections and colonisations with these pathogens were characterised at molecular level by means of multilocus sequence typing (MLST) and the strains that occurred were classified into various sequence types of hospital-associated (HA) *E. faecium*.[6] These hospital-associated pathogens, many of these carry virulence markers (*esp* and/or *hyl*),[7, 8] can be spread readily in a hospital environment.[6] The insertion sequence IS*16* that can be identified by means of PCR can be regarded as a suitable marker to recognise the HA-*E. faecium* isolates;[9] these isolates are further characterised by their resistance to ampicillin and their high-level resistance to fluoroquinolones (MIC $_{\text{ciprofloxacin}}$ > 16 mg/l).[10] Such HA-*E. faecium* strains usually become clinically apparent only after acquiring glycopeptide resistance determinants (*vanA* and *vanB* gene cluster, respectively), but are already present as glycopeptide-susceptible precursor strains in hospitals. Such strains can be spread clonally a in hospital and also between different hospitals (even across different Länder) during patient transfers. However, various clones of these multidrug resistant *E. faecium* strains can also occur within one hospital as a result of horizontal gene transfer of the *vanA* or *vanB* gene cluster.

PEG resistance studies

The results of the resistance studies conducted by the Paul Ehrlich Society for Chemotherapy in 1990, 1995, 1998, 2001, 2004, 2007 and 2010 demonstrate that the prevalences of resistances to some antimicrobials in enterococci have increased over the past 20 years.[3]

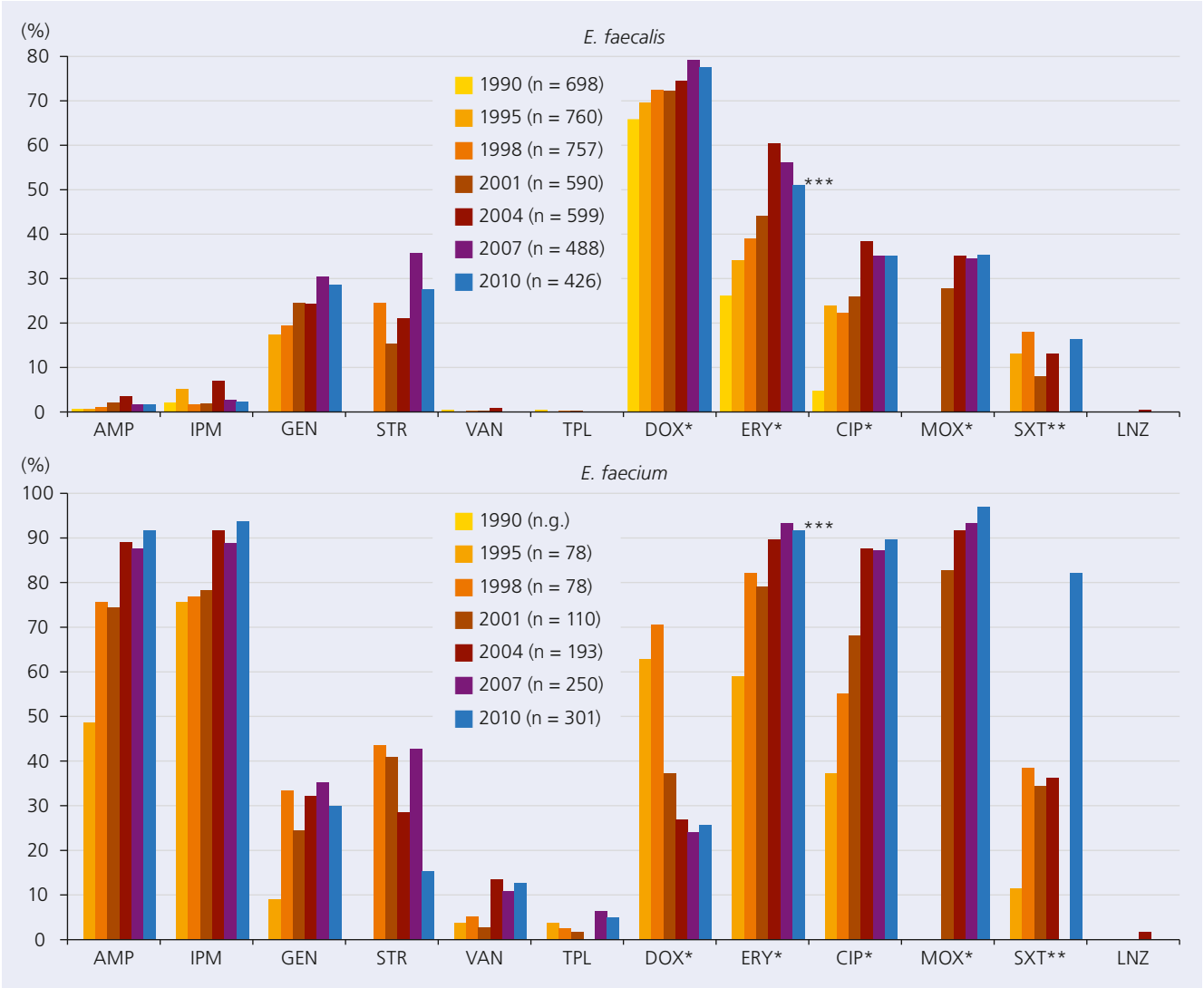


Fig. 4.1.3.1: Prevalence of resistance (%) in *E. faecalis* and *E. faecium* at German hospitals between 1990 (and 1995) and 2010 to selected antimicrobial chemotherapeutics (Source: PEG resistance studies 1990–2010[3])

n.g., not tested; n, number of tested enterococcal isolates; AMP, ampicillin; IPM, imipenem; GEN, gentamicin (high-level resistance, MIC > 500 mg/l); STR, streptomycin (high-level resistance, MIC > 1,000 mg/l); VAN, vancomycin; TPL, teicoplanin; DOX, doxycycline; ERY, erythromycin; CIP, ciprofloxacin; MOX, moxifloxacin; SXT, trimethoprim/sulphamethoxazole (only tested for epidemiological purposes); LNZ, linezolid. * The data for antimicrobials marked with one asterisk is based on the ECOFF values of the wild type (WT≤ x mg/l) of a species to the corresponding antibiotic defined by EUCAST, since EUCAST specifies no clinical breakpoints for these antimicrobials. ** The data only refers to pathogens causing uncomplicated urinary tract infections; the 2007 PEG Study did not provide any data for SXT. *** ECOFF value used in 2010: ≥ 8 mg/l

Among *E. faecalis*, this particularly concerned doxycycline, erythromycin, ciprofloxacin and moxifloxacin (the latter has only been recorded in the PEG studies since 2001); the resistance rates having been determined in each case on the basis of the ECOFF values defined by EUCAST. Antimicrobials for which EUCAST defines no clinical breakpoints were classified on the basis of these ECOFF values in the 2010 resistance study.[11,12] In 2007, 30.3% and 35.7% of the *E. faecalis* strains exhibited high-level resistance to gentamicin and streptomycin, respectively, but this rate declined slightly in 2010 (28.4% and 27.5%, respectively). Throughout the entire period of observation, hardly any ampicillin-, imipenem-, glycopeptide- and linezolid-resistant isolates were detected among these species (Fig. 4.1.3.1).

By contrast, the rate of ampicillin-resistant *E. faecium* increased significantly between 1995 (49%) and 2010 (91.7%), with the rate of vancomycin resistance increasing over the same period, although at a considerably lower level (1995: 3.8%; 1998: 5.1%; 2004: 13.5%; 2007: 11.2%; 2010: 12.6%). Additionally, the rates of teicoplanin resistance in 2007 and 2010 were 8.8% and 5.0%, respectively, indicating a slight increase in the prevalence of vancomycin resistance with a simultaneous drop in the prevalence of teicoplanin resistance in 2010 compared to 2007. This suggests an increased prevalence of *vanB*-positive *E. faecium* strains that are resistant to vancomycin but are susceptible to teicoplanin, as has been observed at hospitals in various European countries. The increase in the overall VRE prevalence is apparently associated with the spread of the above-mentioned *vanA*- or *vanB*-positive HA-*E. faecium* strains showing resistance to ampicillin and high-level resistance to ciprofloxacin starting in mid-2003. The high levels of resistance to erythromycin, ciprofloxacin and moxifloxacin in *E. faecium* were also observed to have increased further; in the absence of clinical MIC breakpoints, these antimicrobials were also classified in 2010 based on the ECOFF values defined by EUCAST (as was the case with *E. faecalis*). However, an ECOFF value deviating by one MIC level was used in 2010 to assess the significance of the prevalence of erythromycin resistance, because the value defined by EUCAST would share the MIC values of the wild population. The prevalence of doxycycline resistance in *E. faecium* dropped (similarly to *E. faecalis*) dramatically (also based on the ECOFF values) from 62.8% in 1995 to 26.9% in 2004; in 2007 and 2010, the resistance rate was 24.0% and 25.6%, respectively.

Linezolid-resistant enterococci were only detected in the 2004 PEG study and had a low prevalence of 0.3% in *E. faecalis* and 1.6% in *E. faecium* isolates (however, subsequent tests only confirmed their presence in one *E. faecium* strain).

In addition to the above-mentioned single resistance of *E. faecalis* and *E. faecium* to relevant antimicrobials, resistance patterns of transferable multidrug resistance in enterococci to ampicillin, gentamicin (high-level resistance), streptomycin (high-level resistance), vancomycin and teicoplanin tested in the PEG studies from 1998 to 2007 as well as in 2010 have also been reported since the 2010 GERMAP report (Fig. 4.1.3.2). This data demonstrates that in 2010: a) a high percentage (> 50%) of *E. faecalis* isolates are still susceptible to these clinically relevant antimicrobials tested in the PEG studies, b) multidrug resistance (involving up to five antimicrobials) is widespread, especially in *E. faecium* and c) ampicillin resistance (total resistance rate made up of ampicillin resistance alone and in combination with other antimicrobials) of *E. faecium* increased from 75.6% to 91.7% over the period of observation. Furthermore, the multidrug resistance patterns of *E. faecium* became considerably more varied in the course of the period 1998–2010, while the percentage of susceptible *E. faecium* isolates dropped from 15.4% in 1998 to 6.6% in 2010 (Fig. 4.1.3.2, bottom row). The prevalence of multidrug resistance in *E. faecalis* also increased over this period (although to a lesser extent), so that the percentage of susceptible isolates dropped from 65.9% in 1998 to 52.7% in 2007, however, increased again slightly to 62.4% in 2010. The total ampicillin resistance rate of *E. faecalis* is (so far) still very low, ranging between 0.9% and 3.3% in the five evaluated PEG studies (1.6% in both 2007 and 2010; Fig. 4.1.3.2, top row).

GENARS

The German Network for Antimicrobial Resistance Surveillance (GENARS) was a network of medical microbiology laboratories established to monitor the antimicrobial resistance of important bacterial pathogens at German hospitals during the period 2002–2006, which was also documented in the 2008 and 2010 GERMAP reports. The GENARS system was replaced by the ARS system in 2008.

ARS

By establishing the Antimicrobial Resistance Surveillance (ARS) network in Germany, a representative, comprehensive monitoring of antimicrobial resistance of clinically relevant bacterial pathogens has been created, covering not only the inpatient but also the outpatient care sector. This makes it possible to continuously record the resistance data of medically relevant bacteria collected in the course of the routine work of laboratories of medical care facilities and private practices. In Germany, the DIN standard 58940 "Susceptibility testing of microbial pathogens to antimicrobial agents" of the Medicine Standards Committee and the US standard of the Clinical Laboratory Standards Institute (CLSI) are being applied simultaneously.[13–16] ARS does not specify which standard is to be used for susceptibility testing and it accepts both qualitative interpretations (classifications: susceptible, intermediate and resistant) and quantitative susceptibility test results (measured MIC values). The evaluations are method-specific, i.e. the results of the susceptibility tests interpreted on the basis of different standards are not mixed with each other. However, ARS strongly encourages the participating laboratories to transmit the results as measured MIC values in order to enable better comparability of the data with other resistance monitoring systems and a swifter response regarding the interpretation of MIC results in the event that MIC breakpoints are adapted. Moreover, the results obtained by ARS can be used to make statements on various structural parameters of healthcare and on regional differences as well as on the epidemiology of antimicrobial resistance in Germany.[17]

Fig. 4.1.3.3 compares the annual antimicrobial resistance data of ARS from 2008 to 2012 for *E. faecalis* and *E. faecium* from the inpatient care sector (all wards) with that of the outpatient care sector. At present, the ARS system can identify multidrug resistant strains on request and provides online information on multidrug resistance in clinically relevant,

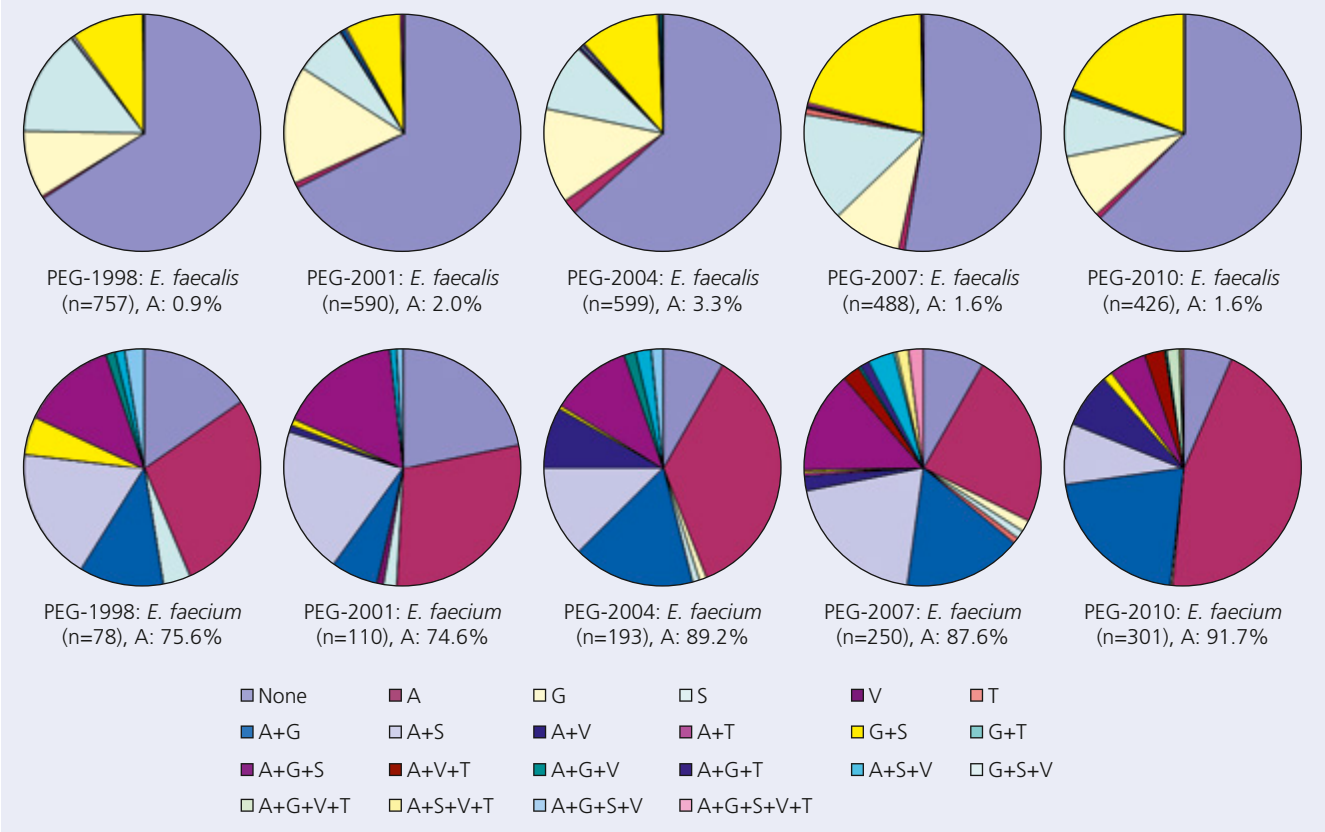


Fig. 4.1.3.2: Prevalence of single and multi-drug resistance to various therapeutically relevant antimicrobials in *E. faecalis* (top row) and *E. faecium* (bottom row) isolates obtained from the resistance studies conducted by Paul Ehrlich Gesellschaft für Chemotherapie e. V. (PEG) in 1998, 2001, 2004, 2007 and 2010 (Source: PEG resistance studies 1990 to 2010)

Resistance to: A, ampicillin; G, gentamicin (high-level resistance); S, streptomycin (high-level resistance); V, vancomycin; T, teicoplanin; none, none of these antimicrobials. The above colour symbols for single and multi-drug resistance rates arranged line by line from left to right correspond to the order of these (multi-drug) resistance rates in the pie charts starting from the top centre and continuing clockwise. In addition, the prevalence of ampicillin resistance in *E. faecalis* and *E. faecium* (total ampicillin resistance calculated on the basis of the single and multi-drug resistance) in the individual years of the PEG resistance studies is indicated below each pie chart.

gram-negative nosocomial bacteria. As expected, there are significant differences in resistance rates to nearly all antimicrobials between isolates from inpatient care and those from outpatient care within the respective enterococcal species during the period 2008–2012, as shown in Fig. 4.1.3.3.

Whereas in inpatient care the rates of resistance (high-level resistance) to the aminoglycosides gentamicin and streptomycin in *E. faecalis* were relatively stable, ranging around 40%, a (slow) increase in resistance rates from 13.8% to 25.3% (gentamicin) and from 28.5% to 32.8% (streptomycin; however, it dropped again to 29.4% in 2012) was observed in isolates from outpatient care. The resistance rates of *E. faecalis* from outpatient care to the fluoroquinolones levofloxacin (12.5% → 24.5%) and moxifloxacin (17.2% → 32.5%) were also subject to a slow increase; in inpatient care, the resistance rates rose from 35.9% → 50.5% (levofloxacin) and from 36.5% → 47.7% (moxifloxacin). The resistance rates of *E. faecalis* to ampicillin, amoxicillin, vancomycin, teicoplanin and linezolid were mostly far below 1% in both care sectors.

The situation was different with *E. faecium* isolates obtained from inpatient and outpatient care between 2008 and 2012 (top and bottom right of Fig. 4.1.3.3). The rate of ampicillin and amoxicillin resistance in *E. faecium* from inpatient care ranged between 92.0% and 96.6%, whereas the rate of ampicillin resistance in isolates from outpatient care rose from 60.7% to 80.7% over the same period. A slow increase in resistance rates of *E. faecium* isolates from outpatient care was observed for gentamicin (27.9% → 35.8%) and streptomycin (52.8% → 65.3%), whereas the rates of isolates from inpatient care dropped over the period of observation 2008–2012 (gentamicin 49.6% → 37.1% and streptomycin 78.2% → 70.4%). High resistance rates to levofloxacin and moxifloxacin, ranging between 85.0% and 94.4%, were documented for *E. faecium* from inpatient care, whereas the rates of isolates from outpatient care mostly ranged between 42.0% and 74.3% (however, with a peak of 90.7% in 2008: 98 of 108 isolates). The rates of glycopeptide resistance increased as well, from 16.2% to 19.1% for vancomycin and from 7.8% to 11.2% for teicoplanin in *E. faecium* isolates from inpatient care as well as from 9.3% to 19.8% for vancomycin und from 4.1% to 6.5% for teicoplanin in *E. faecium* isolates from outpatient care. The already fairly high vancomycin resistance rate of 19.8% in outpatient care suggests that patients take VRE isolates with them into outpatient care when they are discharged. At the same time, these significantly higher rates of resistance to vancomycin compared to teicoplanin also suggest an increased prevalence of *vanB*-positive isolates in both sectors. When such VRE-carrying patients are hospitalised again, these multidrug resistant organisms are brought back to the hospital. Both enterococcal species exhibited very low rates of linezolid resistance, ranging between 0.1% and 1.1% in both care sectors.

Fig. 4.1.3.4 shows the annual prevalence of resistance in *E. faecalis* and *E. faecium* blood culture isolates obtained from hospital patients between 2008 and 2012. Regarding *E. faecalis* isolated from blood cultures, the antimicrobial treatment options were very good to satisfactory because of the extremely low rates of resistance to ampicillin (0.4–1.2%), vancomycin (0.0–1.0%), teicoplanin (0.0–0.7%) and linezolid (0.0–0.8%) during this period as well as the so far still moderate rates of high-level resistance to the aminoglycosides gentamicin (43.6–53.4%) and streptomycin (41.6–58.7%). The situation was different with *E. faecium*: Because of the extensive resistance to ampicillin (95.1–97.7%), the therapeutic combination with aminoglycosides was not active in nearly all *E. faecium* isolates (no synergistic therapeutic effect). In addition, the prevalences of high-level resistance to gentamicin ranged between 34.2% and 49.7% and those to streptomycin were significantly higher (72.0–81.0%). Moreover, resistance rates of 17.8% for vancomycin and 11.3% for

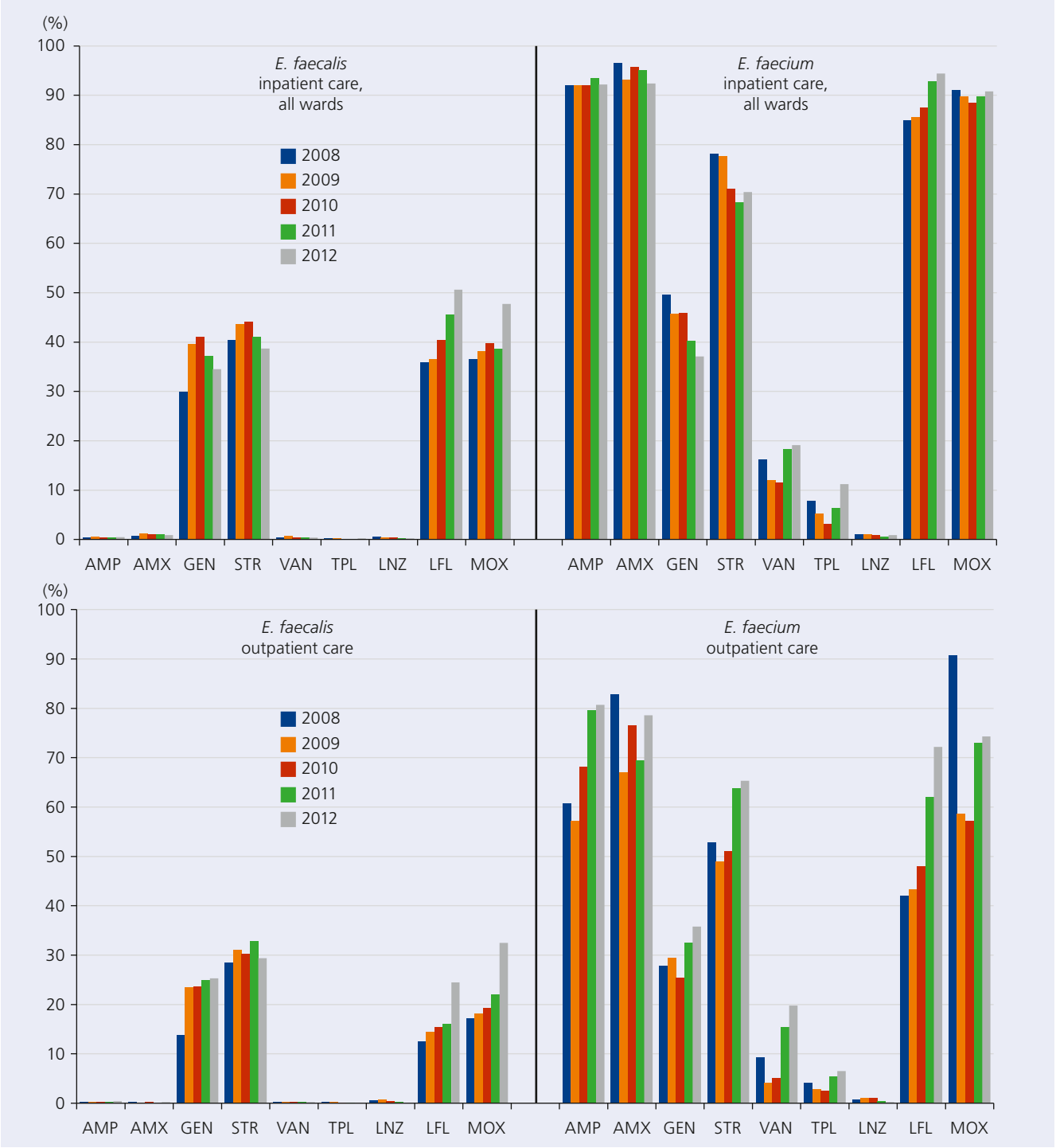


Fig. 4.1.3.3: Prevalence of resistance in *E. faecalis* and *E. faecium* from inpatient (all wards, top) and outpatient (bottom) care between 2008 and 2012 (Source: Robert Koch Institute, ARS, http://ars.rki.de[17])

AMP, ampicillin; AMX, amoxicillin; GEN, gentamicin (high-level resistance); STR, streptomycin (high-level resistance); VAN, vancomycin; TPL, teicoplanin; LNZ, linezolid; MOX, moxifloxacin. It is difficult to specify the number of isolates tested within ARS, since varying numbers of isolates were tested in the four years under review and for each antimicrobial chemotherapeutic. If you wish to receive further detailed information concerning this point, please refer to the original literature (Robert Koch Institute: ARS, https://ars.rki.de[17])

Fig. 4.1.3.4: Prevalence of resistance in *E. faecalis* and *E. faecium* from blood cultures of inpatients between 2008 and 2012 (Source: Robert Koch Institute, ARS, http://ars.rki.de[18])

AMP, ampicillin; GEN, gentamicin (high-level resistance); STR, streptomycin (high-level resistance); VAN, vancomycin; TPL, teicoplanin; LNZ, linezolid; LFL, levofloxacin; MOX, moxifloxacin. It is difficult to specify the number of isolates tested within ARS, since varying numbers of isolates were tested in the four years under review and for each antimicrobial chemotherapeutic. If you wish to receive further detailed information concerning this point, please refer to the original literature (Robert Koch Institute: ARS, https://ars.rki.de[18]).

teicoplanin were documented in 2012; these rates and the existing, though (still) low, rate of resistance to linezolid (1.2% in 2012) suggest that few therapeutic options are left. The above-mentioned high rates of resistance to ampicillin and the fluoroquinolones levofloxacin/moxifloxacin suggest that these isolates are mostly likely HA-*E. faecium* isolates.

SARI

The 2004–2011 results of the SARI project (Surveillance of Antimicrobial Use and Bacterial Resistance in Intensive Care Units) regarding the prevalence of resistance in *E. faecalis* and *E. faecium* isolates from intensive care units of German hospitals to clinically relevant antimicrobials (evaluated according to DIN) are presented in this section.[19] These results also demonstrate the high ampicillin resistance rates of *E. faecium* (increase from 84.5% in 2004 to 96.9% in 2011) compared to *E. faecalis* (resistance rates ranging between 0.2% and 2.7%). *E. faecium* also showed high rates of ciprofloxacin resistance, increasing from 78.2% (2004) to 92.1% (2010) and to 91.0% (2011). These rates of fluoroquinolone resistance were lower in *E. faecalis*. The glycopeptide resistance rates of *E. faecalis* were ≤ 0.5% for vancomycin and ≤ 0.3% for teicoplanin; among *E. faecium*, they rose from 5.9% to 18.1% for vancomycin and from 2.1% to 10.8% for teicoplanin over the period 2004–2011 (with various intermediate stages). The prevalence of resistance in *E. faecium* to ampicillin and ciprofloxacin (in VRE also to glycopeptides) ascertained within the SARI project also suggests the spread of HA-*E. faecium* strains in German intensive care units, as already mentioned previously. Furthermore, the resistance rate of *E. faecium* to quinupristin/dalfopristin dropped between 2004 (4.7%) and 2009 (2.7%); the SARI project provided no data for 2010 and 2011 on this therapeutic combination. Between 2004 and 2011, the prevalence of linezolid-resistant *E. faecium* strains was ≤ 0.4% (Fig. 4.1.3.5).

EARS-Net (formerly EARSS)

The European surveillance studies conducted by EARS-Net (European Antimicrobial Resistance Surveillance Network; formerly: EARSS, European Antimicrobial Resistance Surveillance System) record the prevalence of resistance to relevant antimicrobials in clinically important invasive bacteria, including that in invasive *E. faecalis* and *E. faecium* strains isolated from hospital patients in the participating countries to aminopenicillins (ampicillin), aminoglycosides (high-level gentamicin resistance) and glycopeptides (vancomycin). However, Germany – with a total population of 81.903 million (as of 30 June 2012) – is only represented in EARS-Net by a small and varying number of participating laboratories, which only reflect the resistance situation of invasive pathogens in patients at German hospitals to a limited extent (low coverage).

According to the results of these studies, ampicillin resistance in *E. faecium* increased considerably from 78% in 2003 to 96% in 2011, whereas this rate in *E. faecalis* isolates mostly ranged around 1% (Tab. 4.1.3.1). The prevalence of high-level gentamicin resistance in *E. faecalis* was 41% in 2011; in previous years, this rate ranged between 29% and 67%. In 2011, 42% of the *E. faecium* isolates were found to exhibit high-level resistance to gentamicin; however, this rate varied between 35% and 73% during the period of observation 2003–2011. *E. faecium* is still considered to be the reservoir of glycopeptide resistance (vancomycin) and has been characterised by increasing resistance rates since 2003 (3%), with

peaks of 11%, 10%, 15% and again 11% being reached in 2004, 2005, 2007 and 2011, respectively; in *E. faecalis*, the vancomycin resistance rates between 2003 and 2011 were all below 1% (Tab. 4.1.3.1). Regarding the prevalence and spread of vancomycin-resistant *E. faecium*, German hospitals are now ranking fourth in European comparison (Fig. 4.1.3.6).

Other data sources

The laboratory of Dr. Limbach and colleagues – Medical Care Centre (MVZ) Heidelberg – records the antimicrobial resistance of clinically relevant infectious agents on a semi-annual basis, which also provides an excellent overview of the respective resistance situation of enterococci, thus acting

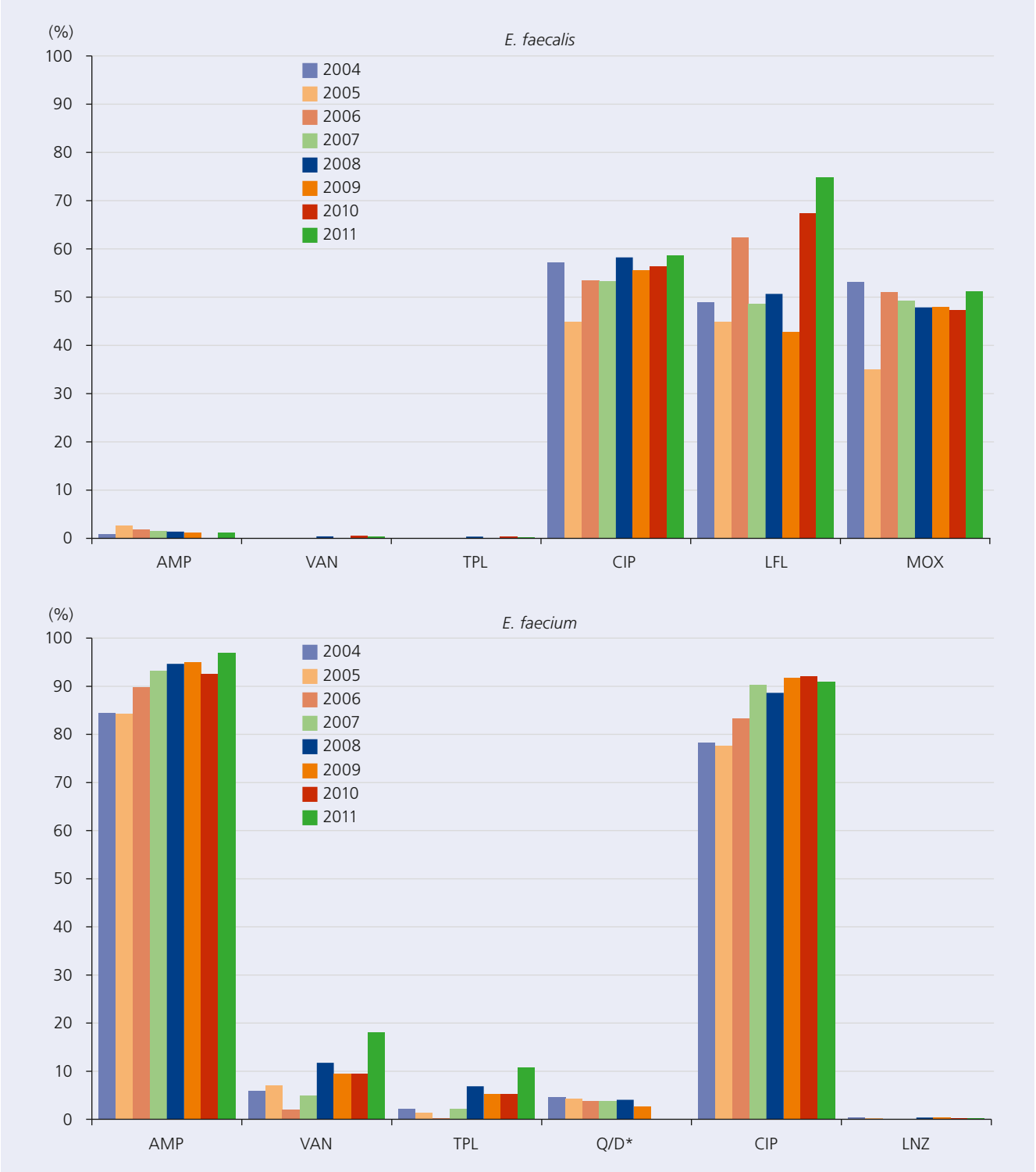


Fig. 4.1.3.5: Prevalence of resistance in *E. faecalis* and *E. faecium* from patients in intensive care units of German hospitals within the SARI project between 2004 and 2011 (Source: SARI project[19])

In the individual years under review, between 497 and 974 *E. faecalis* and between 423 and 761 *E. faecium* isolates were classified based on the DIN standard. AMP, ampicillin; VAN, vancomycin; TPL, teicoplanin; CIP, ciprofloxacin; LFL, levofloxacin; MOX, moxifloxacin; Q/D, quinupristin/dalfopristin (*Q/D was not tested in 2010 and 2011); LNZ, linezolid.

Tab. 4.1.3.1: Prevalence (%) of resistant enterococcal isolates from patients at German hospitals, 2003–2011 (Source: ECDC Surveillance Report 2011: Antimicrobial resistance surveillance in Europe, 2011[20])

Species and antibiotic class	2003 17/347 [a]	2004 22/606 [a]	2005 17/569 [a]	2006 16/529 [a]	2007 12/648 [a]	2008 13/451 [a]	2009 17/952 [a]	2010 16/1009 [a]	2011 17/1231 [a]
E. faecalis									
Aminopenicillin RI [b]	7	7	3	3	7	< 1	3	< 1	< 1
Gentamicin HR [c]	47	42	34	29	67	39	40	47	41
Vancomycin R	< 1	< 1	< 1	< 1	< 1	< 1	< 1	< 1	< 1
E. faecium									
Aminopenicillin RI [b]	78	93	96	94	95	95	94	94	96
Gentamicin HR [c]	47	61	52	38	73	35	45	45	42
Vancomycin R	3	11	10	8	15	6	6	8	11

[a] Number of participating laboratories/number of enterococcal isolates tested; [b] Resistance (R) and intermediate susceptibility (I) together;
[c] High-level gentamicin resistance (HR)

as an early warning system for the incipient development of resistance to individual antimicrobials. The presented glycopeptide resistance rates (vancomycin, teicoplanin) of *E. faecium* from hospitals in the catchment area of this laboratory indicate the emergence and spread of *VanA*- and *VanB*-type HA-*E. faecium* strains starting in the second half of 2003 (Fig. 4.1.3.7). In the second half of 2011, as many as 40% of *E. faecium* isolates were resistant to vancomycin and 10% to teicoplanin; however, this resistance survey conducted at the laboratory of Dr. Limbach and colleagues analysed all *E. faecium* strains (not only invasive isolates like in EARSS-Net). This figure additionally shows the increasing rate of *E. faecium* in all enterococci submitted to this laboratory during the period under review. This rate increased from 3.1% in the first half of 2001 to the present peak of 16.6% in the second half of 2010 over various intermediate stages and dropped slightly to 15.2% in the second half of 2011 and to 12.8% in the second half of 2012, respectively. At the same time, this figure shows the strong increase in the prevalence of vancomycin resistance starting in 2003, with the teicoplanin resistance rate being moderate and sometimes even decreasing. Both latter points are the consequence of the increasing spread of hospital-acquired, especially *vanB*-positive, *E. faecium* strains at many German hospitals.

The increasing prevalence of VRE (*vanA*- and *vanB*-positive *E. faecium* isolates) at German hospitals since 2003/2004, as evidenced by the data reported by the laboratory Dr. Limbach, was also apparent in the number of enterococcal isolates submitted to the Robert Koch Institute Wernigerode. Whereas *vanB*-positive *E. faecium* isolates were very rare in the enterococci submitted until 2003, their prevalence – in all enterococcal isolates submitted to the RKI in the two years mentioned below – increased to as much as 32.8% in 2011 and 40.0% in 2012. The prevalence of *vanA*-positive *E. faecium* isolates submitted in these two years was 43.3% (2011) and 48.0% (2020) (Fig. 4.1.3.8).

Prevalence of resistance to other antimicrobials in *VanA* and *VanB E. faecium* isolates submitted to the RKI Wernigerode

Tab. 4.1.3.2 shows the prevalence of in-vitro resistance to other antimicrobials/chemotherapeutics in *VanA* and *VanB* type *E. faecium* strains submitted to the NRZ for Staphylococci and Enterococci domiciled at the RKI Wernigerode. The MIC values of the strains measured by means of the broth microdilution method were interpreted on the basis of the corresponding clinical MIC breakpoints defined by EUCAST. Antimicrobials for which EUCAST defines no clinical MIC breakpoints were analysed on the basis of the respective ECOFF values also defined by EUCAST.

This resistance data compiled in Tab. 4.1.3.2 shows that there are few antimicrobials left for the treatment of *E. faecium* infections. Some of the *vanA*- and *vanB*-positive *E. faecium* strains additionally exhibit high-level aminoglycoside resistance (gentamicin and/or streptomycin, see Tab. 4.1.3.2). In this connection, the prevalence of high-level gentamicin resistance in VanB strains was apparently decreasing (42.5% → 11.6%), with high-level streptomycin resistance simultaneously increasing (46.6% → 67.7%) over the period under review 2010–2012. The varying rates of high-level gentamicin resistance are assumed to be associated with a varying prevalence of certain strain variants. For example, the VanB resistance of *E. faecium* is associated with a particular strain (MLST-ST192; *esp*- and *hyl*-positive), in which high-level gentamicin resistance is relatively rare: 9 (15.8%) of a representative sample of 57 *vanB*-positive ST192 *E. faecium* isolates showed high-level gentamicin resistance (unpublished data of the NRZ for Staphylococci and Enterococci). VanA and VanB strains were found to differ in terms of prevalence of high-level resistance to both gentamicin and streptomycin. Whereas the rates of high-level resistance of VanA strains ranged between 31.1% and 41.0% during the period 2010–2012, the rates of VanB isolates were significantly lower, showing a downward trend ranging from 13.0% to 8.1%. The resistance situation for quinupristin/dalfopristin in *E. faecium* isolates is also favourable, with the prevalence of low-level resistance decreasing in both VanA isolates (0.7% → 0.2%) and VanB strains (2010: 1.4%, 2011: 8.2%; 2012: 1.1%). The resistance situation for the other second-line antimicrobials linezolid (VanA: dropped from 4.2% to 0.7%, VanB: slightly increased from 0.7% to 1.7%) and tigecycline (VanA: dropped from 2.8% → 0.4%; for VanB: no resistances in 2010–2012) is thus currently still very favourable. Because of the increased mortality rate in clinical studies, the manufacturer (Pfizer) sent a red-hand letter concerning all fields of application of tigecycline in March 2011, which emphasises that the substance is exclusively approved for the treatment of complicated skin and soft tissue infections and complicated intraabdominal infections. The use

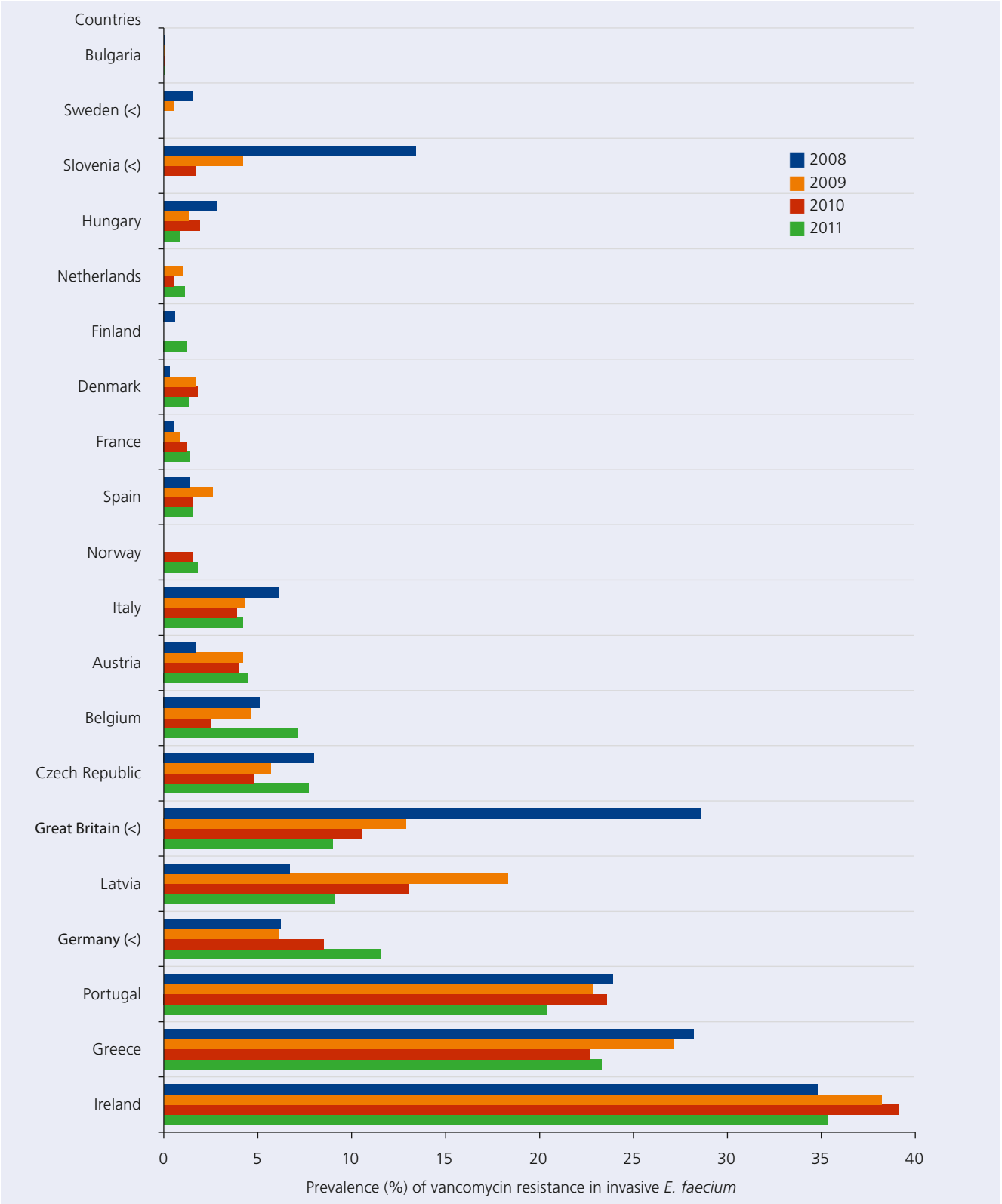
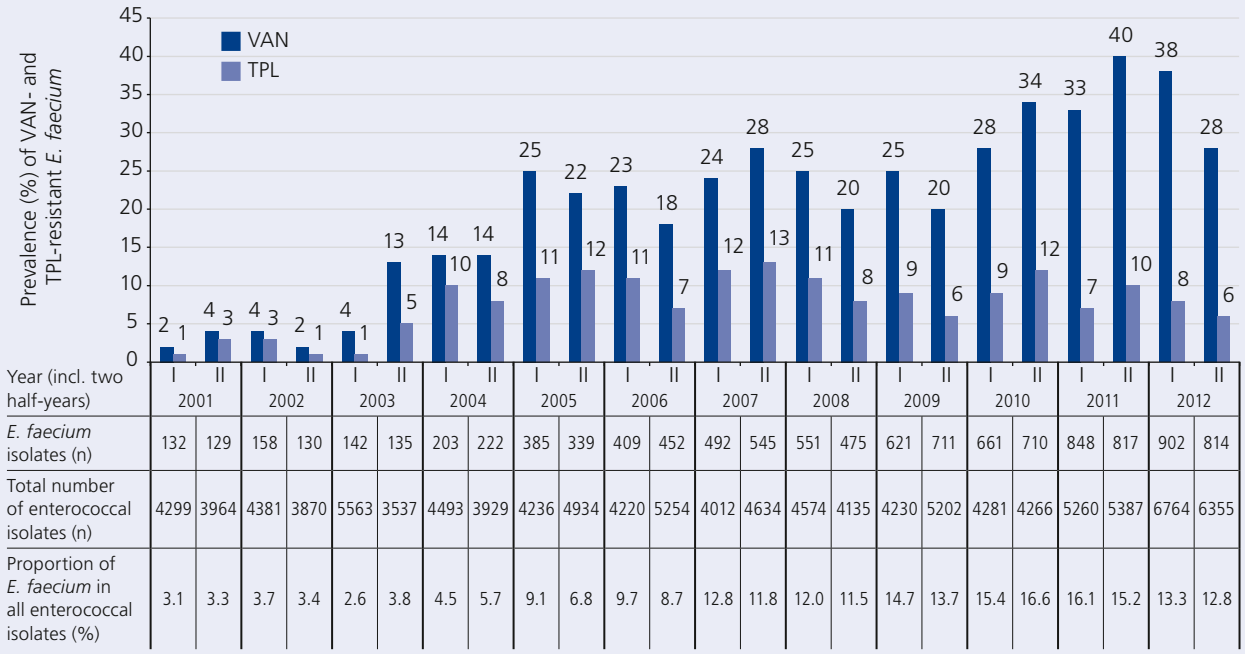


Fig. 4.1.3.6: Comparison between EU/EEA countries 2008–2010 regarding trends in the prevalence of vancomycin resistance in invasive *E. faecium* isolates (Source: ECDC Surveillance Report 2011: Antimicrobial resistance surveillance in Europe, 2011 [20])

Countries that did not report resistance data in any of the years mentioned above (Slovakia) and countries that only reported relevant resistance data for ≤ 19 isolates/year (Cyprus, Estonia, Iceland, Lithuania, Luxembourg, Malta, Poland and Romania) were not included in this analysis. The symbols indicate significant trends (< decrease, > increase) in total vancomycin resistance rates in the laboratories of the respective country that reported resistance data in the four years.

of tigecycline is thus only indicated in rare cases. Chloramphenicol, which was included in the test for epidemiological reasons, also shows a very favourable resistance situation: Based on the wild-type ECOFF value defined by EUCAST (≤ 32 mg/l), neither VanA nor VanB type chloramphenicol-resistant *E. faecium* strains were found during the period 2010–2012. Regarding rifampicin and trimethoprim/sulphamethoxazole, an increasing prevalence of high-level resistance was observed for both Van types (Tab. 4.1.3.2).



Year (incl. two half-years)	I 2001	II 2001	I 2002	II 2002	I 2003	II 2003	I 2004	II 2004	I 2005	II 2005	I 2006	II 2006	I 2007	II 2007	I 2008	II 2008	I 2009	II 2009	I 2010	II 2010	I 2011	II 2011	I 2012	II 2012
E. faecium isolates (n)	132	129	158	130	142	135	203	222	385	339	409	452	492	545	551	475	621	711	661	710	848	817	902	814
Total number of enterococcal isolates (n)	4299	3964	4381	3870	5563	3537	4493	3929	4236	4934	4220	5254	4012	4634	4574	4135	4230	5202	4281	4266	5260	5387	6764	6355
Proportion of *E. faecium* in all enterococcal isolates (%)	3.1	3.3	3.7	3.4	2.6	3.8	4.5	5.7	9.1	6.8	9.7	8.7	12.8	11.8	12.0	11.5	14.7	13.7	15.4	16.6	16.1	15.2	13.3	12.8

Fig. 4.1.3.7: Prevalence (%) of vancomycin (dark blue) and teicoplanin (light blue) resistance in *E. faecium* isolates from patients at Southwestern German hospitals between the 1st half of 2001 and the 2nd half of 2012 as well as percentage of *E. faecium* isolates in all enterococcal strains in the respective half-year (Source: Laboratory Dr. Limbach and colleagues, MVZ Heidelberg)

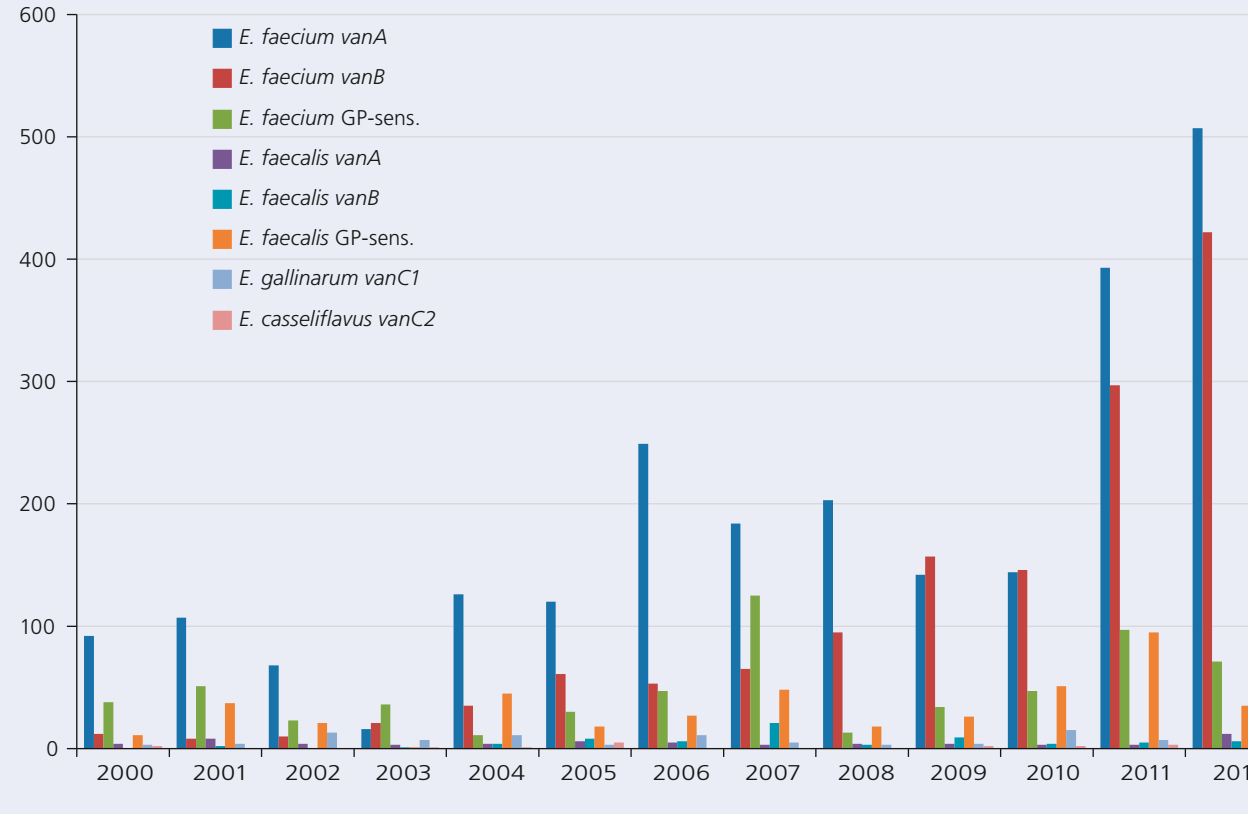


Fig. 4.1.3.8: Number of isolates of various enterococcal species and vancomycin resistance types from infected and colonised inpatients submitted to the RKI Wernigerode between 2000 and 2012 (Source: RKI Wernigerode, NRZ for Staphylococci and Enterococci); GP-sens., glycopeptide-sensitive

Conclusion

During the last 25 years, enterococci have demonstrated increasing prevalences of acquired resistances to various antimicrobials, with some significant differences being observed between the two clinically relevant enterococcal species *E. faecalis* and *E. faecium*, which can be best recognised by the prevalence of resistance to ampicillin and glycopeptides. The anti-enterococcal "second-line antimicrobials" quinupristin/dalfopristin (only against *E. faecium*), linezolid, tigecycline and

Tab. 4.1.3.2: Prevalence of resistance to other antimicrobials/chemotherapeutics in VanA and VanB *E. faecium* isolates submitted to the Robert Koch Institute Wernigerode in 2010, 2011 and 2012 (Source: Robert Koch Institute Wernigerode, NRZ for Staphylococci and Enterococci).

Antibiotic/Chemotherapeutic	Prevalence of resistance (%)a in *E. faecium* isolates of the					
	VanA type			VanB type		
	2010 (n=144)	2011 (n=392)	2012 (n=453)	2010 (n=146)	2011 (n=292)	2012 (n=371)
Penicillin G [b]	99.3	99.5	99.8	100.0	99.7	100.0
Ampicillin [a]	100.0	100.0	99.8	100.0	99.7	100.0
Gentamicin (HR) [a]	56.9	66.1	60.5	42.5	18.8	11.6
Streptomycin (HR) [a]	48.6	45.7	57.4	46.6	41.8	67.7
Gentamicin (HR) [a] and Streptomycin (HR) [a]	34.0	31.1	41.0	13.0	8.6	8.1
Vancomycin [a]	100.0	100.0	100.0	98.6	99.3	95.1
Teicoplanin [a]	99.3	100.0	100.0	0.0	0.0	0.0
Daptomycin [b]	0.0	0.0	0.0	0.0	0.0	0.0
Quinupristin/Dalfopristin [a]	0.7	0.8	0.2	1.4	8.2	1.1
Clindamycin [b]	97.9	98.5	98.2	92.5	93.8	99.2
Erythromycin [b]	98.6	99.5	98.7	92.5	94.9	99.2
Ciprofloxacin [b]	98.6	99.5	100.0	100.0	98.6	100.0
Ciprofloxacin (HR) [c]	97.9	98.5	99.6	99.3	97.3	100.0
Moxifloxacin [b]	99.3	99.5	100.0	100.0	99.0	100.0
Linezolid [a]	4.2	3.9	0.7	0.7	1.7	1.1
Tetracycline [b]	38.2	65.8	60.7	8.2	11.3	16.2
Tigecycline [a]	2.8	0.0	0.4	0.0	0.0	0.0
Rifampicin [b]	74.3	89.2	94.3	78.1	73.6	90.0
Trimethoprim/Sulfamethoxazole [a]	43.1	58.8	60.9	26.0	69.2	81.9
Chloramphenicol [b]	0.0	0.0	0.0	0.0	0.0	0.0

[a] The MIC values were interpreted on the basis of the clinical MIC breakpoints defined by EUCAST (valid from 2013-02-11).
[b] Where EUCAST specified no clinical breakpoints, the MIC values were interpreted on the basis of the epidemiological cut-off (ECOFF) values also defined by EUCAST
[c] Bnterpretation of ciprofloxacin MIC values regarding HR to ciprofloxacin: > 16 mg/l [10]
HR, high-level resistance

apparently also daptomycin are characterised by excellent efficacy against these bacteria. Resistance to these antimicrobials in the corresponding enterococcal isolates from hospital patients has so far only been observed rarely, although it may occasionally occur in vivo after a relatively short period of treatment (e.g. linezolid-resistant *E. faecium*).

The virulence marker-carrying, multidrug resistant HA-*E. faecium* isolates (with or without vancomycin resistance and/or resistance to the above-mentioned "second-line antimicrobials") analysed here regarding prevalence of antimicrobial resistance should be recognised at an early point as part of hospital hygiene measures, epidemiologically relevant isolates should be genotyped (SmaI macrorestriction analysis) and their spread to other hospital patients should be prevented on first emergence by means of accompanying anti-epidemic measures. These measures are also essential to avoid the further spread of multidrug and vancomycin resistance in *E. faecium* (including outbreaks of VRE infections) as well as their transfer to *E. faecalis*, *Staphylococcus aureus* or other clinically relevant gram-positive bacteria. In this process, more restrictive use of antimicrobials without anti-enterococcal activity and of glycopeptides is also of crucial significance.

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4.1.4 *Haemophilus influenzae/ Moraxella catarrhalis*

4.1.4.1 *Haemophilus influenzae*

Haemophilus influenzae is a pathogen that is commonly isolated from respiratory tract infections, but can also cause otitis media, severe soft tissue infections, meningitis and bloodstream infections. Particularly feared infections include epiglottitis in young children, which may have a fatal outcome, as well as meningitis and bloodstream infections. The most important virulence factor is the polyribophosphate capsule, which provides protection against complement and phagocytosis. In the past, most invasive and systemic infections were caused by strains of the capsular type b (Hib). Severe *H. influenzae* infections occur as a result of a lack of antibodies against the capsular antigens, especially in children aged between 6 months and 5 years. This is why vaccination with Hib vaccine is recommended in the first and second year of life. *H. influenzae* infections in adults typically occur as a complication of underlying diseases or in patients with a weakened immune system. Since the Hib vaccination was introduced, the incidence of the infection in children has decreased significantly. By contrast, a slight increase in the incidence of invasive *H. influenzae* infections in elderly people has been observed for several years.[1] They are caused predominantly by non-encapsulated strains. The infection most commonly manifests itself as an acute exacerbation of chronic obstructive bronchitis. *H. influenzae* also frequently causes pneumonia accounting for 5–10% of the pathogens identified as the causative agent of community-acquired pneumonia (CAP).[2]

β-lactam antimicrobials are recommended primarily for treatment. In the event of severe infections, third-generation cephalosporins (group 3 cephalosporins according to the classification of the Paul Ehrlich Society for Chemotherapy (e.g. cefotaxime, ceftriaxone) are indicated. The oral cephalosporins cefalexin, cefadroxil and cefaclor (first-generation/group 1) exhibit no sufficient activity, and most of the cefuroxime MIC values are in the intermediate range, when applying the breakpoints for cefuroxime axetil. By contrast, oral third-generation cephalosporins (cefixime, cefpodoxime proxetil, ceftibuten) are active against *H. influenzae*. Doxycycline and fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) are available as alternatives. Macrolides exhibit no sufficient in-vitro activity against *H. influenzae*, which is why their clinical use is not recommended.

Trends in resistance development

Resistance to aminopenicillins is found most commonly. It is usually associated with β-lactamases. β-lactamase-producing strains are found worldwide. On average, 15% of nearly 15,000 isolates collected over the period 1999–2003 and tested as part of an international surveillance study were found to produce β-lactamase (predominantly TEM-1).[3] β-lactamase was produced by 6% of the 1,711 isolates obtained from German laboratories. When combined with aminopenicillins, the available β-lactamase inhibitors also cover β-lactamase-producing strains.

In β-lactamase-negative ampicillin-resistant strains (BLNAR), the resistance is attributed to changes in the penicillin-binding proteins (PBP) 3A and 3B. In recent years, there has been a considerable increase in the number of reports on the spread of BLNAR.

As part of the 2010 PEG resistance study, 230 clinical isolates from outpatient care, which had been collected over the period from October to December in 25 laboratories across Germany, were tested for antimicrobial susceptibility. The

vast majority of strains (90%) had been isolated from patients with respiratory tract and ENT infections. In 19 cases, the isolates had been obtained from eye swabs. A total of 29 strains (12.6%) were classified as resistant to amoxicillin, whereas all isolates were susceptible to the combination of amoxicillin and clavulanic acid, which suggests the production of β-lactamase as the primary cause of amoxicillin resistance. Amoxicillin-resistant strains were particularly common in the group of patients aged < 5 years, the prevalence of which (18.8%) was more than twice as high as in isolates from other patient groups (9.0%). Third-generation cephalosporins, doxycycline and fluoroquinolones were all tested 100% susceptible (Fig. 4.1.4.1.1). One strain was classified as resistant to cefuroxime (MIC 4 mg/l), whereas the level of resistance to co-trimoxazole reached nearly 30%. As expected, most of the macrolide MIC values were in the intermediate to susceptible range, while the cefaclor values were in the resistant range.[4]

In a Germany-wide study investigating 290 bacterial strains, which had been isolated from outpatients with respiratory tract or ENT infections in the winter of 2007, the percentage of amoxicillin-resistant strains in all isolates was 15.2% (Fig. 4.1.4.1.1).[5] Half of these resistant isolates exhibited the BLNAR phenotype. More than 600 isolates from 2005, 2007 and 2009 were tested for susceptibility to amoxicillin/clavulanic acid and doxycycline as part of the G-TEST (see chapter 4.1.5.1). In this case, 87% of the strains had been cultured from respiratory specimens, 11% from wound swabs and five were blood culture isolates. The percentage of strains resistant to amoxicillin/clavulanic acid was 3.2%, 5.3% and 1.9%, respectively. Resistance to fluoroquinolones was not observed; two strains from 2007 were found to be resistant to doxycycline (Fig. 4.1.4.1.1).[6] Blood culture isolates showed no resistance to amoxicillin/clavulanic acid, doxycycline or fluoroquinolones.

Change in the epidemiological situation of invasive infections in Germany

Since 2008, the Consultant Laboratory for *Haemophilus influenzae* (KLHi) at the Institute of Hygiene and Microbiology of Würzburg University has been testing isolates from invasive *H. influenzae* infections, which must be reported to the health authorities under Section 7 IfSG, on behalf of the Robert Koch-Institute. In this context, isolates from blood or cerebrospinal fluid are considered invasive. The findings of the serotyping are transmitted to the competent health authorities. In 2008, the submission rate of legally recorded invasive *H. influenzae* infections that meet the reference definition of the Robert Koch-Institute was 41% (SurvStat@RKI, data as of 5/12/2012) and improved continuously in the following years to reach 86% in 2011.

The vast majority of the tested isolates were non-encapsulated strains, so-called non-typable *H. influenzae* (NTHi) (altogether 75% throughout the entire study period). The most common capsular type was serotype f (16%), whereas serotype b *H. influenzae* (Hib), which had been the most common type before the vaccination was introduced, was only detected in 6% of the isolates.

65 (12%) of the total of 535 invasive isolates tested were found to be resistant to ampicillin and 55 (10%) isolates were confirmed to produce β-lactamase. 10 isolates (2%) were assumed to exhibit β-lactamase-negative ampicillin resistance (BLNAR). During the period 2008–2011, the prevalence of ampicillin-resistant invasive isolates appears to be largely constant, with the prevalence of BLNAR being very low (Lâm et al., manuscript in preparation).

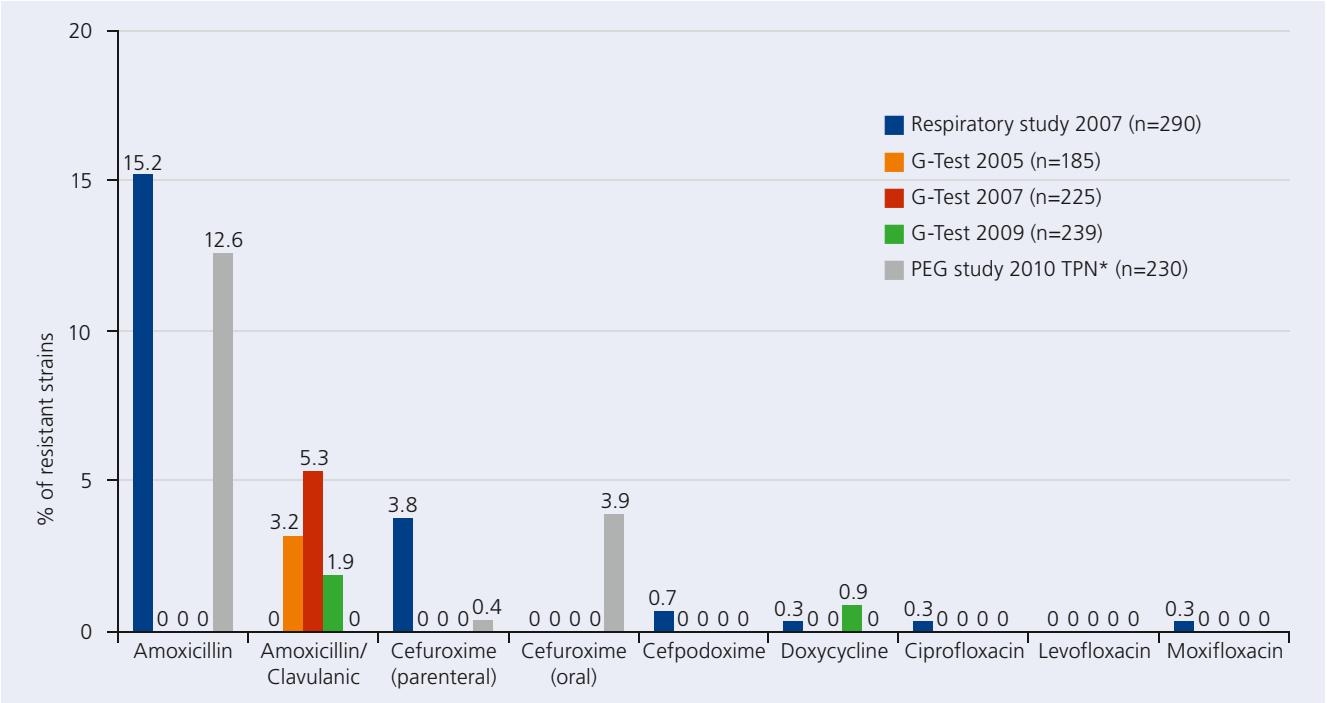

Fig. 4.1.4.1.1: Resistance of *H. influenzae* isolates (EUCAST breakpoints). The difference in the prevalence of strains resistant to cefuroxime (parenteral) and cefuroxime (oral) results from the different breakpoints defined for cefuroxime (parenteral) and cefuroxime (oral).
*TPN, subproject N, outpatient care

Conclusion

Amoxicillin is usually sufficient for the targeted treatment of *H. influenzae* respiratory tract and ENT infections. In the event that β-lactamase-producing strains are detected, a therapeutic combination of an aminopenicillin plus a β-lactamase inhibitor is recommended. Ceftriaxone and cefotaxime continue to be the first-line antimicrobials used for the treatment of meningitis.

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4.1.4.2 *Moraxella catarrhalis*

Moraxella catarrhalis is a pathogen mainly causing infections of the upper respiratory tract, most notably otitis media, conjunctivitis as well as purulent local infections. Behind *Streptococcus pneumoniae* and *Haemophilus influenzae*, it is considered the third most common causative agent of otitis media. *M. catarrhalis* can further cause infections of the lower respiratory tract, especially in patients with underlying diseases such as chronic obstructive pulmonary disease, as well as bloodstream infections and endocarditis. Although *M. catarrhalis* is only rarely identified as the causative agent of community-acquired pneumonia, it colonises the upper respiratory tract of these patients in 10–25% of the cases.[1] Its pathogenic role in mixed infections has not yet been fully understood.

Nearly all strains produce β-lactamase, which is why unprotected penicillins are not suitable for treatment. Combinations of aminopenicillins (ampicillin, amoxicillin) and β-lactamase inhibitors (clavulanic acid, sulbactam) are, however, usually effective. The oral first-generation cephalosporins cefalexin, cefadroxil and cefaclor (group 1 according to the classification of the Paul Ehrlich Society for Chemotherapy) exhibit no sufficient activity. When applying the breakpoints for cefuroxime axetil, (second generation/group 2) most cefuroxime MIC values are in the intermediate range. By contrast, orally administered third-generation (group 3) cephalosporins (cefixime, cefpodoxime proxetil, ceftibuten) as well as co-trimoxazole, doxycycline and fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) prove effective.

Trends in resistance development

As part of the 2010 PEG resistance study, 229 clinical isolates, which had been collected from October to December in 25 laboratories across Germany, were tested for antimicrobial susceptibility.

More than 98% of the isolates were found to produce β-lactamase, all of which were, however, 100% susceptible to amoxicillin/clavulanic acid as well as cefixime and cefuroxime. The majority of the MIC values for co-trimoxazole and erythromycin were in the intermediate range; strains resistant to newer macrolides (azithromycin, clarithromycin, roxithromycin), doxycycline or fluoroquinolones were not detected.[2]

The penicillin resistance is associated with the production of a BRO-type β-lactamase. A distinction is made between BRO-1 and BRO-2. BRO-1 was detected in approx. 95% of the β-lactamase-producing isolates.[3]

Conclusion

The combination of an aminopenicillin and a β-lactamase inhibitor is recommended for the targeted treatment of severe *M. catarrhalis* respiratory tract or ENT infections. Alternative therapeutic agents include oral third-generation cephalosporins as well as newer macrolides in children and doxycycline or fluoroquinolones in adult patients.

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4.1.5 *Escherichia coli* and other *Enterobacteriaceae*

4.1.5.1 *Escherichia coli*

Escherichia coli bacteria are commonly found in the physiological intestinal flora, but can also cause infections, depending on the presence of virulence determinants. They are known to be causative agents of both gastrointestinal diseases and extraintestinal infections (EXPEC). Urinary tract infections caused by uropathogenic *E. coli* (UPEC) are particularly common. In addition, *E. coli* cause ventilator-associated pneumonia and bloodstream infections, less commonly community-acquired pneumonia. Strains that can also be acquired through ventilator-associated pneumonia (SEPEC) account for approximately 25% of the pathogens causing bacteraemic infections.[1] Further extraintestinal *E. coli* infections include surgical site infections, especially in connection with abdominal surgical procedures, and meningitis (MENEC). In the presence of certain adhesins, invasins and toxins, *E. coli* can also cause a number of intestinal diseases. In this respect, a distinction is made between enteropathogenic *E. coli* (EPEC), enterotoxic *E. coli* (ETEC), enteroinvasive *E. coli* (EIEC), enterohaemorrhagic *E. coli* (EHEC) and enteroaggregative *E. coli* (EAEC). The resistance data taken as a basis for this report is obtained mainly from urine and blood culture isolates.

Trends in resistance development

PEG resistance study

Over the period 1995–2010, the percentage of strains resistant to ampicillin in isolates from inpatients (hospital care) increased from approx. 35% to nearly 60%. The prevalence of resistance to trimethoprim/sulphamethoxazole (co-trimoxazole) initially increased steadily as well (from 22.7% in 1995 to 34.4% in 2007). However, the percentage of resistant strains declined slightly after 2007 (Fig. 4.1.5.1.1).2,3

The susceptibility to ciprofloxacin was analysed to evaluate the development of resistance to fluoroquinolones. The percentage of resistant strains in all isolates increased by more than 25%, namely from 5.5% in 1995 to 32.1% in 2010 (Fig. 4.1.5.1.1). The difference in the level of resistance increase in isolates from patients of different age groups is particularly notable (Fig. 4.1.5.1.2). Over the period 1995–2004, the percentage of resistant strains in isolates from patients aged over 60 years increased by approx. 20%, whereas the resistance level of isolates from patients aged below 21 years

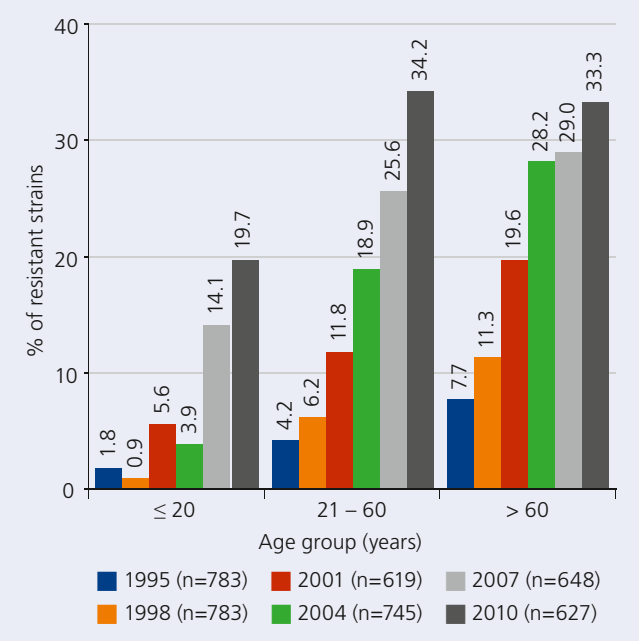

Fig. 4.1.5.1.2: Percentage of ciprofloxacin-resistant *E. coli* strains from hospital care itemised by age of patients (Source: PEG resistance study)

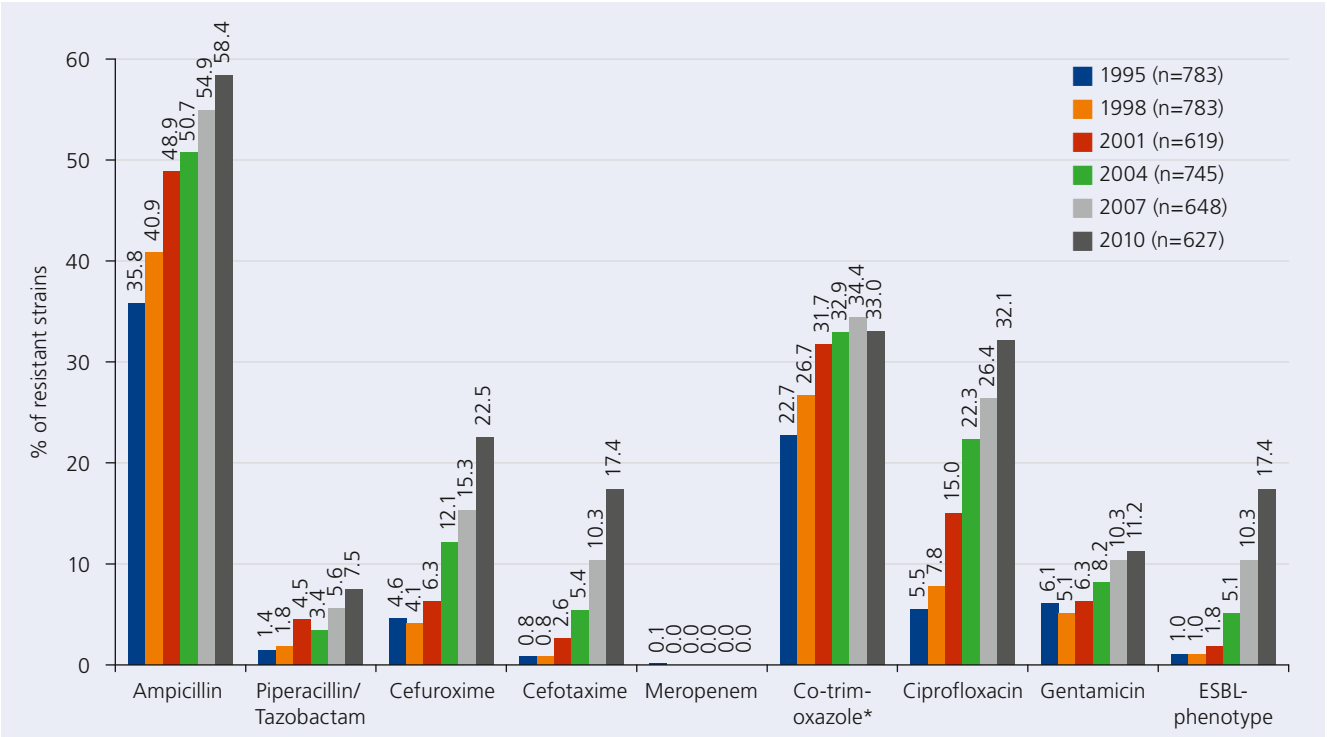

Fig. 4.1.5.1.1: Percentage of resistant *E. coli* strains from hospital care (Source: PEG resistance study)
*Trimethoprim/Sulphamethoxazole

barely changed. After this period, the prevalence of resistance increased slightly in isolates from older patients and strongly in those from adolescent patients. The higher percentage of resistant strains in older patients has so far been explained by the cumulative intake of fluoroquinolones over the years. The observed resistance development may, however, be associated with different clinical manifestations in the various age groups.

The strong increase in fluoroquinolone resistance in isolates from patients aged below 21 years is most likely attributable to the rising number of infections caused by strains with the extended-spectrum β-lactamase (ESBL) phenotype and the simultaneous presence of fluoroquinolone resistance (Fig. 4.1.5.1.3). Whereas the rate of fluoroquinolone resistance was initially proportional to age and the associated extent of antimicrobial exposure, co-resistant strains have also been found in adolescent patients since 2007.

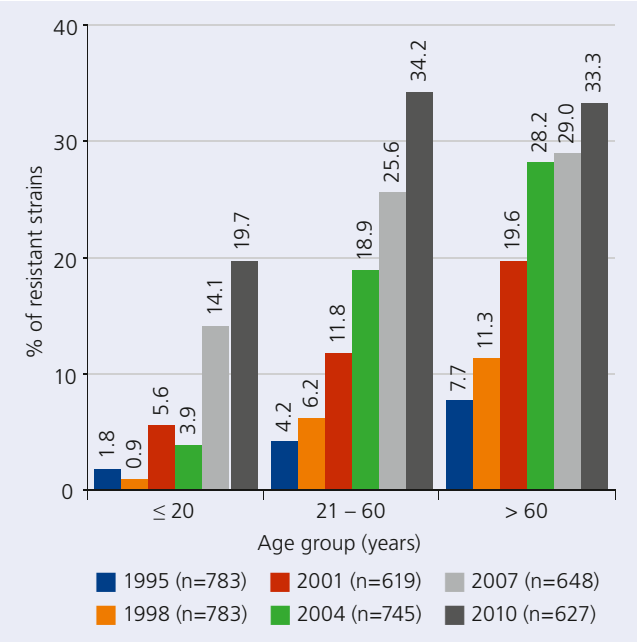

Fig. 4.1.5.1.3: Percentage of *E. coli* strains with an ESBL phenotype from hospital care broken down by age of patients (Source: PEG resistance study)

To identify the ESBL phenotype, isolates with cefotaxime or ceftazidime MIC values of > 1 mg/l were tested for susceptibility to cefotaxime ± clavulanic acid and ceftazidime ± clavulanic acid in accordance with the guidelines of the Clinical and Laboratory Standards Institute (CLSI).[4]

Overall, the percentage of strains with an ESBL phenotype in all *E. coli* isolates from hospital care increased from 1% to 17.4% between 1995 and 2010. At the same time, an increase in the rate of resistance to cefuroxime and cefotaxime from < 5% to 22.5% and from < 1% to 17.4%, respectively, was observed, whereas the susceptibility to carbapenems (e.g. meropenem) remained at a consistently high level of more than 99% (Fig. 4.1.5.1.1). Over the period of observation, the prevalence of resistance to the combination of piperacillin/tazobactam rose from 1.4% to 7.5% and that to gentamicin from 6.1% to 11.2%. The increase in gentamicin resistance is assumed to have been caused by co-selection, given that the consumption of aminoglycosides has strongly decreased over the last two decades.

The real threat posed by resistant strains becomes clear when taking into account not only the prevalence of resistance to individual substances, but also the percentage of multidrug resistant strains. While evaluating the resistance patterns of five selected antimicrobials (ampicillin, cefuroxime, ciprofloxacin, co-trimoxazole, gentamicin) (Fig. 4.1.5.1.4). The percentage of 3MRGN multidrug resistant strains, as defined by KRINKO[5], in all isolates increased from 0.5% in 1995 to 14.4% in 2010. In 2010, however, no strain was classified as 4MRGN.

Colistin, fosfomycin and tigecycline constitute possible alternatives for the treatment of infections caused by multidrug resistant *E. coli* strains. The percentage of strains resistant to fosfomycin was 1.1% in 2010. Colistin-resistant strains were not detected. The testing of isolates with an ESBL phenotype for susceptibility to tigecycline also revealed that all tested isolates were susceptible.

For the first time, the 2010 PEG resistance study also investigated the antimicrobial resistance situation of clinically relevant bacterial species in ambulatory care (outpatients). A total

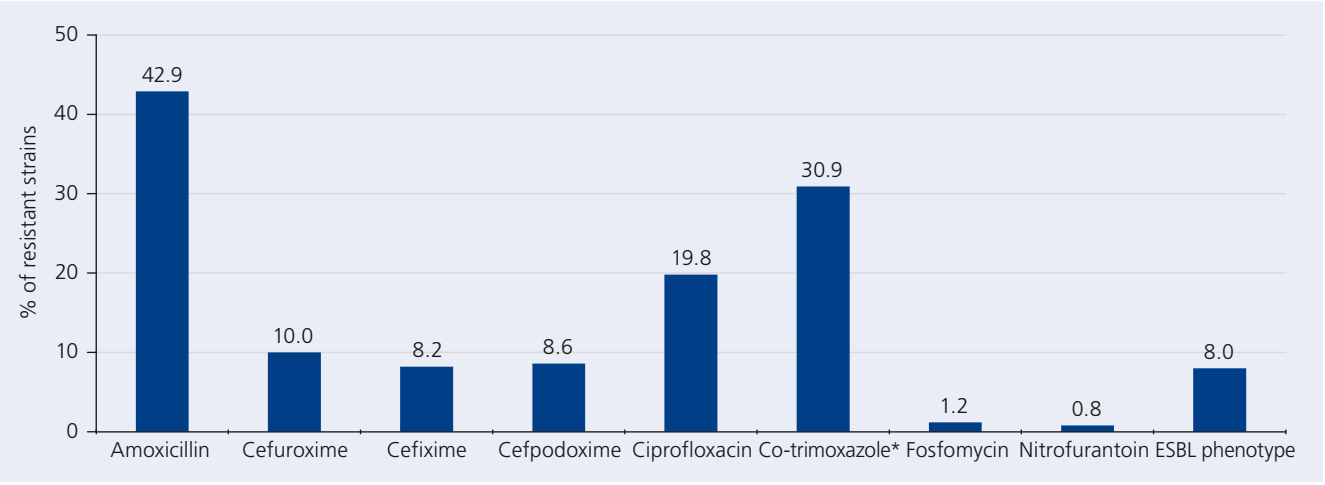

Fig. 4.1.5.1.4: Percentage of resistant *E. coli* urine isolates from outpatient care (n=499) (Source: PEG resistance study 2010)
*Trimethoprim/Sulphamethoxazole

of 499 *E. coli* urine isolates were tested. The prevalence of resistance to the tested antimicrobials varied between 0.8% for nitrofurantoin and 42.9% for amoxicillin (Fig. 4.1.5.1.5). The ESBL phenotype was identified in 40 (8%) isolates.[6]

PEG blood culture study 2006/2007 and GENARS/ARS

The results of the PEG blood culture study and those of the GENARS project were already presented in the 2008 and 2010 GERMAP reports.[7,8]

The resistance data recorded in the laboratories participating in ARS allows its evaluation by care sector (outpatients vs. inpatients) and, given the large number of tested bacterial strains, by level of hospital care. However, the reliability of the data is limited by the fact that the susceptibility to various antimicrobials is tested in different strain collectives.[9]

Under these circumstances, the resistance situation for comparatively expensive antimicrobials in isolates from outpatients is (as expected) much more favourable than in those from inpatients, with the highest resistance levels being observed in pathogens isolated from patients in intensive care units (Fig. 4.1.5.1.6; 2011 data).

As already demonstrated in the 2008 GERMAP report on the basis of the GENARS results, the resistance situation may vary greatly between hospitals and regions. The resistance rate at a hospital depends on both the mix of patients and the specialisation of the respective hospital in certain diseases. The ARS data shows that the highest resistance rates are always found in *E. coli* isolates from patients at tertiary-care hospitals. However, high resistance rates were also found in isolates from patients at primary-care hospitals (Fig. 4.1.5.1.7; 2011 data).

Regarding outpatient care, the ARS data also reveals significant differences in resistance rates between isolates from patients in various care sectors (Fig. 4.1.5.1.8; 2011 data). It is remarkable to see that isolates resistant to certain antimicrobials (ampicillin, co-trimoxazole, ciprofloxacin, gentamicin) are found in patients in specialist outpatient urology clinics just as often as in patients from hospital care.

SARI

The number of bacterial strains isolated from patients in 64 intensive care units during the period 2001–2011 was 171,055[10], 25,935 of which were *E. coli* isolates. However, the presence of copy strains cannot be excluded with certainty. Under these circumstances, the resistance to fluoroquinolones (ciprofloxacin) increased from 8.3% in 2001 to 24.2% in 2008[11] and remained almost constant after this period.12 In 2012, the percentage of fluoroquinolone-resistant strains was 25.55%.[12] The prevalence of resistance to third-generation cephalosporins rose from 1.2% in 2001 to initially 10.5% in 2008[11], and then increased further to reach 17% in 2011.[12] The rate was 13.5% in the last study year.[12]

The resistance density of isolates resistant to third-generation cephalosporins increased from 0.16 per 1,000 patient days in 2011 to 1.39 in 2008[11], with a further increase to 2.6% being observed in 2011.[10] The increase in the rates of resistance to fluoroquinolones and third-generation cephalosporins led to the consumption of carbapenems being nearly doubled.[11] During the period 2001–2012, the percentage of strains resistant to carbapenems (imipenem) was consistently below 1%.[12]

EARS-Net (formerly EARSS)

During the period 2003–2011, between 850 and 3,650 blood culture isolates were tested each year in 12–22 German participating laboratories.[13] The rate of aminopenicillin resistance was 47% at the beginning of the period of observation and 52% at the end. The highest rate observed was 60% (in 2006). The rate of fluoroquinolone resistance initially rose

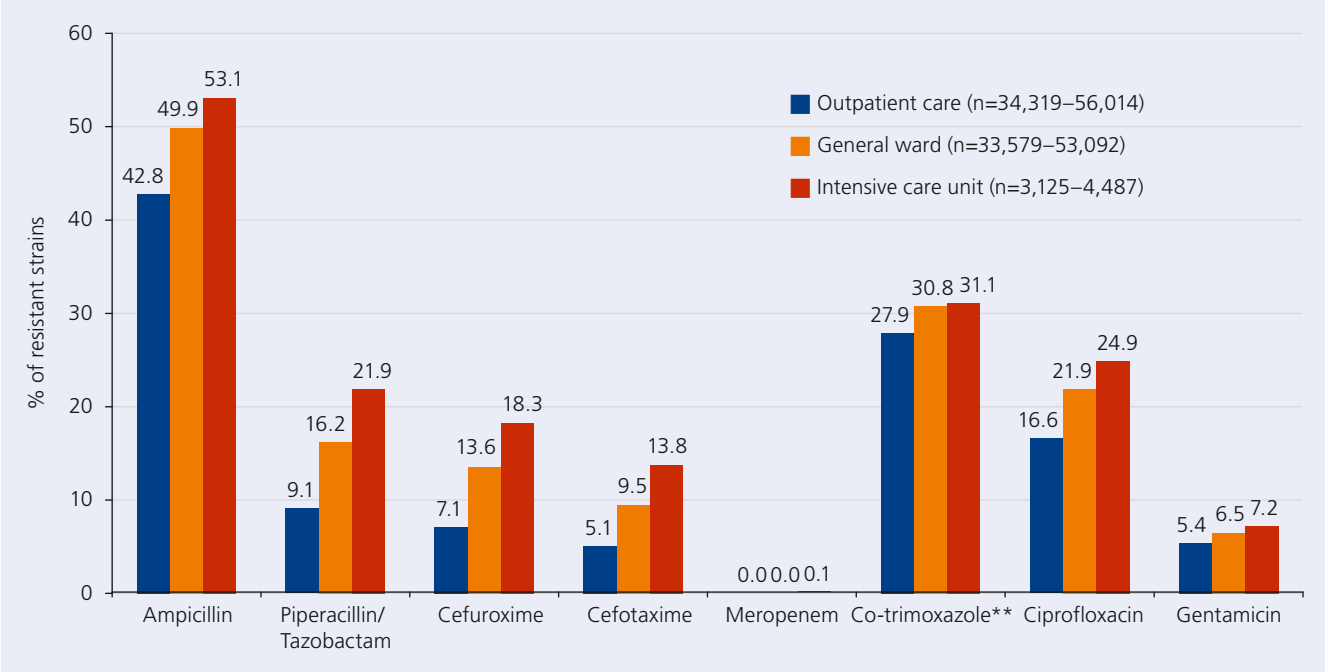

Fig. 4.1.5.1.5: Percentage of resistant *E. coli* strains in outpatient care, on general wards and in intensive care units (Source: ARS, 2010 data*);
*Data as of: 28/05/2013; **Trimethoprim/Sulphamethoxazole

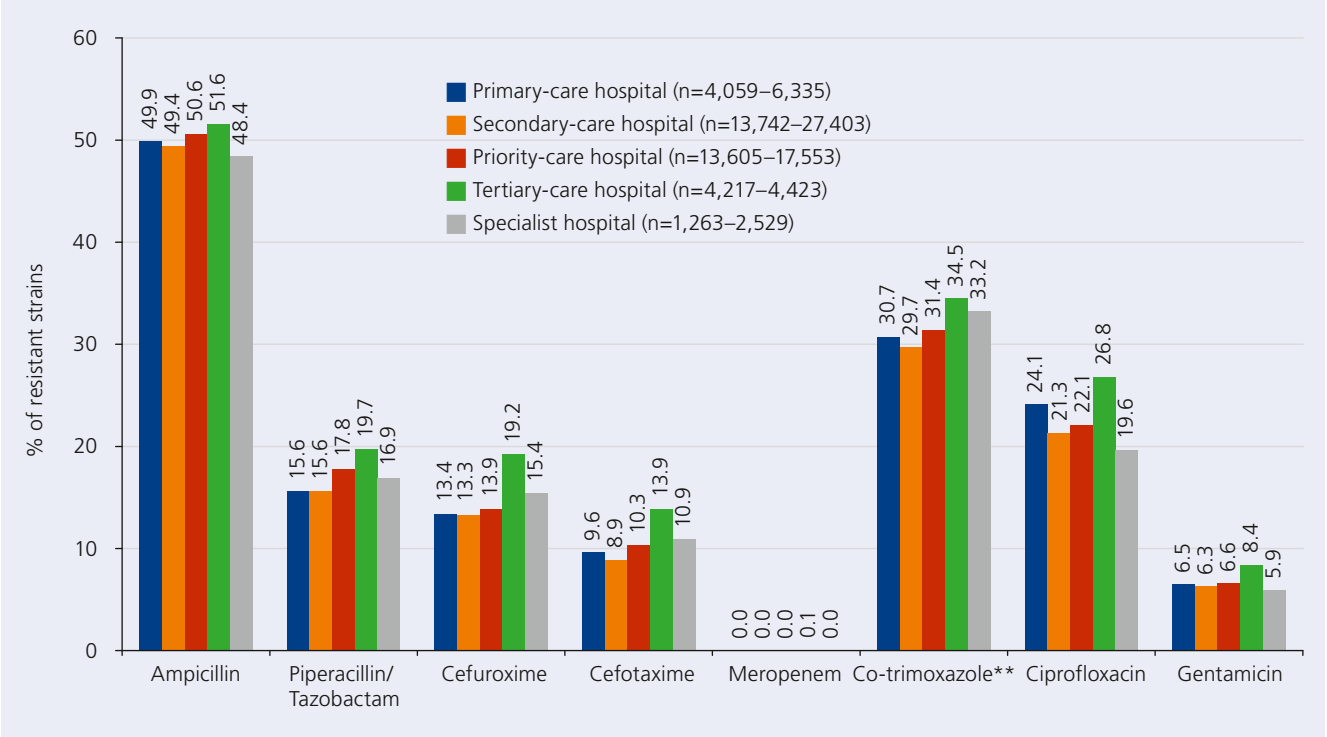

Fig. 4.1.5.1.6: Percentage of resistant *E. coli* strains from hospitals of various levels of care (Source: ARS, 2011 data*); *Data as of: 21/07/2013
**Trimethoprim/Sulphamethoxazole

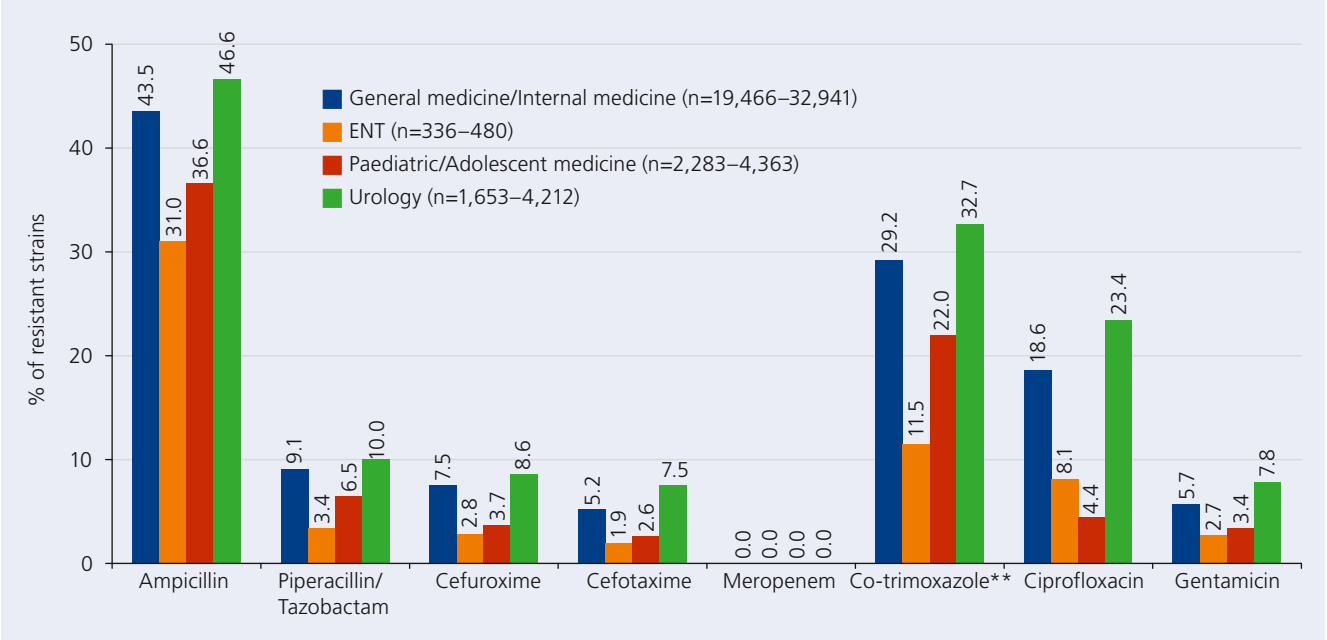

Fig. 4.1.5.1.7: Percentage of resistant *E. coli* strains in various fields of outpatient care (Source: ARS, 2011 data*)
*Data as of: 21/07/2013; **Trimethoprim/Sulphamethoxazole

from 14% to 30% (in 2007) and ranged between 23% and 25% at the end of the study period. The percentage of strains resistant to third-generation cephalosporins initially increased from < 1% in 2003 to 8% in 2007, was 5% in 2008 and subsequently 8% in each year. Until 2008, the prevalence of resistance to aminoglycosides was 4–7% throughout the entire study period; in 2006, however, a resistance rate of 10% was recorded. After 2008, the rate ranged between 7% and 9%.[13]

G-TEST

The prevalence of resistance to tigecycline in *E. coli* isolates was investigated as part of three Germany-wide studies (G-TEST I-III) using isolates from hospitalised patients in 2005 (one year before the introduction of tigecycline), 2007 (one year after the introduction) and 2009. In each of the three study years, approx. 300 *E. coli* isolates were tested for susceptibility to tigecycline and other antimicrobials. In 2005 and 2007, no tigecycline-resistant *E. coli* were detected; in 2009, one strain was found to be resistant to tigecycline (MIC 4 mg/l). The percentage of isolates resistant to fluoroquino-

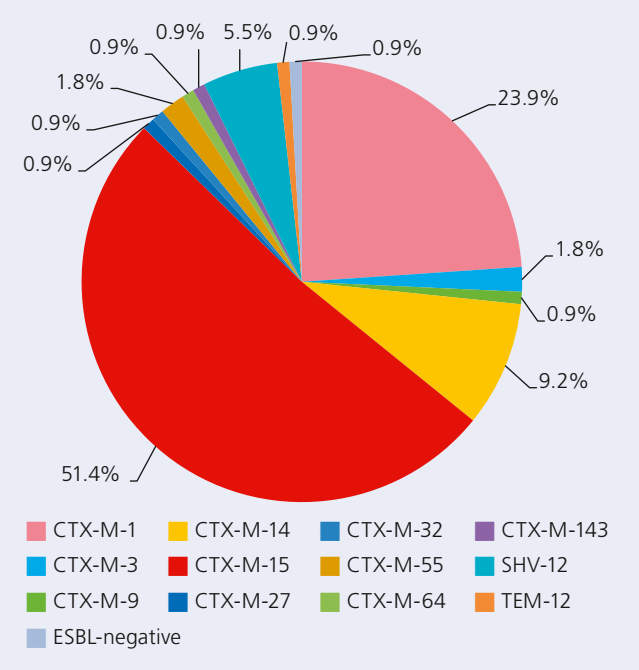

Fig. 4.1.5.1.8: Percentage of ESBL variants of *E. coli* isolates with an ESBL phenotype from hospital care (n=109). No ESBL was detected in one isolate. The MIC values for cefotaxime and ceftazidime were 2 mg/l and 0.5 mg/l, respectively. (Source: PEG resistance study 2010)

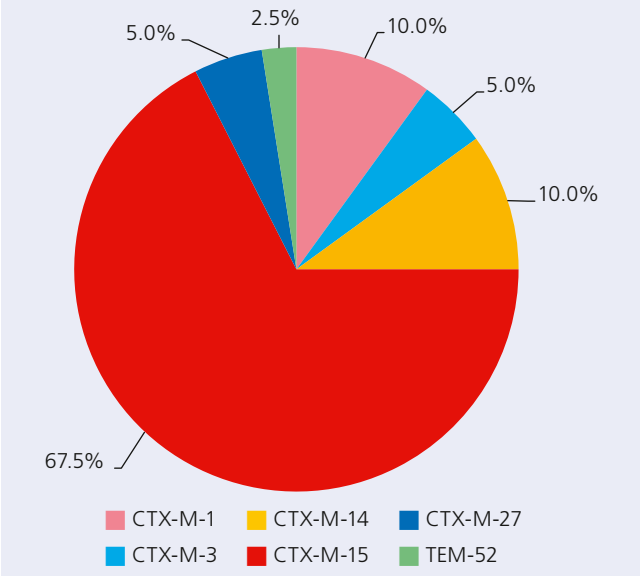

Fig. 4.1.5.1.9: Percentage of ESBL variants of *E. coli* isolates with an ESBL phenotype from outpatient care (n=40). (Source: PEG resistance study 2010)

lones (ciprofloxacin) varied between 21.7% and 28.4% and the percentage of ESBL-producing strains between 5.7% and 13.1%.[14]

Other data sources

The percentage of antimicrobial-resistant strains in some isolates from patients with uncomplicated cystitis was well below the resistance level found in isolates from patients in hospital care. Less than 5% of the 243 strains isolated in Germany within the European ARESC study during the period from September 2003 to June 2006 showed resistance to amoxicillin/clavulanic acid, cefuroxime, ciprofloxacin, fosfomycin and nitrofurantoin. The percentage of isolates resistant to cefuroxime and fosfomycin was even below 1%, whereas the rates of resistance to ampicillin and co-trimoxazole were 34.9% and 25.9%, respectively.[15,16]

ESBL-producing *E. coli*

Nearly all epidemiological studies conducted in recent years reveal an increase in the prevalence of ESBL-producing isolates in Germany.

Molecular characterisation of 109 strains with an ESBL phenotype isolated from inpatients within the 2010 PEG resistance study has demonstrated that more than 90% of the strains produce a CTX-M ESBL (Fig. 4.1.5.1.8). The CTX-M-15 enzyme was detected most frequently (51.4%), followed by CTX-M-1 (23.9%) and CTX-M-14 (9.2%). A similar distribution pattern was observed for the 40 outpatient urine isolates with an ESBL phenotype (Fig. 4.1.5.1.9).

CTX-M-1-producting strains are detected particularly often in veterinary specimens and food.[17] A Dutch study, which used various molecular typing techniques, found that ESBL-producing *E. coli* isolates from poultry samples were closely related to those from stool specimens and blood cultures of patients. CTX-M-1 was the predominant ESBL in each case.[18,19] The results of the study suggest that ESBL-producing *E. coli* can be transmitted from poultry to humans. In this connection, the results of the susceptibility testing of isolates obtained as part of the zoonosis monitoring programme at the Federal Institute for Risk Assessment (BfR) are interesting. Here, an increase in resistance to ceftazidime from 5.9% in 2009 to 13.5% in 2010 was observed in *E. coli* isolates from broilers. However, ESBL-producing *E. coli* were also found in poultry, laying hens, turkey, pork, veal calves as well as in bulk tank milk.[20]

Unlike the spread of CTX-M-1, the occurrence of CTX-M-15 is closely associated with the pandemic spread of the clone O25b-ST131.[21] CTX-M-15 was also the predominant ESBL variant in numerous other studies on human *E. coli* isolates conducted in Germany in 2004, 2008 and 2011.[22] Up to 7% of the general population carry ESBL-producing strains.[22,23] By contrast, outbreaks with ESBL-producing *E. coli* have so far been rare in Germany. An exception to this was the extremely rapid spread of the Shiga toxin-producing *E. coli* serovar O104:H4 featuring additional enteroaggregative properties in 2011, which caused 855 cases of haemolytic-uraemic syndrome and nearly 3,000 cases of EHEC gastroenteritis.[22] This strain was found to produce an CTX-M-15 ESBL.

Carbapenemase-producing *E. coli*

Since mid-2009, microbiology laboratories in Germany have had the opportunity to submit multidrug resistant gram-negative bacteria with suspected presence of a carbapenemase to the National Reference Centre (NRZ) for Gram-Negative Bacteria in Bochum. In 2011 and 2012, the NRZ performed molecular characterisation of the carbapenemase types of 20 and 50 *E. coli* isolates, respectively. In most cases, OXA-48 carbapenemases were detected, although the types KPC-2 and KPC-3 as well as metallo-β-lactamases (predominantly VIM-1 and NDM-1) were identified as well.[24,25]

Conclusion

The prevalence of resistance to antimicrobials widely used at hospitals (broad-spectrum penicillins, cephalosporins, fluoroquinolones) increases further in the hospital sector, whereas the prevalence of resistance to carbapenems continues to be below 1%.

Due to the resistance level of approx. 30%, fluoroquinolones can no longer be recommended for the empiric therapy of infections with suspected involvement of *E. coli*. By contrast, carbapenems still play a major role in the treatment of life-threatening infections. If the rate of ESBL-producing pathogens that can no longer be treated with cephalosporins and often also not with fluoroquinolones were to increase further, it can be assumed that carbapenem consumption will continue to increase even more strongly in the next few years, further increasing the risk of emergence and spread of carbapenem-resistant strains.

In general, the resistance level in outpatient care is significantly lower than in inpatient care, but ESBL-producing and fluoroquinolone-resistant *E. coli* have emerged in this sector, too. Isolates from patients in outpatient urology clinics exhibit almost equally high rates of resistance to numerous antimicrobials as isolates from hospitalised patients. This observation may be explained by the particularly large number of patients with underlying urological diseases, who are predisposed to recurrent urinary tract infections and are therefore likely to have undergone antimicrobial treatment before. Patients with a history of antimicrobial therapy are exposed to a significantly increased risk of acquisition of resistant pathogens. The example of urology patients also points to the fundamental problem of interpreting outpatient resistance data. A large number of specimens submitted to the laboratory most likely come from patients who have undergone previous treatment, i.e. the real extent of the spread of antimicrobial-resistant bacterial pathogens is not reflected in laboratory statistics.[26]

In view of this, the results of epidemiological studies such as the ARESC study[15,16] are interesting. In patients with uncomplicated urinary tract infections, whose urine specimens are usually not subjected to microbiological testing, the resistance situation of *E. coli* is still comparatively favourable. As a result of the detection of multidrug resistant clones, which have spread to epidemic levels in these patients[17, 24], the situation has also worsened in this patient group, as evidenced by the results of the ECO·SENS I (1999–2000) and ECO·SENS II (2007–2008) studies for Austria, where a strong increase in resistance to a great number of antimicrobials was observed, e.g. to ampicillin from 17.5% to 28.8%, to ciprofloxacin from 0% to 4.1% and to co-trimoxazole from 9.5% to 14.4%.[27] Therefore, a more careful use of antimicrobials is urgently needed in order to avoid the selection of (multidrug-) resistant *E. coli*.

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4.1.5.2 Other *Enterobacteriaceae*

Further *Enterobacteriaceae* species commonly causing opportunistic and hospital-associated infections include *Enterobacter cloacae, Klebsiella pneumoniae, Klebsiella oxytoca* and *Proteus mirabilis*. However, they also serve as reservoirs for resistance genes.

Trends in resistance development

PEG resistance study

Fig. 4.1.5.2.1 to 4.1.5.2.4 shows the temporal development of resistance rates of the four *Enterobacteriaceae* species *Enterobacter cloacae, Klebsiella pneumoniae, Klebsiella oxytoca* and *Proteus mirabilis* for up to seven antimicrobials in inpatient care (hospital care) selected as examples (cefuroxime, cefotaxime, piperacillin/tazobactam, meropenem, co-trimoxazole, ciprofloxacin, gentamicin) as well as the rates of the ESBL-producing isolates.[1,2]

Over the period 1995–2010, the percentage of *E. cloacae* strains resistant to cefotaxime initially increased from 30.7% to 43.5% and then dropped to 28.4%. The rate of piperacillin/tazobactam resistance varied between 7.5% and 26.6%. The most common cause of β-lactam resistance in *E. cloacae* is the inducible or constitutive expression of chromosomally mediated AmpC β-lactamases. The rate of ciprofloxacin resistance increased from 2.2% in 1995 to 10.3% in 2001, most recently being 7.7%. The rate of co-trimoxazole resistance also rose initially, namely from < 5% in the 1990s to 17% in 2007, and was 12.5% in the last study year. The rate of meropenem resistance was < 1% in all study years (Fig. 4.1.5.2.1).

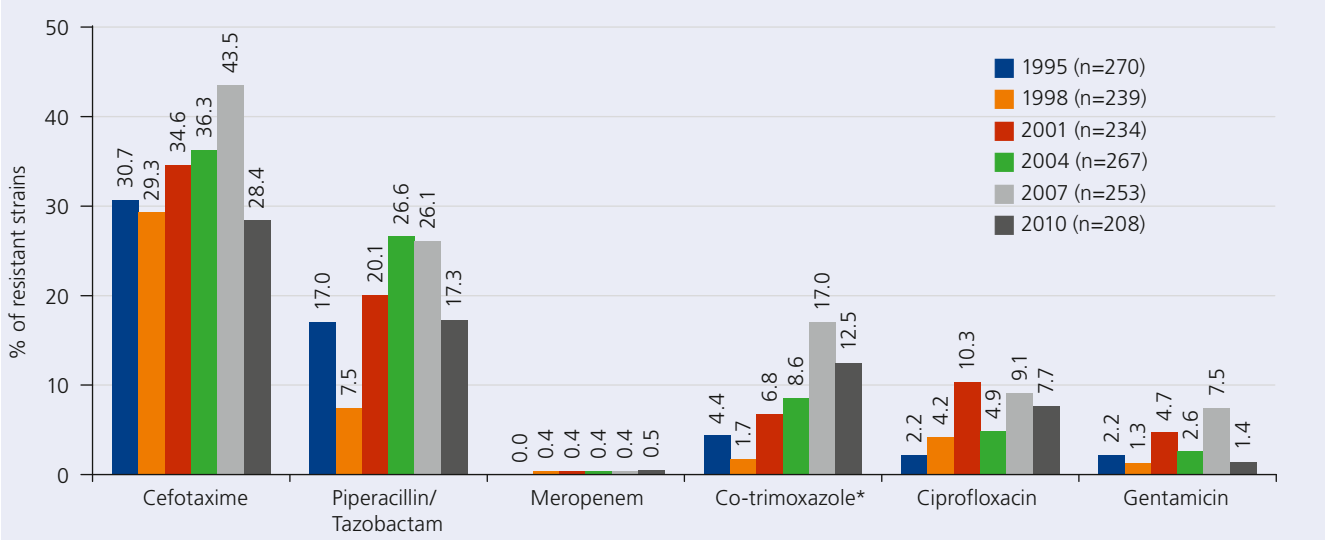

Fig. 4.1.5.2.1: Percentage of resistant *E. cloacae* strains from hospital care (Source: PEG resistance study); *Trimethoprim/Sulphamethoxazole

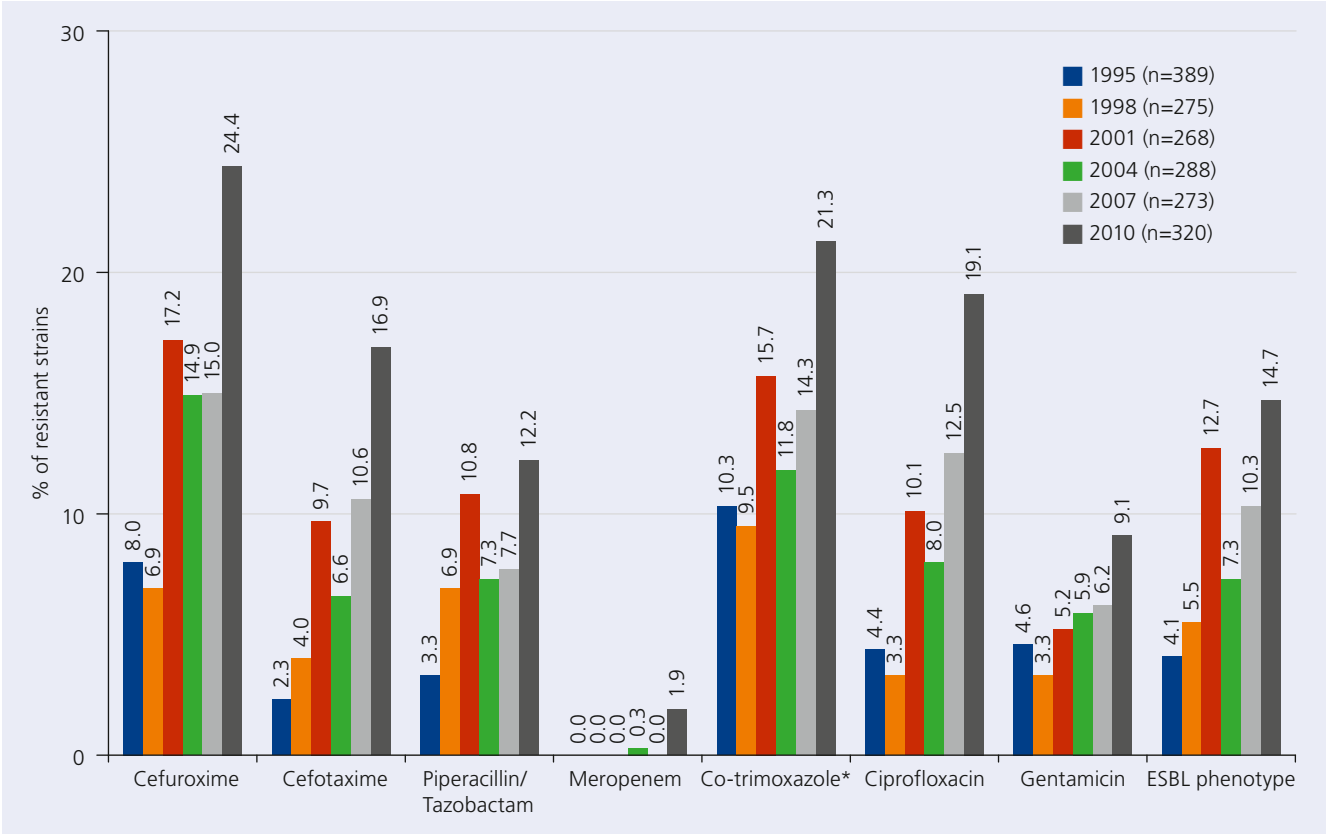

Fig. 4.1.5.2.2: Percentage of resistant *K. pneumoniae* strains from hospital care (Source: PEG resistance study); *Trimethoprim/Sulphamethoxazole

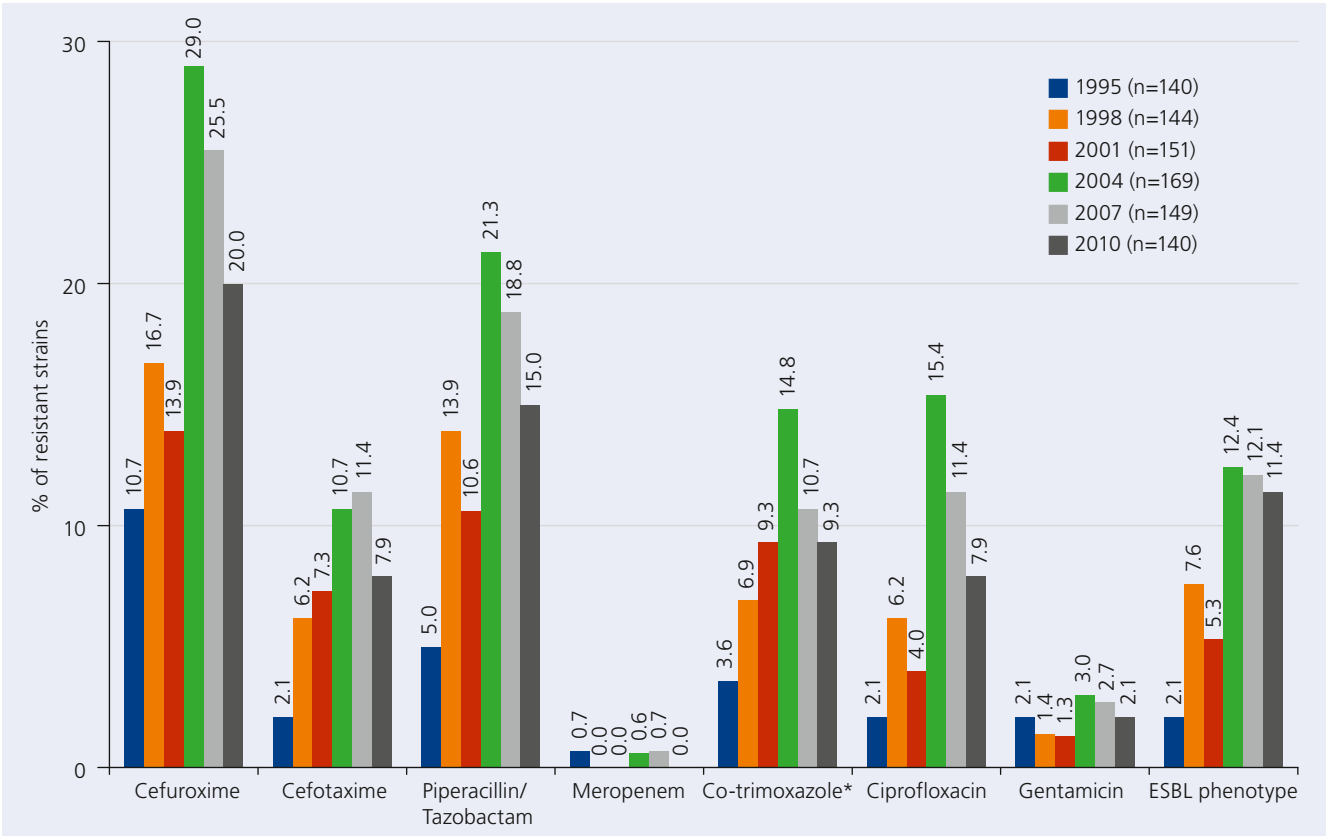

Fig. 4.1.5.2.3: Percentage of resistant *K. oxytoca* strains from hospital care (Source: PEG resistance study); *Trimethoprim/Sulphamethoxazole

Over the 15-year study period, the prevalence of resistance to some antimicrobials in *K. pneumoniae* increased significantly, e.g. to cefuroxime from 8% to 24.4%, to cefotaxime from 2.3% to 16.9%, to piperacillin/tazobactam from 3.3% to 12.2%, to ciprofloxacin from 4.4% to 19.1% and to gentamicin from 4.6% to 9.1% (Fig. 4.1.5.2.3). To identify the ESBL phenotype, isolates with cefotaxime or ceftazidime MIC values of > 1 mg/l were tested for susceptibility to cefotaxime ± clavulanic acid and ceftazidime ± clavulanic acid in accordance with the guidelines of the Clinical and Laboratory Standards Institute (CLSI).3 The percentage of strains with an ESBL phenotype also increased from 4.1% in 1995 to

14.7% in 2010. It is particularly alarming to see that the rate of resistance to first-generation carbapenems (test substance meropenem) was well above 1% for the first time in 2010 (Fig. 4.1.5.2.2).

The development of resistance to cefuroxime in *K. oxytoca* was characterised by an initial increase in the resistance rate from 10.7% in 1995 to 29% in 2004 and a subsequent decline to 25.5% in 2007, followed by another decrease to 20% in 2010. A similar trend in resistance development was observed for co-trimoxazole, ciprofloxacin and piperacillin/tazobactam. The percentage of cefotaxime-resistant strains initially rose from approx. 2% to 11% in 2007 and subsequently dropped to 7.9% in 2010. The percentage of strains with an ESBL phenotype was subject to a comparable trend, while the resistance situation for gentamicin and meropenem remained largely unchanged (Fig. 4.1.5.2.3).

There was hardly any change in the resistance situation of *P. mirabilis* (Fig. 4.1.5.2.4). However, the highest rates of resistance to both ciprofloxacin and gentamicin were observed in the last study year. The percentage of ESLB-producing isolates ranged between 0% and 3.1%.

The percentage of 3MRGN multidrug resistant strains, as defined by KRINKO[4], in all *K. pneumoniae* isolates increased from 1.3% in 1995 to 13.1% in 2010, in *E. cloacae* from 1.1% to 7.7%, in *K. oxytoca* from 0% to 7.1% and in *P. mirabilis* from 1.8% to 2.9%. Seven strains of *K. pneumoniae* (2.2%) as well as one strain of *E. cloacae* (0.5%) were classified as 4MRGN in 2010.

Possible alternatives for the treatment of infections caused by multidrug resistant *Enterobacteriaceae* include colistin, fosfomycin und tigecycline. *P. mirabilis* exhibits intrinsic resistance to colistin and tigecycline. The prevalence of colistin resistance in *E. cloacae* isolates in 2010 was 7.2%, whereas the percentage of colistin-resistant strains in the two *Klebsiella* species was less than 2% each. The percentage of strains resistant to fosfomycin varied between species, amounting to 36.5% in *E. cloacae*, 16.4% in K. oxytoca, 22.5% in *K. pneumoniae* and 18.7% in *P. mirabilis*. The testing of *Klebsiella* strains with an ESBL phenotype for susceptibility to tigecycline revealed that all tested *K. oxytoca* isolates and 93.6% of *K. pneumoniae* isolates were suscpetible.[1]

PEG blood culture study 2006/2007 and GENARS/ARS

The results of the PEG blood culture study and those of the GENARS project were already presented in the 2008 and 2010 GERMAP reports.[7,8]

The resistance data so far recorded in the laboratories participating in ARS also allows its evaluation by care sector (general ward vs. intensive care unit). The resistance situation of *K. pneumoniae* isolates from patients on general wards was more favourable throughout than regarding those from patients in intensive care units, whereas no or only minor differences were observed between these two groups of patients with regards to *E. cloacae, K. oxytoca* and *P. mirabilis*. In some cases, the resistance level on general wards was even higher than in intensive care units (Fig. 4.1.5.2.5–4.1.5.2.8).[7]

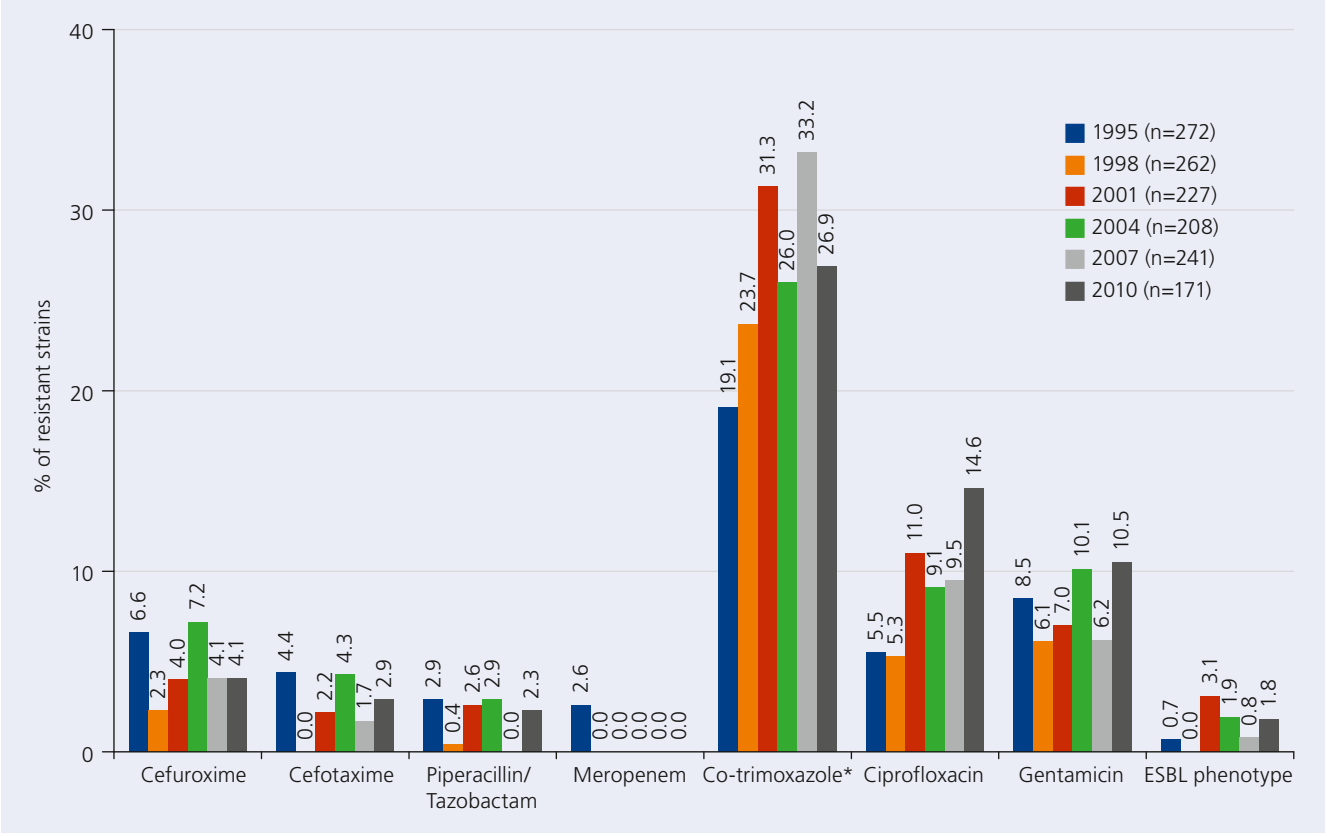

Fig. 4.1.5.2.4: Percentage of resistant *P. mirabilis* strains from hospital care (Source: PEG resistance study); *Trimethoprim/Sulphamethoxazole

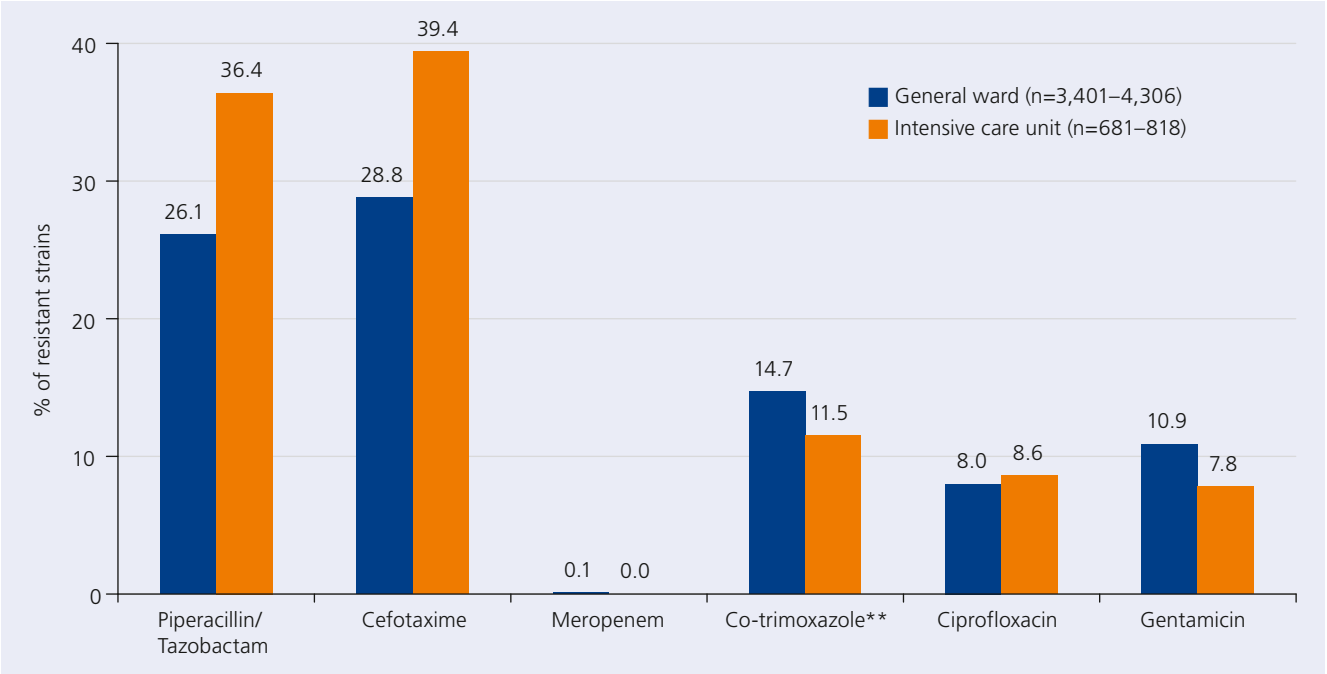

Fig. 4.1.5.2.5: Percentage of resistant *E. cloacae* strains on general wards and in intensive care units (Source: ARS, 2011 data*); *Data as of: 23/10/2012
**Trimethoprim/Sulphamethoxazole

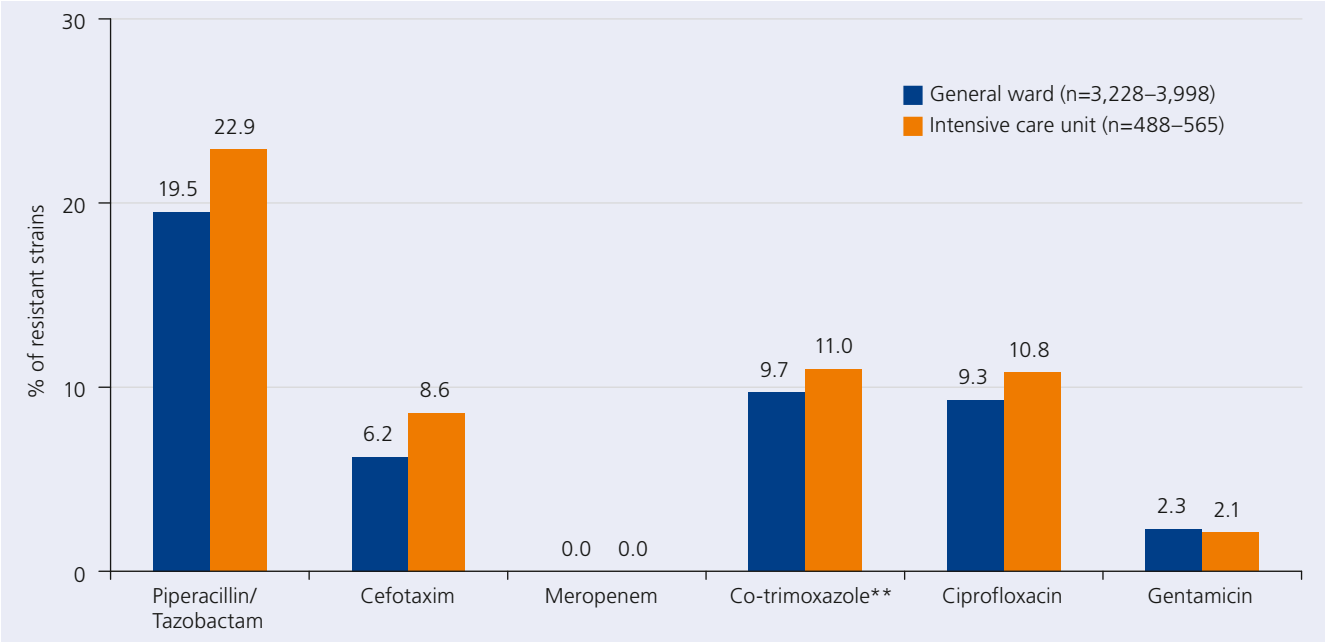

Fig. 4.1.5.2.6: Percentage of resistant *K. oxytoca* strains on general wards and in intensive care units (Source: ARS, 2011 data*); *Data as of: 30/10/2012
**Trimethoprim/Sulphamethoxazole

SARI

The number of bacterial strains isolated from patients in 64 intensive care units during the period 2001–2011 was 171,055[8], 10,146 of which were *K. pneumoniae* isolates. The prevalence of resistance to third-generation cephalosporins in *K. pneumoniae* rose from 3.8% in 2001 to 15.1% in 2008[9], reaching 19.5% in 2011[10] The resistance density of isolates resistant to third-generation cephalosporins increased from 0.25 per 1,000 patient days in 2001 to 0.82 in 2008[9], reaching 1.19 in 2011.[8] The increase in the rates of resistance to third-generation cephalosporins goes hand in hand with a nearly doubled carbapenem consumption. With one exception, the percentage of imipenem-resistant strains in all *K. pneumoniae* isolates up to and including 2010 was always below 1%, increasing slightly to 1.2% (meropenem) and 1.5% (imipenem) in 2011.10 At the beginning of the study period, the rate of fluoroquinolone resistance (test substance ciprofloxacin) was 2.2%, then ranged between 4.2% and 9.9% until 2007 and reached 16.7% in 2011.[10]

The percentage of *E. cloacae* strains resistant to third-generation cephalosporins mostly ranged between 30% and 40% while the percentage of strains resistant to fluoroquinolones (ciprofloxacin) was initially below 5% and then varied between 5.3% and 10.7%.[10]

EARS-Net (formerly EARSS)

During the period 2005–2011, between 105 and 519 *K. pneumoniae* blood culture isolates were tested each year in 12–17 German participating laboratories.[11] Until 2004, neither

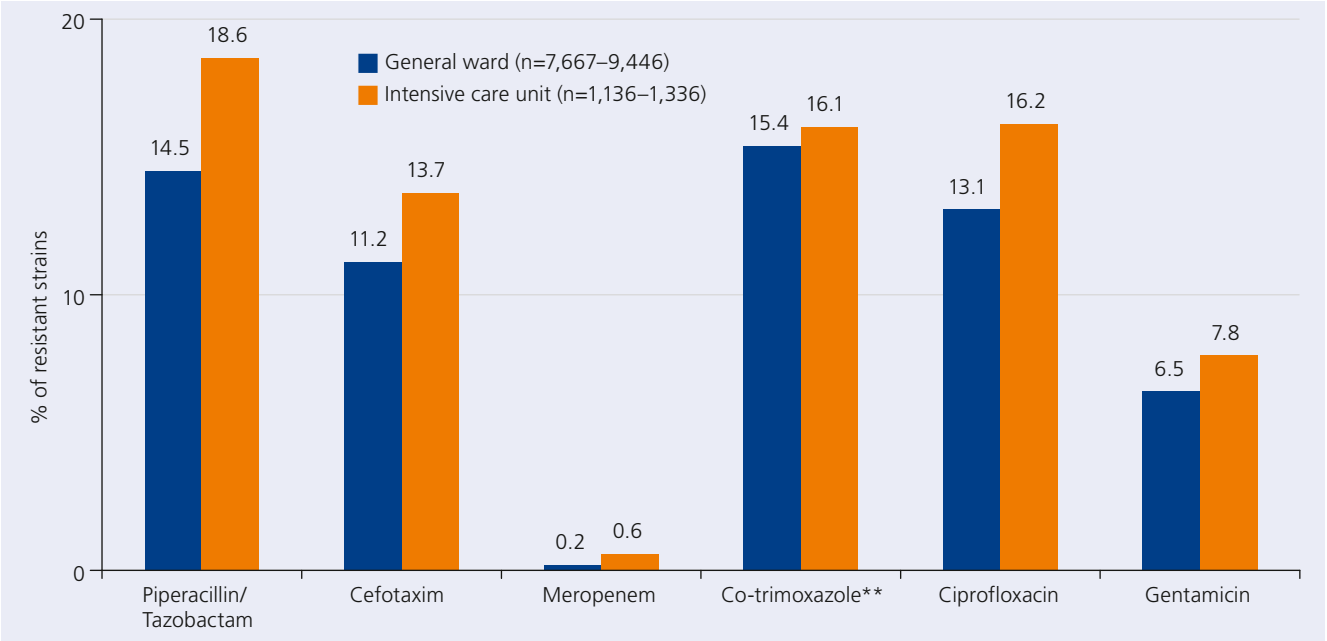

Fig. 4.1.5.2.7: Percentage of resistant *K. pneumoniae* strains on general wards and in intensive care units (Source: ARS, 2011 data*); *Data as of: 06/11/2012
**Trimethoprim/Sulphamethoxazole

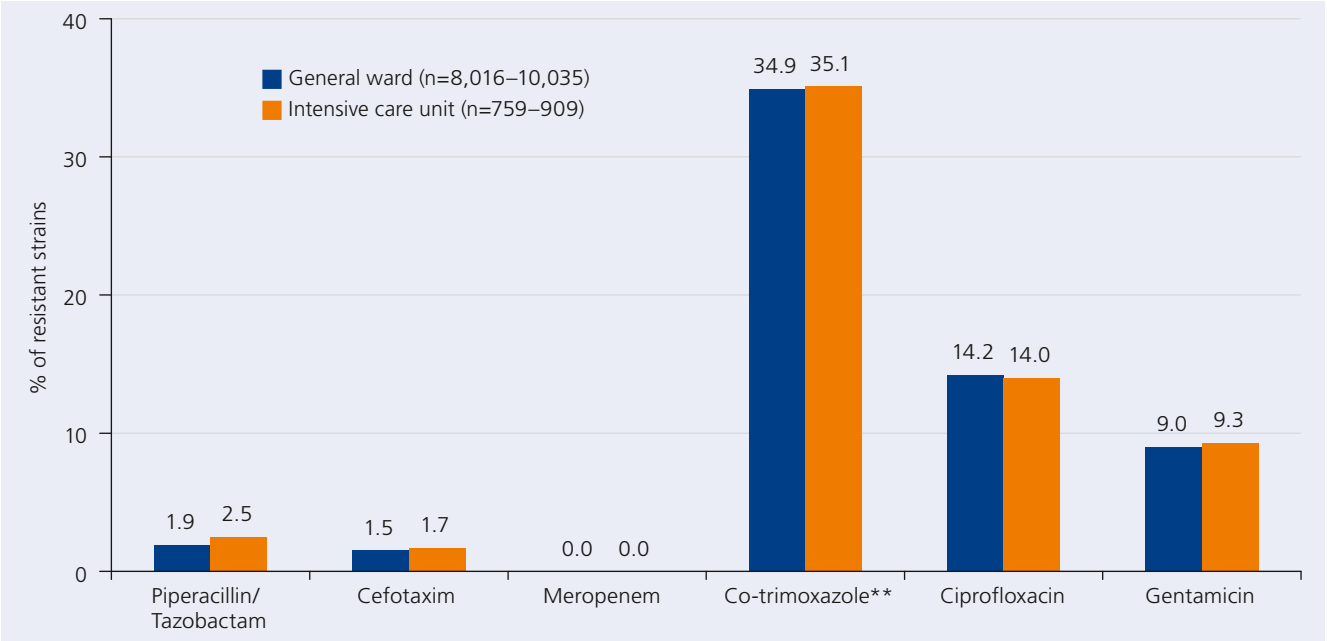

Fig. 4.1.5.2.8: Percentage of resistant *P. mirabilis* strains on general wards and in intensive care units (Source: ARS, 2011 data*); *Data as of: 06/11/2012
**Trimethoprim/Sulphamethoxazole

the number of participating laboratories nor the number of isolates tested by them were representative of the resistance situation in Europe. During the period 2009–2011, the prevalence of resistance to aminoglycosides was 9–10%, to fluoroquinolones 14–15%, to third-generation cephalosporins 13% and to carbapenems < 1%.

G-TEST

In 2005, 2007 and 2009, approx. 230 *E. cloacae* isolates, 100 *K. oxytoca* isolates and 190 *K. pneumoniae* isolates were tested for susceptibility to tigecycline and other antimicrobials.[12] *Proteus* spp. and *Morganella morganii* exhibit intrinsic low susceptibility or resistance to tigecycline, which is why they were not included in this study. 1–2% of the tested *K. oxytoca* isolates showed resistance to tigecycline, as opposed to 6–10% of *E. cloacae* and 7–12% of *K. pneumoniae* isolates. The percentage of *K. oxytoca* isolates with an ESBL phenotype rose from 9% in 2005 to 17.4% in 2007 and dropped to 16.7% in 2009. The percentage of *K. pneumoniae* isolates increased from 4.3% to 14.6% and then dropped to 12.8%. The prevalence of resistance to fluoroquinolones (ciprofloxacin) in *K. oxytoca* increased from 6% to 13.8%, most recently accounting for 11.5%, whereas the fluoroquinolone resistance in *K. pneumoniae* and *E. cloacae* was observed to increase steadily (from 8.1% to 21.4% and from 5.6% to 10.6%, respectively). The additional increase in the rate of piperacillin/tazobactam resistance (from 14% to 23.9%) in *K. oxytoca* between 2005 and 2007 was remarkable, with the subsequent rate being 20.8%. The resistance rate of *K. pneumoniae* varied between 4.8% and 10.3%, whereas the

resistance rate of *E. cloacae* remained nearly unchanged in all three years (approx. 20%). The percentage of ertapenem-resistant *E. cloacae* strains was 4% (2005), 9% (2007) and 5% (2009), while a maximum percentage of 2.1% was observed in all three years in *K. pneumoniae* strains. By contrast, resistance to imipenem was limited to 0.5% of the *K. pneumoniae* strains in the last study year. Carbapenem-resistant *K. oxytoca* strains were not detected during the study period.

ESBL-producing strains

Nearly all epidemiological studies conducted in recent years reveal an increase in the prevalence of ESBL-producing isolates in Germany.

Molecular characterisation of 47 *K. pneumoniae* strains with an ESBL phenotype isolated from inpatients within the 2010 PEG resistance study has demonstrated that 85.1% of the strains produce a CTX-M ESBL (Fig. 4.1.5.2.9). The CTX-M-15 enzyme was detected most frequently (74.5%). One isolate was found to produce the enzyme VEB-1. In three strains (6.4%) with an ESBL phenotype, no ESBL was detected. The MIC values for ceftazidime were all above 1 mg/l and those for cefotaxime all below 0.5 mg/l. Since all three isolates were tested positive for SHV-1 β-lactamase, the resistance is most likely the result of the overexpression of SHV-1.

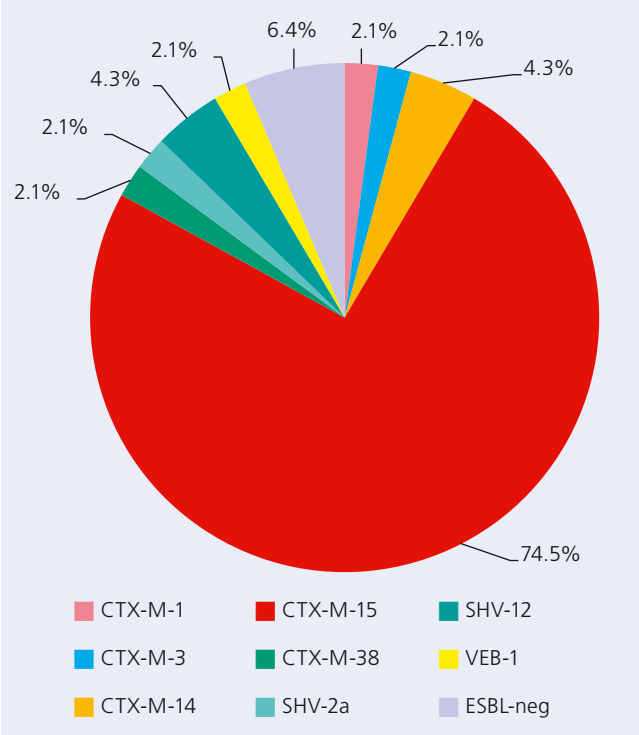

Fig. 4.1.5.2.9: Percentage of ESBL variants of *K. pneumoniae* isolates with an ESBL phenotype from hospital care (n=47). (Source: PEG resistance study 2010)

Merely 5 of the 16 *K. oxytoca* strains with an ESBL phenotype produced an ESBL, which was a CTX-M ESBL in each case. In the remaining 11 strains classified as expressing the ESBL phenotype, this is assumed to be mostly associated with the overexpression of the chromosomal OXY (KOXY, K1) β-lactamase, which simulates the presence of a plasmid-mediated ESBL phenotype.[13] This is evidenced by the presence of resistance to piperacillin/tazobactam as well as the difference in the MIC values for ceftriaxone (≥ 16 mg/l) and cefotaxime (2–8 mg/l).

PER-1 (n=2) and TEM-52 ESBL were detected in the three *P. mirabilis* strains with an ESBL phenotype.

The colonisation of high-risk patients, such as newborns, with ESBL-producing *Enterobacteriaceae* may have fatal consequences. In 2011/2012, for example, the spread of a multidrug resistant CTX-M-15-producing *K. pneumoniae* strain caused several deaths in the neonatal intensive care unit of a hospital in Bremen.[14]

Carbapenemase-producing strains

Resistance or intermediate susceptibility to second-generation carbapenems (ertapenem) was observed in 13% of the *E. cloacae* isolates and 5% of the *K. pneumoniae* isolates obtained from inpatients within the 2010 PEG resistance study. 6 (1.9%) of the *K. pneumoniae* strains were additionally found to be resistant to first-generation carbapenems (doripenem, imipenem, meropenem, see Fig. 4.1.5.2.3). In these strains as well as in one *E. cloacae* strain, the resistance was found to be associated with production of a carbapenemase.[1] Molecular characterisation of the seven strains revealed the presence of the metallo-β-lactamase VIM-1 in *E. cloacae* as well as the carbapenemases KPC-3 (n=3), KPC-2, OXA-48 and VIM-4 in *K. pneumoniae*.

Since mid-2009, microbiology laboratories in Germany have had the opportunity to submit multidrug resistant gram-negative bacteria with suspected presence of a carbapenemase to the National Reference Centre (NRZ) for Gram-Negative Bacteria in Bochum. In 2012, the NRZ performed molecular characterisation of the carbapenemases of 435 *K. pneumoniae*, 44 *E. cloacae* and 25 *K. oxytoca* strains. The most commonly detected carbapenemase in *K. pneumoniae* was OXA-48 (n=166), followed by KPC-2 (n=144) and KPC-3 (n=66), whereas VIM-2 was predominant in *E. cloacae* (n=19) and *K. oxytoca* (n=19).15

In 2012, an alarming development was observed. More than twice as many strains were submitted to the NRZ as in 2011.[16] The strong increase in the number of NDM-1-producing *K. pneumoniae* isolates (from 1 to 25) was remarkable. The increase in the prevalence of KPC-2 in *Enterobacteriaceae* (in particular in *K. pneumoniae*) was particularly noteworthy in Saxony, where this prevalence is now assumed to be endemic. Isolates producing KPC-3 were found predominantly in the Berlin area. Some of the KPC-2- and KPC-3-producing *K. pneumoniae* isolates from Saxony selected as examples have been proved to belong to the *K. pneumoniae* clone ST-258 found worldwide.16

Conclusion

The treatment of Klebsiella infections with third- and fourth-generation cephalosporins is being increasingly limited by the emergence of strains with an ESBL phenotype. The average rate of ESBL-producing strains in all *K. pneumoniae* isolates continues to be estimated at 15%. Isolates that constitutively produce AmpC β-lactamases are commonly found in *Enterobacter* spp., causing resistance to third-generation cephalosporins (cefotaxime, ceftazidime, ceftriaxone) and other antibacterial agents. Third-generation cephalosporins are not

indicated for treatment even in the case of severe infections caused by bacteria with inducible AmpC β-lactamases and in-vitro susceptibility to cefotaxime, as there is a risk of selection of mutants with constitutive (derepressed) expression of AmpC β-lactamase in the course of the treatment. A combination of piperacillin and a β-lactamase inhibitor constitutes no alternative for the treatment of *Enterobacter* infections.

The level of resistance to fluoroquinolones has increased in recent years, but is still below that of *E. coli*. Although the resistance situation for carbapenems is (still) favourable, both the results of the PEG resistance study and the National Reference Centre for Gram-Negative Hospital Pathogens and the increase in carbapenem consumption suggest that the prevalence of carbapenem-resistant strains, in particular *K. pneumoniae* species, is expected to increase to a considerable (in some regions even alarming) extent in the next few years.

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Reviewer: E. Straube

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4.1.6 *Pseudomonas aeruginosa* and other non-fermenting bacteria

4.1.6.1 *Pseudomonas aeruginosa*

Pseudomonas aeruginosa is among the most common causative agents of nosocomial infections. The infections typically affect immunocompromised patients or patients who are ventilated over longer periods of time. *P. aeruginosa* is thus particularly often isolated from patients in intensive care units and on haematology/oncology wards. Common clinical manifestations include pneumonia (especially in ventilated patients), infections of burn wounds, urinary tract infections as well as surgical site infections. Bloodstream infections caused by *P. aeruginosa* are associated with a high mortality rate. Patients suffering from mucoviscidosis (cystic fibrosis) are particularly predisposed to bronchopulmonary infections by alginate-producing *Pseudomonas* strains. The structure of the outer membrane and various efflux pumps are responsible for the fact that *P. aeruginosa* strains exhibit intrinsic resistance to a great number of antimicrobials. The resistance data compiled in this report comes mainly from hospitalised patients. The resistance situation of *P. aeruginosa* in patients with cystic fibrosis (CF patients) is analysed in chapter 4.1.6.2.

Trends in resistance development

PEG resistance study

The period between 1995 and 2010 saw an increase in the resistance to antimicrobials that are often used for the empiric initial treatment of infections with suspected involvement of P. aeruginosa (i.e. β-lactams and fluoroquinolones) (Fig. 4.1.6.1.1).[1,2] The percentage of strains resistant to antipseudomonal cephalosporins (ceftazidime, cefepime) as well as piperacillin (± β-lactamase inhibitor) was well below 10% until 2008, varied between 10% and 15% from 2001 to 2007 and rose to 15–20% in 2010. The rate of resistance to first-generation carbapenems increased significantly towards the end of the study period, amounting to 16.2% (imipenem) and 9.3% (meropenem) in 2010. The percentage of strains susceptible to imipenem and meropenem was nearly identical (77% and 80.1%, respectively).

The prevalence of resistance to ciprofloxacin and levofloxacin varied between 14% and 23% during the study period, with the resistance level being above 20% in the last study years. Before 1990, the percentage of fluoroquinolone-resistant strains in all isolates was still below 3%. By 2001, the rate of aminoglycoside resistance increased, with the resistance level subsequently being either nearly constant (amikacin, tobramycin) or declining (gentamicin). In the last study year, the resistance rates ranged between 3.3% for amikacin and 8.4% for gentamicin (Fig. 4.1.6.1.1).

The percentage of 3MRGN multidrug resistant strains, as defined by KRINKO[3], in all isolates was initially 1.4% in 1995 and 0.7% in 1998, increasing to 6% in 2001 and then further to 8% in 2010. The percentage of 4MRGN strains was initially < 1%, increased to 3.1% in 2001 and was most recently 6.7%.

All isolates from patients in intensive care units showed higher resistance rates than isolates from patients on general wards. However, amikacin demonstrated a higher activity against

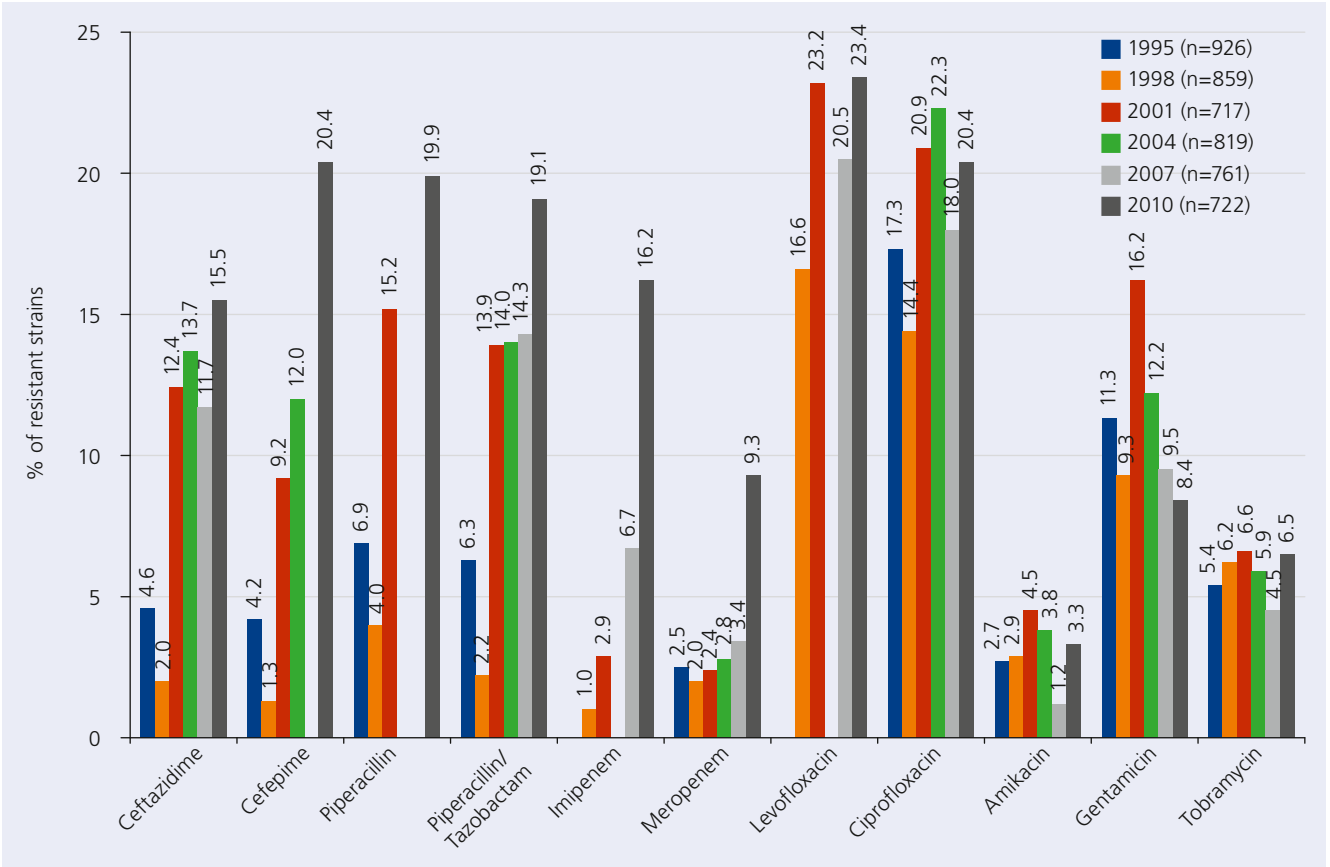

Fig. 4.1.6.1.1: Percentage of resistant *P. aeruginosa* strains from hospital care (Source: PEG resistance study)

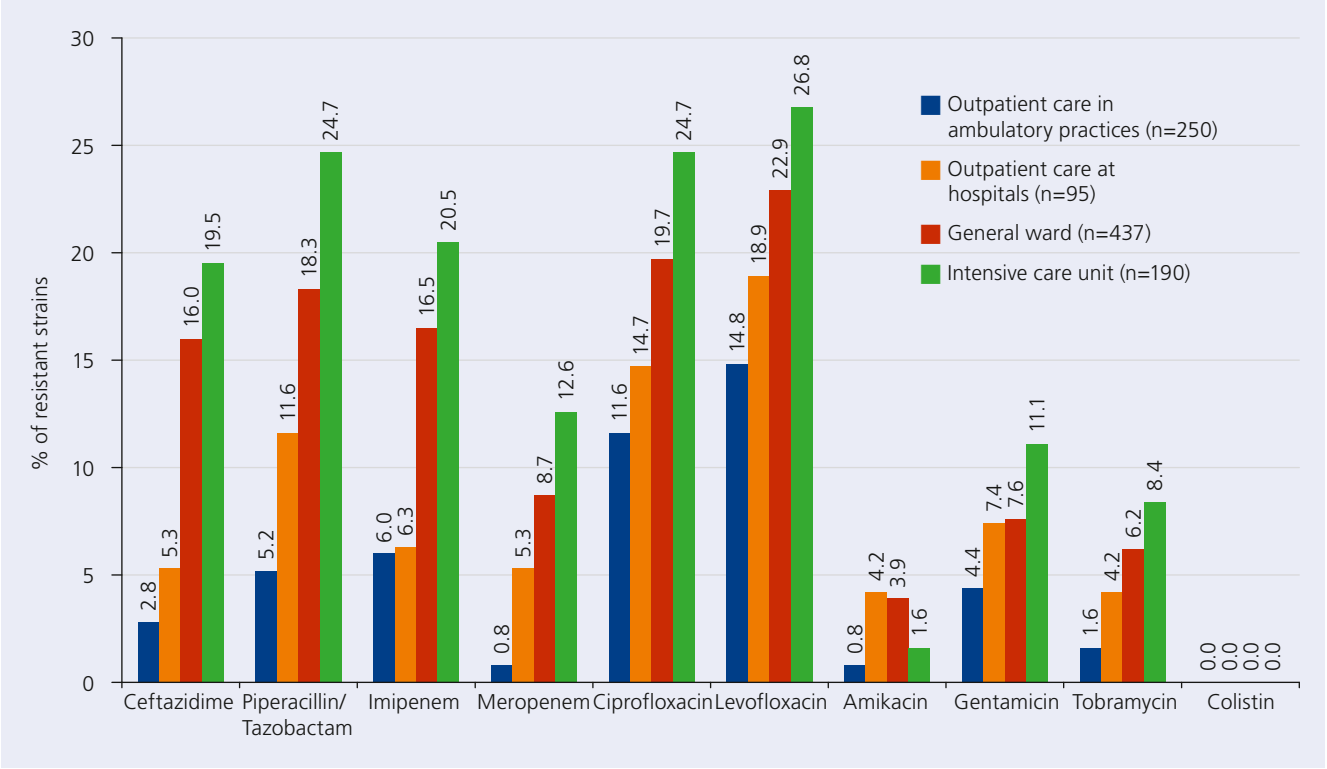

Fig. 4.1.6.1.2: Percentage of resistant *P. aeruginosa* strains in outpatient care, on general wards and in intensive care units (Source: PEG resistance study 2010)

strains from patients in intensive care units than against those from patients on general wards and in outpatient clinics.

For the first time, the 2010 PEG resistance study also investigated the antimicrobial resistance situation of clinically relevant bacterial species in private practices. A total of 250 isolates from non-CF patients were included in the study. The level of resistance to the tested antimicrobials reached a maximum rate of 14.8%.4 Colistin-resistant strains were not detected in any of the care sectors (Fig. 4.1.6.1.2).

PEG blood culture study 2006/2007 and GENARS/ARS

The results of the PEG blood culture study and those of the GENARS project were already presented in the 2008 and 2010 GERMAP reports.

The resistance data so far recorded in the laboratories participating in ARS allows its evaluation by care sector (outpatient care, general ward, intensive care unit). However, the reliability of the data is limited by the fact that the susceptibility to various antimicrobials is tested in different strain collectives.[5]

Under these circumstances, the level of resistance to some of the tested antimicrobials in isolates from patients in intensive care units was significantly higher than in isolates from patients on general wards and in outpatient care (Fig. 4.1.6.1.3; 2011 data). Significant differences in the resistance situation of isolates from patients at primary-, secondary- and tertiary-care hospitals were not observed. As expected, the highest level of resistance to carbapenems was found in isolates from patients at tertiary-care hospitals.

SARI

The number of bacterial strains isolated from patients in 64 intensive care units during the period 2001–2011 was 171,055[10], 17,794 of which were *P. aeruginosa* isolates. No significant change in fluoroquinolone resistance was observed during the study period. The percentage of strains resistant to ciprofloxacin was 19.7%[7] in 2001, 16% in 2008[7] and 21.1% in 2012[8]. The level of resistance to imipenem was stable until 2008 (25%) and then rose to more than 30%.[7,8] The rate of meropenem resistance was 8.9% at the beginning of the study, 16.9% in 2008 and 23.1% in the last study year.[8] The resistance density of isolates resistant to imipenem was initially < 2 per 1,000 patient days (2001–2005) and then increased mostly to 2.5 (2006–2011).[6]

EARS-Net (formerly EARSS)

During the period 2005–2011, between 117 and 389 blood culture isolates were tested each year in 12–17 German participating laboratories.[11] Until 2004, neither the number of participating laboratories nor the number of isolates tested by them were representative of the resistance situation in Europe. During the period 2009–2011, the rate of resistance to aminoglycosides was 7–12%, to fluoroquinolones 17–18%, to piperacillin/tazobactam 13–15%, to ceftazidime 8–11% and to carbapenems 10–13%.[9]

Carbapenemase-producing strains

As part of the 2010 PEG resistance study, a metallo-β-lactamase (MBL), in most cases VIM-2, was confirmed to cause carbapenem resistance in 20/41 (48.8%) strains resistant to imipenem, meropenem and ceftazidime.[1]

Since mid-2009, microbiology laboratories in Germany have had the opportunity to submit multi-resistant gram-negative bacteria with suspected presence of a carbapenemase to the National Reference Centre (NRZ) for Gram-Negative Hospital Pathogens. In 2012, the NRZ performed molecular characterisation of the carbapenemases of 172 strains. In most of

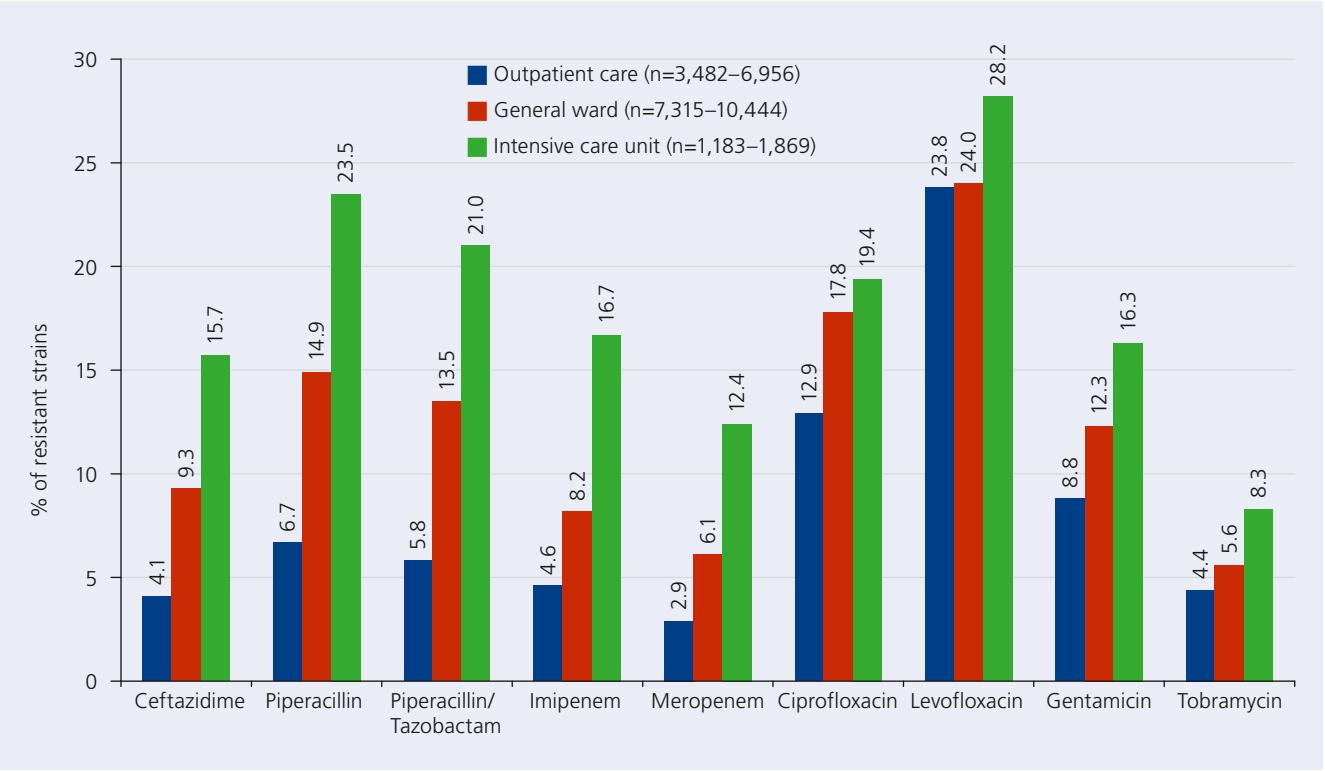

Fig. 4.1.6.1.3: Percentage of resistant *P. aeruginosa* strains in outpatient care, on general wards and in intensive care units (Source: ARS, 2011 data*)
*Data as of: 06/11/2012

the cases, VIM-2 MBL (n=100) were detected, although other MBL, mainly IMP and VIM, were found as well.[10]

Conclusion

The prevalence of resistance to antipseudomonal β-lactams and fluoroquinolones has increased over the last 15 years, whereas a stable or downward trend has been observed for aminoglycosides since 2001. Aminoglycosides, especially amikacin and tobramycin, can thus be recommended for the empiric therapy of infections with suspected involvement of *P. aeruginosa*. The resistance level of all isolates from patients in intensive care units is significantly higher than that observed on general wards and in outpatient care. This predominantly applies to β-lactams. By contrast, resistance rates of < 10% are still often found on general wards, except for fluoroquinolones. In most cases, colistin represents the only therapeutic alternative for the treatment of infections caused by multidrug resistant *P. aeruginosa* strains.

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Reviewer: E. Straube

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4.1.6.2 *Pseudomonas aeruginosa* in CF patients

Resistance situation in CF patients

Resistance situation in CF patients (cystic fibrosis, CF) is one of the most common autosomal recessive hereditary metabolic diseases in Germany. This chronic condition is characterised by a dysfunction of epithelial electrolyte transport (defect of the chloride channel "cystic fibrosis transmembrane conductance regulator") and the resulting production of viscous secretion by all exogenic glands. Facilitated by the viscous bronchial mucus, recurrent bacterial infections of the respiratory tract play a crucial role in the progression of the disease. The colonisation of the CF lung with *Pseudomonas aeruginosa* is the main cause of the morbidity and mortality of the patients. In the course of the disease, most CF patients permanently carry one or more *P. aeruginosa* strains of identical hereditary material (clones). If eradication of the initial colonisation of the CF respiratory tract with *P. aeruginosa* is no longer possible, this chronic infection is treated by regular administration of antimicrobials, mostly given at certain intervals. This is aimed at temporarily reducing the bacterial count in order to delay the chronic-inflammatory impairment of the pulmonary parenchyma, which plays a crucial role in this condition.

Due to the usually lifelong pulmonary persistence of *P. aeruginosa* in the CF lung and the numerous antimicrobial treatments, increasingly adapted subclonal variants of *P. aeruginosa* are selected. In routine microbiology testing, usually performed on a quarterly basis, these predominantly manifest themselves in the form of different morphotypes that exhibit antimicrobial susceptibility to a varying extent. Multidrug resistant variants mostly occur as part of a "polyinfection" together with more susceptible variants. Mucoid isolates, which are characterised by excessive mucus production (alginate) and are usually less resistant to antimicrobials than non-mucoid isolates, are a *P. aeruginosa* morphotype that is typical of the chronic stage of infection.

The resistance situation for the period 2000–2008 regarding both adults and children was already addressed in the 2010 GERMAP report. In the present report, we would like to present the recent development of the last three years (2009–2011), while additionally elaborating on specific factors relevant for lung transplantation in CF patients.

Trends in recent years (patients aged 18 years or older)

Based on the data reported by the consultant laboratories for mucoviscidosis bacteriology (in Northern Germany: Institute of Medical Microbiology and Hospital Epidemiology of the Hanover Medical School, MHH; in Southern Germany: Max von Pettenkofer Institute of Hygiene and Medical Microbiology of Ludwig Maximilian University Munich, MvP), the resistance situation for antipseudomonal antimicrobials that are most commonly used for the treatment of CF was more or less stable during the period 2009–2011. However, the overall resistance rates are higher than in other patient populations, which can be attributed to several factors: Most CF patients carry a *Pseudomonas* clone their whole lives. The numerous interval treatments performed in the course of chronic *P. aeruginosa* infections gradually lead to the selection of ever more resistant *P. aeruginosa* isolates. Moreover, despite careful hygiene measures, there is a possibility that *P. aeruginosa* isolates are transmitted within a patient population. Today,

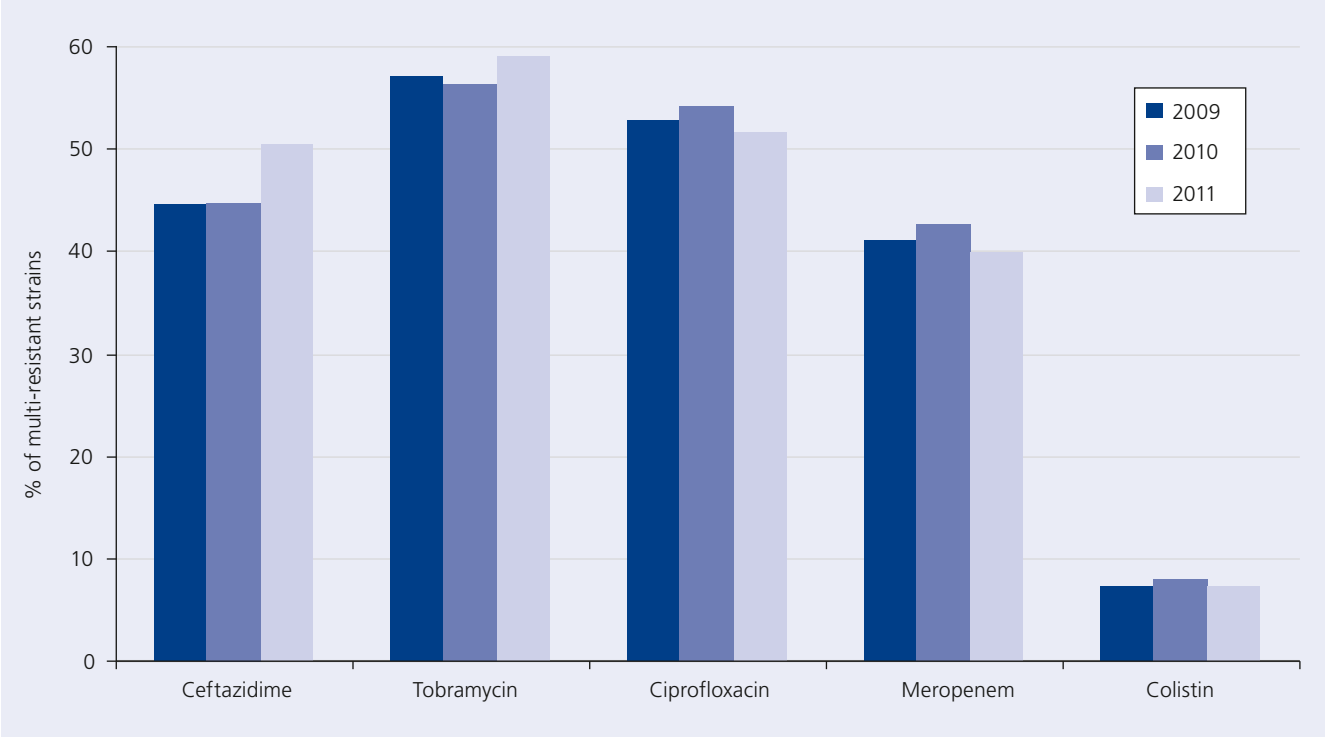

Fig. 4.1.6.2.1: Percentage of *P. aeruginosa* isolates resistant to ceftazidime, tobramycin, ciprofloxacin, meropenem and colistin in CF patients aged 18 years or older (Source: MHH and MvP resistance data)

this risk is minimised by strictly separating *Pseudomonas*-positive patients, non-colonised patients and patients with multidrug resistant isolates.

During the last few years, neither the number of available antipseudomonal antimicrobials nor the therapeutic algorithms applied in the treatment of chronic infections have seen any substantial change. The primary substances used as part of the CF interval therapy regimen are various systemic (especially ceftazidime, meropenem, tobramycin and ciprofloxacin, as a second-line antimicrobial colistin) and inhaled (especially tobramycin and colistin, as a newer substance aztreonam) substances. In the case of acute exacerbation, combination therapy is used additionally in order to cover several resistance variants of a *Pseudomonas* clone and to minimise early resistance development.

Our own data from 2000–2008 shows a slight increase in resistance to most antipseudomonal substances in adult CF patients (18 years or older). By comparison, the resistance rates during the period 2009–2011 were somewhat higher: 44.5–50.4% (2000–2008: 39.4–45.6%) to ceftazidime, 56.4–59.1% (57.4–72.7%) to tobramycin, 51.7–54.2% (43.6–47.9%), to ciprofloxacin, 39.9–42.7% (28.1–36.7%) to meropenem and 7.3–8.0% (4.3–6.3%) to colistin. The aminoglycoside tobramycin represents an exception: Despite consistently high resistance rates (large-scale use of tobramycin for both systemic and inhalation CF therapy), no increasing resistance trend has become apparent in recent years. Among antipseudomonal antimicrobials, ciprofloxacin is the only substance that can also be administered orally, which is why it is particularly suitable for outpatient therapy. This explains the high rates of resistance to this antimicrobial. By contrast, ceftazidime and meropenem (preferably ceftazidime) are usually applied in combination with an aminoglycoside (preferably tobramycin) for the intravenous treatment of exacerbations or for interval therapy. The rates of meropenem resistance, which, given its broad-spectrum activity, is mostly used only for second-line therapy, are comparatively low. The by far lowest rates of resistance are found for colistin, which is primarily used in inhalation therapy (see below). However, colistin resistance in *P. aeruginosa* isolates from CF patients is also higher than in isolates of different origin.

Prevalence of resistance in CF patients aged below 18 years

Unlike in adult CF patients, no significant differences have been observed in recent years in patients aged below 18 years compared to the period 2000–2008. Resistant *P. aeruginosa* strains are already relatively common in this age group. As expected, the rates of resistance to individual antimicrobial classes are somewhat lower than in adult patients, which can be explained by the age-related shorter exposure to antimicrobials. Ciprofloxacin is already approved for the treatment of mucoviscidosis in patients aged below 18 years, which is why resistance is also quite common in this age group (18.2–30.1%). As a result of the yet limited use of ciprofloxacin in children, however, the difference in annual resistance rates compared to adults is more significant than in other antimicrobial classes (24% versus 53% on average).

Colistin

As already mentioned, an exception regarding resistance rates in both adults and children is represented by the peptide antimicrobial polymyxin E (colistin), which has consistently showed significantly lower resistance rates over the years (< 8%). So far, the treatment of mucoviscidosis has exclusively involved colistin inhalation therapy, and colistin has only been used systemically in the exceptional cases of cured respiratory disease. Since 2012, colistin has been approved in Germany for systemic use as well. To what extent this will be reflected in the resistance statistics remains to be seen.

Multidrug resistance (MDR)

At present, there is no uniform international definition of MDR ("multidrug resistance"). In both previous GERMAP reports, a simplified version of the Hanover definition of multidrug resistance was used. Since 2012, a definition by KRINKO (Hygiene measures for infection or colonisation with multidrug resistant gram-negative bacilli, Federal Health Gazette,

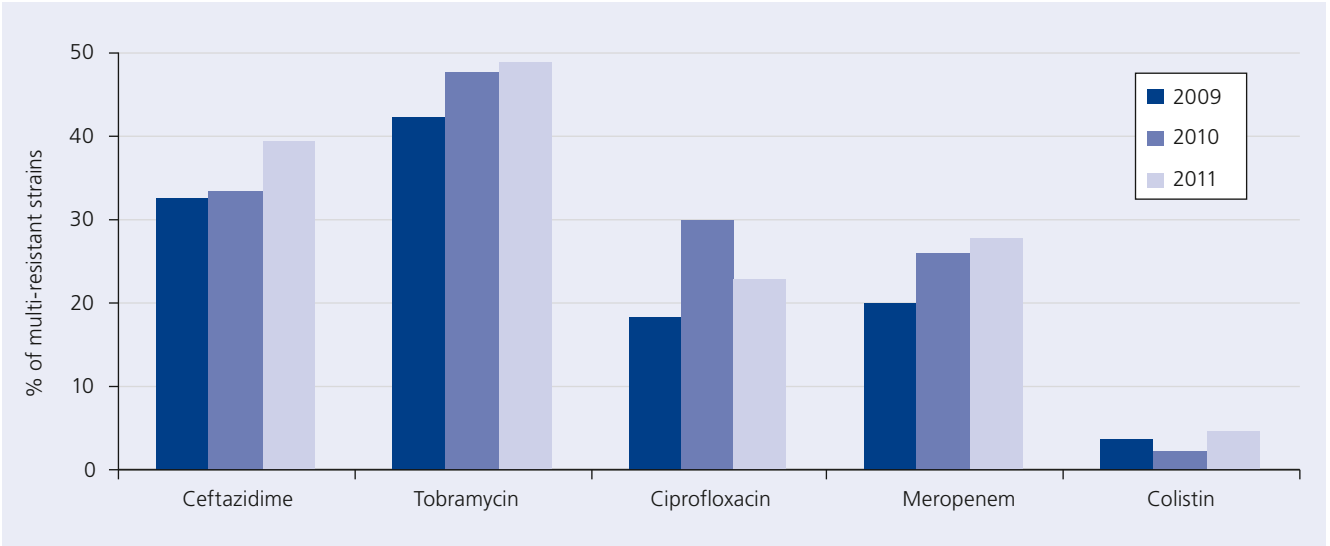

Fig. 4.1.6.2.2: Percentage of *P. aeruginosa* isolates resistant to ceftazidime, tobramycin, ciprofloxacin, meropenem and colistin in CF patients aged below 18 years (Source: MHH resistance data)

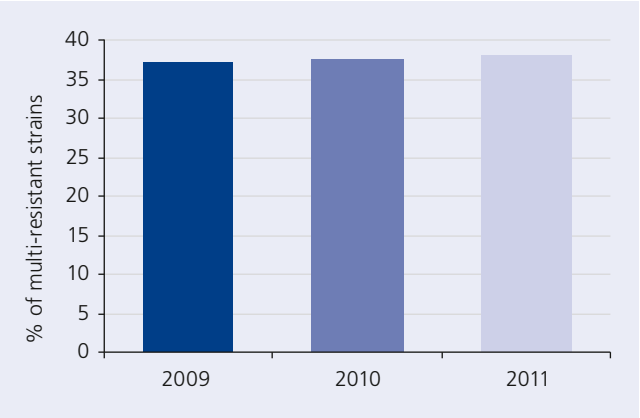

Fig. 4.1.6.2.3: Percentage of multi-drug-resistant *P. aeruginosa* isolates (susceptible to only one or none of the antimicrobials ceftazidime, ciprofloxacin and meropenem). Isolates from CF patients aged > 18 years are shown. Every phenotype was counted only once per patient and per year (Source: MHH and MvP resistance data)

October 2012) has been in place for Germany.[1] This is based on the same principles as the definition previously used in Hanover, but has been developed further, now distinguishing between 3MRGN and 4MRGN (multi-resistant gram-negative bacteria). In the field of CF diagnostics, the restriction of the KRINKO definition to *P. aeruginosa* as the only non-fermenting bacterium is disadvantageous. Moreover, historical data cannot be fully interpreted on the basis of the KRINKO recommendations. The authors nevertheless plan to take account of the KRINKO recommendations in future GERMAP issues.

In this report, we use the term MDR to define *P. aeruginosa* strains that are only susceptible to one or none of the antimicrobials ceftazidime, ciprofloxacin and meropenem. Since tobramycin is only moderately capable of penetrating the lungs and is therefore only used in intravenous treatment in combination with other antimicrobials, it is not considered/included in this definition. In this evaluation, isolates with an identical resistance pattern were only counted once per patient and year. Multidrug resistant *P. aeruginosa* isolates have shown a nearly constant detection rate of approx. 37% over the last three years. This rate of MDR *P. aeruginosa* isolates is the result of the lifelong persistence of individual clones in the respiratory tract of CF patients.

Resistance situation in lung transplantation

A new aspect of resistance statistics is the classification of *P. aeruginosa* isolates obtained from the respiratory tract either after the patient has been listed for lung transplantation (preTX) or during/after lung transplantation (LuTX). Since such isolates, commonly found in the final stage of the lung infection, have previously been exposed to antipseudomonal substances several times, it is not surprising that the corresponding resistance rates are higher than in the overall patient population. Consequently, the highest resistance rates are found in patients before lung transplantation, where the following resistance rates are observed compared to the overall patient population (patients >18 years).

During the period 2009–2011, the rate of resistance to ceftazidime was preTX 52.9%/LuTX 50.1% (overall patient collective >18 years: 46.6%), to tobramycin preTX 66.4%/LuTX 58.7% (57.5%), to ciprofloxacin preTX 71%/LuTX 61.2% (52.9%), to meropenem preTX 57%/LuTX 47.3% (41.2%) and to colistin preTX 3.2%/ LuTX 3.5% (7.5%). The considerable resistance level is significant to the extent that an antimicrobial treatment based on an up-to-date antibiogram is usually administered before lung transplantation in order to reduce the *P. aeruginosa* bacterial count. Furthermore, although

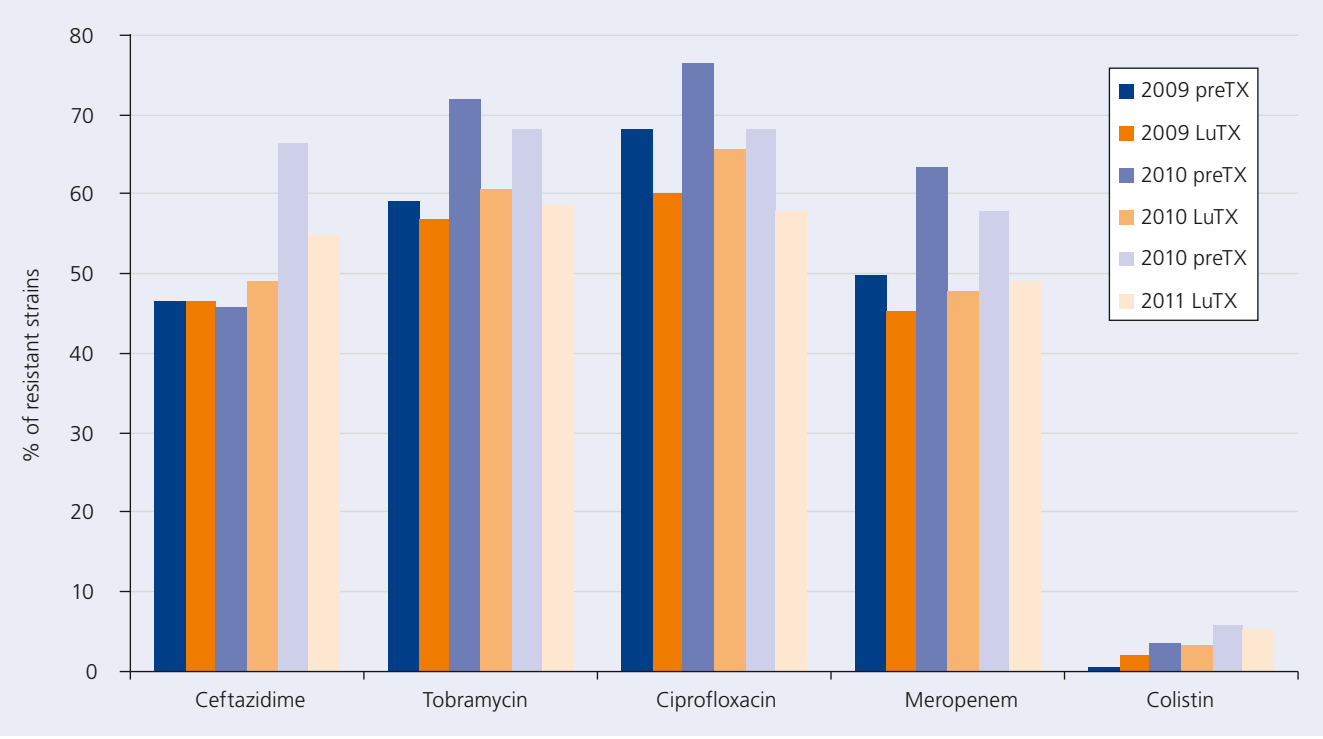

Fig. 4.1.6.2.4: Percentage of *P. aeruginosa* isolates resistant to ceftazidime, tobramycin, ciprofloxacin, meropenem and colistin found in CF patients before lung transplantation (preTX) or during/after lung transplantation (LuTX) (Source: MHH resistance data)

the transplanted lung is not susceptible to pathogens typical of CF, the same (clonally identical) and multidrug resistant pathogens are frequently isolated after lung transplantation: In most patients, however, fewer *Pseudomonas* variants (morphotypes/resistotypes) are detected. The persistent colonisation of the upper respiratory tract (rhinosinusitis) is considered to be the main reservoir.

The clinical relevance of persistent *Pseudomonas* colonisation is characterised by a considerable range of findings. Whereas some colonised patients suffer infectious exacerbations with varying frequency, these virtually never occur in others.

Conclusion

The resistance level of *P. aeruginosa* in CF patients in Germany is high. In recent years, the resistance rates of Pseudomonas isolates from adult CF patients have been observed to increase slightly. To what extent this development will continue needs to be monitored as part of continuous surveillance, in particular to timely recognise any changes in the prevalence and spread of this resistance as well as the resistance development when applying new therapeutic options.

Given the overall high resistance rates in CF patients (especially in patients before/during lung transplantation), regular microbiological testing (isolation of pathogen, resistance profiling) of respiratory specimens is indispensable. Before prescribing antimicrobials to CF patients, it is therefore recommended that bacteriological sputum examination including susceptibility testing be performed and that the substance be selected based on an up-to-date resistance profile. In view of these numerous specific factors, the microbiological CF testing should be performed in specialised laboratories.

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4.1.6.3 *Acinetobacter* spp.

The most important human pathogens of the *Acinetobacter* genus are *Acinetobacter baumannii* as well as *Acinetobacter pittii* (formerly called *Acinetobacter* genomospecies 3) and *Acinetobacter nosocomialis* (formerly called *Acinetobacter* genomospecies 13TU), which are classified into what is called the *Acinetobacter baumannii* group. They predominantly cause nosocomial and only very rarely community-acquired infections, mainly in patients with severe underlying diseases. The associated clinical manifestations include pneumonia, especially in ventilated patients, urinary tract infections, surgical site infections and – often catheter-associated – bloodstream infections. Due to intrinsic resistance mechanisms, the strains of these species are relatively resistant; penicillins and cephalosporins, for example, are usually inactivated through the production of chromosomally mediated AmpC β-lactamases. In addition, resistance to fluoroquinolones and other antimicrobial classes can be acquired by point mutation. Carbapenem resistance is predominantly associated with carbapenemases, the genes of which can be transferred horizontally.

β-lactamase inhibitors, especially sulbactam, exhibit intrinsic activity against pathogens of the *A. baumannii* group. Monotherapy with sulbactam, is, however, not recommended for the treatment of severe infections. The results of the susceptibility testing of *Acinetobacter* isolates to penicillins and cephalosporins in combination with a β-lactamase inhibitor are unreliable, in particular regarding piperacillin/tazobactam. Interpretation of the measured susceptibility is thus not helpful and, in the absence of EUCAST breakpoints, not possible either.

Strains of *A. baumannii*, and, to a lesser extent, also those of the other two species of the *A. baumannii* group, may cause large-scale outbreaks of hospital infections in which only a limited number of epidemic clones play a role. There is now evidence that the majority of carbapenem-resistant *A. baumannii* strains are associated with eight epidemic clones found worldwide (International Clones [IC] 1-8), with IC 2 (also known as European Clone II and as worldwide occurring clone WW2) being detected in nearly 50% of these isolates.[1] β-lactamases most commonly causing carbapenem resistance are the oxacillinases OXA-23, OXA-40, OXA-58 and OXA-143.[1]

Trends in resistance development

PEG resistance study
Information on the susceptibility of isolates of the *A. baumannii* group is available for 2001 (n=158), 2004 (n=176), 2007 (n=168) and 2010 (n=200). When applying the EUCAST breakpoints 3.0, a significant increase in the rate of carbapenem resistance was observed during the period of observation (Fig. 4.1.6.3.1). In 2010, resistance rates of more than 10% were found for fluoroquinolones (ciprofloxacin 19%, levofloxacin 14%) as well as gentamicin (14.5%) and co-trimoxazole (11.5%). The rates of resistance to amikacin, tobramycin as well as imipenem and meropenem ranged between 6.5% and 10%. One strain turned out to be resistant to colistin.[2]

Among the 200 isolates tested in 2010, 95 were identified as *A. baumannii* and 105 as *A. pittii*. *A. baumannii* isolates turned out to be resistant to antimicrobials much more often than *A. pittii* isolates (Fig. 4.1.6.3.2). Among the 21 strains that showed intermediate susceptibility or resistance to imipenem or meropenem, 19 belonged to the *A. baumannii* species and 2 to the A. pittii species.

Colistin represents a therapeutic alternative for the treatment of infections caused by multidrug resistant *A. baumannii*.

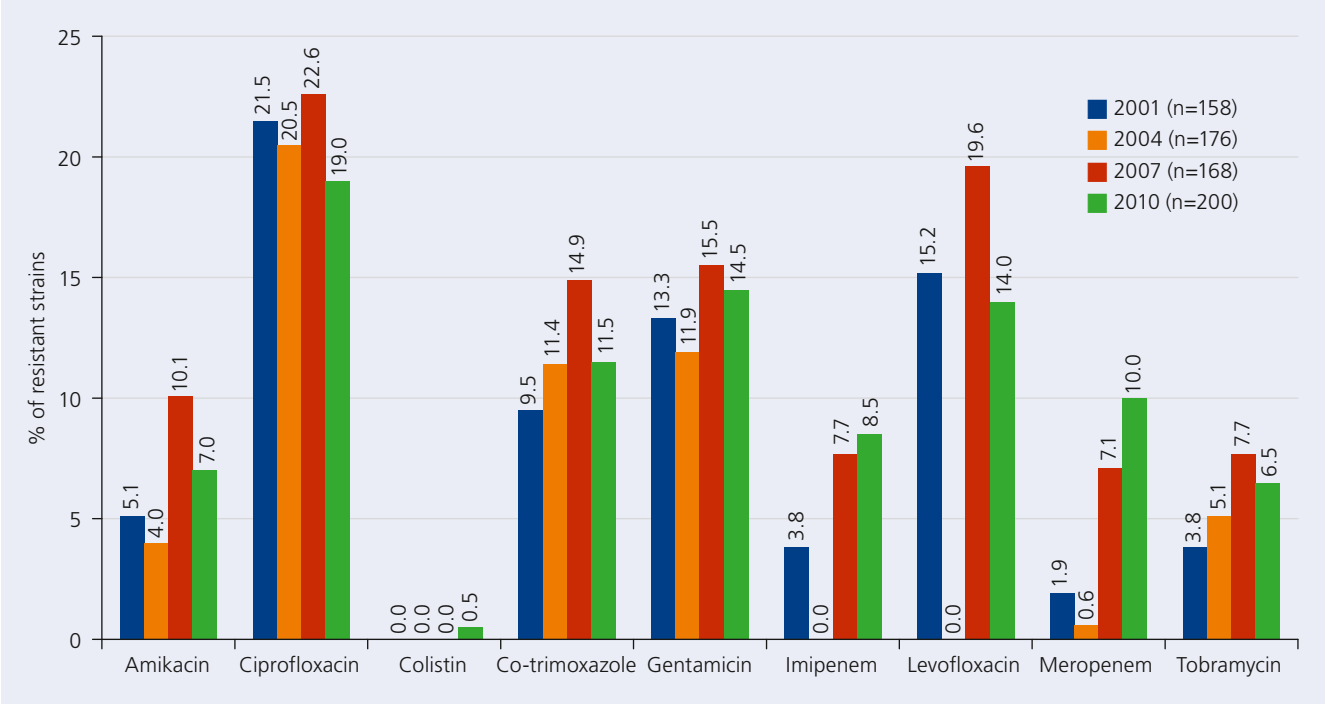

Fig. 4.1.6.3.1: Percentage of resistant strains of the *A. baumannii* group (Source: PEG resistance study, hospital care)

With the exception of one strain, all tested isolates turned out to be susceptible to colistin, whereas tigecycline, in the presence of a concentration of 1 mg/l, exhibited in-vitro activity against only 11 of 21 strains with reduced susceptibility to carbapenem.

PEG blood culture study 2006/2007 and GENARS/ARS

The results of the PEG blood culture study and those of the GENARS project were already presented in the 2008 and 2010 GERMAP reports.

The ARS project provides data for the period 2008–2011.[3] Over the period of observation, the rate of carbapenem resistance (imipenem, meropenem) increased from 12–13% to 16–17% in isolates from patients in intensive care units, from approx. 3% to 9–10% in isolates from patients on normal wards and from < 1% to 2–3% in isolates from outpatients (data as of 23/10/2012). By contrast, the resistance situation for fluoroquinolones (ciprofloxacin, levofloxacin) and co-trimoxazole remained unchanged or showed a downward trend in all care sectors.

The real threat posed by resistant strains becomes clear when taking the percentage of multidrug resistant strains into account. The evaluation of the resistance patterns of the three antimicrobial classes of carbapenems (imipenem and meropenem), fluoroquinolones (ciprofloxacin) and aminoglycosides (gentamicin and tobramycin) revealed an increase in the

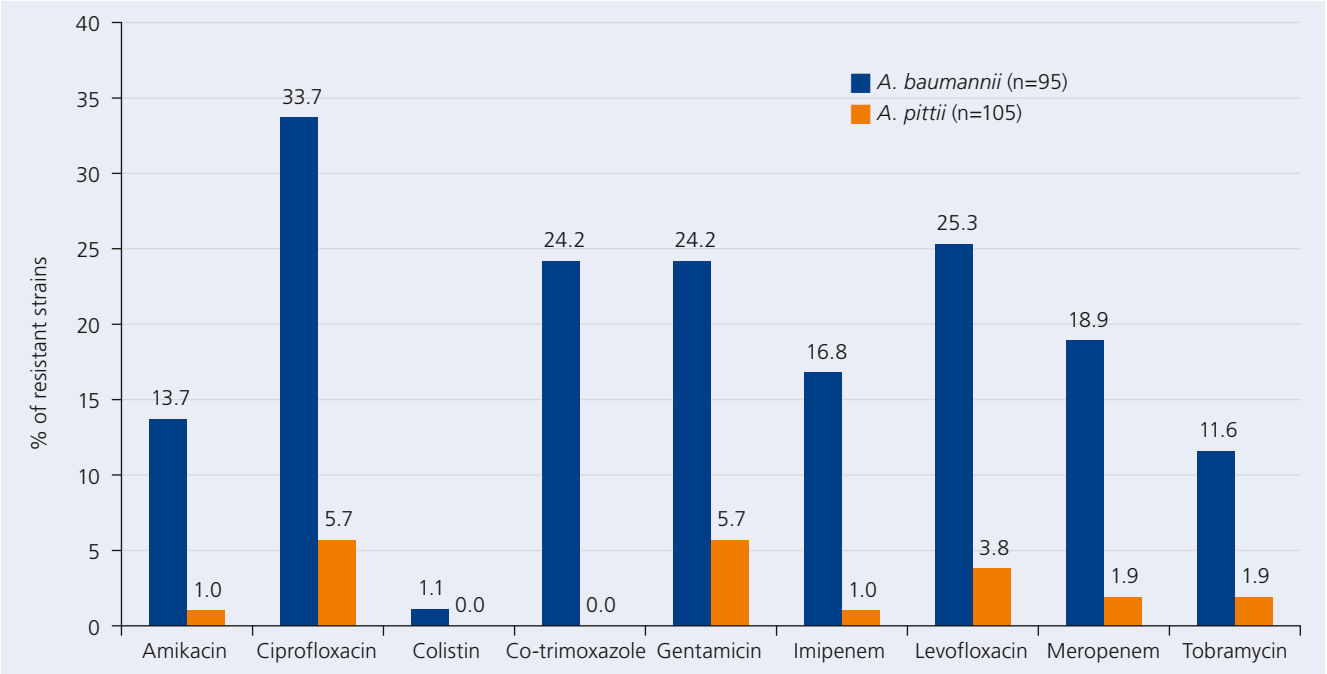

Fig. 4.1.6.3.2: Percentage of resistant *A. baumannii* and *A. pittii* strains in 2010 (Source: PEG resistance study, hospital care)

percentage of the strains from inpatient care that were resistant to none of the three substances (from 69.7% to 79.4%), a decrease in the percentage of strains with single resistance (from 23.6% to 11.0%) and an increase in the percentage of strains with triple resistance (from 1.9% to 5.9%) during the period of observation (data as of 27/03/2013).

However, it should be mentioned that the species identification of *Acinetobacter* spp. using automated devices for the identification of microorganisms does not allow a clear identification at species level, which is why the indicated resistance rates of *A. baumannii* can be regarded as being too low.

G-TEST

As part of the G-TEST, 391 isolates of the *A. baumannii* group obtained in 2005, 2007 and 2009 were tested for susceptibility to tigecycline and other antimicrobials. The in-vitro activity of tigecycline was nearly identical in all study years. The percentage of strains with an MIC value of ≤ 1 mg/l was 99.3% before the introduction of tigecycline, 92.3% one year after its introduction and 97% three years after its introduction.

By contrast, the percentage of isolates resistant to imipenem rose from < 1% in 2005 to 11.1% in 2007, amounting to 8.2% in 2009. However, measured by the $MIC_{50/90}$ values, isolates with reduced susceptibility to imipenem were four times less susceptible to tigecycline than imipenem-susceptible strains (1/2 vs. 0.25/0.5 mg/l). The prevalence of resistance to gentamicin was 13.6% in 2005, 22.2% in 2007 and 15.7% in 2009, whereas the level of resistance to ciprofloxacin dropped from 30% to 21.6%.[4]

When looking at 140 *A. baumannii* isolates separately, the carbapenem resistance was 4.3% in 2005, 25% in 2007 and 23.8% in 2009.[5]

Characterisation of carbapenem-resistant strains

Molecular characterisation of the above-mentioned 21 strains showing intermediate susceptibility or resistance to imipenem and meropenem tested within the 2010 PEG resistance study demonstrated that 16 *A. baumannii* strains expressed an OXA-23-like carbapenemase. One *A. baumannii* strain expressed an OXA-58-like carbapenemase and one *A. pittii* strain an OXA-40-like carbapenemase.[2] No carbapenemase was found in three carbapenem-resistant strains. The majority of isolates were shown to belong to IC 2, the clonal lineage predominant in Europe.[1]

The predominance of OXA-23 also became apparent in the test specimens of *A. baumannii* isolates with suspected carbapenemases submitted to the National Reference Centre for Gram-Negative Hospital Pathogens in 2012. An OXA-23 carbapenemase was detected in 355 of 410 strains. The second and third most common carbapenemases were OXA-72 (n=39) and OXA-58 (n=10), respectively. Some strains harboured the NDM-1 gene.[6] In addition, *A. pittii* strains with the metallo-β-lactamase GIM-1 seem to be widespread in several regions of Germany.

Conclusion

The average prevalence of resistance to carbapenems in strains of the *A. baumannii* group is approx. 10%, with the rate in *A. baumannii* strains being significantly higher than in *A. pittii* strains. Their prevalence in intensive care units is particularly high. Compared to other countries, however, the resistance situation in Germany is still favourable. The targeted therapy of *Acinetobacter* infections is carried out on the basis of an antibiogram. Group 2 carbapenems (according to the PEG classification: doripenem, imipenem, meropenem), if necessary, in combination with a fluoroquinolone, are still recommended for the treatment of severe infections. However, there may be differences regarding susceptibility to the individual antimicrobial agents of both antimicrobial classes. Therefore, the antimicrobials of this class must not be automatically assumed to be generally susceptible if the test substance is found to be susceptible.

In the event of resistance to the first-line antimicrobials, in particular to carbapenems, colistin may be used. Tigecycline is occasionally also considered as an alternative for the treatment of *Acinetobacter* infections.

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Reviewer: E. Straube

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4.1.6.4 *Stenotrophomonas maltophilia*

Besides *Acinetobacter* spp. and *Pseudomonas aeruginosa, Stenotrophomonas maltophilia* is another relevant nosocomial infectious agent belonging to the group of non-fermenting gram-negative bacilli. Although it is not considered highly virulent, *S. maltophilia* exhibits intrinsic resistance to multiple agents. It is frequently associated with biofilm and device-associated infections. It primarily causes pneumonia, in particular ventilator-associated pneumonia, since it is capable of growing in biofilms on respiratory epithelial cells.[3] However, this facultative pathogenic environmental bacterium is commonly isolated from respiratory specimens merely as a colonising organism. *S. maltophilia* also causes catheter-associated bacteraemia. Predisposed patients include those in haematology/oncology departments and intensive care units, catheterised patients and patients receiving broad-spectrum antimicrobials. The organism is commonly isolated at progressive stages of cystic fibrosis; its role in polymicrobial infections is controversial. Its detection rate varies widely in intensive care units compared with other pathogens or per 1,000 patient days, and, according to a multivariate analysis, correlates with the usage density of carbapenems and the size of the ward.[4]

The species population has been classified into various groups on the basis of the imipenem MIC values, 16S rRNA signatures, sequence polymorphisms of the *smeDEF*-encoded efflux pump operon, restriction fragment length polymorphisms and an MLST scheme. Remarkably, this species shows ecotypes that are either isolated exclusively or predominantly from humans or are of non-anthropogenic origin, such as rhizosphere.[5] More recent studies comparing the genome of a blood culture isolate (K279a) with an environmental isolate (R551) revealed a large number of antimicrobial resistance determinants, such as multidrug efflux pumps, β-lactamases and a group of quinolone resistance (*qnr*) determinants.[6,7] Apart from chromosomally mediated resistance, resistance acquired through lateral gene transfer is also of clinical relevance.

S. maltophilia expresses two plasmid-mediated, inducible β-lactamases. The L1 metallo-β-lactamase hydrolyses nearly all β-lactams, except for aztreonam. The L2 serine β-lactamase can be inhibited by clavulanic acid. When expressed together, they hydrolyse most β-lactam antimicrobials. A number of families of multidrug resistance efflux pumps play a major role in resistance to tetracyclines and quinolones, with newer fluoroquinolones such as moxifloxacin appearing to be more efficient that older ones such as ciprofloxacin. The majority of clinical isolates show a colistin MIC of > 4 mg/l (http://mic.eucast.org/Eucast2/regShow.jsp?Id=22939; data as of 03/03/2013).

Therapeutic options and resistance development

In-vitro susceptibility testing of *S. maltophilia* shows discrepancies, in terms of both the comparability of various methods, incubation conditions and the prediction of clinical efficacy.[8,9] The pathogen is significantly more resistant to antimicrobials in biofilms that in planctonic form, which is how it is used in in-vitro susceptibility testing.[10] However, so far, there is no evidence that testing in biofilms improves the predicted clinical efficacy of antimicrobials.

The first-line antimicrobial agent used for treatment of *S. maltophilia* infections is trimethoprim/sulphamethoxazole (co-trimoxazole). Fluoroquinolones available on the German market and, whenever necessary, tigecycline are considered to be alternative substances – for example in patients with a co-trimoxazole allergy. Further alternatives include therapeutic combinations with fluoroquinolones, tigecycline or a colistin inhalation therapy. The combinations ticarcillin/clavulanic acid and aztreonam/clavulanic acid also suggested as alternatives are available abroad. A small number of individual case reports suggest that ceftazidime could also be effective [see review in[11,12,13]].

Initial reports of trimethoprim/sulphamethoxazole resistance and its molecular basis were given particular attention.[14,15] A number of these resistant isolates observed by the SENTRY project came from Europe and one from Germany. Resistance is conferred by mobile genetic elements such as integrons and insertion elements, which may lead to rapid spread of resistance.

Resistance situation

A number of resistance studies in Germany provide a relatively up-to-date picture of the resistance situation (see Tab. 4.1.6.4.1). These include a study on clinical infection isolates conducted in 2010 by the Paul Ehrlich Society, the Antimicrobial Resistance Surveillance project of the Robert Koch Institute (ARS, https://ars.rki.de, data as of 08/01/2013), which provided information on isolates from inpatient care, and the project entitled "Surveillance of Antimicrobial Use and Antimicrobial Resistance in Intensive Care Units" (SARI). They classify pathogens according to clinical categories based on the various antimicrobial testing standards used by the microbiology laboratories (DIN, CLSI or EUCAST). They all agree that the rates of resistance to co-trimoxazole are below 5%. When comparing the last few years, the ARS results reveal a trend of increasing rates of resistance to moxifloxacin, ceftazidime and tigecycline.

Conclusion

The question of which susceptibility testing method is appropriate to predict clinical efficacy has not yet been conclusively resolved. Clinical studies are needed to correlate the in-vitro or animal-experimental data of various antimicrobial classes and their therapeutic combinations with the clinical outcome.

Based on the findings of various resistance studies, in Germany, co-trimoxazole seems to be the first-line antimicrobial agent currently used for (empiric) treatment of infections. The potential spread of various plasmid-mediated resistance mechanisms must be monitored. Therapeutic alternatives available on the German market include tigecycline and moxifloxacin, the efficacy of which seems to be decreasing, without the resistance mechanisms being known. Combinations, e.g. with a colistin inhalation therapy, represent a

Tab. 4.1.6.4.1: Results of various German resistance studies on the number of tested and the percentage of resistant *S. maltophilia* isolates. The various standards taken as a basis for the clinical classification of the in-vitro data are indicated.

Study, period (standard used)	Antibiotic	Number of isolates tested	Resistance rate (%)
PEG IV/2010 (EUCAST)	Co-trimoxazole	234	1.3
SARI 01/2007 - 12/2011 (DIN, CLSI, EUCAST)	Co-trimoxazole	2,280	3.7
	Ceftazidime	2,373	50.0
	Ciprofloxacin	2,247	31.8
	Levofloxacin	776	23.7
ARS 2012 (DIN, CLSI, EUCAST)	Co-trimoxazole	1,693	2.7
	Ceftazidime	1,371	61.3
	Moxifloxacin	311	14.8
	Tigecycline	532	33.5
ARS 2008 (DIN, CLSI)	Co-trimoxazole	789	5.4
	Ceftazidime	754	40.1
	Moxifloxacin	559	9.5
	Tigecycline	100	14.0

clinically effective alternative. Further alternatives used abroad include the combinations ticarcillin/clavulanic acid or aztreonam/clavulanic acid.

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4.1.7 *Neisseria meningitidis*

Neisseria meningitidis is a pathogen causing bloodstream infections and meningitis, especially in infants, toddlers and adolescents. Meningococcal disease, which is a notifiable disease, is feared because of a mortality rate of approx. 8% (Epidemiological Bulletin, No. 39/2012) and an equally high risk of permanent sequelae. Moreover, secondary cases and outbreaks of meningococcal disease have been observed.

The incidence of the infection in Germany is currently approx. 0.5/100,000/a, and can thus be classified as low, even if slight under-reporting has to be assumed. On a global scale, the epidemiology of meningococcal disease is alarming, especially in the African Meningitis Belt where outbreaks are observed, some of which can affect tens of thousands of people.

The most important measure to prevent meningococcal infections with the serogroups A, C, W135 and Y is the provision of vaccines based on native or conjugated capsular polysaccharides. A meningococcal A polysaccharide conjugate vaccine (MenAfriVac™) was introduced successfully in the African Meningitis Belt as part of the *Meningitis Vaccine Project*.[1] Outer membrane protein-specific vaccines against serogroup-B meningococci are available in the event of epidemics.[2] Universal serogroup-B vaccines are currently in clinical trials (phase 2 and 3) or approved for use from the second month of life and were introduced to the German market in December 2013.[3] However, these protein-based vaccines cannot cover all serogroup-B strains.[4] Since 2006, there has been a STIKO (German Standing Committee on Vaccination) recommendation in Germany for the use of meningococcal C conjugate vaccines. If indicated, tetravalent conjugate vaccines (ACWY) are also available to travellers, high-risk individuals, close contacts of patients as well as laboratory staff.

In industrialised countries, β–lactam antimicrobials are the main pillar of the antimicrobial therapy of invasive meningococcal infections. Rifampicin or ciprofloxacin, in pregnant women also ceftriaxone, are used for the prophylactic treatment of close-contact persons (e.g. in the patient's domestic environment (cf. current STIKO recommendations). The use of azithromycin as an alternative is being discussed (see also ECDC Guidance – "Public health management of sporadic cases of invasive meningococcal disease and their contacts" http://www.ecdc.europa.eu/en/publications/publications/1010_gui_meningococcal_guidance.pdf).

In contrast to the situation of the related species *Neisseria gonorrhoeae* (gonococci), the resistance situation of meningococci is not alarming. Only in few cases does the failure of antimicrobial therapy result in lethal infections; in such cases, the antimicrobial therapy cannot stop the rapid toxic progression, despite effective eradication of the bacteria. There is experimental evidence to suggest that both penicillin resistance[5] and rifampicin resistance have a negative influence on the fitness of the bacteria.[6]

The molecular mechanisms of antimicrobial resistance in meningococci are understood to some extent. Reduced susceptibility to penicillin is associated with mutations in the transpeptidase region of the penicillin binding protein 2 (PBP2). A great number of allelic variants of the *penA* gene coding for the penicillin binding protein 2 circulate in meningococci. An international *penA* sequence database has been established and is used in reference laboratories (http://pubmlst.org/neisseria/).[7] Unlike in gonococci, plasmid-mediated β-lactamases do not play a role in meningococci.

The rarely occurring rifampicin resistance is associated with point mutations in the *rpoB* gene, which codes for the β-subunit of the RNA polymerase. Literature references report infections caused by rifampicin-resistant strains in contact persons treated with rifampicin. Resistance to gyrase inhibitors is attributed to alterations in the *gyrA* and *parC* genes. Such a resistance is very rare in Germany. In 2011 and 2012, no invasive strains showing reduced susceptibility to rifampicin or ciprofloxacin were detected by the NRZ for Meningococci. During the period 2002–2012, more than 99% of the tested strains were susceptible to rifampicin and ciprofloxacin.

The NRZ for Meningococci tests all submitted isolates for susceptibility to penicillin G, rifampicin, ciprofloxacin and cefotaxime by means of agar diffusion tests using E-test strips and the EUCAST breakpoints.

Trends in the development of penicillin resistance

Reduced susceptibility to penicillin stands for an MIC of more than 0.06 mg/l. The percentage of penicillin-susceptible strains is observed to be subject to temporal variations (Fig. 4.1.7.1). It is noteworthy that the percentage of strains with a mutated *penA* gene has tripled over the past few years. Between 2002 and 2011, an average of 14% of all tested isolates showed intermediate susceptibility to penicillin, whereas 0.7% were resistant. A noteworthy increase to 25% and 2.2%, respectively, occurred in 2012. This trend is also monitored carefully by the NRZ for Meningococci. The temporal variations may be associated with a varying distribution of the individual clonal complexes of meningococci.

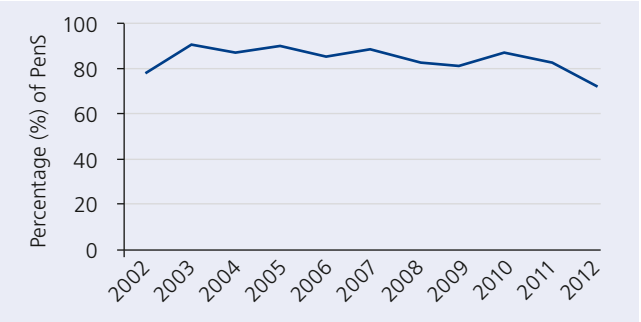

Fig. 4.1.7.1: Development of the percentage of penicillin-susceptible meningococcal strains (2002–2012). Strains with MIC values of up to 0.06 mg/l are considered susceptible.

23% of meningococci belonging to what is called the ST-11 complex, which causes a great number of serogroup-C infections in Germany, are no longer susceptible to penicillin, whereas this rate is only 5% in meningococci belonging to the ST-41/44 complex. This clonal complex is responsible for a large number of serogroup-B infections in Germany. Resistance to cefotaxime has so far not been observed by the NRZ for Meningococci (n=754).

Conclusion

The resistance situation of meningococci continues to be relatively favourable, so treatment and post-exposure prophylaxis can be performed using the approved regimen. However, the increase in the percentage of strains showing intermediate susceptibility to penicillin needs to be monitored further. On an international scale, further standardisation and correlation of geno- and phenotypes is in progress and is being advanced by the *European Monitoring Group on Meningococci* and the IBD-labnet of the ECDC, amongst others. The breakpoints, in particular for rifampicin, require further fine-tuning.[8] The ECDC has issued a guideline on antimicrobial prophylaxis entitled "Public health management of sporadic cases of invasive meningococcal disease and their contacts".

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4.1.8 *Neisseria gonorrhoeae*

Neisseria gonorrhoeae (gonococci) are pathogens causing gonorrhoea, referred to as "the clap" in colloquial language, a sexually transmitted infectious disease that only affects humans. After an incubation period of 2–7 days, gonorrhoea commonly manifests itself as urethritis and/or cervicitis. Oral or anal intercourse with infected people can cause the development of pharyngitis or proctitis. Complications in the further course of the disease include prostatitis and epididymitis in men and salpingitis and peritonitis (PID, pelvic inflammatory disease) in women. A gonococcal infection disseminated through haematogenous spread may be associated with arthritis and haemorrhagic pustulous skin lesions. The frequent asymptomatic progression of the infection, especially in women, facilitates the further spread of the disease. Gonococci are typically transmitted through direct contact during sexual intercourse. By contrast, keratoconjunctivitis (gonoblennorrhoea) in newborns is attributed to infection through direct contact in the birth canal during childbirth. There is no reliable data on the prevalence of gonorrhoea in Germany, since the reporting obligation was cancelled when the Infection Protection Act was adopted in 2001. However, sentinel studies conducted by the RKI suggest a wide spread of gonorrhoea and the "silent epidemic" of sexually transmitted diseases in Germany in general. Based on estimates, an incidence of 25 to 40 cases/100,000 inhabitants is assumed, which is equivalent to approx. 21,000 to 33,000 new infections per year in Germany. In 2010, incidence rates of 0.6 to 30/100,000[1] were estimated in other European countries and 100.8/100,000 in the U.S.[2]

Trends in resistance development

In Germany, little data has been published on the antimicrobial susceptibility of *N. gonorrhoeae*. Moreover, studies conducted before 2010 were limited to specific regions and periods, thus allowing no Germany-wide assessment of the resistance situation and/or resistance development. The comparison of study results is additionally complicated by the fact that the interpretation criteria for antimicrobial susceptibility are derived from different standards (DIN, CLSI, etc.). When looking at the raw data[3, 4, 5] and applying the interpretation criteria shown in Tab. 4.1.8.1, however, the antimicrobial susceptibility of *N. gonorrhoeae* can be estimated and compared over time and between regions (Fig 4.1.8.1).

Previous studies have already reported resistance rates of more than 20% in the Frankfurt am Main area and in Southwestern Germany to penicillin, which used to be the first-line antimicrobial agent for the treatment of gonorrhoea. In addition to 3.5% penicillin-resistant isolates, 22.3% of the gonococcal isolates in the Berlin area were also classified as showing merely intermediate susceptibility to penicillin, which is why penicillin is no longer recommended for empiric therapy. Given the resistance rates ranging between 29.2% and 60.6% and an additional considerable percentage of isolates showing intermediate susceptibility, tetracycline is also not recommended as first-line therapy. Regarding the quinolone ciprofloxacin, an alarming increase in resistance rates became apparent, which was observed over time rather than at regional level (increase in resistance rate from 1.2% to 47.7% within 10 years). This high quinolone resistance rate was

Tab. 4.1.8.1: Breakpoints for interpreting the antibiotic susceptibility of *N. gonorrhoeae* (Source: CLSI, 2009)

Antibiotic	MIC breakpoints (mg/l)		
	Susceptible	Intermediate	Resistant
Penicillin	≤0.06	0.12–1	≥2
Cefixime	≤0.25	–	–
Ceftriaxone	≤0.25	–	–
Tetracycline	≤0.25	0.5–1	≥2
Ciprofloxacin	≤0.06	0.12–0.5	≥1
Spectinomycin	≤32	64	≥128
Azithromycin*			≥1

*Preliminary breakpoint acc. to CDC

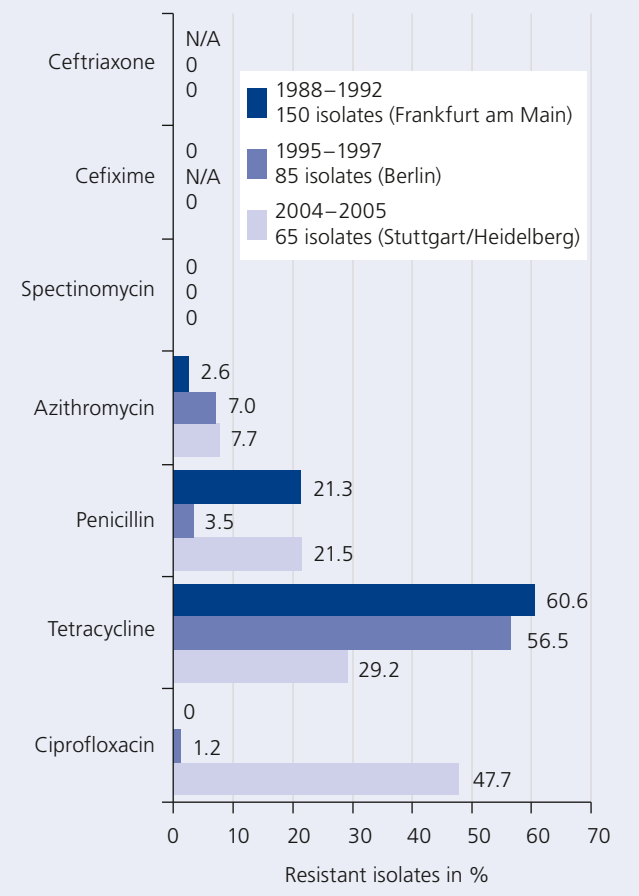

Fig. 4.1.8.1: Temporal and regional development of antibiotic resistance in *N. gonorrhoeae* (Source: References[3-5])

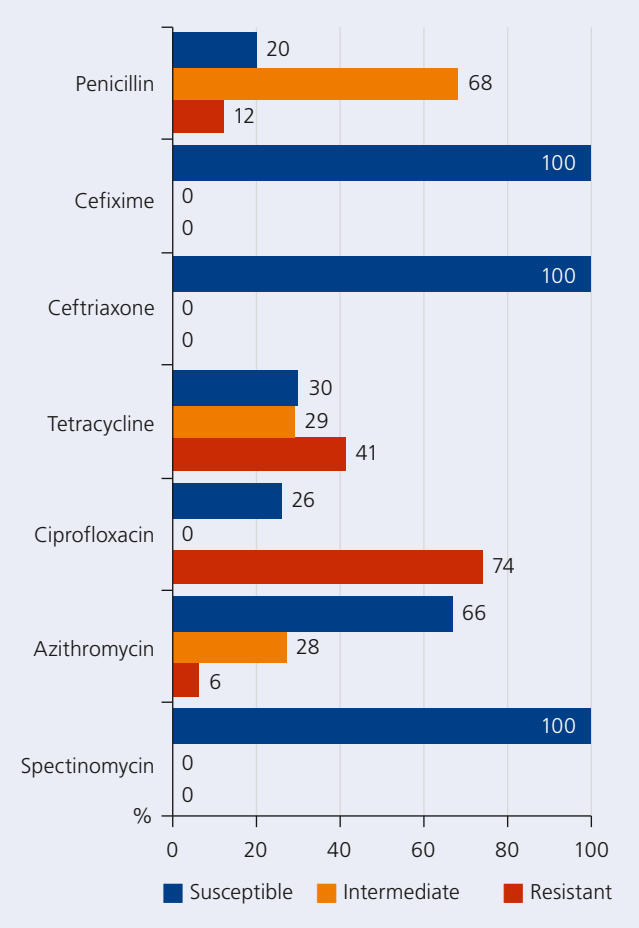

Fig. 4.1.8.2: Antibiotic resistance in *N. gonorrhoeae* (n=213) in Germany. PEG resistance study, 01/10/2010–31/12/2011

confirmed in Northern German surveys, revealing a 34% ciprofloxacin resistance in 1999[6] and in the Rhine-Main region and a 64% ciprofloxacin resistance in 2008[7]. Azithromycin is considered to be a second-line antimicrobial for the treatment of uncomplicated gonorrhoea, but the study conducted in the 1990s already revealed a resistance rate of more than 5% to this azalide. Only third-generation cephalosporins (ceftriaxone and cefixime) as well as the aminoglycoside spectinomycin exhibited 100% in-vitro activity.

A Germany-wide antimicrobial resistance surveillance system for gonococci was established for the first time as part of the 2010 PEG resistance study. During the period from 01/10/2010 to 31/12/2011, 213 gonococcal isolates from 23 centres were submitted to the reference laboratory, the Institute of Medical Microbiology and Hospital Hygiene at the University Hospital of Goethe University in Frankfurt am Main, for the purpose of antimicrobial susceptibility testing and pathogen identification. Preliminary data based on the interpretation criteria for antimicrobial susceptibility defined by EUCAST (Tab. 4.1.8.2) shows 80% non-susceptibility to penicillin, 0% to cefixime, 0% to ceftriaxone, 70% to tetracycline, 74% to ciprofloxacin, 34% to azithromycin and 0% to spectinomycin (Fig. 4.1.8.2).

Since the establishment of the Consultant Laboratory for Gonococci as per 01/01/2010, the antimicrobial susceptibility of *N. gonorrhoeae* has also been monitored in Germany by means of voluntary submission of isolates. According to the data reported by the consultant laboratory, gonococcal isolates with reduced susceptibility to third-generation cephalosporins have been detected in Germany.[8,9,10]

Antimicrobial resistance knows no geographical limits. Reports from the Netherlands on the increasing rate of *N.*

Tab. 4.1.8.2: Breakpoints for interpreting the antibiotic susceptibility of *N. gonorrhoeae* (Source: EUCAST Version 3.0, 2013)

Antibiotic	MIC breakpoints (mg/l)		
	Susceptible	Intermediate	Resistant
Penicillin	≤ 0.06	0.12–1	> 1
Cefixime	≤ 0.12		> 0.12
Ceftriaxone	≤ 0.12		> 0.12
Tetracycline	≤ 0.5	1	> 1
Ciprofloxacin	≤ 0.03	0.06	> 0.06
Spectinomycin	≤ 64		> 64
Azithromycin	≤ 0.25	0.5	> 0.5

gonorrhoeae isolates with reduced susceptibility to cefotaxime (0.125–0.5 mg/l) from 4.8% in 2006 to 12.1% in 2008 as well as reports from France on the emergence of high-level cefixime- and ceftriaxone-resistant *N. gonorrhoeae* are alarming, suggesting potential future limitations in therapy.[11,12]

Conclusion

The antimicrobial susceptibility of *N. gonorrhoeae* was recorded in Germany for the first time as part of a 2010/2011 antimicrobial resistance surveillance system. The assessment of the resistance development and the formulation of effective therapy recommendations require the maintenance and advancement of this surveillance system. The WHO demands that empiric therapy of gonorrhoea yield a therapeutic success of ≥ 95%. In view of the present resistance data of *N. gonorrhoea*, third-generation cephalosporins and spectinomycin seem to be the only options to achieve this goal.

➤ T.A. Wichelhaus
Reviewers: V. Bremer, S. Buder, S. Dudareva-Vizule, P. Kohl

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4.1.9 *Legionella pneumophila*

Legionella are ubiquitous, intracellular bacteria that cause both Pontiac fever, a usually self-limiting feverish systemic disease, and pneumonia. About one-third of the cases are community- or hospital-acquired or travel-associated. *Legionella pneumophila* serogroup 1 causes more than 90% of all Legionella pneumonia infections. *Legionella pneumophila* serogroup 1 strains are extraordinarily heterogeneous in terms of phenotype and genotype. It has been confirmed that a small number of virulent "clones" are responsible for the majority of infections in outpatients. The strain-specific virulence of these clones cannot yet be correlated with defined genetic markers. However, we know that 90% of all community-acquired and travel-associated Legionella infections are caused by strains of *L. pneumophila* serogroup 1, which undergo a reaction with the monoclonal antibody 3/1. This so-called Pontiac group, which is responsible for nearly all reported outbreaks, accounts for only 10–20% of all *Legionella* found in water systems. From this it can be inferred that a large portion of *Legionella* in the environment has low virulence.[1]

Specific patients are predisposed to acquiring a *Legionella* infection. These include in particular immunosuppressed patients after organ transplantation, with malignant diseases, extended corticosteroid therapy or administration of TNF-alpha antagonists.[2] Heavy smokers are also at increased risk. However, about 20% of all *Legionella* infections occur in patients without any typical risk factors.

There are numerous studies providing evidence that *Legionella pneumonia* cannot be distinguished from pneumonia of other aetiology in terms of clinical symptoms. Studies on seroprevalence demonstrate that the approx. 600 cases per year confirmed by laboratory testing and reported under the Infection Protection Act only represent a small fraction of the actually occurring infections. According to the findings of the CAPNETZ pneumonia study, about 4% of all

community-acquired pneumonia infections in Germany are caused by *Legionella*. This study has also demonstrated that the severity of the clinical condition may vary greatly. In some patients suffering from legionellosis, the clinical progression of the disease is complex and severe, involving a considerable mortality rate.[3]

Therapeutic options and resistance development

Legionellosis can be treated with the intracellular antimicrobials tetracycline, macrolides, fluoroquinolones as well as rifampicin. Since *Legionella* are intracellular pathogens, the efficacy of antimicrobials is determined using cell cultures or animal experiments. Fluoroquinolones and newer macrolides such as clarithromycin or azithromycin exhibited the highest activity. A recent study conducted by Bruin et al.[4] determined epidemiological cut-off values (ECOFF) for 183 clinical *L. pneumophila* SG 1 isolates. In this study, fluoroquinolones (most notably levofloxacin), macrolides (most notably clarithromycin) and rifampicin were found to exhibit the highest in-vitro activity.

In-vitro resistance situation

In-vitro susceptibility testing is problematic because of the complex composition of the required culture media for *Legionella*. There are few studies available on susceptibility testing. With the exception of the study conducted by Bruin et al., which reports a clinical wild-type isolate with elevated MIC values for both ciprofloxacin and azithromycin, resistance to the therapeutic agents of the classes of fluoroquinolones, macrolides, tetracyclines or rifampicin has so far not been found among clinical isolates.[4] This one strain should be re-examined using molecular methods. Studies conducted by the Consultant Laboratory for Legionella on 98 *L. pneumophila* strains isolated in Germany between 2002 and 2012 showed no elevated MIC values for these substances either (Lück et al., unpublished).

However, mutants resistant to erythromycin, rifampicin or fluoroquinolones can be cultured under laboratory conditions. These mutants also exhibit the typical mutations in the corresponding genes (*gyrA, rpoB*). Therefore, the resistance development of clinical and environmental isolates requires further monitoring. For the time being, routine antimicrobial susceptibility testing does not seem necessary.

Clinical use

Prospective clinical studies are not available, since the diagnosis is usually too slow and the number of cases is small. A few published observational studies found that levofloxacin was superior to newer macrolides (not significantly).[5]

A combination with rifampicin and the combination of quinolone and azithromycin were tested in a few studies. In general, a combination therapy had no positive influence on the progression of the disease, but it more commonly causedside effects, which is why it cannot be recommended without reservations.[5] The question of whether patients with severe CAP and shock benefit from a combination therapy is still under discussion.

The few clinical reports of a "therapy failure" have so far never been associated with an actual resistance confirmed by in-vitro testing. In these individual cases, diffusion barriers, e.g. in the case of abscesses, or individual patient-specific factors need to be discussed.

Conclusion

The current first-line antimicrobials for the treatment of *Legionella pneumonia* are levofloxacin or another fluoroquinolone administered in the maximum dosage. Newer macrolides, especially azithromycin, are also effective.[6] Therapeutic combinations with rifampicin bring no advantage. In mild cases and on good clinical response, the therapy can be limited to 7–10 days. In immunosuppressed patients or in cases of severe clinical course, prolonged therapy of up to 21 days is recommended.[7]

➤ H. von Baum, C. Lück
Reviewer: D. Jonas

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4.1.10. *Mycobacterium tuberculosis*

Tuberculosis is one of the major causes of diseases and deaths worldwide. The World Health Organisation (WHO) estimates the number of people first diagnosed with tuberculosis (TB) in 2011 at 8.7 million. The number of deaths in the same year amounted to approx. 1.4 million. Most infections affect the lungs and the respiratory tract, and the highly contagious form of microscopically positive pulmonary tuberculosis is found in more than one-third of the cases. However, the pathogen can spread haematogenously from the pulmonary portal of entry to affect all organs.

The drugs and strategies for the treatment of tuberculosis were developed in the second half of the last century. The following first-line antimicrobials are used for the treatment of tuberculosis: isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E) and streptomycin (S), with the latter not being counted by the WHO among the first-line antimicrobials and being used only rarely because of the necessity of parenteral administration. The standard anti-TB therapy (referred to as short-term therapy) commences with a combination of four drugs (HRZE) and is continued after 2(-3) months with two drugs (HR) over another four months (i.e. six months of therapy in total). If drug resistance is suspected to be present, the initial therapy regimen is extended according to patient-specific factors (e.g. previous treatment) and adapted based on the result of the susceptibility testing of the culture isolate.

The major causes of drug resistance development include inadequate treatment, for example the prescription of an ineffective therapy regimen or irregular intake of drugs, which entails insufficient antimicrobial levels. Monotherapy, i.e. the (intended or unintended) administration of only one effective drug, inevitably results in the selection of resistant pathogens. This is due to the fact that a small portion of the bacterial population exhibit intrinsic resistance to a specific anti-TB drug (for example, 1 in 10^6 tuberculosis bacteria is resistant to isoniazid and 1 in 10^8 to rifampicin). In monotherapy, the inherently resistant pathogens can multiply unimpeded, so that the susceptible pathogens eradicated by the antituberculous agent are superseded by resistant bacteria after a short period of time. Unintended monotherapy is first and foremost based on the avoidable lack of knowledge of an existing resistance. For this reason, the pathogen should always be tested for drug susceptibility. This is the only way to ensure adequate treatment and effectively prevent further drug resistance development.

If resistance to first-line antimicrobials is known to exist, second-line antimicrobials need to be used as an alternative. However, these drugs are usually less well tolerated and the therapy takes much longer – in some cases more than two years – since some of these drugs only have a bacteriostatic effect. Treatment with second-line antimicrobials is also much more expensive.

Since the introduction of the Infection Protection Act in 2001, the presence of resistance to the above-mentioned first-line antimicrobials in case of tuberculosis has been recorded and transmitted to the Robert Koch Institute (RKI). In addition to first-line antimicrobials, the recording of resistance to second-line antimicrobials is currently being introduced, so that corresponding data will also be available in the future.

The resistance situation described in this chapter is based on the tuberculosis reporting data transmitted to the RKI by the deadline of 01/08/2012.

Tuberculosis and resistance situation in Germany in 2011

In 2011, a total of 4,317 new tuberculosis cases were notified in Germany that meet the RKI reference definition. This is equivalent to an incidence rate of 5.3 TB cases per 100,000 inhabitants (2010: 4,388 cases, incidence 5.4). The continued downward trend in the case number observed for many years has weakened considerably since 2009, now nearing a plateau with a more or less consistent incidence rate.

The result of the susceptibility testing was available for 2,871 of the 4,317 cases (66.5%) – at least for the two most important first-line antimicrobials isoniazid and rifampicin. To assess the resistance situation, these cases were defined as denominator according to the WHO's definition. In 2011, resistance to at least one of the five first-line antimicrobials ("any resistance" [HRZES]) was observed in 341 cases (11.9%). Multidrug resistant tuberculosis (MDR-TB), defined as resistance to at least isoniazid and rifampicin, was found in 56 cases (2.0%).

Multidrug resistant strains that are additionally resistant to a fluoroquinolone and to one of the three second-line injectable drugs (amikacin, kanamycin or capreomycin) are referred to as "extensively drug-resistant tuberculosis" or XDR-TB. As already mentioned above, the recording of resistance data for second-line antimicrobials as part of the general reporting obligation is currently being implemented, which is why a statement on the prevalence of XDR-tuberculosis in Germany cannot be made yet. According to the WHO's estimates (2012 Global Tuberculosis Report), the percentage of XDR-tuberculosis in all MDR-TB is – based on very limited data available – about 9.0% worldwide, with significant differences being observed between countries. According to the findings of a multicentre, prospective cohort study among eight participating countries conducted by Dalton et al., the average percentage of XDR-TB in all MDR-TB was 6.7%.[1]

The situation appears to be particularly problematic in the countries of the former Soviet Union. According to the data reported by the National Reference Centre (NRZ) for Mycobacteria, individual cases of XDR-TB have also been diagnosed in Germany for several years. XDR-tuberculosis is not only "imported", but sometimes also develops as a consequence of medical treatment errors.

Results of susceptibility tests and molecular-epidemiological studies conducted by the Borstel National Research Centre

During the period 2006–2010, the National Reference Centre for Mycobacteria at the Borstel Research Centre performed susceptibility tests as well as detailed molecular typing (24-loci MIRU-VNTR typing and spoligotyping) for 214 MDR-TB strains isolated from patients living in Germany. A relevant

number of MDR-TB strains was found to be resistant to further antituberculous drugs, e.g. to pyrazinamide (51%), amikacin (15%) or ofloxacin (9%). By means of genotyping, a large number of the strains were classified as the Beijing genotype (55%), followed by the genotypes LAM (13%), Ural (10%) and Delhi/CAS (5%). The total rate of clustered isolates was 58%, with the clustering rate in Beijing strains (76%) being significantly higher than in strains not belonging to the Beijing family (33%). Moreover, approx. 30% of all isolates were classified as belonging to the two largest clusters (Beijing 94-193, 100-32).

The Beijing genotype, which is a main causative agent of resistant tuberculosis in various high-incidence tuberculosis regions, represents a large portion of the MDR strains in Germany as well. The high clustering rate detected and the overall reduced population diversity with two predominant strains suggest a strong clonal spread of certain MDR-TB strains in countries of the former Soviet Union, which is also where the majority of MDR-TB patients in Germany originate from.

Risk factors for resistance development

One main risk factor for resistance development is a previous tuberculosis that may have been treated inadequately or incompletely. For 3,849 (89.2%) of the total of 4,317 cases reported information of a history of tuberculosis were available. About one in five of these patients (742 of 3,849; 19.3%) had previously been diagnosed with tuberculosis. Tab. 4.1.10.1 compares resistance rates between previously treated cases and new cases. It becomes evident that the percentage of resistant tuberculosis in patients with a previous treatment is significantly higher than in patients without a previous tuberculosis and therapy (new cases).

A latent *M. tuberculosis* infection may become active even many years later. For people with an immigration background, the epidemiological tuberculosis situation in the country of origin therefore plays a crucial role in the respective risk of developing active tuberculosis. In the event of progression from latent infection to active disease, the resistance characteristics of the pathogen usually reflect the situation in the country of origin. This is confirmed by the evaluation of the data reported for 2011. The analysis of the resistance situation by country of birth reveals a significantly higher percentage of drug resistant strains in patients from abroad (Tab. 4.1.10.2). Thus, the percentage of multidrug resistant tuberculosis in patients born abroad is approximately six times higher than in those born in Germany (Tab. 4.1.10.2).

Patients who were born in one of the successor states of the former Soviet Union (NIS; Newly Independent States) play a special role. The proportion of drug resistance in patients originating from these countries is particularly high, although the absolute numbers are lower than those found in patients

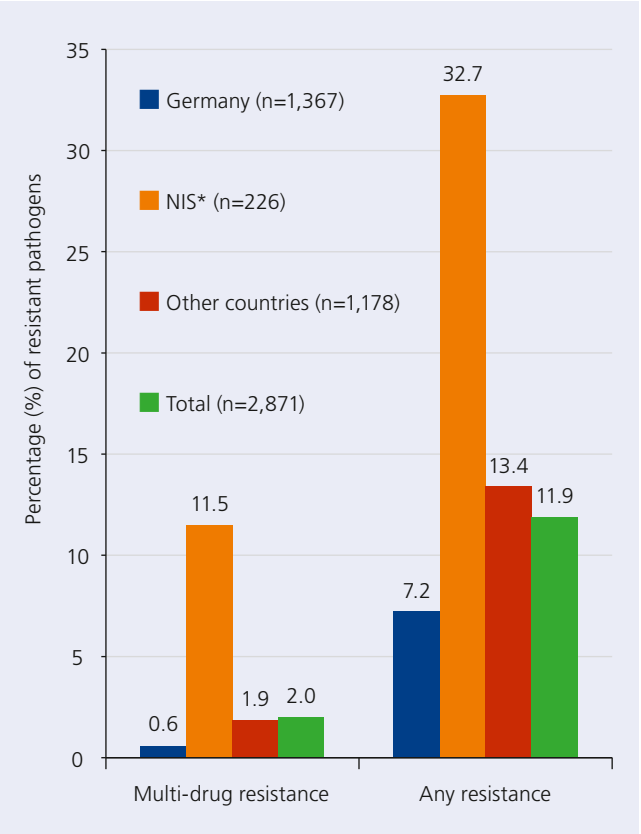


Fig. 4.1.10.1: Percentage of resistant tuberculosis by native country: Germany, NIS, other countries, including resistance information, Germany 2011

* NIS countries: Armenia, Azerbaijan, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Moldavia, Russian Federation, Tajikistan, Turkmenistan, Ukraine, Uzbekistan, Belarus

Tab. 4.1.10.1: Number and percentage of resistant tuberculosis by status of previous infection and previous treatment (Source: Robert Koch Institute, Report on Tuberculosis Epidemiology in Germany for 2011)

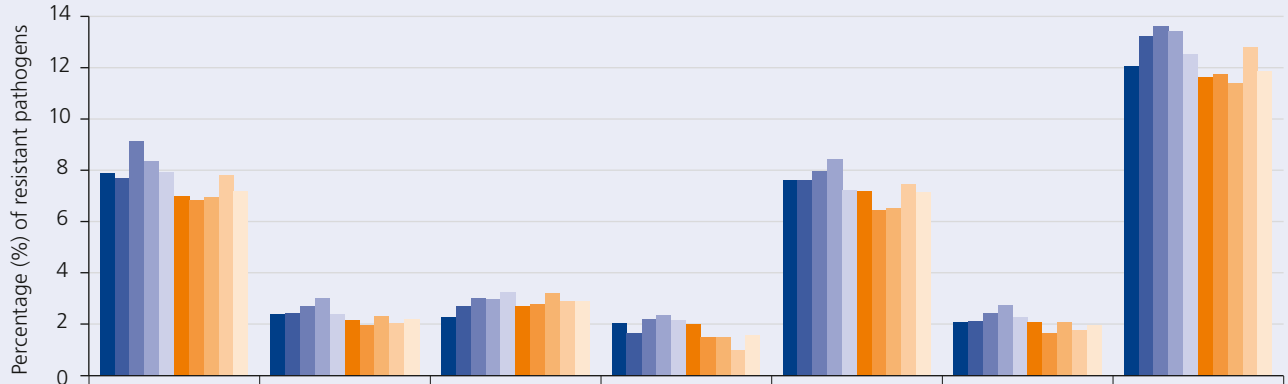
Resistance phenotype	Previous infection (with previous treatment) (n=159)		No previous infection (n=2,176)		Factor previous infection/no previous infection
	Number	Percentage	Number	Percentage	
Isoniazid (H)**	29	18.2	131	6.0	3.0
Rifampicin (R)**	21	13.2	27	1.2	10.6
Pyrazinamide (P)**	12	7.5	57	2.6	2.9
Ethambutol (E)**	11	6.9	23	1.1	6.5
Streptomycin (S)**	23	14.5	133	6.1	2.4
Multi-drug resistance**	18	11.3	23	1.1	10.7
Any resistance excl. PZA (HRES)**	33	20.8	194	8.9	2.3
Any resistance incl. PZA (HRESZ)**	35	22.0	232	10.7	2.1
Poly-resistance excl. PZA (HRES)	6	3.8	56	2.6	1.5

** Significantly higher percentage of resistant pathogens in patients with a previous infection and previous treatment compared to patients without a previous infection ($p < 0.001$)

Tab. 4.1.10.2: Number and percentage of resistant tuberculosis by native country Germany vs. abroad, cases incl. resistance data, 2011 (Source: Robert Koch Institute, 2011 Report on Tuberculosis Epidemiology in Germany)

Resistance phenotype	Germany (n=1.367)		Abroad (n=1.404)		Total (n=2.871)	
	Number	Percentage	Number	Percentage	Number	Percentage
Isoniazid (H)*	43	3.1	158	11.3	206	7.2
Rifampicin (R)*	12	0.9	51	3.6	63	2.2
Pyrazinamide (P)	33	2.4	48	3.4	83	2.9
Ethambutol (E)*	8	0.6	36	2.6	45	1.6
Streptomycin (S)*	49	3.6	150	10.7	205	7.1
Multi-drug resistance*	8	0.6	48	3.4	56	2.0
Any resistance (HRES)*	73	5.3	210	15.0	292	10.2
Any resistance (HRESZ)*	99	7.2	232	16.5	341	11.9
Poly-resistance (HRES)*	16	1.2	62	4.4	81	2.8

*Significantly higher percentage of resistant pathogens in patients born abroad ($p < 0.001$)
Note: No information on native country was available in 100 of the 2,871 tuberculosis cases tested for resistance, which is why these cases were not taken into account in the analysis by native country.



	Isoniazid	Rifampicin	Pyrazinamide	Ethambutol	Streptomycin	Multi-resistance	Any resistance
2002	7.9%	2.4%	2.3%	2.0%	7.6%	2.1%	12.1%
2003	7.7%	2.4%	2.7%	1.7%	7.6%	2.1%	13.2%
2004	9.1%	2.7%	3.0%	2.2%	8.0%	2.4%	13.6%
2005	8.4%	3.0%	3.0%	2.3%	8.4%	2.7%	13.4%
2006	7.9%	2.4%	3.2%	2.1%	7.2%	2.3%	12.5%
2007	7.0%	2.2%	2.7%	2.0%	7.2%	2.1%	11.6%
2008	6.8%	1.9%	2.8%	1.5%	6.4%	1.6%	11.8%
2009	7.0%	2.3%	3.2%	1.5%	6.5%	2.1%	11.4%
2010	7.8%	2.0%	2.9%	1.0%	7.4%	1.7%	12.8%
2011	7.2%	2.2%	2.9%	1.6%	7.1%	2.0%	11.9%

Fig. 4.1.10.2: Percentage of tuberculosis resistant to isoniazid, rifampicin, pyrazinamide, ethambutol, streptomycin as well as multi-drug resistance and any resistance, Germany 2011 (n=2,871) compared to the previous years 2010 (n=2,981), 2009 (n=3,061), 2008 (n=3,046), 2007 (n=3,328), 2006 (n=3,632), 2005 (n=3,900), 2004 (n=4,073), 2003 (n=4,475) and 2002 (n=4,696)

born in Germany. Approximately one-third of the pathogens (32.7%, 74 cases) found in patients from the NIS were resistant to at least one of the five first-line drugs (any resistance [HRESZ]), the percentage of resistant pathogens being about four and a half times higher than in patients born in Germany (7.2%, 99 cases) and more than twice as high than in patients from all other native countries (13.4%, 158 cases; Fig. 4.1.10.2).

This difference is even more pronounced regarding multidrug resistant tuberculosis: MDR-TB in patients from the NIS (11.5%, 26 cases) was nearly 20 times higher than in patients from Germany (0.6%, 8 cases) and six times higher than in patients born in other native countries (1.9%, 22 cases; Fig. 4.1.10.1).

Other factors, e.g. homelessness, imprisonment or addictive diseases (alcoholism, drug addiction) may both increase the risk of progression from latent tuberculosis infection to active diseaseand facilitate the development of resistance. One risk factor for the development of drug resistance is non-adherence to treatment. However, the reported surveillance data at the RKI allows no conclusion concerning this factor.

Trends in drug resistance development between 2002 and 2011

The nationwide recording of resistance data as part of the statutory reporting obligation allows the analysis of the epi-

demiological resistance situation regarding the five first-line antimicrobials over several years.

The evaluation of past years showed an initial slight increase in resistance, which becomes particularly evident when looking at the development of any resistance (with a peak of 13.6% in 2004) and multidrug resistance (peak of 2.7% in 2005). After this period, the resistance rates showed a downward or stable trend (Fig. 4.1.10.2).

At present in 2011, the percentage of multidrug resistant strains is 2.0% (56 cases), which represents a slight increase compared to the previous year (1.7%, 52 cases). On the whole, however, the percentage of MDR-TB during the last five years has stabilised at a relatively low level of around 2% or slightly below (Fig. 4.1.10.2).

A similar stabilisation of rates can be seen regarding any resistance, amounting to just below 12% during the last five years – except for 2010, when a somewhat higher resistance rate of 12.8% was recorded, which, however, dropped again to 11.9% in 2011.

Conclusion

Given the potentially long duration of the diseaseand the treatment as well as the more than 4,000 new diagnoses every year, tuberculosis continues to be one of the most significant infectious diseases in Germany.

The flagging success in reducing the number of new cases observed since 2009 also demonstrates that tuberculosis continues to represent a relevant public health concern.

Although the resistance rates have largely stabilised during the past few years following a slight increase, the rates are still comparatively high. The resistance data proves that an analysis of the cases by immigration background and the knowledge of the resistance situation in the respective countries of origin are of great importance for the assessment of the epidemiological situation in Germany.

For this reason, continued attention and careful analysis are required to anticipate the effects of the global situation as quickly as possible and to adapt the control strategies, if necessary. The significant increase in resistance rates in patients born outside Germany as well as the significantly increased risk of resistance in patients with a history of anti-TB therapy have direct consequences for planning an effective therapy. Early diagnosis and the initiation of an adequate therapy while taking into account the risk factors for the presence of resistance are therefore essential prerequisites for successful tuberculosis control.

Despite the stable or slightly declining rates observed during the past few years, the proportion of multidrug resistant tuberculosis is still relatively high, compared to other Western European countries. In addition, even a small number of XDR-TB cases poses a special challenge for our healthcare sector, in particular regarding the protection of the general population against further spread and in terms of (cost-intensive) management. The recent implementation of the recording of drug resistance data to also include second-line drugs will help, to assess the situation and development in the future even better.us even better anticipate the situation and the future development.

➤ B. Brodhun, D. Altmann, B. Hauer, S. Niemann, S. Rüsch-Gerdes, W. Haas
Reviewer: T. Ulrichs

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4.1.11 *Candida* spp.

Candida spp. represent a major cause of invasive infections in high-risk groups, such as immunosuppressed, oncology or surgery patients. Despite the introduction of echinocandins and newer broad-spectrum azoles, the 15–50% mortality rate associated with invasive candidiasis is still very high all over the world.[1,2] *C. albicans* also continues to represent the most common *Candida* species isolated from bloodstream infections, although an increase in the prevalence of non-albicans *Candida* species has been observed.[2] The species distribution varies between regions, but also depends on the type of the treatment centre and the respective group of patients. For the first time in 2007, the *German National Reference Centre for Systemic Mycoses* published systematically collected epidemiological resistance data for *Candida* isolates from normally sterile specimens in Germany.[3] As part of the MykoLabNet-D study, 561 strains collected from German centres in 2004/2005 were tested by means of the microdilution method in accordance with the M27-A2 protocol of the Clinical and Laboratory Standards Institute (CLSI). *C. albicans* was the most frequently found species, accounting for 58.5% of the isolates, followed by *C. glabrata* (19.1%), *C. parapsilosis* (8.0%), *C. tropicalis* (7.5%), *C. kefyr* (2.0%) and *C. krusei* (1.4%). 3.7% of the tested isolates were resistant to fluconazole and 0.4% to voriconazole. In addition, the resistance situation was found to be favourable for amphotericin B and caspofungin.

In recent years, two other large-scale studies were conducted to investigate the epidemiology of *Candida* infections in German-speaking countries.[4,5] Besides the period of sample collection, these studies differ in terms of the test specimens, the methods of measuring the minimum inhibitory concentration (MIC) and in terms of the clinical breakpoints used.

Study conducted by the Antifungal Susceptibility Testing (AFST) study group

A German-Austrian study determined the species and susceptibility distribution of 1,062 clinical yeast isolates for azoles (fluconazole, posaconazole, voriconazole), echinocandins (anidulafungin, caspofungin, micafungin), flucytosine and amphotericin B. The strains had been collected over the period from October 2008 to March 2009 from ongoing routine testing at 17 study centres and included 184 (17.3%) isolates from normally sterile specimens.[5] The MIC was measured after 48 hours by means of the microdilution method in accordance with the 58940-84 DIN standard.[6,7] However, the selected inoculum was 10 times higher. This is relevant to the extent that, for methodological reasons, the resulting MIC values tend to be higher with the DIN test design than with the corresponding CLSI and EUCAST protocols. The MIC values for amphotericin B measured within the AFST study were interpreted according to the criteria of the European Committee on Antimicrobial Susceptibility Testing (EUCAST), those for fluconazole according to the criteria of the DIN standard[8,9], those for posaconazole, anidulafungin, caspofungin and micafungin according to the criteria published by Pfaller et al.[10,11] and those for flucytosine and voriconazole according to the CLSI criteria.[6,7]

The most commonly isolated species among the isolates was *C. albicans*, accounting for 54%, followed by *C. glabrata* (22%), *C. parapsilosis* (6%), *C. tropicalis* (5.7%) and *C. krusei* (4.3%). None of the isolates showed resistance to all tested antifungals and 519 isolates (48.9%) were susceptible to all antifungals. When taking the non-species-specific EUCAST clinical breakpoints as a basis, the following percentages of *C. albicans* isolates were susceptible: 93.2% (amphotericin B), 95.6% (flucytosine), 84.3% (fluconazole), 83.8% (posaconazole), 91.8% (voriconazole), 96.5% (anidulafungin), 96.2% (caspofungin) and 97.6% (micafungin). Significant rates of resistance were observed for the class of azoles, especially in *C. glabrata, C. krusei, C. parapsilosis* and *C. tropicalis*, whereas resistance to echinocandins and flucytosine was comparatively rare. When applying the species-specific clinical breakpoints, the number of susceptible isolates was observed to fall significantly, especially for azoles. Regarding echinocandins, this effect was observed for *C. glabrata*, but not for *C. albicans*. The recorded resistance rates are summarised in Tab. 4.1.11.1.

2010 resistance study conducted by the Paul Ehrlich Society for Chemotherapy

The "Susceptibility Testing and Resistance" working group of the Paul Ehrlich Society (PEG) for Chemotherapy conducted a multicentre study to investigate the epidemiology and the resistance situation of *Candida* isolates from blood and other normally sterile sites. Over the period from October 2010 to September 2011, 542 yeast isolates, 70.3% of which had been isolated from blood cultures, were collected in 24 German, Austrian and Swiss laboratories. The isolates were tested for susceptibility to amphotericin B, flucytosine, fluconazole, itraconazole, voriconazole, posaconazole, anidulafungin,

Tab. 4.1.11.1: Susceptibility rates (%) of *Candida* isolates (n=1,062) to antifungals (Source: Antifungal Susceptibility Testing (AFST) Study Group[5])

	AMB	FYC	FLC	POS	VOR	ANF	CAS	MCA
C. albicans	93.2[1]	95.6[1]	74.5[2]	30.2[2]	81.9[2]	94.3[2]	94.8[2]	96.0[2]
C. glabrata	86.4[1]	99.2[1]	40.6[1]	37.2[1]	80.3[1]	97.0[2]	76.3[2]	96.6[2]
C. parapsilosis	81.2[1]	90.6[1]	28.1[2]	26.6[2]	71.9[2]	96.9[2]	96.9[2]	96.9[2]
C. tropicalis	83.6[1]	39.3[1]	32.8[2]	0.0[2]	16.4[2]	86.9[2]	85.3[2]	96.7[2]
C. krusei	67.4[1]	6.5[1]	4.4[1]	28.3[1]	50.0[1]	97.8[2]	84.8[2]	97.8[2]

AMB, amphotericin B; FYC, flucytosine; FLC, fluconazole; POS, posaconazole; VOR, voriconazole; ANF, anidulafungin; CAS, caspofungin; MCA, micafungin. Where available, species-specific clinical breakpoints were included in the table.

[1] Non-species-specific clinical breakpoints: AMB (S ≤ 1 mg/l; R > 1 mg/l); FYC (S ≤ 4 mg/l; R > 16 mg/l); FLC (S ≤ 4 mg/l; R > 16 mg/l); POS (S ≤ 1 mg/l; R > 2 mg/l); VOR (S ≤ 1 mg/l; R > 2 mg/l); ANF, CAS, MCA (S ≤ 2 mg/l; R > 2 mg/l)

[2] Species-specific clinical breakpoints: FLC (S ≤ 2 mg/l; R > 4 mg/l); POS (S ≤ 0,06 mg/l; R > 0,06 mg/l); VOR (S ≤ 0,125 mg/l; R > 0,125 mg/l); ANF, CAS, MCA (S ≤ 0,25 mg/l; R ≥ 1,0 mg/l) for *C. albicans, C. krusei, C. tropicalis*; ANF, CAS, MCA (S ≤ 2 mg/l; R ≥ 8 mg/l) for *C. parapsilosis*; ANF, CAS (S ≤ 0,12 mg/l; R ≥ 0,5 mg/l); MCA (S ≤ 0,06 mg/l; R ≥ 0,25 mg/l) for *C. glabrata*

Tab. 4.1.11.2: Susceptibility rates (%) of 542 *Candida* isolates from normally sterile specimens to antifungals (Source: PEG resistance study 2010[4])

	AMB		FLC		POS		VOR		ANF	
	405 nm	450 nm	405 nm	450 nm	405 nm	450 nm	405 nm	450 nm	405 nm	450 nm
C. albicans	99.7	99.4	99.7	99.7	100	100	100	100	100	100
C. glabrata	100	99.1	IE	IE	IE	IE	IE	IE	99.1	99.1
C. parapsilosis	100	100	100	100	100	100	100	100	–	–
C. tropicalis	100	100	100	100	100	100	100	100	100	100
C. krusei	92.3	69.2	–	–	IE	IE	IE	IE	100	100

See Tab. 4.1.11.1 for abbreviations; interpretation according to EUCAST (Antifungal Clinical Breakpoint Table, Version 4.1, of 14/03/2012)
IE, Insufficient Evidence: The antifungal agent exhibits no sufficient activity against the tested species. The measured MIC values can be reported, but are not classified as S, I, or R.
–: The species is not tested for resistance to the antifungal, as it shows no susceptibility to the antifungal agent.

caspofungin and micafungin by means of the microdilution method according to the guidelines of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (Definitive Document EDef 7.1 [www.eucast.org]). The MIC values were determined photometrically at both 405 nm and 450 nm. The measured MIC values were interpreted on the basis of the available species-specific clinical breakpoints (EUCAST Antifungal Clinical Breakpoint Table v. 4.1, of 14/03/2012).

C. albicans (62.5%) was the most commonly isolated species in the study, with *C. glabrata* (21.4%) ranking second, followed by *C. parapsilosis* (5%), *C. tropicalis* (5%) and *C. krusei* (2.4%). At a wavelength of 450 nm, the measured MIC values were typically higher than at 405 nm. For example, 0.38% of the 522 evaluable isolates turned out to be resistant to amphotericin B at 405 nm, compared to 1.34% at 450 nm. One strain each showed resistance to anidulafungin and fluconazole. All strains of *C. albicans, C. parapsilosis* and *C. tropicalis* were susceptible to voriconazole and posaconazole. The resistance rate of *C. albicans* to fluconazole was 0.3%. The highest rate of anidulafungin resistance was found in *C. glabrata* (0.9%). At 450 nm, 30.8% of the *C. krusei* strains were resistant to amphotericin B, with the majority of *C. tropicalis* strains showing reduced susceptibility to flucytosine (70.4%). The resistance rates are summarised in Tab.4.1.11.2.

Conclusion

The studies conducted confirm the continued predominance of the *C. albicans* species in both systemic and superficial yeast infections in Germany. In line with the results of the MykoLabNet-D study, *C. glabrata* continues to be the second most frequently isolated species. The overall resistance situation continues to be favourable. This applies particularly to the first-line antifungals used in Germany for the treatment of systemic *Candida* infections.

However, this data also shows that studies on the assessment of the resistance situation of yeasts still involve methodological problems. Firstly, species-specific and/or clinical breakpoints are not defined for all relevant antifungals, and secondly, the determination of MIC values for fungi substantially depends on the conditions of the test method (e.g. test medium, inoculum, incubation period, wavelength of photometric MIC determination). Therefore, the collection of reliable and comparable epidemiological data requires a standardised test method performed in a reference laboratory.

➤ M. Weig, O. Bader, U. Groß
Reviewer: M. Kresken

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4.2 Gastrointestinal infections

4.2.1 *Helicobacter pylori*

Helicobacter pylori infections are usually acquired within the first 5 years of life, persist lifelong and are accompanied by chronic gastritis. In Germany, the prevalence of *H. pylori* infections ranges between 5% (children) and 24% (adults), and is significantly higher in immigrants (36-86%).[1] Approx. 17% of patients with a *H. pylori* infection develop gastroduodenal ulcers.[2] Moreover, *H. pylori*-positive patients are exposed to a two to three times higher risk of developing gastric carcinoma and have an increased predisposition to the rare mucosa-associated lymphatic tissue (MALT) lymphoma.[3] Since patients with both *H. pylori*-associated peptic ulcers and low-malignancy MALT lymphomas can be cured by an antimicrobial therapy, the national S3 guideline "*Helicobacter pylori* and gastroduodenal ulcers" recommends eradication therapy in patients with these diseases.[1] Combinations of a proton pump inhibitor (PPI), clarithromycin and amoxicillin or metronidazole for at least 7 days are recommended first-line therapies[1] with a 79% to 96% success rate.[4] Besides patient compliance, one of the major causes of therapy failure is resistance to the antimicrobials used. Antimicrobial resistance may have developed either during previous unsuccessful eradication therapies or during therapy of unrelated bacterial infections. The molecular basis of resistance of *H. pylori* primarily is the acquisition of point mutations.[5] If eradication cannot be achieved using the above-mentioned first-line antimicrobials, treatment with amoxicillin, levofloxacin and rifabutin needs to be initiated;[1] the quadruple therapy consisting of a PPI, bismuth subcitrate, metronidazole and tetracycline widely used in the past may also play a more significant role again in the future.[6]

Resistance situation

To test antimicrobial susceptibility, *H. pylori* are cultured from gastric biopsy specimens from corpus and antrum, which are collected predominantly in outpatient care. *H. pylori* is tested for susceptibility to amoxicillin, metronidazole, clarithromycin, levofloxacin, tetracycline and rifabutin, which are commonly used in eradication, by means of the E-test®. Since January 2012, epidemiological cut-off values have been available for susceptibility testing at European level (http://www.eucast.org/clinical_breakpoints/).

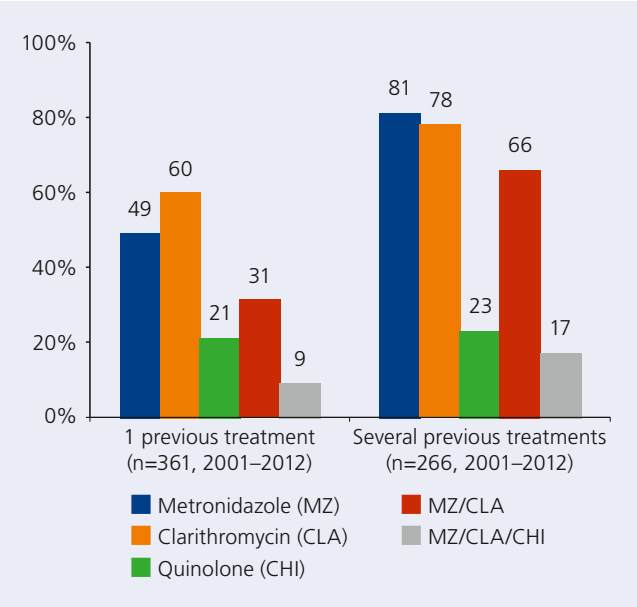

Fig. 4.2.1.1: Resistance rates of *H. pylori* in dependence on the number of previous treatments (data reported by the German-wide *ResiNet* multicentre surveillance study)

In Germany, the estimated primary resistance rates of *H. pylori* are 32% for metronidazole (MZ), 7% for clarithromycin (CLA) and 15% for levofloxacin. Strains with double resistance (to MZ & CLA) are found in as many as 4% of patients without a history of antimicrobial therapy and isolates with triple resistance (resistant to MZ, CLA & levofloxacin) in 1%.[7] This data is obtained from the "Third European multicentre study on antimicrobial susceptibility of *Helicobacter pylori* 2008–2009" and is consistent with the results of the Germany-wide multicentre surveillance study *ResiNet*, which has been continuously supplying data since as early as 2001. Based on this data and the specifications of the Maastricht IV Consensus Report, a combination of a PPI, clarithromycin and amoxicillin or metronidazole is still a first-line therapy.[6]

After one unsuccessful therapy, the resistances to MZ, CLA and quinolones increased to 49%, 60% and 21%, respectively. After more than one unsuccessful eradication therapy, resistances were as high as 81% for MZ, 78% for CLA and 23% for quinolones (data obtained from *ResiNet*, Fig. 4.2.1.1). At the same time, double resistances to MZ/CLA rose from 31% to 66% and the rate of triple resistance to MZ/CLA/CHI from 9% to 17%. Resistance to amoxicillin has so far not been observed in Germany. Resistance to rifampicin/rifabutin is still low (1.4%).[8] Resistance or reduced susceptibility to tetracyclines has so far only been reported in individual cases,[9,10,11] with rifabutin and tetracycline resistance being observed mainly in patients who have undergone multiple previous treatments. Apart from prior unsuccessful therapies, patients' sex constitutes another risk factor for development of resistance. Women carry resistant *H. pylori* more often than men (Fig. 4.2.1.2). This could also be explained by the higher percentage of women with a history of antimicrobial therapies (44%) compared to men with such history (30%). Further risk factors, e.g. the patients' age or clinical diagnosis have no significant influence on the resistance rates.

When looking at the temporal development of resistance in *ResiNet* isolates from patients without a history of antimicrobial therapy, it becomes apparent that the resistance to MZ increased from 24% (2001/2002) to 37% (2011/2012). Over the same period, the CLA resistance also increased from 6% to 12% (Fig. 4.2.1.3). A slight increase in resistance rates from 14% (2001/2002) to 17% (2007/2008) was observed for quinolones. Whether the rather downward trend observed after 2007/2008 will continue remains to be seen (Fig. 4.2.1.3). Reasons for theincreasing primary resistances may include antimicrobial therapies for other bacterial infections, e.g. clarithromycin therapies prescribed for respiratory tract infections.

In addition to phenotypic susceptibility testing, resistance-associated mutations can be also found in certain genes of *H. pylori*. The detection of these mutations correlates well with the results of the phenotype testing.[5] In routine testing,

methods of identifying CLA resistance (23S rRNA genes, real-time PCR) and quinolone resistance (*gyrA* gene, DNA•STRIP® technology) are currently established.[12,13] These methods are primarily used when the bacteria cannot be cultured. To date, more than 5,500 gastric biopsy specimens have been tested in Freiburg for the presence of CLA resistance and more than 500 biopsy specimens for the presence of quinolone resistance. These were collected mainly from patients who had undergone previous treatment. Regarding CLA, resistance-mediating mutations were detected in 45% of the cases, with the A2147G mutation being found most commonly (68%). Regarding quinolones, a resistance-mediating mutation was detected in 36% of the cases, with mutations in the codon 91 being found most frequently (67%).

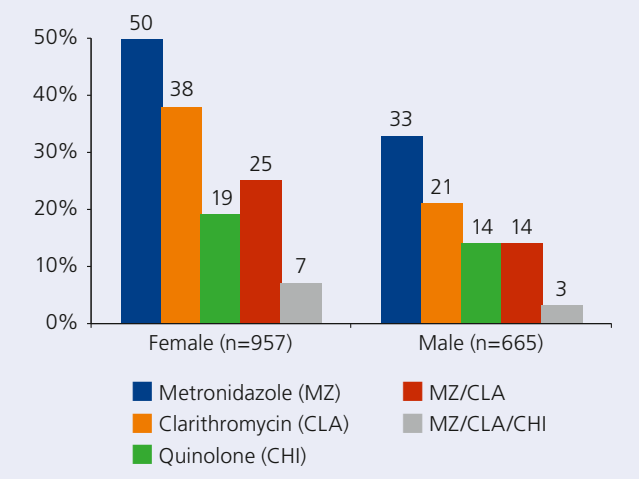

Fig. 4.2.1.2: Resistance rates of *H. pylori* in dependence on sex (data reported by the German-wide *ResiNet* multicentre surveillance study, patients without and with a history of antibiotic therapy)

Conclusion

The introduction of the EUCAST breakpoints marks the first time that standardised breakpoints are available for all antimicrobials used to eradicate *H. pylori*; further standardisation of phenotypic susceptibility testing is nevertheless urgently needed. Compared to other European countries, the resistance situation for first-line antimicrobials is still relatively favourable, making it possible to treat patients without a history of antimicrobial therapy in accordance with the specifications of the national S3 guideline and the Maastricht IV Consensus Report without prior susceptibility testing of the pathogen. However, after the second therapy failure at the latest, the pathogen should be cultured and tested for susceptibility, since previous eradication therapies represent the main risk factor for the development of in *H. pylori*. The increase in primary resistance rates observed over the course of the years makes nationwide surveillance studies indispensable in order to be able to monitor the resistance development in Germany and to identify potential risk factors.

➤ N. Wüppenhorst, E.-O. Glocker
Reviewer: G. Werner

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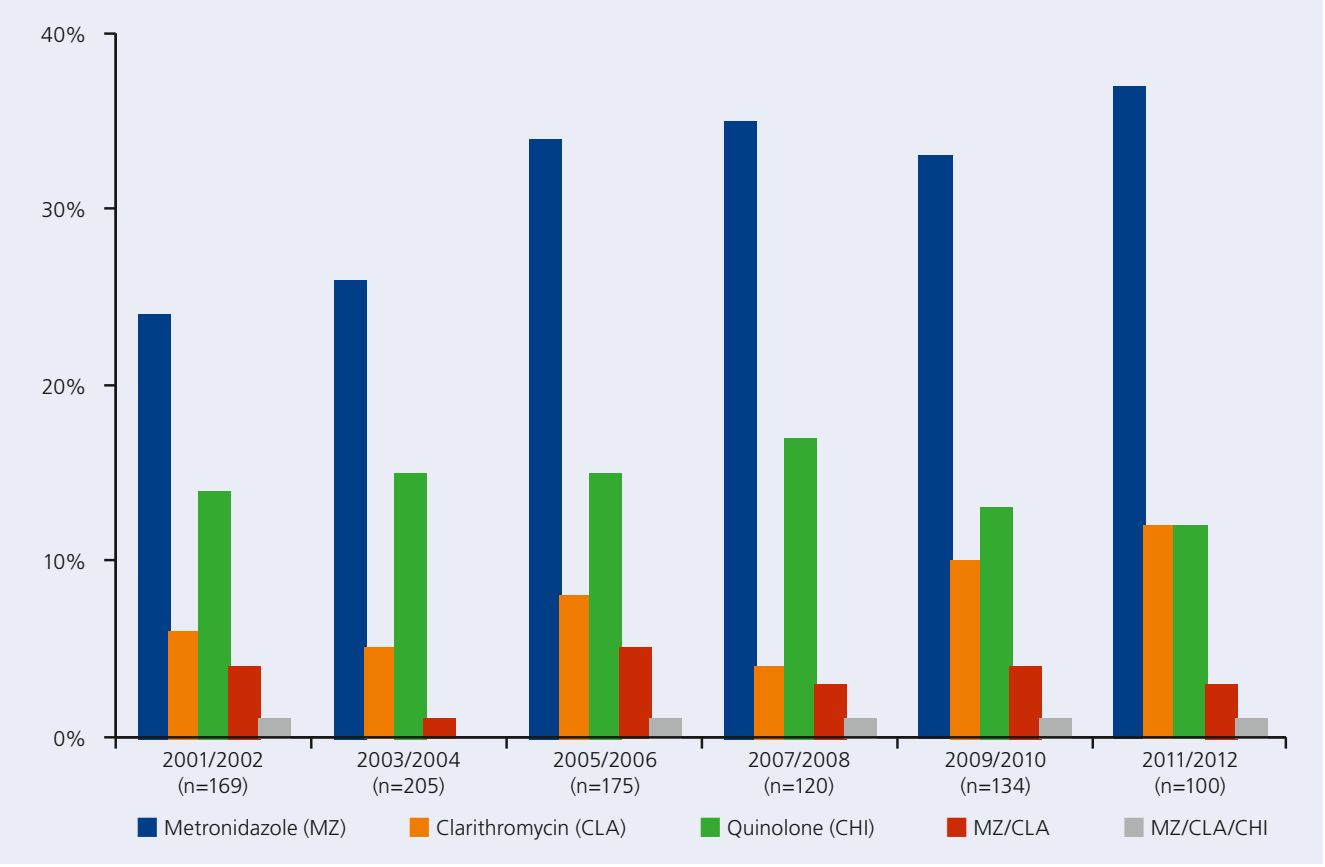

Fig. 4.2.1.3: Temporal trends in resistance development of *H. pylori* (data reported by the German-wide *ResiNet* multicentre surveillance study, patients without a history of antibiotic therapy)

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4.2.2 *Shigella* spp.

The number of *Shigella* infections reported in Germany has been declining for years (http://www3.rki.de/SurvStat). At the same time, the number of *Shigella* isolates submitted to the National Reference Centre for Salmonellae and Other Bacterial Enterics at the Robert Koch Institute, Wernigerode Branch, has been decreasing continuously from 258 in 1998 to 49 in 2011. More than half of these isolates obtained from human diarrhoeal diseases were confirmed to have been caused by travel-associated infections abroad. 77% of the tested *Shigella* strains were *Shigella sonnei*, 19% *Shigella flexneri*, and 4% *Shigella dysenteriae* or *Shigella boidii*. Between 1998 and 2011, a total of 1,714 Shigella strains were tested for susceptibility to 16 antimicrobials. The antibiogram (MIC determination by means of the broth microdilution test) is not created for clinical therapeutic purposes, but serves as an epidemiological marker for pathogen isolates.

Resistance situation

The percentage of *Shigella* isolates tested fully susceptible declined continuously from 20% in 1998 to 2% in 2011. The rates of resistance to some antimicrobials were very high in all *Shigella* spp., with those to streptomycin and co-trimoxazole being subject to a continued upward trend (Tab. 4.2.2.1). The rates of resistance to ampicillin (but not to mezlocillin) as well as to chloramphenicol in *S. flexneri* were significantly higher than in *S. sonnei*. Besides the widespread resistance to streptomycin, very rare cases of resistance to aminoglycosides, in particular to gentamicin, were also found in all *Shigella* spp. Since 2001, resistance to cephalosporins has also been observed in strains of all *Shigella* spp. (mainly from infections abroad). Since 2003, an increasing number of ciprofloxacin-resistant strains have been isolated from all *Shigella* spp. Most of these isolates, which had been obtained mainly from infections acquired abroad, were additionally resistant to eight to twelve other antimicrobials. Since 2005, multidrug resistant *S. dysenteriae* and *S. sonnei* isolates, exhibiting resistance to both fluoroquinolones and third-generation cephalosporins, have also occurred in isolated cases.

Trends in resistance development

Whereas the percentage of fully susceptible strains has continuously decreased over the years to reach 2% in 2011 and the percentage of strains resistant to one or two antimicrobials ranged around 15% between 1989 and 2011, the percentage of multidrug resistant (resistant to more than two of the tested antimicrobials) strains increased from 70% to more than 80% in 2011. The resistance rates of ampicillin and mezlocillin stagnate at a relatively high level (Tab. 4.2.2.1). The rapid increase in resistance to the combination of mezlocillin/sulbactam observed until 2005 has not continued in recent years (Fig. 4.2.2.1). Before 2000, about 90% of mezlocillin-resistant *Shigella* were still susceptible to the combination with the β-lactamase inhibitor. By 2005, this rate dropped to about 30%, which may have been associated with the spread of inhibitor-resistant β-lactamases. In the following years, however, *Shigella* species resistant to mezlocillin/sulbactam were found far less commonly, and about 80% of all mezlocillin-resistant *Shigella* were again susceptible to the combination with the β-lactamase inhibitor in 2011. Resistance to cephalosporins was first observed in 2001. Since then, the rate of resistance to third-generation cephalosporins has also increased continuously, which may have been associated with the increasing spread of extended-spectrum β-lactamases (ESBLs). A significant increase from 0.6% in 1998 to 22% in 2011 is observed in resistance to nalidixic acid. The rate of ciprofloxacin resistance follows this trend at a lower level (Fig. 4.2.2.1).

Tab. 4.2.2.1: Resistance rates of *Shigella* spp. (Source: National Reference Centre for Salmonellae and Other Bacterial Enterics at the Robert Koch Institute, Wernigerode Branch; 1998–2011)

Antibiotic	Breakpoint (mg/l) Resistant (>)	1998–2000 n=691	2001–2003 n=380	2004–2006 n=354	2007–2011 n=289
		% of resistant strains			
Streptomycin	16	76	82	83	88
Co-trimoxazole	16	69	81	87	93
Tetracycline	4	52	65	80	69
Ampicillin	8	41 *sonnei* 28 *flexneri* 68	33 *sonnei* 24 *flexneri* 63	33 *sonnei* 25 *flexneri* 75	29 *sonnei* 21 *flexneri* 69
Mezlocillin	16	25	27	23	18
Mezlocillin/Sulbactam	16	2	7	16	2
Chloramphenicol	8	18 *sonnei* 5 *flexneri* 48	17 *sonnei* 5 *flexneri* 56	20 *sonnei* 5 *flexneri* 75	11 *sonnei* 2 *flexneri* 64
Nalidixic acid	16	1	7	10	19
Ciprofloxacin	2	0	0.3	0.6	5
Gentamicin	4	0.6	0.8	0.9	0.3
Kanamycin	16	0	1.0	0	0
Amikacin	16	0	0.5	0	0
Cefotiam	4	0	1.3	3.4	6
Cefoxitin	16	0	0	1.7	0
Cefotaxime	8	0	1.1	1.6	6
Ceftazidime	16	0	0.5	1.1	1

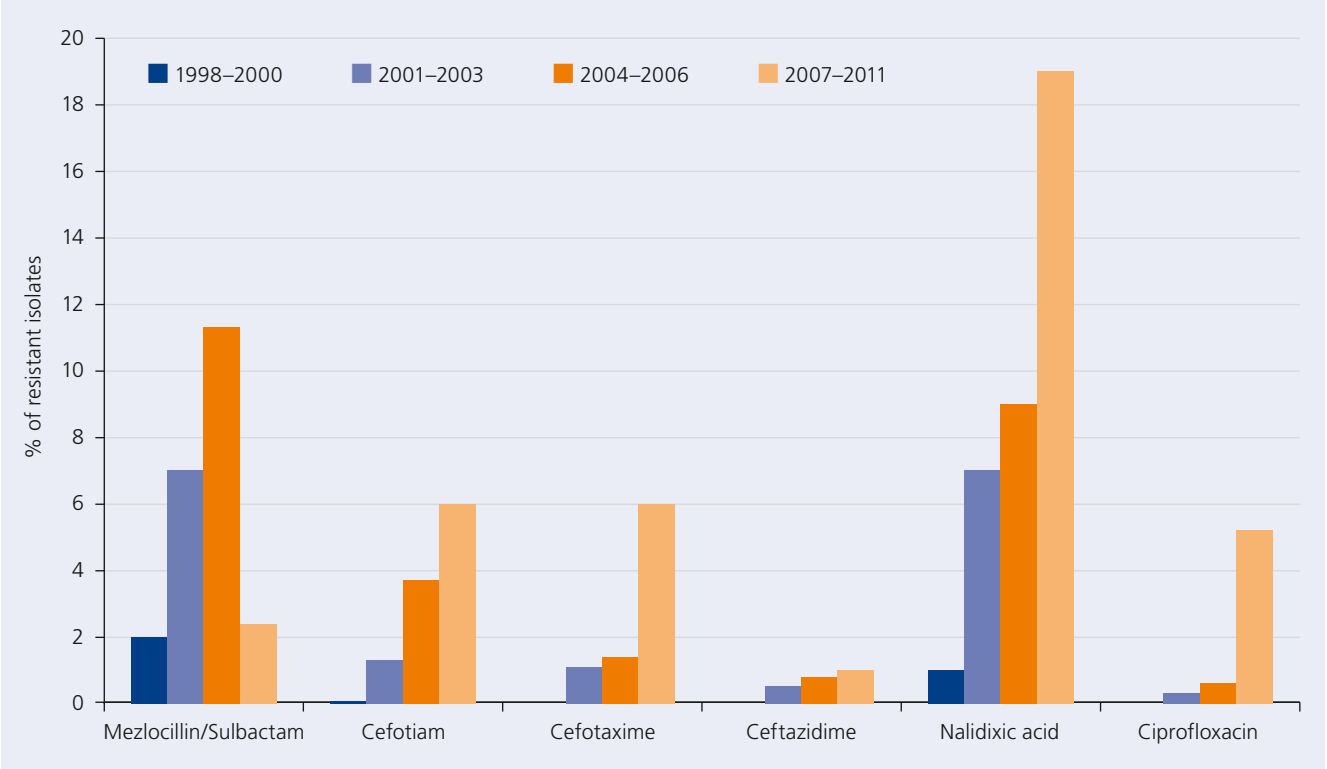

Fig. 4.2.2.1: Temporal development of resistance to some antimicrobials in *Shigella* spp., 1998–2011 (Source: National Reference Centre for *Salmonellae and Other Bacterial Enterics* at the Robert Koch Institute, Wernigerode Branch)

Conclusion

Based on the pathogen isolates tested by the National Reference Centre, the assessment of the resistance situation of *Shigella* consistently covers about 10% of the *Shigella* infections occurring annually, when taking the number of *Shigella* infections reported since 2001 in accordance with the Infection Protection Act as a basis. According to this, *Shigella* isolated in Germany are usually expected to show multidrug resistance. In nearly all cases, the multidrug resistance concerns tetracycline, streptomycin and co-trimoxazole, and, somewhat less commonly, also ampicillin. Increased resistance to ciprofloxacin and/or cephalosporin has to be expected, especially with *Shigella* infections acquired abroad.

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Reviewer: N. Wüppenhorst

4.2.3. *Salmonella enterica* subspecies *enterica*

Despite the downward trend observed, *Salmonella* infections are among the most common causes of bacterial gastroenteritis in Germany, still accounting for 25,000 to 30,000 cases reported annually. In addition to individual infections, *Salmonella enterica* subspecies *enterica* causes a great number of food-associated outbreaks every year, with the serovars Typhimurium (26% in 2008, 34% in 2011) and Enteritidis (53% in 2008, 36% in 2011) being most predominant (http://www3.rki.de/SurvStat). From 1999 to 2011, the National Reference Centre for *Salmonellae and Other Bacterial Enterics* at the Robert Koch Institute, Wernigerode Branch, tested 54,664 *Salmonella* isolates obtained from diarrhoeal diseases in Germany for susceptibility to 16 antimicrobials. The two most common serovars Enteritidis (30–60%) and Typhimurium (30–40%) together accounted for 60–80% of the test specimens, their percentage being nearly constant over the years. The antibiogram (MIC determination by means of the broth microdilution test) is not created for clinical therapeutic purposes, but serves as an epidemiological marker for pathogen isolates.

Resistance situation

As has been the case since 1999, about 95% of the serovar Enteritidis isolates were tested susceptible, whereas a continuous downward trend from 32% susceptible isolates in 1999 to 13% in 2011 was observed for the serovar Typhimurium. The percentage of susceptible strains in the other serovars remained more or less constant (65–75%; 79% in 2011). The resistance situation of salmonellae was thus substantially dependent on the serovar Typhimurium (Fig. 4.2.3.1, Tab. 4.2.3.1). Since 1999, high rates of resistance, which have continued to increase to this day, have been observed for streptomycin, tetracycline as well as for amino- and ureidopenicillins. Whereas about 85% (87% in 2011) of the mezlocillin-resistant serovar Typhimurium strains were still susceptible to the combination with a β-lactamase inhibitor, the corresponding rate in the other serovars (excl. Enteritidis) was only 40–55% (60% in 2011). This suggests an unequal spread of different β-lactam resistance determinants in the various serovars, since nearly 70% of the β-lactam-resistant serovar Typhimurium isolates are attributable to a small number of predominant clones (phage types DT104, DT193) with an inhibitor-susceptible TEM-1 β-lactamase. Resistance to chloramphenicol in about one-third of all serovar Typhimurium isolates was at a high but steadily declining level (20% in 2011), but was only detected in less than 10% of strains of other serovars. The low level of resistance to co-trimoxazole in all serovars (except for Enteritidis) increased slightly to approx. 10% in 2011. The prevalence of resistance to nalidixic acid in the respective serovars was constant over all periods. By contrast, resistance to fluoroquinolones was not detected in the serovars Typhimurium and Enteritidis until 2009. Overall, 95% of the fluoroquinolone-resistant salmonellae were classified as serovar Kentucky; however, six independent serovar Typhimurium isolates resistant to ciprofloxacin have also emerged since 2010. Apart from the widespread resistance to streptomycin, resistance to other aminoglycosides (kanamycin, gentamicin, amikacin) occurred only rarely. Cephalosporin-resistant salmonellae still represent exceptions. In 2011, 0.6% of the tested Salmonella strains showed resistance to cefotaxime

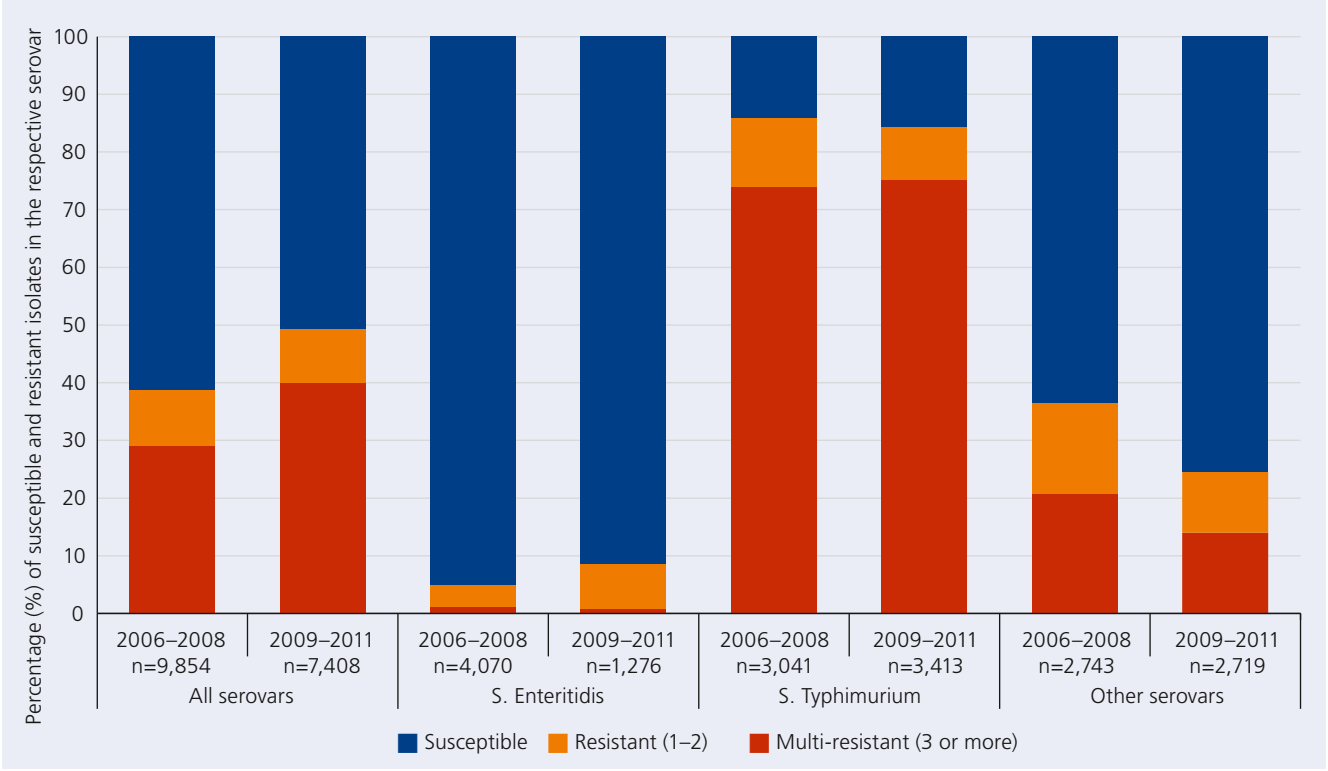

Fig. 4.2.3.1: Percentage of susceptible and (multi-)resistant strains in all *S. enterica* isolates, itemised by the most common serovars Typhimurium and Enteritidis: Comparison of the periods 2006–2008 and 2009–2011 (Source: National Reference Centre for *Salmonellae and Other Bacterial Enterics* at the Robert Koch Institute, Wernigerode Branch)

Tab. 4.2.3.1: Resistance rates of *Salmonella enterica*, subspecies *enterica* (Source: National Reference Centre for *Salmonellae and Other Bacterial Enterics* at the Robert Koch Institute, Wernigerode Branch; 1999–2011)

		1999–2001 n=20,168			2002–2004 n=13,658			2005–2007 n=10,348			2008–2011 n=10,490		
Serovar		Typhimurium	Enteritidis	Other	Typhimurium	Enteritidis	Other	Typhimurium	Enteritidis	Other	Typhimurium	Enteritidis	Other
Percentage (%) during the period		38	48	14	31	52	17	31	42	28	43	22	35
Antibiotic	**Breakpoints (mg/l) Resistant (>)**	% of resistant strains of the respective serovars											
Streptomycin	16	61	2	22	69	1	24	74	1	24	77	0.3	22
Tetracycline	4	63	1	16	65	1	13	73	2	22	75	1	15
Ampicillin	8	54	2	8	61	1	8	71	2	16	77	4	13
Mezlocillin	16	54	1	8	61	1	7	71	1	16	77	4	13
Mezlocillin/Sulbactam	16	11	0.6	4	14	0.3	4	11	0.2	5	10	0.4	5
Chloramphenicol	8	40	1	6	35	1	16	30	1	6	20	0.3	5
Co-trimoxazole	16	7	1	6	11	1	5	17	1	7	10	0.5	9
Nalidixic acid	16	4	3	10	4	4	10	4	3	10	6	3	11
Ciprofloxacin	2	0	0	0.1	0	0	0.2	0	0	0.7	0.1	0	2
Kanamycin	16	2	0.5	3	4	0.2	3	6	0.3	2	3	0.1	2
Gentamicin	4	1	0.5	1	2	0.2	2	1	1	2	1	0.1	2

and 0.3% were additionally resistant to ceftazidime (two multidrug resistant serovar Typhimurium isolates, one Newport, one Goldcoast, one Derby, one Infantis, one Virchow).

Trends in resistance development

Multidrug resistance (resistance to three and more antimicrobials) in serovar Typhimurium strains increased continuously from 44% in 1999 to 78% in 2011 (Fig. 4.2.3.1). Until about 2002, the increase in multidrug resistance followed the spread of a predominant, multidrug resistant strain (phage type DT104) with a chromosomally fixed cluster of genes conferring resistance to tetracycline, streptomycin, chloramphenicol and ampicillin. Since 2002, the spread of the DT104 strains has declined, but the percentage of multidrug resistant strains in serovar Typhimurium isolates has continued to rise. This coincided with the emergence of a new predominant serovar Typhimurium strain (phage type DT193) with chromosomally located genes conferring resistance to tetracycline, streptomycin and ampicillin, but not to chloramphenicol. Accordingly, the rate of chloramphenicol resistance in serovar Typhimurium isolates dropped from 45% in 2001 to 14% in 2011 (Tab. 4.2.3.1). Although the increase in multidrug resistance can again be explained by the increasing prevalence of a single predominant clone, a process involving multiple clones is becoming apparent within the serovar Typhimurium. By contrast, multidrug resistant strains among the serovar Enteritidis remained consistently rare over the years (1% in 2011). The percentage of multidrug resistant isolates in the other serovars ranged between 10% and 20% (14% in 2011), depending on the epidemic situation. The steady increase in rates of resistance to co-trimoxazole from 5% in 1999 to 14% in 2008 in the serovar Typhimurium and from 3% in 1999 to 11% in 2008 in the other serovars (except for Enteritidis) has not continued in recent years (Tab. 4.2.3.1). Whereas a nearly constant rate of resistance to nalidixic acid was observed in all serovars over the years, the emergence of ciprofloxacin-resistant *Salmonella* isolates, which are still very rare but have occurred regularly since 2001, shows an increasing development of resistance to fluoroquinolones as well. Multidrug resistant serovar Kentucky and Paratyphi B/Java strains resistant to both fluoroquinolones and third-generation cephalosporins (e.g. cefotaxime, ceftazidime) were observed in isolated cases.

Conclusion

Based on the pathogen isolates tested by the National Reference Centre, the assessment of the resistance situation of salmonellae consistently covers about 10% of the *Salmonella* infections occurring annually, when taking the number of *Salmonella* infections reported since 2001 in accordance with the Infection Protection Act as a basis. However, the situation of the two most common *Salmonella* serovars in Germany varies greatly. About 95% of serovar Enteritidis isolates are susceptible to all tested antimicrobials, whereas most serovar Typhimurium strains have now become multidrug resistant. The resistance rates of *S. enterica* can thus only be recorded and quantified in relation to serovars. Differences in resistance rates can also reflect differences in selection pressure in the reservoirs of the respective serovars. The investigation of these reservoirs is of great significance in combating the resistance development. It should be noted that, as a rule, antimicrobial treatment is not recommended for uncomplicated enteric forms of salmonellosis.

➤ E. Tietze
Reviewer: N. Wüppenhorst

4.2.4 *Yersinia enterocolitica*

Based on the number of reported cases, about 3,000–5,000 *Yersinia enterocolitica* infections occur every year in Germany (http://www3.rki.de/SurvStat). Between 2005 and 2011, the National Reference Centre for *Salmonellae and Other Bacterial Enterics* at the Robert Koch Institute, Wernigerode Branch, identified and tested 1,521 *Y. enterocolitica* isolates for susceptibility to 16 antimicrobials. About two-thirds of the strains had been isolated from clinically relevant test specimens from patients with gastroenteritis in a German laboratory practice with a supra-regional catchment area of about 1 million inhabitants (sentinel region). The remaining isolates had been obtained from investigation offices from 10 Länder. As was the case in previous years, about three-quarters of the tested strains were classified as serovar O:3, 5–10% as serovar O:9 and 10–20% as the 1A biotype, which is considered non-enteropathogenic. The antibiogram (MIC determination by means of the broth microdilution test) is not created for clinical therapeutic purposes, but serves as an epidemiological marker for pathogen isolates.

Resistance situation

In line with the known non-susceptibility of *Y. enterocolitica* to aminopenicillins, virtually all isolates were resistant to ampicillin (Tab. 4.2.4.1). With the exception of this constitutive resistance, about 60% of the strains were tested fully susceptible, about 30% were found to be resistant to one or two antimicrobials and about 10% were multidrug resistant (resistant to at least three antimicrobials), with these rates being constant over the years. Resistance to mezlocillin was detected in 10% of the strains (Tab. 4.2.4.1); however, nearly all these strains were susceptible to the combination of mezlocillin and the β-lactamase inhibitor sulbactam. 20% of the isolates showed resistance to chloramphenicol. 19% of the *Y. enterocolitica* strains were resistant to streptomycin, whereas the rates of resistance to other aminoglycosides were below 1%. The rates of resistance to tetracycline and cotrimoxazole were also low (< 5%). Resistance to cefotiam, a second-generation cephalosporin, or to the cephamycin cefoxitin was detected in 8% and 7% of the isolates, respectively, whereas resistance to third-generation cephalosporins was only observed in isolated cases among multidrug resistant strains. Most of these strains were not only resistant to cephalosporins, but also to chloramphenicol, tetracycline, nalidixic acid and a number of aminoglycosides such as kanamycin, gentamicin and/or amikacin, but were susceptible to co-trimoxazole, mezlocillin and fluoroquinolones. Since 2005, isolates resistant to nalidixic acid have occurred regularly, although all of them were tested susceptible to the fluoroquinolone ciprofloxacin. A ciprofloxacin-resistant *Y. enterocolitica* strain that was also non-susceptible to all other tested substances, except for mezlocillin, emerged for the first time in 2011.

Trends in resistance development

The resistance situation of *Y. enterocolitica* seems stable. A significant trend towards an increase or decrease in resistance rates cannot be identified for any of the tested antimicrobials (Tab. 4.2.4.1). Although the rates of mezlocillin and cefotiam resistance during the period 2009–2011 were significantly lower than in 2005/2006, monitoring will be required over the next few years to see whether this constitutes a trend. The same applies to the slightly increasing rates of resistance to chloramphenicol and nalidixic acid.

It remains uncertain to what extent the above-described resistance situation of Yersinia isolates, which came mainly from a single large region, can be transferred to the situation in Germany. When comparing the sporadically submitted one-third of the isolates from 10 Länder with the isolates from the sentinel region, however, no significant difference is seen in the resistance situation.

Tab. 4.2.4.1: Resistance rates of *Y. enterocolitica* (Source: National Reference Centre for *Salmonellae and Other Bacterial Enterics* at the Robert Koch Institute, Wernigerode Branch; 2005–2011)

Antibiotic	Breakpoints (mg/l) Resistant (>)	2005–2006 n=365	2007–2008 n=350	2009–2011 n=806
		% of resistant strains		
Ampicillin	8	98	99	100
Mezlocillin	16	15	8	3
Mezlocillin/Sulbactam	16	0	0	0.2
Chloramphenicol	8	14	20	26
Streptomycin	16	14	20	18
Kanamycin	16	1.1	0.9	0.6
Amikacin	16	0.5	0.9	0.7
Gentamicin	4	0.5	0.6	0.6
Tetracycline	4	3	5	4
Co-trimoxazole	16	2	1.4	1.2
Cefotiam	4	12	9	3
Cefoxitin	16	10	5	7
Cefotaxime	8	0	0.3	0.4
Ceftazidime	16	0.3	0.6	0.2
Nalidixic acid	16	1.4	2	3
Ciprofloxacin	2	0	0	0.1

Conclusion

Based on the available data, the percentage of *Y. enterocolitica* isolates resistant to the therapeutically relevant substances co-trimoxazole and tetracyclines as well as to some aminoglycosides is less than 5%. *Y. enterocolitica* can still generally be classified as susceptible to the combination of mezlocillin and sulbactam, ciprofloxacin, but also third-generation cephalosporins. However, isolates that also exhibit resistance to these substances have sporadically emerged during the past two years. It should be noted that, as a rule, antimicrobial treatment is not recommended for uncomplicated enteric forms of yersiniosis.

➤ E. Tietze
Reviewer: N. Wüppenhorst

4.2.5 *Campylobacter jejuni/ Campylobacter coli*

The number of *Campylobacter* infections reported in Germany is increasing and, since 2007, has exceeded the number of salmonella infections reported (http://www3.rki.de/SurvStat). Between 2005 and 2011, the National Reference Centre (NRZ) for *Salmonellae and Other Bacterial Enterics* at the Robert Koch Institute, Wernigerode Branch, tested 1,102 *Campylobacter jejuni* and 592 *Campylobacter coli* isolates for susceptibility to 11 antimicrobials. The pathogen isolates from stool specimens of diarrhoea patients were obtained almost exclusively from a German laboratory practice with a supra-regional catchment area of about 1 million inhabitants. The antibiogram (MIC determination by means of the broth microdilution test) is not created for clinical therapeutic purposes, but serves as an epidemiological marker for pathogen isolates.

Since no generally approved breakpoints are available for *Campylobacter* spp., the isolates were classified as "resistant" based on the DIN values for Enterobacteriaceae and, for some antimicrobials, based on the preliminary MIC90 values for all *Campylobacter* spp. isolates tested so far by the NRZ (Tab. 4.2.5.1). [Editorial note: EUCAST breakpoints for *Campylobacter jejuni* and *coli* have been available since 2013]

Resistance situation

The percentage of fully susceptible strains in all tested *C. jejuni* isolates was 10%; this rate was below 5% in *C. coli* strains (Fig. 4.2.5.1). Consistently high resistance rates in both species were observed for ampicillin, nalidixic acid, ciprofloxacin and tetracycline, while the rates of resistance to erythromycin, clindamycin, chloramphenicol and the aminoglycosides kanamycin, gentamicin and amikacin were significantly lower (Tab. 4.2.5.1). Whereas the rates of resistance to ampicillin, nalidixic acid, ciprofloxacin and chloramphenicol were comparable in *C. coli* and *C. jejuni*, the rates of resistance to tetracycline, erythromycin, clindamycin and the aminoglycosides in *C. coli* were two to ten times higher than in *C. jejuni*. These differences as well as individual higher NRZ-internal MIC_{90} values of *C. coli* necessitated a separate presentation of the resistance situation for the two *Campylobacter* species (Tab. 4.2.5.1). The species-specific differences in the rates of streptomycin and tetracycline resistance are also observed when increasing the MIC breakpoints of *C. coli* by two logs and reducing those of *C. jejuni* by one log, which is why actual differences between the tested populations of the two species are assumed in this case. By contrast, upward correction of the MIC breakpoints of *C. coli* for the other aminoglycosides as well as for erythromycin and clindamycin and/or downward correction of the MIC breakpoints of *C. jejuni* would result in more or less equal rates of resistance to these substances.

Tab. 4.2.5.1: Resistance rates of *Campylobacter* spp.: Comparison of the periods 2005–2008 and 2009–2011 (Source: National Reference Centre for *Salmonellae and Other Bacterial Enterics* at the Robert Koch Institute, Wernigerode Branch)

		2005–2008		2009–2011	
		C. jejuni n=570	*C. coli* n=342	*C. jejuni* n=532	*C. coli* n=250
Antibiotic	Breakpoints (mg/l) Resistant (>)	% of resistant strains of the respective species			
Ampicillin	8	75	67	90	96
Nalidixic acid	16	43	47	55	60
Ciprofloxacin	2	39	43	51	54
Tetracycline	4	19	49	11	44
Erythromycin	4	9	22	5	16
Clindamycin	4	3	9	3	8
Streptomycin	16	5	47	5	50
Kanamycin	16	4	9	4	28
Gentamicin	4	3	5	2	3
Amikacin	16	3	6	2	4
Chloramphenicol	8	4	4	2	4

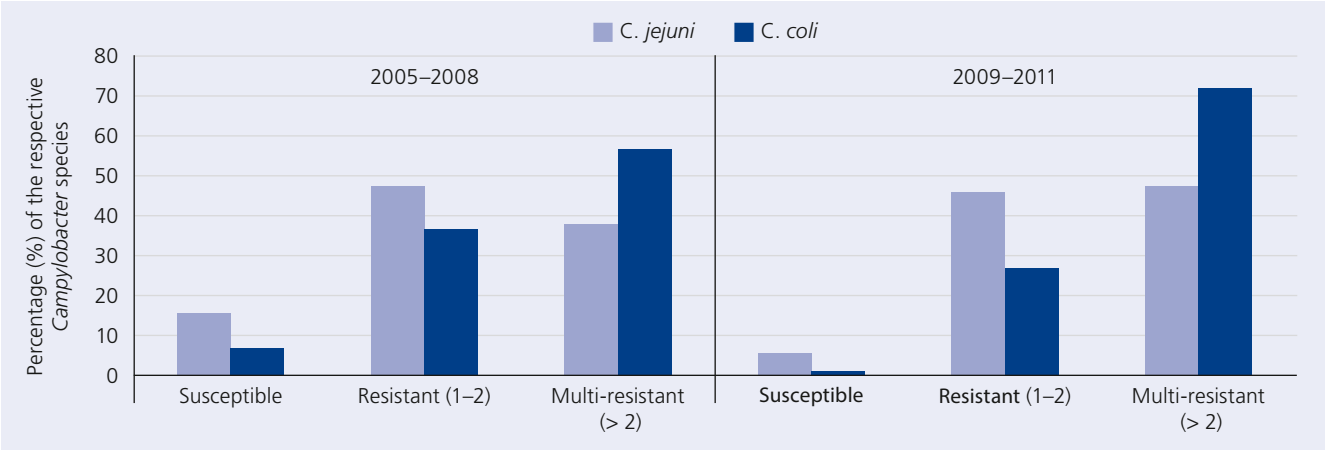

Fig. 4.2.5.1: Change in the prevalence of fully susceptible and resistant (to one to two or three and more of the tested antimicrobials) strains in all *C. jejuni* (n=1,102) and *C. coli* (n=592) strains tested between 2005 and 2011 (Source: National Reference Centre for *Salmonellae and Other Bacterial Enterics* at the Robert Koch Institute, Wernigerode Branch)

The vast majority of the tested *Campylobacter* strains were multidrug resistant (Fig. 4.2.5.1). 43% of the tested *C. jejuni* and 63% of the *C. coli* isolates were resistant to at least three antimicrobials; individual *C. jejuni* and *C. coli* strains were resistant to all tested substances. Co-resistance to ciprofloxacin and erythromycin was found in 5% of the *C. jejuni* and 11% of the *C. coli* strains. Co-resistance to ciprofloxacin and gentamicin, erythromycin and gentamicin, as well as resistance to all three therapeutically relevant antimicrobials was also observed in both species (Fig. 4.2.5.2).

It remains uncertain to what extent the above-described resistance situation of *Campylobacter* isolates, nearly all of which came from a single large region, can be transferred to the situation in Germany. Regional differences, for example between rural regions with large-scale livestock farming and big cities, cannot be excluded.

Trends in resistance development

Given the short monitoring period and the relatively small number of tested strains, only very reserved statements can be made on trends of resistance development in *Campylobacter* spp. The upward trend in ciprofloxacin-resistant isolates among both species from about 25% in 2005 to more than 50% in 2011 (Tab. 4.2.5.1) was yet remarkable. The rate of ampicillin resistance also rose from about 30% in 2005 to more than 90% in 2011.

Conclusion

The available data demonstrates that resistance to ampicillin has to be expected today in nearly all *Campylobacter* spp. strains and that more than 50% of both *C. jejuni* and *C. coli* isolates are resistant to ciprofloxacin. Multidrug resistance is increasingly observed in both species (Fig. 4.2.5.1), in particular co-resistance to the therapeutically relevant fluoroquinolones, macrolides and aminoglycosides (Fig. 4.2.5.2).

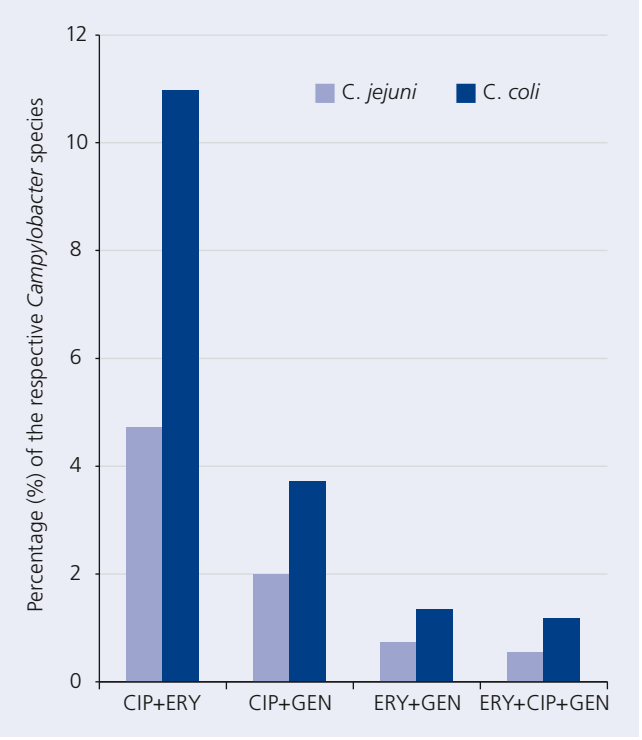

Fig. 4.2.5.2: Prevalence of co-resistance to ciprofloxacin (CIP), erythromycin (ERY) and gentamicin (GEN) in all *C. jejuni* (n=1,102) and *C. coli* (n=592) strains tested between 2005 and 2011 (Source: National Reference Centre for *Salmonellae and Other Bacterial Enterics* at the Robert Koch Institute, Wernigerode Branch)

The definition and standardisation of breakpoints for the susceptibility testing of *Campylobacter* spp. is required not only for therapeutically relevant antimicrobials but also in general. The development of standardised breakpoints – separately for the two *Campylobacter* species – on the basis of population-specific analyses of the minimum inhibitory concentration (MIC_{90}) remains an important task for epidemiological monitoring of the resistance situation, in particular for comparing the data of clinical *Campylobacter* isolates with the situation in strains of non-clinical origin (animals, foods, reservoirs).

➤ E. Tietze
Reviewer: E. Glocker

4.2.6 *Escherichia coli*

The species *Escherichia coli* is commonly found in the physiological intestinal flora. Apart from commensal *E. coli*, there are also pathogenic variants, which characterise themselves by the presence of specific virulence determinants. Among the *E. coli* pathovars causing gastrointestinal infections, Shiga toxin-producing, enterohaemorrhagic *E. coli* (EHEC) are of special significance due to the infection's potential life-threatening complications. During the period 1999–2011, the National Reference Centre for *Salmonellae and Other Bacterial Enterics* at the Robert Koch Institute, Wernigerode Branch, tested a total of 9,993 enteropathogenic *E. coli* isolates from diarrhoeal diseases in Germany for susceptibility to 16 antimicrobials. These were mainly EHEC (subject to a downward trend from about 90% in 1999 to 74% in 2011), which were classified into more than 70 different serovars. The antibiogram (MIC determination by means of the broth microdilution test) is not created for clinical therapeutic purposes, but serves as an epidemiological marker for pathogen isolates.

Resistance situation

Since 1999, about 70% of *E. coli* isolates from clinical stool specimens have been tested fully susceptible every year, about 20% showed resistance to one or two antimicrobials and about 10% were multidrug resistant (resistant to at least

Tab. 4.2.6.1: Resistance rates of enteropathogenic *E. coli* (Source: National Reference Centre for *Salmonellae and Other Bacterial Enterics* at the Robert Koch Institute, Wernigerode Branch; 1999–2011)

		1999–2001 n=2,203	2002–2004 n=2,982	2005–2007 n=2,161	2008–2011 n=2,647*
Antibiotikum	**Breakpoints (mg/l) Resistant (>)**	**% of resistant strains**			
Streptomycin	16	21	21	19	17
Tetracycline	4	17	17	16	15
Ampicillin	8	10	12	12	17
Mezlocillin	16	9	10	11	11
Mezlocillin/Sulbactam	16	2	2	2	3
Chloramphenicol	8	9	14	5	10
Co-trimoxazole	16	6	8	10	10
Kanamycin	16	4	4	3	4
Gentamicin	4	1.4	1.1	1.1	1.3
Amikacin	16	0.4	0.2	0.2	<0.1
Nalidixic acid	16	1.8	2.0	3.4	3.4
Ciprofloxacin	2	0.3	0.2	0.8	0.4
Cefotiam	4	0.6	0.4	1.2	2.4
Cefoxitin	16	0.8	0.3	0.5	0.5
Cefotaxime	8	0.5	0.2	1.1	1.4
Ceftazidime	16	0.5	0.1	0.7	0.6

* The figures for 2011 were corrected to exclude the EHEC O104:H4 outbreak isolates.

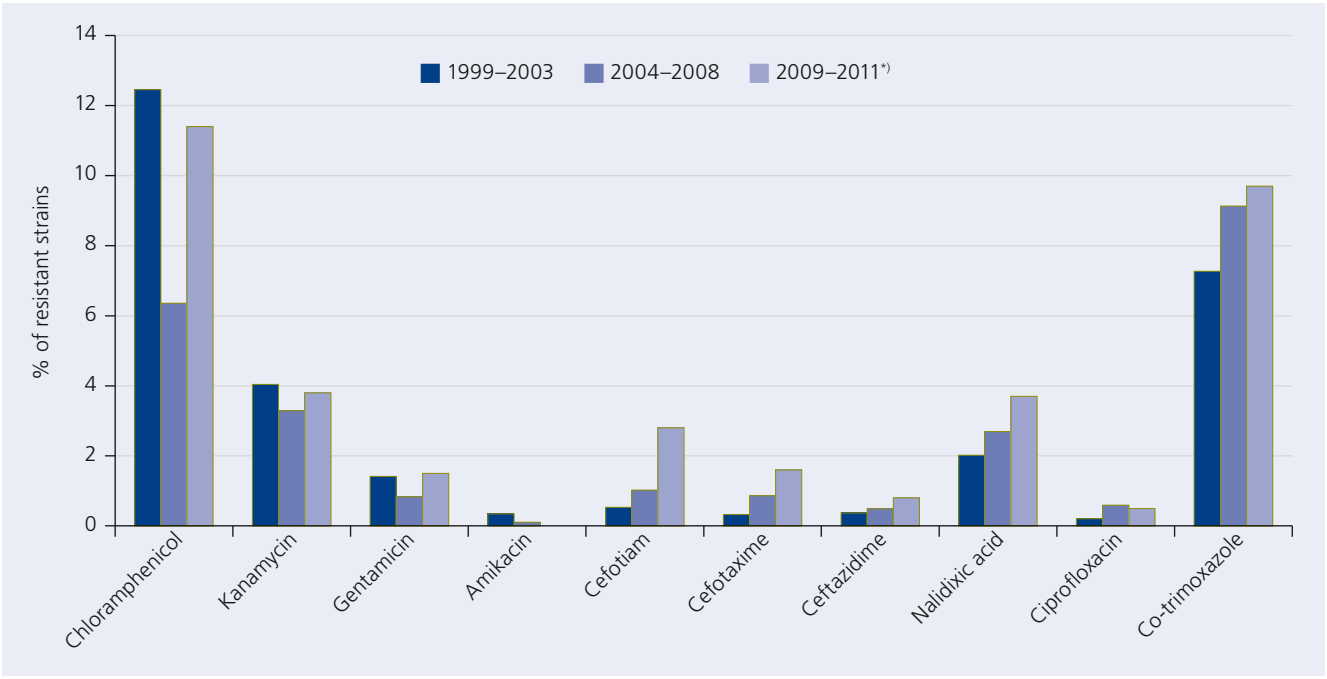

Fig. 4.2.6.1: Resistance rates of enteropathogenic *E. coli* to some selected antimicrobials, comparison of the periods 1999–2003, 2004–2008 and 2009–2011
Source: National Reference Centre for *Salmonellae and Other Bacterial Enterics* at the Robert Koch Institute, Wernigerode Branch)
* The figures for 2011 were corrected by the EHEC O104:H4 outbreak isolates.

three antimicrobials). Streptomycin (20%) and tetracycline (16%) were most frequently affected by resistance (Tab. 4.2.6.1), followed by amino- and ureidopenicillins (10–14%). About 75% of mezlocillin-resistant strains were still susceptible to the combination of mezlocillin and the β-lactamase inhibitor sulbactam. The rates of resistance to chloramphenicol (around 10%) and cotrimoxazole (around 9%) were at nearly the same level. Resistance to the aminoglycosides kanamycin (approx. 4%), gentamicin (approx. 1%) and amikacin < 0.5%) occurred less commonly. Up to and including 2011, the rates of quinolone and cephalosporin resistance were also at a very low level.

Trends in resistance development

A significant trend towards an increase or decrease in resistance rates cannot be identified for any of the tested antimicrobials (Tab. 4.2.6.1). A comparison of cumulative resistance rates for the periods 1999–2003, 2004–2008 and 2009–2011 (Fig. 4.2.6.1) shows a slight variation in the rates of resistance to chloramphenicol as well as to the aminoglycosides kanamycin, gentamicin and amikacin, whereas the rates of resistance to cephalosporins, quinolones and co-trimoxazole were subject to a slight but steady increase. These changes are associated with multiple clones, since they are distributed relatively evenly among more than 70 different serovars of *E. coli* strains. Although the overall percentage of multidrug resistant isolates remained constant over the years, *E. coli* isolates resistant to 10, in isolated cases even to 13, of the tested antimicrobials have occurred repeatedly.

Conclusion

The comparatively moderate resistance situation of pathogenic *E. coli* isolated from diarrhoeal diseases in our test specimens has not seen any significant change since 1999. Resistance to fluoroquinolones and cephalosporins continues to be extremely rare, may, however, occur in a combination within one and the same strain. Antimicrobial treatment of EHEC infections is problematic and is usually not recommended, at least not during the acute diarrhoeal phase. However, the resistance situation shows that these pathogens are also exposed to the ecological selection process of antimicrobial-resistant strains in their reservoirs.

➤ E. Tietze
Reviewer: E. Glocker

Extended-spectrum β-lactamases (ESBLs) in human *Enterobacteriaceae*

Resistance and ESBLs

In recent years, the occurrence of multidrug resistant gram-negative bacteria at German hospitals has been reported with increasing frequency. The percentage of nosocomial *Escherichia coli* and *Klebsiella pneumoniae* with resistance to third-generation cephalosporins has increased notably to 10–15% in Germany over the past 5 years (http://ars.rki.de/).[1] In contrast, the rates of carbapenem-resistant *Enterobacteriaceae* are still low (≤ 1%) although the number of confirmations in Geman hospitals is increasing yearly. Resistance to third-generation cephalosporins (e.g. cefotaxime and ceftazidime) is mainly associated with the production of bacterial enzymes called extended-spectrum β-lactamases (ESBLs), which are capable of hydrolysing cephalosporins and other β-lactams (e.g. aztreonam and various acylaminopenicillins). The ESBL genes are located on plasmids, which are transferable between individuals of the same species as well as between various enterobacterial species.

Since 2004, the Robert-Koch Institute (RKI) in Wernigerode has been performing molecular tests within various studies investigating cephalosporin resistance in gram-negative bacteria to provide deeper insights into the causes of resistance and their spread. The most important results of these efforts are summarised below.

Are all ESBLs alike?

The term "ESBL" refers to a whole range of different β-lactamases that can be produced by bacteria. Generally, β-lactamases are enzymes that cleave β-lactam antimicrobials through hydrolysis. All β-lactam antimicrobials bind to bacterial transpeptidases (penicillin-binding proteins, PBPs) resulting in inhibitition of the cell wall synthesis and thereby causing the death of the bacterium. The inactivation of these β-lactam antimicrobials by β-lactamases lead to bacterial resistance. TEM-1 and SHV-1, the first β-lactamases discovered in the 1960s in *E. coli* and *K. pneumoniae*, are capable of hydrolysing penicillins and narrow-spectrum cephalosporins (ampicillin, cephalothin).[2] Individual point mutations in the bla_{TEM} and bla_{SHV} genes caused changes in the active centre of the enzyme and led to an extension of the substrate spectrum. These new extended-spectrum β-lactamases (ESBLs) are capable of hydrolysing even modern third- and fourth-generation cephalosporins (ceftazidime, cefotaxime, cefepime) as well as aztreonam.[3] More than 190 ESBL variants due to various mutations in the bla_{TEM} and bla_{SHV} genes have been reported to date (http://www.lahey.org/Studies/).

In 1989, another ESBL family called CTX-M enzymes (cefotaximases) was discovered in cefotaxime-resistant *E. coli*. To date, more than 100 CTX-M variants have been identified, divided into five phylogenetic groups.[4] CTX-M enzymes originate from chromosomally encoded β-lactamases of various commensal Kluyvera species.[5] The production of CTX-M ESBL is currently the most commonly reported cause of resistance to third-generation cephalosporins in *E. coli* and *K. pneumoniae* worldwide.[6]

Besides the common ESBL families CTX-M, TEM and SHV, there are many other ESBLs, such as OXA-ESBL, VEB-ESBL or PER-ESBL, which, however, occur far less commonly. All ESBLs share the characteristic of being inhibited by certain enzyme inhibitors, such as clavulanic acid, sulbactam or tazobactam. This is used in diagnostics by employing simple agar diffusion tests (E-test strips, disc tests) or ESBL tests that were integrated into the available automated systems for the phenotypic confirmation of ESBL production in *Enterobacteriaceae*.

ESBL studies in Germany

The use of molecular methods to characterise resistant pathogens allows an accurate assessment of the emergence and spread of individual resistance determinants. For example, one simple method is the PCR amplification and sequencing of resistance genes. To determine the prevalence and geographical distribution of ESBLs in Germany, representative random samples of *E. coli* and *K. pneumoniae* isolates with an ESBL phenotype were tested at the RKI within different studies in 2004 and in 2008. In 2011, further studies on ESBLs in nosocomial and community-acquired *E. coli* were started within the RESET research consortium (www.reset-verbund.de). The results of these analyses showed that CTX-M enzymes are the most common ESBLs in both *E. coli* and *K. pneumoniae*.[7-9] The CTX-M-15 variant, in particular, accounted for approximately half of all ESBLs identified in nosocomial *E. coli* until 2011. The second most common ESBL type is CTX-M-1, accounting for 28% (Tab. 1). These two common ESBL variants, CTX-M-1 and CTX-M-15, were also identified in case-control study in 2011, conducted by Charité Hospital Berlin in patients who had not previously been hospitalised (Tab. 1).[10]

Healthy individuals can also carry ESBL-producing bacteria, at least temporarily. The Bavarian Health and Food Safety Authority (Dr. Valenza) screened 3,344 persons (healthy relatives of patients with gastroenteritis) to investigate the prevalence of ESBL-producing bacteria in the general population. The re-

Tab. 1: Results of the studies of the RKI and collaborative partners on ESBL in humans*

Study	Species	Number of isolates[1]	Common ESBL variants			AmpC[2]	Ref.
			CTX-M-15	CTX-M-1	CTX-M-14	CMY	
RESET Limbach laboratory study	*E. coli*	n=228	n=116 (51%)	n=66 (29%)	n=13 (6%)	– [3]	[10]
RESET case-control study Charité	*E. coli*	n=85	n=26 (31%)	n=37 (44%)	n=11 (13%)	– [3]	[10]
RESET ESBL screening general population (LGL)	*E. coli*	n=211	CTX-M-15: n=97 (46%), CTX-M-1: n=51 (24%); CTX-M-14 n=31 (15%)			n=2 (0,9%)	[11]
ESBL screening (NRZ for Salmonellae)	*S. enterica*	n=150	n=6 (4%)	n=91 (60,7%)	n=12 (8%)	n=8 (5%)	[18]
ESBL screening (RKI)	*P. mirabilis*	n=79	n=6 (8%)	n=6 (8%)	n=2 (3%)	n=51 (65%)	[20]

* Since some of these studies are still ongoing, the results are only preliminary; subject to minor changes.
[1] Isolates with an ESBL phenotype and cefotaxime and/or ceftazidime resistance; [2] Plasmid-mediated CMY-2 AmpC β-lactamases that confer resistance to cefotaxime and ceftazidime; [3] Only isolates with an ESBL phenotype were included in the study. LGL, Bavarian Health and Food Safety Authority; NRZ, National Reference Centre for *Salmonellae and Other Bacterial Enterics*

sults show that 6.3% of the study participants were colonised with ESBL-producing *E. coli*, with CTX-M-15 and CTX-M-1 being the most common variants.11

The partners of veterinary facilities involved in the RESET research consortium determined the ESBL prevalence in companion animals and livestock as well as animal products. The ESBL variant CTX-M-1 was found frequently in *E. coli* from broilers, pigs and cattles. In contrast, the CTX-M-15 type, which is common in human *E. coli* infections, was found rarely and wasoften onlypresent in companion animals.10 The ESBL genes blaCTX-M-1 and blaCTX-M-15 are usually located on conjugative plasmids.[12] Therefore, within the RESET research consortium more detailed and comparative analyses are currently being performed on *E. coli* isolates from humans and animals. with the aim to learn more about the extent of spread of ESBL-producing strains and ESBL gene-carrying plasmids from various sources (humans, animals, food, environment).

The introduction of ESBL-producing *Enterobacteriaceae* into hospitals is inevitable, mainly as the result of unrecognised-known, asymptomatic ESBL colonisation of the patients. To prevent further spread of these resistant bacteria reliable diagnostic and strict compliance with hygiene standards are necessary. Molecular strain typing routinely performed by the RKI on isolates from different hospitals showed that in a specific period of time different ESBL-producing strains were detected in patients within a hospital indicating their external origin. However, identical ESBL-producing strains could be also found in different patients within a hospital. Such a clonal transfer of resistant strains is usually limited to a specific hospital/ward and period of time, since hygiene measures generally were intensified after becoming aware of the problem. ESBL colonisation can have fatal consequences, especially in high-risk patients such as newborns. The massive spread (> 50 colonised patients) of a multidrug resistant, CTX-M-15-producing *K. pneumoniae* strain in a neonatal intensive care unit in Bremen in 2011/2012 demonstrated the importance of fast detection of resistant pathogens in hospitals.[13,14]

ESBL production can rarely be found in bacteria causing gastroenteritis. One example is the Shiga toxin-producing strain *E. coli* serovar O104:H4 with additional enteroaggregative characteristics, which caused 855 cases of haemolytic-uraemic syndrome (HUS) and more than 2,987 cases of EHEC gastroenteritis between Mai and June 2011.[15,16] This *E. coli* O104:H4 strain carried a conjugative plasmid with the ESBL gene blaCTX-M-15. In several affected patients, the analyses of the RKI revealed simultaneous colonisation with non-enteropathogenic *E. coli* that had acquired this resistance plasmid. Such in-vivo plasmid transfer is one of the causes for the rapid spread of ESBL genes.

ESBLs were also identified in *Salmonella enterica* of a wide range of serovars, but in contrast to *E. coli*, the percentage of ESBLs is far below 1%. Analyses of ceftiofur-resistant *S. enterica* isolates from food and livestock indicated the presence of certain ESBL types, such as CTX-M-1, which also occur in *Salmonella* from human infections as well as in nosocomial *E. coli* and *Klebsiella* spp.[17–19] Since ESBLs have also increasingly been identified in other, less common nosocomial pathogens, such as *Proteus mirabilis, Providencia* spp., *Enterobacter cloacae* and *Klebsiella oxytoca*, accurate characterisation of resistance plasmids will be required to answer the question of whether ESBL plasmids are really transferred between *Enterobacteriaceae* of human and animal origin and what role the various gram-negative species play in this process.

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Extended-Spektrum β-Lactamasen (ESBLs) und Carbapenemasen bei *Escherichia coli* von Tieren in Deutschland

In Deutschland werden *Enterobacteriaceae* von Tieren im Rahmen unterschiedlicher Studien hinsichtlich des Vorkommens von ESBLs (β-Lactamasen mit erweitertem Wirkungsspektrum) untersucht. Zu diesen Studien gehören das auf jährlicher Basis vom Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL) durchgeführte nationale Resistenzmonitoring für tierpathogene Erreger GE*RM*-Vet, die einmalig durchgeführte Monitoringstudie BfT-GermVet, aber auch Studien, welche das Vorkommen von ESBL-bildenden *Enterobacteriaceae* bei gesunden Nutz- und Haustieren[1] und bei wildlebenden Tieren[2,3] untersuchen. Der vom Bundesministerium für Bildung und Forschung (BMBF) geförderte und Arbeitsgruppen aus Human- und Veterinärmedizin umfassende Verbund RESET (www.reset-verbund.de) beschäftigt sich mit der Analyse von ESBL-bildenden *Enterobacteriaceae*. Die im Rahmen von RESET durchgeführten Untersuchungen, die auch die Analysen von Stammkollektiven aus GE*RM*-Vet und BfT-GermVet beinhalten, umfassen die Bestimmung der jeweils vorhandenen ESBL-Gene, deren Lokalisation auf Plasmiden oder in der chromosomalen DNA, aber auch die Sequenzierung des genetischen Umfelds der entsprechenden ESBL-Gene. Außerdem wird eine vergleichende Feintypisierung der entsprechenden bei Menschen, Tieren aber auch Lebensmitteln vorkommenden ESBL-bildenden Bakterien durchgeführt.

Für die phänotypische Identifizierung von ESBL- und Carbapenemase-bildenden Bakterien schreibt das Dokument M100-S24 des CLSI bestimmte Screening- und Bestätigungstests vor.[4] Im positiven Falle besagen diese Tests, dass ein bestimmter Erreger eine ESBL bzw. Carbapenemase bildet; diese Tests lassen aber keine sicheren Rückschlüsse auf das bei diesem Erreger vorhandene ESBL- bzw. Carbapenemase-Gen zu. Ähnlich wie beim Menschen findet man auch bei Tieren unterschiedliche ESBL-Gene, die hauptsächlich der $bla_{CTX\text{-}M}$-Gruppe, seltener den Gruppen bla_{TEM} oder bla_{SHV} angehören. Für die Bestimmung der Gruppenzugehörigkeit können entsprechende Multiplex-PCRs eingesetzt werden. Eine korrekte Identifizierung des jeweils vorhandenen Subtyps, z.B. $bla_{CTX\text{-}M\text{-}15}$, setzt allerdings die komplette Sequenzierung des jeweiligen Resistenzgenes (inklusive Start- und Stoppkodon) voraus. Über Carbapenemasen bei

Enterobacteriaceae von Tieren ist bislang wenig bekannt. Für den Nachweis der entsprechenden Gene via Multiplex-PCRs und ihre korrekte Identifizierung gelten jedoch die gleichen Rahmenbedingungen wie für ESBL-Gene.

ESBL-bildende *E. coli* von erkrankten Tieren aus der BfT-GermVet-Studie

Die BfT-GermVet-Studie wurde in den Jahren 2004–2006 in Deutschland durchgeführt und stellte gewissermaßen ein einmaliges Komplement zur parallel laufenden GE*RM*-Vet Studie des BVL dar. In der BfT-GermVet-Studie wurden insgesamt 417 *E.-coli*-Isolate von definierten Krankheitsfällen von Haus- und Nutztieren deutschlandweit gesammelt. Diese umfassten 228 Isolate von Hunden/Katzen, 102 Isolate von Pferden und 87 Isolate von Schweinen.[6] Von den insgesamt 100 Ampicillin-resistenten *E.-coli*-Isolaten erwiesen sich lediglich drei Isolate als ESBL-Bildner.[7] Das erste der drei *E.-coli*-Isolate gehörte dem Multi-Locus-Sequenztyp ST1576 an, stammte von einem Hund mit Pneumonie und verfügte über ein $bla_{\text{CTX-M-1}}$-Gen, das auf dem ca. 50 kb großen IncN-Plasmid pCTX168 lokalisiert war. Das zweite *E.-coli*-Isolat entsprach dem Sequenztyp ST1183, stammte von einem Schwein mit MMA-Syndrom und verfügte über ein $bla_{\text{CTX-M-1}}$-Gen, das auf dem ca. 50 kb großen IncN-Plasmid pCTX246 lokalisiert war. Das dritte *E.-coli*-Isolat zeigte den Sequenztyp ST410, stammte von einem Hund mit einer Harnwegsinfektion und verfügte über ein $bla_{\text{CTX-M-15}}$-Gen, das auf dem ca. 50 kb großen IncF-Plasmid pCTX913 lokalisiert war. Während das Plasmid pCTX913 zusätzlich Gentamicin- und Tetracyclin-Resistenz vermittelte, vermittelten die anderen beiden Plasmide keine weiteren Resistenzeigenschaften.[7]

ESBL-bildende *E. coli* von erkrankten Tieren aus der GE*RM*-Vet Studie

Bisher liegen lediglich für die 1.378 *E.-coli*-Isolate der GE*RM*-Vet Studie 2006–2007 [Schwein (n=538), Geflügel (n=446), Rind (n=183), Hund (n=101), Katze (n=66) Pferd (n=31), Schaf (n=7), Ziege (n=6)] publizierte Daten zu ESBL-Bildnern vor.[8] Von diesen 1.378 Isolaten erwiesen sich 27 (1,96%) als ESBL-Bildner.[8] Diese umfassten je 12 *E.-coli*-Isolate von Schweinen und Rindern, zwei Isolate vom Geflügel sowie ein Isolat von einem Pferd. Die folgenden ESBL-Gene wurden nachgewiesen: $bla_{\text{CTX-M-1}}$ (n=22), $bla_{\text{CTX-M-2}}$ (n=2), $bla_{\text{CTX-M-3}}$ (n=1), $bla_{\text{CTX-M-15}}$ (n=1) und $bla_{\text{TEM-52c}}$ (n=1). Die $bla_{\text{CTX-M-1}}$-Gene befanden sich entweder auf IncN-Plasmiden von ca. 40–50 kb Größe, IncI1-Plasmiden von etwa 83 oder 92 kb, IncF-Plasmiden von ungefähr 50 kb bzw. 70 kb oder auf einem Multireplikon-Plasmid (IncI1, IncN, IncP) von etwa 160 kb. Die 27 ESBL-positiven *E.-coli*-Isolate gehörten vier phylogenetischen Gruppen und 15 unterschiedlichen Sequenztypen an.[8] Die 18 Isolate der phylogenetischen Gruppe A hatten die Sequenztypen ST10 (n=7), ST167 (n=4), ST100 (n=3) sowie ST23, ST83, ST1684 und ST2699 (je n=1). Die sechs *E.-coli*-Isolate der phylogenetischen Gruppe D hatten die Sequenztypen ST648 (n=2), ST57, ST362, ST925 und ST973 (je n=1). Die beiden Isolate der phylogenetischen Gruppe B1 zeigten die Sequenztypen ST453 und ST2698 während das einzige *E.-coli*-Isolat der phylogenetischen Gruppe B2 den Sequenztyp ST131 zeigte. Die Feintypisierung der jeweiligen ESBL-Genregionen wies eine beträchtliche strukturelle Heterogenität auf, die höchstwahrscheinlich auf die Integration von Insertionselementen und Transposons, aber auch auf Rekombinationsereignisse zurückzuführen ist.

Die Raten der phänotypisch bei verschiedenen Tierarten nachgewiesenen ESBL-verdächtigen *E.-coli*-Isolate unterscheiden sich je nach Tierart deutlich. Die höchsten Raten werden bei Isolaten vom Kalb gefunden und stiegen bis 2011 auf bis zu 26% an (Abb. 1).

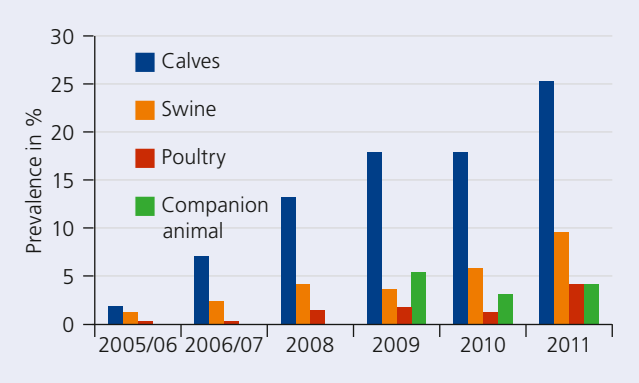

Fig. 1: Prevalence of putative ESBL-producing *E. coli* isolates from various animal species

Es werden jedoch auch bei der Tierart Schwein (bis zu 10%) und beim Geflügel (bis zu 4%) steigende Prävalenzen gefunden. Beim Hund wurden im Studienjahr 2009 erstmals ESBL-verdächtige *E.-coli*-Isolate nachgewiesen.

ESBL-bildende *E. coli* von Wildtieren aus Deutschland

Mehrere Studien beschäftigten sich mit dem Vorkommen von ESBL-bildenden *E. coli* bei Wildtieren in Deutschland. Hier gelang der Nachweis eines $bla_{\text{CTX-M-9}}$-tragenden *E.-coli*-Isolates des Sequenztyps ST131 aus dem Kollektiv von 211 *E.-coli*-Isolaten, die von insgesamt 66 freilebenden Ratten aus Berlin stammten.[2] In einer anderen Studie erfolgte der Nachweis ESBL-bildender *E. coli* bei vier von 172 Isolaten von Wildvögeln. Diese Isolate stammten von Amsel, Blässgans und Felsentaube, verfügten über ein $bla_{\text{CTX-M-15}}$-Gen und gehörten dem Sequenztyp ST648 an.[3]

Carbapenemase-bildende *E. coli* aus Nutztierbetrieben in Deutschland

Im Rahmen des RESET-Projekts wurden verschiedene Longitudinal- und Querschnittsstudien in Geflügel- und Schweinebetrieben durchgeführt. Innerhalb der Population der *E.-coli*-Isolate eines Schweinebetriebs wurden zwei Isolate identifiziert, die über ein $bla_{\text{VIM-1}}$ Carbapenemase-Gen verfügten. Beide *E.-coli*-Isolate repräsentierten den Sequenztyp ST88. Das $bla_{\text{VIM-1}}$-Gen war als Bestandteil eines Klasse 1-Integrons,

welches zusätzlich *aacA4* und *aadA1*-Genkassetten enthielt, auf einem ca. 220 kb großen Plasmid lokalisiert.[9] Interessanterweise wurden im Rahmen dieser Studien auch drei *Salmonella-enterica*-subsp.-*enterica*-Serovar-Infantis-Isolate, die über das gleiche bla_{VIM-1}-tragende Integron verfügten, isoliert. Diese *S.*-Infantis-Isolate stammten aus Staubproben von einem Geflügelbetrieb, aus einem etwa 100 m außerhalb eines Schweinebetriebs genommenen Sockentupfers sowie aus der gepoolten Schweinekotprobe aus dem Betrieb, in dem zuvor die beiden bla_{VIM-1}-positiven *E.-coli*-Isolate gewonnen wurden. In den drei *S.*-Infantis-Isolaten war das bla_{VIM-1}-Integron auf Plasmiden von ca. 300 kb lokalisiert.[10]

Diese beiden Studien weisen bereits auf die Möglichkeit des Interspezies-Austauschs von Carbapenemase-Genen hin. In diesem Zusammenhang ist es wichtig zu wissen, dass auch Bakterien außerhalb der Familie *Enterobacteriaceae* als Spender für Plasmid-lokalisierte Carbapenemase-Gene fungieren können. Bei Studien in China wurde kürzlich ein *Acinetobacter-baumannii*-Isolat aus der Lungenprobe eines Schweins isoliert. Dieses *A.-baumannii*-Isolat verfügte über ein 47.098 bp großes Plasmid, welches neben verschiedenen anderen Resistenzgenen auch das Carbapenemase-Gen bla_{NDM-1} enthielt. Dieses Plasmid erwies sich als konjugativ und transferierte sich problemlos und mit hoher Frequenz in *E. coli*, wo das bla_{NDM-1}-Gen funktionell aktiv war.[11]

Fazit

Aufgrund der meist plasmidären Lokalisation und der Tatsache, dass mitunter auf ESBL-Gen-tragenden Plasmiden auch weitere Resistenzgene lokalisiert sind, bestehen prinzipiell gute Möglichkeiten für einen horizontalen Gentransfer sowie die Co-Selektion und Persistenz von ESBL-Genen auch unter dem durch die Anwendung von Nicht-β-Lactamantibiotika hervorgerufenen Selektionsdruck. Detaillierte Studien zum Vorkommen und zur Ausbreitung von ESBL- und/oder Carbapenemase-positiven *Enterobacteriaceae* sind aufwendig, da sie einerseits die Charakterisierung der entsprechenden Trägerorganismen (z.B. *E. coli*, *S. enterica*), zusätzlich aber auch die Feintypisierung der entsprechenden Plasmide erfordern. Dies ist notwendig um zwischen der klonalen Ausbreitung resistenter Bakterien und der Ausbreitung eines bestimmten ESBL/Carbapenemase-tragenden Plasmids über Stamm-, Spezies- und Genusgrenzen, aber auch über Wirtsgrenzen zu unterscheiden. Mit dem Forschungsverbund RESET steht erstmalig in Deutschland eine Forschungsplattform, die eine umfassende Analyse ESBL-tragender *E.-coli*-Isolate von Menschen und Nutztieren ermöglicht und damit dazu beiträgt, Fragen des wechselseitigen Austauschs entsprechender Gene und der sie beherbergenden mobilen genetischen Elemente zu klären.

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5 Antibiotic resistance in veterinary medicine – Food-producing animals

5.1. Cattle

5.1.1 Respiratory tract infections

The two closely related species *Pasteurella multocida* and *Mannheimia haemolytica* are natural inhabitants of the mucous membranes of the upper respiratory tract of healthy cattle. At the same time, they are diagnosed in both calves and adult cattle as the most common bacterial pathogen causing respiratory tract infections. Together with manifold other factors of animate and inanimate nature, both pathogens play a major role in the complex infectious processes of enzootic bronchopneumonia in cattle as well as in many other infectious respiratory processes causing tremendous economic losses.

5.1.1.1 *Pasteurella multocida*

The 2011 GERM-Vet study included a total of 73 *P. multocida* isolates, 15 of which were obtained from cattle and 58 from young cattle or calves.

The measured MIC values were evaluated collectively for all types of production, since there was hardly any difference in terms of resistance rates.

The level of resistance to nearly all tested antimicrobial agents was in the lower range. The 2011 study found no resistant isolates in the majority of the tested bacterial strains (amoxicillin/clavulanic acid, ceftiofur, enrofloxacin, gentamicin, tilmicosin and tulathromycin). Spectinomycin (9.5%) and tetracycline (12.5%) represented exceptions (Fig. 5.1.1.1.1). One isolate with resistance to florfenicol was detected.

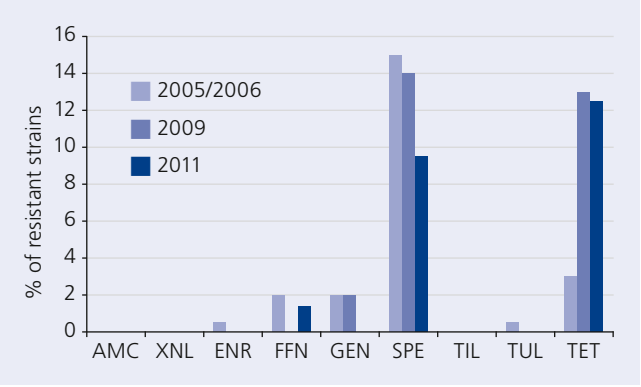

Fig. 5.1.1.1.1: Resistance rates of *P. multocida* from cattle, Germany 2005–2011 (2005/2006 n=188; 2009 n=68; 2011 n=73)

The remaining antimicrobials, which could not be classified based on CLSI breakpoints, are listed in Tab. 5.1.1.1.1. The majority of the measured MIC90 values remain in the lower test range, the only exception being ampicillin, where the MIC_{90} value increased from 0.25 mg/l to 1 mg/l over the study years.

Tab. 5.1.1.1.1: Dairy cattle – MIC_{90} values of *P. multocida* for antimicrobials for which no CLSI-approved breakpoints are available

Antimicrobial	MIC_{90} (mg/l)		
	2005/2006	2009	2011
Ampicillin	0.25	0.5	1
Cefoperazone	0.06	0.06	0.06
Cefotaxime	–	0.015	0.015
Cefquinome	0.06	0.06	0.06
Colistin	4	4	4
Penicillin	0.25	0.25	0.5
Tiamulin	32	16	16
Trimethoprim	0.5	1	0.25
Co-trimoxazole	0.12	0.25	0.25

Conclusion

All isolates from the various types of production are generally characterised by low resistance levels. Resistance rates of more than 10% were only observed for spectinomycin and tetracycline. The antimicrobial agent florfenicol must continue to be monitored carefully, since another resistant isolate was detected after the 2008 study.

➤ H. Kaspar
Reviewer: J. Wallmann

5.1.1.2 *Mannheimia haemolytica*

Trends in resistance development

The 2011 GE*RM*-Vet study tested 33 isolates of the *M. haemolytica* species; these strains were obtained from cattle in various types of production (calf, young cattle and adult cattle).

For the majority of the antimicrobials for which a CLSI breakpoint was available, no resistant isolates were detected in this study, the only exception being tetracycline, to which 13% of the isolates showed resistance (Fig. 5.1.1.2.1).

The remaining antimicrobials, which could not be classified based on CLSI criteria, are listed in Tab. 5.1.1.2.1. The MIC_{90} values for these antimicrobials remained largely unchanged; this particularly applies to the MIC_{90} values for newer cephalosporins.

Tab. 5.1.1.2.1: Cattle – MIC_{90} values of *M. haemolytica* for antimicrobials for which no CLSI-approved breakpoints are available

Antimicrobial	MIC_{90} (mg/l)		
	2006/2007	2009	2011
Ampicillin	≥64	16	0.5
Cefoperazone	0.25	0.25	0.25
Cefotaxime	0.015	0.06	0.015
Cefquinome	0.06	0.12	0.06
Colistin	0.25	0.5	1
Co-trimoxazole	0.25	0.12	0.12

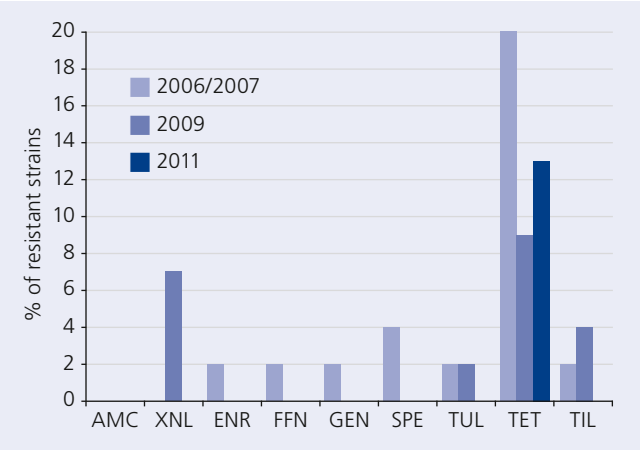

Fig. 5.1.1.2.1: Resistance rates of *M. haemolytica* from cattle, Germany 2006–2011 (2006/2007 n=55; 2009 n=45; 2011 n=33)

Conclusion

On the whole, noteworthy resistance rates are not expected in *M. haemolytica*. A resistance rate of approx. 13% is to be expected for tetracycline. In the 2009 and 2011 studies, the rates of resistance to the remaining antimicrobials were significantly below 10%; in some cases, no resistant isolate was detected at all. However, continued monitoring of the resistance situation is indispensable in order to be able to recognise any adverse changes in the susceptibility situation at an early point.

➤ H. Kaspar
Reviewer: J. Wallmann

5.1.2 Mastitis

In economic terms, mastitis in dairy cattle is one of the infections associated with most serious economic losses in cattle farming. The most frequently isolated pathogens include *Staphylococcus* spp., *Streptococcus* spp. and *Escherichia coli*.

5.1.2.1 *Staphylococcus aureus*

Staphylococcus aureus is among the most common pathogens causing mastitis in cattle. The main route of transmission is the milking process, in addition to transmission through insects and through direct contact with infected cattle. In addition to the subclinical form, catarrhal, necrotising, chronic suppurative or granulomatous forms develop in the course of the disease.

Trends in resistance development

The 2011 GE*RM*-Vet study measured the MIC values of 350 *S. aureus* isolates obtained from dairy cattle with mastitis. The overall resistance level was low. The highest resistance rates were found for ampicillin (14%) and penicillin (13.7%) (Fig. 5.1.2.1.1). The rates of resistance to all other tested antimicrobials were significantly below 10% and the MIC_{50} and MIC_{90} values were low. A 3% rate of resistance was recorded for oxacillin; compared to the 2009 study, the MRSA rate was thus at a similar level.

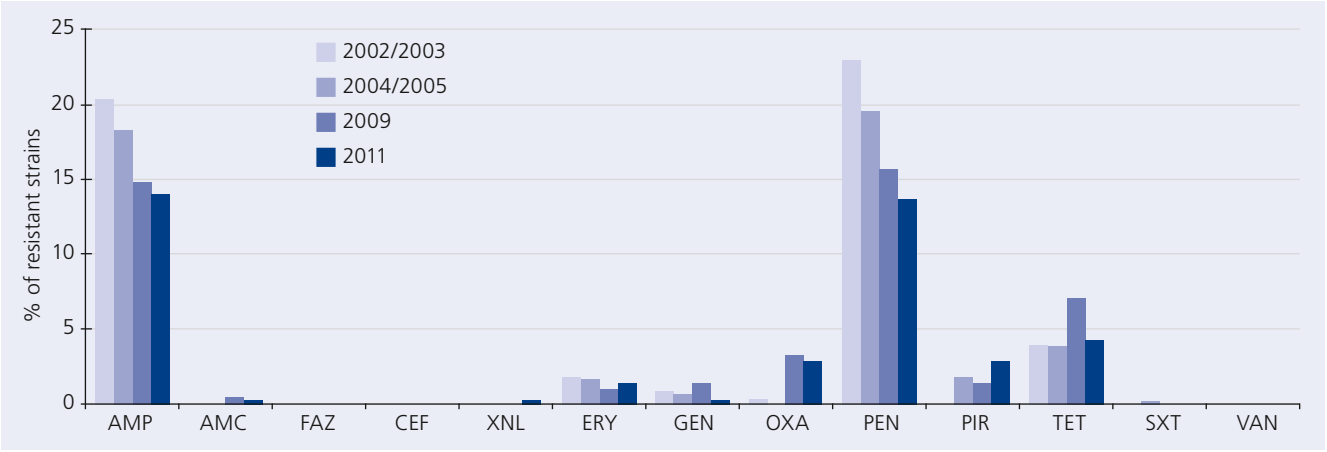

Fig. 5.1.2.1.1: Resistance rates of *S. aureus* from dairy cattle, Germany 2002–2011 (2002/2003 n=227; 2004/2005 n=411; 2009 n=201; 2011 n=350)

Tab. 5.1.2.1.1: Dairy cattle – MIC_{90} values of *S. aureus* for antimicrobials for which no CLSI-approved breakpoints are available

Antimicrobial	MIC_{90} (mg/l)			
	2002/2003	2004/2005	2009	2011
Cefoperazone	2	2	2	1
Cefotaxime	–	–	2	2
Cefquinome	–	0.5	1	1
Clindamycin	–	0.12	0.25	0.25
Enrofloxacin	0.25	0.25	0.25	0.25
Tylosin	–	0.5	1	2

Conclusion

S. aureus isolated from clinical mastitis samples showed high-level susceptibility to most of the tested antimicrobials, in particular to all tested cephalosporins. A slight decline in the rates of ampicillin and penicillin G resistance was observed over the study years. The MRSA rate was consistently approx. 3%.

➤ H. Kaspar
Reviewer: A. Römer

5.1.2.2 *Streptococcus* spp.

Streptococci are the most common infectious agents causing mastitis in dairy cattle, with the species *Streptococcus agalactiae, Streptococcus dysgalactiae* and *Streptococcus uberis* being most significant. *S. agalactiae* exclusively occurs in udders, is transmitted readily and usually causes acute clinical to subclinical chronic forms of mastitis. The two other species, *S. dysgalactiae* and the esculin-positive *S. uberis*, are found mainly in the environment of the animals, where they multiply and, under favourable conditions, can enter the udders to cause acute, subclinical and chronic forms of mastitis. These species were analysed separately in the studies, since they differ considerably in terms of resistance characteristics. These species are currently tested at intervals of three to four years.

Trends in resistance development

S. agalactiae

In the 2009 study year, 40 isolates were tested; the majority of the resistance rates were below 5% (cephalothin and penicillin G 3% each; ceftiofur 2.5%); the rates of erythromycin and pirlimycin resistance were 10% and 18%, respectively. Significantly higher resistance rates were only recorded for gentamicin (83%) and tetracycline (68%) (Fig. 5.1.2.2.1). Isolates resistant to ampicillin, amoxicillin/clavulanic acid, cefazolin and vancomycin were not found. The MIC_{50} and MIC_{90} values for the remaining tested β-lactam antibacterial agents, enrofloxacin and trimethoprim/sulphamethoxazole (co-trimoxazole) were in the susceptible range.

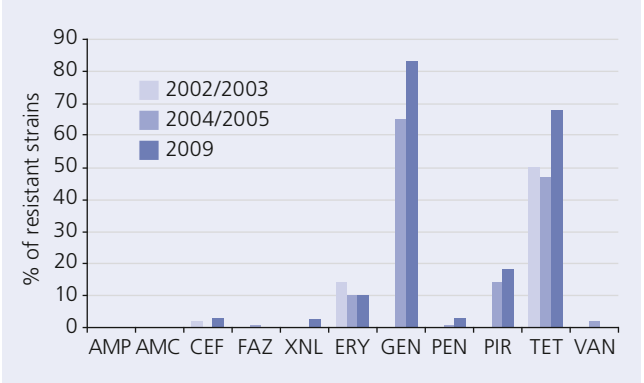

Fig. 5.1.2.2.1: Resistance rates of *S. agalactiae* from dairy cattle, Germany 2002–2009 (2002/2003 n=78; 2004/2005 n=154; 2009 n=40)

S. dysgalactiae

In 2009, 158 isolates of the species *S. dysgalactiae* were tested; the resistance rates were below 10%; both the respective antimicrobials and the resistance rates were more or less identical to those of *S. agalactiae*. Only pirlimycin and tetracycline exceeded the 10% mark (Fig. 5.1.2.2.2). Isolates resistant to β-lactam antibacterial agents were not found; however, 1% of the isolates were resistant to vancomycin. Overall, despite the so far low resistance rates (except for tetracycline), a continued upward trend has been observed for several years.

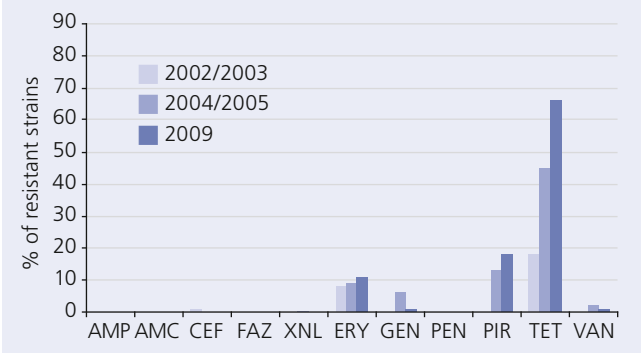

Fig. 5.1.2.2.2: Resistance rates of *S. dysgalactiae* from dairy cattle, Germany 2002–2009 (2002/2003 n=98; 2004/2005 n=259; 2009 n=158)

The MIC_{90} values for the other β-lactam antibacterial agents were in the lower range (Tab. 5.1.2.2.1).

Tab. 5.1.2.2.1: Dairy cattle – MIC_{90} values of *Streptococcus* spp. for antimicrobials for which no CLSI-approved breakpoints are available

Antimicrobial	MIC_{90} (mg/l)		
	S. agalactiae	*S. dysgalactiae*	*S. uberis*
Cefoperazone	0.5	0.25	4
Cefquinome	0.12	0.015	0.015
Clindamycin	4	4	4
Enrofloxacin	2	1	1
Oxacillin	0.5	0.06	0.06
Tilmicosin	4	4	4
Co-trimoxazole	0.25	0.12	0.25
Tylosin	0.5	1	1

S. uberis

In the 2009 study year, 289 S. uberis isolates were tested; in most cases, the resistance rates were again in the very low range (Fig. 5.1.2.2.3). As in the two other tested *Streptococcus* species, increased resistance rates were detected for gentamicin (67%), tetracycline (45%), pirlimycin (27%) and erythromycin (13%).

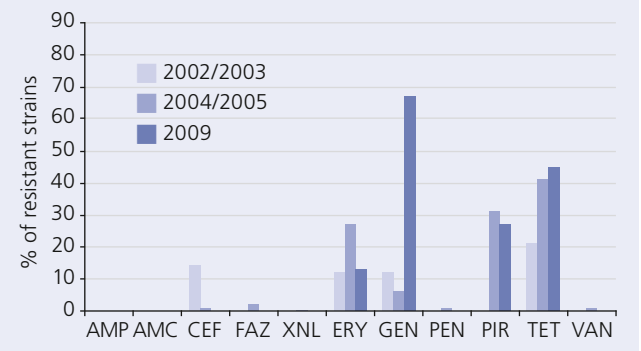

Fig. 5.1.2.2.3: Resistance rates of *S. uberis* from dairy cattle; Germany 2002–2009 (2002/2003 n=43; 2004/2005 n=349; 2009 n=289)

With the exception of cefoperazone, the MIC_{90} values were on the same level with those of the other two *Streptococcus* species. An MIC_{90} value of 4 mg/l was measured for cefoperazone.

Conclusion

Compared to previous studies, the rates of resistance to most of the tested β-lactam antibacterial agents were consistently low. The rates of erythromycin and pirlimycin resistance were also consistent, although somewhat elevated. Increasing resistance rates were found in all three tested species for tetracycline, in particular for gentamicin in *S. agalactiae* and *S. uberis*.

➤ H. Kaspar
Reviewer: U. Steinacker

5.1.2.3 *Enterococcus* spp.

Enterococcus spp. usually enter the udder from the environment, causing clinical or subclinical forms of mastitis. They are diagnosed as mastitis pathogens less commonly than for example *Streptococcus* spp., but have a considerably higher potential of transferring antibiotic resistance to other species.

Trends in resistance development

The 2010 GE*RM*-Vet study tested 14 *Enterococcus faecium* isolates and 36 *Enterococcus faecalis* isolates. Resistance rates of more than 10% were detected for some antimicrobials (Fig. 5.1.2.3.1 and 5.1.2.3.2) and the MIC_{90} values were also frequently elevated (Tab. 5.1.2.3.1). As expected, this predominantly concerned cephalosporins (data not shown) and lincosamides, since *Enterococcus* spp. exhibit an intrinsic resistance to these antimicrobials.

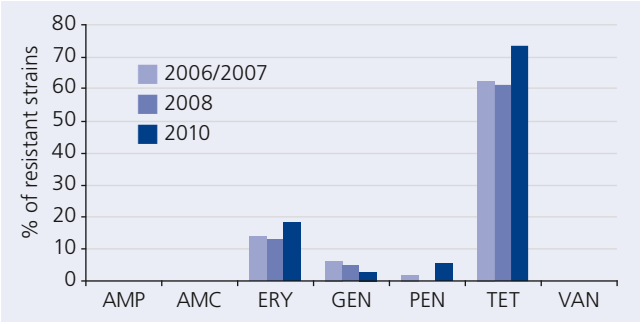

Fig. 5.1.2.3.1: Resistance rates of *E. faecalis* from dairy cattle, Germany 2006–2011 (2006/2007 n=50; 2008 n=39; 2010 n=36)

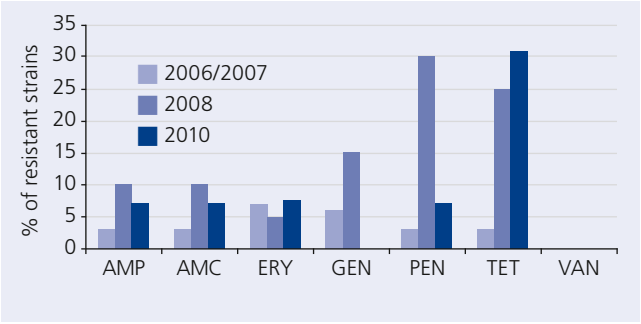

Fig. 5.1.2.3.2: Resistance rates of *E. faecalis* from dairy cattle, Germany 2006–2010 (2006/2007 n=30; 2008 n=20; 2010 n=14)

E. faecalis

Isolates resistant to ampicillin, amoxicillin/clavulanic acid and vancomycin were not found. By contrast, the rates of resistance to erythromycin (18%) and tetracycline (74%) were above 10%. As was the case in the 2006/2007 study, one isolate with high-level gentamicin resistance was detected in the 2010 study.

E. faecium

The rates of resistance to ampicillin, amoxicillin/clavulanic acid and penicillin G were low (7% each). Erythromycin was also in the lower range, with 8% of the isolates being resistant. Similarly to *E. faecalis, E. faecium* showed the highest rates of tetracycline resistance (31%). Overall, these rates were significantly lower than those of *E. faecalis*.

The 2010 study also found differences between *E. faecalis* and *E. faecium* isolates in terms of the MIC_{90} values. Regarding the tested isolates, the macrolide MIC values measured for *E. faecium* isolates were lower than those for *E. faecalis*. The enrofloxacin MIC_{90} values of both species were nearly identical.

Conclusion

Enterococcus spp. isolates from dairy cattle have so far not shown resistance to vancomycin. Both the 2006/2007 and the 2010 studies provided indications of high-level resistance to aminoglycosides, which may signalise a change in the resistance situation.

➤ H. Kaspar, J. Mankertz
Reviewer: U. Steinacker

Tab. 5.1.2.3.1: Dairy cattle – MIC_{90} values of *Enterococcus* spp. for antimicrobials for which no CLSI-approved breakpoints are available

Antimicrobial	MIC_{90} (mg/l)					
	E. faecalis			*E. faecium*		
	2006/2007	2008	2010	2006/2007	2008	2010
Clindamycin	≥ 64	≥ 64	≥ 64	16	16	16
Enrofloxacin	1	1	4	8	8	8
Oxacillin	≥ 8	≥ 8	≥ 8	≥ 8	≥ 8	≥ 8
Pirlimycin	≥ 64	16	≥ 64	16	16	16
Tilmicosin	≥ 64	≥ 128	≥ 128	16	16	16
Co-trimoxazole	0.25	0.25	0.12	0.5	0.5	0.12

5.1.2.4 *Escherichia coli*

Besides *Streptococcus* spp. and *Staphylococcus* spp., *Escherichia coli* are among the most important causative agents of mastitis in cattle. They usually enter the udders from the environment or other sources of infection in cattle, causing severe acute forms of mastitis. The overall well-being of the animals is affected considerably, and deaths may occur as a result of toxic shocks.

Since 2001, the BVL has been testing *E. coli* isolates from dairy cattle with this indication; the 2010 monitoring study included 321 isolates.

Resistance rates of more than 10% were found for ampicillin (12.5%), cephalothin (10%) and tetracycline (11%) (Fig. 5.1.2.4.1). The rates of resistance to the combinations of amoxicillin/clavulanic acid (2.5%) and trimethoprim/sulphamethoxazole (co-trimoxazole) as well as to cefazolin and gentamicin (1.9%) were significantly below 10%. The MIC_{90} values for newer cephalosporins as well as for colistin and enrofloxacin were in the lower range, which is why the probability of occurrence of resistant isolates can be estimated as low (Tab. 5.1.2.4.1).

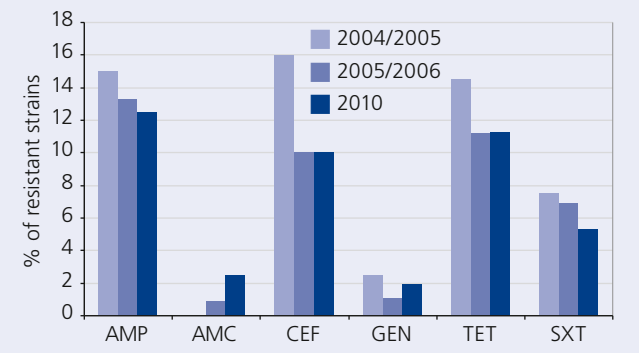

Fig. 5.1.2.4.1: Resistance rates of *E. coli* from dairy cattle, Germany 2004–2010 (2004/2005 n=353; 2005/2006 n=534; 2010 n=321)

Tab. 5.1.2.4.1: Dairy cattle – MIC_{90} values of *E. coli* for antimicrobials for which no CLSI-approved breakpoints are available

Antimicrobial	MIC_{90} (mg/l)		
	2004/2005	2005/2006	2010
Cefoperazone	2	1	0.5
Cefotaxime	1	0.12	0.12
Cefquinome	0.12	0.06	0.12
Ceftiofur	0.5	0.5	0.5
Colistin	0.25	0.5	1
Enrofloxacin	0.06	0.06	0.06
Florfenicol	8	8	16

A comparison of the three study years revealed resistance rates of about the same level: the MIC_{90} values for both newer cephalosporins and enrofloxacin were also in the lower range. Only the colistin MIC90 value saw an increase from 0.25 mg/l to 1 mg/l over the course of the study years; however, colistin is not used for the treatment of mastitis in cattle.

Conclusion

When comparing the resistance rates of mastitis pathogens, *E. coli* shows somewhat higher rates than *Streptococcus* spp.; however, a further increase is currently not being observed, which is why the resistance situation of *E. coli* isolated from mastitis samples is currently expected to be favourable.

➤ H. Kaspar
Reviewer: K. Heidemanns

5.1.2.5 *Klebsiella* spp.

Besides *Escherichia coli* and esculin-positive *Streptococcus* spp., *Klebsiella* spp. are among the environmental mastitis pathogens in cattle. They enter the udders from the environment or other sources of infection in cattle, causing both severe acute and subclinical forms of mastitis. The overall well-being of the animals may be affected considerably, and deaths may occur.

Trends in resistance development

Since the 2005/2006 study year, the GE*RM*-Vet monitoring study has been testing *Klebsiella* spp. isolates from cattle with this indication on an annual basis. The 2011 study year included 51 isolates. The results of the 2006/2007, 2009 and 2011 studies are shown in comparison to demonstrate the trend.

As expected, a high resistance rate and a high MIC*90* value were measured for ampicillin and penicillin, since *Klebsiella* spp. exhibit an intrinsic resistance to amino- and benzylpenicillins. Resistance rates of less than 10% were found for amoxicillin/clavulanic acid, cephalothin, trimethoprim/sulphamethoxazole (co-trimoxazole) (6% each) and tetracycline (8%). The MIC_{90} values for newer cephalosporins as well as for colistin and enrofloxacin were consistently in the lower range, which is why reduced susceptibility is not yet expected in this case (Tab. 5.1.2.5.1).

A comparison with the results of previous GE*RM*-Vet studies revealed an inconsistent trend in resistance rates, with the overall resistance rates being low (with few exceptions, all below 10%). The MIC_{90} values for cephalosporins as well as for enrofloxacin remained stable over the course of the years. A slight increase from 0.5 mg/l to 1 mg/l was observed for colistin (Fig. 5.1.2.5.1). ESBL-positive *Klebsiella* spp. isolates have so far not been detected.

Conclusion

When comparing the data of the study years under review, it became apparent that the resistance rates and MIC_{90} values of *Klebsiella* spp. were in a favourable range. The further de-

Tab. 5.1.2.5.1: Dairy cattle – MIC_{90} values of *Klebsiella* spp. for antimicrobials for which no CLSI-approved breakpoints are available

Antimicrobial	MIC_{90} (mg/l)		
	2006/2007	2009	2011
Cefoperazone	2	2	1
Cefotaxime	0.25	0.06	0.06
Cefquinome	0.12	0.06	0.06
Ceftiofur	0.5	0.5	0.5
Colistin	0.5	0.5	1
Enrofloxacin	0.12	0.12	0.06
Florfenicol	8	8	8
Spiramycin	≥128	≥128	≥128
Tiamulin	≥64	≥64	≥64
Trimethoprim	1	1	–

velopment of ESBLs in both *E. coli* and *Klebsiella* spp. requires particular monitoring in order to be able to anticipate the trend in resistance development.

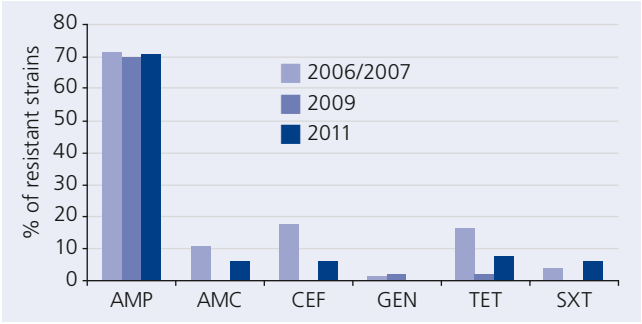

Fig. 5.1.2.5.1: Resistance rates of *Klebsiella* spp. from dairy cattle, Germany 2006–2011 (2006/2007 n=74; 2009 n=50; 2011 n=51)

➤ H. Kaspar
Reviewer: K. Heidemanns

5.1.3 Enteritis

Caused by infections with *Escherichia coli* and *Salmonella* spp., enteritis plays a major role in cattle breeding. The infections often involve substantial economic loss, firstly due to infection-related deaths and secondly due to the stunted growth of the animals after the infection. Although the cause of this clinical condition, which is often accompanied by diarrhoea, is often not determined, the use of antibacterial agents is part of routine practice.

5.1.3.1 *Salmonella enterica* subspecies *enterica*

Trends in resistance development

In the 2009 and 2010 GE*RM*-Vet studies, no *Salmonella enterica* subsp. *enterica* isolates were collected from cattle with "enteritis". In the 2011 study year, only 16 corresponding isolates were submitted, which is why no evaluation is made, given the small number of isolates.

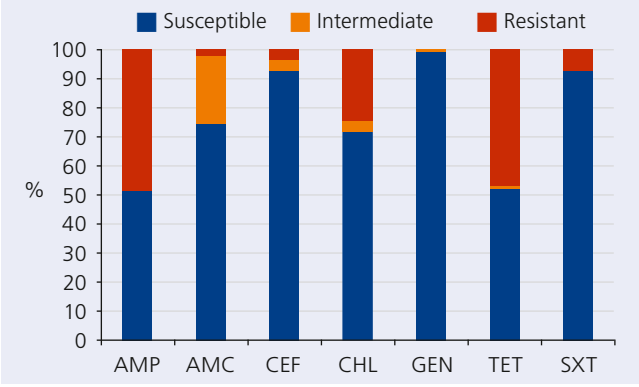

Fig. 5.1.3.1.1: Resistance rates of *Salmonella* spp. from cattle, Germany 2008 (n=82)

In the 2008 study year, a total of 82 *S. enterica* subsp. *enterica* isolates from cattle with enteritis were tested. Because of the small number of isolates, the evaluation was not differentiated by age groups or stages of production. The highest resistance rates were observed for ampicillin and tetracycline

Tab. 5.1.3.1.1: Cattle – MIC_{90} values of *Salmonella* spp. for antimicrobials for which no CLSI-approved breakpoints are available

Antimicrobial	MIC_{90} (mg/l)		
	2005/2006	2006/2007	2008
Apramycin	4	8	4
Cefotaxime	0.12	0.25	0.25
Cefoperazone	0.12	0.12	4
Cefquinome	0.12	0.25	0.12
Ceftiofur	1	1	1
Colistin	4	4	4
Doxycycline	32	64	64
Enrofloxacin	0.06	0.06	0.12
Florfenicol	64	64	64
Nalidixic acid	4	4	4
Spectinomycin	≥ 512	≥ 512	≥ 256
Spiramycin	≥ 128	≥ 128	≥ 128
Trimethoprim	0.5	0.5	0.25
Tulathromycin	16	16	16

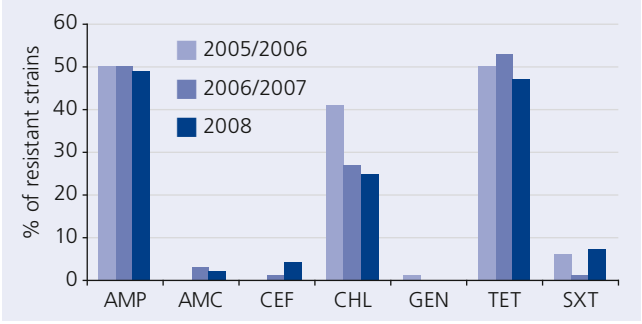

Fig. 5.1.3.1.2: Resistance rates of *Salmonella* spp. from cattle, Germany 2005–2008 (2005/2006 n=102; 2006/2007 n=70; 2008 n=82)

(49% and 48%, respectively, Fig. 5.1.3.1.1). Remarkably, 23% of the isolates showed intermediate resistance to amoxicillin/clavulanic acid. Low MIC_{90} values (Tab. 5.1.3.1.1) and resistance rates were observed for newer cephalosporins, enrofloxacin and gentamicin.

Conclusion

A comparison of the study years 2005–2008 demonstrated nearly constant rates of resistance to ampicillin, amoxicillin/clavulanic acid and tetracycline. The MIC_{90} values also remained stable. The large number of *Salmonella* spp. showing intermediate resistance to the combination of amoxicillin/clavulanic acid requires careful monitoring and susceptibility testing should be performed prior to the therapeutic application of these substances.

➤ U. Steinacker
Reviewer: A. Lübke-Becker

5.1.3.2 *Escherichia coli*

Trends in resistance development

Three GE*RM*-Vet studies provide data for *Escherichia coli* isolates from calves with "enteritis". 160 isolates were tested in 2009, 145 isolates in 2010 and 173 isolates in 2011. Seven antimicrobials were classified on the basis of the CLSI standard.

As was the case in previous study years, the highest resistance rates in the 2011 study were observed for ampicillin (76–79%), tetracycline (68–75%) and trimethoprim/sulphamethoxazole (co-trimoxazole) (48–52%, Fig. 5.1.3.2.1).

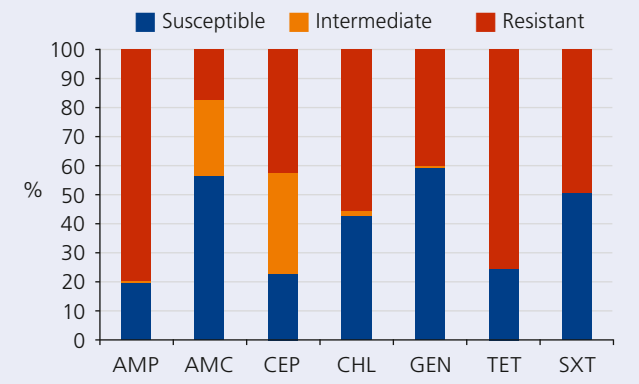

Fig. 5.1.3.2.1: Resistance rates of *E. coli* from calves, Germany 2011

The tested aminoglycosides showed reduced efficacy: The rate of gentamicin resistance rose from 25% in 2009 to 40% in 2011; the apramycin MIC_{90} value increased from 8 mg/l to ≥ 128 mg/l over the period of observation.

The increasing colistin MIC_{90} values since 2009 are noteworthy, suggesting reduced efficacy.

As was the case in the previous study years, the high enrofloxacin MIC_{90} value (≥ 16 mg/l) also indicates reduced efficacy. Moreover, high MIC_{90} values (Tab. 5.1.3.2.1) have been observed for some newer cephalosporins since 2009: ≥ 64 mg/l for cefotaxime and cefquinome as well as ≥ 128 mg/l for ceftiofur. In the 2006/2007 study, the MIC_{90} values for these antimicrobials were still 1 mg/l (cefotaxime), 8 mg/l (cefquinome) and 2 mg/l (ceftiofur).

Both, the increase in cefotaxime MIC_{90} values and the increasing rates of resistance to the combination of amoxicillin/clavulanic acid since 2005 (2005: 7%, 2010: 20%, 2011: 17%; up to 26% intermediate isolates), can be understood as an indication of increased prevalence of ESBL-producing *E. coli*. This is also evidenced by the data on the prevalence of ESBL-producing *E. coli* in calves since 2008. (Fig. 5.1.3.2.2).

Tab. 5.1.3.2.1: Calf – MIC_{90} values of *E. coli* for antimicrobials for which no CLSI-approved breakpoints are available

Antimicrobial	MIC_{90} (mg/l)			
	2006/2007	2009	2010	2011
Apramycin	16	8	8	≥ 128
Cefoperazone	≥ 32	32	≥ 64	≥ 64
Cefotaxime	1	32	≥ 64	≥ 64
Cefquinome	8	≥ 64	≥ 64	≥ 64
Ceftiofur	2	≥ 128	≥ 128	≥ 128
Colistin	0.5	0.5	1	2
Enrofloxacin	≥ 16	≥ 16	≥ 16	≥ 16
Nalidixic acid	≥ 128	≥ 256	≥ 256	≥ 256
Spectinomycin	≥ 512	≥ 512	≥ 512	≥ 512
Trimethoprim	≥ 128	≥ 256	≥ 256	≥ 256

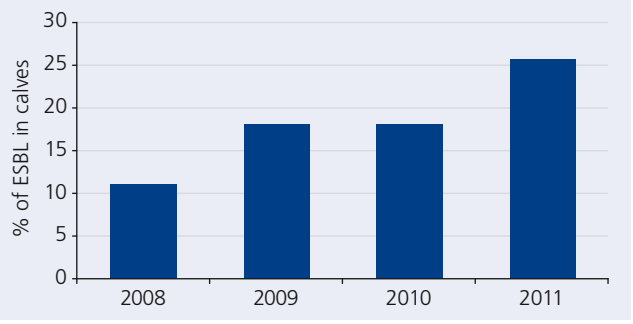

Fig. 5.1.3.2.2: Prevalence of ESBL-producing *E. coli* in calves

Conclusion

Overall, the resistance rates of *E. coli* isolates from calves with enteritis are still fairly high. The resistance to some antimicrobials has increased over the course of the years, while their efficacy has decreased. The further development needs to be monitored closely, in particular regarding the prevalence of ESBL-producing *E. coli* and the reduced efficacy of colistin.

➤ U. Steinacker
Reviewer: A. Lübke-Becker

5.2 Swine (piglet/weaning pig/ fattening pig/breeding pig)

5.2.1 Respiratory tract infections

Since the intensification of pig farming, respiratory tract infections have gained in significance. In this process, both the impairment of the current state of health and the adverse effect on development are relevant. Clinical symptoms of such infections include coughing, sneezing, increased secretion and changed respiratory rates as well as respiratory sounds. Where therapeutic relevance was given, the data was evaluated separately for the individual type of production.

5.2.1.1 *Pasteurella multocida*

Pasteurella multocida is a commensal inhabitant of the mucous membranes of the upper respiratory tract of healthy swine. At the same time, this pathogen is involved in multifactorial infectious processes as well as in the complex of atrophic rhinitis. Consequently, *P. multocida* is one of the most frequently diagnosed bacterial pathogens in swine with symptoms of respiratory infections.

Trends in resistance development

In the 2010 study, a total of 73 *P. multocida* isolates obtained from swine in the individual type of production (piglet, weaning pig, fattening pig) were tested for susceptibility. The species of all isolates were identified by means of a specific multiplex-PCR.

The resistance level of *P. multocida* isolates was classified as low in all three types of production. With the exception of gentamicin and tetracycline, the rates of resistance to the tested antimicrobials were below 5% in all types of production. The rate of resistance to gentamicin was 8% and to tetracycline 35%. When comparing the type of production, significant differences were observed for these two antibacterial agents. The respective rate of gentamicin resistance was 8% in isolates from piglets, 0% in those from weaning pigs and 10% in those from fattening pigs. The rate of tetracycline resistance was 24% in isolates from piglets, 35% in those from weaning pigs and 43% in those from fattening pigs. The susceptibility of *P. multocida* isolates from fattening pigs to a total of four antibacterial agents (amoxicillin/clavulanic acid, ceftiofur, cephalothin, tilmicosin) was not limited at all.

Two isolates from fattening pigs (n=28) were classified as non-susceptible to florfenicol (1 isolate intermediate, 1 isolate resistant) and one isolate from piglets showed intermediate susceptibility.

The MIC_{90} values of *P. multocida* isolates for the tested antibacterial agents were broadly similar in all three types of production (Tab. 5.2.1.1.1), with deviations being observed for cefoperazone, cefquinome and penicillin G. The MIC_{90} values of *P. multocida* isolates from piglets for these three antimicrobials were up to four titre steps higher than in the other stages of production.

Tab. 5.2.1.1.1: MIC_{90} values of *P. multocida* for antimicrobials for which no CLSI-approved breakpoints are available

Antimicrobial	MIC_{90} (mg/l)		
	Piglet	Weaning pig	Fattening pig
Ampicillin	0.5	0.5	1
Apramycin	32	32	32
Cefoperazone	4	0.25	0.12
Cefquinome	0.5	0.06	0.06
Colistin	16	16	8
Doxycycline	2	2	2
Enrofloxacin	0.03	0.03	0.03
Penicillin G	1	1	0.25
Spectinomycin	128	64	64
Tiamulin	32	32	32
Tulathromycin	4	4	4

Compared to the results of the previous study years, a significant increase in resistance rates was observed, which particularly applies to tetracycline. Whereas a resistance rate of 5–10% was recorded 5 years ago (2004/2005 study) and 31% 2 years ago, a resistance rate of approx. 35% was calculated in the current study. A similar – although less pronounced – increase was observed in the MIC_{90} values of *P. multocida* for the following antibacterial agents: 5 years ago, the MIC_{90} value for ampicillin was 0.25 mg/l (2010 study: up to 1 mg/l), for colistin 4 mg/l (2010 study up to 16 mg/l) and for penicillin G 0.25 mg/l (2010 study up to 1 mg/l).

Conclusion

Most of the tested antimicrobials continue to show good efficacy against *P. multocida*. The 2010 study did not find resistance rates of more than 5% of the *P. multocida* isolates in any of the type of production. Irrespective of this, it became evident that the susceptibility of *P. multocida* isolates from fattening pigs to certain antibacterial agents has dropped over the course of the past years. This undesirable development was most pronounced as regards tetracycline and β-lactam antibacterial agents. The detection of two isolates non-susceptible to florfenicol in both the 2008 and the 2010 study should also be viewed critically. In order to be able to recognise future resistance developments within the type of production at an early point, the data needs to be evaluated using the classification selected here.

➤ J. Wallmann
Reviewer: H. Kaspar

5.2.1.2 *Actinobacillus pleuropneumoniae*

Pleuropneumonia caused by *Actinobacillus pleuropneumoniae* (APP) may have a peracute, acute, chronic or subclinical progression, depending on whether additional infection pressure is exerted by other bacterial or viral pathogens in the respective animal population.

Trends in resistance development

In this case, the data was obtained from three GE*RM*-Vet studies (2009–2011) for APP isolates from swine with respiratory tract infections. The tested collective was not evaluated separately for the individual stages of production, since the number of isolates was not sufficient for this purpose.

40 isolates were tested in 2009, 59 in 2010 and 47 in 2011. Nine antimicrobials were classified on the basis of the CLSI standard.

Resistance to tetracycline (17–32%) and gentamicin (4–17%) as well as a significant percentage of isolates showing intermediate resistance to these two antimicrobials were observed. Isolates resistant to ceftiofur were first detected in the 2011 study year (13%, Fig. 5.2.1.2.1 – 5.2.1.2.3).

Tab. 5.2.1.2.1: Swine – MIC_{90} values of APP for antimicrobials for which no CLSI-approved breakpoints are available

Antimicrobial	MIC_{90} (mg/l)		
	2009	2010	2011
Ampicillin	0.5	0.25	0.25
Apramycin	64	32	32
Cefoperazone	0.12	0.12	4
Cefotaxime	0.015	0.015	0.25
Cefquinome	0.03	0.03	0.5
Doxycycline	2	2	8
Enrofloxacin	0.12	0.06	0.06
Nalidixic acid	4	4	4
Penicillin G	1	0.5	4
Spiramycin	64	64	64
Co-trimoxazole	0.25	0.12	0.12
Tulathromycin	32	16	16

Elevated MIC_{90} values were found for apramycin and tulathromycin. No resistance and low MIC_{90} values were observed for the other antimicrobials that play a major role in the treatment of respiratory tract infections in swine, such as amoxicillin/clavulanic acid, florfenicol, cefquinome and enrofloxacin, which suggests good efficacy.

Conclusion

The low level of resistance to most antimicrobials has remained nearly unchanged over the years. However, the development of resistance to tetracycline, gentamicin and ceftiofur requires further careful monitoring.

➤ U. Steinacker
Reviewer: K. Heidemanns

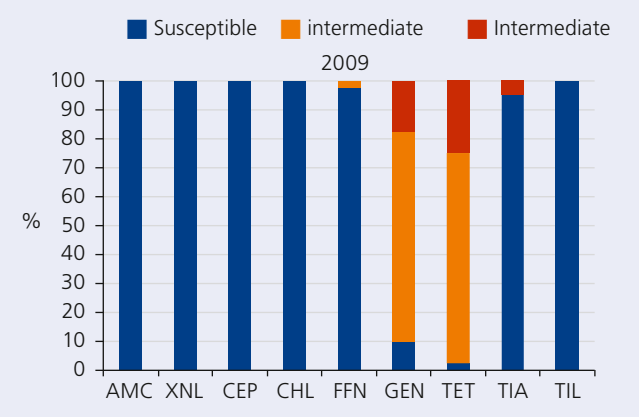

Fig. 5.2.1.2.1: Resistance rates of APP from swine, Germany 2009 (n=40)

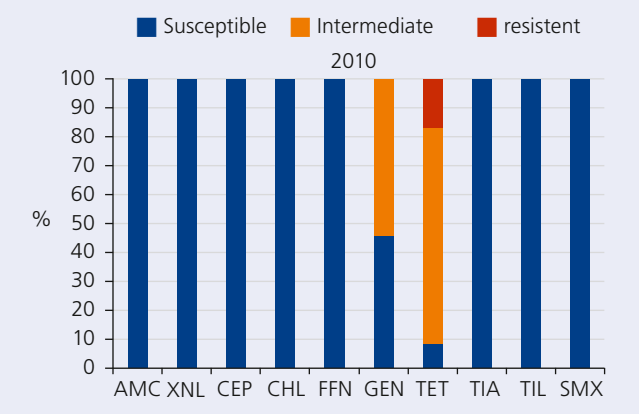

Fig. 5.2.1.2.2: Resistance rates of APP from swine, Germany 2010 (n=59)

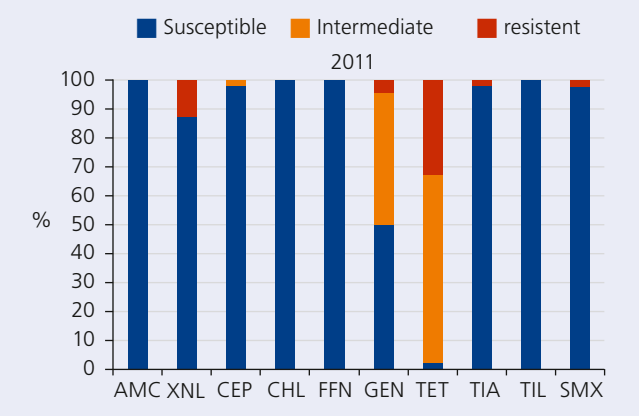

Fig. 5.2.1.2.3: Resistance rates of APP from swine, Germany 2011 (n=47)

5.2.1.3 *Streptococcus suis*

The main reservoir of *Streptococcus suis* is swine. The pathogen colonises the tonsils and the nasal area and is among the most important infectious agents in swine worldwide.

Trends in resistance development

The 2009 GE*RM*-Vet study measured the MIC values of a total of 95 *S. suis* isolates from swine with respiratory tract infections, 47 of which were obtained from piglets and 48 of them from adult pigs (weaning pigs and fattening pigs taken together). More recent data for *S. suis* in swine with respiratory tract infections is not available.

Piglet/Weaning pig/Fattening pig

High rates of resistance across all types of production were only observed for tetracycline (94%). The rate of erythromycin resistance was 53%, and none (cephalothin, vancomycin) or a maximum of 5% of the isolates were found to be resistant to the other tested antimicrobials (ampicillin, amoxicillin/clavulanic acid, ceftiofur, gentamicin and penicillin G) (Fig. 5.2.1.3.1). However, 57% of the isolates showed intermediate resistance to gentamicin.

Tab. 5.2.1.3.1: Swine – MIC_{90} values of *S. suis* for antimicrobials for which no CLSI-approved breakpoints are available

Antimicrobialc	MIC_{90} (mg/l)		
	2005/ 2006	2007/ 2008	2009
Cefoperazone	0.5	1	1
Cefquinome	0.06	0.12	0.06
Clindamycin	64	64	128
Enrofloxacin	0.5	0.5	1
Neomycin	16	64	–
Oxacillin	0.12	0.5	0.5
Pirlimycin	64	64	64
Quinupristin/Dalfopristin	2	2	n.g.
Spiramycin	128	128	128
Co-trimoxazole	0.12	2	2
Tulathromycin	64	64	128
Tylosin	128	128	128

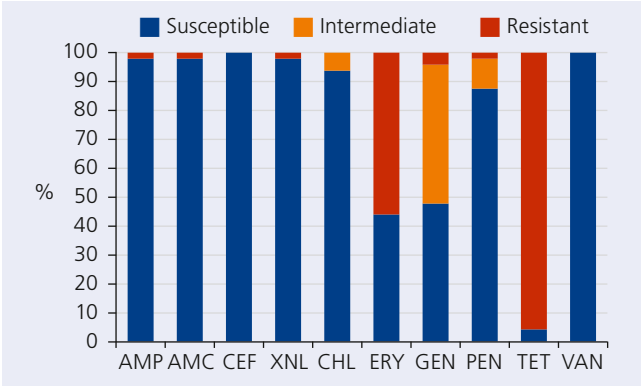

Fig. 5.2.1.3.1: Resistance rates of *S. suis* from swine, Germany 2009 (n=95)

The MIC_{90} values for the other tested β-lactam antibacterial agents, enrofloxacin and trimethoprim/sulphamethoxazole (co-trimoxazole) were low. Consequently, these antimicrobials are expected to be effective.

Elevated MIC_{90} values (Tab. 5.2.1.3.1) were observed for clindamycin, pirlimycin and tulathromycin. Pronounced differences in the resistance characteristics of isolates from various types of production were not recorded, which is why both the MIC_{90} values and the resistance rates are shown collectively for the individual types of production.

Conclusion

When comparing the study years, the rates of resistance to all antimicrobials, except for tetracycline, were at a low level, with some of them showing declining tendencies. However, the high rate of isolates showing intermediate susceptibility to gentamicin requires further monitoring, since an incipient shift in the population regarding resistance characteristics is becoming apparent here.

➤ K. Heidemanns
Reviewer: H. Kaspar

5.2.1.4 *Bordetella bronchiseptica*

Bordetella bronchiseptica causes respiratory tract infections in almost all mammals. Human *B. bronchiseptica* infections have also been reported. However, humans have a very low susceptibility, unlike highly susceptible mammals such as pigs, dogs and guinea pigs. The pathogen is transmitted primarily through direct contact as a droplet infection. The symptoms in swine range from mild rhinitis to severe pneumonia. *B. bronchiseptica* paves the way for infections with other pathogens, e.g. toxigenic *Pasteurella multocida* strains. *B. bronchiseptica* is detected as one of the three most common pathogens in slaughter animals with pneumonia.

Trends in resistance development

In the 2011 GE*RM*-Vet study, a total of 89 *B. bronchiseptica* strains from swine with respiratory tract infections were tested, with high MIC values being measured for most of the tested β-lactam antibacterial agents.

In general, the MIC distribution determined in the 2011 study was similar to that found in previous study years. There was hardly any difference between the MIC_{90} values measured in the individual studies (Tab. 5.2.1.4.1). The rates of florfenicol, gentamicin and tetracycline resistance were below 15%. Resistance rates of up to 20% as well as a high percentage of isolates showing intermediate resistance to cephalothin were observed (Fig. 5.2.1.4.1 – 5.2.1.4.3). Similar rates were found for the antimicrobial agent florfenicol.

Fig. 5.2.1.4.1 to 5.2.1.4.3 compares the percentages of susceptible, intermediate and resistant strains in all three study years.

Tab. 5.2.1.4.1: Swine – MIC_{90} values of *Bordetella* spp. for antimicrobials for which no CLSI-approved breakpoints are available

Antimicrobial	MIC_{90} (mg/l)		
	2009	2010	2011
Ampicillin	32	64	32
Cefquinome	32	32	32
Ceftiofur	128	128	128
Nalidixic acid	8	16	8
Enrofloxacin	0.5	0.5	0.5
Tilmicosin	32	32	32
Trimethoprim	16	8	8
Co-trimoxazole	4	8	8
Tulathromycin	8	16	8

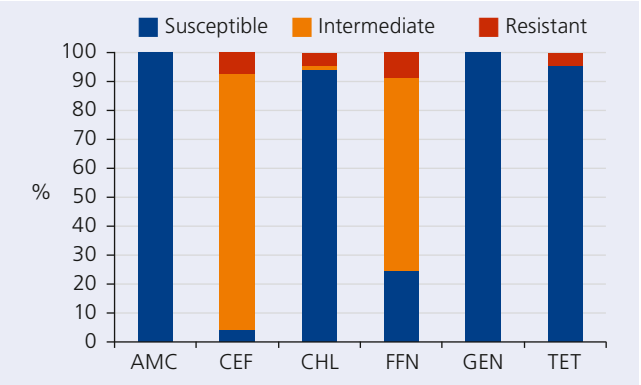

Fig. 5.2.1.4.1: Resistance rates of *B. bronchiseptica* from swine, Germany 2009 (n=69)

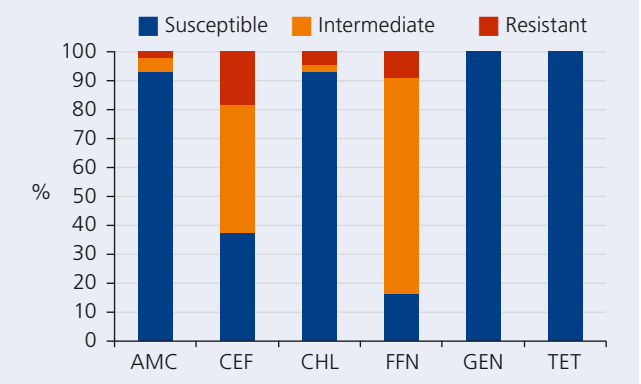

Fig. 5.2.1.4.2: Resistance rates of *B. bronchiseptica* from swine, Germany 2010 (n=43)

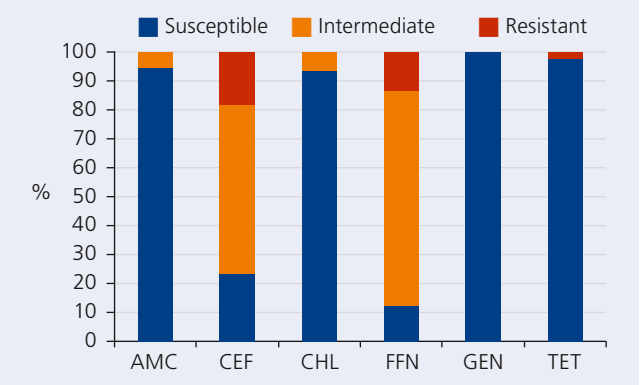

Fig. 5.2.1.4.3: Resistance rates of *B. bronchiseptica* from swine, Germany 2011 (n=89)

Conclusion

B.-bronchiseptica strains isolated from swine show good susceptibility to most antimicrobials, in particular to tetracycline and enrofloxacin. Treatment with penicillins or cephalosporins is not recommended. The high percentage of isolates showing intermediate resistance, especially to florfenicol, requires further monitoring.

➤ K. Heidemanns
Reviewer: H. Kaspar

5.2.2 Enteritis

Enteritis caused by infections with *Escherichia coli* or *Salmonella* spp. plays a major role in pig farming, in particular in rearing of young animals. The symptoms and effects are consistent with those found in cattle.

5.2.2.1 *Escherichia coli*

Trends in resistance development

In the 2010 GE*RM*-Vet study, a total of 237 *E. coli* isolates from swine with the indication of "gastritis/enteritis" were tested and the data was evaluated separately for the three stages of production: piglet (n=156), weaner (n=36) and fattening pig (n=45).

Piglet/Weaner/Fattening Pig

High resistance rates in *E. coli* isolates were observed for tetracycline (60–79%), ampicillin (57–71%) and trimethoprim/sulphamethoxazole (co-trimoxazole) (42–56%) across all stages of production. The rates of cephalothin and chloramphenicol resistance (not approved for use in food-producing animals) ranged between 11% and 30%, with 37–51% of the tested isolates showing intermediate resistance to cephalothin. Resistance rates of more than 10% to amoxicillin/clavulanic acid (11%) and gentamicin (14%) were only observed in isolates from piglets (Fig. 5.2.2.1.1). Overall, isolates from piglets exhibited the highest resistance rates and those from fattening pigs the lowest. Compared to previous studies, the rate of resistance to ampicillin and to the combination of amoxicillin/clavulanic acid has increased (Fig. 5.2.2.1.2).

No CLSI breakpoints were available for the remaining antimicrobials. In 2010, high MIC_{90} values of ≥ 64 and ≥ 512 mg/l were found for the tested aminoglycosides apramycin and spectinomycin, respectively, which suggests no efficacy. Colistin (8 mg/l in piglets and weaners) seems to have limited efficacy, but it can still be regarded as therapeutically effective in fattening pigs (1 mg/l). Furthermore, the consistently high nalidixic acid MIC_{90} values in piglets and fattening pigs (2004/2005: 32 mg/l, 2006/2007 and 2010: 128 mg/l) are remarkable, with the enrofloxacin MIC_{90} values (0.5 mg/l) being stable and significantly lower (Tab. 5.2.2.1.1).

Conclusion

In general, *E. coli* isolates from swine with enteritis showed resistance to a great number of the tested antimicrobials. The efficacy of the therapeutically relevant antimicrobial agent colistin has to be classified as limited, at least when used in piglets and fattening pigs.

➤ A. Römer
Reviewer: A. Lübke-Becker

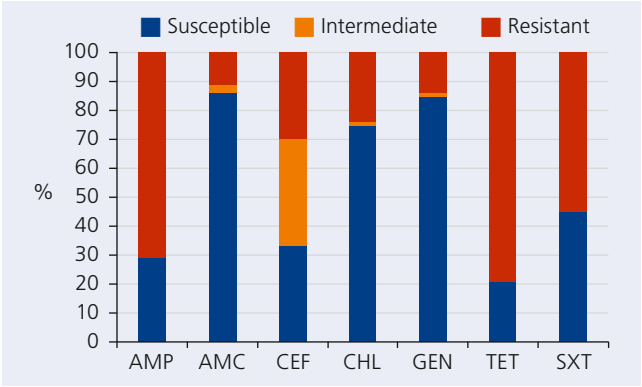

Fig. 5.2.2.1.1: Resistance rates of *E. coli* from piglets with enteritis, Germany 2010 (n=156)

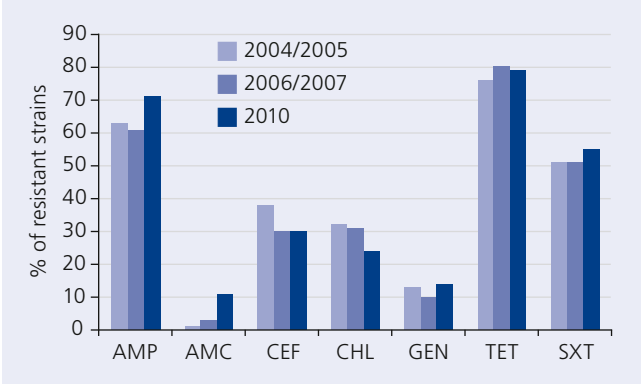

Fig. 5.2.2.1.2: Resistance rates of *E. coli* from piglets with enteritis, Germany 2004–2010 (2004/2005 n=287; 2006/2007 n=333; 2010 n=156)

Tab. 5.2.2.1.1: Swine (piglet) – MIC_{90} values of *E. coli* for antimicrobials for which no CLSI-approved breakpoints are available

Antimicrobial	MIC_{90} (mg/l)		
	2004/2005	2006/2007	2010
Apramycin	16	32	≥ 64
Cefoperazone	16	32	≥ 32
Cefquinome	0.12	0.12	0.12
Ceftiofur	0.5	0.5	0.5
Colistin	0.5	4	8
Enrofloxacin	0.5	0.5	0.5
Florfenicol	8	8	16
Nalidixic acid	32	128	128
Penicillin G	≥ 32	≥ 32	≥3 2
Spectinomycin	512	512	≥ 512
Spiramycin	≥ 128	≥ 128	≥ 128
Tiamulin	≥ 64	≥ 64	≥ 64
Trimethoprim	128	≥ 128	≥ 128
Tulathromycin	32	16	16

5.2.2.2 *Salmonella enterica* subspecies *enterica*

Trends in resistance development

Since 2004, the MIC values of *Salmonella enterica* subsp. *enterica* isolates from swine with the indication of "enteritis" have been measured as part of the GE*RM*-Vet monitoring study. In the 2011 study year, 46 *S. enterica* subsp. *enterica* were tested for in-vitro susceptibility to 24 antimicrobials. CLSI breakpoints were available for eight of the tested antimicrobials, which is why the remaining antimicrobials were classified based on the MIC_{90} values.

High resistance rates were observed for ampicillin (78%) and tetracycline (80%). 30% of the isolates showed resistance and 11% intermediate resistance to chloramphenicol, an antimicrobial agent that is not approved for use in food-producing animals. 26% of the tested isolates were resistant to the combination of trimethoprim/sulphamethoxazole (co-trimoxazole). Only one isolate each was resistant to cephalothin and the combination of amoxicillin/clavulanic acid. However, 15% and 35% of the isolates were classified as intermediate. Isolates resistant to gentamicin were not detected (Fig. 5.2.2.2.1).

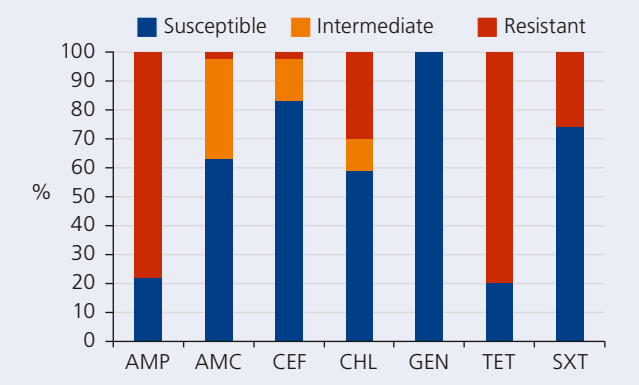

Fig. 5.2.2.2.1: Resistance rates of *S. enterica* ssp. *enterica* from swine with enteritis, Germany 2011 (n=46)

The MIC_{90} values for the newer cephalosporins cefquinome and ceftiofur as well as for enrofloxacin were in the lower range, which is why the occurrence of resistant isolates seems unlikely.

The MIC_{90} values for the polypeptide colistin have been constant for years (2 mg/l). The aminoglycoside apramycin, the macrolides tilmicosin and tulathromycin as well as the pleuromutilin tiamulin showed reduced in-vitro activity (Tab. 5.2.2.2.1).

Tab. 5.2.2.2.1: MIC_{90} values of *S. enterica* ssp. *enterica* isolates for antimicrobials for which no CLSI-approved breakpoints are available

Antimicrobial	MIC_{90} (mg/l)	
	2006/0207	2010
Apramycin	8	4
Cefoperazone	≥ 32	≥ 32
Cefquinome	0,25	0,25
Ceftiofur	1	1
Colistin	2	2
Enrofloxacin	0,12	0,12
Florfenicol	64	64
Nalidixic acid	4	8
Penicillin G	≥ 32	≥ 128
Spiramycin	≥ 128	≥ 256
Sulphamethoxazole	–	≥ 1.024
Tiamulin	≥ 64	≥ 256
Tilmicosin	≥ 128	≥ 128
Trimethoprim	≥ 128	≥ 128
Tulathromycin	16	32

Compared to previous studies, *S. enterica* subsp. *enterica* isolates in the 2011 study year exhibit low rates of resistance to many antimicrobials (Fig. 5.2.2.2.2). However, the resistance rates and MIC_{90} values continue to be at a high level. Moreover, it should be noted that the sample size in the 2011 study year was significantly lower than in previous studies.

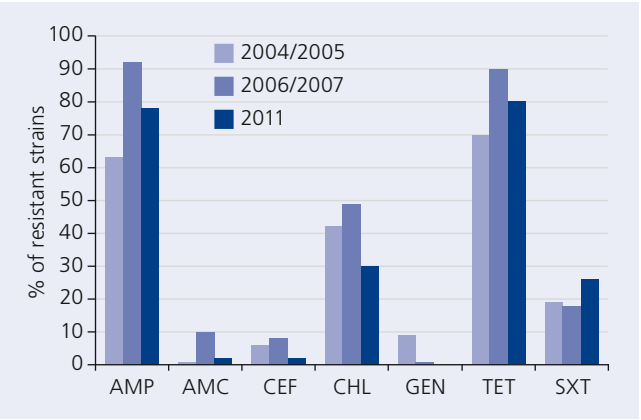

Fig. 5.2.2.2.2: Resistance rates of *S. enterica* ssp. *enterica* from swine with enteritis, Germany 2004–2011 (2004/2005 n=135; 2006/2007 n=120; 2011 n=46)

Conclusion

Overall, the resistance situation is similar for *S. enterica* subsp. *enterica* and *E. coli* from swine with enteritis. Resistance to tetracycline and ampicillin is widespread.

➤ A. Römer
Reviewer: A. Lübke-Becker

5.3 Poultry (chicken, turkey)

5.3.1 Bloodstream infections

5.3.1.1 *Escherichia coli*

Trends in resistance development

The 2010 GE*RM*-Vet study included 262 *Escherichia coli* isolates from diseased poultry, 148 of which were obtained from chickens, 96 from turkeys (3 of them from turkey chicks) and 18 from water fowl.

Among the chicken species, 22 of the isolates were obtained from broiler chicks and 20 from broilers (indication: yolk sac infection/ bloodstream infection). The study included another 106 *E. coli* isolates from pullets and laying hens.

Among the total population of poultry, the resistance rates measured for ampicillin (approx. 35%) and tetracycline (28%) were by far the highest. The rate of enrofloxacin resistance was 4%; 13% of the isolates were classified as "intermediate". Approx. 15% of the strains were resistant to the fixed combination of trimethoprim/sulphamethoxazole (co-trimoxazole) (Fig. 5.3.1.1.1). When evaluating the data by individual animal species and types of production, however, significant differences in susceptibility rates were found in some cases.

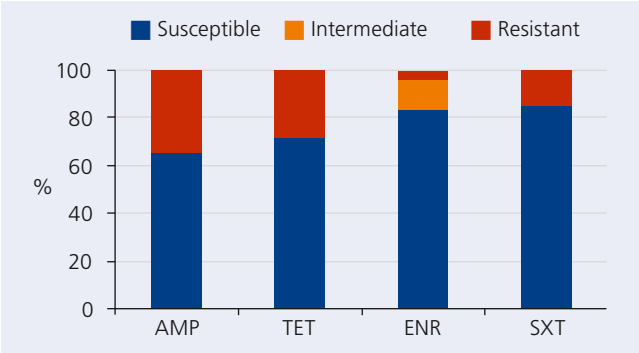

Fig. 5.3.1.1.1: Resistance rates of *E. coli* from poultry (all poultry types and types of production, Germany 2010 (n=262)

Broilers

The bacterial strains isolated from both broiler chicks and broilers showed high rates of resistance to ampicillin (50%) and tetracycline (33%). With the exception of trimethoprim/sulphamethoxazole (19%) and amoxicillin/clavulanic acid (approx. 12% of resistant isolates), the rates of resistance to the other tested antimicrobials were below 10%. 9.5% of the strains were resistant and 31% of the isolates showed intermediate resistance to enrofloxacin (Fig. 5.3.1.1.2).

A comparison of the study years showed that the resistance rates of isolates from broiler chicks ranged at a similar level over the years. The rate of resistance to penicillin, in particular to amoxicillin/clavulanic acid, in broilers increased from 4% in 2004 to 12%.

Laying hens

E. coli isolates from pullets and laying hens showed an overall significantly lower resistance level than found in other types of chicken or turkey use. Resistance to ampicillin was detected

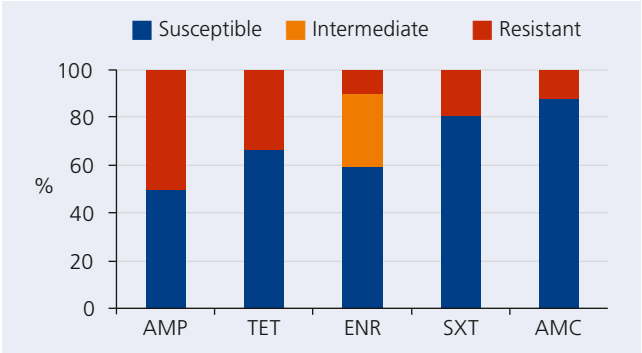

Fig. 5.3.1.1.2: Resistance rates of *E. coli* from broilers, Germany 2010 (n=42)

in 22% (43% resistance in turkeys) and to tetracycline in 16% of the cases (37% resistance in turkeys) (Fig. 5.3.1.1.3). These resistance rates were below those ascertained in the previous years (2004–2007) (ampicillin 18%, tetracycline 25%). The rates of resistance to all other antimicrobials were well below 10% resistant isolates. 1% of the submitted *E. coli* isolates from pullets and laying hens were non-susceptible to enrofloxacin and 5% of the isolates were classified as "intermediate"

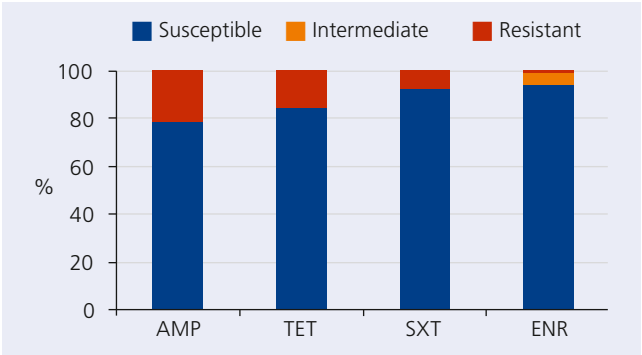

Fig. 5.3.1.1.3: Resistance rates of *E. coli* from laying hens, Germany 2010 (n=148)

Turkeys

The resistance rate in turkeys with the indication of respiratory tract infections was 50% to ampicillin and 47% to tetracycline. The level of resistance to enrofloxacin was 5.4%. 21% of the isolates were classified as "intermediate". The resistance rates in turkeys with the indication of bloodstream infection were somewhat lower. 40% of the isolates were classified as clinically resistant to ampicillin, 35% to tetracycline and 4% to enrofloxacin (Fig. 5.3.1.1.4). With the exception of enrofloxacin, the rates of resistance to the above-mentioned antimicrobials were lower in 2010 than during the period 2004–2007 (ampicillin above 60%, tetracycline above 70%).

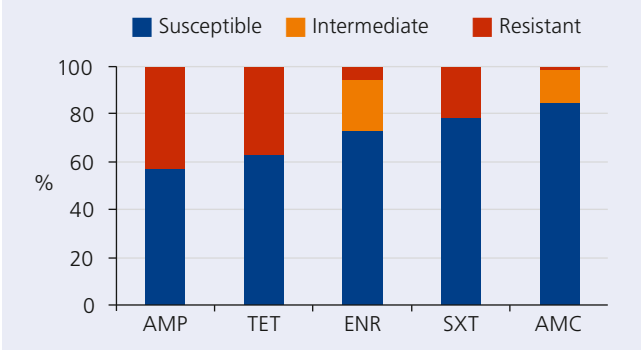

Fig. 5.3.1.1.4: Resistance rates of *E. coli* from turkeys, bloodstream infections and respiratory tract infections, Germany 2010 (n=96)

Water fowl
Only 18 *E. coli* isolates from water fowl were available for susceptibility testing. As was the case with poultry, high resistance rates of approx. 39% were observed for ampicillin and tetracycline and 11% for enrofloxacin. This rate of enrofloxacin resistance is much higher than that found in poultry (approx. 4%).

Conclusion

The resistance rates recorded for avian *E. coli* isolates were observed to strongly depend on the type of production. In relation to each other, isolates from turkey flocks showed higher resistance rates than strains isolated from broiler flocks; the resistance rates found in laying hens were by far the lowest. With the exception of enrofloxacin, a comparison of the study years revealed a consistent resistance level, which should, however, only be regarded as a trend, given the sometimes very small number of isolates. Overall, the ascertained MIC frequency distributions demonstrated that the resistance level of avian *E. coli* isolates exceeded the level determined by the BVL for other veterinary pathogens in other animal species.

The ascertained data cannot completely reflect the resistance characteristics of avian pathogens in Germany, since the number of tested isolates was too small and was not distributed evenly over regions. In order to also obtain reliable data for this production area, the poultry industry's private laboratories, which are mainly in charge of laboratory testing of poultry pathogens in Germany, would have to intensify their participation.

➤ Autor: J. Wallmann
Reviewers: H.M. Hafez, R. Hauck

5.3.1.2 *Staphylococcus aureus*

Trends in resistance development

Poultry/Turkeys
The avian *Staphylococcus aureus* isolates (n=35) tested within the GE*RM*-Vet study were obtained from turkeys (n=26) and broilers (n=9) with the indication of "bloodstream infections" and "diseases of the locomotor system". Given the very small number of isolates, the results were not differentiated by indication or type of production.

High resistance rates were observed for penicillin G (71%), ampicillin and erythromycin (73.5% each) (Fig. 5.3.1.2.1). Even higher resistance rates in the bacterial strains were only found for tetracycline (76.5%). Furthermore, 5 oxacillin-resistant isolates (15%) were detected, which were confirmed as being *mecA*-positive.

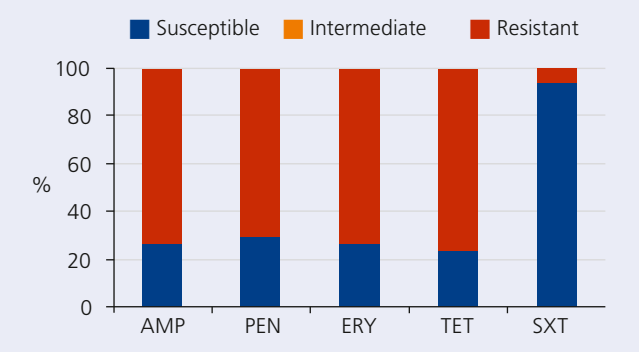

Fig. 5.3.1.2.1: Resistance rates of *S. aureus* from poultry (turkeys and broilers), Germany 2010 (n=35)

Conclusion

A comparison of the study years revealed that the resistance level of some avian *S. aureus* isolates has increased significantly compared to the 2006/2007 study. Whereas the rate of ampicillin and penicillin resistance was about 53% in the 2006/2007 study, this rate rose by approx. 20% by 2010. The rate of erythromycin and tetracycline resistance also increased significantly (2006/2007 37%, currently 73.5%; 2006/2007 59.5%, currently 76.5%). A decrease in the resistance rate (2006/2007 10%, currently 6%) was only observed for trimethoprim/sulphamethoxazole (co-trimoxazole).

Given the very small number of isolates tested in the 2006/2007 and 2010 studies, however, a valid tendency cannot be anticipated. A significantly larger number of isolates need to be tested to verify the results.

➤ J. Wallmann
Reviewers: H.M. Hafez, R. Hauck

5.4 *Escherichia coli* strains from Northwestern Lower Saxony obtained as part of the zoonosis monitoring

Laying hens/Broilers 2011

The study included 91 strains isolated from laying hens and 101 strains isolated from broilers. The tested strains were obtained as part of the General Administrative Regulation on Zoonoses in the Food Chain.[1] The resistance rates of *Escherichia coli* isolated from broilers were significantly higher than those of *E. coli* isolated from laying hens (Fig. 5.4.1). Trimethoprim MIC values of ≥ 64 mg/l were observed in 6.6% of the strains from laying hens and in 59.4% of the strains from broilers.

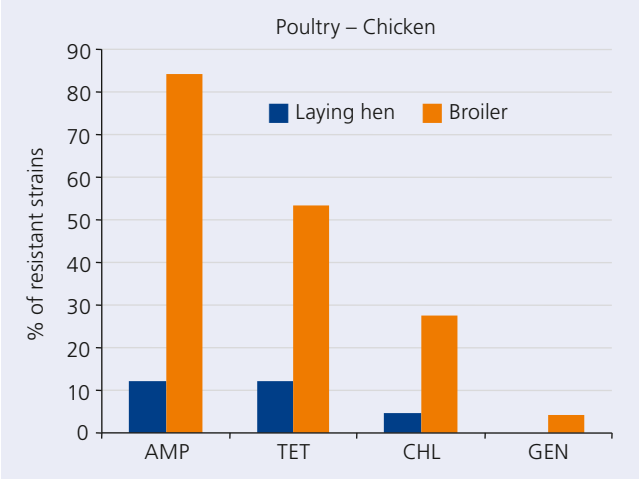

Fig. 5.4.1: Resistance rates of *E. coli* from laying hens (n=91) and broilers (n=101) from northwestern Lower Saxony (2011)

Elevated cephalosporin MIC values (CTX ≥ 0.5 mg/l) were not observed in strains from laying hens; nine strains from broilers exhibited an elevated MIC value (8.9%). High fluoroquinolone MIC values (CIP ≥ 2 mg/l) in strains from laying hens did not occur either; 15.8% of the *E. coli* strains from broilers showed a correspondingly high value.

Turkeys 2011 to 2012

In 2011 and 2012, *E. coli* isolated from turkey farms were also obtained as part of the zoonosis monitoring in the food chain. The rates of resistance to most of the tested antimicrobials remained stable over both years, with the exception of a significant increase in the gentamicin resistance rate (Fig. 5.4.2). Compared to *E. coli* from chickens, *E. coli* from turkeys usually showed higher resistance rates (cf. Fig. 5.4.1). Resistance rates of 41% (2011) and 47.8% (2012) were observed for trimethoprim. Cephalosporin-resistant strains only occurred in isolated cases (MIC CTX ≥ 0.5 mg/l: 2011 n=2, 2012 n=4). By contrast, a number of strains exhibited elevated ciprofloxacin MIC values (Fig. 5.4.2).

Veal calves (< 9 months) 2011 and veal calves/young cattle (< 12 months) 2012

In 2011 and 2012, strains obtained as part of the General Administrative Regulation on Zoonoses in the Food Chain from beef cattle farms were tested. Where several fattening groups were available, two isolates per farm were tested (the youngest and the oldest fattening group in each case). As part of this study, the MIC values of 300 strains were measured in 2011; in 2012, only 59 strains have been tested so far.

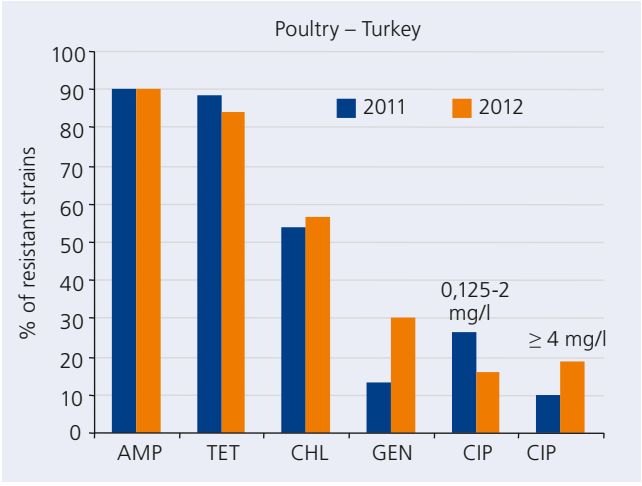

Fig. 5.4.2: Resistance rates of *E. coli* from turkeys from northwestern Lower Saxony in 2011 (n=61) and 2012 (n=69)

Great differences in resistance rates were observed in the two years (Fig. 5.4.3). Whether these differences are based on the deviating number of tested *E. coli* strains, the tested farms, the varying average age of the animals or are actually attributable to a change in the resistance situation cannot be ascertained based on the available data.

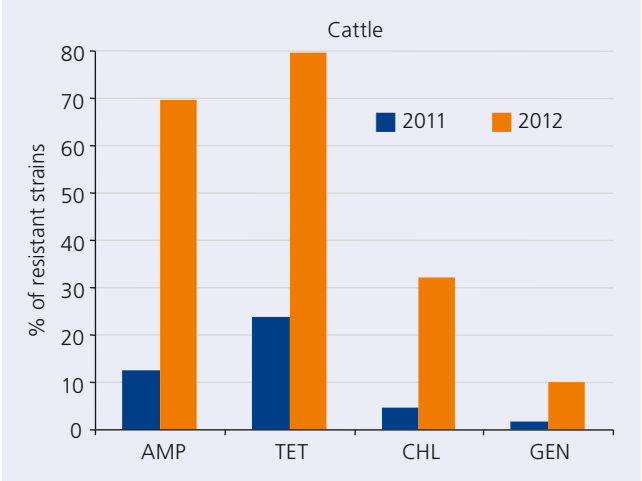

Fig. 5.4.3: Resistance rates of *E. coli* from beef cattle from northwestern Lower Saxony in 2011 (n=300) and 2012 (n=59)

In addition to the resistance rates shown in Fig. 5.4.3, many of the strains tested in 2012 exhibited high trimethoprim MIC values (67.8% at an MIC value of ≥ 64 mg/l; 2011: 16.7%). Ciprofloxacin MIC values of ≥ 4 mg/l were observed in six strains (10.2%) in 2012 and in four strains (1.3%) in 2011. Resistance to ciprofloxacin only occurred in isolated cases.

Fattening pig 2011

Besides veal calves, fattening pigs were also tested for the presence of resistant *E. coli* strains in 2011 as part of the General Administrative Regulation on Zoonoses in the Food Chain. In line with the sampling process for beef cattle, two isolates per farm were obtained from fattening pigs where at least two fattening groups of different age were available. Studies on fattening pigs were not conducted in 2012.

The isolated strains exhibited comparatively high rates of resistance to tetracycline (68.7%), ampicillin (53.0%) and trimethoprim (46.2%) (Fig. 5.4.4). Only low rates of resistance were observed for fluoroquinolones (MIC CIP ≥ 2 mg/l; n=4), cephalosporins (MIC CTX ≥ 0.5 mg/l; n=3) and gentamicin (n=6; 2.3%).

➤ C. Werckenthin
Reviewer: A. Römer

1. Allgemeine Verwaltungsvorschrift über die Erfassung, Auswertung und Veröffentlichung von Daten über das Auftreten von Zoonosen und Zoonoseerregern entlang der Lebensmittelkette (AVV Zoonosen Lebensmittelkette). Bekanntmachung der Neufassung der AVV Zoonosen Lebensmittelkette, vom 10. Februar 2012. http://www.verwaltungsvorschriften-im-internet.de/bsvwvbund_10022012_3289026230009.htm.

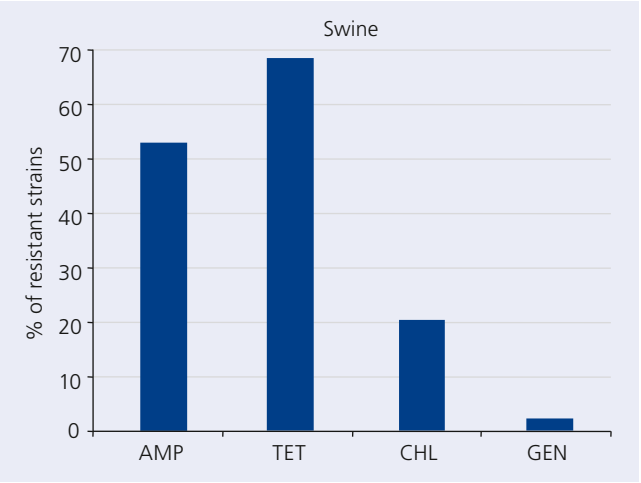

Fig. 5.4.4: Resistance rates of *E. coli* from fattening pigs from northwestern Lower Saxony in 2011 (n=262)

5.5. Prevalence and dynamics of resistance patterns of the lung pathogens *Streptococcus suis, Haemophilus parasuis, Actinobacillus pleuropneumoniae, Pasteurella multocida* and *Bordetella bronchiseptica* isolated from swine herds in Northwestern Germany from 2005 to 2010

Streptococcus suis, Haemophilus parasuis, Actinobacillus pleuropneumoniae (APP), *Pasteurella multocida* and *Bordetella bronchiseptica* belong to the pathogens that are most commonly isolated from cultures of macroscopically altered lung tissue of swine. In the present study, the resistance data measured as minimum inhibitory concentrations of the strains of these five bacterial species isolated from lung tissue, bronchial epithelium and serous skins during the period 2005–2010 as part of routine testing at the Field Station for Epidemiology in Bakum of the University of Veterinary Medicine Hannover was subjected to a retrospective descriptive evaluation. The MIC values were measured using the broth microdilution method in accordance with the CLSI guidelines. The tested antimicrobials are consistent with the large animal layout proposals of the "Antibiotic Resistance" working group of the German Veterinary Association (DVG) (Tab. 5.5.1). The clinical breakpoints for the classification were obtained from the M31-A3 document of the CLSI and the proposal of the DVG "Antibiotic Resistance" working group (2004).

Tab. 5.5.1: Antimicrobial agents/antimicrobial combinations of the tested antimicrobials

Antibiotic class	Antibiotikum		
Macrolides	ERY	TIL	
Pleuromutilins	TIA		
Lincosamides	CLI		
Penicillins/ Aminobenzylpenicillins	PEN	AMP	Amoxicillin
Cephalosporins	CEF (1^{st} gen.)	XNL (3^{rd} gen.)	CQN (4^{th} gen.)
Tetracyclines	TET		
Fluoroquinolones	ENR		
Aminoglycosides	GEN	APR	SPE
Fenicols	FFN		
Combination of diaminopyrimidine/sulphonamide (co-trimoxazole)	SXT (1:19)		
β-lactam antibiotics/ β-lactam inhibitors	AMC (2:1)		

The evaluation of the MIC values revealed species-specific combined resistance patterns of certain antimicrobials for the individual lung pathogens with varying frequency. The following figures list these patterns per pathogen according to their respective frequency. Only resistance patterns that were identified in 5% of the bacterial isolates in the individual study years or throughout the study period of six years were taken into account. Strains susceptible or intermediate to antimicrobials were classified as "non-resistant" and those resistant according to the defined clinical breakpoints as "resistant". Multi-drug resistance was defined as resistance to antimicrobials from more than two antimicrobial classes.

The MIC results of 2,410 S. suis, 1,165 *H. parasuis*, 610 APP, 1,118 *P. multocida* and 829 *B. bronchiseptica* strains were evaluated in the study.

Results

The following sections describe in detail the respective resistance patterns identified in the individual bacterial species. The figures stated refer to the total prevalence of the resistance patterns identified during the study period.

S. suis

During the study period, 8 resistance patterns (M) were identified for *S. suis* (Fig. 5.5.2). Four of the 8 combined resistance patterns showed multi-drug resistance to 3 or 4 antimicrobial classes (Fig. 5.5.1).

M #1: 18% – ERY, TIL, CLI, TET, APR – rose by 8% over the years
M #2: 13% – ERY, TIL, CLI, TET – decreased by 4%
M #3: 11% – TET – increased by 1%
M #4: 9% – APR – decreased by 4%
M #5: 9% – TET, APR – rose by 3%
M #6: 6% – ERY, TIL, CLI, TET, SXT – was characterised by a 2% increase
M #7: 6% – no resistance – rose by 2%
M #8: 5% – ERY, TIL, CLI, TET, SXT, APR – increased by 2%

H. parasuis

The resistance characteristics of *H. parasuis* strains were reflected in 5 resistance patterns (Fig. 5.5.4). Multi-drug resistance was not documented for any of the described combinations (Fig. 5.5.3).

M #1: 36% – SXT – dropped by 23%
M #2: 27% – no resistance – decreased by 2%
M #3: 10% – PEN, SXT – rose by 14%
M #4: 4% – PEN, AMP, SXT – increased by 4%
M #5: 4% – PEN – emained at the same resistance level during the study period

APP

The resistance characteristics of the 610 tested APP strains were expressed in 4 patterns (Fig. 5.5.6). Resistance to more than two antimicrobial classes (multi-drug resistance) was not observed (Fig. 5.5.5).

M #1: 36% – CLI, PEN – increased by 52%
M #2: 28% – PEN – dropped by 57%
M #3: 12% – ERY, CLI, PEN – rose by 2%
M #4: 4% – no resistance – saw a 5% increase

■	■		■							■				■			**M #1** (18%)
■	■		■							■							**M #2** (13%)
										■							**M #3** (11%)
														■			**M #4** (9%)
										■				■			**M #5** (9%)
■	■		■							■	■						**M #6** (6%)
																	M #7 (6%)
■	■		■							■	■			■			**M #8** (5%)
ERY	TIL	TIA	CLI	PEN	AMP	AMC	CEF	CQN	XNL	TET	SXT	ENR	GEN	APR	SPE	FFN	
■ Resistant; Not resistant (susceptible or intermediate)																	

Fig. 5.5.1: *S. suis* resistance patterns #1–#8 during the study period 2005–2010 (n=2,410)

											■						**M #1** (36%)
																	M #2 (27%)
				■							■						**M #3** (10%)
				■	■						■						**M #4** (4%)
				■													**M #5** (4%)
ERY	TIL	TIA	CLI	PEN	AMP	AMC	CEF	CQN	XNL	TET	SXT	ENR	GEN	APR	SPE	FFN	
■ Resistant; Not resistant (susceptible or intermediate)																	

Fig. 5.5.3: *H. parasuis* resistance patterns #1–#5 during the study period 2005–2010 (n=1,165)

			■	■													**M #1** (36%)
				■													**M #2** (28%)
■			■	■													**M #3** (12%)
																	M #4 (4%)
ERY	TIL	TIA	CLI	PEN	AMP	AMC	CEF	CQN	XNL	TET	SXT	ENR	GEN	APR	SPE	FFN	
■ Resistant; Not resistant (susceptible or intermediate)																	

Fig. 5.5.5: APP resistance patterns #1–#4 during the study period 2005–2010 (n=610)

			■														**M #1** (33%)
		■	■														**M #2** (21%)
			■								■						**M #3** (12%)
■		■	■														**M #4** (4%)
ERY	TIL	TIA	CLI	PEN	AMP	AMC	CEF	CQN	XNL	TET	SXT	ENR	GEN	APR	SPE	FFN	
■ Resistant; Not resistant (susceptible or intermediate)																	

Fig. 5.5.7: *P. multocida* resistance patterns #1–#4 during the study period 2005–2010 (n=1,118)

■		■	■	■	■			■	■		■				■		**M #1** (23%)
■		■	■	■	■			■	■						■		**M #2** (19%)
■	■	■	■	■	■			■	■		■				■		**M #3** (11%)
■	■	■	■	■	■			■	■						■		**M #4** (11%)
ERY	TIL	TIA	CLI	PEN	AMP	AMC	CEF	CQN	XNL	TET	SXT	ENR	GEN	APR	SPE	FFN	
■ Resistant; Not resistant (susceptible or intermediate)																	

Fig. 5.5.9: *B. bronchiseptica* resistance patterns #1–#4 during the study period 2005–2010 (n=829)

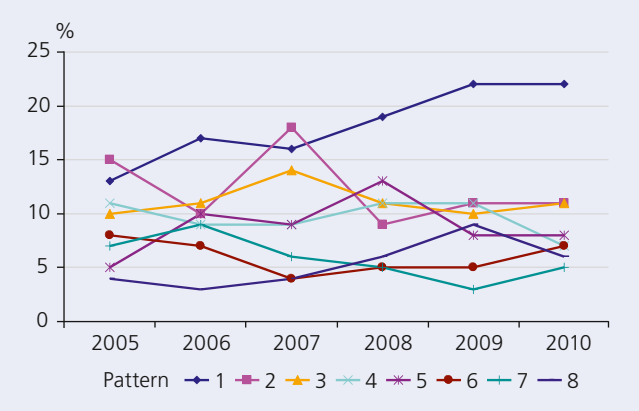

Fig. 5.5.2: Prevalence of resistance patterns #1–#8 in *S. suis* isolates 2005–2010 (n=2,410)

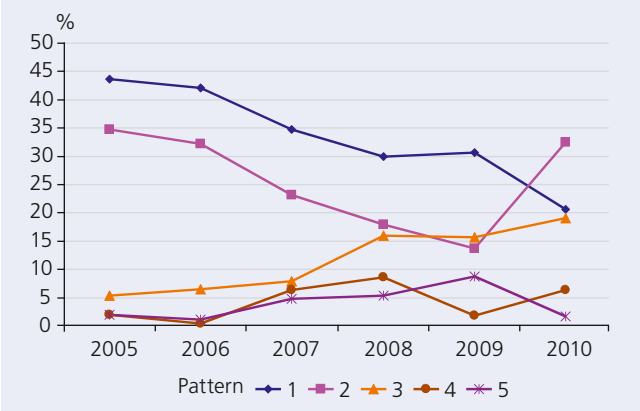

Fig. 5.5.4: Prevalence of resistance patterns #1–#5 in *H. parasuis* isolates 2005–2010 (n=1,165)

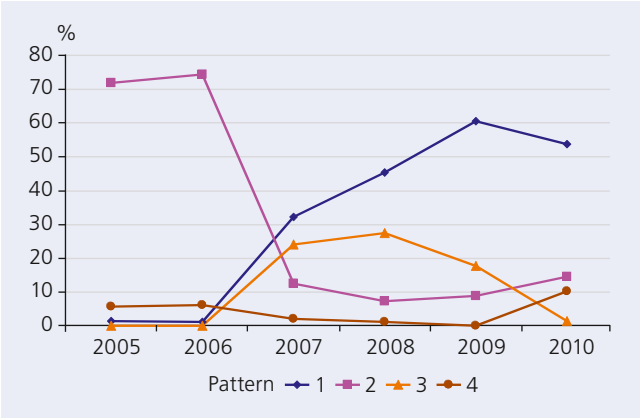

Fig. 5.5.6: Prevalence of resistance patterns #1–#4 in APP isolates 2005–2010 (n=610)

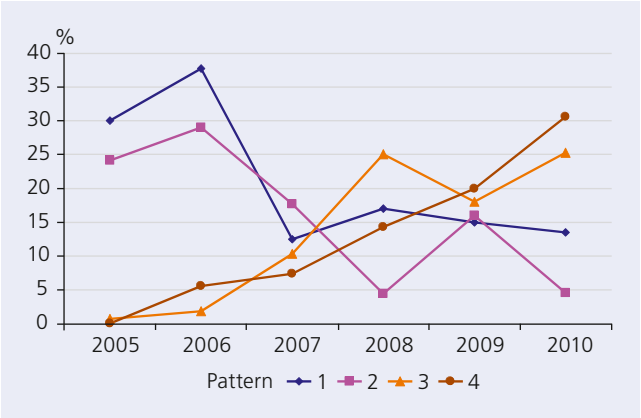

Fig. 5.5.10: Prevalence of resistance patterns #1–#4 in *B. bronchiseptica* isolates 2005–2010 (n=829)

P. multocida

The *P. multocida* strains showed their resistance in 4 patterns during the entire study period (Fig. 5.5.8). Multi-drug resistance did not occur (Fig. 5.5.7)

M #1: 33% – CLI – increased by 6%
M #2: 21% – TIA, CLI – increased by 7%
M #3: 12% – CLI, SXT – decreased by 3%
M #4: 4% – ERY, TIA, CLI – rose by 1%

B. bronchiseptica

The resistance characteristics of the 829 *B. bronchiseptica* strains manifested themselves in 4 patterns (Fig. 5.5.10). The patterns identified characterised themselves by multi-drug resistance to at least four and at most to six antimicrobial classes (Fig. 5.5.9).

M #1: 23% – ERY, TIA, CLI, PEN, AMP, CQN, XNL, SXT, SPE – decreased by 17%
M #2: 19% – ERY, TIA, CLI, PEN, AMP, CQN, XNL, SPE – dropped by 20%
M #3: 11% – ERY, TIL, TIA, CLI, PEN, AMP, CQN, XNL, SXT, SPE – increased by 25%
M #4: 11% – ERY, TIL, TIA, CLI, PEN, AMP, CQN, XNL, SPE – rose by 31%

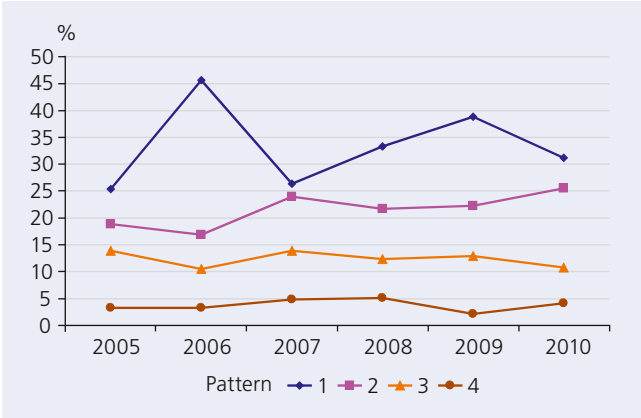

Fig. 5.5.8: Prevalence of resistance patterns #1–#4 in *P. multocida* isolates 2005–2010 (n=1,118)

Trends in resistance development

The data listed for the identified resistance patterns of lung pathogens showed a tendency towards increasing spread of resistance over the six-year study period. The *S. suis* and *B. bronchiseptica* isolates demonstrated a clear tendency to multi-drug resistance, with the increase of pattern #3 (25%) and pattern #4 (31%) being particularly high in the tested *B. bronchiseptica* isolates (Fig. 5.5.10). Among the tested *H. parasuis* and APP strains, the prevalence of resistance against two antimicrobial substances in the patterns increased significantly over the years, as evidenced by pattern #3 (PEN+SXT) of *H. parasuis* (increase by 14%) and pattern #2 (CLI+PEN) of APP (increase by 52%). At the same time, the prevalence of pattern #1 (SXT) of H. parasuis with single resistance dropped by 20% and pattern #2 (PEN) of APP with single resistance by 57%. These statements are shown in Fig. 5.5.4 and 5.5.6.

Conclusion

The identification of phenotypic resistance patterns in pathogenic bacterial strains allows for visualising the resistance characteristics of the individual bacterial strains, making it possible to compare the differences in resistance both between bacterial species and within one species. The identification of resistance patterns is particularly suitable for quantifying changes in the resistance characteristics of individual bacterial species over time. This considerably facilitates the semi-quantitative anticipation of trends in the resistance development of individual bacterial species by animal species and regions.

The current resistance situation of porcine lung pathogens underlines the great significance of monitoring and surveillance programmes in generating reliable basic data to anticipate trends and in implementing strategies for utilising the currently available antibacterial agents, the aim being to counteract further resistance development for the sake of human and animal health.

➤ R. Tegeler, L. Kreienbrock, T. Blaha
Reviewers: J. Wallmann, H. Kaspar

Reducing antibiotic use without taking account of the employed antimicrobials and without simultaneous animal health monitoring is counterproductive

The fact that the prevalence of MRSA (methicillin-resistant *Staphylococcus aureus*) and ESBL (extended-spectrum β-lactamase)-producing *Enterobacteriaceae* has been observed to undoubtedly increase in recent years shows that the problem of resistance development in human and animal bacterial pathogens had been underestimated. One of the main reasons for this is that until recently we have only been looking at resistance development in so-called target bacteria (i.e. bacterial pathogens against which antibacterial agents are used) all over the world. We have become aware of this development in particular through the introduction of systematic surveillance of resistance in the most common target bacteria in humans and animals, but also through the implementation of rules for medically reasonable, prudent use, which were laid down for veterinary medicine in what are referred to as "Guidelines for Antibiotic Use" ("Guidelines for the Prudent Use of Antimicrobial Veterinary Medicinal Products –including Comments" by the Federal Chamber of Veterinarians (BTK) and the TAM working group, updated in June 2010). These guidelines are mandatory for veterinarians. Despite these rules of prudent antibiotic use, however, the intensification of the MRSA problem, especially because of the emergence and worldwide spread of livestock-associated MRSA strains (CC398 mainly in swine, CC1430 in calf and poultry) and the fact that ESBL-producing *Enterobacteriaceae* occur in both animals and humans, have shown that observing the rules of prudent use alone is not sufficient to get the problem of increasing resistance under control.

In general, two phenomena are the reason why resistance cannot be kept under control, even if antibacterial agents are used very responsibly in both humans and animals:

1. **Every**, i.e. even the most "responsible", use of antibacterial agents involves the exposure of billions of commensal or less pathogenic/opportunistic non-target bacteria (at least in veterinary medicine, *Staphylococcus aureus* and common *Enterobacteriaceae* that are potentially capable of producing β-lactamase are no targets of traditional antibiotic administration) to these antibacterial agents and thus their exposure to the same selection pressure as the target bacteria.

2. The rules of prudent antibiotic use can only stipulate what needs to be done when using antibacterial agents – they have no influence on how often humans and animals acquire bacterial infections and how severe these infections are. Veterinarians should use their veterinary knowledge and skills not only to cure infections but also to support farmers in implementing and continuously applying all practices in livestock farming that reduce the prevalence and severity of bacterial infections in farm animals and, to a lesser extent, in humans as well as companion animals.

In fact, we have overlooked both aspects, and we have to accept the growing criticism from society at the extent and frequency of antibiotic use in livestock farming. This means:

a) **Reducing antibiotic use in livestock farming** – starting with animal populations in which above-average amounts of antibacterial agents are used and

b) **Improving animal husbandry and care** to minimise the necessity of antibiotic administration by improving disease prevention and control. This is done by optimising biosafety and hygiene in animal populations, since suboptimal living conditions of animals constantly lead to actually avoidable infectious diseases that reoccur in every production cycle, which, in turn, make the use of antibacterial agents indispensable.

Reducing antibiotic use in livestock farming

The first prerequisite for a targeted reduction of antibiotic use in livestock farming is continuous national monitoring of antibiotic administration per animal species and per animal in the individual animal populations to identify those animal populations in which the antibiotic consumption per animal is extremely high compared to other animal populations. Initial investigations into antibiotic use in livestock farming[1] suggest that, for various reasons, some farmers use much more antibacterial agents than others in comparable animal populations. Various dissertations[2–5] published by the Field Station for Epidemiology at the University of Veterinary Medicine Hanover provide a comparative evaluation of animal health in a wide range of animal populations. This also includes a quantitative evaluation of the use of antimicrobial agents based on the Animal Treatment Index (ATI) (Fig. 1).

$$\text{ATI} = \frac{\text{Number of animals treated} \times \text{Number of antimicrobial agents} \times \text{Number of treatment days}}{\text{Number of animals in the respective animal group}}$$

Fig. 1: Animal Treatment Index

The Animal Treatment Index in the 16th amendment of the Medicinal Products Act specifies the "frequency of treatment": *The ATI is a statistic indicating the number of days on*

which all animals within one population received an antibiotic and the number of different antimicrobial agents it contained.

It became evident that the amount of antibacterial agents used varies between populations, with the professionalism in the respective animal health management, i.e. health-oriented animal husbandry and the level of care provided by farmers, being a far greater determinant for the dependence of livestock farming on routine antibiotic use than all other factors. In a 2008 study evaluating 19 pig populations of comparable size and identical genetic origin, the ATI at animal population level (ATI of all animals in the respective populations within 24 months) ranged from 0 days to 54 (!) days; the populations with an ATI of more than 40 days were in significantly poorer health than those with a lower ATI.

Imposing a reduction of antibiotic use alone may potentially lead to a switch from older antimicrobial classes to highly potent antimicrobial classes (e.g. third- and fourth-generation fluoroquinolones and cephalosporins), which would be the exact opposite of what should be achieved. This must be counteracted through simultaneous monitoring of the applied antimicrobials much in the same way as a reduction in dosages or a shortening in approved treatment times must be counteracted through a simultaneous assessment of animal health.

Improving animal husbandry and care

The most important and readily implementable measures to reduce disease-related antibiotic requirements include in particular:

- Buying animals only from populations of origin with a defined health status, if possible; accommodating animals in properly cleaned and disinfected animal housing according to the all-in/all-out system
- Ensuring that animal groups are as free from pathogens as possible by complying with all known biosafety measures to prevent the introduction of pathogens not present in the respective population (showering before entering the stable, wearing population-specific protective clothing, disinfecting or changing shoes between stable units, restricting visits according to animal contacts prior to visiting a population), performing pest rodent control and keeping wild birds away from feed and livestock
- Continuous hygiene measures including production processes, consistent endo- and ectoparasite control, cleaning and disinfection of water pipes and feed conveyors to prevent biofilms
- Regular testing to identify pathogens BEFORE the condition manifests itself in order to be able to take preventive measures and limit the spread of infections in the animal population through early detection of diseases.

On livestock farms where these measures of modern animal health management are consistently applied, it will be possible to administer antibacterial agents according to the principle of using "as little as possible and only as much as necessary". In order to be able to move this process forward in a purposeful way, it is imperative to monitor the amount of antibacterial agents used, in addition to implementing a benchmarking system that compares herd health to record animal losses, frequency of infections and slaughterhouse findings and to assess animal health by using a herd health index for pig4 and poultry populations. This is done with the aim to provide specific advice for populations with significant animal health deficits and, if that advice is not followed, to subject these populations to official risk-based monitoring.

If the strategies for reducing antibiotic use were to be implemented without taking account of the employed spectrum of antimicrobials and without ensuring a simultaneous improvement in animal health, the resulting reduction in antibiotic use will be counterproductive. Increased veterinary use of modern antimicrobials relevant in human medicine and/or an increase in the prevalence and severity of bacterial infections are "excellent" recipes for a further increase in bacterial resistance.

➤ T. Blaha
Reviewer: J. Wallmann

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6 Antibiotic resistance in veterinary medicine – Non-food-producing animals

6.1 Dog/Cat

6.1.1 Respiratory tract infections /skin, ear and mouth infections

6.1.1.1 *Staphylococcus aureus/ Staphylococcus (pseud)intermedius*

Representatives of the two coagulase-positive *Staphylococcus* spp., *Staphylococcus aureus* and *Staphylococcus (pseud) intermedius*, play an important role in dogs and cats as both a natural inhabitant of the outer skin layer and a pathogen. Whereas *S. aureus* is involved in a multitude of purulent infectious processes, *S. (pseud)intermedius* is most commonly isolated in connection with surgical site infections, otitis externa and canine pyoderma. Both species are also understood to be responsible for post-surgical complications in the form of surgical site infections in veterinary practice. Representatives of both species also cause infections in humans, with a transfer of the respective strains having been observed from humans to dogs/cats and vice versa. Methicillin-resistant *S. aureus* (MRSA) and *S. (pseud)intermedius* (MRSP) strains are particularly significant in this respect due to their zoonotic potential.

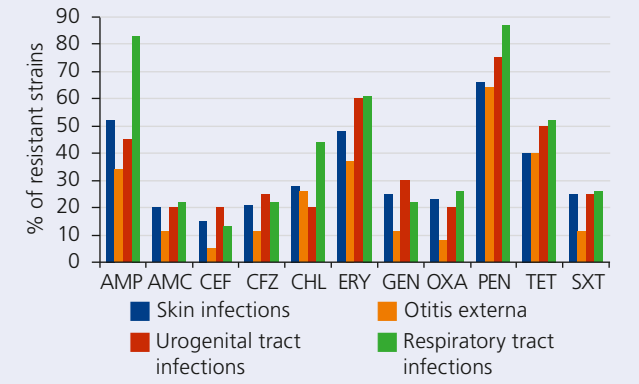

Fig. 6.1.1.1.1: Resistance rates of *S. (pseudo)intermedius* from dogs and cats, Germany 2009 (n=198)

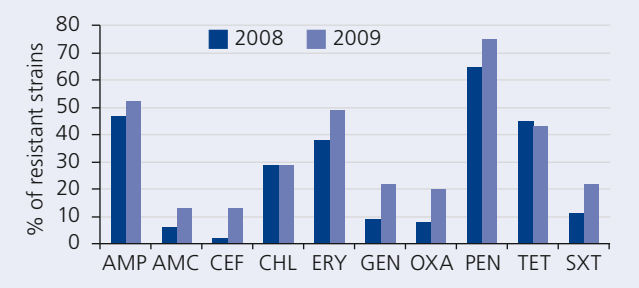

Fig. 6.1.1.1.2: Resistance rates of *S. (pseudo)intermedius* from dogs and cats, Germany 2008–2009 (2008 n=85; 2009 n=198)

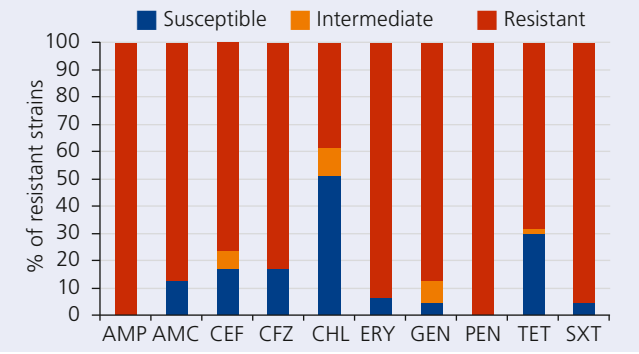

Fig. 6.1.1.1.3: Resistance rates of methicillin-resistant *S. (pseudo)intermedius* from dogs and cats, Germany 2010 (n=47)

Trends in resistance development

S. (pseud)intermedius data is available for the study years 2008–2010. The 2009 study tested 198 canine and feline *S. (pseud)intermedius* isolates with the indication of "skin infections" (n=117), " urogenital tract infections" (n=20), "respiratory tract infections" (n=23) and "otitis externa" (n=38). The highest resistance rates were found for ampicillin (34% to 83%), erythromycin (37% to 61%) and penicillin G (64% to 87%). High resistance rates ranging from 20% to 50% were also observed for the other tested antimicrobials (Fig. 6.1.1.1.1).

A comparison of the various indications showed that some of the isolates from infections of the urogenital and respiratory tract were associated with higher resistance rates than the indication of "otitis externa".

A comparison of the results of the 2009 and 2008 studies (85 tested isolates) showed a noticeable increase in resistance rates to the majority of the tested antimicrobials, especially to cephalothin, erythromycin, gentamicin, oxacillin and penicillin (Fig. 6.1.1.1.2).

In particular, the majority of oxacillin and methicillin-resistant *S. (pseud)intermedius* isolates (MRSI and MRSP) were multi-drug-resistant, for example to chloramphenicol, erythromycin, gentamicin, trimethoprim/sulphamethoxazole (co-trimoxazole) and tetracycline, as was the case with the isolates tested in the 2010 study year (Fig. 6.1.1.1.3). Among 497 *S. (pseud) intermedius* isolates, 47 were found to be MRSP.

More recent MIC results show very high MIC90 values for newer cephalosporins and enrofloxacin (Tab. 6.1.1.1.1), which is why these antimicrobial agents are expected to have a very limited efficacy against *S. (pseud)intermedius* isolates.

Tab. 6.1.1.1.1: Dog/Cat – MIC_{90} values of *S. pseudo(intermedius)* for antimicrobials for which no CLSI-approved breakpoints are available

Antibiotic	MIC_{90} (mg/l)	
	2008 n=85	2009 n=198
Cefoperazone	0.5	≥ 32
Cefotaxime	0.5	≥ 32
Cefquinome	0.5	16
Ceftiofur	0.25	≥ 64
Enrofloxacin	0.5	16
Doxycycline	0.5	1
Spiramycin	≥ 128	≥ 128

In the 2009 study year, 55 canine and feline *S. aureus* isolates with the indication of "skin infection" were tested; in the 2010 study year, 54 isolates were tested. High rates of resistance were found for ampicillin (47% and 65%, respectively) and penicillin (66% and 74%, respectively) (Fig. 6.1.1.1.5). The resistance rates to erythromycin and tetracycline were at 24% in 2009 and at 28% (erythromycin) and 20% (tetracycline) in 2010. A strong increase in resistance was also observed for amoxicillin/clavulanic acid (from 7% to 32%) and oxacillin (from 13% to 35%). The MIC90 values for newer cephalosporins as well as for clindamycin and enrofloxacin also suggest increasing limitations in the efficacy of these antimicrobial agents (Tab. 6.1.1.1.2).

A comparison of the data of *S. (pseud)intermedius* and *S. aureus* showed higher resistance rates for *S. (pseud)intermedius*.

Conclusion

Over the course of the study years, a strong increase in resistance and MIC_{90} values has been observed in various canine and feline *S. (pseud)intermedius* and *S. aureus* isolates, indicating a rather unfavourable resistance situation. Susceptibility testing prior to the start of treatment is therefore strongly recommended.

➤ U. Steinacker
Reviewer: J. Wallmann

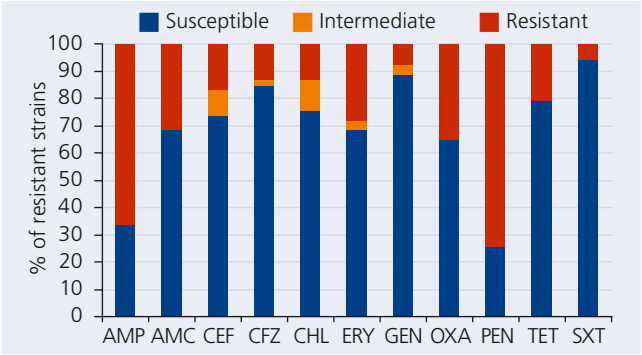

Fig. 6.1.1.1.4: Resistance rates of *S. aureus* from dogs and cats, indication of skin infection, Germany 2010 (n=54)

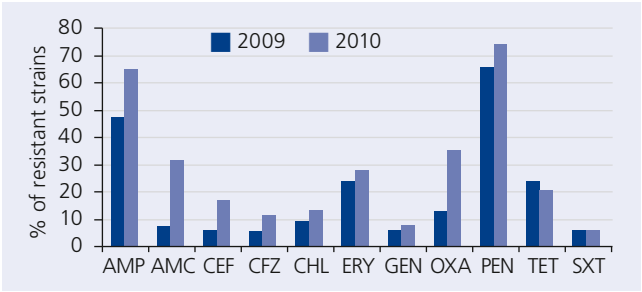

Fig. 6.1.1.1.5: Resistance rates of *S. aureus* from dogs and cats, indication of skin infection, Germany 2009–2010 (2009 n=55; 2010 n=54)

Tab. 6.1.1.1.2: Dog/Cat – MIC_{90} values of *S. aureus* for antimicrobials for which no CLSI-approved breakpoints are available

Antibiotic	MIC_{90} (mg/l)	
	2009 n=55	2010 n=54
Cefoperazone	16	≥ 64
Cefotaxime	16	≥ 64
Cefquinome	2	16
Ceftiofur	2	64
Clindamycin	≥ 128	≥ 128
Enrofloxacin	16	≥ 32

6.1.1.2 *Pasteurella multocida*

The pathogen *Pasteurella multocida* occurs primarily on mucous membranes of humans and animals. It is commonly found in the respiratory tract and in the area of the oropharynx, but may also occur in digestive and reproductive organs. *P. multocida* usually colonises the mucous membranes of the oropharynx of cats (50–70%) and dogs (40–66%). While the infection is usually latent in these species, animal bites may cause infections in humans. Such infections usually start as a localised inflammation at the inoculation site and, in some cases, lead to phlegmons, abscesses, necroses or osteomyelitis. Infections through direct physical contact or contact with airborne droplets are observed less commonly, but have led to acute or subacute forms of bronchitis or pneumonia in isolated cases. *P. multocida* has also been reported to have caused cases of conjunctivitis, stomatitis, enteritis, peritonitis or urinary tract infections.

Trends in resistance development

To date, there are few results available on the pathogen *P. multocida*, which was isolated from dogs or cats with respiratory tract infections (GERMAP 2010).

The latest evaluation includes the isolates from the 2010 GERM-Vet study. A total of 77 *P. multocida* isolates were tested for in-vitro susceptibility to 24 antimicrobial agents, with clinical CLSI breakpoints being available for seven of

them. The isolates were obtained from the respiratory tracts of dogs (n=11) or cats (n=66). All isolates were fully susceptible to cephalothin, chloramphenicol, enrofloxacin, gentamicin as well as amoxicillin/clavulanic acid and tetracycline. Seven isolates were classified as "intermediate" to gentamicin.

The MIC_{50} and MIC_{90} values measured for the remaining antimicrobial agents are listed in Tab. 6.1.1.2.1.

Tab. 6.1.1.2.1: Dog/Cat – $MIC_{50/90}$ values of *P. multocida* for antimicrobials for which no CLSI-approved breakpoints are available

Antimicrobial agent	MIC_{50} (mg/l)	MIC_{90} (mg/l)
Ampicillin	0.25	0.5
Penicillin G	0.25	0.25
Ceftiofur	≤ 0.03	≤ 0.03
Cefquinome	0.03	0.06
Cefoperazone	≤ 0.06	≤ 0.06
Cefotaxime	≤ 0.015	≤ 0.015
Tulathromycin	2	4
Spiramycin	64	128
Apramycin	16	32
Tilmicosin	8	16
Spectinomycin	32	64
Florfenicol	0.25	0.5
Nalidixic acid	1	2
Tiamulin	16	32
Colistin	4	4
Trimethoprim	0.25	0.5
Co-trimoxazole	0.06	0.12
Doxycycline	0.25	0.5

Conclusion

Canine and feline *P. multocida* isolates in Germany were susceptible to most of the tested antimicrobial agents. However, elevated MIC values were observed for macrolides. Over the past five years, there has also been an overall increase in MIC values by one titre step for the antimicrobial agents listed in Tab. 6.1.1.2.1.

➤ J. Wallmann
Reviewer: H. Kaspar

6.1.1.3 *Bordetella bronchiseptica*

Bordetella bronchiseptica s a gram-negative pathogen of the respiratory tract. Transmission occurs primarily through direct contact. Correspondingly, infections most commonly result from close contact with animals in places such as animal shelters or with dog and cat breeders. Diseased animals exhibit respiratory symptoms including sneezing, coughing, mucopurulent discharge from the eyes and nose as well as dyspnoea, with dogs and cats showing a similar range of symptoms. In dogs, *B. bronchiseptica* is a causative agent of kennel cough. Due to the poor clearance rate, dogs and cats are often asymptomatic carriers and shed *B. bronchiseptica* for a long period of time.

Trends in resistance development

Due to the small number of samples, the results of the studies in 2008 (n=10) and 2009 (n=16) as well as 2010 (n=13) and 2011 (n=17) were evaluated collectively.

None of the isolates were found to be resistant to amoxicillin/clavulanic acid, gentamicin and tetracycline. Notably, a high rate of cephalothin-intermediate isolates was observed; however, the CLSI document does not define a species-specific breakpoint for this antimicrobial agent (Fig. 6.1.1.3.1 and 6.1.1.3.2). The first isolates to also exhibit resistance to this antimicrobial agent were found during the study period 2010–2011 (Fig. 6.1.1.3.2).

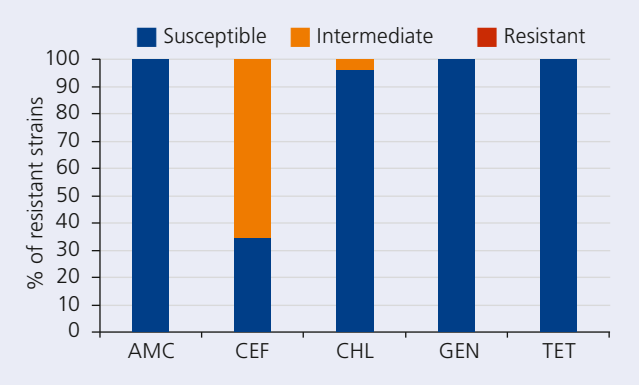

Fig. 6.1.1.3.1: Resistance rates of *B. bronchiseptica* from dogs and cats, Germany 2008–2009 (n=26)

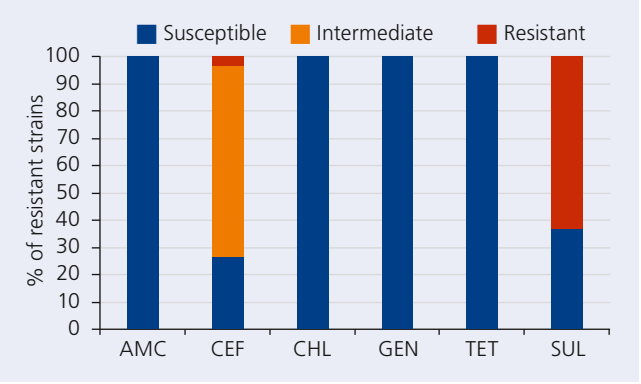

Fig. 6.1.1.3.2: Resistance rates of *B. bronchiseptica* from dogs and cats, Germany 2010–2011 (n=30)

Tab. 6.1.1.3.1: Dog/Cat – MIC_{90} values of *B. bronchiseptica* for antimicrobials for which no CLSI-approved breakpoints are available

Antibiotic	MIC_{90} (mg/l)	
	2008–2009	2010–2011
Ampicillin	32	32
Cefoperazone	8	8
Cefotaxime	≥ 32	≥ 32
Cefquinome	32	32
Ceftiofur	≥ 64	≥ 128
Doxycycline	0,5	1
Enrofloxacin	1	0,5
Florfenicol	4	4
Nalidixic acid	16	8
Penicillin G	≥ 32	≥ 32
Spectinomycin	≥ 256	not tested
Trimethoprim	16	not tested
Co-trimoxazole	4	8
Tulathromycin	16	16

The MIC_{90} values indicated that a great number of β-lactam antibacterial agents can be expected to have reduced efficacy (Tab. 6.1.1.3.1). High MIC_{90} values (8–16 mg/l) were observed for nalidixic acid, which is considered to be an indicator of an incipient fluoroquinolone resistance. The fluoroquinolone enrofloxacin is nonetheless expected to be effective (MIC_{90} 0.5–1 mg/l).

Conclusion

B. bronchiseptica solates showed reduced susceptibility to many β-lactam antibacterial agents. Compared to previous studies, the results for most of the tested antimicrobial agents were in the same range.

➤ U. Steinacker
Reviewer: K. Kadlec

6.1.1.4 *Pseudomonas aeruginosa*

Pseudomonads are gram-negative opportunistic pathogens that are found infrequently as part of the microbiota of the skin, mucous membranes, and gastrointestinal tract of healthy animals and humans and also occur in their environment. In dogs and cats, *Pseudomonas aeruginosa* and *Pseudomonas fluorescens* in particular cause purulent infections in various organ systems – usually as secondary pathogens. Common clinical manifestations include surgical site infections, dermatitis and otitis. *P. aeruginosa* can also play a role as a pathogen causing nosocomial infections in hospitals. It should be noted that this genus is resistant to a great number of antimicrobial agents and disinfectants, which is why only a very limited spectrum of antimicrobials is available for treatment. Many newer antipseudomonal antibacterial agents in human medicine are not available for veterinary medicine, or only in exceptional cases.

Trends in resistance development

Even though current resistance data is of great importance given the limited therapeutic options, the availability of such data is very low.

The 2009 GE*RM*-Vet study tested 46 *Pseudomonas* spp. isolates from the skin, ears and mouths of dogs and cats, 38 strains of these were obtained from dogs (*P. aeruginosa*: n=29, *P. fluorescens*: n=5, *Pseudomonas* spp.: n=4) and eight from cats (*P. aeruginosa*: n=4, *P. fluorescens*: n=2, *Pseudomonas* spp.: n=2). Among the canine isolates, 18 were from otitis, 13 from skin infections and seven from mucosal infections, whereas the feline strains were isolated mainly from mucosal infections (n=6) and one strain each from an otitis and an infection of the outer skin layer.

The isolates were tested for susceptibility to 22 antimicrobials agents and two therapeutic combinations. As expected, nearly all strains exhibited high MIC values for the tested penicillins, older cephalosporins and macrolides. Canine- and feline-specific CLSI breakpoints were available to interpret the measured enrofloxacin MIC values (enrofloxacin-susceptible: ≤ 0.5 mg/l, intermediate: 1–2 mg/l, resistant: ≥ 4 mg/l). At first, all tested *Pseudomonas* spp. isolates were classified regarding susceptibility to gentamicin based on the non-specific CLSI breakpoint; canine *P. aeruginosa* strains were subsequently classified on the basis of the veterinary-specific breakpoint. The susceptibility to further antimicrobial agents was determined based on non-specific CLSI breakpoints.

Using these breakpoints, resistance rates of 96%, 85%, 70% and 20% were recorded for amoxicillin/clavulanic acid, chloramphenicol, tetracycline and enrofloxacin, respectively (Fig. 6.1.1.4.1). It should also be noted that a large number of isolates showing intermediate susceptibility to enrofloxacin were identified (41%, Fig. 6.1.1.4.1). The overall rate of gentamicin resistance was 9% (intermediate 11%); among canine *P. aeruginosa* isolates 14% resistant strains (intermediate: 10%) were detected. The MIC_{50} and MIC_{90} values for the generally effective substances cefotaxime, spectinomycin, colistin and the combination of trimethoprim/sulphamethoxazole (co-trimoxazole) are listed in Tab. 6.1.1.4.1. The MIC values for all other tested antimicrobial agents suggest a high probability of therapeutic inefficacy.

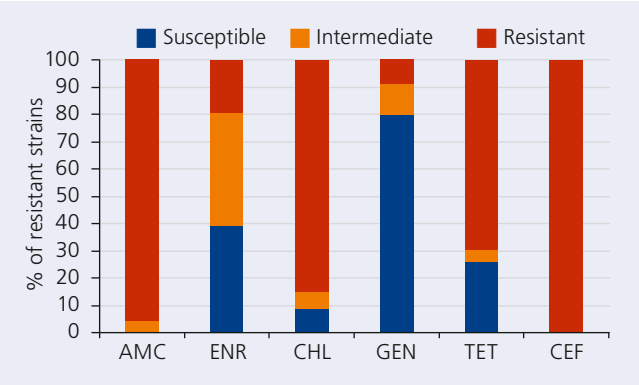

Fig. 6.1.1.4.1: Resistance rates of *Pseudomonas* spp. from otitis and skin/mucosal infections in dogs (n=38) and cats (n=8), Germany 2009

Tab. 6.1.1.4.1: Dog/Cat – $MIC_{50/90}$ values of *Pseudomonas* spp. isolates for antimicrobials for which no CLSI-approved breakpoints are available

Antibiotic	MIC_{50} (mg/l)	MIC_{90} (mg/l)
Cefotaxime	16	≥ 64
Colistin	1	2
Spectinomycin	≥ 512	≥ 512
Co-trimoxazole	8/152	32/608

Fazit

About 9% of the *Pseudomonas* spp. isolates from canine and feline otitis and dermatitis were gentamicin-resistant (14% in canine *P. aeruginosa*). About 20% of the tested pseudomonads showed resistance to enrofloxacin. Additionally, about 41% of the strains were intermediate resistant. These results suggest that the therapeutic options are substantially limited.

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Reviewers: C. Kehrenberg, A. Römer

6.1.2. Urogenital tract infections

6.1.2.1 *Pseudomonas* spp.

Pseudomonas spp. re gram-negative opportunistic pathogens that are found infrequently as part of the microbiota of the skin, mucous membranes, and gastrointestinal tract of healthy animals and humans and also occur in their environment. In dogs and cats, these pathogens may cause skin and surgical site infections as well as infections of the urogenital and respiratory tracts. Infection usually occurs in the presence of an underlying primary disease. *P. aeruginosa* can also act as a nosocomial pathogen, especially in hospitals with intensive care units, which is mainly due to its resistance to many antimicrobial agents and disinfectants. Few antimicrobial agents are available for treatment in veterinary medicine, since the use of newer antipseudomonal antibacterial agents is not permitted in human medicine, or only in exceptional cases.

Trends in resistance development

The 2009 GE*RM*-Vet study collected only 19 *Pseudomonas* spp. isolates from the urogenital tract (16 from dogs: *P. aeruginosa* [n=8], *P. fluorescens* [n=1], *Pseudomonas* spp. [n=7]; 3 from cats: *P. aeruginosa* [n=1], *Pseudomonas* spp. [n=2]), which suggests that the species has only minor significance as a causative agent of urinary tract infections (8 canine and feline isolates) or genital tract infections (11 canine isolates).

The CLSI breakpoints for *Pseudomonas* spp. isolates from skin, ear and mouth infections addressed in chapter 6.1.1.4 were used to determine the susceptibility of *Pseudomonas* spp. isolates from the urogenital tract to selected antibacterial agents. However, no CLSI-approved breakpoints for feline isolates from the urogenital tract are available for enrofloxacin. The tested antimicrobial agents included gentamicin, enrofloxacin, chloramphenicol and tetracycline.

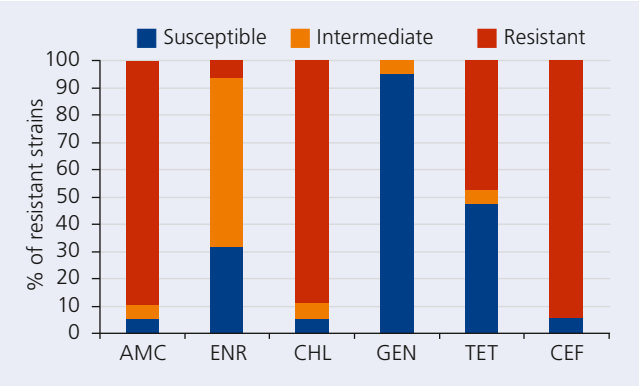

Fig. 6.1.2.1.1: Resistance rates of *Pseudomonas* spp. from urogenital tract infections in dogs (n=16) and cats (n=3); Germany 2009

Among the 19 tested isolates, 17 were resistant to amoxicillin/clavulanic acid and chloramphenicol while 9 isolates were resistant to tetracycline. One of the 16 tested canine isolates was resistant to enrofloxacin. In the absence of breakpoints for feline isolates, only the MIC values of canine isolates were

measured. As was the case with the isolates from otitis and dermatitis, a high percentage of the isolates showed intermediate susceptibility to enrofloxacin (n=10).

None of the tested isolates were gentamicin-resistant. One isolate with intermediate resistance to gentamicin was detected (Fig. 6.1.2.1.1).

In the absence of breakpoints for the generally effective antibacterial agents cefotaxime, spectinomycin, colistin and the combination of trimethoprim/sulphamethoxazole (co-trimoxazole), it was only possible to measure the MIC_{50} and MIC_{90} values (Tab. 6.1.2.1.1).

Tab 6.1.2.1.1 Dog/Cat – $MIC_{50/90}$ values of *Pseudomonas* spp. for antimicrobials for which no CLSI-approved breakpoints are available

Antimicrobial agent	MIC_{50} (mg/l)	MIC_{90} (mg/l)
Cefotaxime	16	≥ 64
Colistin	1	2
Spectinomycin	256	≥ 512
Co-trimoxazole	4/76	16/304

Conclusion

There is very little data available on the susceptibility of canine and feline *Pseudomonas* spp. isolates from urogenital tract infections. The percentage of canine strains resistant to enrofloxacin was 6.3%. Additionally, there was a high percentage of strains showing intermediate resistance to this antimicrobial agent. No gentamicin-resistant isolate and only a moderate percentage of strains with intermediate resistance (5.3%) were detected. The overall resistance situation is therefore only slightly more favourable than in isolates from the skin and the ears.

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Reviewer: C. Kehrenberg

6.1.2.2 *Escherichia coli*

Escherichia coli is the most commonly isolated bacterial pathogen causing infections in the canine and feline urogenital tract. This *Enterobacteriaceae* species is known for its rapid development and transfer of resistance, which explains the need for susceptibility testing and continuous monitoring.

Trends in resistance development

The 2009 and 2010 GE*RM*-Vet studies tested a total of 45 *E. coli* strains from dogs (n=32) and cats (n=13) with urogenital tract infections for their susceptibility to 22 antimicrobial agents and two therapeutic combinations. Clinical CLSI breakpoints were available for seven of the tested antimicrobial agents.

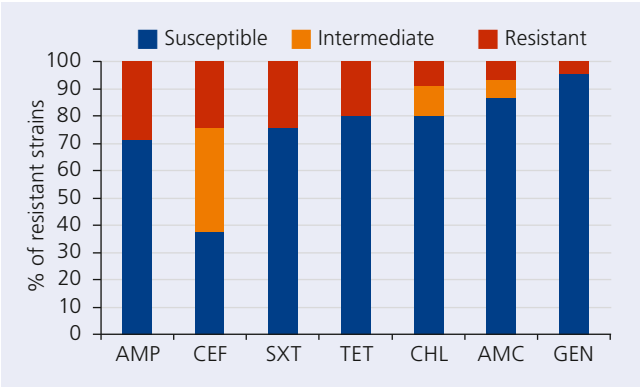

Fig. 6.1.2.2.1: Resistance rates of *E. coli* from the urogenital tract of dogs (n=32) and cats (n=13), Germany 2009 and 2010

Among the tested *E. coli* isolates, 29%, 25%, 24% and 20% were found to be resistant to ampicillin, the potentiated sulphonamides, cephalothin and tetracycline, respectively. It should also be noted that a large number of isolates showing intermediate susceptibility to cephalothin were identified (37.8%, Fig. 6.1.2.2.1). Less than 10% of the strains exhibited MIC values in the resistant range for chloramphenicol (8.9%), amoxicillin/clavulanic acid (6.7%) and gentamicin (4.5%). However, the percentage of intermediate isolates was 11.1% for chloramphenicol and 6.7% for amoxicillin/clavulanic acid (Fig. 6.1.2.2.1).

Only a canine-specific clinical CLSI breakpoint was available for enrofloxacin (susceptible: ≤ 0.5 mg/l, intermediate: 1–2 mg/l, resistant: ≥ 4 mg/l). A resistance rate of 15.6% was recorded for canine isolates. Two feline isolates deviated from the normally distributed population, exhibiting an MIC value of 16 or ≥ 16 mg/l.

The 2006/2007 GE*RM*-Vet study provides representative comparable data for *E. coli* from canine and feline urogenital tract infections; 63 isolates were tested during that period.

In the 2006/2007 study year, the rates of resistance to ampicillin (27%), cephalothin (22%), tetracycline (21%) and gentamicin (5%) were at a similar level. Slightly lower resistance rates were observed for chloramphenicol (5%) and amoxicillin/clavulanic acid (3%) during the 2006/2007 reference period.

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Reviewer: C. Kehrenberg

6.1.3 Enteritis

6.1.3.1 *Escherichia coli*

Escherichia coli s part of the physiological microbiota in the intestinal tract of mammals. Some specific pathovars such as enteropathogenic *E. coli* (EPEC), enterotoxic *E. coli* (ETEC) or Shiga toxin-producing *E. coli* (STEC) may, however, cause serious intestinal infections.

Trends in resistance development

The 2009 and 2010 GE*RM*-Vet studies tested a total of 52 *E. coli* strains from dogs (n=32) and cats (n=20) with intestinal tract infections for their susceptibility to 22 antimicrobial agents and two therapeutic combinations. Clinical CLSI breakpoints were available for seven of the tested antimicrobial agents.

The highest percentages of resistant isolates were observed for ampicillin (total 73%: canine 100%, feline 30%), tetracycline (13.5%), the combination of trimethoprim/sulphamethoxazole (co-trimoxazole, 11.5%) and cephalothin (8%) (Fig. 6.1.3.1.1). Additionally, 44.2% of the isolates were found to show intermediate susceptibility to cephalothin. A resistance rate of 6% was observed for the combination of amoxicillin/clavulanic acid; 4% and 2% of the isolates showed MIC values in the resistant range for chloramphenicol and gentamicin, respectively. 2 isolates (4%) were identified which deviated considerably from the normally distributed population, exhibiting an enrofloxacin MIC value of ≥ 16 mg/l.

The significant difference in resistance rates between canine and feline isolates at a similar MIC distribution is due to the fact that while specific CLSI breakpoints were available for the interpretation of canine MIC values (susceptible: ≤ 0.25 mg/l, intermediate: 0.5 mg/l, resistant: ≥ 1 mg/l), the susceptibility of the feline isolates was determined on the basis of non-specific CLSI breakpoints (susceptible: ≤ 8 mg/l, intermediate: 16 mg/l, resistant: ≥ 32 mg/l).

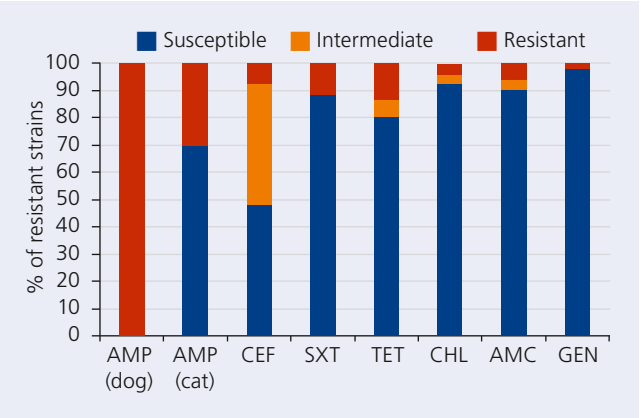

Fig. 6.1.3.1.1: Resistance rates of *E. coli* from the gastrointestinal tract of dogs (n=32) and cats (n=20), Germany 2009 and 2010

The 2006/2007 GE*RM*-Vet study provides representative comparable data for *E. coli* from canine and feline gastrointestinal tract infections. The 2006/2007 resistance rates to ampicillin (canine 100%), tetracycline (14%), trimethoprim/sulphamethoxazole (13%), cephalothin (8%), chloramphenicol (4%) and gentamicin (1% intermediate isolates, no resistant isolates) were at a comparable level. While the rate of resistance to amoxicillin/clavulanic acid (3%) was slightly lower during the 2006/2007 reference period, the percentage of ampicillin-resistant feline isolates was significantly lower (17%). However, in 2009/2010, only half as many feline isolates were tested.

➤ A. Lübke-Becker, L.H. Wieler
Reviewer: C. Kehrenberg

6.2 Horse

6.2.1 Respiratory tract infections/Skin, ear and mouth infections

6.2.1.1. *Pseudomonas* spp.

Pseudomonas spp. are gram-negative opportunistic pathogens in humans and animals. In addition to skin and surgical site infections, they may also cause urogenital and respiratory tract infections – usually as secondary pathogens. It should be noted that pseudomonas exhibit widespread non-susceptibility to a great number of antimicrobial agents.

Trends in resistance development

In 2011, 22 isolates from horses with various indications were tested and compared with the results of the previous years (2009 n=31, 2010 n= 50).

Throughout that period (Fig. 6.2.1.1.1 to 6.2.1.1.3), very high rates of resistance were recorded for amoxicillin/clavulanic acid (up to 97%), chloramphenicol (up to 97%) and cephalothin (up to 100%). The tetracycline resistance rate also increased significantly between 2009 and 2011 (from 22% in 2009 to 72% in 2011). Declining resistance rates were only observed for gentamicin. By contrast, the MIC_{90} values (Tab. 6.2.1.1.1) remained stable, except for cefotaxime (from 64 mg/l to 16 mg/l) and nalidixic acid (from 128 mg/l to 64 mg/l).

However, the number of isolates tested in 2011 was too small to infer a significant change in resistance rates.

Tab. 6.2.1.1.1: Horse – MIC_{90} values of *Pseudomonas* spp. for antimicrobials for which no CLSI-approved breakpoints are available

Antibiotic	MIC_{90} (mg/l)		
	2009	2010	2011
Ampicillin	≥ 64	≥ 64	≥ 64
Cefoperazone	32	32	8
Cefotaxime	≥ 32	32	16
Cefquinome	16	8	8
Ceftiofur	64	64	32
Colistin	8	2	4
Florfenicol	256	256	256
Doxycycline	32	32	32
Nalidixic acid	128	≥ 128	64
Enrofloxacin	2	8	2
Trimethoprim	≥ 128	2	-
Co-trimoxazole	≥ 32	≥ 32	16
Tulathromycin	≥ 64	≥ 64	≥ 64

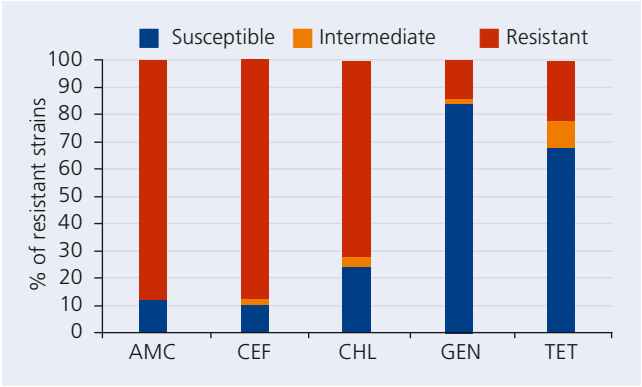

Fig. 6.2.1.1.1: Resistance rates of *Pseudomonas* spp. from horses (n=31), Germany 2009

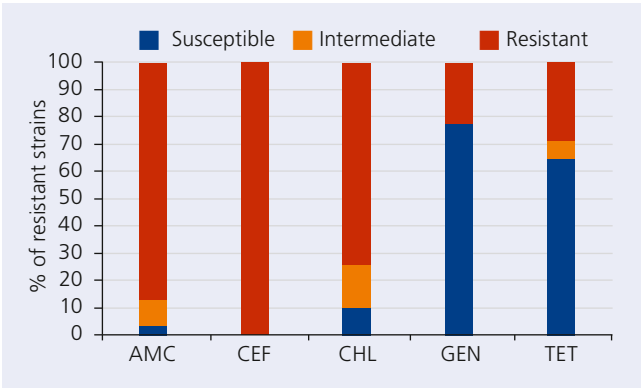

Fig. 6.2.1.1.2: Resistance rates of *Pseudomonas* spp. from horses (n=50), Germany 2010

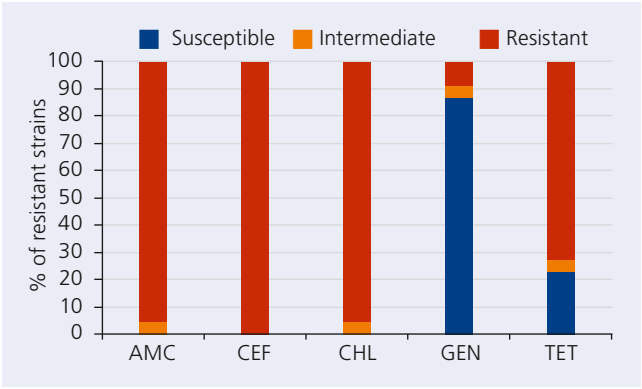

Fig. 6.2.1.1.3: Resistance rates of *Pseudomonas* spp. from horses (n=22), Germany 2011

Conclusion

As expected, the resistance data of equine *Pseudomonas* spp. isolates indicates resistance to the majority of the tested antimicrobial agents.

➤ K. Heidemanns
Reviewer: A. Römer

6.2.1.2 *Staphylococcus aureus*

Staphylococcus aureus is a facultative pathogen found worldwide. In humans and many animal species, it is an inhabitant of the upper respiratory tract and the skin. It is one of the most significant causes of hospital-associated surgical site infections at equine hospitals and can be transferred from humans to animals and vice versa.

Trends in resistance development

The 2011 GE*RM*-Vet study tested 36 isolates from horses with various indications (2009 n=36, 2010 n=38).

As in previous study years, the highest resistance rates were identified for ampicillin and penicillin.

Unlike in 2009 and 2010, the tested S. aureus isolates did not exhibit any resistance to erythromycin, whereas amoxicillin/clavulanic acid resistance increased considerably over the years. The noticeable increase in oxacillin resistance from less than 20% (2009) to 34.5% in 2011 may be associated with the growing number of MRSA infections in horses (Fig. 6.2.1.2.1–6.2.1.2.3).

Regarding MIC_{90} values, an increase in MIC values was observed for third- and fourth-generation cephalosporins. The increase of the enrofloxacin MIC_{90} value to 4 mg/l should be given further attention (Tab. 6.2.1.2.1).

Tab. 6.2.1.2.1: Horse – MIC_{90} values of *S. aureus* for antimicrobials for which no CLSI-approved breakpoints are available

Antibiotic	MIC_{90} (mg/l)		
	2009	2010	2011
Cefoperazone	8	16	32
Cefotaxime	8	8	16
Cefquinome	2	2	4
Ceftiofur	4	8	8
Clindamycin	0.25	0.25	0.12
Enrofloxacin	0.25	0.12	4
Pirlimycin	1	1	0.5
Quinupristin/Dalfopristin	0.5	0.5	0.5
Spiramycin	8	8	4
Tulathromycin	16	8	8
Tilmicosin	2	2	2
Tylosin	1	2	2

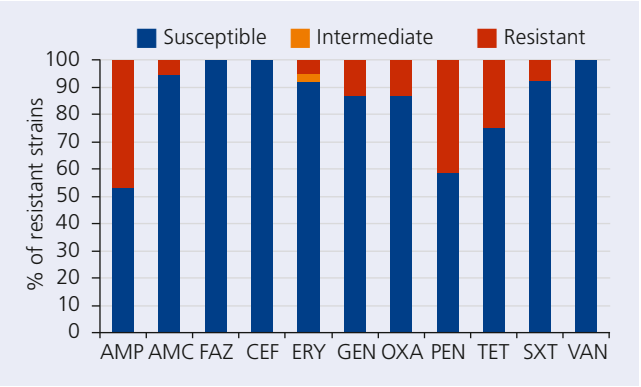

Fig. 6.2.1.2.1: Resistance rates of *S. aureus* from horses (n=36), Germany 2009

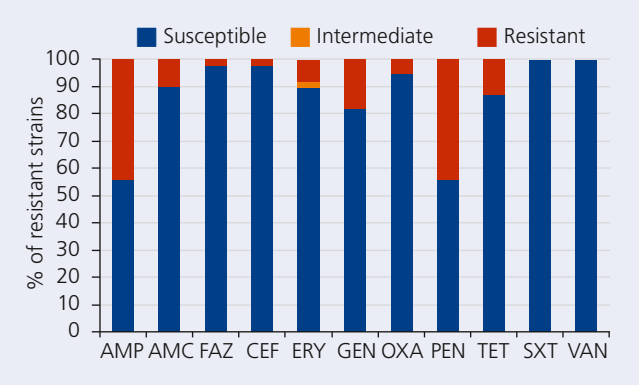

Fig. 6.2.1.2.2: Resistance rates of *S. aureus* from horses (n=38), Germany 2010

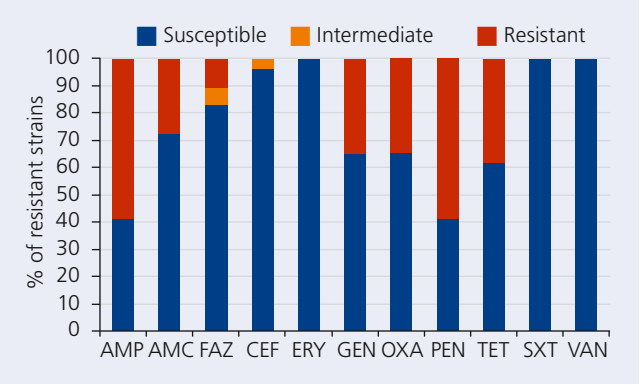

Fig. 6.2.1.2.3: Resistance rates of *S. aureus* from horses (n=36), Germany 2011

Conclusion

Equine *S. aureus* isolates have been included in the BVL's monitoring programme since 2009. Throughout the study period, a noticeable increase in resistance rates was recorded for penicillins, gentamicin and tetracycline. Macrolides, clindamycin and the combination of trimethoprim / sulphamethoxazole (co-trimoxazole) are expected to show good efficacy.

➤ K. Heidemanns
Reviewer: A. Römer

6.2.2 Urogenital tract infections

6.2.2.1 *Klebsiella* spp.

Klebsiella spp. are regularly isolated from cervical swabs in mares. Even asymptomatic genital tract infections can lead to reduced food intake and miscarriages.

Trends in resistance development

In the 2008 and 2009 study years, 14 and 16 *Klebsiella* spp. isolates, respectively, were isolated from the genital tract of mares and evaluated collectively due to the small number of isolates. As expected, a high resistance rate and a high MIC_{90} value (77% and $MIC_{90} \geq 32$mg/l, respectively) were recorded for ampicillin and penicillin G as a result of intrinsic resistance to these antimicrobials. No resistant isolates were detected for gentamicin and trimethoprim/sulphamethoxazole (co-trimoxazole), while one resistant isolate each was found for cephalothin, amoxicillin/clavulanic acid, chloramphenicol and tetracycline (Fig. 6.2.2.1.1).

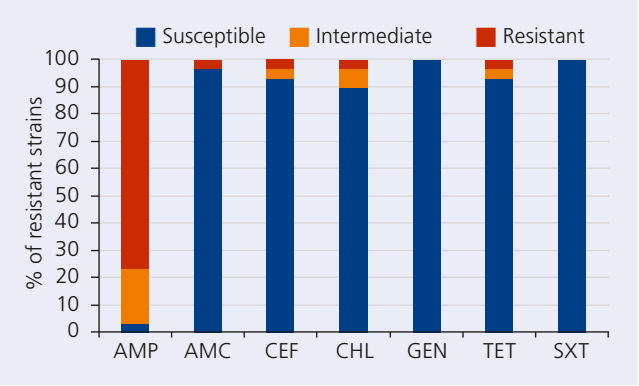

Fig. 6.2.2.1.1: Resistance rates of *Klebsiella* spp. from horses (n=30), Germany 2009

The enrofloxacin and cephalosporin MIC_{90} values were in the low range (Tab. 6.2.2.1.1).

Tab. 6.2.2.1.1: Horse – MIC_{90} values of *Klebsiella* spp. for antimicrobials for which no CLSI-approved break-points are available

Antibiotic	MIC_{90} (mg/l)
	2008/2009
Apramycin	4
Cefoperazone	0.5
Cefotaxime	0.06
Cefquinome	0.06
Ceftiofur	0.5
Colistin	0.5
Doxycycline	4
Enrofloxacin	0.12
Nalidixic acid	4
Penicillin G	≥ 32
Florfenicol	8
Trimethoprim	1

Conclusion

The resistance data collected on *Klebsiella* spp. from genital tract infections indicates good efficacy for nearly all of the tested antimicrobial agents.

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Reviewer: A. Römer

Interpretation of data on the susceptibility of bacteria to antimicrobial agents: Clinical breakpoints versus epidemiological cut-off values

Public discussion often makes no distinction between clinical resistance, which refers to the treatability of human or animal diseases, and microbiological resistance, which is used for preventive consumer protection. This section is designed to explain the different terms used for the interpretation of bacterial susceptibility in a comprehensible manner and to suggest a standard terminology – based on existing guidelines – to avoid confusion.

Resistance is defined as the gradually varying non-susceptibility of bacteria to antimicrobial agents. Depending on the method used, the result of the susceptibility test is expressed as inhibition zone diameter (IZD) in mm (agar diffusion test) or as minimum inhibitory concentration (MIC) in mg/l (broth micro- and macrodilution, agar dilution or E-test).[1–3]

The interpretation of these test results requires interpretation criteria that specify for each particular case whether the pathogen is susceptible or resistant to the antimicrobial agent. For interpretation of the IZD and MIC values, a general distinction is made between the terms "clinical breakpoint" and "epidemiological cut-off value" (ECOFF) defined by the European Committee on Antimicrobial Susceptibility Testing.[1,4–6]

Clinical breakpoints

Clinical breakpoints in human and veterinary medicine serve to interpret the results of the in-vitro susceptibility testing of microorganisms with regards to the potential therapeutic success when using the corresponding antimicrobial agents. When applying clinical breakpoints, infectious agents are classified as "susceptible", "intermediate" or "resistant". Depending on the antimicrobial agent and the pathogen, the "intermediate" category may be omitted.[4,7–9]

Susceptible

The "susceptible" classification implies that infections caused by this pathogen are most likely to be treated successfully using the corresponding antimicrobial agent in the approved dosage.[1]

Intermediate

The "intermediate" classification implies that infections caused by this pathogen can be treated successfully, provided that the antimicrobial agent is applied at the infection site in sufficient concentration or in a higher dosage.[1] At easily accessible infection sites (e.g. urinary tract), an infection may be eliminated by administering the regular dosage, whereas the same pathogen at difficult-to-access infection sites (e.g. lungs, meninx) may not be eliminated even when applying the maximum approved dosage. This category additionally represents a buffer zone to avoid that slight technical variations inherent in the test systems lead to substantial differences in the interpretation of the test results.

Resistant

The "resistant" classification means that the maximum approved dosage of the corresponding antimicrobial agent that can be reached at the infection site is not sufficient to efficiently inhibit the growth of the pathogen or to eradicate it.[1] Therapeutic success with this antimicrobial agent is thus rather unlikely. Pathogens classified as "clinically resistant" often exhibit special resistance mechanisms.

By using clinical breakpoints to interpret the antibiogram, the attending physician/veterinarian can predict which antimicrobials are suitable for the treatment of the respective disease and which are not. Clinical breakpoints thus constitute an important aid for selecting the best suitable antimicrobial agent on a case-by-case basis.[1,5,6]

Clinical breakpoints are specific to a combination of antimicrobial agent, infectious agent, type of infection and human or animal species. The development of clinical breakpoints is a laborious and complex process, in which it is necessary to take account of the dosage of the antimicrobial agent, the method and route of administration, pharmacokinetic and pharmacodynamic parameters, the achievable antimicrobial concentration at the infection site as well as the MIC values of the pathogen to be eradicated and the results of the clinical efficacy tests.[1–3,6]

In human medicine, the clinical breakpoints defined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are increasingly gaining significance (www.eucast.org). For this purpose, a National Antimicrobial Susceptibility Testing Committee (NAK) was established in June 2012 on the initiative of representatives of the German Society for Hygiene and Microbiology (DGHM), the Paul Ehrlich Society for Chemotherapy (PEG) and the Robert Koch Institute (RKI). One major goal of the NAK is the nationwide establishment of the clinical EUCAST breakpoints in all German laboratories engaged in human medicine. The use of standardised meth-

ods and breakpoints is an essential prerequisite for harmonising the interpretation of the results of in-vitro susceptibility tests. Statements that are based on different test methods and non-standardised breakpoints cannot be compared with each other.[1–4]

In veterinary medicine, the clinical breakpoints published by the U.S. Clinical and Laboratory Standards Institute (CLSI) are currently used both in monitoring studies of veterinary pathogens (e.g. GE*RM*-Vet, antimicrobial-specific studies) and as part of the marketing authorisation of veterinary antimicrobials, in the absence of European interpretation criteria.[9] At present, there is no statutory obligation to apply these breakpoints in monitoring the susceptibility of veterinary pathogens in Germany, which is to provide information on therapeutic options to veterinarians. In monitoring the resistance characteristics of zoonotic agents, human-specific breakpoints are to be used for interpretation.

Epidemiological cut-off values (ECOFFs)

ECOFF values make a distinction between a natural, susceptible "wild-type population" and a "non-wild-type population" on the basis of IZD or MIC values. The "wild-type population" comprises the population of microorganisms with the lowest MIC values and the highest IZD values, which are assumed to exhibit no acquired or mutational resistance mechanisms. The so-called "non-wild-type population" includes microorganisms with higher MIC values and lower IZD values. Bacteria in the "non-wild-type population" are assumed to exhibit acquired or mutational resistance mechanisms.[1,4] These bacterial strains are also referred to as "microbiologically resistant". The use of ECOFF values makes it possible to recognise shifts in MIC or IZD values within a bacterial population at an early point, thereby gaining important information suggesting potential resistance development. It should be noted that ECOFF values allow no statements on the potential therapeutic success.[2–4] This means that microorganisms in the "wild-type population" are not automatically susceptible to a particular antimicrobial agent; in turn, microorganisms in the "non-wild-type population" with resistance mechanisms are not automatically clinically resistant and non-treatable with the respective antimicrobial agent.

The Regulation 2003/99/EC on the monitoring of zoonoses and zoonotic agents requires EU member states to record comparable data on the prevalence of antibiotic resistance in zoonotic agents from animals and foods originating from them. From this it follows that this data has to be interpreted on an epidemiological basis using human-specific breakpoints. This data is transmitted by the member states to the European Food Safety Authority (EFSA) on an annual basis and is published in the EU Report on Antimicrobial Resistance. Antibiotic resistance monitoring under the Regulation 2003/99/EC is carried out in line with the EFSA recommendations[10,11] and the Commission's guidelines for monitoring antimicrobial resistance in *Salmonella* and *Campylobacter* developed on their basis (decisions 2007/407 and 2007/516).[12,13]

The zoonotic agents come from healthy animals and foods originating from them, which is why the recommendations for the interpretation of the results generally differ from the recommendations for antibiotic resistance monitoring in bacteria from diseased animals. The zoonosis monitoring is aimed at obtaining indications of resistance mechanisms for new antimicrobials at an early point and detecting bacterial isolates that do not belong to the "wild-type population" for established antimicrobials.

Comparison of clinical breakpoints and ECOFF values (clinical and microbiological resistance)

The interpretation criteria to be used – clinical breakpoints or ECOFF values – depend on the test objective.[2,3] The use of clinical breakpoints is recommended for tests aimed at helping to select the best possible treatment (e.g. when testing bacteria from acute infectious processes). The use of ECOFF values is helpful for testing microorganisms without a clinical context to recognise any changes in resistance development [e.g. bacteria found in the physiological flora (commensal organisms) or bacteria from foods and/or the environment] (Fig. 1).[1–6] If the significance of these bacteria for human health needs to be identified, the use of clinical breakpoints is again recommended.

New data and insights could result in the adaptation of breakpoints. Therefore, the currently applicable breakpoints should always be used.[1–3] In this connection, it should be noted that the method of MIC or IZD determination specified in a document and the clinical breakpoints or ECOFF values listed in the same document form one unit. Performing the susceptibility tests based on a particular method (e.g. CLSI) and evaluating the results based on interpretation criteria stipulated in another implementing regulation (e.g. EUCAST, BSAC) is not permissible.[1–3]

Clinical breakpoints and ECOFF values may be very similar or even identical, but there are also examples of great divergence between these two types of interpretation criteria.

The GERMAP reports have so far only comprised data on the spread of antibiotic resistance in diseased humans and animals that is interpreted on the basis of clinical breakpoints.

➤ H. Kaspar, M. Kresken, B. Pfefferkorn, S. Schwarz, J. Wallmann
Reviewers: B. Wiedemann, A. Römer

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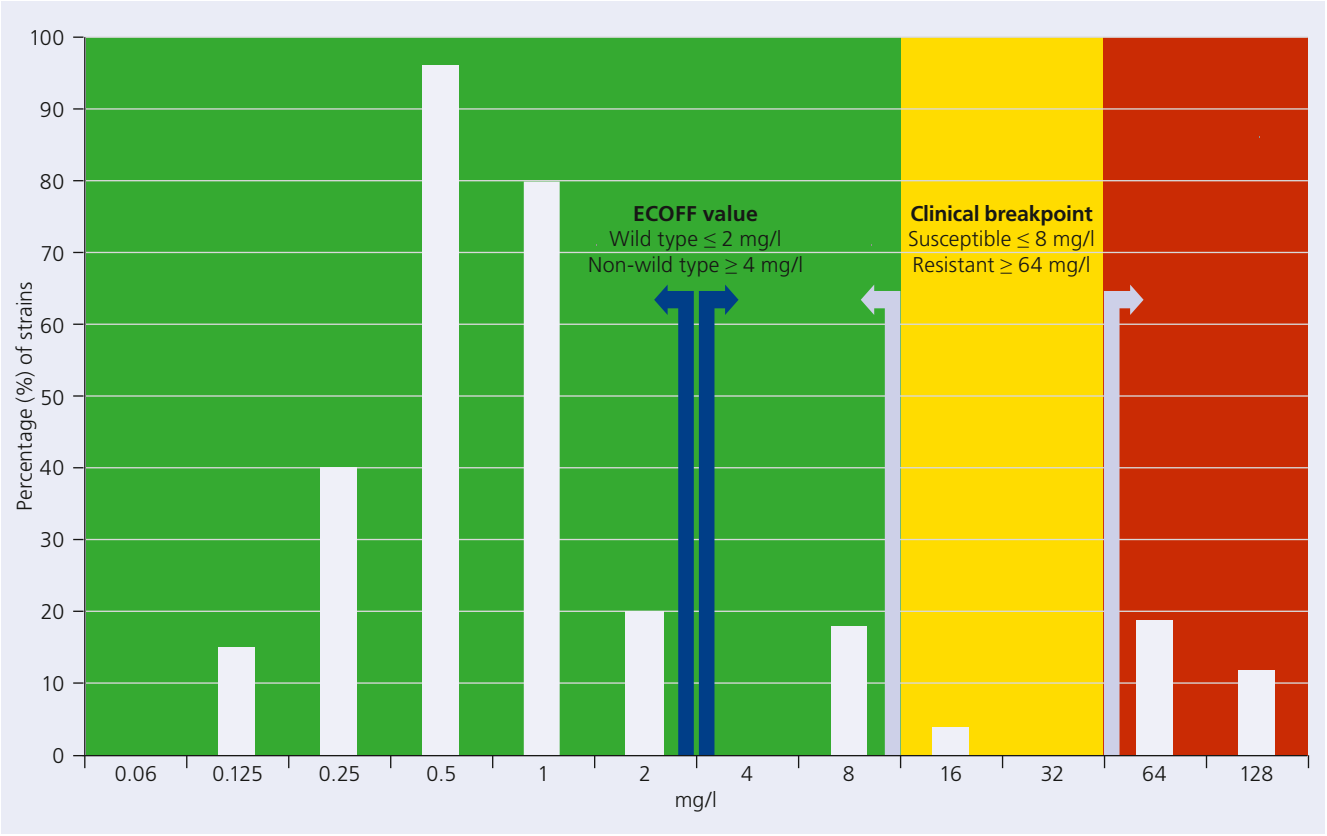

Fig. 1: Classification of bacterial strains based on the MIC values for an antimicrobial agent using epidemiological cut-off values (ECOFF values) and clinical breakpoints

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12. EFSA: The Communitiy Summary Report on antimicrobial resistance in zoonotic and indicator bacteria from animals and food in the European Union in 2008. ESFA Journal 2010;8:1658, (S. 13)
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7 Demographic data and data sources

7.1 Resistance surveillance studies in human medicine

The majority of available data is obtained from prospective, multicentre studies conducted in Germany during the period 1995–2011 (in some cases also in 2012). Furthermore, the resistance data reported by the National Reference Centres (NRZ) was included in the analysis. The respective NRZ and the most important resistance surveillance programmes and systems in Germany are presented below.

PEG studies

Resistance study
The Working Group "Susceptibility Testing and Resistance" in the Paul-Ehrlich-Gesellschaft für Chemotherapie e.V. (PEG) has been investigating the resistance situation of various bacterial species in Central Europe since 1975 as part of a longitudinal study. The surveys have been conducted at three-year intervals since 1995, most recently in 2010/2011. Mainly laboratories in Germany as well as a number of centres in Switzerland and Austria participate in the studies.

The study is characterised by a high quality standard, which is ensured by the fact that all isolates collected within one survey period are identified and tested for antimicrobial susceptibility on the basis of harmonised and standardised methods. The use of uniform methods and breakpoints is an essential prerequisite for the interpretation of the test results, since statements that are based on different test methods and non-uniform breakpoints are difficult to compare. Another improvement in data quality was achieved by testing all strains collected within the last study in a reference laboratory.

The results of the study can be seen on the website of the working group (http://www.p-e-g.org/econtext/resistenzdaten/), where they can also be viewed in an interactive database. These results allow for describing the respective extent of and temporal variations in the resistance situation. The data analysis is to show tendencies in resistance development, while also contributing to understanding the respective prevalent mechanisms that play a role in the spread of resistant bacteria.

The last study was conducted in four subprojects with the participation of more than 50 laboratories. A total of approx. 8,500 bacterial strains and more than 500 *Candida* isolates from outpatient and inpatient care were tested for antimicrobial susceptibility.

1. Project with isolates from hospitalised patients (subproject H),
2. Project with isolates from ambulatory care patients (outpatients) (subproject N),
3. Project with Candida isolates from blood and other sterile sites (subproject C),
4. Project with gonococci (subproject G)

The strains of the respective species that are isolated during the recruitment period are consecutively included in the study. This is intended to avoid overrepresentation of strains with unusual characteristics in the study. Of bacterial species that are found very frequently, such as *Escherichia coli*, however, only every other, every third, etc. isolate is included in the study.

As the method of susceptibility testing, the microdilution method according to the DIN EN ISO 20776-1 (formerly DIN 58940) standard is applied using industrially produced microtitre plates that contain the antimicrobials in vacuum-dried form. In order to be able to recognise methodological errors and determine the reproducibility of the MIC results, reference strains are also included in the susceptibility testing.

The results of the identification and susceptibility testing (MIC values) are documented in data sheets, along with information on the type and origin of the test specimens as well as on the age and sex of the patients, and are evaluated using the statistical analysis software SAS.

For classifying the bacterial isolates as "susceptible", "intermediate" or "resistant", the respective applicable species-specific clinical MIC breakpoints defined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) have been applied since 2010. Previously, the data was evaluated based on the breakpoints defined by the DIN Standards Committee Medicine applicable at that time. This change in breakpoints has the consequence that the resistance rates for the years up to 2007 (inclusively) stated in this report may deviate from the data provided in the 2008 and 2010 GERMAP reports.

*Project with isolates from hospitalised patients (**subproject H**)*

The protocol is consistent with that of previous resistance surveys, which is why the results can be compared with each other without any limitations. Approx. 60–65% of the tested bacterial strains were obtained from patients on general

wards, approx. 25% from patients in intensive care units and 10–15% from outpatients. The results of the 2007 and 2010 surveys show that the pathogens were cultured mainly from wound specimens (approx. 25%), respiratory tract specimens (20%), urinary tract specimens (15-18%) and blood cultures (11–12%). The majority of patients were male (56–58%). The average (median) age of the patients has increased in recent years, most recently amounting to 64 years.

*Project with isolates from ambulatory care patients (outpatients) (**subproject N**)*

The prevalence of resistance in various bacterial pathogens from outpatient care submitted to the microbiology laboratories was investigated for the first time in 2010. These included *Escherichia coli* (only urine isolates), *Haemophilus influenzae, Moraxella catarrhalis, Pseudomonas aeruginosa* (non-CF isolates) as well as *Staphylococcus aureus* and streptococci. The collected data is to provide a basis for recognising resistance trends in upcoming years.

Further information on the subprojects H and N as well as on all other subprojects can be found in the final reports, which are available for free download on the PEG website. The resistance study is funded using contributions from the pharmaceutical industry as well as the PEG's own resources.

➔ www.p-e-g.org/econtext/resistenzdaten/

Blood culture study
The working group has conducted four studies since 1983. The fourth PEG blood culture study in 2006/2007 included a total of 7,652 pathogens from 7,310 episodes of bloodstream infection. 13 laboratories from Germany and one laboratory from Austria participated in the study. All aetiologically relevant blood culture isolates were included as non-copy strains. Bacteria that are found in the resident skin flora (e.g. coagulase-negative staphylococci) and can be contaminants were only taken into account when detected several times. Each institute cultured and identified the bacteria using its own standard laboratory methods. The antimicrobial susceptibility was determined on the basis of the MIC results of 11 laboratories, which used industrially produced antimicrobial-containing microtitre plates in line with the specifications of the working group. The applied breakpoints are largely consistent with those used in the PEG resistance study. The results were published in the Chemotherapy Journal (Becker A, Rosenthal E, Studiengruppe. Antibiotikaempfindlichkeit von Sepsis-Erregern 2006–2007. Chemother J 2010;19:28-39).

GENARS
In 1999, the German Society for Hygiene and Microbiology (DGHM), the PEG and the Germany Society for Infectiology (DGI) established and funded a resistance epidemiology network entitled German Network for Antimicrobial Resistance Surveillance (GENARS). From 2002 to 2005, the project was funded by the Federal Ministry of Health (BMG) and was managed by the Robert Koch-Institute from July 2005 to the end of 2006. GENARS was a Germany-wide network of medical microbiology laboratories at university hospitals. GERNARS was concluded as a standalone project in 2006. The basic idea is carried forward in ARS (Antimicrobial Resistance Surveillance, see below) with a greater number of participating laboratories.

This project was aimed at continuously recording the resistance data of all isolates from the whole range of clinical specimens from laboratory routine, measuring antimicrobial resistance by means of MIC determination, reporting the (not interpreted) actually measured MIC values (to be able to recognise resistance developments at an early point) and evaluating the data as quickly as possible. Since isolates obtained from different test specimens are not always given the same clinical relevance in clinical microbiology laboratory routine, not every laboratory included all isolated bacteria in the susceptibility testing agreed for the GENARS project. The resistance data pooled in GENARS came from Frankfurt, Hanover, Jena, Leipzig, Kiel, Cologne and Ulm.

➔ www.genars.de

EARS-Net
EARS-Net (European Antimicrobial Resistance Surveillance Network), formerly EARSS, is a network funded by the European Union that pools and analyses the data reported by the national surveillance systems of the EU member states. EARS-Net collects data from laboratory routine on the resistance situation of blood culture isolates for seven "indicator" bacterial species to certain antimicrobials: *Streptococcus pneumoniae, S. aureus, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Klebsiella pneumoniae* and *P. aeruginosa*.

In 2011, 19 microbiology laboratories, which take care of 189 hospitals, participated in EARS-Net. Various methods of susceptibility testing are applied according to the DIN standard or the CLSI guidelines. Interlaboratory tests are performed by the United Kingdom National External Quality Assessment Service (UK NEQAS) for the purpose of quality assurance.

The national surveillance programme is coordinated by the RKI.

➔ www.ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/index.aspx

ARS
By initiating the ARS surveillance system, a continuous laboratory-based resistance surveillance project has been established at the Robert Koch-Institute, which builds on the organisational structures and methodological experience of the EARS-Net and GENARS surveillance systems, integrates them and places them on a broader basis. The primary goal of the resistance surveillance programme is to record and provide reference data on the resistance situation in both inpatient and outpatient care.

The surveillance programme covers all clinically relevant bacterial pathogens from the whole range of specimens. ARS is based on the results of the susceptibility tests performed by the participating laboratories as part of laboratory routine. At present, the network comprises 24 laboratories. ARS does not specify the clinical relevance of the isolates and which methods are to be used for pathogen identification and/

or susceptibility testing (ISO 20776-1 standard; DIN 58940 standards, guidelines of the U.S. Clinical Laboratory Standards Institute [CLSI]). Both qualitative (SIR interpretations) and quantitative (MIC values) susceptibility test results are accepted. Most laboratories now use the EUCAST breakpoints for the SIR interpretations. The standard evaluations are based on SIR interpretations; in this process, the interpretation results obtained on the basis of different standards are consolidated. As part of EARS-Net, the ARS laboratories participate in interlaboratory tests performed by the United Kingdom National External Quality Assessment Service (UK NEQAS) for the purpose of external quality assessment.

In 2012, 16 laboratories participated actively in ARS; they transmitted data of approx. 875,000 clinical specimens from 329 hospitals as well as of approx. 372,000 clinical specimens from 5,950 medical practices. The results of the susceptibility testing of the most common bacterial pathogens in outpatient and inpatient care are made available to the public via an interactive database.

From 2007 to mid-2010, ARS was funded externally by the Federal Ministry of Health; since then, it has been carried forward in accordance with the guidelines of the German Antimicrobial Resistance Strategy DART as an ongoing task of the RKI.

➔ https://ars.rki.de/

SARI

SARI (Surveillance of Antimicrobial Use and Bacterial Resistance in Intensive Care Units) was part of a research network investigating the spread of nosocomial infections and resistant pathogens, which was initially (2000–2006) funded by the Federal Ministry of Education and Research (BMBF) and is now carried forward at the Institute of Hygiene and Environmental Medicine of Charité – University Hospital Berlin. SARI focuses on intensive care units, i.e. high-risk areas, in terms of antimicrobial consumption and the resistance situation at hospitals. Both the resistance rates of the 13 most common pathogens to selected antimicrobials and the antimicrobial consumption are recorded on a monthly basis (excluding "copy strains"). As part of the semi-annual evaluation and feedback to the participants, not only resistance rates but also resistance densities (resistant pathogens/1,000 patient days as the unit of measuring the burden of resistance) are calculated.

At present, SARI comprises data of 100 intensive care units in Germany (60 wards take part in SARI and 40 wards in SARI-light). The susceptibility tests are performed based on either the DIN method (D centres) or the CLSI method (C centres).

➔ http://sari.eu-burden.info/

ResiNet (*Helicobacter pylori*)

ResiNet is a nationwide, multicentre, prospective surveillance study recording and analysing antimicrobial resistance development and the risk factors associated with Helicobacter pylori in Germany. The study was initiated in 2001 by the National Reference Centre (NRZ) for Helicobacter pylori and has since then been carried forward as one of the essential tasks of the NRZ funded by the Robert Koch-Insitute.

The study is aimed at identifying risk factors for the development of resistance in *H. pylor*i, identifying suitable intervention measures to control the resistance development and gaining a solid data basis to be able to give evidence-based recommendations for the diagnosis and treatment of *H. pylori* infections.

ResiNet is a prospective study collecting pseudonymised clinical (clinical manifestation) and anamnestic data (including sociodemographic data, previous diseases, previous antimicrobial treatments in connection with *H. pylori* or other infections) by means of a standardised questionnaire. In addition, the pathogen is cultured from gastric biopsy specimens of the study patients and the isolates are tested for susceptibility to antimicrobials that are suitable for treatment.

At present, 11 microbiology centres across Germany are involved in ResiNet. Each centre has two to three affiliated gastroenterologists, who recruit patients in previously scheduled study weeks to undergo spectroscopy and biopsy, provided that a medical indication is given. The microbiology centres perform a microbiological culture of the pathogen for subsequent susceptibility testing. For this purpose, all centres use harmonised, standardised methods, identical quality control strains and, within the respective study week, identical batches of culture media.

All data, including the results of the respective susceptibility test, is transmitted to the NRZ for *Helicobacter pylori*, where it is recorded in a central database and evaluated. The results are made available to all interested on the website of the NRZ. The study results are used as an essential basis for developing national guidelines for the clinical management of *H. pylori* infections.

➔ www.uniklinik-freiburg.de/mikrobiologie/live/NRZ.html

G-TEST

G-TEST (German Tigecycline Evaluation Surveillance Trial) is a resistance surveillance programme initiated by the German subsidiary of the company Wyeth (now Pfizer). As part of three Germany-wide studies in 2005, 2007 and 2009, a total of more than 6,000 bacterial isolates from selected aerobic gram-positive and gram-negative bacterial species, collected before as well as one year and three years after tigecycline was introduced to the market, were tested for susceptibility to this antimicrobial agent in comparison with other antimicrobials. Each study involved 15 medical microbiology laboratories located across Germany. Each laboratory was asked to include a maximum of 200 isolates from hospitalised patients with community-acquired or nosocomial infections in the study. The pathogens were identified using standard laboratory methods. The susceptibility tests were performed in a central laboratory. The MIC values were measured by means of microdilution in accordance with the DIN-ISO standard. The MIC values were interpreted primarily on the basis of the breakpoints defined by EUCAST (European Committee on Antimicrobial Susceptibility Testing).

National reference centres

In the course of restructuring the sector of infection epidemiology in Germany, National Reference Centres (NRZ) entrust-

ed with the surveillance of important infectious agents have been appointed by the Federal Ministry of Health since 1995. The centres are appointed for a three-year period in consultation with representatives of the Robert Koch-Institute (RKI), the Commission for Infection Epidemiology and medical-scientific associations. An up-to-date overview of the appointed NRZ can be found on the RKI website.

➔ www.rki.de

The present report was created using the resistance data reported by the following NRZ:

- National Reference Centre for Gram-Negative Hospital Pathogens
  ➔ http://memiserf.medmikro.ruhr-uni-bochum.de/nrz/
- National Reference Centre for *Helicobacter pylori*
  ➔ www.uniklinik-freiburg.de/mikrobiologie/live/NRZ.html
- National Reference Centre for Meningococci
  ➔ www.meningococcus.de
- National Reference Centre for Mycobacteria
  ➔ http://www.fz-borstel.de/cms/forschungszentrum/nationales-referenzzentrum-fuer-mykobakterien.html
- National Reference Centre for Salmonellae and Other Bacterial Enterics
  ➔ http://www.rki.de/DE/Content/Infekt/NRZ/Salmonellen/salmo_node.html
- National Reference Centre for Staphylococci
  ➔ http://www.rki.de/DE/Content/Infekt/NRZ/Staphylokokken/staphylo_node.html
- National Reference Centre for Streptococci
  ➔ www.streptococcus.de
- National Reference Centre for Systemic Mycoses
  ➔ www.nrz-myk.de
  (formerly: www.nrz-mykosen.de)
- National Reference Centre for the Surveillance of Nosocomial Infections
  ➔ www.nrz-hygiene.de

List of general tasks (not all tasks are assumed by every NRZ)

1. Development and improvement of testing methods, coordination in the standardisation and distribution of generally applicable test methods; initiation of quality assurance tests
2. Testing going beyond routine and detailed typing of pathogens including molecular tests for the identification of epidemiological correlations
3. Maintenance of a strain bank and submission of reference strains and/or test-specific reference drugs, except for strains of the ATCC (American Type Culture Collection) and the DSMZ (German Collection of Microorganisms and Cell Cultures)
4. Establishment and coordinating maintenance of a network of testing facilities
5. Provision of advisory services to the Public Health Service, laboratories, private physicians, hospitals and research institutes; further training and public relations
6. Collaboration with reference laboratories of other countries as well as the WHO collaborating centres, including participation in international interlaboratory tests
7. Evaluation and interpretation of data in consultation with the RKI with the aim to show a representative picture of the epidemiological situation in Germany; initiation of and participation in surveillance projects
8. Monitoring of incoming data with the aim to promptly detect outbreaks or outbreak risks as well as immediate reporting to the RKI; support of the Public Health Service and the RKI in supplementary tests as part of outbreak investigations
9. Epidemiological analysis and assessment of resistance and virulence development
10. Regular reporting and advice to the RKI regarding the corresponding factual issues; assistance in the development of RKI recommendations for testing, treatment and prevention and generally in applied infection epidemiology

➤ M. Kresken, E. Straube, E. Meyer
Reviewer: M. Mielke

7.2 Resistance surveillance studies in veterinary medicine

System of susceptibility testing

Since 2001, the Federal Office of Consumer Protection and Food Safety (BVL) has been testing bacterial pathogens isolated from food-producing animals with acute diseases for susceptibility to selected antimicrobials throughout Germany as part of the National Resistance Monitoring programme (GE*RM*-Vet). Since the 2006/2007 study year, isolates from diseased companion animals have been tested as well. As part of annual studies, data is collected that is suitable to recognise changes in the susceptibility of bacteria and the spread of resistance at an early stage. Since 2001 and 2006, comprehensive and evidence-based resistance data has been available in Germany for all important animal species and therapeutically relevant bacterial pathogens for at least 25 indications.

Test design

The decision of what bacterial species to identify for what clinical condition is based primarily on the role of the pathogen in the respective pathological process. The bacterial isolates are submitted by external institutions (veterinary investigation offices, animal health services of the Länder, academic institutions, private veterinary laboratories) in accordance with a detailed sampling plan. Bacterial strains from animals that received antibiotic treatment in the last four weeks before the sample collection are not taken into account in the study. In order to exclude the testing of "copy-strains", a maximum of two strains of the same bacterial species or genus from each animal herd are included in the study. This parameter is controlled using fixed herd numbers. The regional proportion of the number of bacterial strains to be tested per species/genus depends on the number of animals in the individual Länder. Epidemiological parameters, such as herd size, type of use, type of husbandry as well as the age and sex of the animals are recorded for each bacterial strain so that further important information is available for the assessment of potential influence factors on the development and further spread of resistance.

Sample size

The accuracy of estimating the incidence rate of a new resistance in a bacterial population depends on the prevalence of the characteristic in the bacterial population. If the average prevalence of a resistance in a population is estimated at 10% and the sample size is n=280 bacterial strains, the actual prevalence ranges between 7% and 13% in 95 of 100 cases. This sample size is sufficient to identify annual changes with sufficient certainty. This sample size is suitable to identify a "minor" effect with sufficient statistical power. If further influence factors need to be considered in view of the target statement, the sample size has to be increased accordingly. If only a one-time resistance situation is to be investigated, a smaller sample size can be selected. Since the sample size has a substantial influence on the reliability of the results, the calculations are carried out using a significance level of $\alpha = 0.05$ and a statistical power of $1-\beta = 0.80$.

Method of susceptibility testing

The susceptibility of the tested bacterial strains to the various antibacterial agents is determined using the broth microdilution method in accordance with the information provided in the M31-A3 approved standard document of the Clinical Laboratory and Standards Institute (CLSI, 2008).[1] Cation-adjusted Müller-Hinton broth is used to produce the inoculum. 2% lysed horse blood (Oxoid GmbH, Wesel) is supplemented for the susceptibility testing of *Streptococcus* spp., *Enterococcus* spp., *Pasteurella multocida* and *Mannheimia haemolytica*. The inoculum density of $2–8\times10^5$ CFU/ml is set in accordance with the CLSI standard and is checked on a regular basis by means of bacterial counts. As susceptibility testing systems, industrially produced microtitre plates (MCS Diagnostics, Sensititre, UK) are used that contain the antimicrobials in vacuum-dried form. The inoculated microtitre plates are incubated for 16–24 h at 34–38°C under aerobic conditions and are then read off visually. For the purpose of quality assurance, the reference strains specified in the CLSI document are included as well.

As part of the GE*RM*-Vet programme, a total of 22 individual antimicrobials and 2 therapeutic combinations are tested in 10 and 12 dilutions, respectively, per bacterial strain, taking account of the therapeutic aspects in human and veterinary medicine. For reasons of feasibility, all bacterial strains are always tested for susceptibility to 24 substances, which is why it occasionally occurs that the testing also includes antimicrobials that may not be relevant for the respective bacterial species or that the respective bacterial species exhibits intrinsic resistance to an antimicrobial agent within the clinically achievable antimicrobial concentration (e.g. inefficacy of penicillin G or erythromycin against *E. coli*). The withdrawal of the marketing authorisation for an antimicrobial agent (e.g. ban on the use of chloramphenicol in food-producing animals) is not taken into account either.

Breakpoints

The measured MIC values are classified into the categories "susceptible", "intermediate" or "resistant" using clinical breakpoints, as stated in the M31-A3 and M100-S18 documents. At the time of the evaluation, the CLSI document M31-A3 was the only internationally approved document containing veterinary-specific clinical breakpoints, but it should be noted that the majority of these breakpoints, in particular those for older antibacterial agents, had been adopted from human medicine. The veterinary-specific breakpoints listed in the CLSI document apply exclusively to the indicated combination of bacterial species/indication/animal species. Antimicrobials for which the CLSI document M31-A3 (CLSI, 2008[1]) and/or M100-S18 (CLSI, 2007[2]) define no fixed breakpoints are not classified into the categories "susceptible", "intermediate" or "resistant" (Tab. 7.2.1). Instead, the MIC_{50} and MIC_{90} values calculated on the basis of the MIC distribution

of the population are used to determine the susceptibility of the bacteria. These two values indicate at which MIC value at least 50% and 90% of the tested population are inhibited by the corresponding antimicrobial agent.[3]

For some antimicrobials, only canine-specific breakpoints are available. Unless stated otherwise, these breakpoints were also used for the evaluation of feline isolates.

Tab. 7.2.1: Antimicrobial agents/antimicrobial combinations, test ranges and breakpoints for antimicrobials tested in the veterinary part

Antibiotic class	Antimicrobial agent	Abbreviation	Test range (mg/l)	Breakpoint resistant from (mg/l)
Penicillins	Benzylpenicillin	PEN	0.015–32	≥ 0.25[a] ≥ 4[b] ≥ 16[c]
Aminopenicillins	Ampicillin	AMP	0.03–64	≥ 32[d] ≥ 0.5[a] ≥ 8[b] ≥ 16[c] ≥ 1[e]
β-lactam/β-lactamase inhibitors	Amoxicillin/Clavulanic acid (ratio 2:1)	AMC	0.03/0.015–64/32	≥ 8/4[a] ≥ 32/16[f]
Isoxazolyl penicillins	Oxacillin +2% NaCl	OXA	0.015–8	≥ 4[g] ≥ 0.5[a]
Cephalosporins	Cephalothin	CEF	0.06–128	≥ 32
	Cefazolin	CFZ	0.03–64	≥ 32
	Cefoperazone	CFP	0.06–32	
	Cefotaxime	CTX	0.015–32	
	Ceftiofur	XNL	0.03–64	≥ 8[h.i.j]
	Cefquinome	CQN	0.015–32	
Tetracyclines	Tetracycline	TET	0.12–256	≥ 8[b.h] ≥ 16[f] ≥ 2[i]
	Doxycycline	DOX	0.06–128	
Macrolides	Erythromycin	ERY	0.015–32	≥ 8[a.c] ≥ 1[b]
	Spiramycin	SPI	0.06–128	
	Tilmicosin	TIL	0.06–128	≥ 32[k]
	Tulathromycin	TUL	0.03–64	≥ 64[h]
	Tylosin tartrate	TYL	0.06–128	
Lincosamides	Pirlimycin	PIR	0.03–64	≥ 4[l]
	Clindamycin	CLI	0.03–64	≥ 4[a]
Aminoglycosides	Gentamicin	GEN	0.12–256	≥ 16[f] ≥ 8[l]
	Apramycin	APR	0.03–64	
	Spectinomycin	SPE	0.12–256	≥ 128[h]
Phenicols	Florfenicol	FFN	0.12–256	≥ 8[h.m]
	Choramphenicol	CHL	0.5–256	≥ 16[b] ≥ 32[f]
Pleuromutilins	Tiamulin	TIA	0.03–64	≥ 32[n]
(Fluoro)quinolones	Enrofloxacin	ENR	0.008–16	≥ 2[h.o]
	Nalidixic acid	NAL	0.06–128	≥ 4[a.d.r]
Glycopeptides	Vancomycin	VAN	0.015–32	≥ 32[a.c]
Diaminopyrimidines	Trimethoprim	TMT	0.06–128	≥ 16[a]
Streptogramins	Quinupristin/Dalfopristin	Q/D	0.015–32	≥ 4[p]
Polypeptides	Colistin	COL	0.03–16	
Sulphonamides	Sulphamethoxazole	SUL	0.5–1024	
Carbapenems	Imipenem	IPM	0.06–128	≥ 16[p]
Combinations of diaminopyrimidine/sulphonamide	Trimethoprim/ Sulphamethoxazole (co-trimoxazole) (1:19)	SXT	0.015/0.29–32/608	≥ 4/76[a.d]

[a] Applies to (other) *Staphylococcus* spp.; [b] Applies to *Streptococcus* spp.; [c] Applies to *Enterococcus* spp.; [d] Applies to *Enterobacteriaceae*; [e] Applies to *E. coli* (dog); [f] Applies to other bacteria; [g] Applies to *S. aureus* and *S. (pseudo)intermedius*; [h] Applies to *M. haemolytica* and *P. multocida* (cattle); [i] Applies to APP, *P. multocida* and *S. suis* (swine); [j] Applies to *S. aureus, S. uberis, S. agalactiae, S. dysgalactiae* and *E. coli* (mastitis); [k] Applies to *M. haemolytica* (cattle), APP and *P. multocida* (swine); [l] Applies to *Enterobacteriaceae* and *P. aeruginosa* (dog and horse); [m] Applies to APP, *P. multocida, B. bronchiseptica* and *S. suis* (swine); [n] Applies to APP (swine); [o] Applies to *P. multocida* and *E. coli* (dog and turkey); [p] human-medical breakpoint; [q] Applies to *S. aureus, S. uberis, S. agalactiae* and *S. dysgalactiae* (mastitis); [r] Applies to other organisms in dogs

➤ H. Kaspar
Reviewers: J. Wallmann, R. Hauck

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Veterinary Laboratory Ankum	Ankum
State Veterinary Investigation Office Arnsberg	Arnsberg
State Veterinary Investigation Office/Diagnostic Centre	Aulendorf
LABOKIN GmbH & Co KG	Bad Kissingen
Thuringia State Office of Food Safety and Consumer Protection (TLLV)	Bad Langensalza
University of Veterinary Medicine Hanover, Field Station for Epidemiology	Bakum
Berlin-Brandenburg State Laboratory	Berlin
Saxony State Investigation Bureau, Veterinary Diagnostics, Chemnitz	Chemnitz
Chemical and Veterinary Investigation Office East Westphalia-Lippe	Detmold
LVL Lebensmittel- und Veterinärlabor GmbH	Emstek
Bavarian Health and Food Safety Authority (LGL)	Erlangen
Chemical and Veterinary Investigation Office Stuttgart Fellbach	Fellbach
Brandenburg State Laboratory, Frankfurt/Oder	Frankfurt/Oder
State Office Laboratory Hesse (LHL)	Gießen
Veterinärlabor Heidemark Mästerkreis GmbH	Haldensleben
LAVES Veterinary Institute Hanover	Hannover
University of Veterinary Medicine Hanover, Institute of Food Quality and Safety	Hannover
Thuringia State Office of Food Safety and Consumer Protection (TLLV)	Jena
Landwirtschaftliche Untersuchungs- und Forschungsanstalt ITL GmbH	Kiel
Rhineland-Palatinate State Investigation Office, Institute for Diagnosis of Animal Diseases	Koblenz
Rhineland-Palatinate State Investigation Office, Institute for Foods of Animal Origin	Koblenz
Chemical and Veterinary Investigation Office Rhine-Ruhr-Wupper	Krefeld
State Investigation Bureau for Health and Veterinary Affairs	Leipzig
Vet Med Laboratory, Institute of Clinical Diagnostics	Ludwigsburg
Ludwig Maximilian University, Faculty of Veterinary Medicine, Institute of Infection Medicine and Zoonoses	München
Chemical and Veterinary Investigation Office Münsterland-Emscher-Lippe	Münster
Schleswig-Holstein State Laboratory, Food, Veterinary and Environmental Diagnostics	Neumünster
Bavarian Health and Food Safety Authority (LGL)	Oberschleißheim
Veterinary Institute Oldenburg, Lower Saxony State Office of Consumer Protection and Food Safety	Oldenburg
Tiergesundheitsdienst Bayern e.V.	Poing
Mecklenburg-Western Pomerania State Office for Agriculture, Food Safety and Fishery (LALLF)	Rostock
Saxony-Anhalt State Office of Consumer Protection, Department 4 Veterinary Diagnostics and Epidemiology	Stendal

7.3 Antimicrobial consumption data – Methodology and sources

Methodology of consumption data in human medicine

There is a whole range of sources of antimicrobial consumption data available in human medicine, which are, however, primarily suitable for market research purposes. These sources state sales figures (e.g. number of packages) and/or sales volume (in €). Only in exceptional cases is such data available and stated in amounts suitable for use in healthcare research. The corresponding institutes pursue predominantly commercial interests and offer the data to pharmaceutical manufacturers/distributors and market research institutions.

In order to guarantee comparability (between hospital departments, regions, countries, etc.), the amounts usually need to be converted into so-called daily doses and brought down to a common denominator (e.g. days of care or hospital cases). Daily doses are, in turn, expressed as defined daily doses, abbreviated as DDD. Furthermore, the drugs available on the market need to be classified. In this respect, the "Anatomical Therapeutic Chemical Classification" (ATC) of the World Health Organisation (WHO) is useful as a methodological basis, which specifies DDDs for nearly all substances (www.whocc.no/atcddd).

For the purpose of analysing the German outpatient pharmaceutical market, this classification was extended to cover not only certain substances or their combinations which would otherwise not be taken into account, but also the daily doses of pharmaceutical substances, specifically for children. DDDs specified in the ATC-WHO are primarily based on the doses commonly prescribed in the outpatient setting. Several studies have demonstrated that the use of DDDs in inpatient care results in the actual use density being overestimated by ~30%. In recent years, the official adaptation of the DDDs to the doses commonly prescribed in the inpatient sector has been hesitant and sporadic. For this reason, the inpatient use density is usually expressed as recommended daily doses (RDD) or even as actually prescribed daily doses (PDD).

The outpatient antimicrobial use density can be best expressed as DDD per 1,000 (insured or inhabitants or the like) and year or, preferably, day (DDD/1,000/day); in isolated cases, we also used prescription figures expressed as number of prescriptions per 100 or 1,000 insured and year. For the hospital sector, we usually used DDD per 100 days of care (DDD/100), in addition to stating RDD per 100 days of care (RDD/100) at some points. It should be considered that the denominator of "days of care" (unlike number of cases used as the denominator) strongly depends on the length of stay, i.e. shorter lengths of stay lead to an increase in use density, which is not the case when calculating the consumption in relation to the number of cases. There is hardly any data available on actual prescribing rates (number of antimicrobial prescriptions per patient and unit of time); this is mainly statistical data stating the amounts dispensed by pharmacies in both outpatient and inpatient care, which is then converted.

Sources in human medicine – Outpatient care

Outpatient prescribing data (relating to the prescription antimicrobials that are dealt with in this report) is recorded primarily in pharmacy data processing centres and is prepared and made available via ABDATA (or another service provider). ABDATA Pharma-Daten-Service is a division of Werbe- und Vertriebsgesellschaft Deutscher Apotheker mbH, engaged in the development and production of pharmaceutical data (www.abdata.de). The most important institutes using such primary data for market research purposes and commercially offering corresponding programmes include IMS Health (www.imshealth.de) and Insight Health (www.insight-health.de).

SHI Drug Index
The most important sources for non-commercial applications in outpatient care include the healthcare research projects of the health insurance funds, most notably the SHI Drug Index project. This project is conducted by the Research Institute of the AOK (WIdO, www.wido.de) on behalf of the National Associations of Statutory Health Insurance Funds (SHI) and the Central Research Institute of Ambulatory Health Care in Germany. It has been investigating the pharmaceutical market in the Federal Republic of Germany since 1980, the aim being to enhance transparency and economic efficiency. The data basis is the prescriptions under statutory health insurance within one calendar year that are filled in public pharmacies. Until 2001, one representative sample of prescriptions by panel physicians was taken for all of Germany; the data obtained this way is extrapolated using the dispensing statistics of statutory health insurance funds. Since 2001, all prescribing data has been available to the SHI Drug Index, allowing for in-depth analyses – for example at regional level from Regional Associations of Panel Physicians – to be conducted within the research project. On the initiative of the Department of Infectiology at the University Hospital Freiburg and the WIdO, an analysis of outpatient antimicrobial consumption in Germany, taking account of region-specific factors, was presented for the first time in 2003.

Rapid Prescription Feedback System of the SHI (GAmSi)
The analysis system (www.gamsi.de) developed by the WIdO allows the monthly evaluation of all drug prescriptions submitted by pharmacies to health insurance funds pursuant to Section 300 SGB V [Book V of the German Social Security Code]. All 17 Regional Associations of Panel Physicians receive a regional report from the National Associations of Statutory Health Insurance Funds on a monthly basis. The data is available for evaluation about eight weeks after the end of the month. This makes it possible to compare regions on the basis of key figures.

Drug Prescription Report
Issued annually by U. Schwabe and D. Paffrath, the "Drug Prescription Report" has been reporting the drug prescriptions by panel physicians since 1985. Numerous experts from pharmacology, medicine and economics comment on the prescribing behaviour of physicians. The primary goal of this publication is to improve market and cost transparency. Wherever possible, drugs are classified based on the criteria of evidence-based medicine. Every year, the Drug Prescription Report contains about 50 therapeutic and four market-related

chapters dealing with the 3,000 leading drugs available on the German pharmaceutical market that account for 96% of all prescriptions. The WIdO's SHI Drug Index project supports this standard work by providing both prescribing and classification data and their own contributions.

GEK Drug Report
This brochure, which has been issued by Gmünder ErsatzKasse (GEK) for several years, is processed by the Bremen Centre for Social Policy Research and contains analyses of the pharmaceutical consumption of GEK members (approx. 1.6 million).

Pharmaceutical Atlas
Created by the Institute for Health and Social Research (IGES) and funded by the Association of Research-Based Pharmaceutical Companies, the Pharmaceutical Atlas has been issued since 2006. It analyses changes in sales of pharmaceuticals prescribed to insured covered by SHI.

ESAC/ESAC-Net
ESAC stands for "European Surveillance of Antimicrobial Consumption". This project was launched in 2001 using EU funding; after the third EU funding phase 2007–2010, it is now financed by the ECDC (*European Centre for Disease Prevention and Control*, Stockholm) and is domiciled there under the name ESAC-Net. ESAC-Net collects national data on antimicrobial use and analyses it at European level. Antimicrobial consumption data of the participating countries can be viewed in an interactive database based on the ATC classification. Access to the corresponding database is available on request. The data sources are generally heterogeneous; over-the-counter antimicrobials are not included in the analyses in countries where such antimicrobials are available. Comprehensive or representative hospital consumption data is available from few countries and is listed accordingly.

Sources in human medicine – Inpatient care

The availability of non-commercial data on antimicrobial use density at German hospitals is very limited. Regarding use density per days of care, an older study conducted by Janknegt et al. is available, comparing hospitals of various sizes in the Netherlands, Belgium and North Rhine-Westphalia. Based on the ATC-WHO definition of daily doses at that time, a use density of 38 DDD/100 was ascertained for German hospitals, which is higher than in the Netherlands, but lower than in Belgium (34 and > 50 DDD/100, respectively). Concerning the prescribing of antimicrobial treatments (incl. antifungal and antiviral agents), a survey conducted in 1994 at four Southwestern German university hospitals revealed a daily prevalence of 33% in internal medicine, 28% in surgery and 40% in paediatric medicine. The NIDEP study with a representative sample of hospitals conducted in 1997 showed that 17% of all registered hospital patients received an antimicrobial therapy. In a national reference study on nosocomial infections (NI) and antimicrobial use conducted in 2011 by the NRZ for the Surveillance of Nosocomial Infections as part of the European prevalence studies initiated by the ECDC, the prevalence of antimicrobial use was 25.5% at all 132 participating hospitals.

More recent data for the entire German hospital sector is collected by the MABUSE network ("Medical Antimicrobial Use Surveillance and Evaluation") and the ADKA-if-RKI project in accordance with Sections 4 and 23 of the Infection Protection Act. Separate consumption data for intensive care units is collected within the SARI project ("*Surveillance of Antimicrobial Use and Resistance in Intensive Care*").

MABUSE network /ADKA-if-RKI project
The network was established on the initiative of Infectiology Freiburg and is based on previous studies conducted at Baden-Württemberg university hospitals and, later on, at non-university hospitals in Southwestern Germany. Further studies at university hospitals (INTERUNI-II) as well as pilot studies in collaboration with IMS Health (and its affiliate GPI Krankenhausforschung) followed (some of them supported by the BMBF 2002–2008), using 2003 and 2004 data. These analyses included 145 hospitals with 688 evaluable wards (2003) and 184 hospitals with 843 evaluable wards (2004). The distribution of the participating hospitals in the 2004 study, the results of which are published here in comparison with the ADKA-if-RKI project, is shown in greater detail in Tab. 7.3.1. Overall, data is thus available for a population of 19,319,623 days of care (equivalent to 2,748,162 cases). This is equivalent to a "sample" in the magnitude of approx. 10% of all days of care at (non-paediatric and non-psychiatric) acute-care hospitals. The evaluation only included hospitals that were able to provide comprehensive pharmacy dispensing and administrative data for at least 10 months in 2004.

Since 2007, the MABUSE network has been collaborating with the Association of German Hospital Pharmacists (ADKA) within a project for the prospective collection of hospital consumption data (quarterly data) (www.if-freiburg.de bzw. www.adka.de). In 2010, the so-called ADKA-if project entered into collaboration with the Robert Koch Institute (ADKA-if-RKI project; www.antiinfektiva-surveillance.de). For the first time in 2011, it was possible to analyse 75 hospitals with 705 evaluable wards, which provided comprehensive pharmacy dispensing and administrative data for antimicrobials over the whole year. 66 hospitals with 551 evaluable wards reported data on antifungals. Continuous national hospital antimicrobial surveillance at about 150 to 250 hospitals is planned to be established as part of the German Antimicrobial Resistance Strategy (DART).

The amendment of the Infection Protection Act to the effect of collecting antimicrobial consumption data was to support the establishment. The participating departments and/or wards within the ADKA-if-RKI projects differ considerably from the 2004 hospital cohort in terms of type, speciality and number of installed beds (see Tab. 7.3.2 and 7.3.3). The present report contains an evaluation of hospitals that were able to provide comprehensive quarterly data on consumption (antimicrobials, antifungals) and days of care for 2011.

SARI
Originally funded by the BMBF (2000–2006), SARI (www.antibiotika-sari.de) continuously (aggregated monthly data) collects resistance and antimicrobial consumption data in intensive care units of selected hospitals, the aim being to improve antimicrobial use and thereby prevent and control

Tabelle 7.3.1: Details of hospitals that participated in the 2004 study (MABUSE Network in cooperation with IMS Health)

Region	Hospitals (n)				Departments/Wards (n)			
	Total	Bed capacity			Total	Type/Speciality		
						General ward		Intensive care unit
		< 400	400–800	> 800		Non-surgical	Surgical	
East	31	12	7	7+5 [a]	166	59	60	47
West	72	43	14	10+5 [a]	328	113	130	85
South	81	54	17	7+3 [a]	349	113	150	86
Total	**184**	**109**	**38**	**24+13 [a]**	**843**	**285 [b]**	**340 [c]**	**218 [d]**

[a] Figures for university hospitals are shown separately; all 13 university hospitals had a bed capacity of > 800
[b] Incl. 47 haematology/oncology departments/wards and 179 general internal medicine departments/wards
[c] Incl. 180 general surgical departments/wards
[d] Incl. 160 surgical/interdisciplinary intensive care units and 58 non-surgical (conservative) intensive care units

nosocomial infections. The project was started in February 2000 with 12 intensive care units and now covers more than 40 wards which are distributed over more than 20 German hospitals and provide data over at least 6 months, including 15 intensive care units of various specialities at university hospitals. This project is planned to be merged with the ADKA-if-RKI project in the medium term (see above).

Methodology and sources of sales data in veterinary medicine

Society for Consumer Research (GfK)

In 2005, the "veterinary panel" of the Society for Consumer Research (GfK) in Nuremberg was available to estimate the sales of veterinary antimicrobials. The veterinary panel was based on a random testing of the purchasing behaviour of practicing veterinarians. The random test attempted to record the amount of veterinary pharmaceuticals purchased as precisely as possible and extrapolated these amounts to the population of practicing veterinarians. The individual antimicrobials were merged into antimicrobial classes, so that individual products could not be identified. Antimicrobials that entered Germany via imported shrimp or aquaculture fish as well as sales via public pharmacies were not taken into account. Based on the above-described method, veterinary antimicrobial sales of approx. 785 t were reported for 2005. The detailed data was published in GERMAP 2008.

Veterinary Drug Index (TAR) – DIMDI-AMV

2011 marked the first time that pharmaceutical companies and wholesalers were required to report the annual sales of veterinary antimicrobials to the DIMDI under the Medicinal Products Act (AMG)[30] and the DIMDI Regulation on Medicinal Products (DIMDI-AMV)[31], so that comprehensive data is now available. The data is evaluated by the Federal Office of Consumer Protection and Food Safety (BVL), itemised by region and, if possible, published in the following year.

The 2011[32] and 2012[33] data provided in this report only constitutes a starting point for the development and interpretation of veterinary antimicrobial sales in Germany in the next few years. Trends in development can only be identified in the following years.

European Surveillance of Veterinary Antimicrobial Consumption (ESVAC)

For the first time, the European Surveillance of Veterinary

Tab. 7.3.2: Details of hospitals that participated in the 2011 ADKA-if-RKI project (MABUSE Network in cooperation with ADKA and RKI) and provided data on antibiotic use

Bed capacity	Departments/Wards (n)				
	Total	Type/Speciality			
		General ward		Intensive care unit	
		Non-surgical	Surgical	Non-surgical	Surgical
< 400	213	64	107	5	37
400–800	293	98	138	24	33
> 800	199	59	93	16	31
Total	**705**	**221**	**338**	**45**	**101**

Tab. 7.3.3: Details of hospitals that participated in the 2011 ADKA-if-RKI project (MABUSE Network in cooperation with ADKA and RKI) and provided data on antifungal consumption

Bed capacity	Departments/Wards (n)				
	Total	Type/Speciality			
		General ward		Intensive care unit	
		Non-surgical	Surgical	Non-surgical	Surgical
< 400	141	46	61	4	30
400–800	252	86	112	22	32
> 800	158	49	71	14	24
Total	**551**	**181**	**244**	**40**	**86**

Antimicrobial Consumption project (ESVAC) has published data for nearly all 25 member states of the European Union (EU) for 2011.[34]

The comparability of data between the individual member states is to be ensured by relating the antimicrobial sales data to the animal population (Eurostat data)[35]. For this purpose, a correction factor [Population Correction Factor (PCU)] has been introduced, which is calculated by multiplying the number of animals reported and slaughtered in the respective country by the estimated weight of the animals at the time of treatment. It is nevertheless difficult to compare the data, since France, Ireland and the Netherlands have not implemented a statutory obligation to report antimicrobial sales data.

Since most veterinary antimicrobials are approved for use in several animal species, the data allows no conclusion as to the possible use of antimicrobials in individual animal species.

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7.4 Basic key figures of inpatient hospital care in Germany with particular reference to nosocomial infections (2010)

In 2010, about 18 million patients on approx. 142 million days of care were treated in Germany at 2,064 hospitals, in addition to medical treatments as part of outpatient medical care and at other care facilities. Medical care and treatment at all these facilities is associated with a risk of infections which depends on the type of care and cannot be ruled out completely.

According to the 12th coordinated population projection by the Federal and State Statistical Offices (variant "lower limit of the average population")[1], about one-third (37%) of Germany's population will be 60 years of age or older by 2030. For inpatient hospital care, this means that the number of hospital cases is expected to increase due to ageing and the associated risk of diseases alone. According to available calculations, the number of hospital cases – with the total population decreasing – could increase from currently approx. 18 million cases to 19.3 million cases by 2030. This would account for an increase of about 7%. If the nosocomial infection rate were to remain constant, the absolute number of nosocomial infections would thus be expected to increase as well.

Some treatment-associated infections can be avoided by taking appropriate preventive measures. Such measures are developed by the Committee for Hospital Hygiene and Infection Prevention at the Robert Koch Institute (RKI) in collaboration with other experts and are published by the RKI along with additional useful information (www.rki.de > Prevention of Infection > Hospital Hygiene). The documentation of decreasing or low infection and resistance rates helps objectivise the achievement of prevention goals (Federal Health Gazette 11/12 Volume 55 2012).

This section is designed to present important basic key data of inpatient hospital care to allow extrapolations (comprehensible estimates) regarding the extent of the problem of nosocomial infections in Germany.

The internationally proven and generally approved measures of prevention and control of nosocomial infections also include an established surveillance system. With this goal in mind, the recording and evaluation of nosocomial infections and pathogens with special resistance mechanisms, including feedback to the respective organisational units in Germany, has been embedded in the Infection Protection Act (Section 23 IfSG), and a National Reference Centre (NRZ) for the Surveillance of Nosocomial Infections has been established (see web links at the end of this section), from where the Hospital Infection Surveillance System (KISS) based on voluntary participation is managed and coordinated. The voluntary and anonymous participation serves to ensure high data quality. Furthermore, a representative point prevalence survey on nosocomial infections and antimicrobial use was conducted in 2011. The final report can be seen on the website of the NRZ for the Surveillance of Nosocomial Infections ("German National Point Prevalence Study on Nosocomial Infections and Antimicrobial Use", 2011; final report). When reading this report, it should be considered that data from prevalence surveys cannot be related directly to data from incidence surveys.

Multidrug resistant pathogens that spread at hospitals and may also be transmitted between hospitals and other care facilities as a result of patient transfers are of special significance. The antimicrobial treatment options for infections with these pathogens are considerably limited. In Germany, this problem currently concerns in particular methicillin (oxacillin)-resistant *Staphylococcus aureus* strains (MRSA) as well as – subject to regional variations – vancomycin-resistant enterococci (VRE), in addition to *Escherichia coli* and *Klebsiella* strains producing extended-spectrum β-lactamases (ESBLs). Not only gram-negative bacteria that are capable of producing carbapenemase, but also multidrug resistant strains of *Pseudomonas* spp. and *Acinetobacter* spp. as well as the increasing rate of infections with toxin-producing *Clostridium difficile* require special attention.

Due to the close association of the selection pressure caused by antimicrobial use and the prevalence of resistant pathogens, the systematic recording and evaluation of isolates with certain resistance and multidrug resistance mechanisms in accordance with Section 23 IfSG also represents a tried and tested method to recognise corresponding high-risk areas and clusters as well as outbreaks with these pathogens.

In order to estimate the extent of the problem, more specific data is often requested, e.g. on the number of hospitals and other care facilities, the number of patients treated and the procedures performed on them as well as the nosocomial infections observed. On the following pages, we therefore compiled useful tables of basic key figures on inpatient hospital care as well as information on the KISS surveillance system of the NRZ for the Surveillance of Nosocomial Infections (further tables can be seen at www.rki.de). The algorithm stated allows extrapolations on the basis of the current figures.[2]

Due to the reporting obligation for MRSA detected in blood cultures or cerebrospinal fluid introduced in mid-2009 (Section 7 Clause 1 Sentence 1 IfSG), reliable figures are now also available for this parameter which indicates severe forms of infection with pathogens which are difficult to treat.

General notes

A calculation, as suggested in Tab. 7.4.1, can only be made in respect of catheter-associated urinary tract infections. The data from ITS-KISS can be regarded as representative. The data from peripheral wards (DEVICE-KISS) on ventilator-associated pneumonia and catheter-associated bloodstream infections is not representative of all peripheral wards to the same extent. The prevalence of such infections per 1,000 patient days on these wards can hardly be transferred (extrapolated) to wards with a lower incidence of ventilations or catheter applications. The algorithm provided in Tab. 7.4.1 is therefore not suitable to calculate the total number of ventilator-associated pneumonia and catheter-associated bloodstream infections.

Overall, it should be considered that the KISS reference data usually covers a 5-year period, unless stated otherwise (i.e. in this case 2006 - 2010).

Tab. 7.4.1: Algorithm for extrapolation/estimation of nosocomial infections (NI) based on the data provided by the Hospital Infection Surveillance System (KISS) and the Federal Statistical Office

		Data source	Calculation formula	Example
1	**Patient days in inpatient facilities per year in total (A)**	Federal Statistical Office (subject-matter series 12, series 6.1.1, tables 1.1 and 2.2.3)	Available directly in the data source	**For 2010** A: 141.941.665
1.1	**Patient days in intensive care units per year (A_1)**		Available directly in the data source	**For 2010** A_1: 7.413.503
1.2	**Patient days on peripheral wards per year (A_2)**	Lines 1 and 1.1 of this table	$A–A_1$	**For 2010** A_2: 134.528.162 (141.941.665–7.413.503)
2	**Incidence of device-associated nosocomial infections (B)** (device-associated NI rate per patient day)	Reference data of ITS-KISS and DEVICE-KISS on all wards	Number of device-associated infections/number of patient days	**For urinary tract infections and lower respiratory tract infections based on the 2006–2010 reference data** **For primary bloodstream infections based on the 2008–2010 reference data**
2.1	**Incidence of nosocomial infections in intensive care units (B_1)**			**For urinary tract infections** B_1: 0,001549 (10.014/ 6.464.496) **For lower respiratory tract infections** B_1: 0,002489 (16.092/ 6.464.496) **For primary bloodstream infections** B_1: 0,000847 (3.570/ 4.217.565)
2.2	**Incidence of nosocomial infections on peripheral wards (B_2)**			**For urinary tract infections** B_2: 0,000815 (1.873/ 2.299.358)
3	**Number of catheter-associated urinary tract infections per year in Germany** (hospital-wide)	Lines 1.1, 1.2, 2.1 and 2.2 of this table	$(A_1xB_1) + (A_2xB_2)$	**For urinary tract infections** 121.124 (7.413.503 x 0,001549 + 134.528.162x0, 000815)

Surgical site infections

The number of surgical site infections can also be extrapolated for 2010: The surgical site infection rate for 2010, calculated on the basis of the OP-KISS (surgical site infection surveillance) 2006 2010 reference data, amounted to 1.6420 surgical site infections/100 surgeries. This surgical site infection rate relates to 14,937,120 surgical procedures performed in Germany in 2010. This yields an estimated (extrapolated) number of 245,268 surgical site infections in Germany in 2010. However, it should be considered that the range of surgeries covered by OP-KISS is not identical to the range of surgeries performed in total.

MRSA prevalence

Extrapolations in respect of MRSA prevalence can be made as follows: hospital patients (number of cases) in Germany in 2010: 18,032,903, patient days in Germany in 2010: 141,941,665.

Given an average MRSA prevalence of 0.982% (MRSA cases/100 patients) at hospitals in 2010 (Source: MRSA-KISS; 40,955 MRSA cases in 4,171,014 patients), the extrapolation yields 177,083 hospital patients (cases) carrying MRSA (readmissions are counted again).

The MRSA incidence density of nosocomial cases in 2010 amounted to 0.21 MRSA/1,000 patient days (Source: MRSA-KISS; 6,608 nosocomial MRSA cases on 31,011,609 patient days). When extrapolating this figure, this yields 29,808 MRSA cases in 2010 that were first acquired in the course of the respective stay and were classified as "hospital-acquired", as defined in MRSA-KISS. At this point, it should be mentioned that still more than 95% of MRSA detected in Germany in hospital patients on admission or in the further course of the hospital stay are HA-MRSA (report of the NRZ for Staphylococci for 2008).

According to MRSA-KISS, the percentage of infections in the MRSA cases in 2007 was 26.4% (recorded for the last time, see next paragraph); among the MRSA cases first detected in the course of the hospital stay, the percentage of patients with an MRSA infection was 39%. The higher percentage of MRSA detected in connection with infections in the nosocomial MRSA cases is most likely attributable to the fact that swab tests are generally not performed in the course of an inpatient stay unless an infection is suspected.

Detection of MRSA in blood cultures and cerebrospinal fluid

According to the regulation to adapt the reporting obligation pursuant to Section 7 IfSG to the epidemiological situation, MRSA in blood cultures and cerebrospinal fluid detected in laboratory testing have been subject to reporting since 01/07/2009 in order to monitor the prevalence of invasive

MRSA infections. In 2010, a total of 3,977 cases (98.8% blood cultures) were reported, equivalent to a nationwide annual incidence of 4.9 cases/100,000 inhabitants. The regional, state-specific incidence of MRSA cases ranges between 1.1 and 8.3 cases/100,000 inhabitants and year, with significant differences being observed within the individual Länder when breaking the incidence down to administrative district level. The reasons for the regional differences are manifold (e.g. density and type of hospitals in a particular region, frequency of blood culture sampling) and cannot be explained by the collected surveillance data alone. Apart from infants aged below one year, the incidence increases with age, with men being affected much more often than women. The average age is 71 years; more than two-thirds (73.6%) of the patients are aged > 65 years. Within the age group of < 15 years, infants aged < 1 year exhibit the highest incidence rates (1.5/100,000 inhabitants/year).

At the time of diagnosis, 88.7% of the patients were in inpatient care and 11.3% received outpatient medical care. The transmitted data allows no conclusion as to whether the infection was acquired at the hospital, at another care facility or in outpatient care. However, it can be assumed that a large number of outpatients with that diagnosis have previously come into contact with a care facility (e.g. previous inpatient hospital stay, treatment at a dialysis facility).

For the first time, the data provided as part of the MRSA reporting obligation allows an estimation of the population-specific burden posed by severe invasive MRSA infections. As an indicator for the overall burden posed by all MRSA infections at hospitals, the presence of MRSA in blood helps anticipate the future development and trends in prevalence and distribution.

Ratio of MRSA detected in blood cultures to other MRSA infections in intensive care units

Since 2009, the MRE-KISS submodule (MDRO surveillance) within ITS-KISS has no longer made a distinction between infections and colonisations, which is why the most recent data on this comes from the 2004-2008 reference data:

A total of 4,472 MRSA infections were indicated, 844 of which were found in patients with an MRSA-positive blood culture (462 times as part of primary bloodstream infections, 382 times as part of secondary bloodstream infections). This yields a ratio of 3,628 to 844 or 4.3 to 1 or, expressed in other terms, there is a ratio of one positive MRSA blood culture to an average of four other MRSA infections in intensive care units.

In summary, based on the above-stated extrapolations for 18 million inpatient hospital stays, this results in:

- approx. 121,000 catheter-associated urinary tract infections
- approx. 245,000 surgical site infections.

Based on the above extrapolations, the MRSA prevalence at German hospitals in 2010 amounted to approx. 177,000 cases (colonisation and infection; readmissions are counted again). The ratio of MRSA detected in blood cultures to other MRSA infections was approx. 1:4.

Extensive further information, in particular additional statistics on the basic key figures in this connection, can be found at:

- **www.rki.de**
  > Prevention of Infection > Hospital Hygiene (there: …)
- **www.destatis.de**
- **www.nrz-hygiene.de**
  > Surveillance
- **https://ars.rki.de/**

➤ C. Geffers, U. Bölt, B. Schweickert, M. Mielke

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Basic key figures of inpatient hospital care in Germany

Tab. 7.4.2: Inpatient care between 1991 and 2010
Selected key figures of hospitals differentiated by year and country

Year/Country	Hospitals			Patient movement[1]				
	Total	Total number of installed beds		Number of cases		Billing/ Occupancy days	Average length of stay	Average occupancy rate
	Number		per 100,000 inhabitants[2]	Number	per 100,000 inhabitants[2]	in 1,000	in days	in percent
1991	2,411	665,565	832	14,576,613	18,224	204,204	14.0	84.1
1992	2,381	646,995	803	14,974,845	18,581	198,769	13.3	83.9
1993	2,354	628,658	774	15,191,174	18,713	190,741	12.6	83.1
1994	2,337	618,176	759	15,497,702	19,034	186,049	12.0	82.5
1995	2,325	609,123	746	15,931,168	19,509	182,627	11.5	82.1
1996	2,269	593,743	725	16,165,019	19,739	175,247	10.8	80.6
1997	2,258	580,425	707	16,429,031	20,023	171,837	10.5	81.1
1998	2,263	571,629	697	16,847,477	20,538	171,802	10.2	82.3
1999	2,252	565,268	689	17,092,707	20,823	169,696	9.9	82.2
2000	2,242	559,651	681	17,262,929	21,004	167,789	9.7	81.9
2001	2,240	552,680	671	17,325,083	21,041	163,536	9.4	81.1
2002	2,221	547,284	664	17,432,272	21,135	159,937	9.2	80.1
2003	2,197	541,901	657	17,295,910	20,960	153,518	8.9	77.6
2004	2,166	531,333	644	16,801,649	20,365	146,746	8.7	75.5
2005	2,139	523,824	635	16,539,398	20,056	143,244	8.7	74.9
2006	2,104	510,767	620	16,832,883	20,437	142,251	8.5	76.3
2007	2,087	506,954	616	17,178,573	20,883	142,893	8.3	77.2
2008	2,083	503,360	613	17,519,579	21,334	142,535	8.1	77.4
2009	2,084	503,341	615	17,817,180	21,762	142,414	8.0	77.5
2010	**2,064**	**502,749**	**615**	**18,032,903**	**22,057**	**141,942**	**7.9**	**77.4**
Of which (2010):								
Baden-Württemberg	289	58,045	540	2,022,271	18,815	16,040	7.9	75.7
Bavaria	373	75,789	605	2,762,631	22,061	21,285	7.7	76.9
Berlin	79	19,782	574	755,185	21,909	5,897	7.8	81.7
Brandenburg	52	15,244	608	538,880	21,490	4,480	8.3	80.5
Bremen	14	5,224	791	202,161	30,610	1,482	7.3	77.7
Hamburg	47	11,897	668	448,176	25,178	3,605	8.0	83.0
Hesse	181	35,844	591	1,271,478	20,967	10,016	7.9	76.6
Mecklenburg-Western Pomerania	39	10,454	635	407,018	24,723	3,034	7.5	79.5
Lower Saxony	198	41,978	530	1,591,130	20,076	12,433	7.8	81.1
North Rhine-Westphalia	404	121,780	682	4,194,541	23,494	33,517	8.0	75.4
Rhineland-Palatinate	98	25,451	635	878,578	21,924	6,745	7.7	72.6
Saarland	24	6,548	642	259,106	25,403	2,050	7.9	85.8
Saxony	80	26,383	635	978,892	23,555	7,730	7.9	80.3
Saxony-Anhalt	50	16,527	705	594,250	25,343	4,599	7.7	76.2
Schleswig-Holstein	94	15,743	556	569,348	20,103	4,532	8.0	78.9
Thuringia	42	16,060	716	559,260	24,950	4,496	8.0	76.7
Change compared to the previous year (in %):								
Germany	**-1.0**	**-0.1**	**0.0**	**1.2**	**1.4**	**-0.3**	**-1.5**	**-0.2**
Baden-Württemberg	–	-0.7	-0.7	1.1	1.1	-0.4	-1.5	0.3
Bavaria	-1.1	-0.1	-0.3	1.0	0.8	-0.2	-1.2	-0.1
Berlin	–	0.6	0.2	2.6	2.2	1.1	-1.5	0.5
Brandenburg	–	-0.2	0.2	0.3	0.7	-0.1	-0.4	0.1
Bremen	–	-0.5	-0.4	2.7	2.8	-0.7	-3.3	-0.2
Hamburg	-4.1	0.8	0.7	5.1	5.0	3.1	-1.8	2.3
Hesse	-0.5	0.9	0.9	1.6	1.5	-0.4	-1.9	-1.3
Mecklenburg-Western Pomerania	–	-0.4	0.2	1.5	2.1	-0.8	-2.3	-0.4
Lower Saxony	–	0.8	0.9	1.4	1.6	-0.1	-1.5	-0.9
North Rhine-Westphalia	-2.2	-0.4	-0.2	1.2	1.4	-0.6	-1.7	-0.1
Rhineland-Palatinate	–	-0.5	-0.2	0.2	0.5	-0.9	-1.0	-0.3
Saarland	-4.0	-2.1	-1.5	1.0	1.6	-0.9	-1.9	1.2
Saxony	-2.4	-0.4	0.1	1.0	1.5	-0.3	-1.2	0.2
Saxony-Anhalt	–	0.2	1.2	0.4	1.3	-0.5	-0.9	-0.7
Schleswig-Holstein	-1.1	0.5	0.5	0.9	0.9	-1.6	-2.4	-2.1
Thuringia	–	-0.1	0.6	0.2	0.9	-1.3	-1.5	-1.2

1) Number of cases and billing/occupancy days including hour cases, 2) Calculated for the general population
Source: Basic Data of Hospitals, © Federal Statistical Office (Destatis), Wiesbaden, 2011

Tab. 7.4.3: Number of installed beds, occupancy rate, billing/occupancy days by specialist department (including intensive care beds)

Specialist department	Total number of specialist depart-ments[1]	Number of installed beds		Occupancy rate[2]		Billing/Occupancy days[2]	
		Total	Of which intensive care beds	Total	Of which intensive care beds	Total	Of which intensive care beds
	Number			In percent		Number	
Total number of specialist departments[3]	**8,447**	**502,749**	**24,974**	**77.4**	**81.3**	**141,941,665**	**7,413,503**
Of which:							
Total number of general departments							
Ophthalmology	**323**	**4,872**	**2**	**64.4**	**121.0**	**1,145,735**	**883**
Surgery	**1,252**	**107,544**	**6,847**	**74.3**	**80.0**	**29,159,640**	**2,000,419**
Of which: Vascular surgery	246	7,761	444	74.4	80.4	2,107,374	130,281
Thoracic surgery	66	2,623	352	72.9	84.6	697,785	108,636
Trauma surgery	404	23,056	991	83.8	72.7	7,049,859	262,902
Visceral surgery	169	8,582	789	73.0	84.8	2,287,988	244,098
Gynaecology and obstetrics	**925**	**35,228**	**287**	**59.6**	**63.2**	**7,659,547**	**66,247**
Of which: Gynaecology	536	12,208	117	52.8	67.0	2,350,756	28,619
Obstetrics	453	8,785	25	65.8	111.9	2,109,031	10,213
Otorhinolaryngology	**730**	**11,128**	**135**	**63.4**	**75.5**	**2,574,031**	**37,185**
Skin and venereal diseases	**116**	**4,744**	**4**	**77.6**	**59.2**	**1,343,733**	**864**
Cardiac surgery	**70**	**4,446**	**1,234**	**84.0**	**84.8**	**1,363,732**	**381,778**
Of which: Thoracic surgery	5	140	54	90.1	91.7	46,059	18,073
Internal medicine	**1,299**	**154,213**	**9,171**	**79.4**	**83.6**	**44,673,248**	**2,800,060**
Of which: Angiology	32	862	22	73.0	88.3	229,736	7,090
Endocrinology	30	989	16	77.1	96.4	278,373	5,631
Gastroenterology	226	13,133	435	79.7	77.8	3,820,961	123,531
Haematology and internal oncology	153	7,376	251	83.4	69.7	2,244,222	63,864
Cardiology	280	20,532	2,269	87.4	87.4	6,551,280	723,734
Nephrology	114	3,666	221	83.3	78.8	1,115,038	63,580
Pneumology	106	6,616	460	82.1	82.7	1,982,550	138,779
Rheumatology	64	2,426	5	71.9	52.7	636,450	962
Geriatric medicine	**226**	**12,128**	**90**	**90.6**	**74.4**	**4,011,692**	**24,448**
Paediatric surgery	**80**	**1,941**	**131**	**59.2**	**63.9**	**419,592**	**30,563**
Paediatric medicine	**363**	**19,297**	**2,630**	**66.3**	**75.9**	**4,670,683**	**728,574**
Of which: Paediatric cardiology	30	573	135	68.4	75.8	142,976	37,363
Neonatology	150	2,465	855	79.7	84.2	717,173	262,649
Oral maxillo-facial surgery	**194**	**2,191**	**45**	**63.3**	**81.4**	**506,461**	**13,370**
Neurosurgery	**177**	**7,000**	**858**	**80.4**	**87.1**	**2,053,715**	**272,861**
Neurology	**410**	**22,098**	**1,551**	**84.5**	**89.6**	**6,815,229**	**507,118**
Nuclear medicine	**112**	**921**	**2**	**54.0**	**82.7**	**181,653**	**604**
Orthopaedics	**420**	**24,018**	**504**	**72.5**	**66.9**	**6,352,031**	**123,079**
Of which: Rheumatology	18	650	16	65.6	71.6	155,609	4,181
Plastic surgery	**131**	**1,943**	**63**	**65.5**	**83.5**	**464,615**	**19,198**
Radiotherapy	**162**	**3,154**	**2**	**68.7**	**112.5**	**790,784**	**821**
Urology	**513**	**15,002**	**400**	**72.6**	**74.6**	**3,972,702**	**108,845**
Other specialist departments/ general beds	**216**	**4,086**	**996**	**72.9**	**79.9**	**1,087,542**	**290,289**
Total number of psychiatric departments							
Of which:							
Paediatric/Adolescent psychiatry and psychotherapy	**137**	**5,460**	**–**	**91.7**	**–**	**1,826,587**	**1**
Psychiatry and psychotherapy	**412**	**54,035**	**22**	**93.3**	**78.4**	**18,401,734**	**6,293**
Of which: Addiction	97	4,552	–	86.1	–	1,430,905	3
Psychotherapeutic medicine	**179**	**7,300**	**–**	**92.6**	**–**	**2,466,979**	**3**

[1] Multiple answers or double counts possible. If a hospital has more than one main focus within a speciality, the speciality is counted only once. The sum of the main focuses is thus not necessarily consistent with the figure stated for the corresponding speciality.

[2] Number of billing/occupancy days included from 2002 hour cases. This also has an influence on the key figures ascertained on the basis of these two reference figures.

Source: Basic Data of Hospitals, © Federal Statistical Office (Destatis), Wiesbaden, 2011

Tab. 7.4.4: Types of treatment at hospitals

Year	Treatment cases[1)]				Outpatient surgeries
	Inpatient	Semi-inpatient	Pre-inpatient	Post-inpatient	
	Number				
2002	17,432,272	376,473	1,169,529	747,206	575,613
2003	17,295,910	502,470	1,417,411	755,096	724,310
2004	16,801,649	511,137	1,670,652	661,274	1,160,573
2005	16,539,398	527,213	1,965,027	654,277	1,371,708
2006	16,832,883	623,657	2,266,670	703,488	1,513,716
2007	17,178,573	675,082	2,714,169	781,197	1,638,911
2008	17,519,579	702,649	2,991,986	820,371	1,758,305
2009	17,817,180	667,093	3,298,544	875,259	1,813,727
2010	18,032,903	673,080	3,510,861	905,602	1,854,125

[1)] Before the 1st amendment of the KHStatV [Hospital Statistics Regulation] took effect, only the number of patients discharged from semi-inpatient care was counted.
Source: Basic Data of Hospitals, Federal Statistical Office (Destatis), Wiesbaden, 2011

Tab. 7.4.5: Selected key figures of hospitals by bed capacity and type of funding body, 2010

Bed capacity/Type of funding body	Total number of hospitals	Number of installed beds	Number of installed beds per 100,000 inhabitants
	Number		
Total number of hospitals	**2,064**	**502,749**	**615**
Hospital with 0 beds[1)]	61	–	–
Hospital with 1 to 49 beds	372	7,490	9
Hospital with 50 to 99 beds	274	20,026	24
Hospital with 100 to 149 beds	268	32,736	40
Hospital with 150 to 199 beds	200	34,501	42
Hospital with 200 to 299 beds	302	73,626	90
Hospital with 300 to 399 beds	204	69,948	86
Hospital with 400 to 499 beds	142	63,283	77
Hospital with 500 to 599 beds	82	44,643	55
Hospital with 600 to 799 beds	69	46,802	57
Hospital with 800 and more beds	90	109,694	134
Public hospitals	**630**	**244,254**	**299**
Under private law	368	138,535	169
Under public law	262	105,719	129
Legally dependent	119	38,766	47
Legally independent	143	66,953	82
Non-profit hospitals	**755**	**173,457**	**212**
Private hospitals	**679**	**85,038**	**104**

[1)] Day or night hospitals exclusively offering semi-inpatient care
Source: Basic Data of Hospitals, Federal Statistical Office (Destatis), Wiesbaden, 2011

Tab. 7.4.6: General hospitals by bed capacity, 2010

General hospitals	In total 1,758	Beds 462,457
> 100 beds	543	22,631
100 to < 200 beds	406	58,723
200 to < 500 beds	572	182,900
500 to < 800 beds	148	89,585
≥ 800 beds	89	108,618

Source: Basic Data of Hospitals, Federal Statistical Office (Destatis), Wiesbaden, 2011

Tab. 7.4.7: Distribution of age and sex of inpatients in Germany (2001–2010) Key patient figures at a glance

Subject of proof	Reporting year									
	2010	2009	2008[a]	2007[a]	2006[a]	2005[a]	2004[a]	2003	2002	2001
	Number									
Total number of treatment cases[b]	**18,489,998**	**18,231,569**	**17,937,101**	**17,568,576**	**17,142,476**	**17,033,775**	**17,233,624**	**17,313,222**	**17,398,538**	**17,259,596**
- Men	8,705,679	8,569,023	8,392,426	8,188,483	7,995,913	7,923,621	7,968,271	7,907,222	7,899,301	7,813,749
- Women	9,784,155	9,662,423	9,544,617	9,379,967	9,146,276	9,110,081	9,265,287	9,405,898	9,498,237	9,445,553
Treatment cases excl. patients with foreign/ unknown place of residence, of unknown sex and age	**18,412,117**	**18,161,404**	**17,869,372**	**17,497,527**	**17,078,512**	**16,970,819**	**17,159,213**	**17,244,171**	**17,331,212**	**17,183,495**
- Men	8,662,490	8,530,096	8,354,296	8,149,525	7,960,327	7,889,241	7,929,456	7,871,052	7,864,291	7,774,416
- Women	9,749,627	9,631,308	9,515,076	9,348,002	9,118,185	9,081,578	9,229,757	9,373,119	9,466,921	9,409,079
Treatment cases per 100,000 inhabitants[e]	**22,520**	**22,182**	**21,760**	**21,270**	**20,735**	**20,580**	**20,799**	**20,897**	**21,012**	**20,869**
- Men	21,602	21,254	20,762	20,228	19,744,	19,553	19,652	19,507	19,509	19,332
- Women	23,404	23,074	22,719	22,270	21,685	21,564	21,897	22,226	22,448	22,336
Treatment cases per 100,000 inhabitants (standardised)[c, e]	**20,684**	**20,513**	**20,291**	**20,003**	**19,651**	**19,629**	**19,962**	**20,030**	**20,256**	**20,230**
- Men	18,618	18,496	18,263	17,990	17,753	17,744	17,992	17,859	17,977	18,066
- Women	22,287	22,082	21,883	21,589	21,144	21,122	21,549	21,821	22,100	22,057
Average age of patients (in years)[d]	**53.8**	**53.6**	**53.2**	**52.8**	**52.5**	**52.1**	**51.9**	**52.7**	**52.3**	**51.8**
- Men	53.1	52.4	52.4	52.0	51.6	51.2	51.0	51.9	51.3	50.8
- Women	54.3	54.2	53.9	53.5	53.2	52.9	52.7	53.5	53.1	52.7
Age-specific rate per 100,000 inhabitants[e]										
- Below 15 years	16,171	15,867	16,052	15,810	15,427	15,284	14,678	11,386	11,416	11,559
- 15 to less than 45 years	13,395	13,197	12,891	12,634	12,361	12,348	12,783	13,512	13,857	13,969
- 45 to less than 65 years	19,872	19,710	19,544	19,339	19,319	19,498	20,319	21,372	21,785	21,802
- 65 to less than 85 years	44,458	44,033	43,336	42,622	41,772	41,971	42,775	43,665	43,573	43,049
- 85 years or older	66,364	66,124	65,415	63,964,	61,604	61,171	59,913	61,838	62,259	61,067
Average length of stay (in days)	**7.9**	**8.0**	**8.1**	**8.3**	**8.4**	**8.6**	**8.6**	**9.0**	**9.3**	**9.4**
Hour cases within one day	**528,461**	**516,298**	**504,116**	**493,400**	**493,861**	**506,891**	**606,418**	**687,725**	**732,721**	**740,280**
Short-stay patients (1 to 3 days)	**6,828,023**	**6,568,703**	**6,279,504**	**5,944,592**	**5,631,308**	**5,401,207**	**5,406,254**	**5,262,823**	**5,086,019**	**4,896,539**
Number of deaths	**407,473**	**408,310**	**400,943**	**395,169**	**389,339**	**392,715**	**384,805**	**404,526**	**400,510**	**391,408**
Coverage (%)	**99.8**	**99.7**	**99.6**	**99.4**	**98.9**	**100.9**	**100.0**	**100.1**	**99.6**	**99.6**

[a] Including healthy newborns
[b] Treatment cases including patients of unknown sex
[c] Standardised with the standard population "Germany 1987"
[d] Average age between 2000 and 2002 based on a 10% sample
[e] Excl. patients domiciled abroad, of unknown sex and unknown age
Source: Basic Data of Hospitals, Federal Statistical Office (Destatis), Wiesbaden, 2011

Tab. 7.4.8: Most common surgeries[1] differentiated by type of procedure (2010; four-digit level)				
Rank	**OPS code**	**Operation**	**Number**	**Percent**
		Total number of surgeries[2]	**14,937,120**	**100**
1	5-469	Other surgeries of intestines	321,734	2.2
2	5-812	Arthroscopic surgeries of articular cartilage and menisci	281,177	1.9
3	5-032	Access to lumbar vertebral column, sacrum and coccyx	271,236	1.8
4	5-893	Surgical wound toilet (wound debridement) and excision of diseased dermal or hypodermal tissue	267,374	1.8
5	5-758	Reconstruction of female genitals after rupture, postpartum [perineal rupture]	246,817	1.7
6	5-513	Endoscopic surgeries of bile ducts	224,260	1.5
7	5-794	Open reposition of multi-fragment fractures near the joint of a long tubular bone incl. osteosynthesis	215,683	1.4
8	5-820	Hip joint replacement	213,697	1.4
9	5-511	Cholecystectomy	192,825	1.3
10	5-749	Other caesarean sections	187,065	1.3
11	5-787	Removal of osteosynthesis material	178,098	1.2
12	5-530	Closure of inguinal hernia	176,693	1.2
13	5-811	Arthroscopic surgeries of synovial membrane	174,481	1.1
14	5-831	Excision of diseased intervertebral cartilage	171,729	1.1
15	5-810	Arthroscopic revision of joints	170,910	1.1
16	5-790	Closed reposition of fractures or separation of epiphysis incl. osteosynthesis	160,496	1.1
17	5-822	Knee joint replacement	158,100	1.1
18	5-800	Open-surgical revision of joints	157,462	1.0
19	5-839	Other surgeries of vertebral column	153,884	1.0
20	5-215	Surgeries of nasal concha (Concha nasalis]	147,179	1.0
21	5-385	Elimination, excision and stripping of varices	146,279	0.9
22	5-452	Local excision and destruction of diseased colon tissue	138,521	0.9
23	5-793	Open reposition of simple fractures near the joint of a long tubular bone	134,956	0.9
24	5-144	Extracapsular cataract extraction [ECCE]	130,368	0.9
25	5-892	Other dermal and hypodermal incisions	128,475	0.9
26	5-788	Surgeries of the metatarsus and phalanx of the feet	127,071	0.8
27	5-399	Other surgeries of blood vessels	125,790	0.8
28	5-916	Temporary coverage of soft tissue	125,450	0.8
29	5-900	Simple restoration of dermal and hypodermal surface continuity	125,108	0.8
30	5-895	Radical and extended excision of diseased dermal and hypodermal tissue	123,255	0.8

[1] Excl. duplicates
[2] The total number of surgeries also includes the positions 5–93…5–99 (additional information on surgeries), which are, however, not shown here separately
Source: DRG Statistics, Federal Statistical Office (Destatis), Wiesbaden, 2011

Tab. 7.4.9: Most common surgeries[1)] differentiated by body area (2010; three-digit level)

Rank	OPS code	Surgery	Number	Percent
	5	**5 Surgeries[1), 2)]**	**14,937,120**	**100**
1	5-81	Arthroscopic joint surgeries	807,303	5.4
2	5-78	Surgeries of other bones	740,186	5.0
3	5-83	Surgeries of the vertebral column	685,081	4.6
4	5-89	Surgeries of the dermis and hypodermis	661,800	4.4
5	5-79	Reposition of fractures and luxations	632,665	4.2
6	5-82	Endoprosthetic joint and bone replacement	516,029	3.5
7	5-51	Surgeries of the gall bladder and bile ducts	437,087	2.9
8	5-38	Incision, excision and closure of blood vessels	411,168	2.8
9	5-03	Surgeries of the medulla, meninx and spinal canal	404,948	2.7
10	5-46	Other surgeries of small intestines and colon	403,884	2.7
11	5-80	Open joint surgeries	336,496	2.3
12	5-21	Surgeries of the nose	314,186	2.1
13	5-53	Closure of abdominal hernia	297,115	2.0
14	5-90	Surgical restoration and reconstruction of dermis and hypodermis	294,892	2.0
15	5-45	Incision, excision, resection and anastomosis of small intestines and colon	292,784	2.0
16	5-75	Other obstetric surgeries	280,412	1.9
17	5-39	Other surgeries of blood vessels	275,389	1.8
18	5-74	Caesarean section and child development	273,467	1.8
19	5-57	Surgeries of the urinary bladder	257,644	1.7
20	5-85	Surgeries of muscles, tendons, fascia and bursa	252,212	1.7
21	5-37	Arrhythmia surgeries and other surgeries of the heart and pericardium	195,308	1.3
22	5-15	Surgeries of the retina, choroid and vitreous body	192,590	1.3
23	5-68	Incision, excision and extirpation of the uterus	186,056	1.2
24	5-28	Surgeries in the nasopharyngeal and oropharyngeal area	184,378	1.2
25	5-06	Surgeries of the thyroid gland and the parathyroid gland	184,283	1.2
26	5-73	Other surgeries for induction of labour and during labour	177,850	1.2
27	5-54	Other surgeries in the abdominal area	173,240	1.2
28	5-91	Other surgeries of the dermis and hypodermis	172,473	1.2
29	5-65	Surgeries of the ovary	167,851	1.1
30	5-49	Surgeries of the anus	165,087	1.1

[1)] Excl. duplicates
[2)] The total number of surgeries also includes the positions 5–93…5–99 (additional information on surgeries), which are, however, not shown here separately
Source: DRG Statistics, Federal Statistical Office (Destatis), Wiesbaden, 2011

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List of abbreviations

ABS	Antibiotic Stewardship
ACME-Cluster	Arginine catabolic mobile element
ADKA	Association of German Hospital Pharmacists
AFST	Antifungal Susceptibility Testing
AG TAM	Working Group for Veterinary Medicinal Products
AMB	Amphotericin B
AMC	Amoxicillin/Clavulanic acid
AMG	German Medicinal Products Act
AMIS	Drug Information System
AMP	Ampicillin
ANF	Anidulafungin
AOK	General local health insurance fund
APR	Apramycin
AQUA	Institute for Applied Quality Improvement and Research in Health Care
AQUIK	Outpatient Quality Indicators and Key Figures
ARESC	Antimicrobial Resistance Epidemiological Survey on Cystitis
ARMIN	Antibiotic Resistance Monitoring in Lower Saxony
ARS	Antibiotic Resistance Surveillance
AT	Austria
ATC	Anatomical Therapeutic Chemical Classification
ATI	Animal Treatment Index
AVV	General Administrative Regulation
BE	Belgium
BfR	Federal Institute for Risk Assessment
BfT	Federal Association for Animal Health
BG	Bulgaria
BLNAR	β-lactamase-negative ampicillin resistance
BMBF	Federal Ministry of Education and Research
BQS	Federal Institute for Quality Assurance
BSAC	British Society for Antimicrobial Chemotherapy
BTK	Federal Chamber of Veterinarians
BVL	Federal Office of Consumer Protection and Food Safety
cAMB	Conventional amphotericin B
CA-MRSA	Community-associated MRSA
CAP	Community-acquired pneumonia
CAPNETZ	Competence Network Community-Acquired Pneumonia
CAS	Caspofungin
CC	Clonal complex
CDC	Centers for Disease Control
CDI	*Clostridium difficile* infection
CEF	Ceftiofur
CF	Cystic fibrosis
CFR	Choramphenicol/Florfenicol resistance gene
CFZ	Cefazolin
CH	Switzerland
CHI	Quinolone
CHL	Choramphenicol
CIP	Ciprofloxacin
CLA	Clarithromycin
CLI	Clindamycin
CLSI	Clinical and Laboratory Standards Institute
COL	Colistin
CPZ	Cefoperazone
CQN	Cefquinome
CTC	Chlortetracycline

CTX	Cefotaxime
CY	Cyprus
CZ	Czech Republic
DDD	Defined daily doses
DE	Germany
DGHM	German Society for Hygiene and Microbiology
DIMDI	German Institute of Medical Documentation and Information
DIN	German Institute for Standardisation
DK	Denmark
DOX	Doxycycline
DVG	German Veterinary Medicine Society
EAEC	Enteroaggregative *E. coli*
EARS-Net	European Antimicrobial Resistance Surveillance Network
ECDC	European Centre for Disease Prevention and Control
ECOFF	Epidemiological cut-off values
EE	Estonia
EFSA	European Food Safety Authority
EHEC	Enterohaemorrhagic *E. coli*
EIEC	Enteroinvasive *E. coli*
EL	Greece
ENR	Enrofloxacin
EOD	Early-onset disease
EPEC	Enteropathogenic *E. coli*
ERY	Erythromycin
ES	Spain
ESAC	European Surveillance of Antimicrobial Consumption
ESBL	Extended-spectrum β-lactamases
ESPED	Survey Unit for Rare Paediatric Diseases in Germany
ESVAC project	European Surveillance of Veterinary Antimicrobial Consumption
ETEC	Enterotoxic *E. coli*
EUCAST	European Committee on Antimicrobial Susceptibility Testing
EXPEC	Extraintestinal pathogenic *E. coli*
FFN	Florfenicol
FI	Finland
FLC	Fluconazole
FOS	Fosfomycin
FPA	Food-producing animals
FR	France
FYC	Flucytosine
GBS	Group-B streptococci
GEN	Gentamicin
GENARS	German Network for Antimicrobial Resistance Surveillance
GERM-Vet	National Resistance Monitoring of Veterinary Pathogens
G-TEST	German Tigecycline Evaluation Surveillance Trial
HABS	Hospital Antibiotic Stewardship
HACEK	Group of gram-negative bacteria causing endocarditis that, due to the special growth conditions required, only grow in the laboratory after a longer incubation period
HA-MRSA	Hospital-acquired MRSA
HCA-MRSA	Hospital-associated community onset MRSA
HDD	Inhibition zone diameter
Hib	*H. influenzae* of serotype b
HR	Croatia
HU	Hungary
HUS	Haemolytic-uraemic syndrome
IAP	Intrapartum antibiotic prophylaxis
IE	Insufficient evidence
IE	Ireland
if	Infectiology Freiburg
IfSG	German Infection Protection Act
IGES	Institute for Health and Social Research

IPM	Imipenem
IS	Iceland
IT	Italy
KBV	Federal Association of Panel Physicians
KISS	Hospital Infection Surveillance System
KLHi	Consultant Laboratory for *H. influenzae*
KNS	Coagulase-negative *Staphylococcus* spp.
KRINKO	Commission for Hospital Hygiene and Infection Prevention
KV	Regional Association of Panel Physicians
L-AMB	Liposomal amphotericin B
LA-MRSA	Livestock-associated MRSA
LFL	Levofloxacin
LIN	Lincomycin
LNZ	Linezolid
LOD	Late-onset disease
LT	Lithuania
LU	Luxembourg
LuTX	During/After lung transplantation
MABUSE	Medical Antibiotic Use Surveillance and Evaluation
MALT lymphoma	Mucosa-associated lymphatic tissue lymphoma
MCA	Micafungin
MDR	Multi-drug resistance
MDR-TB	Multi-drug-resistant tuberculosis
MENEC	Meningitis-associated *E. coli*
MHK	Minimum inhibitory concentration
MLST	Multilocus sequence typing
MMA	Mastitis-Metritis-Agalactiae complex
MOX	Moxifloxacin
MPM	Meropenem
MRA	Macrorestriction Analysis
MRGN	Multi-resistant gram-negative bacteria
MRSA	Methicillin-resistant *S. aureus*
MRSI	Methicillin-resistant *S. intermedius*
MRSP	Methicillin-resistant *S. pseudintermedius*
MSM	Men who have sex with men
MZ	Metronidazole
NAK	National Antimicrobial Susceptibility Testing Committee
NAL	Nalidixic acid
NAMed	Medical Standardisation Committee
NEO	Neomycin
N-FPA	Non-food-producing animals
NI	Nosocomial infections
NIT	Nitrofurantoin
NL	Netherlands
NLGA	State Health Office of Lower Saxony
NO	Norway
NRZ	National Reference Centre
NTHi	Non-typable *H. influenzae*
NUS	NIS, Newly Independent States
OIE	World Organisation for Animal Health
OXA	Oxacillin
PBP	Penicillin-binding protein
PCR	Polymerase chain reaction
PCU	Number of food-producing animals multiplied by their estimated weight at the time of treatment
PDD	Prescribed daily doses
PEG	Paul Ehrlich Society for Chemotherapy
PEN	Penicillin
PFGE	Pulsed-field gel electrophoresis
PID	Pelvic inflammatory disease
PIR	Pirlimycin

PL	Poland
POS	Posaconazole
PPI	Proton-pump inhibitor
PPS	Point prevalence survey
preTX	Before lung transplantation
PROTEKT	Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin
PT	Portugal
PVL	Panton-Valentine leukocidin
Q/D	Quinupristin/Dalfopristin
QISA	Quality Indicator System for Outpatient Care
RDD	Recommended daily doses
RESET	Research Association for ESBL and (Fluoroquinolone) Resistance in *Enterobacteriaceae*
ResiNet	Study for monitoring the resistance situation and identifying risk factors for the resistance development of *H. pylori*
RIF	Rifampicin
RKI	Robert Koch Institute
RNA	Ribonucleic acid
rRNA	Ribosomal RNA
RU	Russia
SARI	Surveillance of Antibiotic Use and Resistance in Intensive Care
SE	Sweden
SEPEC	Septicemic *E. coli*
SHI	Statutory health insurance
SI	Slovenia
SK	Slovakia
spa	Gene coding for the protein A in *S. aureus* (*S. aureus* protein A)
SPE	Spectinomycin
SPI	Spiramycin
SPN analyses	Single nucleotide polymorphism (analyses)
ST	Sequence type
STEC	Shiga toxin-producing *E. coli*
STIKO	Standing Committee on Vaccination
STR	Streptomycin
SUL	Sulphamethoxazole
SXT	Trimethoprim/Sulphamethoxazole (co-trimoxazole)
TEE	Transoesophageal echocardiography
TEL	Telithromycin
TEM-1	The name TEM is derived from a Greek patient named Temoniera, in whom a bacterial strain with this β-lactamase was isolated for the first time.
TET	Tetracycline
TIA	Tiamulin
TIL	Tilmicosin
TPL	Teicoplanin
TRI	Trimethoprim
TUL	Tulathromycin
TYL	Tylosin
UK	United Kingdom
UPEC	Uropathogenic *E. coli*
VAN	Vancomycin
VetCAb	Veterinary Consumption of Antibiotics
VOR	Voriconazole
VRE	Vancomycin-resistant enterococci
WHO	World Health Organisation
WIdO	Research Institute of the AOK
WINEG	Research Institute of Techniker Krankenkasse for Benefit and Efficiency in Health Care
XDR-TB	Extensively drug-resistant tuberculosis
XNL	Ceftiofur
ZI	Central Research Institute of Ambulatory Health Care in Germany