GERMAP 2015

Antimicrobial Resistance and Consumption

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

GERMAP 2015

Antimicrobial Resistance and Consumption

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

Editors

Bundesamt für Verbraucherschutz und Lebensmittelsicherheit
Dienstsitz Berlin
Mauerstraße 39-42, 10117 Berlin
www.bvl.bund.de
Persons responsible: Dr. Heike Kaspar, Dr. Jürgen Wallmann

Paul-Ehrlich-Gesellschaft für Chemotherapie e.V.
Campus Hochschule Bonn-Rhein-Sieg
Von-Liebig-Straße 20, 53359 Rheinbach
www.p-e-g.org
Person responsible: Prof. Dr. Michael Kresken

Scientific advisory board

Publisher

Antiinfectives Intelligence Gesellschaft für klinisch-mikrobiologische Forschung und Kommunikation mbH
Von-Liebig-Straße 20, 53359 Rheinbach
www.antiinfectives-intelligence.de

Graphic design

federbusch-design, Bonn
www.federbusch-design.de

Copyright

Edition

October 2016 / **ISBN** 978-3-9818383-0-5
English Version June 2017

Suggested citation

Federal Office of Consumer Protection and Food Safety, Paul-Ehrlich-Gesellschaft für Chemotherapie e.V., GERMAP 2015 – Report on the consumption of antimicrobials and the spread of antimicrobial resistance in human and veterinary medicine in Germany. Antiinfectives Intelligence, Rheinbach, 2016.

Bundesamt für Verbraucherschutz und Lebensmittelsicherheit

Paul-Ehrlich-Gesellschaft für Chemotherapie e. V.
www.p-e-g.org

With the friendly assistance of Deutsches Zentrum für Infektionsforschung (DZIF)

DZIF

Bundesministerium für Gesundheit (BMG)

Bundesministerium für Ernährung und Landwirtschaft (BMEL)

Bundesinstitut für Risikobewertung (BfR)

Deutsche Gesellschaft für Hygiene und Mikrobiologie e.V. (DGHM)

Deutsche Gesellschaft für Infektiologie e.V. (DGI)

Deutsche Gesellschaft für Pädiatrische Infektiologie e.V. (DGPI)

Wissenschaftliches Institut der AOK (WIdO)

Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)

Friedrich-Loeffler-Institut (FLI)

Robert Koch-Institut (RKI)

Authors and reviewers

Prof. Dr. Thomas Alter
Institute of Food Hygiene
Free University of Berlin

Doris Altmann
Robert Koch Institute, Berlin

PD Dr. Isabelle Bekeredjian-Ding
Division of Microbiology
Paul Ehrlich Institute, Langen

Dr. Alice Bender
Unit 304 Post-Marketing
Federal Office of Consumer Protection and Food Safety, Berlin

Prof. Dr. Reinhard Berner
Department of Paediatrics
University Hospital Carl Gustav Carus

Ute Bölt
Federal Statistical Office, Bonn

Dr. Viviane Bremer
Robert Koch Institute, Berlin

Dr. Bonita Brodhun
Robert Koch Institute, Berlin

Dr. Susanne Buder
Consultant Laboratory for Gonococci
Vivantes Clinic of Dermatology and Venereology, Berlin

PD Dr. Heike Claus
National Reference Centre for Meningococci and Haemophilus influenzae
Institute of Hygiene and Microbiology
University of Würzburg

Dr. Christiane Cuny
National Reference Centre for Staphylococci and Enterococci
Robert Koch Institute, Wernigerode

Dr. Dr. Katja de With
Clinical Infectiology
University Hospital Dresden

Sandra Dudareva-Vizule
Robert Koch Institute, Berlin

PD Dr. Lüppo Ellerbroek
Federal Institute for Risk Assessment, Berlin

Prof. Dr. Christa Ewers
Institute of Hygiene and Infectious Diseases of Animals
University of Gießen

Dr. Matthias Fellhauer
Schwarzwald-Baar Hospital, Villingen-Schwenningen

Dr. Angelika Fruth
Robert Koch Institute, Wernigerode

PD Dr. Christine Geffers
National Reference Centre for the Surveillance of Nosocomial Infections
Charité University Hospital Berlin

PD Dr. Erik-Oliver Glocker
Institute of Laboratory Medicine
Municipal Hospital Brandenburg

Prof. Dr. Andreas Groll
Clinic of Paediatric and Adolescent Medicine –
Paediatric Haematology and Oncology and Centre for Bone Marrow Transplantation
University Hospital Münster

Prof. Dr. Walter Haas
Robert Koch Institute, Berlin

PD Dr. Rüdiger Hauck
Auburn University Animal Science
Poultry Science Building, Auburn, Alabama

Dr. Barbara Hauer
Robert Koch Institute, Berlin

Dr. Wiebke Hellenbrand
Robert Koch Institute, Berlin

Dr. Julia Hermes
Robert Koch Institute, Berlin

Dr. Torsten Hoppe-Tichy
University Hospital Heidelberg

Prof. Dr. Johannes Hübner
Hauner Clinic and Outpatient Clinic of Paediatric Medicine
University Hospital Munich

PD Dr. Matthias Imöhl
National Reference Centre for Streptococci
Institute of Med. Microbiology
University Hospital RWTH Aachen

Dr. Klaus Jansen
Robert Koch Institute, Berlin

Prof. Dr. Daniel Jonas
Infection Prevention and Hospital Hygiene
University Hospital Freiburg

Dr. Martin Kaase
Central Department of Hospital Hygiene and Infectiology
University Medical Centre Göttingen

Prof. Dr. Annemarie Käsbohrer
Federal Institute for Risk Assessment, Berlin

Dr. Anne-Kathrin Karaalp
Unit 505 Monitoring of Resistance to Antibiotics
Federal Office of Consumer Protection and Food Safety, Berlin

Dr. Heike Kaspar
Unit 505 Monitoring of Resistance to Antibiotics
Federal Office of Consumer Protection and Food Safety, Berlin

Prof. Dr. Winfried V. Kern
Division of Infectious Diseases
University Hospital and Medical Center Freiburg

Prof. Dr. Manfred Kist
Institute of Med. Microbiology and Hygiene
University Hospital Freiburg

Dr. Ingo Klare
National Reference Centre for Staphylococci and Enterococci
Robert Koch Institute, Wernigerode

Dr. Sabine Klee
Unit 304 Post-Marketing
Federal Office of Consumer Protection and Food Safety, Berlin

Dr. Barbara Körber-Irrgang
Antiinfectives Intelligence GmbH, Rheinbach

Dr. Evelyn Kramme
Clinic of Infectiology and Microbiology
Campus Lübeck

Prof. Dr. Michael Kresken[1,2]
[1] Antiinfectives Intelligence GmbH, Rheinbach
[2] Rheinische Fachhochschule Köln GmbH, Cologne

Prof. Dr. Oliver Kurzai
National Reference Centre for Invasive Mycoses
Leibniz Institute for Natural Product Research and Infection Biology
Hans Knöll Institute, Jena

Dr. Thiên-Trí Lâm
National Reference Centre for Meningococci and Haemophilus influenzae
Institute of Hygiene and Microbiology
University of Würzburg

Fabian Lander
Department of Paediatrics
University Hospital Carl Gustav Carus

Dr. Franziska Layer
National Reference Centre for Staphylococci and Enterococci
Robert Koch Institute, Wernigerode

Dr. Ulf Lenski
Federal Institute for Risk Assessment, Berlin

PD Dr. Christoph Lübbert
Department of Infectiology and Tropical Medicine
Clinic of Gastroenterology and Rheumatology
University Hospital Leipzig

Dr. Antina Lübke-Becker
Institute of Microbiology and Epizootics
Free University of Berlin

Dr. Christian Lück
Consultant Laboratory for Legionella
Institute of Med. Microbiology and Hygiene
University Hospital of TU Dresden

Dr. Matthias Merker
Molecular and Experimental Mycobacteriology
Borstel Research Centre
Leibniz Centre for Medicine and Biosciences

PD. Dr. Elisabeth Meyer
Institute of Hygiene and Environmental Medicine
Charité – University Hospital Berlin

Dr. Geovana Brenner Michael
Institute of Microbiology and Epizootics
Free University of Berlin

Prof. Dr. Martin Mielke
Robert Koch Institute, Berlin

Dr. Alexander Mischnik
Division of Infectious Diseases
University Hospital and Medical Center Freiburg

Prof. Dr. Stephan Niemann
National Reference Centre for Mycobacteria
Borstel Research Centre

Dr. Yvonne Pfeifer
Robert Koch Institute, Wernigerode

Prof. Dr. Mathias W. Pletz
Centre of Infectiology and Hospital Hygiene
University Hospital Jena

Inke Reimer
Unit 304 Post-Marketing
Federal Office of Consumer Protection and Food Safety, Berlin

Prof. Dr. Ralf René Reinert
National Reference Centre for Streptococci
Institute of Med. Microbiology
University Hospital RWTH Aachen

Dr. Antje Römer
Unit 505 Monitoring of Resistance to Antibiotics
Federal Office of Consumer Protection and Food Safety, Berlin

Dr. Sabine Rüsch-Gerdes
formerly: National Reference Centre for Mycobacteria
Leibniz Centre for Medicine and Biosciences
Borstel Research Centre

Julia Schaufler
Research Institute of the AOK, Berlin

PD Dr. Frieder Schaumburg
Institute of Med. Microbiology
University Hospital Münster

PD Dr. Norbert Schnitzler
Public Health Department, District Düren

Dr. Ludwig Sedlacek
Institute for Medical Microbiology and Hospital Epidemiology
Hannover Medical School

Prof. Dr. Harald Seifert
Institute of Med. Microbiology, Immunology and Hygiene
University Hospital Cologne

Prof. Dr. Dr. Bhanu Sinha
Medical Microbiology
University Medical Centre Groningen

Prof. Dr. Barbara Spellerberg
Institute of Med. Microbiology and Hygiene
University Hospital Ulm

Michaela Steib-Bauert
Centre of Infectiology and Travel Medicine
University Hospital Freiburg

Dr. Ulrike Steinacker
Unit 505 Monitoring of Resistance to Antibiotics
Federal Office of Consumer Protection and Food Safety, Berlin

Dr. Bernd Stephan
Antimicrobial Development Department
Bayer Animal Health GmbH

Dr. Kerstin Stingl
National Reference Laboratory for Campylobacter
Federal Institute for Risk Assessment, Berlin

Inka Stolle
Institute of Hygiene and Infectious Diseases of Animals
University Hospital Gießen

Prof. Dr. Eberhard Straube
Jena

Dr. Birgit Strommenger
National Reference Centre for Staphylococci and Enterococci
Robert Koch Institute, Wernigerode

Prof. Dr. Sebastian Suerbaum
Institute for Medical Microbiology and Hospital Epidemiology
Hannover Medical School

Dr. Carsten Telschow
Research Institute of the AOK, Berlin

Dr. Erhard Tietze
Robert Koch Institute, Wernigerode

Prof. Dr. Matthias Trautmann
Institute of Hospital Hygiene
Clinical Centre Stuttgart

Prof. Dr. Andrew J. Ullmann
Medical Clinic and Outpatient Clinic II
University Hospital Würzburg

Prof. Dr. Dr. Timo Ulrichs[1,2]
[1] Akkon University of Human Sciences, Berlin
[2] Koch Metschnikow Forum, Berlin

Dr. Mark van der Linden
National Reference Centre for Streptococci
Institute of Med. Microbiology
University Hospital RWTH Aachen

Prof. Dr. Ulrich Vogel
National Reference Centre for Meningococci and Haemophilus influenzae
Institute of Hygiene and Microbiology
University of Würzburg

Petra Vogt
Federal Institute for Risk Assessment, Berlin

Prof. Dr. Heike von Baum
Institute of Med. Microbiology and Hygiene
University Hospital Ulm

Dr. Jürgen Wallmann
Unit 306 Drug Resistance
Federal Office of Consumer Protection and Food Safety, Berlin

Dr. Jan Walter
Robert Koch Institute, Berlin

Dr. Grit Walther
National Reference Centre for Invasive Mycoses
Leibniz Institute for Natural Product Research and Infection Biology
Hans Knöll Institute, Jena

Dr. Armin Weiser
Federal Institute for Risk Assessment, Berlin

Prof. Dr. Tobias Welte
Clinic of Pneumology
Hannover Medical School

Prof. Dr. Constanze Wendt
Medical Care Centre Laboratory Dr. Limbach & Kollegen GbR, Heidelberg

PD Dr. Christiane Werkenthin
Lower Saxony State Office of Consumer Protection and Food Safety, Oldenburg

Prof. Dr. Guido Werner
National Reference Centre for Staphylococci and Enterococci
Robert Koch Institute, Wernigerode

Prof. Dr. Dr. Thomas A. Wichelhaus
Institute of Med. Microbiology and Infection Control
University Hospital Frankfurt, Goethe University

Dr. Stefan Ziesing
Institute for Medical Microbiology and Hospital Epidemiology
Hannover Medical School

The editors would like to thank **Julia Fritz** (Antiinfectives Intelligence GmbH) for her comprehensive editorial support in creating GERMAP 2015!

Preface

GERMAP 2015 is the fourth issue of a report that provides a summary of data on the consumption of antimicrobials and the spread of antimicrobial resistance in human and veterinary medicine in Germany. Last year, the significance of GERMAP within the "One Health" approach in Germany was documented in a special way by GERMAP having been listed as a "best practice" example in the document entitled "Combating Antimicrobial Resistance" of the meeting of the G7 countries in Germany.[1]

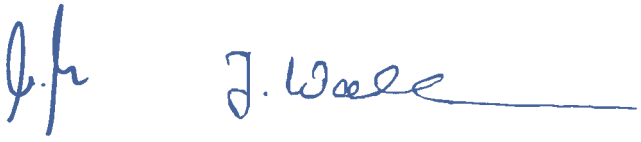
The information provided in the present report primarily covers the period 2011–2013, including some data from 2014. Many of the previously described trends have continued unbroken. In human medicine, broad-spectrum antimicrobials, most notably cephalosporins and fluoroquinolones, still have a very large share in total consumption. This applies to antimicrobials used in both outpatient and inpatient care. As is known, cephalosporins and fluoroquinolones strongly promote the selection of multidrug-resistant organisms. According to the findings of the PEG resistance study, however, the percentage of 3MRGN multidrug-resistant strains (as defined by the KRINKO [Commission for Hospital Hygiene and Infection Prevention], 2012)[2] in all *Escherichia coli* isolates has not increased further since the publication of GERMAP 2012, but stayed below the level found in the 2010 study, amounting to 11% in 2013. 4MRGN *E. coli* strains, which show resistance to carbapenems, were not detected in the last study either. The percentage of 3MRGN strains in *Klebsiella pneumoniae* isolates has increased further, amounting to 13% in 2013. However, the percentage of 4MRGN strains remained at approx. 2%. Accounting for 5% in 2013, the percentage of 4MRGN strains among *Pseudomonas aeruginosa* isolates was 2% below the 2010 level. However, a trend reversal towards stagnant or even decreasing carbapenem resistance rates cannot be assumed on the basis of these figures. Rather, the goal must remain to reduce the share of cephalosporins and fluoroquinolones in the treatment of infectious diseases in all care sectors. This particularly applies to antimicrobials with a comparatively low bioavailability, such as the orally administered cefuroxime axetil. Moreover, it has so far not been possible to reduce the use of antimicrobials in the treatment of acute respiratory tract infections in outpatient care to the desired extent.

In veterinary medicine, reliable data on total antimicrobial sales was made available for the first time in 2011. To date, data from four years has been available, showing that the total amount of antimicrobials sold to veterinarians has so far continuously dropped by 27%; however, the total sales volume of fluoroquinolones increased by 50% and the sales volume of newer cephalosporins remained constant over the same period. However, the sales data reported by the pharmaceutical companies allows no conclusion as to the actual use of the various antimicrobial classes in various animal species, since veterinary drugs are often approved for use in several animal species. The development of antimicrobial resistance in veterinary pathogens is first and foremost characterised by increasing rates of ESBL and MRSA.

The detection of carbapenemase-producing bacteria in animals[3,4] proves that antimicrobial-resistant bacteria or resistance genes can be transferred between humans and animals and vice versa. The plasmid-mediated resistance to polymyxins (colistin) among *E. coli* isolates, detected for the first time in 2015, is another example of the negative trend in the efficacy of antimicrobials.[5] Should the use of antimicrobials not finally be limited to the extent required for treatment and metaphylaxis, further legal interventions into the therapeutic freedom of veterinarians must be expected.

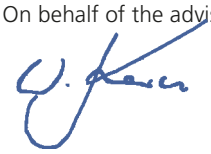
Again, many colleagues from human and veterinary medicine were involved in the creation of this report. We want to thank all involved for their great work, especially those colleagues who followed our invitation to take a closer look at specific aspects in the field of antimicrobial consumption and resistance. You will find these contributions in this issue under the heading "GERMAP *spezial*".

On behalf of the editors:



Michael Kresken Jürgen Wallmann

On behalf of the advisory board:



Winfried Kern

1. G7 GERMANY 2015, Combating Antimicrobial Resistance, Examples of Best-Practices of the G7 Countries. http://www.bundesgesundheitsministerium.de/fileadmin/dateien/Downloads/G/G7-Ges.Minister_2015/Best-Practices-Broschuere_G7.pdf.
2. Empfehlung der Kommission für Krankenhaushygiene und Infektionsprävention (KRINKO) beim Robert Koch-Institut (RKI). Hygienemaßnahmen bei Infektionen oder Besiedlung mit multiresistenten gramnegativen Stäbchen. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2012;55:1311-54.
3. Fischer J, Rodríguez I, Schmoger S, Friese A, et al. *Escherichia coli* producing VIM-1 carbapenemase isolated on a pig farm. J Antimicrob Chemother 2012;67:1793-5.
4. Fischer J, Rodríguez I, Schmoger S, Friese A, et al. *Salmonella enterica* subsp. *enterica* producing VIM-1 carbapenemase isolated from livestock farms. J Antimicrob Chemother 2013;68:478-80.
5. Liu YY, Wang Y, Walsh TR, Yi LX, et al. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study, 2015. Lancet Infect Dis 2016;16:161-8.

Vorwort

Mit GERMAP 2015 steht jetzt bereits zum vierten Mal eine Zusammenfassung von Daten über den Antibiotikaverbrauch und die Verbreitung von Antibiotikaresistenzen in der Human- und Veterinärmedizin in Deutschland zur Verfügung. Die Bedeutung von GERMAP im Rahmen des „One Health"-Ansatzes in Deutschland wurde im letzten Jahr in besonderer Weise auch dadurch dokumentiert, dass GERMAP als ein „Best Practice"-Beispiel im Dokument „Combating Antimicrobial Resistance" des Treffens der G7-Staaten in Deutschland gelistet worden ist.[1]

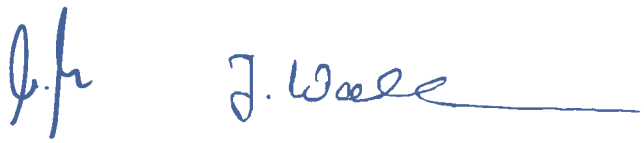
Die Angaben in dem vorliegenden Bericht beziehen sich zumeist auf den Zeitraum 2011 bis 2013 und teilweise auch auf das Jahr 2014. Viele der bereits zuvor beschriebenen Trends haben sich fortgesetzt. In der Humanmedizin ist der Anteil der Antibiotika mit einem breiten Wirkungsspektrum am Gesamtverbrauch – 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. Nach den Angaben der PEG-Resistenzstudie hat sich der Anteil multiresistenter Stämme vom Typ 3MRGN (gemäß Definition der KRINKO von 2012)[2] an allen *Escherichia-coli*-Isolaten seit der Veröffentlichung von GERMAP 2012 aber nicht weiter erhöht, sondern lag im Jahr 2013 mit 11% unter dem Niveau der Studie des Jahres 2010. *E.-coli*-Stämme vom Typ 4MRGN, die eine Resistenz gegen Carbapeneme zeigen, wurden auch in der letzten Studie nicht entdeckt. Bei den *Klebsiella-pneumoniae*-Isolaten nahm der Anteil von 3MRGN-Stämmen weiter zu und betrug 13% im Jahr 2013. Der Anteil von 4MRGN-Stämmen lag jedoch unverändert bei ca. 2%. Der Anteil von 4MRGN-Stämmen unter den *Pseudomonas-aeruginosa*-Isolaten lag im Jahr 2013 mit 5% um 2%-Punkte unter dem Niveau von 2010. Eine Trendumkehr zu stagnierenden oder gar sinkenden Carbapenem-Resistenzraten kann aus diesen Zahlen aber nicht abgeleitet werden. Vielmehr muss es weiterhin das Ziel sein, den Anteil von Cephalosporinen und Fluorchinolonen für die Therapie von Infektionskrankheiten in allen Versorgungsbereichen zu senken. Dies gilt vor allem für solche Antibiotika, die wie das oral applizierbare Cefuroximaxetil eine vergleichsweise geringe Bioverfügbarkeit besitzen. Zudem ist es in der ambulanten Versorgung bisher nicht in dem gewünschten Umfang gelungen, den Antibiotikaeinsatz bei akuten Atemwegsinfektionen zu reduzieren.

Für den Bereich der Veterinärmedizin wurden für das Jahr 2011 erstmals verlässliche Daten über die Gesamtmengenabgabe von Antibiotika zur Verfügung gestellt. Bis heute liegen Angaben aus vier Jahren vor, die zeigen, dass die Gesamtabgabemengen von Antibiotika an Tierärzte kontinuierlich bis heute um 27% zurückgegangen sind; die Abgabemengen für Fluorchinolone sind allerdings im gleichen Zeitraum um 50% gestiegen und die Abgabemengen für die neueren Cephalosporine sind konstant geblieben. Die von den pharmazeutischen Unternehmern mitgeteilten Abgabemengen lassen jedoch keinen sicheren Rückschluss auf den tatsächlichen Einsatz der verschiedenen Antibiotikagruppen bei den unterschiedlichen Tierarten zu, da Tierarzneimittel häufig für mehrere Tierarten zugelassen sind.

Die Resistenzentwicklung bei tierpathogenen Bakterien wird u.a. auch von steigenden ESBL- und MRSA-Raten gekennzeichnet. Die Beobachtung, dass Carbapenemase bildende Bakterien vereinzelt 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. Die 2015 zum ersten Mal diagnostizierte plasmidvermittelnde Resistenz gegen Polymyxine (Colistin) bei *E.-coli*-Isolaten ist ein weiteres Beispiel für die Negativentwicklung bzgl. der Wirksamkeit von Antibiotika.[5] Sollte nicht endlich der Einsatz von Antibiotika auf das für Therapie und Metaphylaxe notwendige Maß beschränkt werden, muss auch mit weiteren gesetzlichen Eingriffen in die Therapiefreiheit des Tierarztes gerechnet werden.

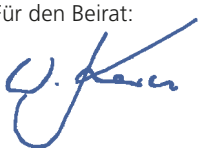
An der Erstellung des vorliegenden Berichtes waren erneut zahlreiche Kolleginnen und Kollegen aus der Human- und Veterinärmedizin beteiligt. Für die geleistete Arbeit danken wir allen Beteiligten sehr herzlich, insbesondere denjenigen Kolleginnen und Kollegen, die unserer Einladung gefolgt sind, ausgewählte 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

Für den Beirat:



Winfried Kern

1. G7 GERMANY 2015, Combating Antimicrobial Resistance, Examples of Best-Practices of the G7 Countries. http://www.bundesgesundheitsministerium.de/fileadmin/dateien/Downloads/G/G7-Ges.Minister_2015/Best-Practices-Broschuere_G7.pdf.
2. Empfehlung der Kommission für Krankenhaushygiene und Infektionsprävention (KRINKO) beim Robert Koch-Institut (RKI). Hygienemaßnahmen bei Infektionen oder Besiedlung mit multiresistenten gramnegativen Stäbchen. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2012;55:1311-54.
3. Fischer J, Rodríguez I, Schmoger S, Friese A, et al. *Escherichia coli* producing VIM-1 carbapenemase isolated on a pig farm. J Antimicrob Chemother 2012;67:1793-5.
4. Fischer J, Rodríguez I, Schmoger S, Friese A, et al. *Salmonella enterica* subsp. *enterica* producing VIM-1 carbapenemase isolated from livestock farms. J Antimicrob Chemother 2013;68:478-80.
5. Liu YY, Wang Y, Walsh TR, Yi LX, et al. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study, 2015. Lancet Infect Dis 2016;16:161-8.

1 Summary

Human Medicine

The total amount of antimicrobials used in human medicine in Germany is estimated to range between 700 and 800 tonnes per year.

When extrapolated to the population, the outpatient prescription volume accounts for approx. 85% of the total antimicrobial consumption (500-600 tonnes) in human medicine. According to the data reported by the Research Institute of the AOK (WIdo), there were nearly 45 million antimicrobial prescriptions under statutory health insurance in 2014, accounting for 448 million DDD (defined daily doses) and a sales volume of € 920 million. However, these figures cannot be compared with those stated in previous GERMAP reports, because the consumption of locally applied antimicrobials has now also been taken into account. The use density in 2014 was 17.4 DDD per 1,000 insured and day, showing a basically unchanged level since 2005. However, the prescription volume of extended-spectrum β-lactams (oral cephalosporins, aminopenicillin/β-lactamase inhibitor combinations and flucloxacillin) has more than doubled over the last 10 years, which is attributed to the strong increase in cefuroxime (axetil). Furthermore, significant regional differences are still being observed, with the consumption of β-lactam antimicrobials being significantly higher in western Länder compared to eastern ones. Based on daily doses, amoxicillin continues to be the most commonly prescribed antimicrobial, followed by the second-line antimicrobial cefuroxime (axetil), although none of the German practice guidelines lists this substance as a drug of choice. Fluoroquinolones continue to be prescribed mainly to elderly patients.

The ADKA-if-DGI surveillance project is currently the most important data source for quantifying hospital antimicrobial consumption. Overall, the inpatient antimicrobial use density seems to have increased in recent years, with non-university acute-care hospitals, irrespective of their size, showing a median consumption of 59 DDD/100 days of care and university hospitals a consumption of 84 DDD/100 days of care in 2013/2014. In 2014, β-lactams and fluoroquinolones were the most frequently prescribed antimicrobials at hospitals. The use density in intensive care units was twice as high as on general wards.

The majority of the data used to assess the resistance situation is obtained from studies conducted by the Paul Ehrlich Society for Chemotherapy (PEG) as well as from the laboratory-based surveillance systems ARS, SARI and EARS-Net. Furthermore, the resistance data reported by the National Reference Centres (NRZ) entrusted with the surveillance of important infectious agents was included in the analysis.

Since the publication of the first GERMAP report containing data on the resistance situation that dates back to 2006/2007, the resistance situation of a number of pathogens has changed substantially. The prevalence of macrolide resistance in pneumococci isolated from patients with invasive infections dropped from 16.2% (adults) and 20.8% (children) in 2007 to below 10% in both age groups in 2013 and 2014. For several years, the percentage of penicillin-resistant isolates from children (3–4%) has been ranking well above the rate in adults (approx. 1%). Nearly all penicillin-resistant isolates concerned meningitis cases. Compared to the situation in other European countries, however, penicillin-resistant pneumococci are still rare in Germany. An average of 14% of meningococcal isolates obtained over the period 2002-2011 showed intermediate susceptibility to penicillin, whereas 0.7% of them were resistant. In 2012, these rates increased to 25% and 2.2%, respectively. In 2013, the percentage of strains showing intermediate susceptibility to penicillin increased further to 40%, but dropped again to 22% in 2014, whereas the percentage of penicillin-resistant strains reached a level similar to that of 2012 in both years. The variations over time can be explained by the variable occurrence of meningococcal clones or clonal complexes. For example, 23% of the meningococci belonging to the so-called ST-11 complex, which is responsible for the majority of the serogroup-C diseases in Germany, are no longer susceptible to penicillin. By contrast, this is the case with only 5% of the meningococci belonging to the ST-41/44 complex. This clonal complex is responsible for the majority of serogroup-B diseases in Germany.

The antimicrobial susceptibility of *N. gonorrhoeae* was systematically investigated in Germany for the first time as part of the PEG resistance study in 2010. Since then, the continuous surveillance of the antimicrobial susceptibility of *N. gonorrhoeae* has been ensured by the Consultant Laboratory for Gonococci and the GORENET Resistance Network. The WHO demands that empiric therapy of gonorrhoea yields a therapeutic success of at least 95%. At present, third-generation cephalosporins and spectinomycin seem to be the only options to achieve this goal.

In 2013, the incidence of new tuberculosis diagnoses was 5.3 cases per 100,000 inhabitants. Amounting to 3.4%, the percentage of multi-drug-resistant tuberculosis (MDR-TB) cases has reached the highest level since the registration of resistant tuberculosis in 2001. The resistance situation of the two most common *Salmonella* serovars in Germany still varies greatly. About 95% of serovar Enteritis isolates are susceptible to all tested antimicrobials. By contrast, most serovar Typhimurium strains have now become multi-drug resistant.

The percentage of MRSA in *Staphylococcus aureus* isolates continues to show a downward trend in Germany. According to the data reported by EARS-Net, the average percentage of MRSA in *S. aureus* blood culture isolates was 11.8% in 2014. With the exception of fluoroquinolones, co-resistance in MRSA to antimicrobials other than β-lactams also shows a downward trend. This decline can be explained by the recently increasing emergence of new variants (isolates of the clonal lineage ST22 ["Barnim Epidemic Strain"] and ST225 ["Rhine-Hesse Epidemic Strain"]) with a significantly narrower resistance spectrum than previous epidemic MRSA. Up to 90% of MRSA isolates in hospital care and approx. 70% in outpatient care belong to the group of HA-MRSA (in outpatient care referred to as HCA-MRSA). The dynamic emergence and spread of CA-MRSA clones as well as the upward trend in the prevalence of livestock-associated LA-MRSA, in particular in regions with extensive livestock farming, still require special attention. The zoonotic reservoir also plays a

significant role in the introduction of new mec variants (*mecC*) and new resistance genes such as *cfr*. Because of the possible transfer to HA-MRSA, the emergence of *cfr*-mediated linezolid resistance in *Staphylococcus epidermidis* at German hospitals requires particular attention.

The trend towards increasing resistance in *Escherichia coli* isolates from inpatient care to numerous antimicrobial classes commonly used in empiric therapy (e.g. piperacillin/tazobactam, cephalosporins, fluoroquinolones) has not continued. According to the findings of the PEG resistance study, the percentage of strains producing extended-spectrum β-lactamase (ESBL) was 17.4% in 2010 and 14.9% in 2013. In both years, the predominant ESBL was the enzyme CTX-M-15, accounting for more than 50%. The spread of CTX-M-15 is closely associated with the pandemic spread of strains of the clonal lineage O25b-ST131, the percentage of which is > 30% of all ESBL-positive *E. coli* in inpatient and outpatient care as well as in nursing homes. CTX-M-1 is detected among ESBL-positive *E. coli* as the second most common enzyme. CTX-M-1-producing strains are also often isolated from veterinary specimens and detected in food (e.g. poultry). Investigations in the Netherlands suggest that CTX-M-1-producing *E. coli* can be transmitted from poultry to humans. The resistance level of fluoroquinolones is still high, which is why they are only recommended to a limited extent for the empiric therapy of infections with suspected involvement of *E. coli*. By contrast, carbapenems continue to play a major role in the treatment of life-threatening infections due to the still very favourable resistance situation (< 1%). The prevalence of resistance to tigecycline and colistin also continues to be below 1%. Following the emergence of isolates with a plasmid-mediated resistance mechanism in various regions (including Germany), however, the spread of colistin resistance needs to be carefully monitored. 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. However, the "real" extent of the spread of antimicrobial-resistant *E. coli* in outpatient care is not reflected adequately by the existing resistance surveillance systems, since a disproportionately large number of specimens submitted to microbiology laboratories are obtained from patients with risk factors for carriage of resistant organisms. Up to 7% of the general population carry ESBL.

The treatment of *Klebsiella pneumoniae* infections is also being increasingly limited by the emergence of ESBL-producing strains, most of which show resistance not only to cephalosporins but also to numerous other antimicrobials (e.g. piperacillin/tazobactam, fluoroquinolones, gentamicin). CTX-M-15 is again the predominant ESBL. According to the findings of the PEG resistance study, the ESBL rate has increased from 14.7% to 17.4% over the period 2010-2013. By contrast, the resistance situation for carbapenems was still favourable.

Among *Pseudomonas aeruginosa*, great differences continue to be observed in resistance levels between isolates obtained from patients in intensive care units and those from patients on general wards. During recent years, the resistance situation of antipseudomonal antimicrobials has either remained unchanged or has even become more favourable than it was some years ago. The steady decline in gentamicin resistance, which has been observed for more than 10 years, is remarkable. By contrast, the prevalence of carbapenem resistance among *Acinetobacter baumannii* has now reached 30%.

All in all, it can be stated that antimicrobial consumption has not seen any significant change during the last few years. This observation as well as the predominant use of broad-spectrum antimicrobials, in particular cephalosporins and fluoroquinolones, indicate the need to continue the activities in the field of rational antimicrobial prescribing (Antibiotic Stewardship [ABS]). Nevertheless, it should be noted that the resistance situation of many bacterial pathogens has by now stabilised, although at a significantly higher level than prior to the beginning of the last wave of globalisation in the 1990s.

Veterinary Medicine

The present resistance data relating to veterinary pathogens in Germany is predominantly based on the results of the national resistance monitoring of veterinary pathogens, GE*RM*-Vet, conducted by the Federal Office of Consumer Protection and Food Safety (BVL) and the findings of some additional studies. The GE*RM*-Vet monitoring, an annual German wide programme, has been investigating the resistance characteristics of bacteria isolated from both food-producing and companion animals since 2001. Only resistance data of isolates from diseased animals is included in these studies.

The assessment of susceptibility data from veterinary medicine has clearly demonstrated how important it is to differentiate the study results by host species, type of production, bacterial species and organ systems.

Staphylococcus aureus strains isolated from dairy cattle were susceptible to most antimicrobials, in particular to all tested newer cephalosporins. Since 2008, the MRSA rate has increased from 1% to approx. 6%. By contrast, *S. aureus* isolates from poultry showed resistance rates of up to 70% to penicillins, tetracycline and erythromycin, whereas companion animals (dogs and cats) were found to have resistance rates of approx. 66% only to penicillins. The percentage of MRSA in *S. aureus* was approx. 6% in 2013, showing a clear downward trend compared to the 2012 study year (18%). This rate was 25% in companion animals. The percentage of methicillin (oxacillin)-resistant *Staphylococcus pseudintermedius* (MRSP) in *S. pseudintermedius* strains was still 10%.

Bovine *Enterococcus* spp. strains isolated from mastitis samples showed good susceptibility to most antimicrobials, whereas resistance rates of well above 10% were found to erythromycin (26%) and gentamicin (61%). In addition, approx. 30% of the *E. faecalis* isolates were found to show intermediate resistance to gentamicin. The enrofloxacin MIC_{90} values of *E. faecium* isolates were 8 mg/l and those of *E. faecalis* isolates two dilutions lower.

Bordetella bronchiseptica strains isolated from swine as well as from dogs and cats with respiratory tract infections showed high

MIC values for most tested ß-lactam antimicrobials. 88% of the isolates from swine were found to show intermediate resistance to florfenicol. Amounting to 16 mg/l, the MIC_{90} value for marbofloxacin, which was tested for the first time in the 2012/2013 study years, was quite high, whereas the MIC_{90} value of 0.5 mg/l for enrofloxacin suggests good efficacy of this antimicrobial.

Regardless of their host species, the most important bacterial pathogens causing respiratory infections, namely *Pasteurella multocida*, *Mannheimia haemolytica* and *Actinobacillus pleuropneumoniae*, also showed good susceptibility to newer antimicrobials. Florfenicol-resistant bovine and porcine *P. multocida* isolates were not detected.

In 2013, the highest resistance rates among *Escherichia coli* strains (indication enteritis) isolated from dogs and cats were found to ampicillin (71% in total; dogs 100%, cats 38%), tetracycline and trimethoprim/sulphamethoxazole (cotrimoxazole) (24% each). These values were below those of food-producing animals as regards the indication of both "enteritis" and "urogenital tract infections". The resistance rates to the combination of amoxicillin/clavulanic acid varied greatly depending on the animal species and/or the type of use. The lowest resistance rates were found in dairy cattle (2%) as well as in turkeys and laying hens (approx. 5-10%). The highest resistance rates of *E. coli* to this combination were detected in broilers (35%), piglets and porkers (70%). The *E. coli* isolates from small animals rarely showed resistance to amoxicillin/clavulanic acid (10%) and the isolates from store pigs were 100% susceptible. ESBL-producing *E. coli* from calves were detected in 7% of the cases in 2006/2007 and in as many as 28% of the cases in 2013.

Nationwide data on the sales of veterinary antimicrobials has been collected since 2011. Since then, pharmaceutical companies and wholesalers have been required under the Medicinal Products Act (AMG)[1] and the DIMDI Regulation on Medicinal Products[2] to report the annual sales of antimicrobials. In the following year, the sales data is published itemised by region. In 2011, 1,706 t of antimicrobials (primary antimicrobial agent) were sold in total. The most commonly sold antimicrobials were tetracyclines (564 t), aminopenicillins (528 t), sulphonamides (185 t) and macrolides (173 t).[3] The evaluation of the 2012 data has shown that the total sales of veterinary antimicrobials (primary antimicrobial agent) amounted to 1,619 t in 2012.[4] In the two following years, 2013 and 2014, the sales volumes once again dropped, with the total sales volume amounting to 1,452 t in 2013 and 1,238 t in 2014. This means that the total sales volume dropped by approx. 27% within a period of 4 years[5]. The sales volume of fluoroquinolones rose from 8.2 t to 12.3 t during the same period. In spite of the regionalised data, a correlation to the corresponding resistance situation in various animal species cannot be established, since veterinary drugs are often approved for use in several animal species.

Preserving the efficacy of antimicrobials currently available in veterinary medicine is and will continue to be one of our top-priority tasks. This can only be ensured by responsible and intelligent use of antimicrobials in line with the applicable guidelines on antimicrobial use[6].

In vitro susceptibility testing is indispensible before selecting a suitable antimicrobial for therapy, especially before applying antimicrobials that have been observed to have limited efficacy.

Better husbandry conditions, good herd management and optimised hygiene concepts are the most important instruments to achieve a restrictive use of antimicrobials. Calling for a reduction of antimicrobial use alone is not adequate to address this complex problem of the development and spread of antimicrobial resistance.

➤ J. Wallmann
Reviewer. H. Kaspar

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;1230-4.
4. Wallmann J, Reimer I, Bender A, Römer A, et al. Abgabemengenerfassung antimikrobiell wirksamer Stoffe in Deutschland 2012. Dtsch Tierärtzebl 2014;184-6.
5. Wallmann J, Bender A, Reimer I, Heberer T. Abgabemengenerfassung antimikrobiell wirksamer Stoffe in Deutschland 2014. Dtsch Tierärtzebl 2015;1260-5.
6. Anonymous: Leitlinien für den sorgfältigen Umgang mit antimikrobiell wirksamen Tierarzneimitteln; Dtsch Tierärztebl, Beilage Okt. 2010.

1 Zusammenfassung

Humanmedizin

Die Gesamtmenge der im humanmedizinischen Bereich in Deutschland eingesetzten Antibiotika dürfte ca. 700–800 Tonnen pro Jahr betragen.

Das Verordnungsvolumen im ambulanten Bereich macht, hochgerechnet auf die Bevölkerung, ca. 85% des gesamten Antibiotikaverbrauchs (500–600 Tonnen) in der Humanmedizin aus. Im Jahr 2014 wurden nach den Angaben des Wissenschaftlichen Instituts der AOK (WIdO) hier nahezu 45 Mio. Antibiotikaverordnungen mit 448 Mio. definierten Tagesdosen (defined daily doses, DDD) und einem Umsatz von 920 Mio. € im Bereich der gesetzlichen Krankenversicherung getätigt. Diese Zahlenwerte sind allerdings nicht mit den Angaben in früheren GERMAP-Berichten vergleichbar, da aktuell auch der Verbrauch von lokal angewendeten Antibiotika berücksichtigt wurde. Die Verordnungsdichte im Jahr 2014 betrug 17,4 DDD pro 1.000 Versicherte und Tag und zeigt seit 2005 ein im Wesentlichen unverändertes Niveau. Jedoch hat sich das Verordnungsvolumen bei den β-Lactamen mit erweitertem Spektrum (Oralcephalosporine, Aminopenicillin/β-Lactamase-Inhibitor-Kombinationen und Flucloxacillin) in den letzten 10 Jahren mehr als verdoppelt, was auf die sehr starke Zunahme von Cefuroxim(axetil) zurückzuführen ist. Ferner sind nach wie vor große regionale Unterschiede, mit einem deutlich höheren Verbrauch von β-Lactamantibiotika in den westlichen als in den östlichen Bundesländern, zu beobachten. Nach Tagesdosen ist Amoxicillin weiterhin das meistverordnete Antibiotikum. An zweiter Stelle folgt aber bereits das „Reserveantibiotikum" Cefuroxim(axetil), obwohl die Substanz in keiner deutschen Behandlungsleitlinie Mittel der Wahl ist. Der Verordnungsschwerpunkt der Fluorchinolone liegt weiterhin bei den älteren Patienten.

Die wichtigste z.Zt. verfügbare Datenquelle für die Darstellung des Antibiotikaverbrauchs im Krankenhaus stellt das ADKA-if-DGI-Surveillance-Projekt dar. Insgesamt scheint die Verbrauchsdichte im stationären Sektor in den letzten Jahren angestiegen zu sein. Dabei zeigten im Zeitraum 2013/14 nichtuniversitäre Akutkrankenhäuser, unabhängig von der Größe, im Median einen Verbrauch von 59 DDD/100 Pflegetage und Universitätskliniken von 84 DDD/100 Pflegetage. Die im Krankenhaus am häufigsten verordneten Antibiotika im Jahr 2014 waren β-Lactame und Fluorchinolone. Die Verbrauchsdichte auf Intensivstationen war mindestens doppelt so hoch wie auf Normalstationen.

Das Datenmaterial zur Bestimmung der Resistenzsituation stammt größtenteils aus den Studien der Paul-Ehrlich-Gesellschaft für Chemotherapie (PEG) sowie aus den laborgestützten Surveillance-Systemen ARS, SARI und EARS-Net. Darüber hinaus wurden die Resistenzdaten der Nationalen Referenzzentren (NRZ) zur Überwachung wichtiger Infektionserreger analysiert.

Seit der Veröffentlichung des ersten GERMAP-Berichtes mit Angaben zur Resistenzsituation bis zu den Jahren 2006/7 hat sich die Resistenzsituation bei mehreren Erregern z.T. erheblich geändert. Die Häufigkeit der Makrolid-Resistenz bei den Pneumokokken von Patienten mit invasiven Erkrankungen sank von 16,2% (Erwachsene) bzw. 20,8% (Kinder) im Jahr 2007 auf jeweils unter 10% in den Jahren 2013 und 2014. Der Anteil der Penicillin-resistenten Isolate von Kindern liegt seit einigen Jahren mit 3–4% deutlich über der Rate bei Erwachsenen (ca. 1%). Bei nahezu allen Penicillin-resistenten Isolaten handelte es sich um Meningitis-Fälle. Im europäischen Vergleich ist die Resistenzsituation bei den Pneumokokken gegenüber Penicillin in Deutschland aber nach wie vor sehr günstig. Von den Meningokokken aus dem Zeitraum 2002–2011 zeigten durchschnittlich 14% intermediäre Empfindlichkeit gegenüber Penicillin und 0,7% waren resistent. Im Jahr 2012 gab es dann einen Anstieg auf 25% bzw. 2,2%. In 2013 erhöhte sich der Anteil Penicillin-intermediärer Stämme weiter auf 40%, sank jedoch in 2014 wieder auf 22%, während der Anteil Penicillin-resistenter Stämme in den beiden Jahren ein ähnlich hohes Niveau erreichte wie 2012. Die Schwankungen über die Zeit lassen sich mit dem variablen Auftreten von Meningokokken-Klonen oder klonalen Komplexen erklären. So sind 23% der Meningokokken, die zum sogenannten ST-11-Komplex gehören, der einen Großteil der Serogruppe-C-Erkrankungen in Deutschland verursacht, nicht mehr sensibel gegenüber Penicillin. Im Gegensatz dazu ist dies nur bei 5% der Meningokokken der Fall, die zum ST-41/44-Komplex gehören. Dieser klonale Komplex ist für einen großen Teil der Serogruppe-B-Erkrankungen in Deutschland verantwortlich.

Die Antibiotikaempfindlichkeit von *Neisseria gonorrhoeae* wurde in Deutschland erstmalig durch die PEG-Resistenzstudie im Jahr 2010 systematisch erfasst. Seitdem ist eine kontinuierliche Surveillance der Antibiotikaempfindlichkeit von *N. gonorrhoeae* durch das Konsiliarlabor für Gonokokken und das Resistenz-Netzwerk GORENET gegeben. Die WHO fordert von einer kalkulierten suffizienten Therapie der Gonorrhoe einen Heilungserfolg von mindestens 95%. Dieses Ziel scheint z.Zt. nur mit Cephalosporinen der Gruppe 3 und Spectinomycin sicher erreichbar.

Die Inzidenz neu diagnostizierter Erkrankungen an Tuberkulose lag im Jahr 2013 bei 5,3 Erkrankungen je 100.000 Einwohner. Dabei erreichte der Anteil der Fälle von multiresistenter Tuberkulose (MDR-TB) mit 3,4% den höchsten Wert seit der Erfassung der resistenten Tuberkulose im Jahr 2001. Die Resistenzlage bei den beiden häufigsten *Salmonella*-Serovaren in Deutschland stellt sich nach wie vor sehr unterschiedlich dar. Serovar-Enteritis-Isolate sind zu etwa 95% sensibel gegen alle getesteten Antibiotika. Dagegen sind heute die weitaus meisten Serovar-Typhimurium-Stämme mehrfachresistent.

Der Anteil von MRSA an den *Staphylococcus-aureus*-Isolaten lässt für Deutschland einen weiter rückläufigen Trend erkennen. Im Jahr 2014 lag, nach den Angaben des EARS-Net, der Anteil von MRSA an den *S.-aureus*-Blutkulturisolaten im Mittel bei 11,8%. Die Koresistenzen bei MRSA gegen andere Antibiotika als β-Lactame zeigen mit Ausnahme der Fluorchinolone ebenfalls rückläufige Tendenz. Dieser Rückgang ist darauf zurückzuführen, dass die in den letzten Jahren verstärkt auftretenden Varianten (Isolate der klonalen Linie ST22 [„Barnimer Epidemiestamm"] und ST225 [„Rhein-Hessen-Epidemiestamm"]) ein deutlich schmaleres Resistenzspektrum zeigen als ältere epidemische MRSA. Im Krankenhausbereich gehören bis zu 90% der MRSA-Isolate zur Grup-

pe der HA-MRSA und im ambulanten Versorgungsbereich sind es ca. 70%, die hier als HCA-MRSA bezeichnet werden. Besonderer Aufmerksamkeit bedarf nach wie vor die Dynamik im Auftreten und der Verbreitung von CA-MRSA-Klonen sowie von tierassoziierten LA-MRSA, insbesondere in Regionen mit intensiver Nutztierhaltung. Das zoonotische Reservoir ist aber auch für das Einbringen neuer *mec*-Varianten (*mecC*) und neuer Resistenzgene wie *cfr* bedeutend. Insbesondere das Auftreten der *cfr*-kodierten Linezolid-Resistenz bei *Staphylococcus epidermidis* in deutschen Krankenhäusern bedarf wegen der möglichen Übertragung auf HA-MRSA besonderer Aufmerksamkeit.

Bei den *Escherichia-coli*-Isolaten aus dem stationären Bereich hat sich der Trend zur Zunahme der Resistenz gegen die häufig zur kalkulierten Therapie verwendeten Antibiotikagruppen (z.B. Piperacillin/Tazobactam, Cephalosporine, Fluorchinolone) nicht weiter fortgesetzt. Nach den Angaben der PEG-Resistenzstudie lag der Anteil der Stämme, die eine Extended-Spektrum-β-Lactamase (ESBL) bilden, im Jahr 2010 bei 17,4% und im Jahr 2013 bei 14,9%. In beiden Jahren war die dominierende ESBL das Enzym CTX-M-15, mit einem Anteil von jeweils über 50%. Die Ausbreitung von CTX-M-15 steht in engem Zusammenhang mit der pandemischen Verbreitung von Stämmen der klonalen Linie O25b-ST131, deren Anteil im stationären und ambulanten Bereich sowie in Pflegeheimen bei > 30% aller ESBL-positiven *E. coli* liegt. CTX-M-1 wird als zweithäufigstes Enzym bei ESBL-positiven *E. coli* nachgewiesen. CTX-M-1-bildende Stämme werden häufig auch aus veterinärmedizinischem Material angezüchtet und in Nahrungsmitteln (z.B. Geflügelfleisch) gefunden. Untersuchungen aus den Niederlanden deuten darauf hin, dass CTX-M-1-bildende *E. coli* über Geflügelfleisch auf den Menschen übergehen können. Das Resistenzniveau bei den Fluorchinolonen liegt nach wie vor in einem solchen Bereich, dass sie nur bedingt zur kalkulierten Therapie von Infektionen bei Verdacht einer Beteiligung von *E. coli* in Betracht kommen. Demgegenüber besitzen die Carbapeneme aufgrund der unverändert sehr günstigen Resistenzsituation (< 1%) weiterhin einen hohen Stellenwert in der Therapie lebensbedrohlicher Infektionen. Die Resistenzhäufigkeit gegen Tigecyclin und Colistin liegt ebenfalls weiterhin unter 1%. Allerdings muss die Verbreitung der Colistin-Resistenz nach dem Auftreten von Isolaten mit einem Plasmid-kodierten Resistenzmechanismus in verschiedenen Regionen (einschließlich Deutschland) sorgfältig beobachtet werden. Das Resistenzniveau im ambulanten Bereich ist im Allgemeinen deutlich niedriger als im stationären Bereich, aber auch dort sind ESBL bildende und Fluorchinolon-resistente *E. coli* verbreitet. Gleichwohl wird das „wahre" Ausmaß der Ausbreitung Antibiotika-resistenter *E. coli* im ambulanten Bereich durch die verfügbaren Resistenz-Surveillance-Systeme aber nur unzureichend abgebildet, da ein überproportional hoher Anteil der an das mikrobiologische Labor gesendeten Proben von Patienten mit Risikofaktoren für resistente Erreger stammt. In der Normalbevölkerung sind bis zu 7% der Personen mit ESBL besiedelt.

Die Therapie von *Klebsiella-pneumoniae*-Infektionen wird ebenfalls durch das Auftreten ESBL bildender Stämme eingeschränkt, die zumeist nicht nur gegen Cephalosporine, sondern häufig auch gegen zahlreiche andere Antibiotika (z.B. Piperacillin/Tazobactam, Fluorchinolone, Gentamicin) resistent sind. CTX-M-15 ist auch hier die dominierende ESBL. Nach den Angaben der PEG-Resistenzstudie hat sich die ESBL-Rate in dem Zeitraum 2010–2013 von 14,7% auf 17,4% erhöht. Demgegenüber zeigte sich eine unverändert günstige Resistenzsituation für die Carbapeneme.

Bei *Pseudomonas aeruginosa* wurden weiterhin große Unterschiede im Resistenzniveau zwischen den Isolaten von Patienten aus dem Intensivpflegebereich und solchen von Patienten von Allgemeinstationen beobachtet. Die Resistenzsituation bei den *Pseudomonas*-wirksamen Antibiotika war in den letzten Jahren entweder unverändert oder stellt sich sogar günstiger dar als vor einigen Jahren. Auffällig ist vor allem der seit mehr als 10 Jahren zu beobachtende stetige Rückgang der Gentamicin-Resistenz. Demgegenüber hat die Resistenzhäufigkeit bei *Acinetobacter baumannii* gegenüber Carbapenemen inzwischen eine Niveauhöhe von 30% erreicht.

Insgesamt ist festzustellen, dass sich der Antibiotikaverbrauch in den letzten Jahren nicht wesentlich verändert hat. Diese Beobachtung sowie der weiterhin hohe Anteil von Breitspektrum-Antibiotika, insbesondere von Cephalosporinen und Fluorchinolonen, geben Anlass, die Aktivitäten im Bereich rationale Verschreibung (Antibiotic Stewardship [ABS]) fortzusetzen. Gleichwohl ist zu konstatieren, dass bei vielen bakteriellen Infektionserregern inzwischen eine Stabilisierung der Resistenzlage, gleichwohl auf einem deutlich höheren Niveau als vor dem Beginn der letzten Globalisierungswelle in den 1990er-Jahren, erreicht worden ist.

Veterinärmedizin

Die vorliegenden Resistenzdaten tierpathogener Bakterien in Deutschland basieren vor allem auf den Resultaten des nationalen Resistenzmonitorings für tierpathogene Bakterien GE*RM*-Vet, durchgeführt vom Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL), sowie auf einigen zusätzlichen Studienergebnissen. Das GE*RM*-Vet-Monitoringprogramm untersucht seit dem Jahr 2001 in jährlichen Studien deutschlandweit das Empfindlichkeitsverhalten von Bakterien gegenüber Antibiotika, die sowohl von Lebensmittel liefernden Tieren stammen als auch von Heimtieren. Es gehen ausschließlich Resistenzdaten von Bakterienisolaten erkrankter Tiere in die Untersuchungen ein.

Bei der Bewertung der Empfindlichkeitsdaten aus der Veterinärmedizin zeigt sich sehr deutlich, wie wichtig die differenzierte Darstellung der Untersuchungsergebnisse getrennt nach Tierarten, Produktionsrichtung, Bakterienspezies und Organsystemen ist.

Staphylococcus-aureus-Stämme vom Milchrind waren empfindlich gegenüber den meisten Wirkstoffen, insbesondere auch gegenüber allen geprüften neueren Cephalosporinen. Die MRSA-Rate stieg seit 2008 von 1% auf ca. 6%. *S.-aureus*-Isolate vom Geflügel hingegen zeigten Resistenzraten bis zu knapp 70% gegenüber den Penicillinen, Tetracyclin und Erythromycin, während bei den Heimtieren (Hund und Katze) nur gegenüber

Penicillinen Resistenzraten von ca. 66% ermittelt wurden. Der Anteil von MRSA bei *S. aureus* lag beim Geflügel 2013 bei ca. 6% und zeigte damit einen deutlichen Rückgang zum Studienjahr 2012 mit 18%. Beim Heimtier lag die Rate bei 25%. Der Anteil von Methicillin (Oxacillin)-resistentem *Staphylococcus pseudintermedius* (MRSP) bei den *S.-pseudintermedius*-Stämmen lag beim Heimtier weiterhin bei 10%.

Die bovinen *Enterococcus*-spp.-Stämme, isoliert aus Mastitiden, wiesen gegenüber den meisten Wirkstoffen eine gute Empfindlichkeit auf. Resistenzraten von deutlich über 10% wurden hingegen für Erythromycin (26%) und Gentamicin (61%) ermittelt. Gegenüber Gentamicin wurden bei *E. faecalis* zudem ca. 30% intermediär-resistente Isolate diagnostiziert. Die MHK_{90}-Werte für Enrofloxacin lagen für *E.-faecium*-Isolate bei 8 mg/l, bei Isolaten von *E.-faecalis* zwei Tierstufen darunter.

Bordetella-bronchiseptica-Stämme, isoliert von Schweinen bzw. von Hunden und Katzen mit einer respiratorischen Erkrankung, zeigten hohe MHK-Werte gegenüber den meisten getesteten β-Lactamantibiotika. Bei den Isolaten vom Schwein wurde für Florfenicol ein Anteil von 88% intermediär-resistenten Isolaten festgestellt. Der MHK_{90}-Wert für das erstmals in den Studienjahren 2012/2013 untersuchte Marbofloxacin mit 16 mg/l war recht hoch, während von einer guten Wirksamkeit von Enrofloxacin mit einem MHK_{90}-Wert von 0,5 mg/l auszugehen war.

Die wichtigsten bakteriellen Erreger von Atemwegsinfektionen *Pasteurella multocida*, *Mannheimia haemolytica* und *Actinobacillus pleuropneumoniae* zeigten unabhängig von der tierartlichen Herkunft eine gute Empfindlichkeit auch für die neueren Wirkstoffe. Florfenicol-resistente *P.-multocida*-Isolate wurden von Rindern und Schweinen nicht diagnostiziert.

Die höchsten Resistenzraten bei den *Escherichia-coli*-Stämmen (Indikation Enteritis) von Hund und Katze wurden 2013 für Ampicillin (insgesamt 71%: Hund 100%, Katze 38%), Tetracyclin und Trimethoprim/Sulfamethoxazol (Cotrimoxazol) (jeweils 24%) ermittelt. Diese Werte lagen unter denen der Lebensmittel liefernden Tiere, sowohl bei der Indikation „Enteritis" als auch bei „Erkrankungen des Urogenitaltraktes". Gegenüber der Kombination Amoxicillin/Clavulansäure wurden in Abhängigkeit von der Tierart bzw. Nutzungsrichtung sehr unterschiedliche Werte diagnostiziert. Die niedrigsten Resistenzraten wurden sowohl beim Milchrind (2%) als auch bei der Pute und Legehenne (ca. 5–10%) protokolliert. Die höchsten Resistenzraten bei *E. coli* gegenüber dieser Kombination wurden bei Broiler (35%), Ferkel und Mastschwein (70%) verzeichnet. Die *E.-coli*-Isolate vom Kleintier zeigten gegenüber Amoxicillin/Clavulansäure selten Resistenz (10%) und die Isolate vom Läufer waren zu 100% empfindlich. ESBL bildende *E. coli* vom Kalb wurden 2006/2007 in 7% der Fälle und 2013 bereits in 28% der Fälle detektiert.

Bundesweite Daten zu den Abgabemengen von Antibiotika an Tierärzte werden seit dem Jahr 2011 erfasst. Seit diesem Zeitpunkt müssen die pharmazeutischen Unternehmer und Großhändler gemäß AMG[1] und der DIMDI-Arzneimittelverordnung[2] die abgegebenen Mengen an Antibiotika pro Jahr melden. Im Folgejahr werden die regional aufgegliederten Abgabemengen veröffentlicht. Insgesamt wurden im Jahr 2011 1.706 t Antibiotika (Grundsubstanz) abgegeben. Die am häufigsten abgegebenen Wirkstoffe waren: Tetracycline (564 t), Aminopenicilline (528 t), Sulfonamide (185 t) und Makrolide (173 t).[3] Die Auswertung der Daten für 2012 ergab, dass in 2012 insgesamt 1.619 t Antibiotika (Grundsubstanz) an Tierärzte abgegeben wurden[4]. In den beiden folgenden Jahren 2013 und 2014 sanken die Abgabemengen erneut, sodass für 2013 eine Gesamtabgabemenge von 1.452 t und für 2014 von 1.238 t errechnet wurde. Damit sank die Gesamtabgabemenge im Zeitraum von 4 Jahren um ca. 27%.[5] Im gleichen Zeitraum stieg die Abgabemenge an Fluorchinolonen von 8,2 t auf 12,3 t an. Eine Korrelation zu den entsprechenden Resistenzdaten aus dem Tierbereich kann trotz regionalisierter Abgabemengendaten nicht hergestellt werden, da die Präparate häufig für mehrere Tierarten zugelassen sind.

Eine unserer Aufgaben mit höchster Priorität wird auch in Zukunft der Erhalt der Wirksamkeit der derzeit für die Veterinärmedizin verfügbaren antibakteriellen Wirkstoffe sein. Sichergestellt werden kann dies nur durch einen verantwortungsbewussten und intelligenten Einsatz der Wirkstoffe gemäß den gültigen Antibiotika-Leitlinien.[6]

Vor der Auswahl eines geeigneten Antibiotikums zur Therapie, insbesondere vor Anwendung von Wirkstoffen, von denen bekannt ist, dass eine eingeschränkte Wirksamkeit vorhanden sein könnte, ist eine Testung der in vitro-Empfindlichkeit unverzichtbar.

Verbesserte Haltungsbedingungen, ein gutes Herdenmanagement und optimierte Hygienemaßnahmen sind die wichtigsten Instrumente, um einen restriktiven Einsatz von Antibiotika zu erreichen. Die alleinige Forderung nach Verringerung der Menge an eingesetzten Wirkstoffen wird der komplexen Problematik der Antibiotikaresistenzentwicklung und -ausbreitung nicht gerecht.

➤ J. Wallmann
Reviewer: H. Kaspar

1. Arzneimittelgesetz in der Fassung der Bekanntmachung vom 12. Dezember 2005 (BGBl. 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 Tierärztebl 2013;9:1230-4.
4. Wallmann J, Reimer I, Bender A, Römer A, et al. Abgabemengenerfassung antimikrobiell wirksamer Stoffe in Deutschland. Dtsch Tierärztebl 2014;2:184-6.
5. Wallmann J, Bender A, Reimer I, Heberer T. Abgabemengenerfassung antimikrobiell wirksamer Stoffe in Deutschland 2014. Dtsch Tierärztebl 2015;9:1260-5.
6. 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 in previous years, antimicrobials were among the top-selling drugs prescribed in outpatient care under statutory health insurance (SHI) in 2014. In terms of prescribing rate by number of packages prescribed, they have been taking a leading position among the five most frequently prescribed active drug 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]

Prescription volume

The development of the 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 had initially dropped since 2005 before significantly increasing again from 2012 onwards. In 2014, 45 million prescriptions, accounting for 448 million DDD and a sales volume of € 920 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. Compared to previous reports, the classification system has been changed in the present issue; for example, the group of topical antimicrobials has been added. The current data thus cannot directly be compared with the evaluations published in previous GERMAP issues.

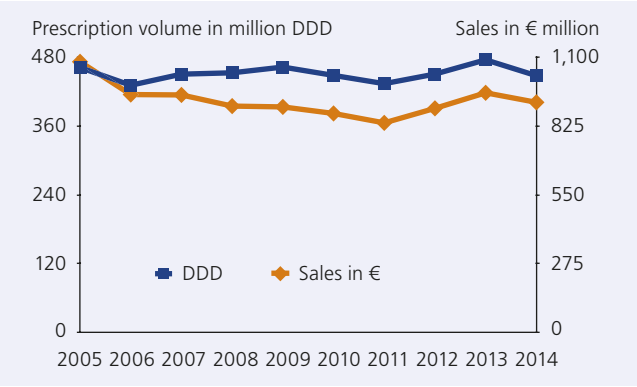


Fig. 2.1.1: Development of prescription volume (in DDD) and antimicrobial sales (in €) over the last ten years (Sources: WIdO, SHI Drug Index)

In 2014, basic penicillins again took first place, followed by topical antimicrobials, tetracyclines and macrolides (Tab. 2.1.1). Accounting for 85 million DDD, amoxicillin (without the marketed combination therapies for *Helicobacter* eradication that include this drug) was the antimicrobial agent with the highest prescription volume in 2014. Accounting for 55.1 million DDD, cefuroxime replaced doxycycline (48.4 million DDD) to rank second.

As regards antimicrobial classes, the increase in the prescription volume of extended-spectrum β-lactams (oral cephalosporins aminopenicillin/β-lactamase inhibitor and flucloxacillin) over the last 10 years is particularly high (+111.3%), whereas the prescription volume of basic penicillins remained nearly constant, and that of tetracyclines and folic acid antagonists (incl. co-trimoxazole) dropped over the same period. The most significant increase in prescription volume over the last 10 years has been observed for cefuroxime axetil (Fig 2.1.2), although this substance is not recommended for first-line therapy in any of the German practice guidelines.[1]

Tab. 2.1.1: Antimicrobials prescribed (by daily dose) in 2014 under statutory health insurance (Source: WIdO)

	Prescribed daily doses (million DDD)	Average DDD costs in €
Basic penicillins (oral penicillins and/or aminopenicillins)	105.8	1.14
Oral cephalosporins, aminopenicillin/ β-lactamase inhibitor, flucloxacillin	89.0	2.7
Topical antimicrobials	70.0	1.4
Tetracyclines	54.2	0.8
Newer macrolides/ketolides/azalides	42.0	2.3
Quinolones	34.5	3.1
Erythromycin and other older macrolides	22.4	2.6
Special urinary tract antimicrobials	13.6	2.6
Folic acid antagonists (incl. co-trimoxazole)	12.9	2.0

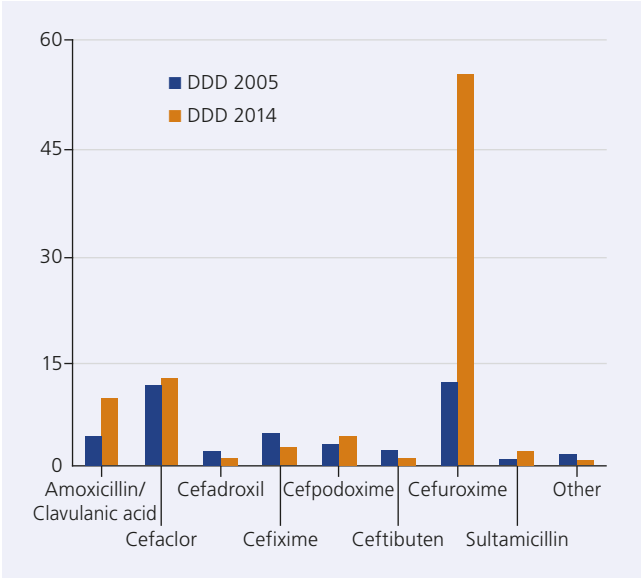


Fig. 2.1.2: Development of prescription volume (in million DDD) of selected β-lactam antimicrobials 2005-2014 (Sources: WIdO, SHI Drug Index)

The share of tetracyclines in the total antimicrobial prescription volume has long since been declining, accounting for 28% (all DDD) in 1991 before dropping to 19% and 12% in 2005 and 2014, respectively.

During the last 3 years, the overall changes have been less dramatic. However, the consumption of oral cephalosporins and special urinary tract antimicrobials (among them nitrofurantoin and fosfomycin-trometamol) has continued to increase (Tab. 2.1.2).

When looking at the prescription volume of systemic antimicrobials, i.e. without taking the DDD into account, oral cephalosporins

Tab. 2.1.2: Changes in the outpatient prescription volume (by daily dose) of certain antimicrobial classes between 2012 and 2014 (Sources: WIdO, SHI Drug Index)

	Change in %
Basic penicillins (oral penicillins and/oraminopenicillins)	+1.8%
Oral cephalosporins, aminopenicillin/ β-lactamase inhibitor, flucloxacillin	+9.3%
Tetracyclines	-9.1%
Newer macrolides/ketolides/azalides	-5.3%
Quinolones	-6.5%
Erythromycin and other older macrolides	-9.4%
Special urinary tract antimicrobials	+6.1%
Folic acid antagonists (incl. co-trimoxazole)	-8.5%

accounted for nearly 22% and basic penicillins only for about 18%. This "predominance" in the prescription volume of oral cephalosporins over penicillins has been observed for many years and is very remarkable in international comparison.

Use density

The figures relating to outpatient antimicrobial consumption can be described as use density expressed in DDD per insured persons and year or DDD per 1,000 insured persons and day, which allows for comparing both the longitudinal and cross-sectional data on a both regional and international scale. These figures are available for the approximately 70 million insured covered by SHI (87% of the population living in Germany). Data for such evaluations is not available from private health insurers.

The development of outpatient antimicrobial use density in Germany over the last 10 years is shown in Fig. 2.1.3. In terms of insured covered by SHI, about 17.4 DDD per 1,000 insured and day were prescribed in 2014 (Fig. 2.1.3). When evaluating the data from previous publications for a comparison with more recent data, it should be noted that these figures may be based on previous DDD definitions which no longer apply today and that topical antimicrobials have now been included as well. When applying the current dose definitions retrospectively (Fig. 2.1.3), a slight increase in use density (all antimicrobials incl. topical forms of application) over the last ten years and up to 2013 becomes apparent.

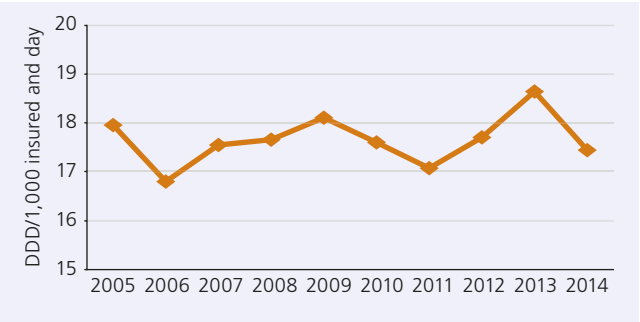


Fig. 2.1.3: Outpatient antimicrobial use density (in DDD per 1,000 insured and day) in Germany since 2005 (Sources: WIdO, SHI Drug Index, systemic and topical antimicrobials)

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 at hospitals 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 in Germany is estimated to range between 700 and 800 tonnes per year. However, the reliability of consumption data expressed in tonnes is limited. The daily doses vary greatly between substances and substance classes and may therefore have a considerable influence on the "tonnage", even if the changes in daily doses are minor.

Outpatient prescriptions in European comparison

Compared to other European countries, Germany is still ranking in the lower third with an outpatient use density of < 16 DDD/1,000 insured/day (exclusively systemic antimicrobials, i.e. excluding topical substances) – along with the Netherlands, Austria, the Scandinavian and Baltic countries, Slovenia and Hungary (Fig. 2.1.4). Greece and Romania as well as France, Italy, Belgium and Luxembourg were among the European top users in 2011, 2012 as well as in 2013.[4] This is also likely to be the case in 2014. Physicians in these countries prescribed more than twice as many antimicrobials as German ones. The orders of magnitude have only seen minor changes during the last few years (Fig. 2.1.4).

The figures for the Netherlands (approx. 10-11 DDD/1,000) and Switzerland[5] show the possible "lower" end of the use density in a modern society without any recognisable detrimental effects on quality. They may point to potential room for optimisation in the German healthcare system – however, it cannot be ruled out that this seemingly very low consumption could at least to some extent be compensated for by the inpatient use density. Similarly low use densities are observed in the Baltic States.

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 the cases, an antimicrobial therapy is not indicated. The "*Choosing wisely*" campaign (*www.choosingwisely.org*) as well as other guidelines and recommendations also call for avoiding the unnecessary use of antimicrobials, especially in this indication. Studies have provided sufficient evidence that the use of antimicrobials in upper respiratory tract infections is only indicated and beneficial in exceptional cases. A good example is a relatively recent study which impressively demonstrates that in elderly patients suffering from cough for several days without suspected pneumonia amoxicillin is not more effective than a placebo.[6]

When comparing the antimicrobial consumption in the Netherlands and Germany, the special organisation of medical care in the Netherlands should be taken into account. Moreover, there are significant differences between the two countries as regards qualified staff incl. specialists. In the Netherlands, measures to prevent antimicrobial resistance are implemented in a uniform manner on the basis of current guidelines. Recommendations/guidelines for antimicrobial therapy are issued and regularly updated by a commission (Stichting Werkgroep Antibiotikabeleid; www.swab.nl).

Use density by region

Significant regional differences in antimicrobial consumption within Germany were evaluated specifically and described in

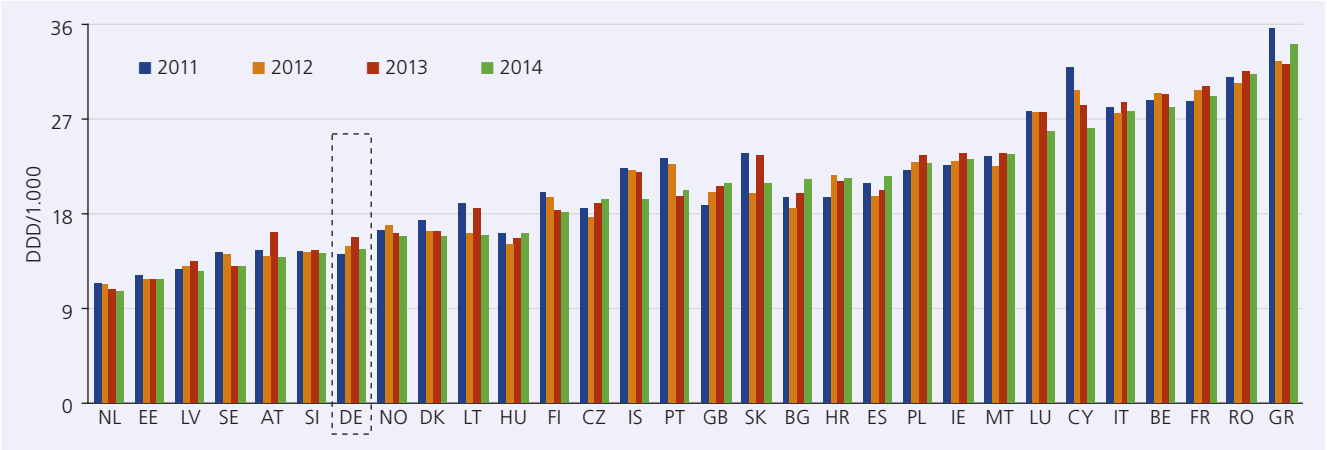


Fig. 2.1.4: Use density of systemic antimicrobials used in outpatient care in Germany (DE, edged) compared to other European countries at population level, expressed as DDD per 1,000 insured or inhabitants and day (Source: ESAC-Net, 2011-2014 data)

greater detail for the first time in 2011.[7] Especially in the western federal states, physicians prescribed significantly more antimicrobials than in the five "new" (after reunification) states in the east.

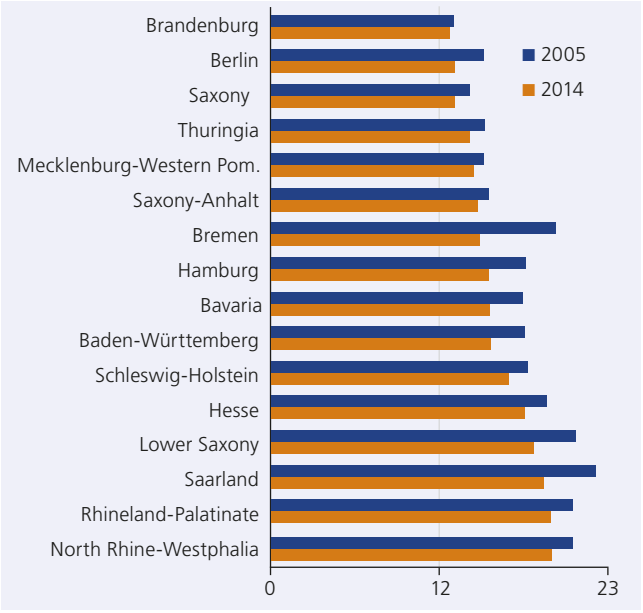


Fig. 2.1.5: Regional antimicrobial use density in 2005 and 2014 (DDD/1,000 insured/day) (Sources: WIdO, SHI Drug Index, systemic and topical antimicrobials)

These regional differences have since then seen no substantial change.[8-13] In 2005, for example, the use density in the "old" states ranged between 17.2 DDD/1,000/day (Bavaria) and 22.2 DDD/1,000/day (Saarland), thus significantly exceeding that in the "new" states (between 12.5 and 14.8 DDD/1,000/day).

The 2014 figures show a range from 12.2 DDD/1,000/day in Brandenburg to 19.2 DDD/1,000/day in North Rhine-Westphalia (Fig. 2.1.5 and 2.1.6), which has superseded Saarland at the top of the list. In all regions, especially in the western states, fewer antimicrobials were prescribed in 2014 than in 2005.

Notably, β-lactam consumption (basic penicillins and oral cephalosporins) continues to be higher in the western region, and penicillin consumption, in particular, is comparatively low in the eastern states, 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. There are distinct differences in the preference for certain antimicrobials, e.g. fluoroquinolones, between the regions: for example, the three major high-consumption regions of moxifloxacin in 2011 were the eastern federal states of Mecklenburg-Western Pomerania, Brandenburg and Saxony-Anhalt, with Saarland, Rhineland-Palatinate and Baden-Württemberg being the leaders in levofloxacin consumption (Fig. 2.1.6).

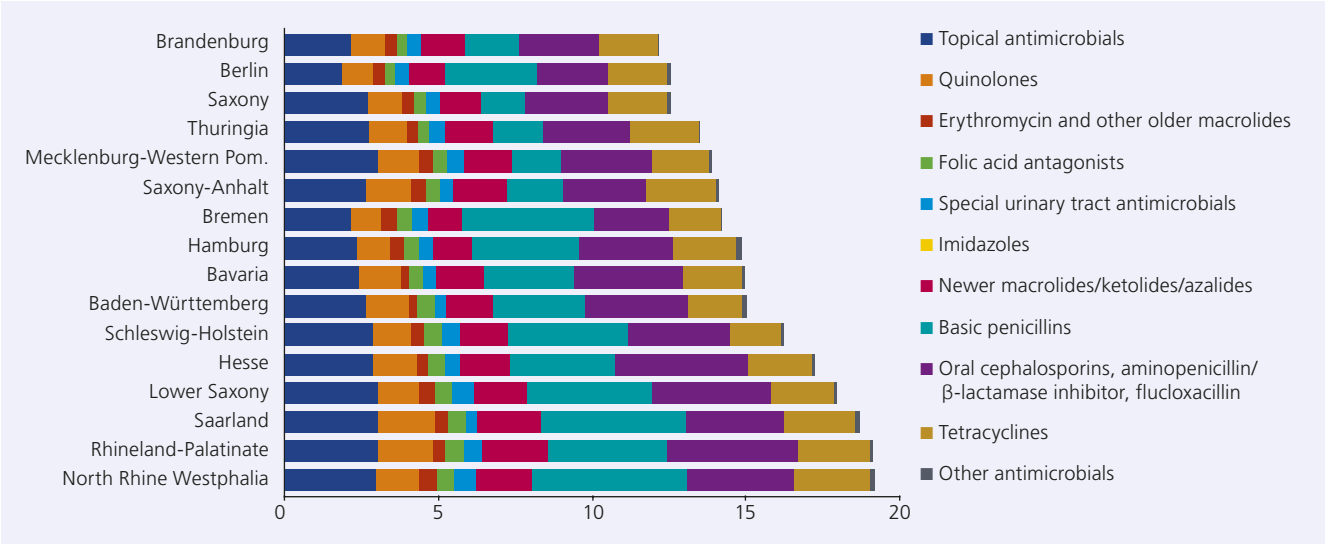


Fig. 2.1.6: Antimicrobial use density (in DDD per 1,000 insured and day) in 2014 by KV regions; excl. prescriptions by dentists (Source: WIdO)

Tab. 2.1.3: Regional differences in the prescribing of certain antimicrobial classes in 2014 in DDD/1,000 insured and day (Source: WIdO)

	East	South	West
Basic penicillins (oral penicillins and/oraminopenicillins)	1.9	2.9	4.3
Oral cephalosporins, aminopenicillin/ β-lactamase inhibitor, flucloxacillin	2.6	3.5	3.7
Topical antimicrobials	2.5	2.9	2.9
Tetracyclines	2.0	1.8	2.2
Newer macrolides/ketolides/azalides	1.4	1.5	1.8
Quinolones	1.2	1.3	1.4
Special urinary tract antimicrobials	0.5	0.4	0.6
Folic acid antagonists (incl. co-trimoxazole)	0.4	0.5	0.6
Erythromycin and other older macrolides	0.4	0.3	0.5

East: Berlin, Brandenburg, Saxony, Saxony-Anhalt, Mecklenburg-Western Pomerania, Thuringia; South: Bavaria, Baden-Württemberg; West: North Rhine-Westphalia, Lower Saxony, Bremen, Hamburg, Schleswig-Holstein, Hesse, Rhineland-Palatinate, Saarland

Use density by specialist group

Prescriptions by general practitioners in Germany accounted for approx. 46% of all antimicrobial prescriptions (in DDD) in 2014 (Fig. 2.1.7). They were responsible for 45% of the total penicillin consumption, 49% of all macrolide prescriptions and 54% of all quinolone prescriptions. They were followed by internists working as general practitioners, paediatricians and dentists ranking second, third and fourth, respectively.

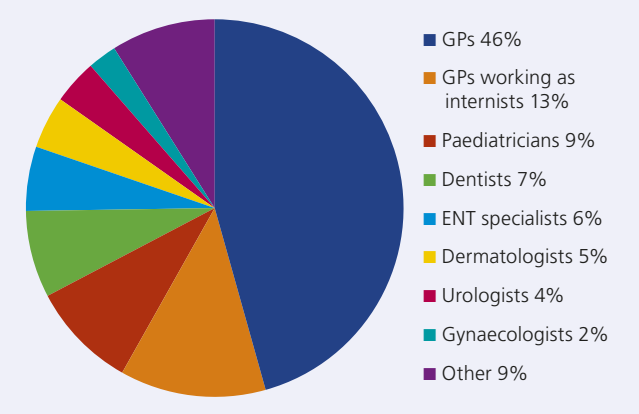


Fig. 2.1.7: Share of individual specialist groups in total antimicrobial consumption in Germany in 2014 (Sources: WIdO, SHI Drug Index, systemic and topical antimicrobials)

The various specialist groups set different priorities in selecting antimicrobials: penicillins and oral cephalosporins accounted for 45% of all daily doses prescribed by general practitioners. ENT specialists also focussed on these antimicrobial classes, accounting for 62% of the prescribed daily doses of antimicrobials. Paediatricians also preferably prescribed these antimicrobial classes (47%), with topical antimicrobials, mainly gentamicin and kanamycin (as eye drops), having been prescribed particularly often (40%). By contrast, the prescribing behaviour of urologists was expectedly entirely different: quinolones accounted for 25% and other urinary tract antimicrobials for 31% of the prescribed DDD of antimicrobials. Dermatologists prescribe tetracyclines by far the most frequently (47%); this is explained by the use of doxycycline and other tetracyclines in the treatment of acne.

The highest antimicrobial prescription volume (by daily dose) per physician was demonstrated by ENT specialists and paediatricians, followed by urologists, dermatologists and general practitioners (Tab. 2.1.4).

Tab. 2.1.4: Antimicrobial prescription volume per physician of certain specialist groups in 2014 (Source: WIdO)

Specialist group	DDD of antimicrobials prescribed per specialist
ENT specialists	5,563
Paediatricians	5,533
Urologists	5,309
Dermatologists	5,243
GPs	5,003
All physicians	2,186

Use density by age group

Based on daily doses, antimicrobials are prescribed more often in childhood (< 5 years) and in old age (≥ 80 years) 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.

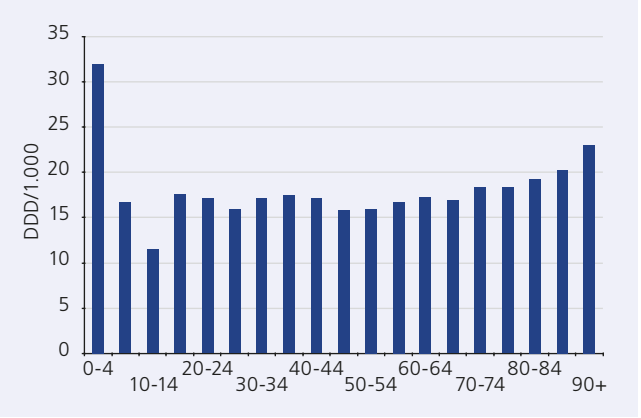


Fig. 2.1.8: Antimicrobial use density (in DDD per 1,000 insured and day) in dependence on age (age groups in years) in 2014 (Sources: WIdO, SHI Drug Index, systemic and topical antimicrobials)

The prescribing rate (in %) in childhood is considerable: In 2010, antimicrobials were prescribed to nearly 70% of all children aged < 5 years. This rate is approximately twice as high as in other age groups.[14] In 2010, the prescribing rate in the age group of ≤ 15 years was 39%, compared to a rate of < 30% in the age group of 40-74 years.[15]

In addition to topical antimicrobials, basic penicillins and oral cephalosporins were used predominantly in childhood. Up to the age of 15 years, the consumption of topical antimicrobials drops significantly in favour of penicillins, which represent the most commonly prescribed antimicrobial class in the age group of 5-44 years, accounting for more than 30%. Not until the age of 60 years does its rate drop to below 20%. Accounting for more than 20%, oral cephalosporins play a significant role in all age groups. Above the age of 15 years, tetracyclines are prescribed at a constant rate of approx. 15%, which does not decrease until the age of 75 years. Fluoroquinolones increasingly gain significance with age, reaching a rate of more than 10% in patients aged ≤ 50 years. By contrast, macrolides lose significance with increasing age (Fig. 2.1.9).

Especially as regards the prescribing rates in children, relatively high rates (2010 data) – unlike in adults – are observed in some of the new states in the east, namely Thuringia, Saxony-Anhalt and Mecklenburg-Western Pomerania.[12] The reasons for this are not quite clear. This observation has also been made for Saxony-Anhalt and Mecklenburg-Western Pomerania in previous studies.[13]

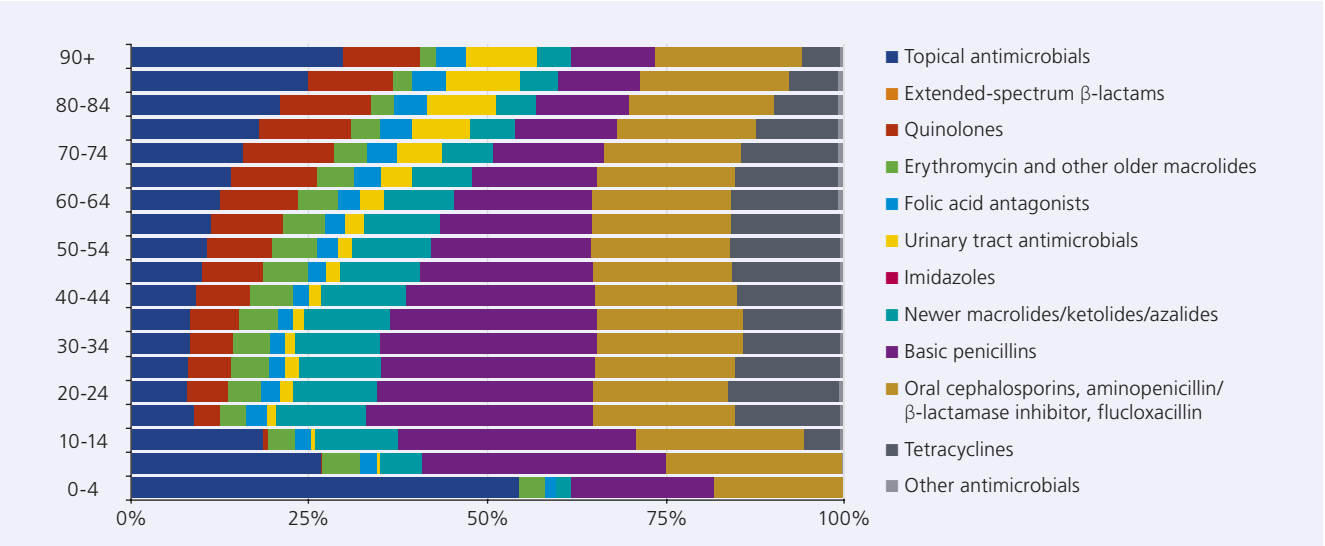


Fig. 2.1.9: Prescribing rate of antimicrobial classes (in DDD) in dependence on age (age groups in years) in 2014 (Sources: WIdO, SHI Drug Index, systemic and topical antimicrobials)

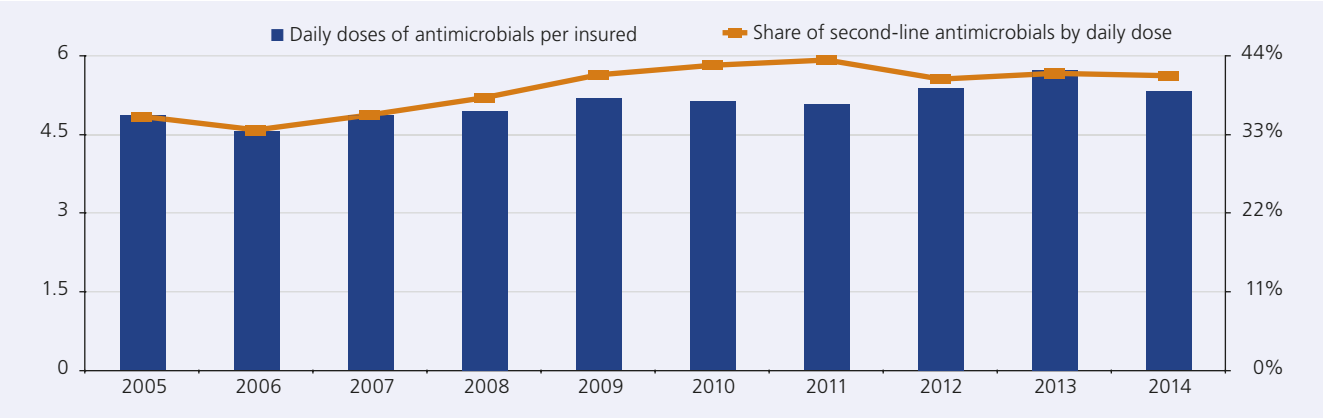


Fig. 2.1.10: Antimicrobial consumption in DDD per insured and year and share of second-line antimicrobials by DDD during the period 2005-2014 (Source: WIdO, SHI Drug Index)

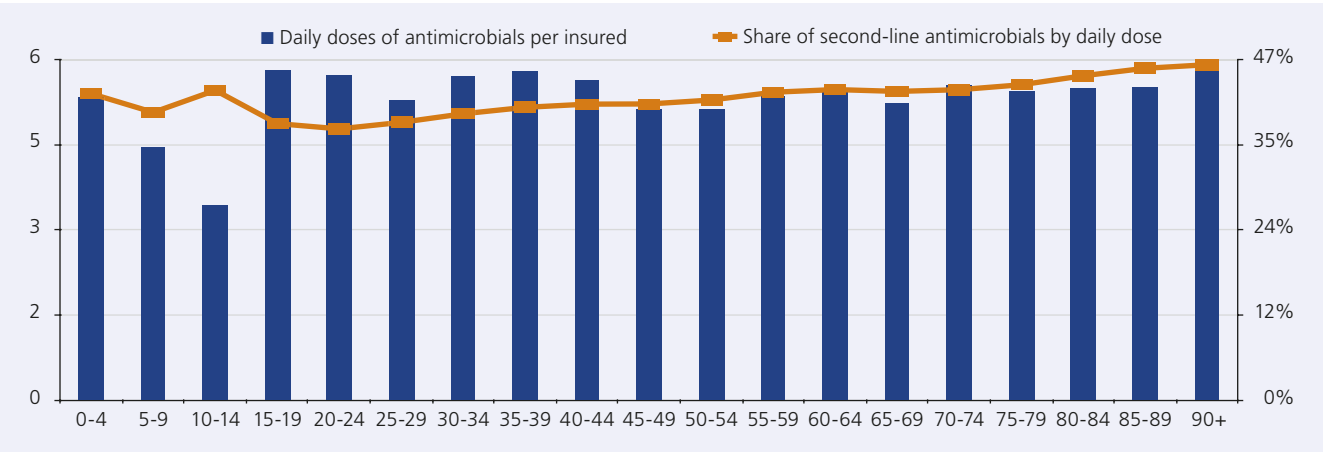


Fig. 2.1.11: Antimicrobial consumption in DDD per insured and year and share of second-line antimicrobials by DDD in 2014 (Source: WIdO, SHI Drug Index)

Consumption of second-line antimicrobials

When defining extended-spectrum β-lactams (incl. oral cephalosporins), newer macrolides and fluoroquinolones as second-line antimicrobials, the share of this group, based on daily doses of systemic antimicrobials, had been increasing slowly but steadily for many years until 2011 and has remained nearly constant since 2012, accounting for 41% in 2014 (Fig. 2.1.10).

It is interesting to see that this share, based on age groups, increases with age, whereas it amounts to approx. 38% in the age group of 15-19 years, it rises to above 46% in the age group of > 90 years (Fig. 2.1.11).

There are also regional differences: the share of second-line antimicrobials so defined is the lowest in Bremen (35%) and is significantly higher in Mecklenburg-Western Pomerania (52%)

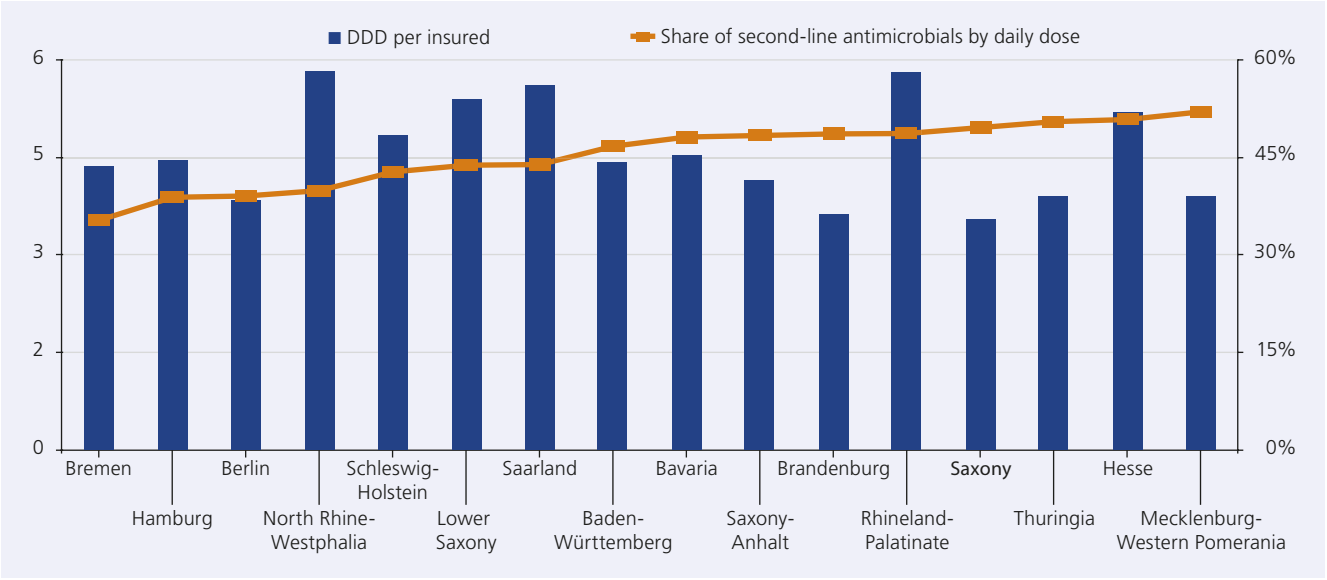


Fig. 2.1.12: Regional antimicrobial consumption in DDD per insured and year and share of second-line antimicrobials by DDD in 2014; excl. prescriptions by dentists (Source: WIdO, SHI Drug Index)

(Fig. 2.1.12). These figures are not adjusted for various influence factors, such as the age of the respective population.

Tab. 2.1.5 lists the ten most commonly prescribed systemic second-line antimicrobials, as defined above (ATC group J01). Altogether, these make up nearly 40% of the total prescription volume of all systemic antimicrobials by daily doses.

Conclusion

Showing an outpatient systemic antimicrobial consumption of 16 DDD per 1,000 insured and day, Germany remains in the lower third compared to other European countries – on a similar level with the Netherlands, Austria, the Scandinavian and Baltic countries, Slovenia and Hungary. Western states, predominantly those bordering France, Luxembourg and Belgium, remain the high-consumption regions within Germany; however, Saarland 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, with a slight decline being observed in 2014. The increase particularly applies to fluoroquinolones and oral cephalosporins 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, may be potential reasons for the differences in use density and prescription profile in Germany.

The overall consumption appears to be high, especially in view of the fact that second-line antimicrobials should only be prescribed for second-line therapy, i.e. once the first-line therapy has failed or seems to be unsuitable[15,16]. Newer macrolides, cephalosporins and fluoroquinolones are frequently prescribed for diseases that can be treated relatively easily with other antimicrobial classes, and often even for diseases that can be treated without antimicrobials at all. The high outpatient prescribing rates of these antimicrobials indicate the need to reconsider the prescription patterns, because the unjustified use of antimicrobials accelerates the development of resistance in bacteria, thereby contributing to the selection of multidrug-resistant pathogens.

Tab. 2.1.5: Prescriptions, sales and daily doses (DDD) of the ten leading so-called second-line antimicrobials in 2014 (Sources: WIdO, SHI Drug Index)

Antimicrobial	Prescriptions in '000	Sales in million EUR	Daily doses in million DDD
Cefuroxime	4,695	92.0	55.1
Ciprofloxacin	3,947	60.2	20.1
Clarithromycin	1,597	24.4	15.9
Azithromycin	2,713	37.5	13.5
Cefaclor	1,651	31.7	12.4
Roxithromycin	1,380	21.3	11.8
Levofloxacin	1,212	18.6	8.1
Cefpodoxime	727	17.9	4.3
Moxifloxacin	439	20.2	3.1
Cefixime	366	8.7	2.6
Total	18,728	332.5	146.8
Total of all second-line antimicrobials	19,902	420.8	153.9

➤ W.V. Kern, J. Schaufler, C. Telschow
Reviewer: R. Berner, M. Kresken

1. Schwabe U, Paffrath D (Hrsg): Arzneiverordnungs-Report 2015: Aktuelle Daten, Kosten, Trends und Kommentare. Springer-Verlag, Berlin, Heidelberg 2015.
2. Kern WV, Steib-Bauert M, de With K. Comment on: hospital consumption of antibiotics in 15 European countries: results of the ESAC Retrospective Data Collection (1997–2002). J Antimicrob Chemother 2006;58:900-1.
3. Adriaenssens N, Coenen S, Versporten A, Muller A, et al. European Surveillance of Antimicrobial Consumption (ESAC): outpatient antibiotic use in Europe (1997-2009). J Antimicrob Chemother 2011;66 Suppl 6:vi3-12.
4. ECDC. Summary of the latest data on antibiotic consumption in the European Union, November 2015. ESAC-Net. http://ecdc.europa.eu/en/eaad/antibiotics-get-informed/antibiotics-resistance-consumption/Documents/antibiotics-consumption-EU-data-2015.pdf.
5. Achermann R, Suter K, Kronenberg A, Gyger P, et al. Antibiotic use in adult outpatients in Switzerland in relation to regions, seasonality and point of care tests. Clin Microbiol Infect 2011;17:855-61.
6. Little P, Stuart B, Moore M, Coenen S, et al. Amoxicillin for acute lower-respiratory-tract infection in primary care when pneumonia is not suspected: a 12-country, randomised, placebo-controlled trial. Lancet Infect Dis 2013;13:123-9.

7. Günther J, Kern WV, Nink K, Schröder H, et al. Solange sie noch wirken… Analysen und Kommentare zum Antibiotikaverbrauch in Deutschland. WIdO Bonn/Universitat Freiburg 2003.
8. de With K, Schröder H, Meyer E, Nink K, et al. Antibiotic use in Germany and European comparison. Dtsch Med Wochenschr 2004;129:1987-92.
9. GERMAP 2012: Bundesamt für Verbraucherschutz und Lebensmittelsicherheit, Paul-Ehrlich-Gesellschaft für Chemotherapie e.V., Infektiologie Freiburg. Bericht über den Antibiotikaverbrauch und die Verbreitung von Antibiotikaresistenzen in der Human- und Veterinärmedizin in Deutschland, Antiinfectives Intelligence, Rheinbach, 2014. http://www.p-e-g.org/econtext/germap.
10. Glaeske G, Schicktanz C, Janhsen K. GEK-Arzneimittel-Report 2008. Asgard-Verlag, St. Augustin 2008.
11. Glaeske G, Hoffmann F, Koller D, Tholen K, et al. Faktencheck Gesundheit - Antibiotika-Verordnungen bei Kindern. Bertelsmann Stiftung, Gütersloh 2012.
12. Augustin J, Mangiapane S, Kern WV. A regional analysis of outpatient antibiotic prescribing in Germany in 2010. Eur J Public Health 2015; 25:397-9.
13. Kern WV, de With K, Nink K, Steib-Bauert M, et al. Regional variation in outpatient antibiotic prescribing in Germany. Infection 2006;34:269-73.
14. Schröder H. Hände weg von der eisernen Reserve. Gesundheit und Gesellschaft 2011;7-8/11:20-6.
15. Höffken G, Lorenz J, Kern WV, Welte T, et al. Guidelines for the epidemiology, diagnosis, antimicrobial therapy and management of community- acquired pneumonia and lower respiratory tract infections in adults. Dtsch Med Wochenschr 2010;135:359-65.
16. WHO The evolving threat of antimicrobial resistance - Options for action 2012. http://www.who.int/patientsafety/implementation/amr/publication/en/.

2.2 Hospital antimicrobial consumption

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. These changes 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 observed over the past years – merely due to the fact that the number of cases has increased while the length of stay has decreased.

The primary data sources used to describe hospital antimicrobial consumption in Germany include the data collected within the ADKA-if-DGI (until 2015 ADKA-if-RKI) surveillance project (www.antiinfektiva-surveillance.de), which evolved out of the MABUSE network. The number of participants in this surveillance project has increased considerably since 2011 – as a result of the accelerated, quarterly data evaluation (individual antimicrobial report) thanks to the RKI's support in 2014/2015 and result of the greater willingness to participate in the surveillance project since the amendment of the Infection Protection Act in 2011 (Fig. 2.2.1). The participating hospitals often present the data for the last calendar year (4 quarters) with a considerable delay. The most recent comparative evaluation of data from 4 full quarters in both 2013 or 2014 is available for 141 acute-care hospitals. Paediatric and psychiatric departments were not included in this evaluation.

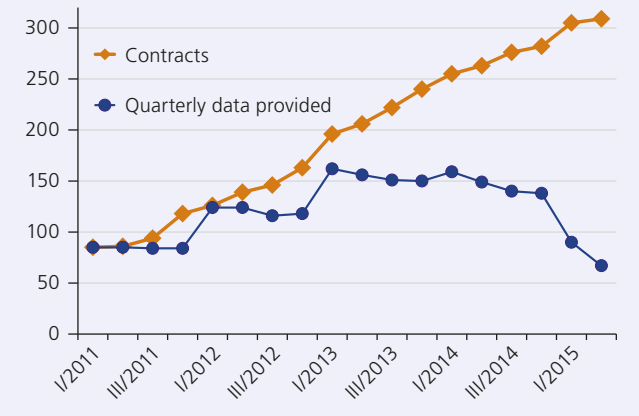


Fig. 2.2.1: Participating hospitals (contracts) and data provided (full quarterly data) within the ADKA-if-DGI project (Source: Infectiology Freiburg)

As before, inpatient antimicrobial use density can be best calculated as "recommended daily doses" (RDD) or – for the purpose of international comparison – as defined daily doses (DDD, according to ATC-WHO) per 100 patient days (RDD/100 or DDD/100) or per hospital case. However, the use of DDD remains problematic, since they often do not correspond to the daily doses commonly used and prescribed at hospitals – especially regarding the frequently used β-lactams, here, in turn, mainly penicillins.[1,2] The currently applicable DDD definitions of the WHO as well as the RDD definitions used herein are provided in chapter 7.3.

In the present report, the most recent 2013/2014 data is again compared with the 2004 data (survey conducted by the MABUSE network using IMS data of 184 acute-care hospitals). However, it should be considered that the 2004 and 2013/2014 hospital cohorts are not congruent.

According to the recent data, the median antimicrobial use density at German acute-care hospitals in 2013/2014 amounted to 40 RDD/100 patient days. Expressed in DDD/100 patient days, the corresponding figure was 60 DDD/100 (Tab. 2.2.1). As expected and demonstrated in previous reports, university hospitals show significantly higher use densities, whereas no difference is observed between non-university hospitals with different bed capacities (Tab. 2.2.1, Fig. 2.2.2).

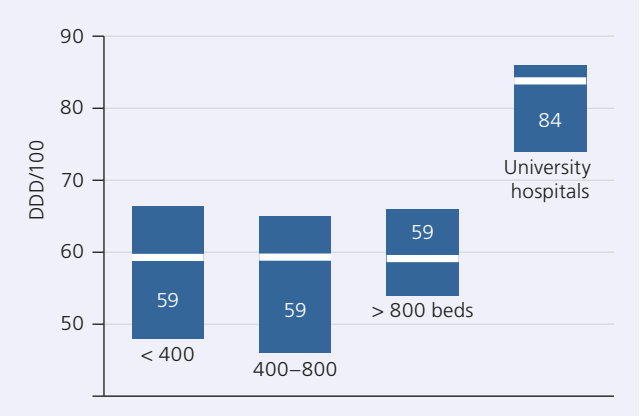


Fig. 2.2.2: Total antimicrobial use density in dependence on the hospital size (number of beds) (medians and interquartile ranges) in 2013/2014 (Source: ADKA-if-DGI Surveillance)

A comparison with the 2004 data reveals an increase in virtually all departments (Tab. 2.2.2), in particular on general wards and to a lesser extent in intensive care units. However, it should be noted that this is not a real longitudinal study, but two cross-sectional studies in which the participating hospitals were not identical.

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. 2.2.3). However, there are very few evaluations available in the form of DDD/100.

Tab. 2.2.1: Use density of systemic antimicrobials at German acute-care hospitals in daily doses per 100 patient days in 2013/2014 (Source: ADKA-if-DGI Surveillance)

		RDD/100		DDD/100	
Hospital size/type	**n**	**Median**	**Interquartile range**	**Median**	**Interquartile range**
Non-university hospitals	128				
< 400 beds	80	39.8	33.4–45.2	58.7	48.4–66.8
400–800 beds	33	37.9	29.6–43.7	58.8	46.1–65.1
> 800 beds	15	40.9	35.2–43.6	58.8	53.7–66.0
University hospitals	13	55.3	52.5–58.3	83.6	74.3–85.7
Total	141	40.4	34.1–45.9	60.3	49.1–69.0

Tab. 2.2.2: Average antimicrobial use densities by type of hospital, ward and department. The figures provided include the median and interquartile ranges in RDD/100 for 2004 and 2013/2014 (Sources: MABUSE Network [2004 data] and ADKA-if-DGI Surveillance)

	2004		2013/14	
General surgical ward				
University hospitals	35	(29–44)	48	(40–51)
Non-university hospitals	27	(20–34)	35	(30–43)
General non-surgical ward				
University hospitals				
Haematology/Oncology	96	(66–128)	107	(94–117)
General internal medicine	39	(43–46)	45	(41–47)
Other non-surgical specialities	25	(24–28)	45	(41–47)
Non-university hospitals				
Haematology/Oncology	38	(29–58)	53	(38–65)
General internal medicine	31	(25–38)	37	(30–42)
Other non-surgical specialities	21	(13–26)	37	(30–42)
Intensive care unit				
University hospitals	85	(62–116)	94	(89–111)
Non-university hospitals	74	(58–95)	81	(70–92)

Tab. 2.2.3: National surveys on antimicrobial use density at hospitals (data in DDD/100 from 2012 or later)

	DDD/100
Sweden 2013 (n=80)	60
Germany 2013 (n=141)	60
Netherlands 2012 (n=72)	71
Denmark 2014 (n=66)	104

Sources: SWEDRES-SVARM 2013, NETHMAP 2014, DANMAP 2014, ADKA-if-DGI Surveillance

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 (http://ecdc.europa.eu/en/healthtopics/antimicrobial-resistance-and-consumption/antimicrobial-consumption/ESAC-Net/Pages/ESAC-Net.aspx). However, only a few, predominantly small countries are able to provide comprehensive data for the hospital sector, which is why the information available to date remains incomplete.

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 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 department/ward

As expected, the antimicrobial use density varied between departments (Tab. 2.2.2). The use density was particularly high in haematology/oncology departments of university hospitals (median rate 107 RDD/100) as well as in intensive care units (median rate 81 and 94 RDD/100 at non-university hospitals and university hospitals, respectively). It was about twice as high in intensive care units as on general wards (Tab. 2.2.2 and Tab. 2.2.4). However, the proportion of antibiotics used in intensive care units per total hospital consumption was < 20% at both university and non-university hospitals (Tab. 2.2.4).

Antimicrobial classes and agents

In 2013/2014, the most commonly used drug classes were β-lactams and fluoroquinolones, followed by macrolides/clindamycin. By contrast, aminoglycosides and tetracyclines were used rarely (Tab. 2.2.5).

Cephalosporins number 1 at hospitals

Among β-lactams, first- and second-generation cephalosporins (especially cefuroxime) had the largest share at both university and non-university hospitals (Tab. 2.2.5). The prescribing rate of third-generation cephalosporins varied greatly (Fig. 2.2.3), with the median rate being 3.4 RDD/100 (non-university hospitals) and 4.3 RDD/100 (university hospitals). The use densities of the various penicillin classes also vary greatly. Overall, combinations of aminopenicillin/β-lactamase inhibitor are used more commonly than piperacillin (± inhibitor).

The ratio of penicillins and cephalosporins at the 141 hospitals altogether – expressed in RDD – was 50:50 (expressed in DDD, this ratio was 54:46). Compared to the hospital sector in other European countries, cephalosporins seem to be predominant at German hospitals (Fig. 2.2.4).

Tab. 2.2.4: Use density of systemic antimicrobials expressed in recommended daily doses per 100 patient days (RDD/100) in various departments/sections and their share in total consumption (% of RDD) in 2013/2014 (Source: ADKA-if-DGI Surveillance)

		RDD/100		Share in total consumption
	n	Median	Interquartile range	
Non-university hospitals				
Non-surgical departments (general wards)	339	36.6	29.6–42.2	35%
Haematology/Oncology	41	52.6	37.9–64.6	5%
Surgical departments (general wards)	545	35.4	29.8–42.8	48%
Intensive care units	204	80.8	70.3–92.3	12%
University hospitals				
Non-surgical departments (general wards)	96	45.3	41.3–46.8	23%
Haematology/Oncology	13	107.3	94.4–117.1	11%
Surgical departments (general wards)	147	47.6	39.6–51.4	48%
Intensive care units	82	94.0	88.9–111.4	19%

Tab. 2.2.5: Use density of certain antimicrobial classes expressed in recommended daily doses per 100 patient days (RDD/100) in 2013/2014 (Source: ADKA-if-DGI Surveillance)

	Non-university hospitals		University hospitals	
	Median	Interquartile range	Median	Interquartile range
Carbapenems	1.3	0.9–2.1	3.7	3.6–5.0
Broad-spectrum penicillins	3.2	1.8–4.3	5.9	4.5–6.7
Cephalosporins 3rd/4th generation	3.4	2.0–5.5	4.3	3.0–5.3
Cephalosporins 1st/2nd generation	6.9	4.5–8.8	8.0	5.6–10.4
Aminopenicillin/BLI combinations*	5.6	3.2–7.8	6.5	4.5–9.0
Narrow-spectrum penicillins#	1.4	0.9–1.8	1.9	1.6–2.1
Fluoroquinolones	5.1	3.8–6.4	8.0	6.6–8.5
Glycopeptides incl. daptomycin	0.7	0.5–0.9	2.4	1.9–2.7
Aminoglycosides	0.2	0.1–0.3	0.5	0.4–0.6
Macrolides and clindamycin	3.8	2.6–5.2	4.6	4.2–4.9
Tetracyclines	0.4	0.3–0.8	0.6	0.4–0.7
Folic acid antagonists/sulphonamides	1.1	0.8–1.6	2.3	2.1–3.1
Others	3.2	2.4–4.4	3.9	3.5–4.7
among them metronidazole	2.8	2.0–3.7	2.5	2.1–3.5

* BLI= β-lactamase inhibitor; # penicillin, ampicillin, amoxicillin, flucloxacillin

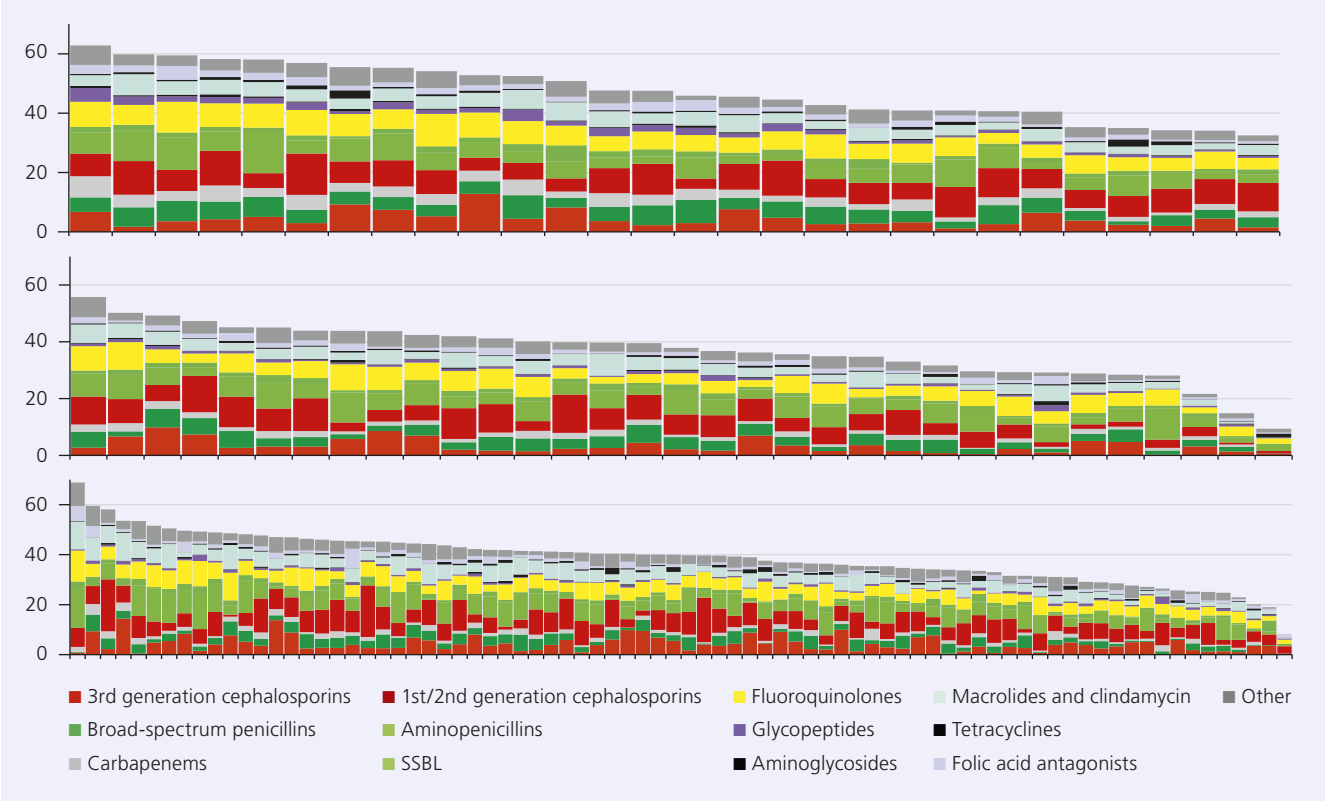


Fig. 2.2.3: Distribution of total antimicrobial use density (in RDD/100) at 141 acute-care hospitals incl. statement of the consumption of various antimicrobial classes in dependence on the hospital size (number of beds). Top row: > 800 beds, middle row: 400-800 beds, bottom row: < 400 beds (Source: ADKA-if-DGI Surveillance)

In 2013/2014, the leader of the TOP-5 list and the most commonly used antimicrobial agent was cefuroxime (oral and parenteral taken together). Interestingly, this had already been the case in 2004, although most other antimicrobial agents on the TOP-5 list, except for ciprofloxacin, have changed over the course of time (Tab. 2.2.6).

Several studies have demonstrated that the nosocomial CDI rate can be reduced by specifically restricting the use of cephalosporins and/or fluoroquinolones.[3] Corresponding studies from Germany are not available and it will be of great interest to correlate the CDI prevalence with certain antimicrobial consumption patterns at German hospitals as well as to plan and evaluate potential changes in antimicrobial prescribing strategies. In Sweden, for example, the use of cephalosporins at hospitals was reduced

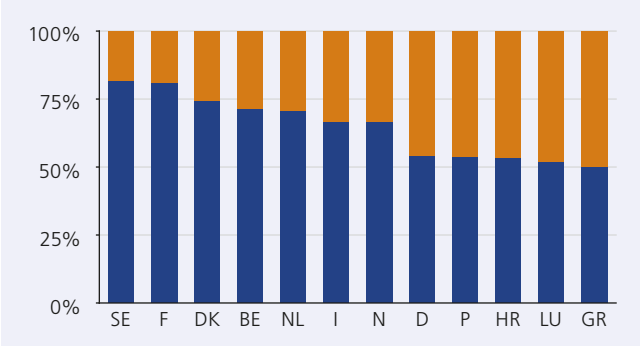


Fig. 2.2.4: Relative share of penicillins (in blue) and cephalosporins (in orange) by DDD in hospital care in various European Countries (Sources: ECDC Surveillance of Antimicrobial Consumption in Europe 2012, ADKA-if-DGI Surveillance [2013/2014 data]

Tab. 2.2.6: The TOP-5 antimicrobials (by RDD) prescribed at hospitals and their respective shares in total consumption (in % of RDD) in 2004 and 2013/2014 (Sources: MABUSE Network [2004 data] and ADKA-if-DGI Surveillance)

2004	%	2013/14	%
Cefuroxime	13.8%	Cefuroxime	15.3%
Co-trimoxazole	7.9%	Piperacillin/tazobactam	9.3%
Ampicillin/sulbactam	6.8%	Ciprofloxacin	8.2%
Amoxicillin/clavulanic acid	5.9%	Ceftriaxone	7.8%
Ceftriaxone	5.5%	Metronidazole	6.5%

by > 50% between 2006 and 2013; the cephalosporin use density is now only about 6 DDD/100[4] – compared to well above 10 DDD/100 in our present survey. A similar significant reduction in consumption, in particular of second-generation cephalosporins, has also been achieved in Great Britain.[5]

Low aminoglycoside, tetracycline and glycopeptide consumption

The average use density of aminoglycosides and tetracyclines in 2013/2014 was < 1 RDD/100. Glycopeptides were also used sparingly at non-university hospitals (< 1 RDD/100) (Tab. 2.2.5), whereas they were prescribed much more frequently in intensive care units and in haematology/oncology departments of larger hospitals.

Conclusion

Inpatient antimicrobial use density in Germany seems to have increased over the past 10 years. In 2013/2014, non-university hospitals showed a use density of < 60 DDD/100 patient days, compared to a use density of > 80 DDD/100 patient days at university hospitals. In 2013/2014, the most frequently prescribed antimicrobials in the hospital sector were again intermediate-spectrum β-lactams (mainly cefuroxime) and fluoroquinolones. Cephalosporins are particularly predominant in surgical departments. In line with expectations, the antimicrobial use density in intensive care units is about twice as high as on general wards. However, the consumption in intensive care units only accounts for < 20% of the total hospital antimicrobial consumption. The data basis has improved significantly.

➤ W.V. Kern, K. de With, M. Fellhauer, M. Steib-Bauert
Reviewer: B. Sinha, E. Kramme, M. Kresken

1. Muller A, Monnet DL, Talon D, Hénon T, et al. Discrepancies between prescribed daily doses and WHO defined daily doses of antibacterials at a university hospital. Br J Clin Pharmacol 2006;61:585-91.
2. de With K, Bestehorn H, Steib-Bauert M, Kern WV. Comparison of defined versus recommended versus prescribed daily doses for measuring hospital antibiotic consumption. Infection 2009;37:349-52.
3. Feazel LM, Malhotra A, Perencevich EN, Kaboli P, et al. Effect of antibiotic stewardship programmes on Clostridium difficile incidence: a systematic review and meta-analysis. J Antimicrob Chemother 2014;69:1748-54.
4. SWEDRES-SVARM 2013. Use of antimicrobials and occurrence of antimicrobial resistance in Sweden. http://www.folkhalsomyndigheten.se/publicerat-material/publikationer/SWEDRESSVARM-2013/ (last accessed on 1 March 2015).
5. Cooke J, Stephens P, Ashiru-Oredope D, Charani E, et al. Longitudinal trends and cross-sectional analysis of English national hospital antibacterial use over 5 years (2008-13): working towards hospital prescribing quality measures. J Antimicrob Chemother 2015;70:279-85.

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). This is also confirmed by the most recent 2014 figures (15.8 million DDD). Systemic azoles were prescribed less commonly. In 2014, itraconazole was used less frequently (1.7 million DDD) than fluconazole (2 million DDD)[1,2], and both were prescribed much more frequently than voriconazole and posaconazole (< 0.2 million DDD each) (Fig. 2.3.1).[1]

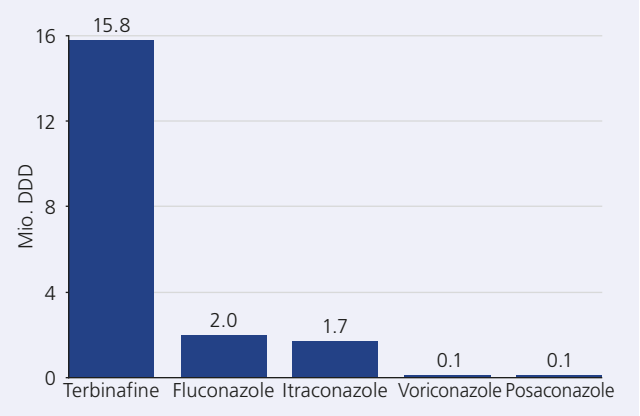


Fig. 2.3.1: Consumption of systemic antifungals in outpatient care in 2014 (Source: WIdO, SHI Drug Index)

An older 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).[2] 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.

As was the case in previous years, 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 again prescribed much more frequently in 2014 than systemic antifungals.[1]

In 2014, the most commonly prescribed substance for the treatment and prevention of oral candidiasis and other mucosal fungal infections again appears to have been topical amphotericin B (2.4 million DDD).[1] However, there is no reliable consumption data available for these groups. 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. Accounting for 1.2 million DDD, clotrimazole was used relatively often – mainly in gynaecology.

Inpatient use densities

Most previous surveys conducted at German acute-care hospitals were limited to university hospitals or intensive care units.[3] Subsequent surveys in 2004 confirmed that the highest consumption rates at non-university hospitals were also observed in haematology/oncology departments, followed by intensive care units.[4] At that time, the median rates in intensive care units were 20 DDD/100 (university hospitals) and 5 DDD/100 (non-university acute-care hospitals). 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 order of magnitude.[5]

The 2012 GERMAP report included 2011 data on a total of 66 hospitals. The median total use density amounted to 0.9 DDD/100 (interquartile range 0.5-1.5), being much higher in intensive care units (median rate 6.1 in surgical intensive care units and 4.5 in non-surgical intensive care units) and on haematology/oncology wards (median rate 5.8) than in other departments.

For the 2013/2014 period, data from 4 full quarters is available for 124 hospitals (excluding paediatric and psychiatric departments). As expected, the antifungal use density strongly depends on the hospital size (Tab. 2.3.1), ranging between 0.3 (median rate at hospitals with < 400 beds), 0.7 (hospitals with 400-800 beds) and 2.7 DDD/100 (hospitals with > 800 beds) across all hospital departments.

Tab. 2.3.1: Antifungal consumption (RDD/100, median values and interquartile ranges) in total and in various specialities/sections at 124 German acute-care hospitals* of various sizes (number of beds) in 2013/2014 (Source: ADKA-if-DGI Surveillance)

Speciality/Section	RDD/100					
	<400 beds		400–800 beds		>800 beds	
Total*	0.3	(0.2–0.7)	0.7	(0.4–1)	2.7	(1.2–4.5)
Intensive care units*						
Surgical/Anaesthesiological	2.8	(0–8.6)	6.4	(2.2–11.9)	7.6	(4.6–13)
Other surgical and interdisciplinary	3.7	(2–6.2)	4.6	(3.2–7.1)	8.5	(0.6–14.4)
Internal	1.3	(0.2–3.2)	2.6	(1.9–4.3)	8.4	(3.1–17.2)
Other non-surgical	< 0.1	–	0.7	(0–1.7)	0.9	(0.3–3.5)
General wards*						
General surgery	0.1	(0–0.2)	0.2	(0.1–0.4)	0.7	(0.5–1.5)
Urology	0.1	(0–0.5)	0.4	(0.1–0.6)	0.7	(0.3–1.1)
Orthopaedics/Traumatology	< 0.1	–	< 0.1	–	0.4	(0.1–0.6)
Other general surgical wards	0.1	(0–0.4)	0.2	(0.1–0.3)	0.3	(0.2–0.5)
General internal medicine	0.2	(0.1–0.5)	0.4	(0.1–0.6)	1.1	(0.3–2.3)
Haematology/Oncology	2.1	(1.1–3)	2.6	(1.9–3)	23.6	(7.5–38.7)
Other non-surgical specialities	0.1	(0–0.2)	0.2	(0.1–0.3)	0.4	(0.1—0.9)

*Excl. paediatric and psychiatric wards

Antifungal classes at hospitals

Fluconazole still number 1 at hospitals.

Azoles were by far most commonly used in all hospital departments both in 2004 and during the period 2007-2011. In 2013/2014, the situation was similar (Tab. 2.3.2) with two exceptions: Caspofungin was used somewhat more often in internal intensive care units of larger hospitals (> 800 beds) and voriconazole and posaconazole were prescribed more frequently in haematology/oncology departments of larger hospitals. In the 2008 and 2009 ESAC point prevalence surveys, fluconazole was again identified as most frequently prescribed systemic antifungal at hospitals.[6]

Tab. 2.3.2: Relative prescribing rate of various antifungals (in % of all RDD and DDD of systemic antifungals) at German acute-care hospitals* (general wards and intensive care units) in 2009, 2011 and 2013/2014 (Source: ADKA-if-DGI Surveillance)

Antimicrobial	Percentage of RDD (DDD)		
	2009	2011	2013/14
Fluconazole	62 (70)	50 (66)	45 (61)
Voriconazole	22 (13)	22 (15)	14 (9)
Caspofungin	7 (4)	12 (8)	16 (11)
Posaconazole	6 (3)	7 (5)	12 (8)
L-AmB	5 (3)	4 (2)	5 (4)
Anidulafungin	4 (2)	2 (2)	3 (2)
Itraconazole	3 (4)	1 (2)	1 (2)
cAmB	2 (1)	1 (1)	< 1 (< 1)
Flucytosin	< 1 (< 1)	< 1 (< 1)	< 1 (< 1)
Micafungin	–	1 (1)	3 (2)

*Excl. paediatric and psychiatric wards

Overall, echinocandins were prescribed with increasing frequency (Tab. 2.3.2); however, anidulafungin and micafungin continued to be prescribed relatively rarely compared to caspofungin. Conventional amphotericin B was barely used. Flucytosin, ketoconazole, itraconazole and terbinafine also play a very insignificant role in the inpatient setting.

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 has also been observed in a similar magnitude during the last 10 years. In our recent 2013/2014 survey, the median rates ranged between 1 and 9 RDD/100, depending on the hospital size and the type of intensive care unit. In individual cases, use densities of > 20 RDD/100 were observed. As mentioned above, fluconazole was also the most commonly used substance in intensive care units, except for internal intensive care units of larger hospitals. In non-surgical intensive care units, voriconazole was also still used to some extent (Tab. 2.3.3).

Tab. 2.3.3: Use density of selected azoles and echinocandins (in RDD/100, weighted average) in intensive care units in 2013/2014 (Source: ADKA-if-DGI Surveillance)

Antimicrobial	RDD/100	
	Surgical intensive care units	Non-surgical intensive care units
Fluconazole	3.5	2.5
Voriconazole	0.8	1.5
Caspofungin	2.4	2.5
Anidulafungin	0.6	0.6

Tab. 2.3.4: Use density of selected (systemic) antifungals (in RDD/100, weighted average) on haematology/oncology wards in 2013/2014 (Source: ADKA-if-DGI Surveillance)

Antimicrobial	RDD/100	
	Non-university hospitals	University hospitals
Total	4.9	40.1
Fluconazole	1.5	13.2
Voriconazole	0.9	7.3
Posaconazole	1.4	9.4
Itraconazole	0.2	< 0.1
Caspofungin	0.8	3.6
Anidulafungin	< 0.1	0.1
Micafungin	< 0.1	2.3
L-AmB	0.1	4.0

Haematology/oncology as high-consumption areas

On haematology/oncology wards, more antifungals are used than on other internal general wards (Tab. 2.3.1). The median rate in 2009 was 8 DDD/100 (equivalent to 6 RDD/100). In 2011, the median rate was 5.8 DDD/100 (equivalent to 4.2 RDD/100). The recent rates range between 4.9 RDD/100 and about 40 RDD/100, depending on whether it is a university or non-university hospital (Tab. 2.3.4).

The use pattern also appears to have changed slightly: 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 reliability of the figures for the outpatient sector is 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 of the applied substances differs or has changed, while the use density has remained constant.

➤ W.V. Kern
Reviewer: A. Ullmann, T. Hoppe-Tichy

1. Kern WV. Antibiotika und Chemotherapeutika. In: Schwabe U, Paffrath D (Hrsg): Arzneiverordnungs-Report 2015. Springer-Verlag, Berlin 2015, pp. 359-88.
2. Adriaenssens N, Coenen S, Muller A, Vankerckhoven V, et al. European Surveillance of Antimicrobial Consumption (ESAC): outpatient systemic antimycotic and antifungal use in Europe. J Antimicrob Chemother 2010; 65:769-74.
3. de With K, Steib-Bauert M, Knoth H, Dörje F, et al. Hospital use of systemic antifungal drugs. BMC Clin Pharmacol 2005;5:1.

4. GERMAP2008 Antibiotika-Resistenz und -Verbrauch. http://www.bvl.bund.de/SharedDocs/Downloads/08_PresseInfothek/Germap_2008.pdf?__blob=publicationFile&v=2.
5. Meyer E, Schwab F, Gastmeier P, Ruden H, et al. Antifungal use in intensive care units. J Antimicrob Chemother 2007;60:619-24.
6. Zarb P, Amadeo B, Muller A, Drapier N, et al. Antifungal therapy in European hospitals: data from the ESAC point-prevalence surveys 2008 and 2009. Clin Microbiol Infect 2012;18:389-95.

3 Antimicrobial consumption in veterinary medicine

3.1 Veterinary antimicrobial sales

Surveillance of antimicrobial sales

Resistance occurs in both human and veterinary medicine. However, there is no clear sharp distinction 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.

Concerning goal 3 "Retaining and improving therapy options", the Federal Government states in the DART 2020 document that the surveillance of veterinary antimicrobial sales should be continued.[1]

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 (DIMDI Regulation on Medicinal Products – DIMDI AMV) of 24 February 2010 to the German Institute of Medical Documentation and Information. 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 German Drug Information System (AMIS). The data recorded and aggregated 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 the amount of primary antimicrobial agent sold is calculated, if possible.

In addition to the national recording and evaluation of antimicrobial sales data, the BVL also transmits the data to the European Surveillance of Veterinary Antimicrobial Consumption [ESVAC] project. Within the ESVAC project, antimicrobial sales data for 25 EU member states were published for the first time in 2011.[2] By now, two additional reports on antimicrobial sales data in Europe have been published for 2012 and 2013.[3,4]

Results of the surveillance of antimicrobial sales in Germany in 2011, 2013 and 2014 (TAR)

The total amount of primary antimicrobial agents (excluding medicated premixes approved for the production of medicated feed) sold to German-based veterinarians was 1,706 t in 2011 and 1,238 t in 2014. Among the 875 veterinary medicinal products approved and subject to reporting in Germany, sales data was reported for 586 (67%) drugs in 2014. Similar figures were reported for 2013 as follows: Of the 763 veterinary medicinal products approved and subject to reporting in Germany, sales data was reported for 583 (76.4%) drugs. The drugs for which no sales data was reported were approved in Germany but were not sold in the year under review.

Of the 586 veterinary medicinal products for which sales data was reported in 2014, 418 drugs are approved for use in food-producing animals (FPA) and 168 drugs exclusively for the treatment of non-food-producing animals (N-FPA).

Antimicrobial agents and classes

In both years under review (2013 and 2014), the largest portion of antimicrobial agents was made up of penicillins with 473 t and 450 t, respectively, and tetracyclines with 454 t and 342 t, respectively, with sulphonamides (2013 152 t; 2014 121 t), macrolides (2013 126 t; 2014 109 t) and polypeptide antimicrobials (2013 125 t; 2014 107 t) following far behind. Further sales included 39 t (2013) and 38 t (2014) of aminoglycosides, 24 t (2013) and 19 t (2014) of trimethoprim, 17 t (2013) and 15 t (2014) of lincosamides, 15 t (2013) and 13 t (2014) of pleuromutilins, 12.1 t (2013) and 12.3 t (2014) of fluoroquinolones as well as approx. 5 t of fenicols in both years. 5.8 t of cephalosporins were reported, 3.7 t of which were third- and fourth-generation cephalosporins (2013, 2014). Nitroimidazoles, nitrofurans and fusidic acid were sold in amounts of less than 1 t. A detailed overview of the reported antimicrobials is provided in Tab. 3.1.1. The amounts sold between 2011 and 2014 as well as the differences in sales between 2011 and 2014 are also shown to allow a comparison.

Classification of antimicrobial sales according to animal species

A clear classification of the reported 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 approx. 99% of the total sales of primary antimicrobial agents during the period 2011-2014. It must be noted that a veterinary drug is classified as approved for use in FPA if at least

Tab. 3.1.1: Amount of primary antimicrobial agents per antimicrobial class [t] sold to Germany-based dispensing veterinarians, 2011-2014

Antimicrobial class	Amount sold in 2011	Amount sold in 2012	Amount sold in 2013	Amount sold in 2014	Difference between 2011 and 2014
Aminoglycosides	47	40	39	38	-9
Cephalosporins 1st gen.	2.0	2.0	2.0	2.1	+0.1
Cephalosporins 3rd gen.	2.1	2.5	2.3	2.3	+0.2
Cephalosporins 4th gen.	1.5	1.5	1.5	1.4	-0.1
Fluoroquinolones	8.2	10.4	12.1	12.3	+4.1
Folic acid antagonists	30	26	24	19	-11
Lincosamides	17	15	17	15	-2
Macrolides	173	145	126	109	-64
Penicillins	528	501	473	450	-78
Phenicols	6.1	5.7	5.2	5.3	-0.8
Pleuromutilins	14	18	15	13	-1
Polypeptide antimicrobials	127	124	125	107	-20
Sulphonamides	185	162	152	121	-64
Tetracyclines	564	566	454	342	-222
Total*	1.706	1.619	1.452	1.238	-468

* any deviations are due to rounding

one of the animal species for which it is approved is a food-producing animal species.

The number of approved drugs per animal species reported as part of the surveillance of antimicrobial sales is listed in Tab. 3.1.2. 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 the treatment of one animal species in 2013 and 2014.

Regionalised sales data

The DIMDI Regulation on Medicinal Products stipulates that the sales data reported be itemised by the first two digits of the postcode of the veterinarians' addresses. 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]). It does not allow a clear classification according to Länder because there are several over-

Tab. 3.1.2: Number of drugs per target animal species reported within the surveillance of antimicrobial sales in 2013 and 2014 (multiple answers possible according to the marketing authorisation)

Animal species	Number of drugs reported in 2013	Number of drugs reported in 2014
Carrier pigeon	11	10
Duck	2	4
Pheasant	1	1
Fish	1	1
Goose	1	1
Poultry	2	1
Chicken	78	76
Dog	202	204
Rabbit	8	7
Cat	95	95
Guinea pig	4	0
Horse	47	48
Turkey	35	37
Cattle	305	310
Sheep	48	50
Pig	286	287
Pigeon	13	12
Goat	14	14

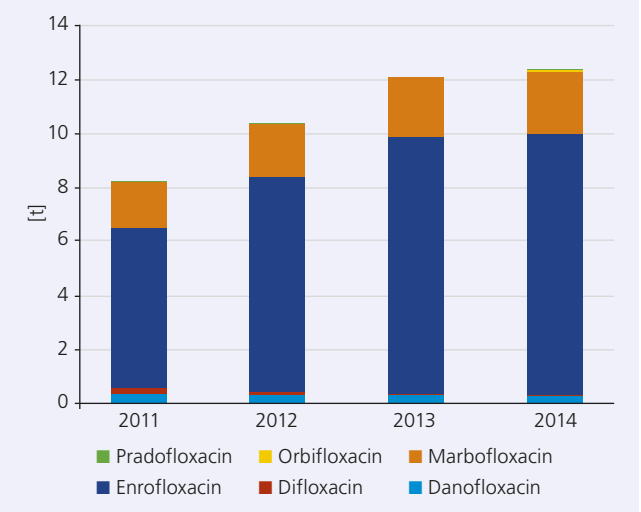


Fig. 3.1.1: Comparison of sales of primary antimicrobial agents in fluoroquinolones [t] in Germany, 2011-2014

lapping postcode areas. Almost half of the total of antimicrobial agents was supplied to veterinarians in the postcode areas 48 (northern North Rhine-Westphalia, 80 t) and 49 (western Lower Saxony, 505 t). A regionalisation of sales data according to the two-digit postcodes is provided in Fig. 3.1.2.

ESVAC data

The European Surveillance of Veterinary Antimicrobial Consumption project (ESVAC) published data for 19 EU member states for the first time in 2010 (no data from Germany included).[5] By now, data for 2012 from 25 member states and data for 2013 from 26 member states have been published.

When calculating the amount of antimicrobial agent (mg), ESVAC uses a defined correction factor PCU (population correction unit = number of FPAs multiplied by the estimated weight at the time of treatment) to allow better comparability of the data reported by the individual member states. The corresponding data is shown in Tab. 3.1.3 to allow a European comparison. The amounts sold in Germany, expressed in mg of amount sold per PCU, were 211 mg/PCU in 2011, 205 mg/PCU in 2012 and 179 mg/PCU in 2013.

Conclusion

The sales data shows that the vast majority of sales account for what are called "old" agents, whereas fluoroquinolones and third- and fourth-generation cephalosporins (antimicrobial agents with special relevance for human medicine) play a rather subordinate role in veterinary medicine, compared to the total antimicrobial sales. About 94% of all antimicrobial agents were sold for oral administration. Approx. 62.5 t (approx. 5%) were sold for parenteral administration.

The drop in sales by 27% over the period 2011-2014 should not be interpreted as an indication of fewer antimicrobial therapies. The drop in total antimicrobial sales during the period under review may be a direct consequence of the public discussion about antimicrobial resistance and the call for reduced antimicrobial use. In addition, livestock farms were required for the first time in the second half of 2014 to report the frequency of treatment to the competent state authorities in accordance with the 16th amendment of the Medicinal Products Act (AMG). The measure of treatment frequency reporting is intended to reduce antimicrobial consumption in animal production. The reduction in antimicrobial sales by 468 t (2011 1,706 t; 2014 1,238 t) over the period 2011-2014 is accompanied by an increase in the sales of fluoroquinolones by approx. 4 t, which is equivalent to an increase of approx. 50%. This mainly concerns enrofloxacin, where the sales were observed to increase from 5.9 t in 2011 to 9.6 t in 2014, equivalent to an increase of approx. 63% (Fig. 3.1.1). At the same time, an increase in the sales of third-generation cephalosporins by nearly 10% (2.1 t in 2011, 2.3 t in 2014) is observed.

A comparison of the various doses of antimicrobial agents in this connection, e.g. tetracyclines with a dose of up to 80 mg/kg of BW, fluoroquinolones with approx. 2.5-10 mg/kg of BW and third-generation cephalosporins with 1-2 mg/kg of BW, makes clear the extent of the increase in the sales of these antimicrobial agents calculated here. The reduction in total antimicrobial sales may also have been compensated by the increased use of antimicrobial agents applied in a lower dose per kg of BW.

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 dispensing veterinarians 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 identical to the region where these are used. The actual consumption cannot be determined, nor is a classification according to individual animal species possible, since the majority of the drugs are approved for use in several animal species.

At first glance, a reduction in antimicrobial use appears desirable. However, attributing the development and spread of bacterial resistance solely to antimicrobial sales is not appropriate, because the corresponding mechanisms are much more complex and cannot be reduced solely to the amount of antimicrobials sold or used. From a scientific point of view, the mere calling for reduced antimicrobial use without taking any accompanying measures to

Tab. 3.1.3: Comparison of sales of antimicrobial agents used in food-producing animals in mg per correction factor (mg/PCU) and of the population correction unit (PCU; estimated weight of all food-producing animals at the time of treatment) for 2011 in 25 and for 2012 and 2013 in 26 European member states (ESVAC)*

Member state	2011		2012		2013	
	mg/PCU	PCU [in 1,000 t]	mg/PCU	PCU [in 1,000 t]	mg/PCU	PCU [in 1,000 t]
Austria	55	977	55	966	57	957
Belgium	175	1,695	161	1,658	157	1,657
Bulgaria	104	399	99	388	116	401
Cyprus	408	127	397	113	426	113
Czech Republic	83	732	80	673	82	697
Denmark	43	2,479	44	2,424	45	2,418
Estonia	66	114	56	131	62	137
Finland	24	520	24	511	24	514
France	117	7,643	103	7,419	95	7,165
Germany	212	8,600	205	8,338	179	8,526
Hungary	192	767	246	727	230	763
Iceland	6	114	6	116	5	115
Ireland	49	1,770	58	1,725	57	1,762
Italy	370	4,497	341	4,500	302	4,372
Latvia	35	171	41	162	37	167
Lithuania	42	337	40	339	37	339
Luxembourg	–	–	44	50	54	51
Netherlands	114	3,186	75	3,279	70	3,226
Norway	4	1,680	4	1,851	4	1,789
Poland	120	3,929	132	3,908	151	3,806
Portugal	161	1,016	157	996	187	958
Slovakia	44	247	43	235	63	248
Slovenia	43	182	37	183	22	180
Spain	249	7,135	242	6,996	317	6,944
Sweden	14	835	14	783	13	796
United Kingdom	51	6,724	66	6,749	62	6,799

* ©European Surveillance of Veterinary Antimicrobial Consumption, 2013. Sales of veterinary antimicrobial agents in 25 EU/EEA countries in 2011 (EMA/236501/2013), European Surveillance of Veterinary Antimicrobial Consumption, 2014. Sales of veterinary antimicrobial agents in 26 EU/EEA countries in 2012 (EMA/333921/2014), European Surveillance of Veterinary Antimicrobial Consumption, 2015. Sales of veterinary antimicrobial agents in 26 EU/EEA countries in 2013 – 5th ESVAC report (EMA/387934/2015)

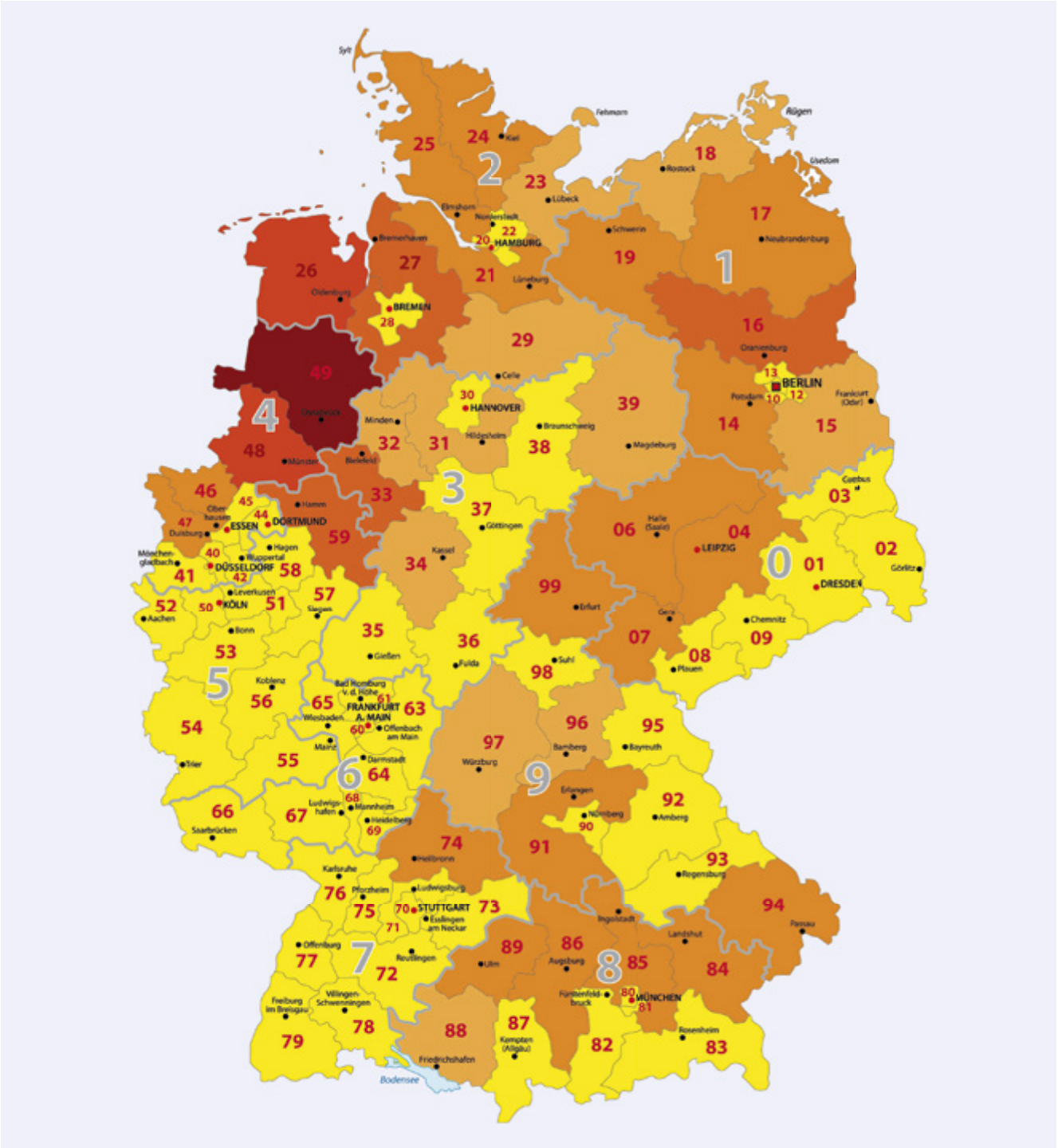


Fig. 3.1.2: Amount of primary antimicrobial agents sold [t] per postcode area in Germany, 2014

ensure their prudent and proper use is not expedient to control antimicrobial resistance. The evidence-based assessment of antimicrobial use and the resulting consequences requires comprehensive, detailed antimicrobial consumption data (including designation of medicinal product, animal species, number of animals treated, indication and dose).

The European Medicines Agency (EMA) has recently published data on defined daily doses in veterinary medicine (defined daily dose for animals, DDDvet and defined course dose for animals, DCDvet) on its website.[5,6] These parameters can help compare the antimicrobial consumption data in a standardised manner. At the same time, the surveillance of antimicrobial consumption would also include drugs purchased by veterinarians from abroad (e.g. via the Internet).

➤ J. Wallmann
Reviewer: A. Bender, I. Reimer

1. DART2020 Antibiotika-Resistenzen bekämpfen zum Wohl von Mensch und Tier: http://www.bmg.bund.de/fileadmin/dateien/Publikationen/Ministerium/Broschueren/BMG_DART_2020_Bericht_dt.pdf2.
2. European Medicines Agency, European Surveillance of Veterinary Antimicrobial Consumption, 2013. Sales of veterinary antimicrobial agents in 25 EU/EEA countries in 2011 (EMA/236501/2013): http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/10/WC500152311.pdf.
3. European Medicines Agency, European Surveillance of Veterinary Antimicrobial Consumption, 2014. Sales of veterinary antimicrobial agents in 26 EU/EEA countries in 2012 (EMA/333921/2014): http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/10/WC500175671.pdf.
4. European Medicines Agency, European Surveillance of Veterinary Antimicrobial Consumption, 2015. Sales of veterinary antimicrobial agents in 26 EU/EEA countries in 2013 – Fifth ESCAC report (EMA/387934/2015).

5. European Medicines Agency, 2012. Sales of veterinary antimicrobial agents in 19 EU/EEA countries in 2010 (EMA/88728/2012): http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/10/WC500133532.pdf.
6. Principles on assignment of defined daily dose for animals (DDDvet) and defined course dose for animals (DCDvet), EMA/710019/2014, Veterinary Medicines Division (2015). http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/06/WC500188890.pdf.

3.2 Animal Treatment Index (ATI) – Surveillance of treatment frequency

There is a multitude of legal provisions as well as supplementary guidelines and recommendations for the use and sale of antimicrobials in veterinary practice. The most important statutory basis is the Medicinal Products Act (AMG). Further regulations are set forth in the Veterinary House Dispensary Ordinance (TÄHAV) and the Ordinance on the Recording Obligations of Livestock Owners for Medicinal Products Intended for Use in Animals (ANTHV).[1]

With the 16th amendment of the Medicinal Products Act coming into force on 1 April 2014, further veterinary-specific regulations were added to the Medicinal Products Act (AMG, 2013).[2] The main goals are to reduce the use of antimicrobials in livestock farming to limit the risk of the development and spread of antimicrobial resistance, thereby contributing to maintaining the efficacy of antimicrobials.

The regulations for calculating the Animal Treatment Index (ATI) are primarily directed at livestock owners, who are responsible for the recording and reporting as well as the performance of the measures (Fig. 3.2.1). Veterinarians mainly act in an advisory function, but livestock owners can also transfer the responsibility to report the antimicrobial use to them. The data to be recorded is pooled in an extensive database of the Origin and Information System for Livestock (HI Tier) (https://www.hi-tier.de/). All cattle, pig, chicken and turkey farms exceeding a certain size (20 beef cattle, 250 fattening pigs, 1,000 meat turkeys and 10,000 broilers) are subject to the reporting obligation (Ordinance on the Submission of Notifications pursuant to Sec. 58a and 58b of the Medicinal Products Act, TAMMitDurchfV).[3] As regards cattle, a distinction is additionally made between veal calves aged up to 8 months and beef cattle aged above 8 months, and as regards swine, between piglets with a weight of up to and including 30 kg and fattening pigs with a weight of more than 30 kg (AMG, 2013).[2]

As regards the duration of treatment with antimicrobials with a therapeutic drug level of longer than 24 hours, 7 treatment days must be documented, unless the veterinarian determines a deviating number of treatment days based on the duration of the therapeutic drug level in accordance with Sec. 58b (3) AMG.

Based on the information provided on the use of antimicrobials in relation to the average number of animals kept in a half-yearly period, the competent state authority calculates the half-yearly Animal Treatment Index (ATI) per farm and carries out a benchmarking between comparable farms (animal species/age group). HI-Tier transmits the individual ATI in anonymised form to the Federal Office of Consumer Protection and Food Safety (BVL), which ascertains nationwide parameters and promulgates them in the Federal Gazette. By comparing the ATI calculated for their farms, livestock owners are then able to determine whether their farms are below or above the median (parameter 1: value below which 50% of all farms fall) or below or above the third quartile (parameter 2: value below which 75% of all farms fall). If parameter 1 is exceeded, the livestock owner has to identify the reasons for the excessive use of antimicrobials in collaboration with a veterinarian and check whether the antimicrobial use can be reduced. If parameter 2 is exceeded, a written action plan for minimising the antimicrobial use must be drawn up within two months, which also has to be presented to the competent state authority (AMG, 2013).[2]

Conclusion

The first surveillance period extended from 1 July 2014 to 31 December 2014 and the second one from 1 January 2015 to 30 June 2015, which is why results from two surveillance periods were available for the first time in 2015. The results were published in the Federal Gazette (Tab. 3.2.1, Tab. 3.2.2).[4,5]

The parameters do not allow a statement on the average number of treatment days per animal and half-year, nor are they suitable to compare the frequency of antimicrobial use between individual animal species and types of use. A correlation of this data or the data from the individual farms with the regional resistance situation is not possible, because information required for a corresponding classification is not available.

➤ J. Wallmann
Reviewer: I. Reimer

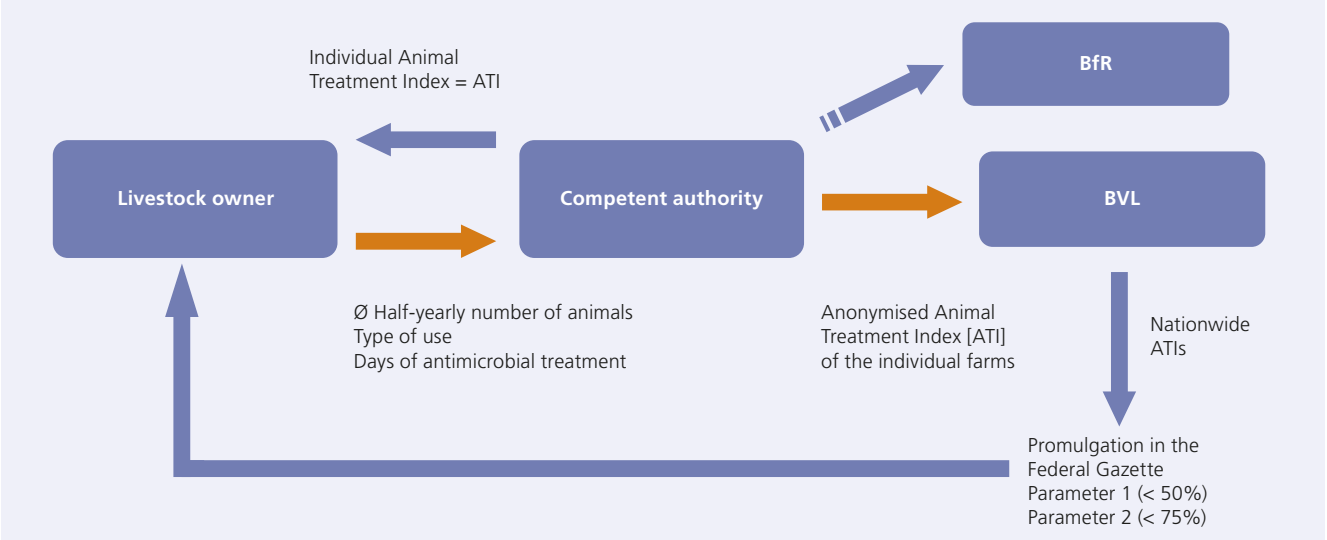


Fig. 3.2.1: System of recording the Animal Treatment Index

Tab. 3.2.1: Median and third quartile of the nationwide treatment frequencies of beef cattle, fattening pigs, broilers and meat turkeys recorded from 1 July 2014 to 31 December 2014 in accordance with Sec. 58c (4) of the Medicinal Products Act (AMG)

Animal species/Type of use	Median	Third quartile
Veal calves aged up to 8 months	0.000	5.058
Beef cattle aged above 8 months	0.000	0.015
Piglets weighing up to 30 kg	4.793	26.191
Fattening pigs weighing more than 30 kg	1.199	9.491
Broilers	19.558	35.032
Meat turkeys	23.030	47.486

Tab. 3.2.2: Median and third quartile of the nationwide treatment frequencies of beef cattle, fattening pigs, broilers and meat turkeys recorded from 1 January 2015 to 30 June 2015 in accordance with Sec. 58c (4) of the Medicinal Products Act (AMG)

Animal species/Type of use	Median	Third quartile
Veal calves aged up to 8 months	0.000	2.676
Beef cattle aged above 8 months	0.000	0.000
Piglets weighing up to 30 kg	5.930	20.611
Fattening pigs weighing more than 30 kg	0.757	6.474
Broilers	16.712	27.114
Meat turkeys	21.791	40.225

1. Sigge C, Richter A, Wallmann J, Klein G. Rechtliche Grundlagen und Leitlinien. In: Der Praktische Tierarzt 95, 2014;Suppl. 5:4-6.
2. Arzneimittelgesetz (AMG): 16. Gesetz zur Änderung des Arzneimittelgesetzes vom 10. Oktober 2013 (16. AMG-Novelle), BGBl. I. Seite 3813; zuletzt geändert durch Berichtigung der 16. AMG-Novelle vom 24.03.2014, BGBl. I. 272.
3. Tierarzneimittel-Mitteilungendurchführungsverordnung (TAMMitDurchfV): Verordnung über die Durchführung von Mitteilungen nach §§ 58a und 58b des Arzneimittelgesetzes vom 18. Juni 2014, BGBl. I. S. 797.
4. Bundesanzeiger (BAnz): Bekanntmachung des BVL zur ersten Erfassung der Therapiehäufigkeit vom 31. März 2015. BAnz AT 31.03.2015 B11. http://www.bvl.bund.de/SharedDocs/Downloads/05_Tierarzneimittel/bekanntmachungen/2015_03_31_Bekanntmachung_BAnz.pdf?__blob=publicationFile&v=2.
5. Bundesanzeiger (BAnz): Bekanntmachung des BVL zur zweiten Erfassung der Therapiehäufigkeit vom 30. September 2015. BAnz AT 30.09.2015 B4 http://www.bvl.bund.de/DE/05_Tierarzneimittel/05_Fachmeldungen/2015/2015_09_30_Fa_Antibiotikaabgabemenge_1HJ2015.html.

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 diseases, 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 2014 (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 1.3% 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 largely stabilised by 2014. The clindamycin resistance rate was very low throughout the entire period.

Conclusion

All *S. pyogenes* strains detected between 1999 and 2014 were susceptible to penicillin G. The rate of macrolide resistance during the study period ranged between 1.3% and 13.6%; the slight drop in the resistance rate observed in recent years has largely stabilised. The rate of resistance to clindamycin was even lower than to macrolides.

➤ M. Imöhl, R.R. Reinert, M. van der Linden
Reviewer: M. Pletz, T. Welte

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

Year		Penicillin G			Macrolide			Clindamycin		
	Isolates (n)	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
2012	320	100	0	0	98.1	0.6	1.3	99.7	0.0	0.3
2013	359	100	0	0	97.2	0.0	2.8	98.6	0.0	1.4
2014	245	100	0	0	94.7	0.0	5.3	98.8	0.0	1.2

4.1.1.2. *Streptococcus agalactiae*

Streptococcus agalactiae (group B streptococci, GBS) infections can generally be subdivided into neonatal infections and infections beyond the newborn period. In Germany and all other industrialised countries, GBS is by far the most common pathogen causing neonatal bloodstream infections. According to the most recent results of a national study conducted in Germany from 2008 to 2010, the incidence of blood or cerebrospinal fluid culture-positive GBS infections appears to be in decline, currently accounting for 0.34 per 1,000 live births, whereas it was still 0.47 during the period 2001-2003.[1] By contrast, the neonatal GBS cases have been observed to increase in recent years from 0.2/1,000 (1987) to 0.32/1,000 (2011) in the Netherlands.[2] Interestingly, a significantly larger number of isolates from 2011 belonged to a clonal lineage, referred to as clonal complex (CC)17, which is classified as particularly virulent.

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. Whereas EOD is formally defined as manifestation between the 1st and 6th day after birth, infections occurring after the 6th day of life are referred to as late-onset bloodstream infections (late-onset disease, LOD, between the 7th and 90th day after birth). 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 35th -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 the cases being fatal.[1] According to most recent U.S. data, neonatal GBS meningitis is associated with long-term effects in more than 40% of all affected patients.[2]

The above-mentioned national 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. Adult, predominantly older patients accounted for three-quarters of the 1,085 invasive isolates submitted to the central study laboratory: 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.[4] All tested isolates were highly susceptible to penicillin, ampicillin and cefotaxime. About 10% of the isolates were resistant to erythromycin and nearly 6% were resistant to clindamycin. Given that these antibiotics are used as alternatives for IAP in pregnant women who are allergic to penicillin, this observation is 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 second 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 and 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, a significant 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 (23%) found at a single center study in Germany performed in 2011.[5] The inducible clindamycin resistance rate was 6.1%.[5] Interestingly, the erythromycin resistance rate in isolates from newborns was 32%, while the rate in isolates from pregnant women was only 21%.[5] In the nationwide RKI study (2008-2010), only 16% of the neonatal isolates, but 23% of the adult isolates were found to be resistant to erythromycin.

The results of a 2013 resistance study conducted by the Paul Ehrich Society revealed a macrolide resistance rate of 32%; the inducible clindamycin resistance rate remained nearly unchanged (6.5%). The doxycycline resistance rate was 78% in this study.[6]

In the U.S. and Asia, GBS strains with reduced susceptibility to penicillin have been observed in the past and confirmed by the corresponding reference laboratories. In addition, isolated cases of vancomycin-resistant GBS isolates have been reported in the U.S. Fortunately, such isolates have so far not been detected in Germany.

Tab.4.1.1.2.1: Antimicrobial susceptibility of 976 invasive GBS isolates (2008–2010)

	Resistant [%]	MIC [mg/l]			
		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	≤ 1.0
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.

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 pregnant women 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
Review: N. Schnitzler

1. Fluegge K, Siedler A, Heinrich B, Schulte-Moenting J, et al. Incidence and clinical presentation of invasive neonatal group B streptococcal infections in Germany. Pediatrics 2006;117:1139-45.
2. Bekker V, Bijlsma MW, van de Beek D, Kuijpers RW, et al. Incidence of invasive group B streptococcal disease and pathogen genotype distribution in newborn babies in the Netherlands over 25 years: a nationwide surveillance study. Lancet Infect Dis 2014;14:1083-9.
3. Libster R, Edwards KM, Levent F, Edwards MS, et al. Long-term outcomes of group B streptococcal meningitis. Pediatrics 2012;130:8-15.
4. Fluegge K, Supper S, Siedler A, Berner R. Antibiotic susceptibility in neonatal invasive isolates of Streptococcus agalactiae from a nationwide surveillance study in Germany over 2 years. Antimicrob Agents Chemother 2004;48:4444-6.
5. Kunze M, Zumstein K, Markfeld-Erol F, Elling R, et al. Comparison of pre- and intrapartum screening of group B streptococci and adherence to screening guidelines: a cohort study. Eur J Pediatr 2015 ;174:827-35.
6. http://www.p-e-g.org/econtext/resistenzdaten

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 the 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 avirulent. Some pneumococcal infections are associated with a clustering of specific serotypes. In children, for example, about 10-15 serotypes have been responsible for 80-90% of all invasive infections before the pneumococcal conjugate vaccine was introduced. *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 the cases, causes the greatest burden of disease. 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 anatomical and functional 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). For persons aged 60 years or older, one-time vaccination against pneumococci with a pneumococcal polysaccharide vaccine is recommended by the STIKO as a standard vaccination.

In very young children, older patients with a weakened immune system and immunocompromised individuals, the effect of polysaccharide vaccines is weaker than in the rest of the population. By conjugating the polysaccharide antigens to a carrier protein, a T cell-dependent immune response is induced, resulting in higher antibody concentrations, not only in young children. Memory B cells are also produced, leading to a stronger immune response on repeated contact with the antigens. The great number of serotypes, of which only a limited number can be introduced into the conjugate vaccine, constitutes a challenge in the production of conjugate vaccines.

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) for the respective year, especially since the EUCAST breakpoints were not available before 2009.

Adults

The available data on adults cover the period from 1992 through December 2014. During the period 1992-2007, 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 upward 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, during the period 2008-2014, 4.6-16.2% of all meningitis cases were penicillin G-resistant, whereas most of the isolates found in non-meningitis cases were intermediate (0.3-0.7%), with resistant isolates being detected only sporadically (0.0-0.1%). 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 7.6% resistant isolates in 2014 (Tab. 4.1.1.3.1, Fig. 4.1.1.3.2).

Children

The evaluated data on children were collected from 1997 through December 2014. The rate of resistance to penicillin G during the period 1997-2007 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

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

Year	Isolates (n)	Penicillin G			Makrolide		
		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
2012	1,925	98.1	0.7	1.2	89.2	0.0	10.8
2013	2,251	98.8	0.4	0.8	92.5	0.0	7.5
2014	2,151	98.3	0.6	1.1	92.4	0.0	7.6

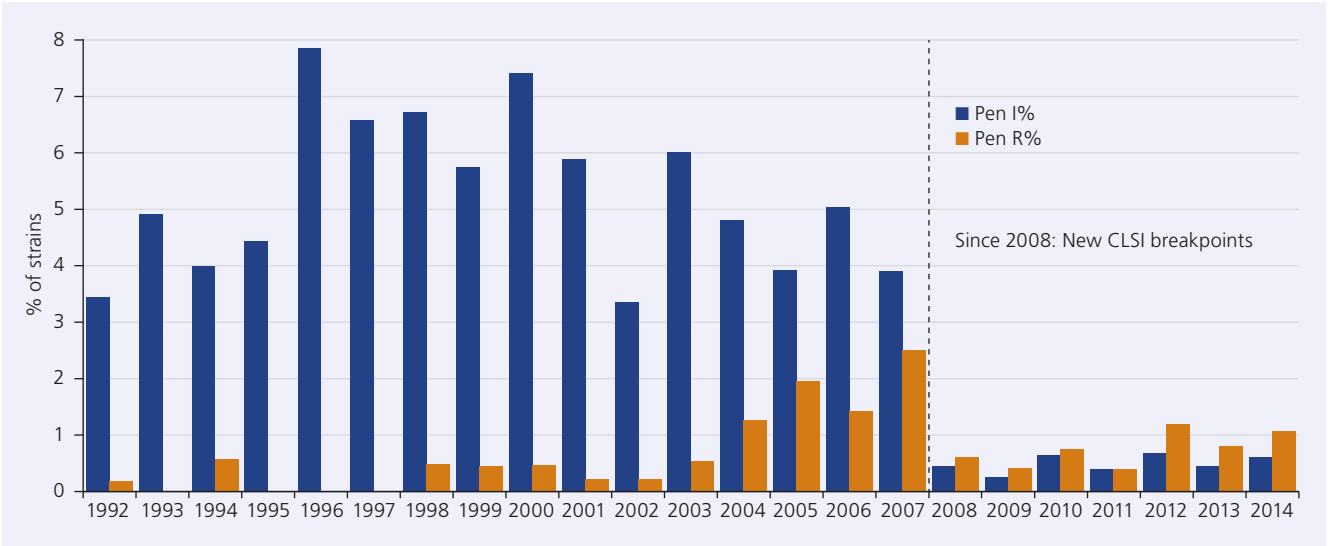


Fig. 4.1.1.3.1: Isolates from adults with reduced susceptibility to penicillin
Pen I%, % of penicillin-intermediate isolates; Pen R%, % of penicillin-resistant isolates

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			Isolates (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
2012	142	83.8	0.0	16.2	1,783	99.3	0.7	0.0
2013	140	89.3	0.0	10.7	2,111	99.4	0.5	0.1
2014	146	84.2	0.0	15.8	2,005	99.4	0.6	0.0

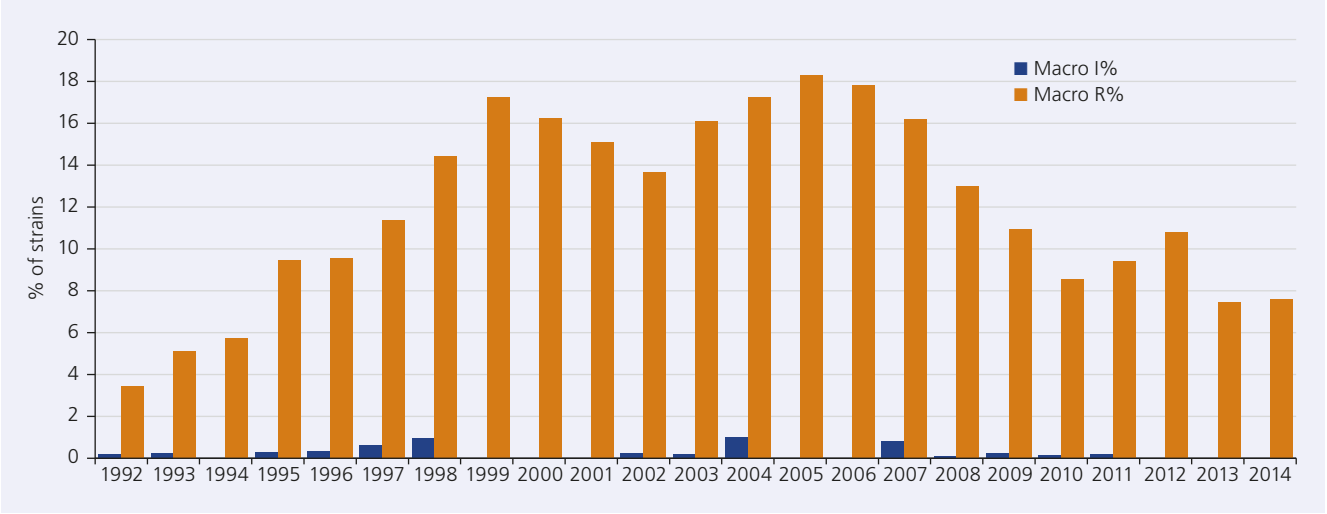


Fig. 4.1.1.3.2: Isolates from adults with reduced susceptibility to macrolides
Macro I%, % of macrolide-intermediate isolates; Macro R%, % of macrolide-resistant isolates

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
2012	173	93.6	0.6	5.8	91.9	0.0	8.1
2013	189	96.3	0.0	3.7	93.1	0.0	6.9
2014	153	95.4	1.3	3.3	91.5	0.0	8.5

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 only led to a temporary drop in the average resistance rate (Tab. 4.1.1.3.3, Fig. 4.1.1.3.3). During the period 2008-2014, 3.3-16.1% of all meningitis cases in children were penicillin G-resistant, whereas most of the isolates found in non-meningitis cases were intermediate (0.0-2.2%), with one resistant isolate (0.7%) being detected in 2011 (Tab. 4.1.1.3.4).

The prevalence of macrolide resistance in children increased significantly between 1997 (10.6%) and 2005 (33.4%), but fortunately it gradually decreased again between 2006 (29.8%) and 2014 (8.5%). 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).

Resistance and serotype distribution

The serotype distribution, shown based on the 2008 and 2014 data, respectively, confirms that a few years after the recom-

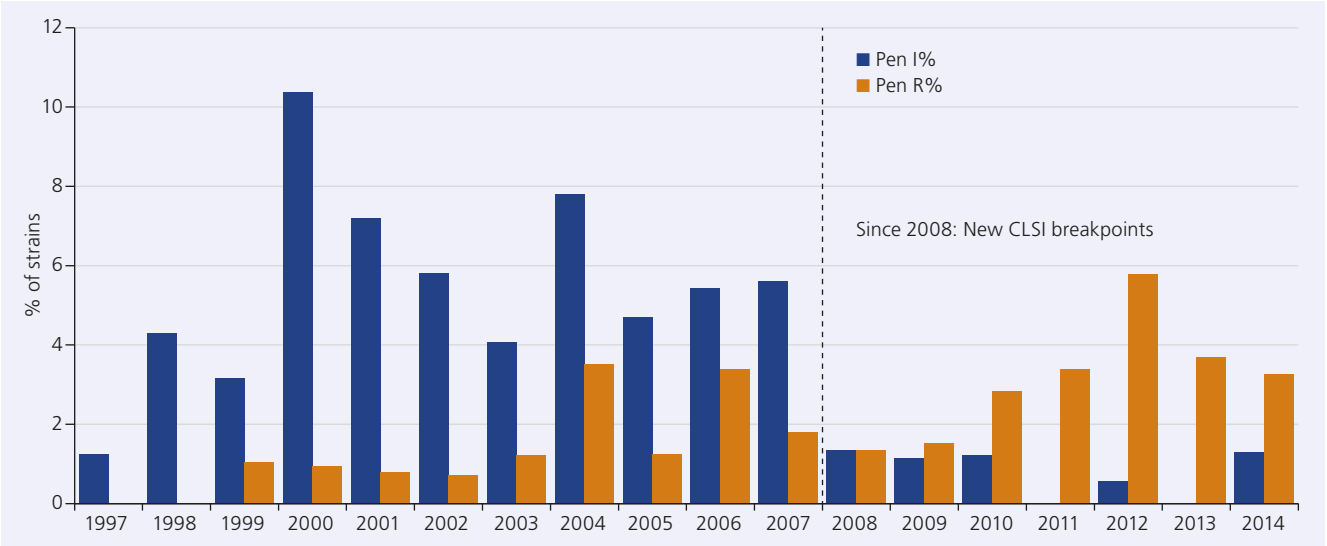


Fig. 4.1.1.3.3: Isolates from children with reduced susceptibility to penicillin
Pen I%, % of penicillin-intermediate isolates; Pen R%, % of penicillin-resistant isolates

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			Isolates (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
2012	62	83.9	0.0	16.1	111	99.1	0.9	0.0
2013	65	89.2	0.0	10.8	124	100.0	0.0	0.0
2014	55	90.9	0.0	9.1	98	98.0	2.0	0.0

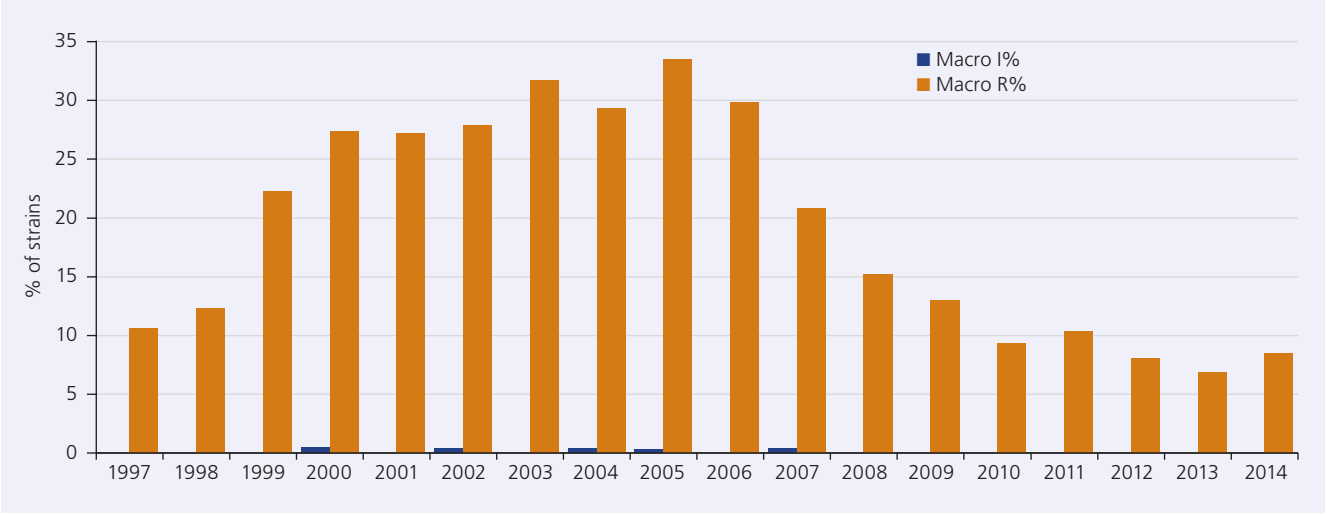


Fig. 4.1.1.3.4: Isolates from children with reduced susceptibility to macrolides
Macro I%, % of macrolide-intermediate isolates; Macro R%, % of macrolide-resistant isolates

mendation for vaccination the serotype distribution has changed significantly in both children and adults (herd protection).

At present, only 5.2% of the isolates in children are covered by the 7-valent conjugate vaccine (7v PnC), 11.8% by the 10-valent conjugate vaccine (10v PnC) and 27.5% by the 13-valent conjugate vaccine (13v PnC). The most common serotypes in 2014 were 24F (11.1%), 12F (8.5%), 3 (7.8%) and 19A (7.2%) (Tab. 4.1.1.3.5).

In adults, 5.6% of the isolates are currently covered by the 7v PnC, 11.2% by the 10v PnC and 71.6% by the 23-valent polysaccharide vaccine (23v PnP). The most common serotypes in 2014 were 3 (16.2%), 12F (8.4%), 22F (8.0%), 19A (5.9%), 8 (5.8%) and 9N (5.3%) (Tab 4.1.1.3.6).

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, Tab 4.1.1.3.8).

By contrast, the prevalence of penicillin resistance in children slightly increased from 1.3% in 2008 to 3.3% in 2014, with 1.3% intermediate isolates being detected in both years (Tab. 4.1.1.3.9)

Tab. 4.1.1.3.5: Serotype distribution in children in 2008 and 2014

Sero-type	In PnC vaccine	2008		2014	
		Isolates (n)	%	Isolates (n)	%
4	7v, 10v, 13v	1	0.4	0	0.0
6B	7v, 10v, 13v	10	4.5	2	1.3
9V	7v, 10v, 13v	3	1.3	1	0.7
14	7v, 10v, 13v	12	5.4	1	0.7
18C	7v, 10v, 13v	14	6.3	0	0.0
19F	7v, 10v, 13v	8	3.6	4	2.6
23F	7v, 10v, 13v	5	2.2	0	0.0
Total	7v	53	23.7	8	5.2
1	10v, 13v	29	12.9	7	4.6
5	10v, 13v	2	0.9	0	0.0
7F	10v, 13v	32	14.3	3	2.0
Total	10v	116	51.8	18	11.8
3	13v	12	5.4	12	7.8
19A	13v	10	4.5	11	7.2
6A	13v	12	5.4	1	0.7
Total	13v	150	67.0	42	27.5
38	no	9	4.0	6	3.9
10A	no	7	3.1	10	6.5
15B	no	5	2.2	3	2.0
15C	no	5	2.2	9	5.9
24F	no	5	2.2	17	11.1
12F	no	4	1.8	13	8.5
9N	no	4	1.8	1	0.7
22F	no	3	1.3	3	2.0
23A	no	3	1.3	4	2.6
33F	no	3	1.3	9	5.9
35F	no	3	1.3	2	1.3
NT	no	3	1.3	0	0.0
11A	no	2	0.9	2	1.3
16F	no	2	0.9	0	0.0
17F	no	2	0.9	3	2.0
18A	no	2	0.9	0	0.0
8	no	1	0.4	5	3.3
21	no	1	0.4	0	0.0
31	no	1	0.4	0	0.0
39	no	1	0.4	0	0.0
15A	no	1	0.4	4	2.6
23B	no	1	0.4	5	3.3
28A	no	1	0.4	0	0.0
28F	no	1	0.4	2	1.3
33A	no	1	0.4	0	0.0
35A	no	1	0.4	0	0.0
35B	no	1	0.4	2	1.3
6C	no	1	0.4	1	0.7
12A	no	0	0.0	1	0.7
27	no	0	0.0	1	0.7
34	no	0	0.0	5	3.3
37	no	0	0.0	3	2.0
Total		224	100,0	153	100.0

Tab. 4.1.1.3.6: Serotype distribution in adults in 2008 and 2014

Sero-type	In Pn vaccine	2008		2014	
		Isolates (n)	%	Isolates (n)	%
4	7v, 10v, 13v, 23v	94	5.2	23	1.1
6B	7v, 10v, 13v, 23v	42	2.3	11	0.5
9V	7v, 10v, 13v, 23v	71	3.9	8	0.4
14	7v, 10v, 13v, 23v	169	9.3	19	0.9
18C	7v, 10v, 13v, 23v	49	2.7	13	0.6
19F	7v, 10v, 13v, 23v	59	3.2	34	1.6
23F	7v, 10v, 13v, 23v	82	4.5	12	0.6
Total	7v	566	31.1	120	5.6
1	10v, 13v, 23v	153	8.4	38	1.8
5	10v, 13v, 23v	13	0.7	1	0.0
7F	10v, 13v, 23v	179	9.8	82	3.8
Total	10v	911	50.1	241	11.2
3	13v, 23v	226	12.4	348	16.2
19A	13v, 23v	76	4.2	128	5.9
6A	13v	56	3.1	20	0.9
Total	13v	1,269	69.8	737	34.2
8	23v	61	3.4	124	5.8
9N	23v	51	2.8	113	5.3
10A	23v	36	2.0	85	3.9
11A	23v	49	2.7	59	2.7
12F	23v	31	1.7	181	8.4
15B	23v	19	1.0	29	1.3
20	23v	8	0.4	25	1.2
22F	23v	59	3.2	173	8.0
33F	23v	17	0.9	35	1.6
Total	23v	1,544	84.9	1,541	71.6
35F	no	34	1.9	40	1.9
23A	no	32	1.8	50	2.3
24F	no	31	1.7	83	3.9
6C	no	24	1.3	57	2.6
38	no	22	1.2	26	1.2
31	no	9	0.5	25	1.2
34	no	9	0.5	12	0.6
15A	no	7	0.4	80	3.7
16F	no	7	0.4	19	0.9
23B	no	4	0.2	68	3.2
33A	no	4	0.2	1	0.0
35B	no	4	0.2	41	1.9
13	no	3	0.2	2	0.1
10B	no	3	0.2	5	0.2
17F	no	3	0.2	23	1.1
35A	no	3	0.2	0	0.0
7C	no	3	0.2	1	0.0
15C	no	2	0.1	18	0.8
18A	no	2	0.1	6	0.3
25F	no	2	0.1	0	0.0
NT	no	2	0.1	3	0.1
29	no	1	0.1	1	0.0
39	no	1	0.1	0	0.0
10F	no	1	0.1	1	0.0
11B	no	1	0.1	1	0.0
12A	no	1	0.1	10	0.5
18F	no	1	0.1	0	0.0
24B	no	1	0.1	1	0.0
7B	no	1	0.1	3	2.0
28F	no	0	0.0	4	2.6
37	no	0	0.0	3	2.0
21	no	0	0.0	2	1.3
28A	no	0	0.0	2	1.3
15F	no	0	0.0	1	0.7
19B	no	0	0.0	1	0.7
6D	no	0	0.0	1	0.7
Total		1,818	100.0	2,152	100.0

and in adults from 0.6% in 2008 to 1.1% in 2014, with 0.4% (2008) and 0.6% (2014) intermediate isolates being detected (Tab. 4.1.1.3.10). It is remarkable that isolates non-susceptible to penicillin were predominantly of non-vaccine serotypes (15A, 23B) in meningitis cases and of vaccine serotypes (6A, 6B, 14, 19A, 19F) in non-meningitis cases.

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

Tab. 4.1.1.3.7: Macrolide resistance of 7v, 10v and 13v PnC serotypes and other serotypes in children in 2008 and 2014

Category	2008		2014	
	Isolates (n)	%	Isolates (n)	%
7v PnC serotypes				
Susceptible	34	64.2	3	37.5
Intermediate	0	0.0	0	0.0
Resistant	19	35.8	5	62.5
10v PnC serotypes				
Susceptible	90	77.6	13	72.2
Intermediate	0	0.0	0	0.0
Resistant	26	22.4	5	27.8
13v PnC serotypes				
Susceptible	122	81.3	35	83.3
Intermediate	0	0.0	0	0.0
Resistant	28	18.7	7	16.7
Other serotypes				
Susceptible	68	91.9	105	94.6
Intermediate	0	0.0	0	0.0
Resistant	6	8.1	6	5.4
Total number				
Susceptible	190	84.8	140	91.5
Intermediate	0	0.0	0	0.0
Resistant	34	15.2	13	8.5

Tab. 4.1.1.3.8: Macrolide resistance of 7v, 10v and 13v PnC serotypes, 23v PnPS serotypes and other serotypes in adults in 2008 and 2014

Category	2008		2014	
	Isolates (n)	%	Isolates (n)	%
7v PnC serotypes				
Susceptible	516	91.2	82	68.3
Intermediate	0	0.0	0	0.0
Resistant	50	8.8	38	31.7
10v PnC serotypes				
Susceptible	714	78.4	200	83.0
Intermediate	2	0.2	0	0.0
Resistant	195	21.4	41	17.0
13v PnC serotypes				
Susceptible	1.050	82.7	659	89.4
Intermediate	2	0.2	0	0.0
Resistant	217	17.1	78	10.6
23v PnPS serotypes				
Susceptible	1.324	85.6	1.462	93.5
Intermediate	2	0.1	0	0.0
Resistant	221	14.3	102	6.5
Other serotypes				
Susceptible	206	95.8	511	90.0
Intermediate	0	0.0	0	0.0
Resistant	9	4.2	57	10.0
Total number				
Susceptible	1.581	87.0	1.989	92.4
Intermediate	2	0.1	0	0.0
Resistant	235	12.9	163	7.6

Tab. 4.1.1.3.9: Penicillin resistance of 7v, 10v and 13v PnC serotypes and other serotypes in children in 2008 and 2014

Category	2008		2014	
	Isolates (n)	%	Isolates (n)	%
7v PnC serotypes				
Susceptible	50	94.3	6	75.0
Intermediate	2	3.8	2	25.0
Resistant	1	1.9	0	0.0
10v PnC serotypes				
Susceptible	113	97.4	16	88.9
Intermediate	2	1.7	2	11.1
Resistant	1	0.9	0	0.0
13v PnC serotypes				
Susceptible	144	96.0	40	95.2
Intermediate	3	2.0	2	4.8
Resistant	3	2.0	0	0.0
Other serotypes				
Susceptible	74	100.0	106	95.5
Intermediate	0	0.0	0	0.0
Resistant	0	0.0	5	4.5
Total number				
Sensibel	218	97.3	146	95.4
Intermediär	3	1.3	2	1.3
Resistent	3	1.3	5	3.3

Tab. 4.1.1.3.10: Penicillin resistance of 7v, 10v and 13v PnC serotypes, 23v PnPS serotypes and other serotypes in adults in 2008 and 2014

Category	2008		2014	
	Isolates (n)	%	Isolates (n)	%
7v PnC serotypes				
Susceptible	551	97.3	115	95.8
Intermediate	8	1.4	5	4.2
Resistant	7	1.2	0	0.0
10v PnC serotypes				
Susceptible	896	98.4	236	97.9
Intermediate	8	0.9	5	2.1
Resistant	7	0.8	0	0.0
13v PnC serotypes				
Susceptible	1.252	98.7	724	98.2
Intermediate	8	0.6	12	1.6
Resistant	9	0.7	1	0.1
23v PnPS serotypes				
Susceptible	1.530	98.9	1.549	99.0
Intermediate	8	0.5	12	0.8
Resistant	9	0.6	3	0.2
Other serotypes				
Susceptible	213	99.1	548	96.5
Intermediate	0	0.0	0	0.0
Resistant	2	0.9	20	3.5
Total number				
Susceptible	1.798	98.9	2.116	98.3
Intermediate	8	0.4	13	0.6
Resistant	12	0.7	23	1.1

comparatively low. The rapid increase in macrolide resistance has been halted in recent years. The resistance rates in both children and adults decreased relatively continuously between 2006 and 2014, being well below 10% in both age groups in 2014.

➤ M. Imöhl, R.R. Reinert, M. van der Linden
Reviewer: M. Pletz, T. Welte

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 colonisers or infectious agents until after discharge; these are then termed hospital-associated community-onset MRSA (HCA-MRSA). Additionally, MRSA occurring in the population outside and independently from inpatient care facilities (*community-associated* MRSA, CA-MRSA) differ from those that have their original reservoir in livestock farming (*livestock-associated MRSA*, LA-MRSA).[1-3]

Trends in resistance development

The percentage of methicillin-resistant *S. aureus* in the *S. aureus* population has been declining for several years. This trend is also reflected in the data reported by a number of national and international surveillance systems.

European Antimicrobial Resistance Surveillance Network (EARS-Net)

EARS-Net records data from various national antimicrobial resistance surveillance systems to present the resistance situation of selected pathogens in Europe over time and to identify trends for various European countries and regions. In 2012, 2013 and 2014, Germany reported resistance data for 2,563, 3,070 and 3,146 *S. aureus* isolates from blood cultures, respectively, ascertained in 22 laboratories (covering about 200 hospitals). Whereas the data on the prevalence of methicillin-resistant *S. aureus* collected within EARS-Net during the period 1999-2005 showed a continuous increase (from 8.3 to 21.4%), a declining trend has been observed since 2006. Recent EARS-Net data reveals a rate of methicillin-resistant *S. aureus* isolates from blood cultures of 15.4% for 2012, 12.7% for 2013 and 11.8% for 2014.[4] Fig. 4.1.2.1 summarises the prevalence of MRSA during the period 2010-2014 in Germany and in other European countries. In general, the MRSA rates in Northern Europe are lower than in Southern and Southeast Europe. A significant increase is observed in Denmark and Slovenia, whereas the MRSA rates are declining in eight countries. However, the MRSA rates in 2014 are still > 25% in seven countries, in one of them (Romania) even > 50%.

Data from the mandatory national surveillance system for invasive MRSA infections

Since July 2009, MRSA detected in blood cultures and cerebrospinal fluid have been subject to reporting in Germany. Under the laboratory reporting obligation, 4,498 cases were reported in 2012 and 4,372 in 2013, equivalent to an incidence of 5.6 and 5.3 cases per 100,000 inhabitants, respectively. In 2014, the incidence dropped to 4.8 cases per 100,000 inhabitants (3,841 reported cases). The incidence of MRSA cases shows regional differences which cannot be explained by the collected surveillance data (https://survstat.rki.de/).[5]

Antimicrobial Resistance Surveillance System (ARS)

ARS is a laboratory-based surveillance system that continuously collects resistance data from medical routine on clinically relevant bacterial pathogens. At present, this network comprises 28 laboratories of inpatient and outpatient care. The ARS national surveillance system determined MRSA rates of 20.2% in 2012 and 17.1% in 2013 for all specimens obtained from inpatient care; when looking only at MRSA from blood culture isolates in inpatient care, the rates dropped from 17.0% in 2012 to 13.9% in 2013. With a rate of 12.7%, the downward trend continues in 2014 (https://ars.rki.de, data as of 23/02/2016).

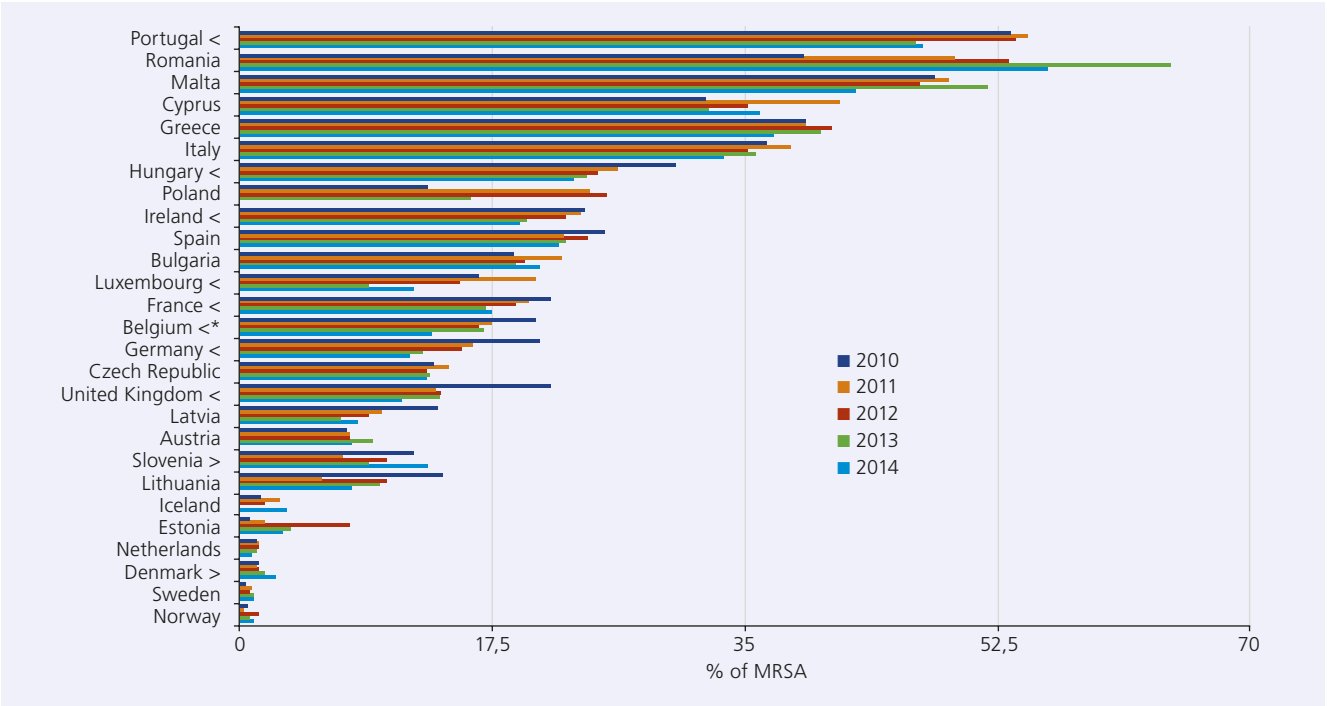


Fig. 4.1.2.1: Percentage of MRSA in *S. aureus* isolates from blood cultures in various European countries (2010-2014)[4] The < and > symbols indicate a significant increase or decrease in resistance. The >* symbol indicates a significant trend when taking the data from all laboratories into account. However, the trend was not significant when only data was taken into account from laboratories that participated in the study every four years.

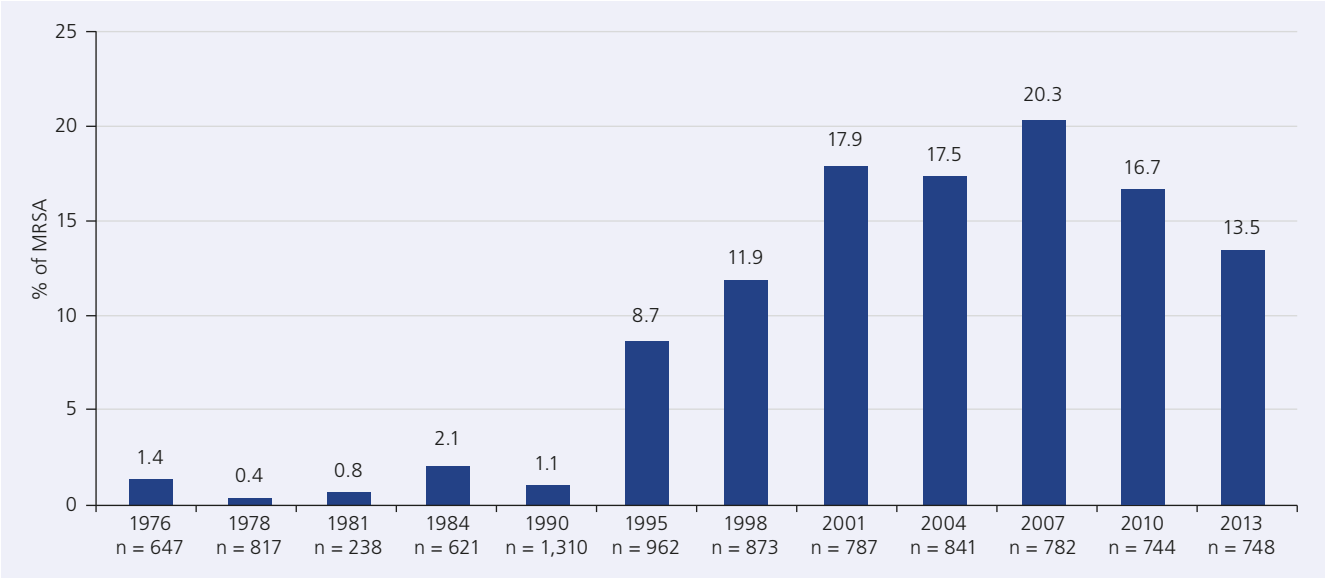


Fig. 4.1.2.2: Percentage of MRSA in all tested *S. aureus*; data obtained from the resistance studies by the Paul Ehrlich Society (1976-2013)

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. Over the last few years, a slight but steady decline in the incidence density of nosocomial MRSA cases has been observed in German intensive care units (data reported by MRSA-KISS; www.nrz-hygiene.de/). The MRSA rate in all nosocomial *S. aureus* infections in intensive care patients (ITS-KISS) and in patients who have undergone surgery (OP-KISS) dropped from 33% in 2007 to 27% in 2012. The MRSA prevalence in northern and western parts of Germany is higher than in southern and eastern federal states.[6]

Resistance study conducted by the Paul Ehrlich Society for Chemotherapy (PEG)

Since 1975, the Susceptibility Testing and Resistance Working Group of the PEG has been regularly collecting data on antimicrobial resistance in important bacterial species, among them *S. aureus*, isolated from clinical specimens. Between 2007 and 2010, the MRSA rate was observed to drop from 20.3% to 16.7%; with an MRSA rate of 13.5% in *S. aureus* from the hospital sector, this trend continued in 2013 (Fig. 4.1.2.2). The prevalence of co-resistance in MRSA in 2010 and 2013 is shown in Fig. 4.1.2.3. This confirms the downward trend in the prevalence of MRSA resistant to several substances, which reflects the decline in extensively drug-resistant clones among epidemic MRSA clones. The MRSA rate in *S. aureus* from ambulatory care was 8% in 2013. The prevalence of co-resistance in MRSA to other substances was 76.7% for ciprofloxacin, 56.7% for erythromycin and 43.3% for clindamycin. MRSA resistant to vancomycin, linezolid or co-trimoxazole were not detected either at hospitals or in the ambulant sector. MRSA showing high-level mupirocin resistance were not identified in 2013; however, one MSSA showing high-level resistance to mupirocin was detected in outpatient care (MIC > 256 mg/l).[7,8]

Molecular characterisation of MRSA isolates from the hospital sector yielded a classification as HA-MRSA in 84.2% of the cases in 2013, among them 37.6% MRSA with the *spa* type t003

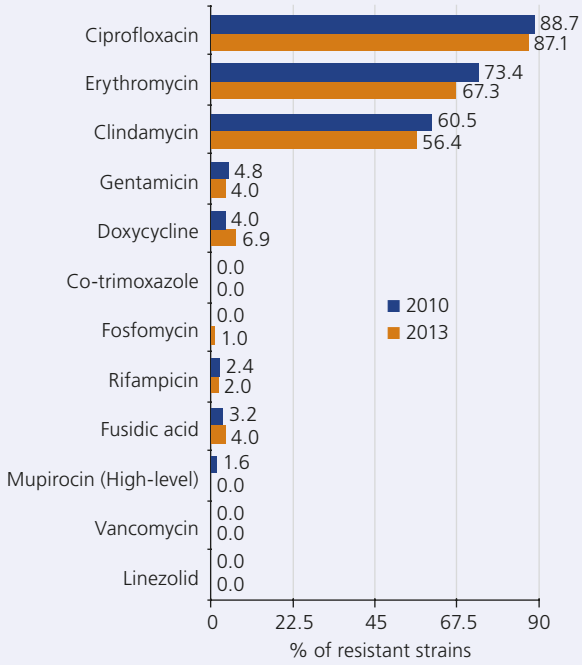


Fig. 4.1.2.3: Co-resistance to important antimicrobials in MRSA; data obtained from the resistance studies by the Paul Ehrlich Society (2010 and 2013)

(clonal lineage ST225; "Rhine-Hesse Epidemic Strain") and 27.1% with the *spa* type t032 (clonal lineage ST22; "Barnim Epidemic Strain"). 5% of the strains, exhibiting the *spa* types t011, t034, t899 and t2576, belong to the livestock-associated clonal complex CC398. 10.9% of the strains were classified as CA-MRSA, in 7% of which the genetic determinants for the production of Panton-Valentine leukocidin were detected. In outpatient care, HA-MRSA (among them *spa* t003 and t032, 26.7% each) were identified in 70% of the cases; in this environment these clones are referred to as HCA-MRSA. Furthermore molecular typing revealed one LA-MRSA and eight strains which were classified as CA-MRSA.[7,8]

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

Emergence of epidemic MRSA at German hospitals

HA-MRSA occur as epidemic MRSA and they are assigned to specific clonal lineages using molecular typing techniques. It has been observed for several decades, that there is a dynamic change in epidemic HA strains.[9]

Staphylococci from about 250 diagnostic facilities all over Germany are sent to the NRC every year. As was the case in previous years, HA-MRSA of certain clonal lineages are found at nearly all hospitals (Tab. 4.1.2.1), with MRSA of the clonal lineages ST22 ("Barnim Epidemic Strain") and ST225 ("Rhine-Hesse Epidemic Strain") being most prevalent. MRSA of the clonal lineages ST8 and ST45 ("Berlin Epidemic Strain") occur far less commonly at hospitals than other epidemic MRSA. In 2013/2014, MRSA ST228 ("Southern German Epidemic Strain") were only detected in isolated cases, with a significant decline of this clonal lineage being observed at German hospitals.

The vast majority of MRSA strains, where the clinical indication was submitted, were isolated from surgical site infections, followed by bloodstream infections, abscesses and pneumonia. Most of these isolates were grouped to the clonal lineages ST225 and ST22, thus reflecting the predominance of these two epidemic MRSA strains at German hospitals; a correlation between a particular clonal lineage and specific indication is not apparent. A study that performed typing of *S. aureus* from blood cultures involving staphylococci reference laboratories from 25 European countries revealed that different HA-MRSA are predominant in the various countries. However, some clonal lineages are found throughout Europe. When comparing the 2006 and 2011 data of this study, an increase in the prevalence of MRSA ST22 is becoming apparent Europe-wide.[10]

Due to the endemic spread of specific HA-MRSA clones, other molecular typing methods than *spa*-typing are needed to resolve the dissemination of these strains e.g. in outbreak investigations.[11] The NRC is currently conducting pilot projects for NGS (Next Generation Sequencing)-based strain typing, the main focus being placed on the extraction of diagnostically relevant information from whole genome data (prediction of resistance, identification of important virulence markers) as well as core genome-based typing (cgMLST).

Resistance to other antimicrobial classes in HA-MRSA

Tab. 4.1.2.2 summarises the prevalence of resistance to indicator substances of various antimicrobial classes other than β-lactam antimicrobials. In 2014, 80% of all MRSA from nosocomial infections were resistant to ciprofloxacin and moxifloxacin, 58.2% to erythromycin and 50.3% to clindamycin. The rates of resistance to a number of antimicrobials were below 10%.

Tab. 4.1.2.2: Resistance to other antimicrobials (in addition to resistance to β-lactam antimicrobials) in HA-MRSA, 2012-2014

Antimicrobial	2012 (%)	2013 (%)	2014 (%)
Ciprofloxacin	86.6	81.8	80.0
Moxifloxacin	86.1	80.8	79.3
Erythromycin	65.7	58.9	58.2
Clindamycin	58.8	50.6	50.3
Gentamicin	5.7	5.0	6.6
Tetracycline	7.4	7.2	8.6
Rifampicin	1.4	0.8	1.5
Co-trimoxazole	0.5	0.4	0.8
Fusidic acid-sodium	3.5	4.0	4.7
Fosfomycin	0.4	0.2	0.5
Linezolid	0	0.1	0.03
Tigecycline	0.13	0.04	0.23
Daptomycin	1.0	2.7	2.9
Mupirocin	6.7*	6.2*	I: 5.8 / R: 1.2
Vancomycin	0.2	0.04	0.03
Teicoplanin	0.3	0.3	0.13

I, intermediate, R, resistant; * I + R

The rate of resistance to mupirocin was 1.2% in 2014, with 5.8% of the isolates being classified as intermediate based applying EUCAST breakpoints. The horizontally acquired resistance determinant *ileS*-2 was detected in the majority of the resistant isolates, whereas intermediate isolates predominantly exhibited resistance-associated polymorphisms in the native *ileS*. To what extent *S. aureus* isolates with low-level mupirocin resistance is associated with a possible failure of decolonisation measures is currently not yet clear.

In 2013/2014, three linezolid-resistant HA-MRSA were submitted which were tested negative for the presence of the *cfr* resistance gene.

Tab. 4.1.2.1: Prevalence of epidemic MRSA with nationwide spread at German hospitals

Clonal complex	Clonal lineage	2012	2013	2014	Frequent resistance phenotypes
CC5	ST228, t001, Southern German Epidemic Strain	10.0%	2.0%	0%	PEN, OXA, GEN, ERY, CLI, CIP, MOX, (PHO), (MUP)
	ST5, t002, Rhine-Hesse Epidemic Strain	26.0%	28.6%	28.9%	PEN, OXA, ERY, CLI, CIP, MOX
	ST225, t003, Rhine-Hesse Epidemic Strain	70.0%	67.3%	62.2%	PEN, OXA, ERY, CLI, CIP, (MOX), (MUP), (FUS)
CC8	ST8, t008	24.0%	24.5%	28.9%	PEN, OXA, (ERY), (CLI), (CIP), (MOX)
	ST239, t037, t030, Vienna Epidemic Strain	16.0%	2.0%	6.7%	PEN, OXA, GEN, ERY, CLI, TET, CIP, SXT, (RAM), MOX
CC22	ST22, t005,t020, t022, Barnim Epidemic Strain	40.0%	42.9%	53.3%	PEN, OXA, ERY, CLI, CIP, (MOX)
	ST22, t032, Barnim Epidemic Strain	88.0%	85.7%	84.4%	PEN, OXA, ERY, CLI, CIP, (MOX), (MUP), (FUS)
CC45	ST45, u.a. t004, t038, t065, Berlin Epidemic Strain	28.0%	20.4%	17.8%	PEN, OXA, CIP, (MOX), (GEN), (ERY), (CLI)
Total number of hospitals		n = 50	n = 49	n = 45	

Phenotypes in brackets: detected only in some of the isolates

The prevalence of daptomycin-resistant MRSA in 2014 was 2.9%, thus being at a similarly high level as in 2013. These isolates were often multidrug-resistant and predominantly belonged to the currently most widespread clonal lineages of HA-MRSA (ST22 and ST225). However, the increasing number of submissions of daptomycin-resistant MSSA, some of which also exhibit elevated MIC values for glycopeptides, is remarkable. Most of these isolates belong to clonal lineages which are known as "typical" nasal colonisers.

In 2013/2014, resistance to tigecycline was detected in eight cases; three of these isolates belonged to the so-called "Vienna Epidemic Strain" (ST239), which is characterised by a particularly broad resistance phenotype. In these two years, we additionally received two MRSA that were resistant to vancomycin and teicoplanin (*van*A- and *van*B-negative). These strains were additionally daptomycin-resistant; this suggests the presence of mutations which can cause cross-resistance to glycopeptides and daptomycin.

As part of a research project supported by the Federal Ministry of Health, *spa* types and antimicrobial resistance profiles of 1,952 bacteraemia-associated MRSA from hospitals in North Rhine-Westphalia were determined during the period 2011-2013.[12] A total of 96% of these strains were resistant to fluoroquinolones, 78% to erythromycin, 70% to clindamycin, 4% to gentamicin and 2% to rifampicin. Resistance to last-resort antimicrobials occurred rarely. MRSA of the clonal lineages ST225 and ST22 were again predominant; however, regional differences in the distribution of the spa types became apparent.

Ceftaroline is a fifth-generation cephalosporin with activity against MRSA, which has been available in Germany since October 2012. As part of a study investigating the in-vitro susceptibility of *S. aureus* to ceftaroline before its approval, the NRC tested 160 clinical isolates representative of the German *S. aureus* and MRSA population by means of agar diffusion, broth microdilution and E-test® (EUCAST breakpoints for ceftaroline: susceptible ≤ 1 mg/l; resistant > 1 mg/l).[13] Whereas, as expected, all tested MSSA isolates were susceptible to ceftaroline, the results within the MRSA population were strongly dependent on the clonal lineage of the tested isolates. Isolates of the clonal lineages ST239 and ST228 showed particularly high $MIC_{50/90}$ values (minimum inhibitory concentration) of 2.5/3.33 mg/l. The $MIC_{50/90}$ values of MRSA lineages that are highly prevalent in Germany (ST22, ST225) ranged at 1/1.5 mg/l. Hence, some of these isolates exhibited MIC values within the range of the current EUCAST breakpoint for ceftaroline, which has made the final classification as susceptible or resistant difficult. As regards ceftaroline-resistant isolates in particular, the various susceptibility testing methods produced significantly different results, i.e. the E-test® only identified resistant isolates in few cases. The results of other international studies confirm these observations and also describe ceftaroline susceptibility testing as a current diagnostic challenge.[14,15]

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

CA-MRSA occur in the population outside hospitals and independently of HA-MRSA-associated risk factors. The clinical symptoms of CA-MRSA 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 less commonly, but are associated with a high mortality.

In 2013/2014, most CA-MRSA submitted to the NRC were isolated from deep skin and soft tissue infections (abscesses, furuncles, carbuncles, surgical site infections), with CA-MRSA of the clonal lineages CC5, CC8, CC80 and CC30 being most predominant (Tab. 4.1.2.3). Clusters of CA-MRSA infections within families occurred occasionally. For the first time in 2013, it was also possible to detect transmission chains of CA-MRSA at hospitals. A CA-MRSA ST22 strain was isolated from abscesses of three patients on a surgical ward and from the tracheal secretion of another patient. The personnel screening revealed two staff members carrying this clone. Three mothers and two newborns

Tab. 4.1.2.3: Prevalence of clonal lineages of CA-MRSA occurring within infections in 2013/2014

Clonal lineage	2013 (n)	2014 (n)	spa types	lukPV-positive (n)	Country of origin or travel history of patients (n = cases)
CC1	21	12	t127, t174, t321, t386, t5100	17/33	Libya (2), Croatia (1), Romania (1)
CC5	19	55	t002, t010, t045, t105, t315, t548, t653, t856, t954, t1062, t2069, t2646, t3235, t14207	46/51	Libya (12), Syria (2), Saudi Arabia (1)
CC8	49	46	t008, t024, t121, t190, t304, t334, t363, 1617, t1578, t11985	87/95	UAE (1), Kuwait (1), Venezuela (1), USA (3), UK (1), Hungary (1)
CC22	20	27	t005, t016, t223, t309, t449, t566, t852, t891, t2336, t4573, t5047, t13545	35/47	Libya (1), Kuwait (1), Romania (1)
CC30	13	32	t017, t018, t019, t021, t138, t318, t665, t685, t5447, t6278, t12633	40/45	Turkey (1)
ST59	12	20	t216, t437, t2365	27/32	Poland (1), Thailand (1)
ST72	2	1	t324, t791	2/3	–
CC80	34	39	t044, t131, t376, t4955, t1200, t1247, t1759	72/73	Egypt (2), Libya (2), Kuwait (1)
ST88	9	15	t186, t690, t692, t786, t1814, t4015, t4045, t4158, t5041, t12154, t13831	22/24	Kenya (2), Somalia (2), Egypt (1), China (1)
ST97	1	13	t267, t359, t426, t2112	0/14	Libya (1), Kuwait (1)
ST121	1	4	t159, t272, t314, t4169	2/5	–
ST152	9	5	t355, t4272, t4690, t4741, NT	10/14	–
ST188	2	1	t189	0/3	Saudi Arabia (1)
ST239	–	4	t037	0/4	Libya (4)
ST398	29	21	t011, t034, t899, t1451, t2011	2/50	–
ST772	5	10	t345, t657, t2085, t8882	15/15	Pakistan (1)

on a neonatal ward were tested positive for CA-MRSA ST8. A spatial and temporal connection was established in all five cases. The personnel screening identified two persons who also carried this clone.

CA-MRSA still spread predominantly in the family environment of patients, often during stays in endemic regions. In some cases, the assumption that the strain has been imported from countries in which these CA-MRSA were first reported or are found more commonly was confirmed. In one case, MRSA were imported by patients who had come to Germany as refugees and directly received medical treatment at German hospitals.[16]

Even if the recent data does not reveal a significant increase and/or spread of specific CA-MRSA clones in Germany, the detection and molecular typing of these strains is essential to be able to recognise trends early.[17,18]

Emergence and spread of livestock-associated MRSA (LA-MRSA) in Germany

LA-MRSA CC398 increasingly occur as nasal colonisers and infectious agents in humans in regions with a high livestock density[19,20], which is also confirmed by the isolates submitted to the NRC. Among all MRSA submitted from all over Germany, the rate of CC398 was 3.4% in 2013 and 2014. LA-MRSA may cause skin and soft tissue infections; nosocomial infections may also occur as a result of nasal colonisation.

Molecular typing of bacteraemia-associated MRSA from hospitals in North Rhine-Westphalia (2011-2013, 1,952 MRSA) revealed an MRSA CC398 rate of 1.7%. Regional clusters of LA-MRSA correlated with areas characterised by a high density of pig farms.[12] In about 20-38% of all MRSA CC398 cases, however, people in these rural areas are not exposed to any risk factors to suggest an acquisition in agriculture, which points to different routes of transmission. Compared to classic HA-MRSA, MRSA CC398 show lower transmission rates in hospitals, which may be attributed to the fact that patients colonised with MRSA CC398 at hospital-admission are younger, stay shorter at the hospital and less frequently require intensive care than patients colonised with HA-MRSA.[19] Recent publications on the virulence of MRSA CC398 clearly demonstrate their potential pathogenicity in humans and their capability of adapting to the respective hosts, for example by acquiring or losing specific gene clusters and prophages.[21,22]

Other *Staphylococcus* spp.

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 coagulase-negative staphylococci (CNS).[7] Fig. 4.1.2.4 summarises the rates of resistance to selected antimicrobials in *S. epidermidis* and *S. haemolyticus* ascertained as part of the last three surveys. In 2013, 74.5% of all *S. epidermidis* and 92.6% of all *S. haemolyticus* were resistant to oxacillin (methicillin). The resistance rate of *S. haemolyticus* to ciprofloxacin was at a similar level in 2013 as it was in 2010 (89.5%); the resistance rate of *S. epidermidis* was observed to decrease during this period (2010: 70.5%, 2013: 62.6%). Compared to 2010, 5% less clindamycin-resistant *S. epidermidis* were detected in 2013. The resistance rates of both species to erythromycin hardly differed in all three surveys. The observed change in the percentage of gentamicin-resistant strains of both *S. haemolyticus* and *S. epidermidis* was marginal when comparing 2010 and 2013. However, there was a notable increase in the resistance rate of both species to teicoplanin in 2013 (*S. epidermidis* from 10.8% (2010) to 35.8% (2013); *S. haemolyticus* from 16% (2010) to 37.9% (2013)). Strains resistant to linezolid and vancomycin were not detected in these studies.

Data reported by the National Reference Centre for Staphylococci and Enterococci

Compared to previous years, a relatively large number of CNS were submitted to the NRC in 2013/2014 for testing their susceptibility to linezolid and daptomycin. 122 isolates were confirmed to be resistant to linezolid, with most strains being multidrug-resistant *S. epidermidis*. The plasmid-mediated resistance determinant *cfr* was detected in 37 of these *S. epidermidis* strains.

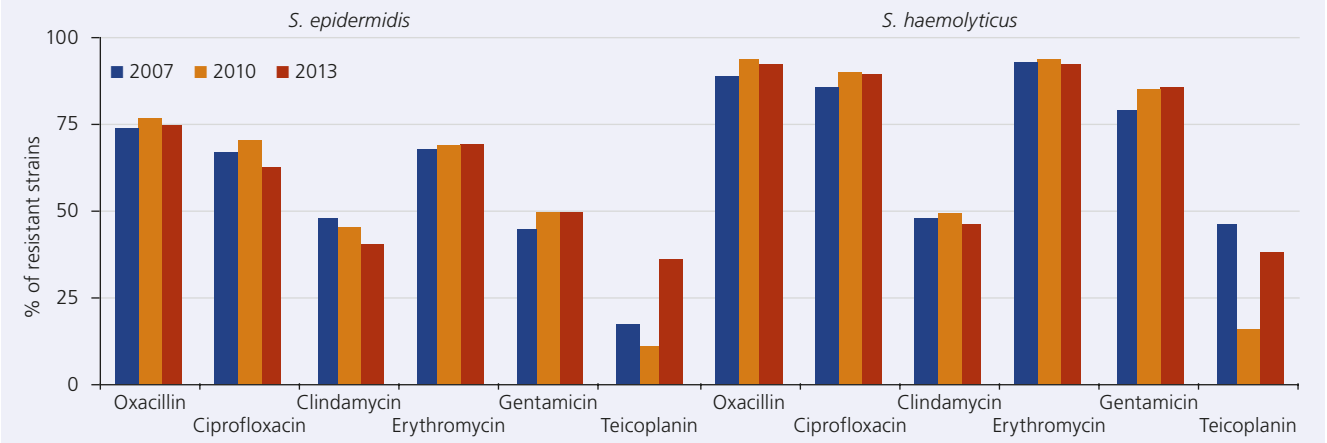


Fig. 4.1.2.4: Resistance to important antimicrobials in *S. epidermidis* and *S. haemolyticus*; data obtained from the resistance studies by the Paul Ehrlich Society (2007-2013)

Resistance to daptomycin was confirmed in 35 CNS isolates. An increase in linezolid and daptomycin-resistant CNS does not become apparent in other "conventional" surveillance systems (ARS, PEG resistance study).

Besides requests for confirmation of resistance, an increasing number of requests were submitted for molecular typing of linezolid-resistant *S. epidermidis* from clusters of colonisations/infections at hospitals.[23] These strains were typed by means of MLST and PFGE after *Sma*I macrorestriction analysis. In addition to the *cfr* resistance gene, various mutations in ribosomal genes were detected, which could also be the cause of linezolid resistance. At one hospital, the antimicrobial consumption on the affected ward was analysed, showing an increased use of linezolid; nearly all patients received linezolid during their stay (NRC; unpublished data).

Conclusion

The downward trend in the MRSA rate in *S. aureus* infections continues in 2013/2014. At hospitals, epidemic MRSA strains of the clonal lineages ST225 and ST22 are predominant; these clones also have a high prevalence in MRSA from ambulatory care as so-called hospital-associated community-onset (HCA) MRSA.

The emergence and spread of CA-MRSA clones requires special attention, as currently refugees from various crisis regions receive medical care in Germany.

The widespread use of last-resort antibiotics requires the detection and characterization of antibiotic resistances against these substances (from both *S. aureus* and CNS), as those trends are not detected early in conventional surveillance studies. At present, this applies specifically to linezolid-resistant strains, since the patent for linezolid expired in 2016 and the cost reduction will very likely lead to an increased consumption.

➤ F. Layer, B. Strommenger, C. Cuny, G. Werner
Reviewer: M. Kresken

1. Köck R, Becker K, Cookson B, van Gemert-Pijnen JE, et al. Methicillin-resistant *Staphylococcus aureus* (MRSA): burden of disease and control challenges in Europe. Euro Surveill 2010;15:19688.
2. Morgan M. Methicillin-resistant *Staphylococcus aureus* and animals: zoonosis or humanosis? J Antimicrob Chemother 2008;62:1181-7.
3. Köck R, Mellmann A, Schaumburg F, Friedrich AW, et al. The epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) in Germany. Dtsch Arztebl Int 2011;108:761-7.
4. Antimicrobial resistance surveillance in Europe 2014. Annual Report of the European Antimicrobial resistance Surveillance Network (EARS-Net). Stockholm, ECDC, 2015.
5. Robert Koch-Institut: Infektionsepidemiologisches Jahrbuch für 2014. Berlin, 2015.
6. Meyer E, Schroder C, Gastmeier P, Geffers C. The reduction of nosocomial MRSA infection in Germany: an analysis of data from the Hospital Infection Surveillance System (KISS) between 2007 and 2012. Dtsch Arztebl Int 2014;111:331-6.
7. Kresken M, Hafner D, Körber-Irrgang B für die Studiengruppe. Epidemiologie und Resistenzsituation bei klinisch wichtigen Infektionserregern aus dem Hospitalbereich gegenüber Antibiotika. Bericht über die Ergebnisse einer multizentrischen Studie der Paul-Ehrlich-Gesellschaft für Chemotherapie e.V. aus dem Jahre 2013. Antiinfectives Intelligence, Rheinbach 2016. Verfügbar unter http://www.p-e-g.org/econtext/Berichte%20der%20Studien.
8. Kresken M, Hafner D, Körber-Irrgang B für die Studiengruppe. Resistenzsituation bei klinisch wichtigen Infektionserregern aus dem ambulanten Versorgungsbereich gegenüber Antibiotika. Bericht über die Ergebnisse einer multizentrischen Studie der Paul-Ehrlich-Gesellschaft für Chemotherapie e.V. aus dem Jahre 2013. Antiinfectives Intelligence, Rheinbach 2016. Verfügbar unter http://www.p-e-g.org/econtext/Berichte%20der%20Studien.
9. Witte W, Cuny C, Klare I, Nübel U, et al. Emergence and spread of antibiotic-resistant Gram-positive bacterial pathogens. Int J Med Microbiol 2008;298:365-77.
10. Grundmann H, Schouls LM, Aanensen DM, Pluister GN, et al. The dynamic changes of dominant clones of *Staphylococcus aureus* causing bloodstream infections in the European region: results of a second structured survey. Euro Surveill 2014;19.
11. Strommenger B, Braulke C, Heuck D, Schmidt C, et al. spa Typing of *Staphylococcus aureus* as a frontline tool in epidemiological typing. J Clin Microbiol 2008;46:574-81.
12. Cuny C, Layer F, Werner G, Harmsen D, et al. State-wide surveillance of antibiotic resistance patterns and spa types of methicillin-resistant *Staphylococcus aureus* from blood cultures in North Rhine-Westphalia, 2011-2013. Clin Microbiol Infect 2015;21:750-7.
13. Strommenger B, Layer F, Klare I, Werner G. Pre-Use Susceptibility to Ceftaroline in Clinical *Staphylococcus aureus* Isolates from Germany: Is There a Non-Susceptible Pool to be Selected? PLoS One 2015;10:e0125864.
14. Livermore DM, Mushtaq S, Warner M, James D, et al. Susceptibility testing challenges with ceftaroline, MRSA and a 1 mg/L breakpoint. J Antimicrob Chemother 2015;70:3259-66.
15. Lahiri SD, McLaughlin RE, Whiteaker JD, Ambler JE, et al. Molecular characterization of MRSA isolates bracketing the current EUCAST ceftaroline-susceptible breakpoint for *Staphylococcus aureus*: the role of PBP2a in the activity of ceftaroline. J Antimicrob Chemother 2015;70:2488-98.
16. Leistner R, Denkel L, Gastmeier P, Werner G, et al. Prevalence of MRSA and Gram-negative bacteria with extended-spectrum beta-lactamases (ESBLs) and carbapenemases in patients from Northern Africa at a German hospital. Journal of Antimicrobial Chemotherapy 2015;70:3161-4.
17. Glasner C, Pluister G, Westh H, Arends JP, et al. *Staphylococcus aureus* spa type t437: identification of the most dominant community-associated clone from Asia across Europe. Clin Microbiol Infect 2015;21:163e1-8.
18. Nurjadi D, Friedrich-Janicke B, Schafer J, Van Genderen PJ, et al. Skin and soft tissue infections in intercontinental travellers and the import of multi-resistant *Staphylococcus aureus* to Europe. Clin Microbiol Infect 2015;21:567e1-10.
19. Köck R, Ballhausen B, Bischoff M, Cuny C, et al. The impact of zoonotic MRSA colonization and infection in Germany. Berl Munch Tierarztl Wochenschr 2014;127:384-98.
20. Bundesamt für Verbraucherschutz und Lebensmittelsicherheit, Paul-Ehrlich-Gesellschaft für Chemotherapie e.V., Infektiologie Freiburg. GERMAP 2012-Bericht über den Antibiotikaverbrauch und die Verbreitung von Antibiotikaresistenzen in der Human- und Veterinärmedizin in Deutschland. Antiinfectives Intelligence, Rheinbach, 2014.
21. Ballhausen B, Jung P, Kriegeskorte A, Makgotlho PE, et al. LA-MRSA CC398 differ from classical community acquired-MRSA and hospital acquired-MRSA lineages: functional analysis of infection and colonization processes. Int J Med Microbiol 2014;304:777-86.
22. Cuny C, Abdelbary M, Layer F, Werner G, et al. Prevalence of the immune evasion gene cluster in *Staphylococcus aureus* CC398. Vet Microbiol 2015;177:219-23.
23. Bender J, Strommenger B, Steglich M, Zimmermann O, et al. Linezolid resistance in clinical isolates of *Staphylococcus epidermidis* from German hospitals and characterization of two *cfr*-carrying plasmids. J Antimicrob Chemother 2015;70:1630-8.

4.1.3 Enterococci

Enterococci are gram-positive, catalase-negative bacteria that are as inhabitants of the intestinal tract a part of the natural gut flora of animals and humans. However, they can also cause a number of partly severe infections: urinary tract infection, surgical site infection (especially in the abdominal area; often polymicrobial), bloodstream infection and endocarditis. Occasionally, enterococci are also found in the vaginal flora and the biliary tract, but only rarely in the oropharynx. Enterococcal infections particularly affect premature infants and newborns, elderly patients as well as patients with an underlying disease and/or immunosuppression. As a result of medical progress and better living conditions, people are becoming older and older (often multimorbid patients), especially in highly developed countries. This leads to a rising number of risk patients for enterococcal infections.

Enterococci are the second to third most common bacterial genus in hospital infections (nosocomial infections). However, *Enterococcus* (*E.*) *faecalis* and *E. faecium* still possess the highest clinical relevance among the currently known more than 50 enterococcal species: *E. faecalis* is found in 60-95%, *E. faecium* in 5-40% of all enterococcal infections. However, the proportion of *E. faecium* compared to *E. faecalis* has been increasing steadily over the last years. As part of the so-far six antimicrobial resistance studies conducted by Paul-Ehrlich-Gesellschaft für Chemotherapie e.V. (PEG), the proportion of *E. faecium* isolates (in relation to all tested enterococcal strains) increased as follows: 9.3% (1998) → 15.7% (2001) → 24.4% (2004) → 33.9% (2007) → 41.4% (2010) → 43.0 % (2013).[1]

The prevalences of these two major enterococcal species in hospital patients can be influenced by the following factors a) type of the hospital and its departments, b) pool of patients (rising number of predominantly affected older and/or immunosuppressed patients), c) antimicrobial selective pressure prevailing at the hospital and/or in the respective clinical disciplines, d) deficiencies in the implementation of hygiene measures in case of emergence of multidrug-resistant bacterial strains, e.g. vancomycin-resistant enterococci (VRE, especially among *E. faecium*).

Previous treatments with antimicrobials that exhibit an "enterococcal gap" (i.e. drugs to which enterococci are intrinsically resistant, e.g. all cephalosporins) can contribute to colonisations or infections of patients with enterococci (including VRE). Longer hospital stays involving diverse antimicrobial chemotherapies, severe underlying diseases as well as intraabdominal or cardiac/thoracic surgical procedures are also considered to be risk factors for enterococcal/VRE infections. Furthermore, stays of patients in specific hospital units (internal medicine, surgical departments with or without intensive care unit, transplantation units, haematology/oncology, urology/nephrology, neonatology) are also associated with a high risk of enterococcal/VRE colonisations or infections.

Trends in resistance development

Enterococci are characterised by natural (intrinsic) and acquired resistance to numerous antimicrobials.

Natural resistance: Enterococci are intrinsically resistant to *all* cephalosporins (of the first to the fourth generation), semisynthetic penicillins (e.g., oxacillin), monobactams, aminoglycosides (low-level resistance type), (most) lincosamides, polymyxins, streptogramins (e.g., quinupristin/dalfopristin in *E. faecalis*, but not in *E. faecium*) as well as to vancomycin (low-level resistance type) in *E. gallinarum* and *E. casseliflavus*.

Acquired resistance: Enterococci can exhibit acquired resistance, e.g. to ampicillin (especially in *E. faecium*), macrolides, tetracyclines, aminoglycosides (high-level resistance), chloramphenicol, fluoroquinolones, glycopeptides (especially in *E. faecium*), streptogramins (e.g., quinupristin/dalfopristin in *E. faecium*), oxazolidinones (linezolid), and glycylcyclines (tigecycline). However, resistance to the last two second-line antimicrobials (especially to tigecycline) has so far occurred relatively rarely in enterococci (see below).[2,3]

E. faecium is considered to be the primary reservoir of *vanA*- and *vanB*-mediated glycopeptide resistance, respectively. Since the middle of 2003/the beginning of the 2004, an increased prevalence of VRE has been observed at hospitals in various European countries. Additionally, the occurrence of outbreaks of infections with these multidrug-resistant pathogens continues to be of great interest. The increased occurrence and clustering of ampicillin/vancomycin-resistant *vanA*- or *vanB*-positive *E. faecium* strains at German hospitals was confirmed by genotyping these VRE isolates by means of *Sma*I-macrorestriction analysis (MRA).

These hospital-acquired pathogens, some of which carry virulence markers (*esp* and/or *hyl* as markers for enterococcal surface protein and putative hyaluronidase, respectively), can spread readily in a hospital environment.[4-6] The insertion sequence IS*16* which can be identified by means of PCR is a suitable marker to recognise hospital-associated (HA) *E. faecium* isolates[7]; additionally, these isolates are characterised by their resistance to ampicillin and their high-level resistance to fluoroquinolones (ciprofloxacin MIC > 16 mg/l).[8] HA-*E. faecium* strains usually become clinically apparent only after acquiring glycopeptide resistance determinants (*vanA* and *vanB* gene cluster, respectively), but are often already present in hospitals as glycopeptide-susceptible precursor strains. Such strains can spread clonally between hospitals, for example after patient transfers. As a result of horizontal gene transfer of the *vanA* or *vanB* gene cluster, respectively, various clones of these multidrug-resistant *E. faecium* strains can also occur within one hospital.

PEG resistance studies

The results of the resistance studies conducted by Paul-Ehrlich-Gesellschaft für Chemotherapie e.V. (PEG) in 1990 as well as every three years during the period 1995-2013 demonstrate that the prevalence of resistance to some antimicrobials in enterococci has increased over the past about 20 years.[1]

Among *E. faecalis*, this particularly concerned doxycycline, erythromycin, ciprofloxacin, and moxifloxacin (the latter has only been included in the PEG studies since 2001). The variations in the prevalence of doxycycline resistance are also attributable to the use of different clinical breakpoints of the corresponding susceptibility testing standards while evaluating the MIC values. The DIN[9,10] MIC breakpoints were taken as a basis in 2004 and 2007 and the epidemiological cut-off (ECOFF) value for doxycycline defined by EUCAST in 2010 and 2013[11], because EUCAST

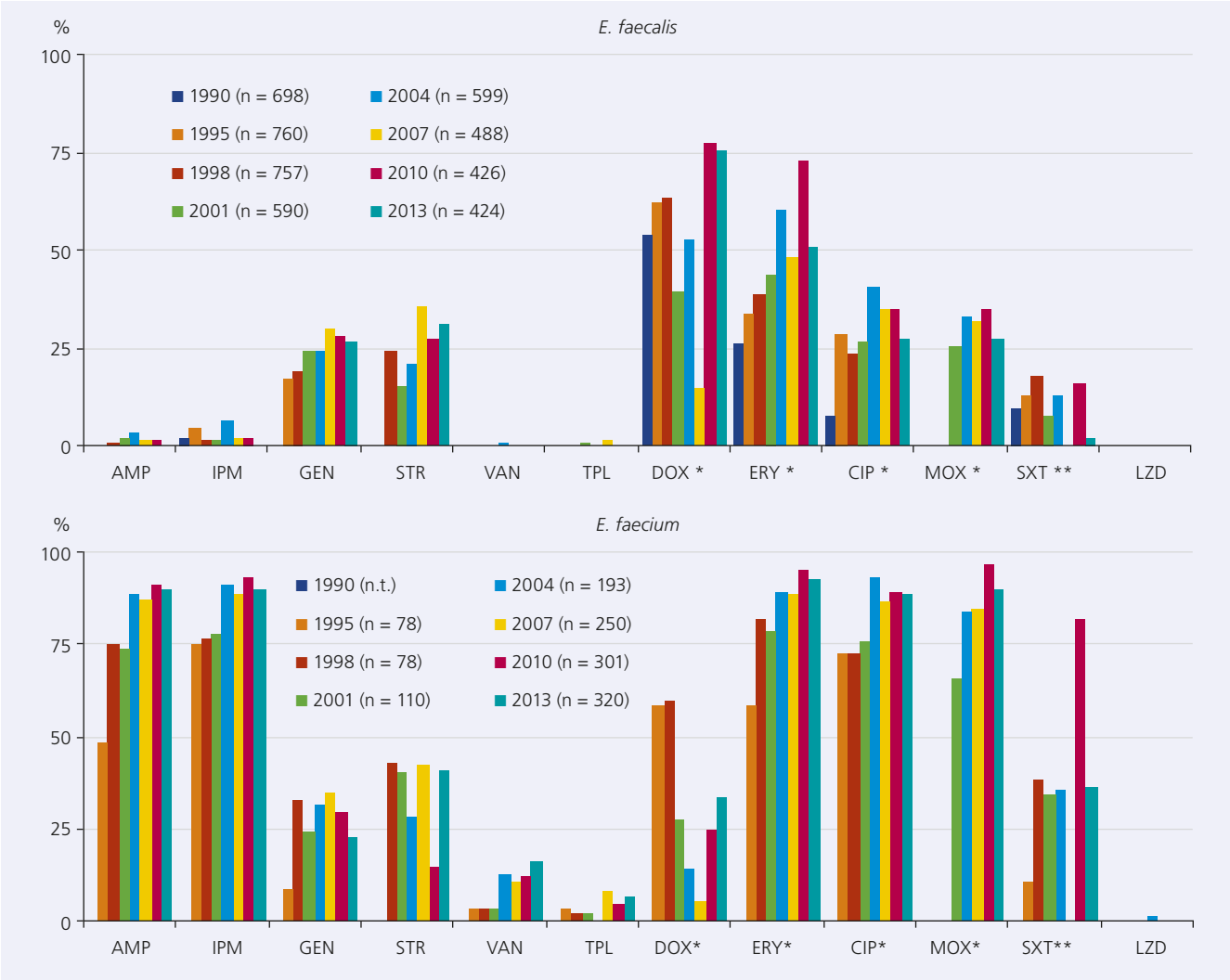


Fig. 4.1.3.1: Prevalence of resistance (%) in *E. faecalis* and *E. faecium* at German hospitals between 1990 (and 1995) and 2013 to selected antimicrobial chemotherapeutics (Source: PEG resistance studies 1990-2013)[1]

n.t., not tested; n, number of tested enterococcal isolates; AMP, ampicillin; IPM, imipenem; GEN, gentamicin (high-level resistance); STR, streptomycin (high-level resistance); VAN, vancomycin; TPL, teicoplanin; DOX, doxycycline; ERY, erythromycin; CIP, ciprofloxacin; MOX, moxifloxacin; SXT, trimethoprim/sulphamethoxazole (only tested for epidemiological purposes); LZD, linezolid. * For better comparability with older data, the resistance rates of the 2007 PEG study for the antimicrobials marked with one asterisk were calculated on the basis of the 2004 MIC breakpoints (DIN). *The 2010 and 2013 resistance rates for antimicrobials marked with one asterisk are based on the ECOFF values of the wild type (WT≤ x mg/l) of a species to the corresponding antimicrobial defined by EUCAST, since EUCAST specifies no clinical breakpoints for these antimicrobials for 2010 and 2013. ** The 2007 PEG study did not provide any data for SXT.

does not specify any clinical MIC breakpoints for doxycycline and some other antibiotics. Antimicrobials for which EUCAST defines clinical breakpoints were also evaluated on the basis of these breakpoints in the 2010 and 2013 resistance studies.[12] In 2007, 30% and 36% of the *E. faecalis* strains exhibited high-level resistance to gentamicin and streptomycin, respectively, but this rate declined slightly in the years thereafter. Throughout the entire study period, still hardly any ampicillin-, imipenem-, glycopeptide- and linezolid-resistant isolates were detected among this species (Fig. 4.1.3.1).

By contrast, the rate of ampicillin-resistant *E. faecium* increased significantly between 1995 (49%) and 2010 as well as 2013 (above 90% each). The frequency of vancomycin resistance in *E. faecium* increased over the same period (1995: 3.8%; 1998: 3.8%; 2001: 3.6%; 2004: 13.5%; 2007: 11.1%; 2010: 12.6%; 2013: 16.6%). The rates of teicoplanin resistance in 2010 and 2013 were 5.0% and 7.5%, respectively. This indicates a significant increase in the prevalence of vancomycin resistance and a slight increase in the prevalence of teicoplanin resistance in 2013 compared to 2010. It suggests an increased prevalence of *vanB*-positive (this means vancomycin-resistant but teicoplanin-susceptible) *E. faecium* strains. 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, the ECOFF values defined by EUCAST (as was the case with *E. faecalis*) were used to determine the rates of resistance to these antimicrobials in both 2010 and 2013. The prevalence of doxycycline resistance in *E. faecium* dropped (similarly to *E. faecalis*) dramatically from 59.0% in 1990 and 60.3% in 1995 to 14.5% in 2004 and 6% in 2007, however, these rates were determined on the basis of the 2004 DIN MIC breakpoints. In the absence of clinical EUCAST MIC breakpoints, the ECOFF value was used to evaluate the 2010 and 2013 PEG data relating to doxycycline resistance in *E. faecium*; according to this, the rates of resistance are 25.6% (2010) and 34.1% (2013).

Linezolid-resistant enterococci were only detected in the 2004 and 2013 PEG studies and had a low prevalence: 0.3% of the 426 *E. faecalis* and 1.6% of the 301 *E. faecium* isolates tested in 2004 and of 0.0% of the *E. faecalis* (n=424) and 0.3% of the *E. faecium* (n=320) isolates tested in 2013.

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 2013 have also been reported since the 2010 GERMAP Report (Fig. 4.1.3.2). This data demonstrates that also in 2013: a) a high percentage (63%) of the *E. faecalis* isolates are still susceptible to these therapeutically relevant antimicrobials tested in the PEG studies, b) multidrug resistance (involving up to 5 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) in *E. faecium* increased from 75.6% to more than 90% over the study period. Furthermore, the multidrug resistance patterns of *E. faecium* became considerably more varied in the course of the period 1998-2013, while the percentage of susceptible *E. faecium* isolates dropped from 15.4% in 1998 to 7.5% in 2013 (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, but increased again slightly to 62.5% in 2013. The total ampicillin resistance rate of *E. faecalis* is still very low, ranging between 0.0% and 3.3% in the six evaluated PEG studies Fig. 4.1.3.2, top row).

ARS

Antimicrobial Resistance Surveillance in Germany (ARS) monitors the antimicrobial resistance of clinically relevant bacterial pathogens, covering not only the inpatient but also the outpatient care sector. This makes it possible to record the resistance data of medically relevant bacteria collected in clinical and microbiology laboratories and medical practices in Germany (more details at: https://ars.rki.de).[13] At present, the ARS system identifies multidrug-resistant strains on request, which is also planned to be offered online in the future.

Fig. 4.1.3.3 shows the annual antimicrobial resistance data of ARS from 2008 to 2014 for *E. faecalis* and *E. faecium* from the inpatient care sector (here: isolates from blood cultures) and the outpatient care sector.[13] As expected, there are significant differences in resistance rates to nearly all tested antimicrobials between isolates from blood cultures and those from the outpatient care sector within the respective enterococcal species during the period 2008-2014.

The rates of resistance (high-level resistance) to the aminoglycosides gentamicin and streptomycin in *E. faecalis* from blood cultures dropped from more than 50% in 2010 to approx. 35% in 2014; a decline in the resistance rates to these antimicrobials was also observed at a lower level for isolates from outpatient care. Compared to outpatient *E. faecalis* isolates, the blood culture isolates of these species showed significantly higher resistance rates to levofloxacin and moxifloxacin. The resistance rates of *E. faecalis* to ampicillin, amoxicillin, vancomycin, teicoplanin and linezolid were mostly below 1% in both care sectors (Fig. 4.1.3.3).

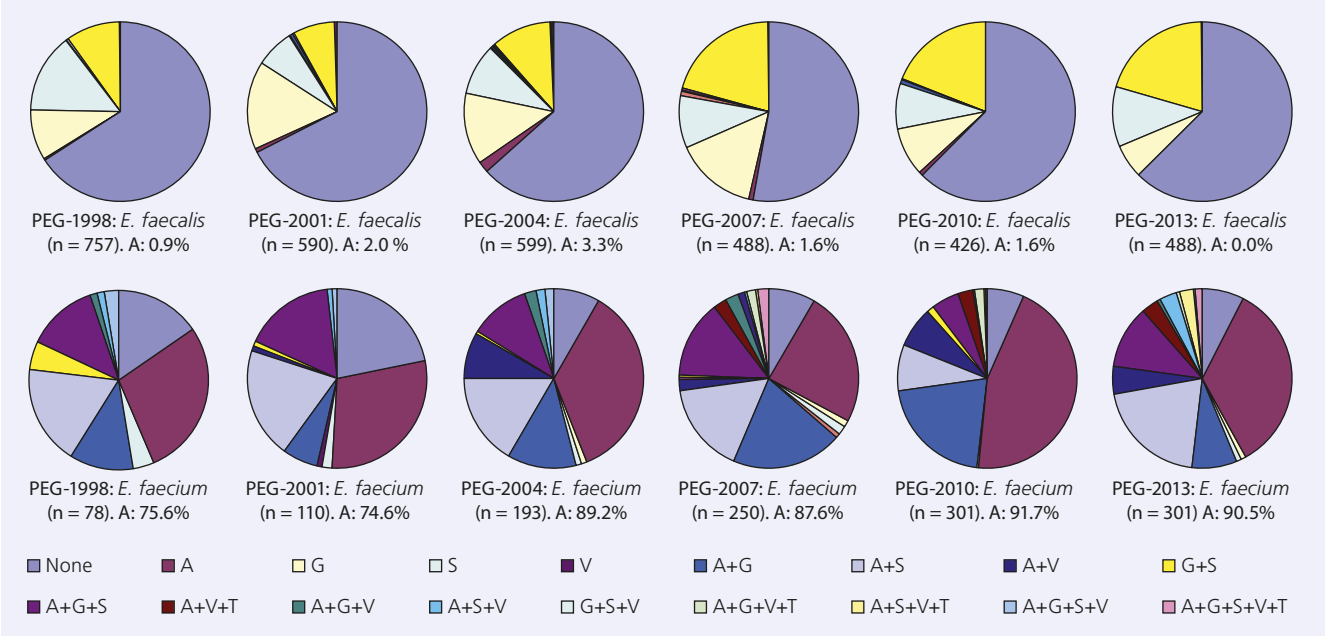


Fig. 4.1.3.2: Prevalence of single and multidrug resistance to various therapeutically relevant antimicrobials in *E. faecalis* (top row) and *E. faecium* (bottom row) isolates obtained from the resistance studies conducted by Paul Ehrlich Gesellschaft für Chemotherapie e. V. (PEG) in 1998, 2001, 2004, 2007, 2010 and 2013 (Source: PEG resistance studies 1990 to 2013)[1]

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 multidrug resistance rates arranged line by line from left to right correspond to the order of these (multidrug) 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 multidrug resistance) in the individual years of the PEG resistance studies is indicated below each pie chart.

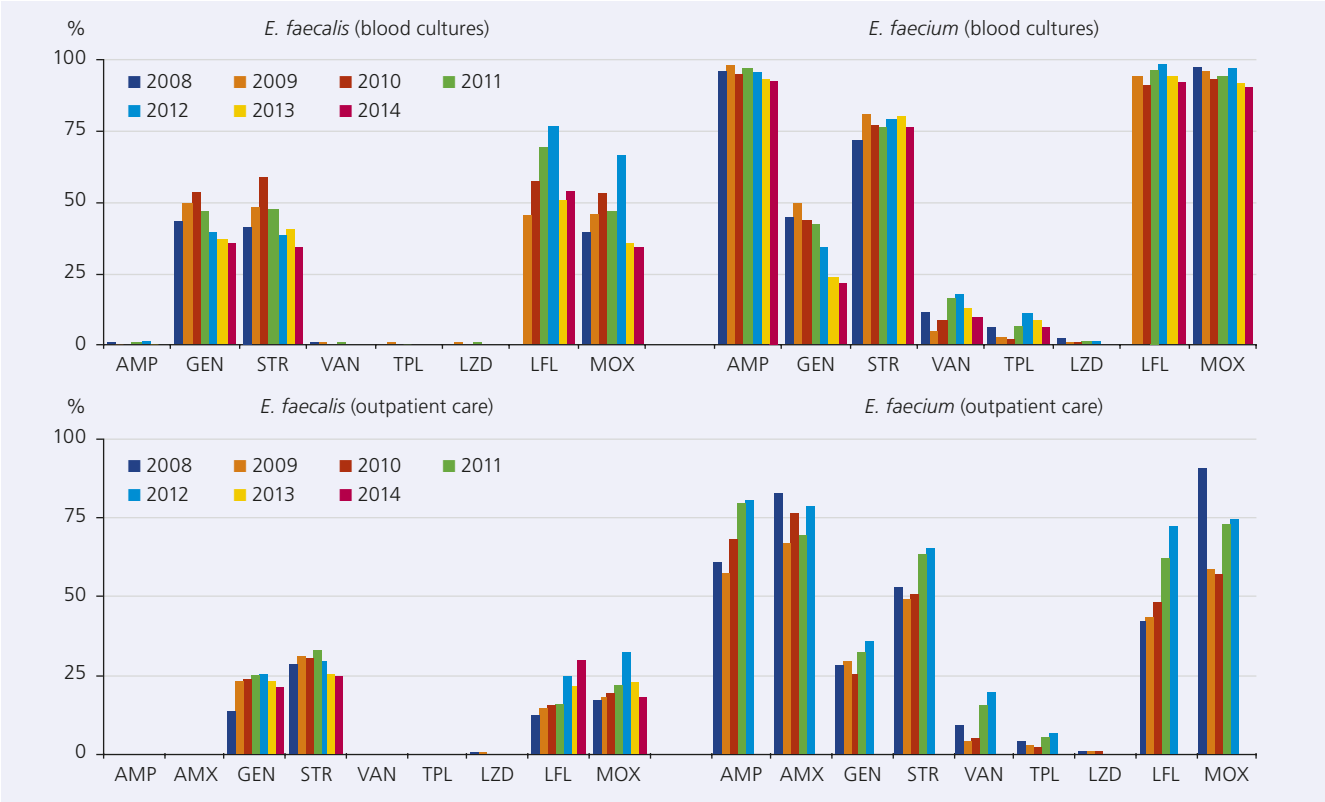


Fig. 4.1.3.3: Prevalence of resistance in *E. faecalis* and *E. faecium* from inpatient (blood cultures, top) and outpatient (bottom) care during the period 2008-2014 (Source: Robert Koch Institute, ARS, http://ars.rki.de)[13]

AMP, ampicillin; AMX, amoxicillin; GEN, gentamicin (high-level resistance); STR, streptomycin (high-level resistance); VAN, vancomycin; TPL, teicoplanin; LZD, 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 individual 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). ARS did not indicate any resistance rates for *E. faecium* from outpatient care in 2013 and 2014, because only data for fewer than 50 isolates was available to ARS; ARS indicates no linezolid resistance rates for enterococci in 2013 and 2014 (see https://ars.rki.de).

The situation was different with *E. faecium* isolates obtained from blood cultures and outpatient care between 2008 and 2014 (right side of Fig. 4.1.3.3). The rate of ampicillin and amoxicillin resistance in *E. faecium* from blood cultures ranged between 92.4% and 97.7%, whereas the rate of resistance to these two penicillins in isolates from outpatient care ranged between 57.2% and 82.8% over the above period. ARS did not ascertain any resistance rates for *E. faecium* from outpatient care for 2013 and 2014, since fewer than 50 isolates were available for evaluation in both years. An increase in resistance rates (high-level resistances) to gentamicin and streptomycin was observed in *E. faecium* from outpatient care, whereas the high-level resistance to gentamicin in blood culture isolates dropped considerably over the study period. High resistance rates of more than 90% to the two quinolones levofloxacin and moxifloxacin were documented for *E. faecium* from blood cultures during the period 2008-2014, whereas these rates in isolates from outpatient care mostly ranged between 42% and 74% (however, ARS did not have any resistance data for 2013 and 2014). The rates of resistance to vancomycin in *E. faecium* isolates from blood cultures dropped from 17.8% (2012) to 12.9% (2013) and to 9.7% (2014) and those to teicoplanin from 11.3% (2012) to 8.5% (2013) and to 6.1% (2014). In the absence of ARS data for 2013 and 2014, more recent evaluations of the rates of resistance to vancomycin and teicoplanin are not available for the outpatient care sector. However, the already fairly high resistance rates of 15.4% (2011) and 19.8% (2012) to vancomycin as well as of 5.4% (2011) and 6.5% (2012) to teicoplanin in outpatient care suggest that patients apparently take VRE isolates with them into outpatient care when they are discharged from hospital. At the same time, the 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 can be brought back to the hospital. The rates of resistance to linezolid in *E. faecium* isolates from both sectors ranged between 0.2% and 1.1% (outpatient) and between 0.9% and 2.6% (blood cultures). The resistance situation for linezolid in *E. faecium* isolates submitted to the NRZ for Staphylococci and Enterococci was very different (see below).

SARI

The prevalence of resistance in *E. faecalis* and *E. faecium* isolates from intensive care units of German hospitals to therapeutically relevant antimicrobials is examined as part of the SARI project (Surveillance of Antimicrobial Use and Bacterial Resistance in Intensive Care Units)[14] and is presented in this section for the period 2004-2014 (Fig. 4.1.3.4). These data demonstrate the high ampicillin resistance rates of *E. faecium* – in contrast to *E. faecalis* – increasing from 85.2% (2004) through various intermediate stages to 95.9% (2011) and to 92.7% (2014). *E. faecium* also showed high rates of ciprofloxacin resistance, increasing from 81.5% (2004) to 94.2% (2010) and to 93.1% (2014). By contrast, the rates of fluoroquinolone resistance in *E. faecalis* were lower and the rates of resistance to fluoroquinolones in *E. faecalis* have been observed to drop significantly since 2012, compared to previous years (2014: ciprofloxacin 47.9%, levofloxacin 28.1%

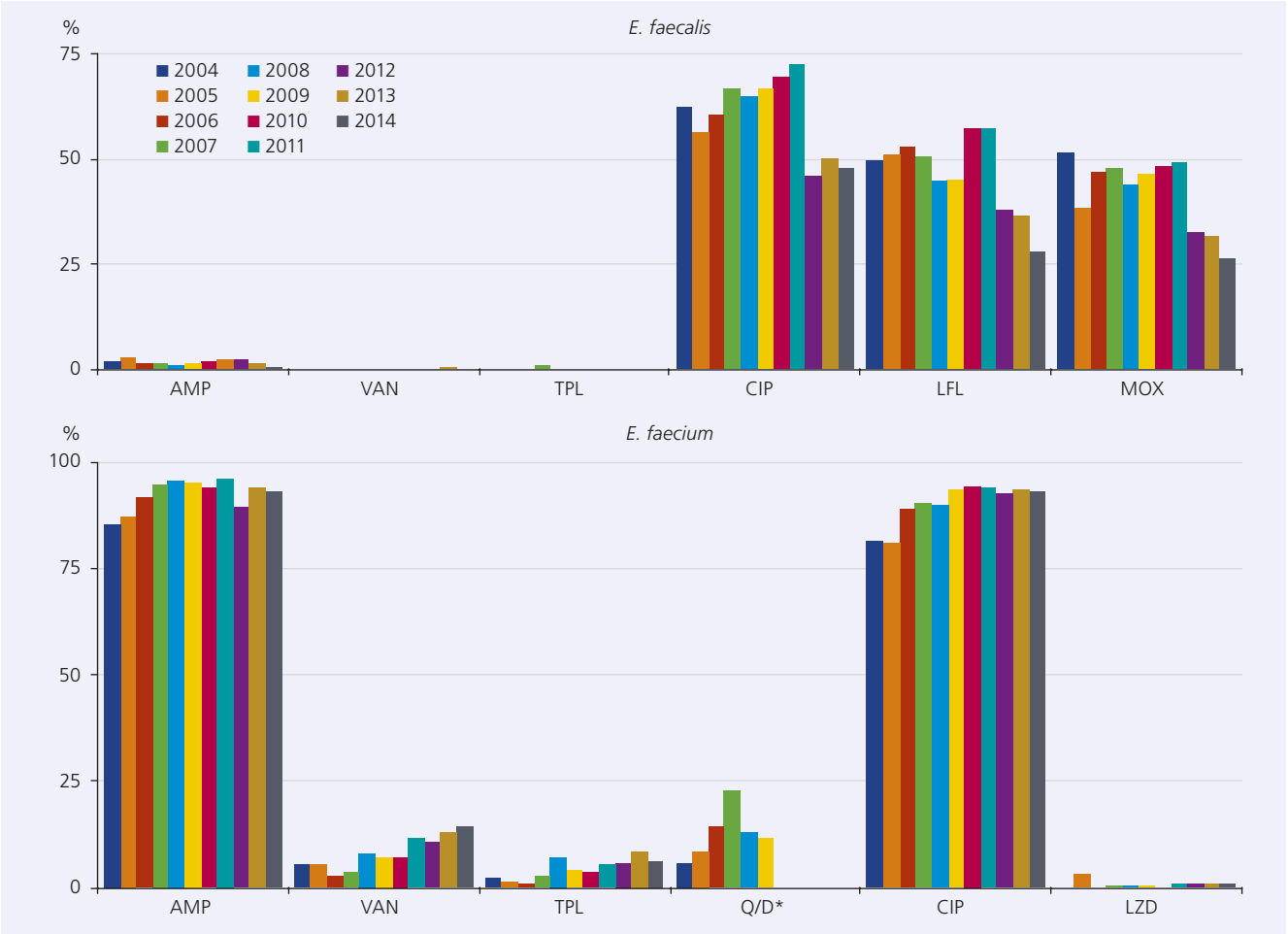


Fig. 4.1.3.4: Prevalence of resistance in *E. faecalis* (top) and *E. faecium* (bottom) from intensive care units of German hospitals within the SARI project during the period 2004-2014 (Source: SARI project)[14]

During the period 2004-2014, 1,273-2,795 *E. faecalis* and 611-1,833 *E. faecium* isolates were classified within SARI.

AMP, ampicillin; VAN, vancomycin; TPL, teicoplanin; CIP, ciprofloxacin; LFL, levofloxacin; MOX, moxifloxacin; Q/D, quinupristin/dalfopristin (* Q/D was no longer tested from 2010 on); LZD, linezolid

and moxifloxacin 26.1%). The glycopeptide resistance rates of *E. faecalis* were ≤ 0.5% for vancomycin and mostly ≤ 0.4% for teicoplanin during the study period; the rates of resistance in *E. faecium* were observed to increase for vancomycin (2013: 12.8%; 2014: 14.3%) and teicoplanin (2013: 8.3%; 2014: 6.1%). The prevalence of resistance in *E. faecium* to ampicillin and ciprofloxacin (in VRE also to glycopeptides) ascertained within the SARI project also suggests the above-mentioned spread of HA-*E. faecium* strains in German intensive care units. The prevalence of linezolid-resistant *E. faecium* strains was 1.1% in both 2013 and 2014 (Fig. 4.1.3.4).

EARS-Net (formerly EARSS)

The prevalence of resistance to relevant antimicrobials in clinically important invasive bacteria is recorded in the European EARS-Net surveillance studies (European Antimicrobial Resistance Surveillance Network[15]; formerly: EARSS, European Antimicrobial Resistance Surveillance System), including resistance to amino-penicillins (ampicillin), aminoglycosides (high-level gentamicin resistance) and glycopeptides (vancomycin) in invasive *E. faecalis* and *E. faecium* strains isolated from hospital patients in the participating countries.

According to the results of the EARS-Net studies, the prevalence of ampicillin resistance in *E. faecium* isolates from patients at German hospitals increased considerably from 78% in 2003 to 96% in 2005 and 2011 as well as to 93% in 2013, whereas this rate in *E. faecalis* ranged below 1% of the isolates in recent years (Tab. 4.1.3.1). The prevalence of high-level gentamicin resistance in *E. faecalis* was 39% in 2013; during the period 2003-2012, this rate ranged between 29% and 67%. In 2013, 27% of the *E. faecium* isolates were found to show high-level resistance to gentamicin; however, this rate varied between 32% and 73% during the period 2003-2012. *E. faecium* is still considered to be the primary reservoir of glycopeptide resistance (vancomycin); the resistance rates were also observed in EARS-Net to increase from 3% in 2003 through various intermediate stages to 16% in 2012 and to 15% in 2013. In *E. faecalis*, the vancomycin resistance rates were below 1% during the entire study period (Tab. 4.1.3.1). In European comparison, German hospitals rank fourth regarding the prevalence and spread of vancomycin-resistant *E. faecium* in 2013, with an upward trend having been observed over the last few years (Fig. 4.1.3.5).

Tab. 4.1.3.1: Prevalence (%) of resistant enterococcal isolates from patients at German hospitals, 2003-2013 (Source: ECDC Surveillance Report 2013: Antimicrobial resistance surveillance in Europe, Nov 2014)[15]

Species and antimicrobial 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 16/1,009[a]	2011 17/1,231[a]	2012 21/1,499[a]	2013 22/1,841[a]
E. faecalis											
Aminopenicillin RI[b]	7	7	3	3	7	< 1	3	< 1	< 1	< 1	< 1
Gentamicin HR[c]	47	42	34	29	67	39	40	47	41	36	39
Vancomycin R	< 1	< 1	< 1	< 1	< 1	< 1	< 1	< 1	< 1	< 1	< 1
E. faecium											
Aminopenicillin RI[b]	78	93	96	94	95	95	94	94	96	93	93
Gentamicin HR[c]	47	61	52	38	73	35	45	45	42	32	27
Vancomycin R	3	11	10	8	15	6	6	8	11	16	15

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

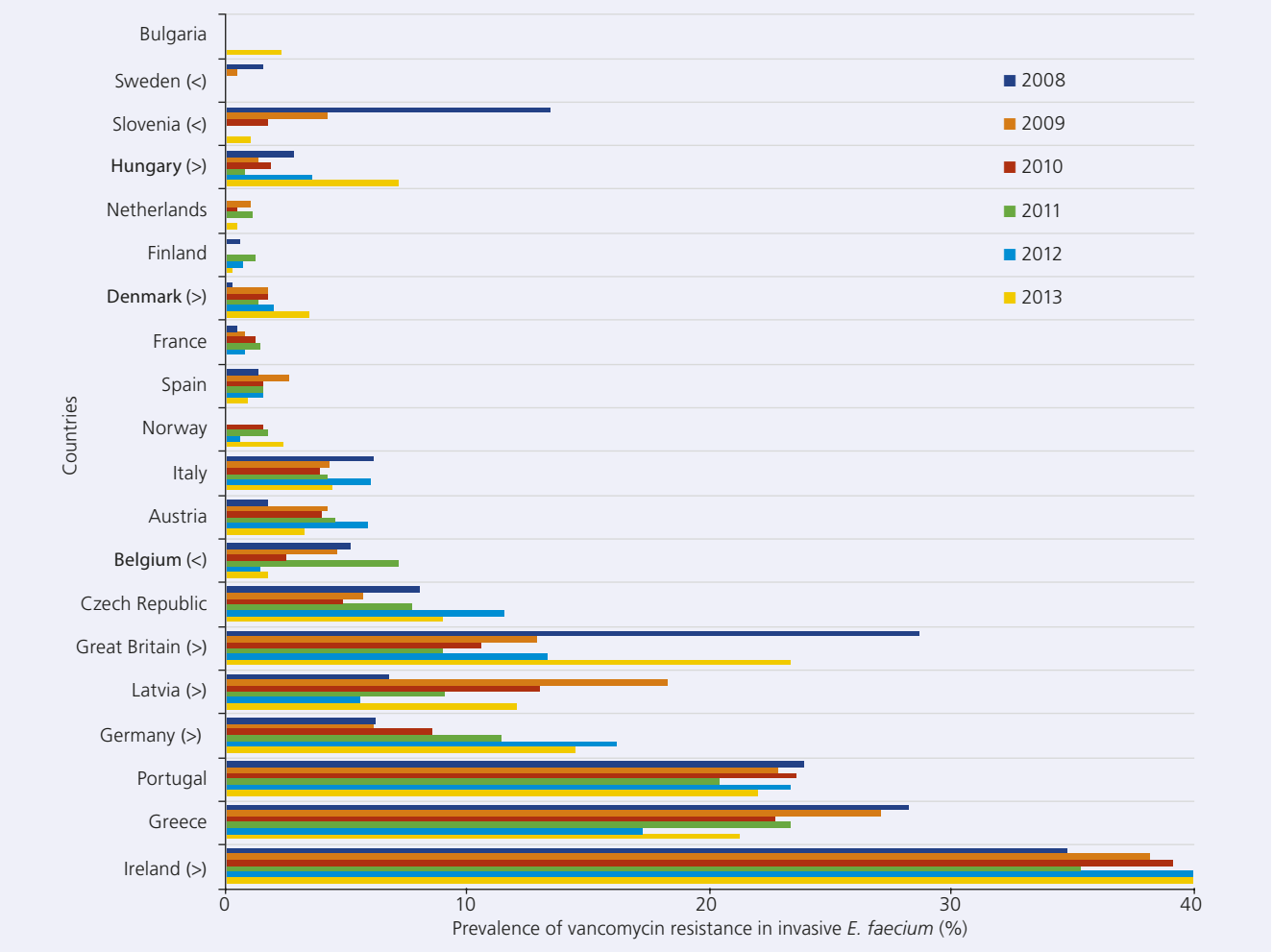


Fig. 4.1.3.5: Comparison of EU/EEA countries 2008-2013 regarding trends in the prevalence of vancomycin resistance in invasive *E. faecium* isolates (Source: ECDC Surveillance Report 2013: Antimicrobial resistance surveillance in Europe)[15]

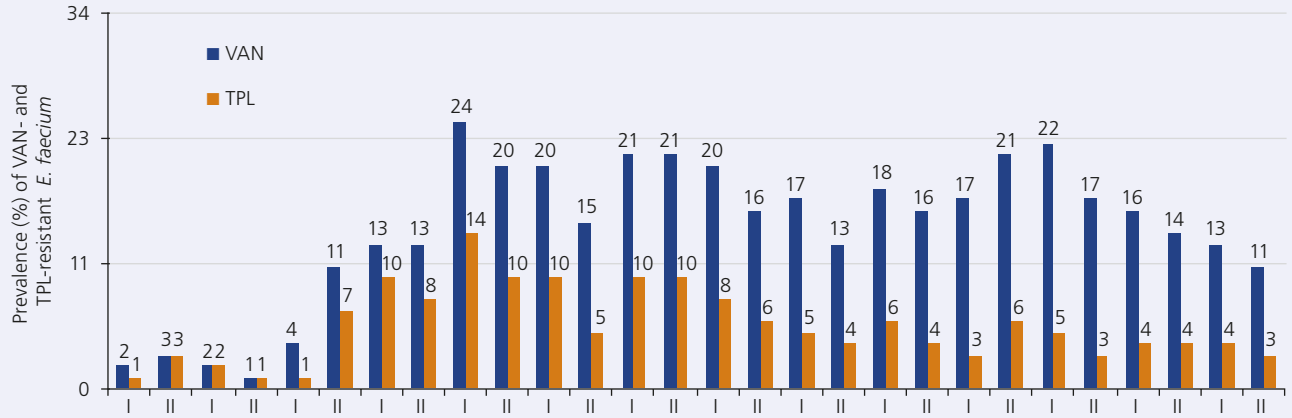
Countries that did not report resistance data in all years mentioned above and countries that only reported relevant resistance data for ≤ 19 isolates/year were not included in this analysis. The symbols indicate significant trends (< decrease, > increase) in total vancomycin resistance rates in invasive *E. faecium* in the laboratories of the respective country that reported resistance data in these years.

Other data sources

Resistance rates of glycopeptide-resistant *E. faecium* reported by the Laboratory Dr. Limbach and Colleagues, Heidelberg

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. The presented resistance rates to the glycopeptides vancomycin and teicoplanin in *E. faecium isolates* from patients at hospitals in the catchment area of this laboratory indicate the strong increase in the emergence and spread of *vanA*- and *vanB*-type HA-*E. faecium* strains since the second half of 2003 (Fig. 4.1.3.6).

In the first half of 2005, 24% of the *E. faecium* isolates were resistant to vancomycin and 14% to teicoplanin; after various intermediate stages, relatively high rates of vancomycin (22%) and teicoplanin (5%) resistance were again reached in the first half of 2012. Over the following years, the rates of glycopeptide resistance in *E. faecium* isolates gradually decreased, with 11% of them being resistant to vancomycin and 3% to teicoplanin in



Year (incl. half-years I + II)	2001		2002		2003		2004		2005		2006		2007		2008		2009		2010		2011		2012		2013		2014	
E.-faecium-isolates (n)	128	118	132	135	128	123	194	212	367	324	386	421	471	493	517	454	573	555	549	531	684	597	698	687	775	679	700	683
Total number of enterococcal-isolates (n)	3,405	3,519	3,610	3,560	3,494	3,651	3,485	4,065	4,814	4,740	4,825	5,088	4,748	5,482	5,466	5,008	5,263	5,513	5,377	5,427	5,736	5,746	6,233	5,884	6,322	6,311	6,288	6,037
Percentage of *E. faecium* in all enterococcal isolates (%)	3.8	3.4	3.7	3.8	3.7	3.4	5.6	5.2	7.6	6.8	8.0	8.3	9.9	9.0	9.5	9.1	10.9	10.1	10.2	9.8	11.9	10.4	11.2	11.7	12.3	10.8	11.1	11.3

Fig. 4.1.3.6: Prevalence (%) of vancomycin (VAN) and teicoplanin (TPL) resistance in *E. faecium* isolates from patients at Southwestern German hospitals between the 1st half of 2001 and the 2nd half of 2014 (Source: Laboratory Dr. Limbach and Colleagues, Heidelberg) – data does not include screening specimens

the second half of 2014. The significant increase in vancomycin resistance rates compared to the teicoplanin resistance rates observed from about 2009/2010 indicates the increased prevalence of *vanB*-positive (and thus teicoplanin-susceptible) *E. faecium* isolates at many hospitals.

Fig. 4.1.3.6 additionally shows the increasing portion of the species *E. faecium* in all enterococcal isolates submitted to this laboratory during the period under review. This *E. faecium* rate rose from 3.8% in the first half of 2001 through various intermediate stages to the so-far highest value of 12.3% in the first half of 2013 and ranged at 11.3% in the second half of 2014.

VRE/Enterococci submitted to the NRC for Staphylococci and Enterococci at the RKI Wernigerode

The above-described increased prevalence of VRE (*vanA* and *vanB* isolates of *E. faecium*) observed at German hospitals since 2003/2004 was also apparent in the number of enterococcal isolates submitted to the Robert Koch Institute Wernigerode [where the National Reference Centre (NRC) for Staphylococci and Enterococci has been established since May 2012]. Whereas *vanB*-positive *E. faecium* isolates were very rare among the enterococcal isolates submitted before 2003, their prevalence – in all enterococcal isolates submitted to the RKI Wernigerode in both years – increased to as much as 32.8% and 40.0% in 2011 and 2012, respectively. The ratio of *vanA*- and *vanB*-positive isolates in vancomycin-resistant *E. faecium* isolates submitted in 2013 and 2014 was about 50:50 (Fig. 4.1.3.7).

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

The *vanA*- and *vanB*-type *E. faecium* strains submitted to the RKI Wernigerode during the period 2010-2014 were tested for the prevalence of in-vitro resistance to other antimicrobials/chemotherapeutics. 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 evaluated on the basis of the respective ECOFF values also defined by EUCAST.

The results presented in Tab. 4.1.3.2 show that most *vanA*- and *vanB*-type *E. faecium* strains submitted to the RKI Wernigerode during the period 2010-2014 exhibit high rates of resistance to the antimicrobials/chemotherapeutics tested by the RKI Wernigerode. Nearly all vancomycin-resistant *E. faecium* strains tested here are resistant to ampicillin and are characterised by high-level ciprofloxacin resistance (MIC > 16 mg/l) as hospital-associated strains. Some of the *vanA*- and *vanB*-positive *E. faecium* strains additionally exhibit high-level resistance to aminoglycosides (gentamicin and/or streptomycin). During the study period 2010-2014, the rates of high-level streptomycin resistance increased in both VRE types. The varying rates of high-level gentamicin resistance observed during this period are apparently associated with a varying prevalence of certain strain variants. The *vanB*-encoded resistance of *E. faecium* is associated with particular strains; for example, high-level gentamicin resistance is comparatively rare in MLST ST192 (*esp*- and *hyl*-positive): 9 (15.8%) of a representative sample of 57 *vanB*-positive ST192 *E. faecium* isolates showed high-level gentamicin resistance (unpublished data of the NRC

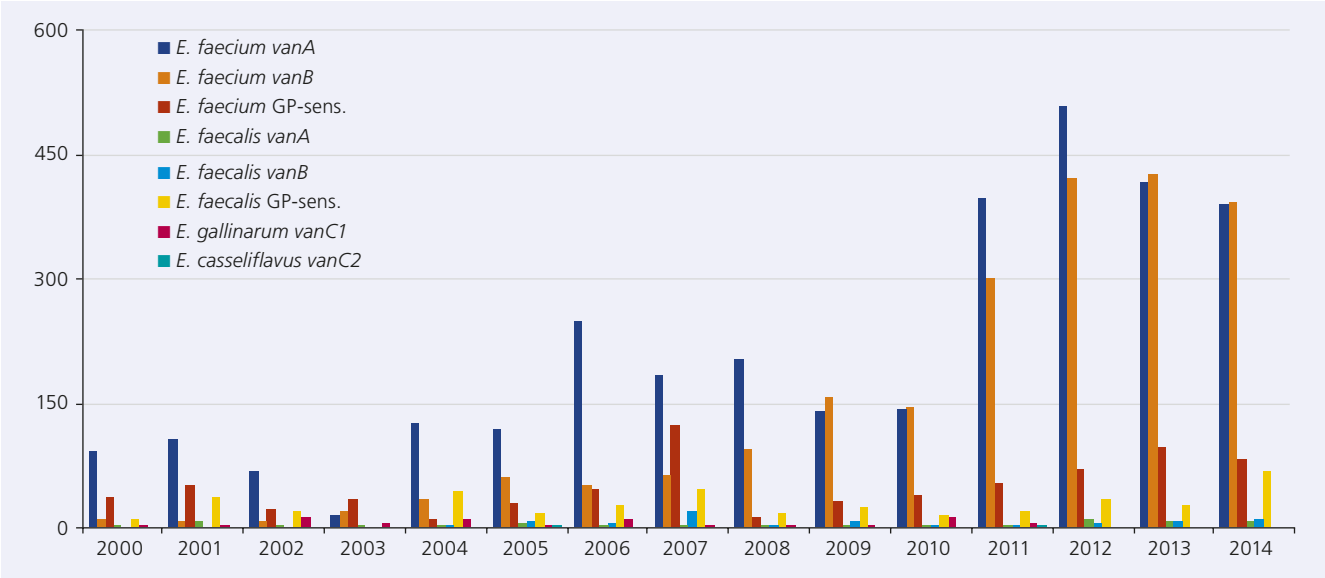


Fig. 4.1.3.7: Number of isolates of various enterococcal species* and vancomycin resistance types* isolated from infected and colonised inpatients and submitted to the RKI Wernigerode during the period 2000-2014 (Source: RKI Wernigerode, NRC for Staphylococci and Enterococci)

GP-sens., glycopeptide-sensitive

* In addition to the enterococcal species and vancomycin resistance types shown here, individual, rather rare species and/or resistance types occurred in 2011 to 2014, such as in 2011/2012: 2 *E. avium* and 1 *E. cecorum* (all 3 isolates susceptible to glycopeptides), 7 *E. faecium* with *vanA* plus *vanB*; 2013: 3 *E. gallinarum* with *vanC1* plus *vanA*, 1 *E. gallinarum* with *vanC1* plus *vanB*, 3 *E. avium* with *vanA*, 7 *E. avium* (susceptible to glycopeptides), 1 *E. raffinosus* (susceptible to glycopeptides); 2014: 5 *E. faecium* with *vanA* plus *vanB*, 2 *E. faecium* with *vanD*, 1 *E. durans* with *vanA*, 1 *E. gallinarum* with *vanC1* plus *vanA*, 2 *E. avium* (1 strain with *vanB* and 1 strain susceptible to glycopeptides), 1 *E. pseudoavium* (susceptible to glycopeptides). For the sake of clarity, these isolates are not included in this figure.

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 from 2010 to 2014 (Source: Robert Koch Institute Wernigerode, NRC for Staphylococci and Enterococci)

Antimicrobial/ Chemotherapeutic	Prevalence of resistance (%)[a] in *E. faecium* isolates of the									
	VanA-type					*VanB*-type				
	2010 (n=144)	2011 (n=392)	2012 (n=453)	2013 (n=418)	2014 (n=391)	2010 (n=146)	2011 (n=292)	2012 (n=371)	2013 (n=424)	2014 (n=393)
Penicillin G [b]	99.3	99.5	99.8	99.5	100.0	100.0	99.7	100.0	100.0	100.0
Ampicillin [a]	100.0	100.0	99.8	99.5	100.0	100.0	99.7	100.0	100.0	100.0
Gentamicin (HR) [a]	56.9	66.1	60.5	55.7	38.4	42.5	18.8	11.6	24.5	32.1
Streptomycin (HR) [a]	48.6	45.7	57.4	63.9	72.6	46.6	41.8	67.7	81.1	75.3
Gentamicin (HR) [a] and Streptomycin (HR) [a]	34.0	31.1	41.0	41.9	30.4	13.0	8.6	8.1	20.8	26.7
Vancomycin [a]	100.0	100.0	100.0	100.0	100.0	98.6	99.3	95.1	98.1	99.5
Teicoplanin [a]	99.3	100.0	100.0	100.0	100.0	0.0	0.0	0.0	0.2 [d]	1.5 [d]
Daptomycin [b]	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3
Quinupristin/Dalfopristin [a]	0.7	0.8	0.2	0.7	1.3	1.4	8.2	1.1	0.7	3.8
Clindamycin [b]	97.9	98.5	98.2	96.9	97.2	92.5	93.8	99.2	96.9	95.4
Erythromycin [b]	98.6	99.5	98.7	97.4	96.7	92.5	94.9	99.2	97.9	98.7
Ciprofloxacin [b]	98.6	99.5	100.0	99.0	100.0	100.0	98.6	100.0	99.8	100.0
Ciprofloxacin (HR) [c]	97.9	98.5	99.6	99.0	99.5	99.3	97.3	100.0	99.8	100.0
Moxifloxacin [b]	99.3	99.5	100.0	99.0	100.0	100.0	99.0	100.0	99.5	100.0
Linezolid [a]	4.2	3.9	0.7	4.5	4.6	0.7	1.7	1.1	2.4	1.8
Tetracycline [b]	38.2	65.8	60.7	64.6	62.7	8.2	11.3	16.2	14.9	16.0
Tigecycline [a]	2.8	0.0	0.4	0.7	3.1	0.0	0.0	0.0	0.2	0.5
Rifampicin [b]	74.3	89.2	94.3	93.3	99.7	78.1	73.6	90.0	93.6	98.7
Trimethoprim/Sulphamethoxazole [a]	43.1	58.8	60.9	61.7	67.5	26.0	69.2	81.9	84.0	57.5
Chloramphenicol [b]	0.0	0.0	0.0	0.0	3.6	0.0	0.0	0.0	0.0	1.5

[a] The MIC values were interpreted on the basis of the clinical MIC breakpoints defined by EUCAST.

[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] Interpretation of ciprofloxacin MIC values regarding HR to ciprofloxacin: > 16 mg/l.[10]

[d] In rare cases, *vanB E. faecium* strains may constitutively express the *vanB*-encoded vancomycin resistance and are then also resistant to teicoplanin

HR, high-level resistance

for Staphylococci and Enterococci). The *vanA* and *vanB* strains submitted to the RKI Wernigerode (NRZ for Staphylococci and Enterococci) during the period 2010-2014 were found to differ in terms of prevalence of high-level resistance to both gentamicin and streptomycin: Whereas the rates of high-level resistance in *vanA* strains ranged between 30.4% and 41.9%, the rates of

vanB isolates were significantly lower, ranging between 8.1% and 26.7%.

The resistance situation for the second-line antimicrobials linezolid and tigecycline varies. Whereas the prevalence of linezolid-resistant isolates in *vanA*-type *E. faecium* isolates submitted to the NRC slightly increased (2014: 4.6%), the prevalence of linezolid-resistant isolates was significantly lower among the submitted *vanB*-type *E. faecium* isolates (between 0.7% and 2.4% during the study period; 2014: 1.8%). As discussed above, the rates of resistance to linezolid ascertained in resistance surveillance systems (PEG studies, ARS, SARI) have so far been very low (often ≤ 1%). Such strains are nevertheless already present at German hospitals, as evidenced by the increased number of linezolid-resistant enterococci submitted to the RKI Wernigerode (Tab. 4.1.3.2). The majority of linezolid-resistant enterococcal isolates (especially *E. faecium*) submitted to the NRZ is susceptible to vancomycin (see 2014 Annual Report of the NRC for Staphylococci and Enterococci).

The rates of resistance to tigecycline in both *van* types of *E. faecium* submitted to the RKI Wernigerode are still very favourable, although the rates of tigecycline resistance in these isolates were observed to slightly increase in 2014 (3.1% of the *vanA* and 0.5% of the *vanB* strains).

The rates of resistance to chloramphenicol, which was included in the test for epidemiological reasons, in the VRE strains submitted to the RKI are also very favourable: 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 2010-2013; in 2014, 3.6% of the *vanA*- and 1.5% of the *vanB*-positive *E. faecium* isolates were resistant to chloramphenicol. An increasing prevalence of high-level resistance was observed for rifampicin and co-trimoxazole in *E. faecium* isolates of both *van* types during the period 2010-2014 (Tab. 4.1.3.2).

The in-vivo therapeutic efficacy of daptomycin is subject to controversy, which is why EUCAST does not specify clinical MIC breakpoints, but a wild-type ECOFF breakpoint of ≤ 4 mg/l. Based on this ECOFF value, the enterococcal database of the NRC for Staphylococci and Enterococci comprising 6,357 enterococcal isolates from hospital patients tested for daptomycin so far contains six *E. faecium* isolates and one *E. faecalis* isolate for which daptomycin MIC values of > 4 mg/l were measured by means of the broth microdilution test and E-test (total in-vitro resistance rate 0.11%). Hence, the prevalence of daptomycin resistance in enterococci currently appears to be extremely low.

Conclusion

During the last 25 years, enterococci have demonstrated increasing rates of resistance to various antimicrobials, with some significant differences being observed between the two clinically relevant enterococcal species *E. faecalis* and *E. faecium*. This can be best recognised by the prevalence of resistance to ampicillin and glycopeptides. The most important second-line antimicrobials, namely linezolid, tigecycline and daptomycin, are characterised by excellent in-vitro activity against these bacteria. Resistance to individual antimicrobials may, however, occur in vivo after a relatively short period of treatment (e.g., linezolid-resistant *E. faecium*). Second-line antimicrobials should be applied selectively and restrictively to prevent the development of selective pressure for the corresponding second-line antimicrobial agent. However, a more restrictive use of antimicrobials without anti-enterococcal activity and of glycopeptides is also of great significance.

➤ I. Klare, C. Wendt, G. Werner
Reviewer: J. Hübner

1. Kresken M, Hafner D, Schmitz FJ, Wichelhaus TA für die Studiengruppe PEG-Resistenzstudie: Resistenzsituation bei klinisch wichtigen Infektionserregern gegenüber Antibiotika in Deutschland und im mitteleuropäischen Raum. Bericht über die Ergebnisse einer multizentrischen Studie der Arbeitsgemeinschaft Empfindlichkeitsprüfungen & Resistenz der Paul-Ehrlich-Gesellschaft für Chemotherapie e.V. aus dem Jahre 1998/2001/2004/2007/2010/2013 (Online: http://www.p-e-g.org/ag_resistenz/main.htm).
2. Seedat J, Zick G, Klare I, Konstabel C, et al. Rapid emergence of resistance to linezolid during linezolid therapy of an *Enterococcus faecium* infection. Antimicrob Agents Chemother 2006;50:4217–9.
3. Werner G, Gfrörer S, Fleige C, Witte W, et al. Tigecycline-resistant *Enterococcus faecalis* strain isolated from a German ICU patient. J Antimicrob Chemother 2008;61:1182–3.
4. Willems RJL, Top J, van Schaik W, Leavis H, et al. Restricted gene flow among hospital subpopulations of *Enterococcus faecium*. mBio 2012;3:1–10.
5. Willems RJ, Homan W, Top J, van Santen-Verheuvel M, et al. Variant *esp* gene as a marker of a distinct genetic lineage of vancomycin-resistant *Enterococcus faecium* spreading in hospitals. Lancet 2001;357:853–5.
6. Rice LB, Carias L, Rudin S, Vael C, et al. A potential virulence gene, *hyl*Efm, predominates in *Enterococcus faecium* of clinical origin. J Infect Dis 2003;187:508–12.
7. Werner G, Fleige C, Geringer U, van Schaik W, et al. IS element IS*16* as a molecular screening tool to identify hospital-associated strains of *Enterococcus faecium.* BMC Infect Dis 2011;11:80.
8. Werner G, Fleige C, Ewert B, Laverde-Gomez JA, et al. High-level ciprofloxacin resistance among hospital-adapted *Enterococcus faecium* (CC17). Int J Antimicrob Agents 2010;35:119–25.
9. DIN – Deutsches Institut für Normung e. V. (2004) DIN 58940-8: Empfindlichkeitsprüfung von mikrobiellen Krankheitserregern gegen Chemotherapeutika, Teil 8: Mikrodilution. In: DIN-Taschenbuch 222 – Medizinische Mikrobiologie und Immunologie, Diagnostische Verfahren, Beuth-Verlag Berlin, Wien, Zürich, S 342–53.
10. DIN – Deutsches Institut für Normung e. V. (2004) DIN 58940-4: Empfindlichkeitsprüfung von mikrobiellen Krankheitserregern gegen Chemotherapeutika, Teil 4: Bewertungsstufen für die minimale Hemmkonzentration, Beiblatt 1: MHK-Grenzwerte von antibakteriellen Wirkstoffen. In: DIN-Taschenbuch 222 – Medizinische Mikrobiologie und Immunologie, Diagnostische Verfahren, Beuth-Verlag Berlin, Wien, Zürich, S 307–23.
11. EUCAST, European Committee on Antimicrobial Susceptibility Testing, MIC distributions: Antimicrobial wild type distributions of microorganisms.
12. EUCAST, European Committee on Antimicrobial Susceptibility Testing, Clinical breakpoints bacteria (version 3.1).
13. ARS (Antibiotika-Resistenz-Surveillance in Deutschland), Datenbank: Resistenzübersicht *E. faecium, E. faecalis*; Blutkulturen bzw. ambulanter Bereich, 2008–2014 (https://ars.rki.de/).
14. SARI, Surveillance der Antibiotika-Anwendung und der bakteriellen Resistenzen auf Intensivstationen, 2004–2014; www.nrz-hygiene.de/surveillance/sari/ .
15. ECDC Surveillance Report 2013: Antimicrobial resistance surveillance in Europe, Nov. 2014; http://www.ecdc.europa.eu/en/activities/surveillance/EARS-Net.

MRSA and VRE prevalence in Africa and Asia – a selective literature search regarding the most recently published colonisation and infection rates

In addition to the published data from industrialised countries, an increasing amount of data on the epidemiology of resistant gram-positive bacteria in Africa[1] and Asia is now available. Among gram-positive bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) are of particular clinical and infection control significance because the antimicrobial alternatives are often limited particularly in cases of infection and not merely colonisations.[2] The two tables below show the results of a selective and comprehensive literature search from 2015. In each case, the most recently published and PubMed-listed publication on MRSA and VRE colonisation and infection was evaluated. The evaluation included only data that did not originate from clusters or outbreak events and did not report imported infections or colonisations.

For Africa, only the MRSA colonisation and infection rates were included, because the available data on VRE are insufficient, with some of the information coming from unreliable sources.[3-11] For Asia, the amount of data on VRE prevalence is considerably larger and the data sources are more reliable. Therefore, only the MRSA and VRE infection rates were included for Asia to provide a better overview, while the available data on colonisation were not included for the sake of clarity. The countries were categorised based on the classification of the United Nations (UN). Overall, the median MRSA rate in *S. aureus* infections in Africa appears to be slightly lower in western Africa (14.5%) compared to other African regions (21.3-25.4%). By contrast, the MRSA colonisation rate is comparable across all African regions.

However, we were unable to fully evaluate the quality of the studies to assess how representative the available data are. Therefore, the conclusion should be critically appraised. In most countries, no national surveillance data are available, but only selective regional studies; for some countries, no data were available at all. Moreover, there is no sufficient information available to evaluate the microbiological standards in the individual countries, i.e. the technical resources and the related validation processes used for reproducible in vitro susceptibility testing and molecular or phenotypic characterisation of resistance mechanisms are unknown.

➤ F. Schaumburg, A. Mischnik, C. Lübbert, I. Bekeredjan-Ding
Reviewer: W.V. Kern, G. Werner

1. Schaumburg F, Alabi AS, Peters G, Becker K. New epidemiology of *Staphylococcus aureus* infection in Africa. Clin Microbiol Infect 2014;20:589-96.
2. Mutters NT, Werner G, Tacconelli E, Mischnik A. Treatment options for serious infections caused by vancomycin-resistant enterococci. Dtsch Med Wochenschr 2015;140:42-5.
3. Aamodt H, Mohn SC, Maselle S, Manji KP, et al. Genetic relatedness and risk factor analysis of ampicillin-resistant and high-level gentamicin-resistant enterococci causing bloodstream infections in Tanzanian children. BMC Infect Dis 2015;15:107.
4. Hashem YA, Yassin AS, Amin MA. Molecular characterization of *Enterococcus* spp. clinical isolates from Cairo, Egypt. Indian J Med Microbiol 2015;33:80-86.
5. Isendahl J, Manjuba C, Rodrigues A, Xu W, et al. Prevalence of community-acquired bacteraemia in Guinea-Bissau: an observational study. BMC Infect Dis 2014;14:3859.
6. Ahoyo TA, Bankole HS, Adeoti FM, Gbohoun AA, et al. Prevalence of nosocomial infections and anti-infective therapy in Benin: results of the first nationwide survey in 2012. Antimicrob Resist Infect Control 2014;3:17.
7. Seni J, Najjuka CF, Kateete DP, Makobore P, et al. Antimicrobial resistance in hospitalized surgical patients: a silently emerging public health concern in Uganda. BMC Res Notes 2013;6:298.
8. Kateete DP, Kabugo U, Baluku H, Nyakarahuka L, et al. Prevalence and antimicrobial susceptibility patterns of bacteria from milkmen and cows with clinical mastitis in and around Kampala, Uganda. PLoS One 2013;8:e63413.
9. Djahmi N, Boutet-Dubois A, Nedjai S, Dekhil M, et al. Molecular epidemiology of *Enterococcus* sp. isolated in a university hospital in Algeria. Scand J Infect Dis 2012;44:656-62.
10. Dromigny JA, Nabeth P, Perrier Gros Claude JD. Distribution and susceptibility of bacterial urinary tract infections in Dakar, Senegal. Int J Antimicrob Agents 2002;20:339-47.
11. von Gottberg A, van Nierop W, Duse A, Kassel M, et al. Epidemiology of glycopeptide-resistant enterococci colonizing high-risk patients in hospitals in Johannesburg, Republic of South Africa. J Clin Microbiol 2000;38:905-9.
12. Djoudi F, Benallaoua S, Aleo A, Touati A, et al. Descriptive epidemiology of nasal carriage of *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* among patients admitted to two healthcare facilities in Algeria. Microbial Drug Resist 2015;21:218-23.
13. Alioua MA, Labid A, Amoura K, Bertine M, et al. Emergence of the European ST80 clone of community-associated methicillin-resistant *Staphylococcus aureus* as a cause of healthcare-associated infections in Eastern Algeria. Med Mal Infect 2014;44:180-3.
14. Abou Shady HM, Bakr AE, Hashad ME, Alzohairy MA. *Staphylococcus aureus* nasal carriage among outpatients attending primary health care centers: a comparative study of two cities in Saudi Arabia and Egypt. Braz J Infect Dis 2015;19:68-76.
15. Ahmed EF, Gad GF, Abdalla AM, Hasaneen AM, et al. Prevalence of methicillin resistant *Staphylococcus aureus* among Egyptian patients after surgical interventions. Surg Infect (Larchmt) 2014;15:404-11.
16. Al-haddad OH, Zorgani A, Ghenghesh KS. Nasal carriage of multidrug resistant Panton-Valentine leucocidin-positive methicillin-resistant *Staphylococcus aureus* in children in Tripoli-Libya. Am J Trop Med Hyg 2014;90:724-7.
17. Buzaid N, Elzouki AN, Taher I, Ghenghesh KS. Methicillin-resistant *Staphylococcus aureus* (MRSA) in a tertiary surgical and trauma hospital in Benghazi, Libya. J Infect Dev Ctries 2011;5:723-6.
18. Oumokhtar B, Elazhari M, Timinouni M, Bendahhou K, et al. *Staphylococcus aureus* nasal carriage in a Moroccan dialysis center and isolates characterization. Hemodial Int 2013;17:542-7.
19. El Shallaly GH, Hassan AN, Siddig NO, Mohammed RA, et al. Study of patients with community-acquired abscesses. Surg Infect (Larchmt) 2012;13:250-6.
20. Ben Slama K, Gharsa H, Klibi N, Jouini A, et al. Nasal carriage of *Staphylococcus aureus* in healthy humans with different levels of contact with animals in Tunisia: genetic lineages, methicillin resistance, and virulence factors. Eur J Clin Microbiol Infect Dis 2011;30:499-508.
21. Kechrid A, Perez-Vazquez M, Smaoui H, Hariga D, et al. Molecular analysis of community-acquired methicillin-susceptible and resistant *Staphylococcus aureus* isolates recovered from bacteraemic and osteomyelitis infections in children from Tunisia. Clin Microbiol Infect 2011;17:1020-6.
22. Loeto D, Matsheka MI, Gashe BA. Enterotoxigenic and antibiotic resistance determination of *Staphylococcus aureus* strains isolated from food handlers in Gaborone, Botswana. J Food Prot 2007;70:2764-8.
23. Truong H, Shah SS, Ludmir J, Twananana EO, et al. Staphylococcus aureus skin and soft tissue infections at a tertiary hospital in Botswana. South Afr Med J 2011;101:413-6.
24. Nurjadi D, Olalekan AO, Layer F, Shittu AO, et al. Emergence of trimethoprim resistance gene *dfrG* in *Staphylococcus aureus* causing human infection and colonization in sub-Saharan Africa and its import to Europe. J Antimicrob Chemother 2014;69:2361-8.

Tab. 1: Most recently published MRSA colonisation and infection rates in Africa by UN region

UN-Region	Country	Colonisation			Infection		
		Percentage of MRSA / *S. aureus* isolates	Survey period	Source	Percentage of MRSA / *S. aureus* isolates	Survey period	Source
North Africa	Algeria	6%	unknown before 2015	12	62%	2010	13
	Egypt	61%	2011	14	24%	unknown before 2012	15
	Libya	34%	2009–2010	16	31%	2007	17
	Morocco	3%	2010	18	No data		
	Sudan	No data			24%	2009–2010	19
	Tunisia	2%	2008–2009	20	22%	2006–2008	21
	Western Sahara	No data			No data		
South Africa	Botswana	16%	unknown before 2007	22	23%	2000–2007	23
	Lesotho	No data			No data		
	Namibia	7%	2008–2009	24	10%	2008–2009	24
	Republic of South Africa	77%	2002	25	36%	2012–2013	26
	Swaziland	No data			No data		
West Africa	Benin	No data			25%	2009–2011	27
	Burkina Faso	No data			No data		
	Ivory Coast	5%	2012	28	25%	1998–2001	29
	Gambia	No data			0%	2003–2005	30
	Ghana	2%	2011–2012	31	3%	2010–2012	32
	Guinea-Conakry	No data			No data		
	Guinea-Bissau	No data			0%	2010	5
	Cabo Verde	0%	1997	33	0%	1997	33
	Liberia	No data			No data		
	Mali	1%	2005	34	No data		
	Mauritania	No data			No data		
	Niger	No data			No data		
	Nigeria	16%	2008–2010	35	29%	2010	36
	St. Helena	No data			No data		
	Senegal	0%	2012	37	15%	2000	10
	Sierra Leone	No data			No data		
	Togo	No data			36%	2003–2005	38
Central Africa	Angola	58%	2012	39	No data		
	Equatorial Guinea	No data			No data		
	Democratic Republic of Congo	16%	2011	40	64%	2013	41
	Gabon	2%	2010–2013	42	3%	2012	43
	Cameroon	No data			21%	1996–1997	44
	Republic of Congo	No data			No data		
	São Tomé and Príncipe	27%	2010–2012	45	No data		
	Chad	No data			No data		
	Republic of Central Africa	No data			No data		
East Africa	Ethiopia	44%	2010–2011	46	49%	2011–2012	47
	Burundi	No data			No data		
	Djibouti	No data			No data		
	Eritrea	0%	unknown before 2012	48	9%	unknown before 2009	49
	Kenya	7%	2011	50	84%	2005–2007	51
	Comoros	No data			No data		
	Madagascar	15%	unknown before 2011	52	6%	2001–2005	53
	Malawi	No data			1%	1994–1999	54
	Mauritius	No data			No data		
	Mayotte	No data			No data		
	Mozambique	No data			9%	2010–2011	55
	Réunion	No data			13%	2005	56
	Rwanda	No data			82%	2013	57
	Zambia	No data			No data		
	Seychelles	No data			No data		
	Zimbabwe	No data			No data		
	Somalia	No data			No data		
	South Sudan	No data			No data		
	Tanzania	11%	unknown before 2013	58	44%	2011–2012	59
	Uganda	No data			38%	2011–2012	60

Tab. 2: Most recently published MRSA and VRE rates in clinical isolates in Asia by UN region

		MRSA rates in clinical isolates			VRE rates in clinical isolates		
UN region	Country	Percentage of MRSA / *S. aureus* isolates	Survey period	Source	Percentage of VRE / *Enterococcus* isolates	Survey period	Source
East Asia	China	41% 68%	2007–2012 2011	61 62	5%	2010	63
	Mongolia	76%	No data	64	No data		
	Korea	73%	2011	65	26%	2011	65
	Japan	45%	2011	65	0%	2011	65
	Taiwan	74%		66	25%	2010	67
Southeast Asia	Myanmar	No data			No data		
	Laos	0%	2000–2011	68	No data		
	Thailand	53%	2011	65	2%	1999–2009	69
	Cambodia	No data			No data		
	Vietnam	19%	2008–2009	70	No data		
	Indonesia	28%	2011	65	0%	2011	65
	East Timor	No data			No data		
	Singapore	52%	2011	65	0,4–0,7%	2006–2010	71
	Malaysia	32%	2011	65	9%	2010–2011	72
	Philippines	59%	2011	65	No data		
South Asia	India	45% 54%	2011 2010–2011	65 73	14%	2011–2014	74
	Nepal	43%	No data	75	0,3%	2010–2011	76
	Pakistan	48%	2009–2010	77	12%	2011–2012	78
	Bangladesh	32-63%	2005	79	0%	2009–2010	80
	Bhutan	No data			No data		
Central Asia	Kazakhstan	No data			No data		
	Uzbekistan	No data			No data		
	Turkmenistan	No data			No data		
	Afghanistan	51%	2010–2012	81	No data		
	Kirgizstan	No data			No data		
	Tajikistan	No data			No data		
Russia and Caucasus	Russia	48%	2006–2007	82	9–10%		83

25. Cotton MF, Wasserman E, Smit J, Whitelaw A, et al. High incidence of antimicrobial resistant organisms including extended spectrum beta-lactamase producing Enterobacteriaceae and methicillin-resistant *Staphylococcus aureus* in nasopharyngeal and blood isolates of HIV-infected children from Cape Town, South Africa. BMC Infect Dis 2008;8:40.
26. Fortuin-de Smidt MC, Singh-Moodley A, Badat R, Quan V, et al. *Staphylococcus aureus* bacteraemia in Gauteng academic hospitals, South Africa. Int J Infect Dis 2015;30:41-8.
27. Sina H, Ahoyo TA, Moussaoui W, Keller D, et al. Variability of antibiotic susceptibility and toxin production of *Staphylococcus aureus* strains isolated from skin, soft tissue, and bone related infections. BMC Microbiol 2013;13:188.
28. Schaumburg F, Pauly M, Anoh E, Mossoun A, et al. *Staphylococcus aureus* complex from animals and humans in three remote African regions. Clin Microbiol Infect 2015;21:345.
29. Akoua-Koffi C, Guessennd N, Gbonon V, Faye-Kette H, et al. Methicillin-resistance of *Staphylococcus aureus* in Abidjan (1998-2001): a new hospital problem. Med Mal Infect 2004;34:132-6.
30. Hill PC, Onyeama CO, Ikumapayi UN, Secka O, et al. Bacteraemia in patients admitted to an urban hospital in West Africa. BMC Infect Dis 2007;7:2.
31. Egyir B, Guardabassi L, Esson J, Nielsen SS, et al. Insights into nasal carriage of *Staphylococcus aureus* in an urban and a rural community in Ghana. PLoS One 2014;9:e96119.
32. Egyir B, Guardabassi L, Sorum M, Nielsen SS, et al. Molecular epidemiology and antimicrobial susceptibility of clinical *Staphylococcus aureus* from healthcare institutions in Ghana. PLoS One 2014;9:e89716.
33. Aires De Sousa M, Santos Sanches I, Ferro ML, De Lencastre H. Epidemiological study of staphylococcal colonization and cross-infection in two West African Hospitals. Microbial Drug Resist 2000;6:133-41.
34. Ruimy R, Maiga A, Armand-Lefevre L, Maiga I, et al. The carriage population of *Staphylococcus aureus* from Mali is composed of a combination of pandemic clones and the divergent Panton-Valentine leukocidin-positive genotype ST152. J Bacteriol 2008;190:3962-8.
35. Olalekan AO, Schaumburg F, Nurjadi D, Dike AE, et al. Clonal expansion accounts for an excess of antimicrobial resistance in *Staphylococcus aureus* colonising HIV-positive individuals in Lagos, Nigeria. Int J Antimicrob Agents 2012;40:268-72.
36. Shittu A, Oyedara O, Abegunrin F, Okon K, et al. Characterization of methicillin-susceptible and -resistant staphylococci in the clinical setting: a multicentre study in Nigeria. BMC Infect Dis 2012;12:286.
37. Fall C, Richard V, Dufougeray A, Biron A, et al. *Staphylococcus aureus* nasal and pharyngeal carriage in Senegal. Clin Microbiol Infect 2014;20:239-41.
38. Kombate K, Dagnra AY, Saka B, Mouhari-Toure A, et al. Prevalence of methicillin-resistant *Staphylococcus aureus* in community-acquired skin infections in Lome, Togo. Med Trop (Mars) 2011;71:68-70.
39. Conceicao T, Coelho C, Santos-Silva I, de Lencastre H, et al. Epidemiology of methicillin-resistant and -susceptible *Staphylococcus aureus* in Luanda, Angola: first description of the spread of the MRSA ST5-IVa clone in the African continent. Microbial Drug Resist 2014;20:441-9.
40. De Boeck H, Vandendriessche S, Hallin M, Batoko B, et al. *Staphylococcus aureus* nasal carriage among healthcare workers in Kisangani, the Democratic Republic of the Congo. Eur J Clin Microbiol Infect Dis 2015;34:1567-72.
41. Iyamba JM, Wambale JM, Lukukula CM, za Balega Takaisi-Kikuni N. High prevalence of methicillin resistant staphylococci strains isolated from surgical site infections in Kinshasa. Pan Afr Med J 2014;18:322.
42. Schaumburg F, Alabi AS, Mombo-Ngoma G, Kaba H, et al. Transmission of *Staphylococcus aureus* between mothers and infants in an African setting. Clin Microbiol Infect 2014;20:390-6.
43. Alabi AS, Frielinghaus L, Kaba H, Kosters K, et al. Retrospective analysis of antimicrobial resistance and bacterial spectrum of infection in Gabon, Central Africa. BMC Infect Dis 2013;13:455.
44. Kesah C, Ben Redjeb S, Odugbemi TO, Boye CS, et al. Prevalence of methicillin-resistant *Staphylococcus aureus* in eight African hospitals and Malta. Clin Microbiol Infect 2003;9:153-6.
45. Conceicao T, Santos Silva I, de Lencastre H, Aires-de-Sousa M. *Staphylococcus aureus* nasal carriage among patients and health care workers in Sao Tome and Principe. Microbial drug resistance 2014;20:57-66.
46. Shibabaw A, Abebe T, Mihret A. Antimicrobial susceptibility pattern of nasal *Staphylococcus aureus* among Dessie Referral Hospital health care workers, Dessie, Northeast Ethiopia. Int J Infect Dis 2014;25:22-5.
47. Kahsay A, Mihret A, Abebe T, Andualem T. Isolation and antimicrobial susceptibility pattern of *Staphylococcus aureus* in patients with surgical site infection at Debre Markos Referral Hospital, Amhara Region, Ethiopia. Arch Public Health 2014;72:16.

48. Ghebremedhin B, Koenig W. Comparative study of nasal bacterial carriage in pediatric patients from two different geographical regions. Eur J Microbiol Immunol (Bp) 2012;2:205-9.
49. Naik D, Teclu A. A study on antimicrobial susceptibility pattern in clinical isolates of *Staphylococcus aureus* in Eritrea. Pan Afr Med J 2009;3:1.
50. Aiken AM, Mutuku IM, Sabat AJ, Akkerboom V, et al. Carriage of *Staphylococcus aureus* in Thika Level 5 Hospital, Kenya: a cross-sectional study. Antimicrobial Resist Infect Control 2014;3:22.
51. Maina EK, Kiiyukia C, Wamae CN, Waiyaki PG, et al. Characterization of methicillin-resistant *Staphylococcus aureus* from skin and soft tissue infections in patients in Nairobi, Kenya. Int J Infect Dis 2013;17:115-9.
52. Rasamiravaka T, Rasoanandrasana S, Zafindraibe NJ, Rakoto Alson AO, et al. Evaluation of methicillin-resistant *Staphylococcus aureus* nasal carriage in Malagasy patients. J Infect Dev Ctries 2013;7:318-22.
53. Randrianirina F, Soares JL, Ratsima E, Carod JF, et al. In vitro activities of 18 antimicrobial agents against *Staphylococcus aureus* isolates from the Institut Pasteur of Madagascar. Ann Clin Microbiol Antimicrob 2007;6:5.
54. Komolafe OO, James J, Kalongolera L, Makoka M. Bacteriology of burns at the Queen Elizabeth Central Hospital, Blantyre, Malawi. Burns 2003;29:235-8.
55. van der Meeren BT, Millard PS, Scacchetti M, Hermans MH, et al. Emergence of methicillin resistance and Panton-Valentine leukocidin positivity in hospital- and community-acquired *Staphylococcus aureus* infections in Beira, Mozambique. Trop Med Int Health 2014;19:169-76.
56. Picot S, Rakotomalala RS, Farny K, Simac C, et al. Evolution of resistance to antibiotics from 1997 to 2005 in the Reunion Island. Med Mal Infect 2010;40:617-24.
57. Ntirenganya C, Manzi O, Muvunyi CM, Ogbuagu O. High prevalence of antimicrobial resistance among common bacterial isolates in a tertiary healthcare facility in rwanda. Am J Trop Med Hyg 2015;92:865-70.
58. Moyo SJ, Aboud S, Blomberg B, Mkopi N, et al. High nasal carriage of methicillin-resistant *Staphylococcus aureus* among healthy Tanzanian under-5 children. Microbial Drug Resist 2014;20:82-8.
59. Moremi N, Mushi MF, Fidelis M, Chalya P, et al. Predominance of multi-resistant gram-negative bacteria colonizing chronic lower limb ulcers (CLLUs) at Bugando Medical Center. BMC Res Notes 2014;7:211.
60. Seni J, Bwanga F, Najjuka CF, Makobore P, et al. Molecular characterization of *Staphylococcus aureus* from patients with surgical site infections at Mulago Hospital in Kampala, Uganda. PLoS One 2013;8:e66153.
61. Yang Z, Wang J, Wang W, Zhang Y, et al. Proportions of *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* in patients with surgical site infections in mainland China: a systematic review and meta-analysis. PLoS One 2015;10:e0116079.
62. Li T, Song Y, Zhu Y, Du X, et al. Current status of *Staphylococcus aureus* infection in a central teaching hospital in Shanghai, China. BMC Microbiol 2013;13:153.
63. Zhao C, Sun H, Wang H, Liu Y, Hu B, et al. Antimicrobial resistance trends among 5608 clinical Gram-positive isolates in China: results from the Gram-Positive Cocci Resistance Surveillance program (2005-2010). Diagn Microbiol Infect Dis 2012;73:174-81.
64. Wang LF, Li JL, Ma WH, Li JY. Drug resistance analysis of bacterial strains isolated from burn patients. Genet Mol Res 2014;13:9727-34.
65. Mendes RE, Mendoza M, Banga Singh KK, Castanheira M, et al. Regional resistance surveillance program results for 12 Asia-Pacific nations (2011). Antimicrob Agents Chemother 2013;57:5721-6.
66. Chou YH, Lee MS, Lin RY, Wu CY. Risk factors for methicillin-resistant *Staphylococcus aureus* skin and soft-tissue infections in outpatients in Taiwan. Epidemiol Infect 2015;143:749-53.
67. Wang JT, Chang SC, Wang HY, Chen PC, et al. High rates of multidrug resistance in *Enterococcus faecalis* and *E. faecium* isolated from inpatients and outpatients in Taiwan. Diagn Microbiol Infect Dis 2013;75:406-11.
68. Anderson M, Luangxay K, Sisouk K, Vorlasan L, et al. Epidemiology of bacteremia in young hospitalized infants in Vientiane, Laos, 2000-2011. J Trop Pediatr 2014;60:10-6.
69. Thongkoom P, Kanjanahareutai S, Chantrakooptungool S, Rahule S. Vancomycin-resistant enterococci (VRE) isolates isolated in Rajavithi Hospital between 1999 and 2009. J Med Assoc Thai 2012;95:S7-15.
70. Thwaites GE. The management of *Staphylococcus aureus* bacteremia in the United Kingdom and Vietnam: a multi-centre evaluation. PLoS One 2010;5:e14170.
71. Cai Y, Chan JP, Fisher DA, Hsu LY, et al. Vancomycin-resistant Enterococci in Singaporean hospitals: 5-year results of a multi-centre surveillance programme. Ann Acad Med Singapore 2012;41:77-81.
72. Getachew Y, Hassan L, Zakaria Z, Zaid CZ, et al. Characterization and risk factors of vancomycin-resistant Enterococci (VRE) among animal-affiliated workers in Malaysia. J Appl Microbiol 2012;113:1184-95.
73. Eshwara VK, Munim F, Tellapragada C, Kamath A, et al. *Staphylococcus aureus* bacteremia in an Indian tertiary care hospital: observational study on clinical epidemiology, resistance characteristics, and carriage of the Panton-Valentine leukocidin gene. Int J Infect Dis 2013;17:1051-5.
74. Bhatt P, Patel A, Sahni AK, Praharaj AK, et al. Emergence of multidrug resistant enterococci at a tertiary care centre. Med J Armed Forces India 2015;71:139-44.
75. Ansari S, Nepal HP, Gautam R, Rayamajhi N, et al. Threat of drug resistant *Staphylococcus aureus* to health in Nepal. BMC Infect Dis 2014;14:157.
76. Ghosh AN, Bhatta DR, Ansari MT, Tiwari HK, et al. Application of WHONET in the Antimicrobial Resistance Surveillance of Uropathogens: A First User Experience from Nepal. J Clin Diagn Res 2013;7:845-8.
77. Ahmad MK, Asrar A. Prevalence of methicillin resistant *Staphylococcus aureus* in pyogenic community and hospital acquired skin and soft tissues infections. J Pak Med Assoc 2014;64:892-5.
78. Babar N, Usman J, Munir T, Gill MM, et al. Frequency and antibiogram of vancomycin resistant *enterococcus* in a tertiary care hospital. J Coll Physicians Surg Pak 2014;24:27-9.
79. Haq JA, Rahman MM, Asna SM, Hossain MA, et al. Methicillin-resistant *Staphylococcus aureus* in Bangladesh-a multicentre study. Int J Antimicrob Agents 2005;25:276-7.
80. Akhter S, Asna ZH, Rahman MM. Prevalence and antimicrobial susceptibility of *enterococcus* species isolated from clinical specimens. Mymensingh Med J 2011;20:694-9.
81. Tariq TM. Bacteriologic profile and antibiogram of blood culture isolates from a children's hospital in Kabul. J Coll Physicians Surg Pak 2014;24:396-9.
82. Baranovich T, Zaraket H, Shabana, II, Nevzorova V, et al. Molecular characterization and susceptibility of methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* isolates from hospitals and the community in Vladivostok, Russia. Clin Microbiol Infect 2010;16:575-82.
83. Jones RN, Flonta M, Gurler N, Cepparulo M, et al. Resistance surveillance program report for selected European nations (2011). Diagn Microbiol Infect Dis 2014;78:429-36.

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). Invasive *H. influenzae* infections occur as a result of a lack of antibodies against the capsular antigens, especially in infants and young children. Hib meningitis/bloodstream infections occur most frequently in the first two years of life, epiglottitis in the third to fourth year of life. This is why vaccination with Hib vaccine is recommended in the first and second year of life as part of basic immunisation. *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. *H. influenzae* accounts for 5-10% of the pathogens identified as the causative agent of community-acquired pneumonia.[2]

β-lactam antimicrobials are recommended primarily for treatment. In the event of severe infections, third-generation cephalosporins (group 3a according to the classification of the Paul Ehrlich Society for Chemotherapy), such as cefotaxime and ceftriaxone, are indicated. The oral cephalosporins cefalexin, cefadroxil and cefaclor (first generation/group 1) exhibit no sufficient activity, and most of the cefuroxime (second-generation/group 2) MIC values are in the intermediate range, when applying the breakpoints for cefuroxime axetil. By contrast, third-generation (group 3) oral 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, 20.2% of the nearly 15,000 isolates collected over the period 2004-2012 and tested as part of an international surveillance study were found to produce β-lactamase.[3] β-lactamase was produced by 14.8% of the 6,322 isolates obtained from European 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 the international surveillance study, the rate of BLNAR in all isolates was 1.5% (Europe 1.6%).[3]

As part of the 2013 PEG resistance study, 236 pathogen 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 25 cases, the isolates had been obtained from eye swabs. A total of 21 isolates (8.9%) 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. The rate of amoxicillin-resistant strains was 6.5% in the group of patients aged < 5 years, compared to 10.9% in other patients. Four isolates (1.7%) were classified as resistant to cefixime and two isolates (0.8%) showed resistance to fluoroquinolones. 100% susceptibility was found for cefpodoxime and doxycycline (Fig. 4.1.4.1.1).[4] In the 2010 PEG resistance study, 12.6% of the 230 tested isolates were resistant to amoxicillin, all of which were β-lactamase-producing strains (Fig. 4.1.4.1.1).[5]

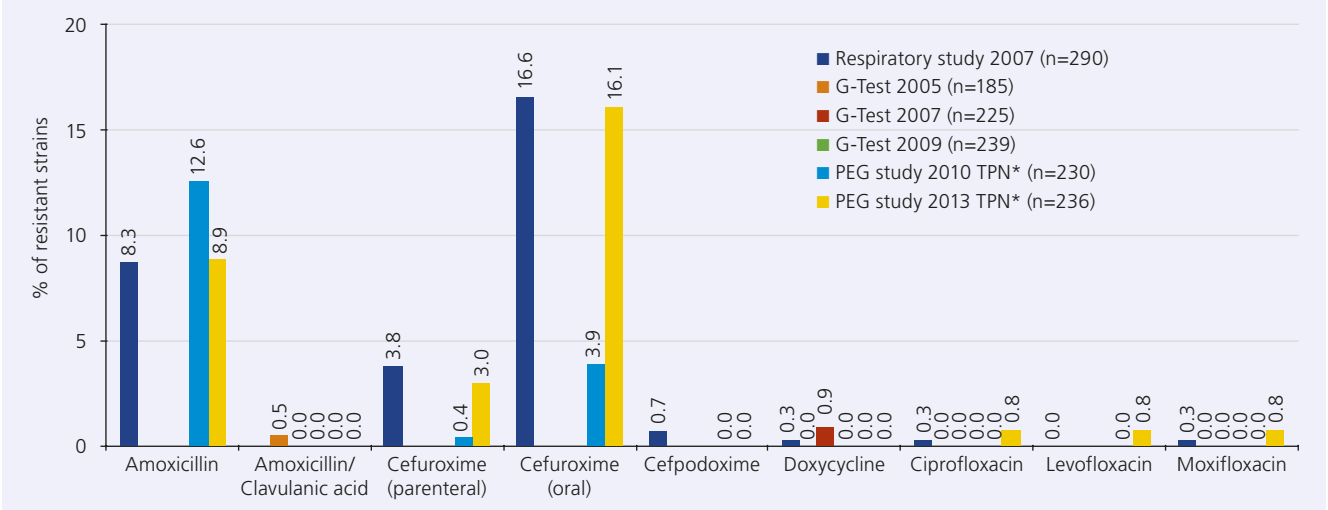


Fig. 4.1.4.1.1: Resistance of *H. influenzae* isolates (EUCAST breakpoints, version 6.0). The difference in the prevalence of strains resistant to cefuroxime (parenteral) and cefuroxime (oral) results from the different breakpoints defined for cefuroxime (parenteral) and cefuroxime (oral).
*TPN, subproject ambulatory care

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 8.3% (Fig. 4.1.4.1.1).[6] As part of G-TEST (see chapter 7.1), more than 600 isolates obtained from hospitalised patients in 2005, 2007 and 2009 were tested for susceptibility to amoxicillin/clavulanic acid, doxycycline and fluoroquinolones. In this case, 87% of the strains had been cultured from respiratory specimens, 11% from wound swabs and five were blood culture isolates. One isolate from 2005 showed resistance to amoxicillin/clavulanic acid and two strains from 2007 were found to be resistant to doxycycline. Resistance to fluoroquinolones was not observed; (Fig. 4.1.4.1.1).[7] The blood culture isolates showed no resistance to amoxicillin/clavulanic acid, doxycycline or fluoroquinolones.

Epidemiological situation of invasive infections in Germany

In 2013, the Consultant Laboratory for *Haemophilus influenzae* was merged with the National Reference Centre (NRZ) for Meningococci and has since then been called NRZ for Meningococci and H. influenzae (NRZMHi). Since 2008, it has been testing isolates from invasive *H. influenzae* infections, which must be reported to the health authorities under Sec. 6 and 7 IfSG, on behalf of the Robert Koch Institute. The findings of the serotyping are transmitted to the competent health authorities. The submission rate of legally recorded *H. influenzae* infections that meet the reference definition of the Robert Koch Institute increased from originally 41% in 2008 to 77% in 2014 (SurvStat@ RKI, data as of 10/06/2015).

During the study period 2009-2014, non-encapsulated, so-called non-typable *H. influenzae* (NTHi) constituted the majority of the tested invasive isolates (altogether 81%). The most common capsular type was serotype f (12%), whereas serotype b *H. influenzae* (Hib), which had been the most common type before the vaccination was introduced, was only detected in 4% of the isolates.

In 2014, 75 (21%) of the total of 349 invasive isolates tested were found to exhibit phenotypic resistance to ampicillin, 54 (15%) of which were confirmed to produce β-lactamase. 21 isolates (6%) were assumed to be BLNAR. During the period 2009-2012, the overall prevalence of ampicillin-resistant invasive isolates was constant, with the prevalence of BLNAR being comparatively low.[8]

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 aminopenicillin and a β-lactamase inhibitor is recommended. In case of invasive infections, isolates with β-lactamase-negative ampicillin resistance are also commonly detected. Ceftriaxone and cefotaxime continue to be the first-line antimicrobials used for the treatment of meningitis.

➤ M. Kresken, B. Körber-Irrgang, U. Vogel, T.T. Lâm
Reviewer: R. Berner, E. Straube

1. Vogel U, Elias J, Claus H. Invasive Erkrankungen durch *Haemophilus influenzae* im Jahr 2008. Robert Koch-Institut. Epid Bull 2009(35),357-8.
2. Welte T, Köhnlein T. Global and local epidemiology of community-acquired pneumonia: the experience of the CAPNETZ Network. Semin Respir Crit Care Med 2009;30:127–35.
3. Tomic V, Dowzicky MJ. Regional and global antimicrobial susceptibility among isolates of *Streptococcus pneumoniae* and *Haemophilus influenzae* collected as part of the Tigecycline Evaluation and Surveillance Trial (T.E.S.T.) from 2009 to 2012 and comparison with previous years of T.E.S.T. (2004-2008). Ann Clin Microbiol Antimicrob 2014;13:52.
4. Kresken M, Hafner D, Körber-Irrgang B für die Studiengruppe. Resistenzsituation bei klinisch wichtigen Infektionserregern aus dem ambulanten Versorgungsbereich gegenüber Antibiotika. Bericht über die Ergebnisse einer multizentrischen Studie der Paul-Ehrlich-Gesellschaft für Chemotherapie e.V. aus dem Jahre 2013. Antiinfectives Intelligence, Rheinbach, 2016. Verfügbar unter http://www.p-e-g.org/econtext/Berichte%20 der%20 Studien.
5. Kresken M, Hafner D, Körber-Irrgang B für die Studiengruppe. Resistenzsituation bei klinisch wichtigen Infektionserregern aus dem ambulanten Versorgungsbereich gegenüber Antibiotika. Bericht über die Ergebnisse einer multizentrischen Studie der Paul-Ehrlich-Gesellschaft für Chemotherapie e.V. aus dem Jahre 2010. Antiinfectives Intelligence, Rheinbach, 2013. Verfügbar unter http://www.p-e-g.org/econtext/Berichte%20 der%20 Studien.
6. Kresken M, Brauers J, Körber-Irrgang B. Resistance among isolates of *Haemophilus influenzae* to orally administered β-lactams and fluoroquinolones: results of an nationwide surveillance study in Germany, winter 2007. 18th European Congress of Clinical Microbiology and Infectious Diseases, Barcelona, April 2008, Poster 2054. Clin Microbiol Infect 2008;13:604–5.
7. Kresken M, Becker K, Seifert H, Leitner E, et al. Resistance trends and in vitro activity of tigecycline and 17 other antimicrobial agents against Gram-positive and Gram-negative organisms, including multidrug-resistant pathogens, in Germany. Eur J Clin Microbiol Infect Dis 2011;30:1095–103.
8. Lâm TT, Claus H, Elias J, Frosch M, et al. Ampicillin resistance of invasive *Haemophilus influenzae* isolates in Germany 2009-2012. Int J Med Microbiol 2015;305:748-55.

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 – in very rare cases – 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, most cefuroxime (second-generation/group 2) MIC values are in the intermediate range. By contrast, cefixime (third-generation/group 3) and macrolides as well as co-trimoxazole, doxycycline and the fluoroquinolones ciprofloxacin, levofloxacin and moxifloxacin prove effective.

Trends in resistance development

As part of the 2013 PEG resistance study, 242 pathogen isolates, which had been collected from October to December in 25 laboratories across Germany, were tested for antimicrobial susceptibility. More than 96% of the isolates were found to produce β-lactamase, all of which were, however, 100% susceptible to amoxicillin/clavulanic acid as well as to cefixime and cefuroxime (i.v.). Cefpodoxime ($MIC_{50/90}$ 0.5/1 mg/l) showed a lower in vitro activity than cefixime ($MIC_{50/90}$ 0.125/0.25 mg/l). As expected, the MIC values for cefuroxime (oral) were in the intermediate range ($MIC_{50/90}$ 1/2 mg/l). The majority of the isolates were additionally susceptible to macrolides (azithromycin 99%, clarithromycin 95%, erythromycin 95%, roxithromycin 98%) and co-trimoxazole (88%). Isolates resistant to 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 (group 3) cephalosporins (cefixime) as well as newer macrolides in children and doxycycline or fluoroquinolones in adult patients. Because of their capability of selecting ESBL-producing Enterobacteriaceae, however, oral second- and third-generation (group 2 and 3) cephalosporins as well as fluoroquinolones are not suitable for first-line treatment.

➤ M. Kresken, B. Körber-Irrgang
Reviewer: R. Berner, E. Straube

1. Sy MG, Robinson JL. Community-acquired *Moraxella catarrhalis* pneumonia in previously healthy children. Pediatr Pulmonol 2010;45:674-8.
2. Kresken M, Hafner D, Körber-Irrgang B für die Studiengruppe. Resistenzsituation bei klinisch wichtigen Infektionserregern aus dem ambulanten Versorgungsbereich gegenüber Antibiotika. Bericht über die Ergebnisse einer multizentrischen Studie der Paul-Ehrlich-Gesellschaft für Chemotherapie e.V. aus dem Jahre 2013. Antiinfectives Intelligence, Rheinbach, 2016. Verfügbar unter http://www.p-e-g.org/econtext/Berichte%20der%20Studien.
3. Khan MA, Northwood JB, Levy F, Verhaegh SJ, et al. *bro* β-lactamase and antibiotic resistances in a global cross-sectional study of *Moraxella catarrhalis* from children and adults. J Antimicrob Chemother 2010;65:91-7.

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* strains with special virulence determinants may cause ventilator-associated pneumonia and bloodstream infections, less commonly community-acquired pneumonia. Strains causing bloodstream infections (SEPEC), which can also be acquired through ventilator-associated pneumonia, but more commonly through urinary tract infections, 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 continuously from approx. 35% to nearly 60%. In 2013, the percentage then dropped to 50.8% for the first time. 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 was observed to decline to 29% after 2007 (Fig. 4.1.5.1.1).[2,3]

The susceptibility to ciprofloxacin was analysed to evaluate the development of resistance to fluoroquinolones. Over the period 1995-2010, 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 rate then dropped to 24.7% in 2013. The difference in the dynamics of resistance development 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 > 60 years increased by approx. 20%, whereas the resistance level of isolates from patients aged < 21 years barely changed. After this period, the prevalence of resistance increased slightly in isolates from older patients and strongly in those from adolescent patients. The highest resistance level was reached in 2010, amounting to nearly 20% in patients aged < 21 years and to more than 30% in both patients aged 21-60 years and those aged > 60 years. Subsequently, the resistance rate in patients aged < 21 years dropped by nearly 18% to reach the 1995 level (< 2%), whereas a reduction in resistance rates of approx. 10% and 5% was observed in patients aged 21-60 years and in patients aged > 60 years, respectively. 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.

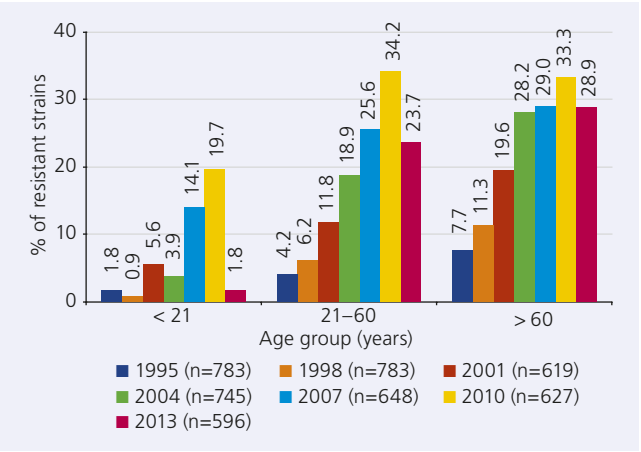


Fig. 4.1.5.1.2: Percentage of ciprofloxacin-resistant *E. coli* strains from hospital care itemised by age of patients, 1995-2013 (Source: PEG resistance study)

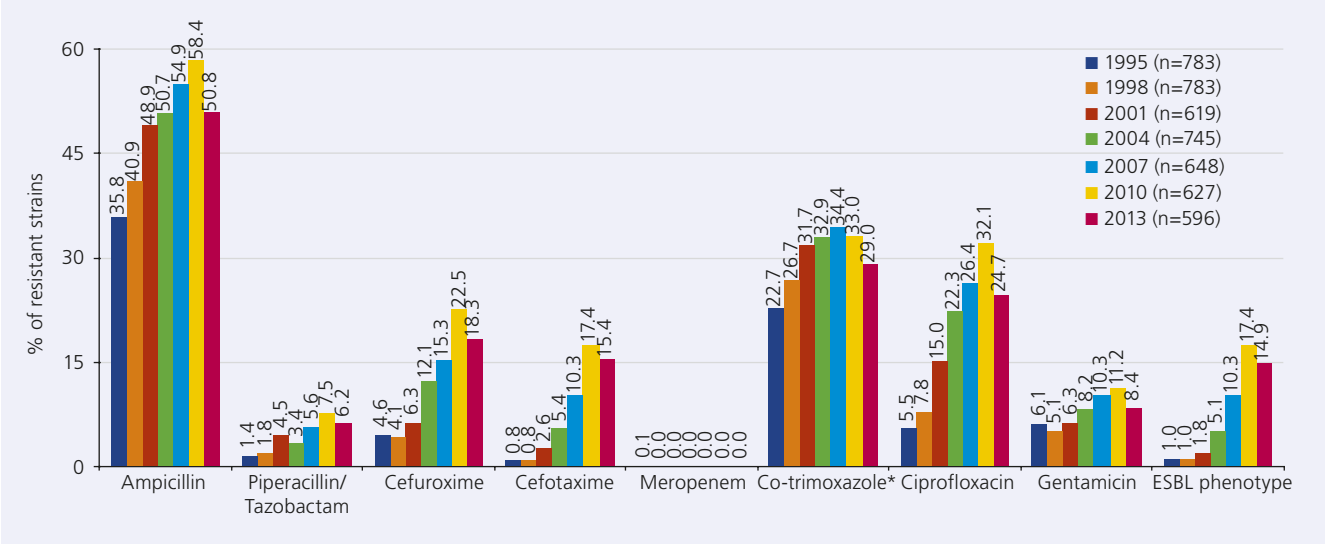


Fig. 4.1.5.1.1: Percentage of resistant *E. coli* strains from hospital care, 1995-2013 (Source: PEG resistance study)
*Trimethoprim/Sulfamethoxazole

The initial strong change in the fluoroquinolone resistance rates in isolates from patients aged < 21 years is most likely attributable to the varying prevalence 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 were also increasingly detected in adolescent patients in 2007 and 2010.

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]

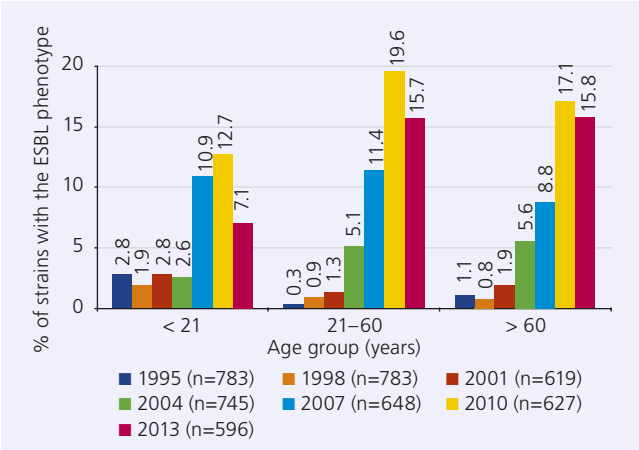


Fig. 4.1.5.1.3: Percentage of *E. coli* strains with the ESBL phenotype from hospital care itemised by age of patients, 1995-2013 (Source: PEG resistance study)

Between 1995 and 2010, the percentage of strains with an ESBL phenotype in all *E. coli* isolates from the hospital sector was observed to increase steadily (from 1% to 17.4%) (Fig. 4.1.5.1.1). At the same time, the prevalence of resistance to cefuroxime and cefotaxime increased from < 5% to 22.5% and from < 1% to 17.4%, respectively. In the 2013 study year, the percentage of strains with an ESBL phenotype dropped for the first time (14.9%). Simultaneously, the rate of resistance to cefuroxime and cefotaxime dropped to 18.3% and 15.4%, respectively. Over the entire study period, carbapenems (e.g. meropenem) showed high susceptibility rates of more than 99%. By contrast, the prevalence of resistance to the combination of piperacillin/tazobactam rose from 1.4% in 1995 to 7.5% in 2010, most recently amounting to 6.2%, whereas the prevalence of resistance to gentamicin increased from 6.1% to 11.2%, ranging at 8.4% at the end of the study period. The development of 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), the percentage of strains resistant to all five substances was initially observed to decrease steadily from 56.4% in 1995 to 37.5% in 2010. In the last study year, the percentage again rose to 43.1%. Conversely, the percentage of strains resistant to three or more antimicrobial agents initially increased from 7.0% (1995) to 29.5% (2010) and then dropped again to 22.7%. The percentage of strains resistant to all five antimicrobials was initially 0.4%, reached 5.3% in 2010, ranging at 3.4% in 2013 (Fig. 4.1.5.1.4). The percentage of 3MRGN multidrug-resistant strains, as defined by the KRINKO[5], in all isolates increased from 0.6% in 1995 to 14.5% in 2010 and then decreased to 10.9% in 2013. In 2013, no strain was classified as 4MRGN.

Colistin, fosfomycin and tigecycline constitute possible alternatives for the treatment of infections caused by multidrug-resistant *E. coli*. The percentage of *E. coli* isolates resistant to fosfomycin was 1.8% in 2013. One isolate was found to be resistant to colistin, with the transferable gene *mcr-1* being detected as the resistance gene. The testing of isolates with an ESBL phenotype for susceptibility to tigecycline revealed that all tested isolates were susceptible.

The 2010 and 2013 PEG resistance studies also investigated the antimicrobial resistance situation of clinically relevant bacterial species in ambulatory care (outpatients). Nearly 500 *E. coli* urine isolates were tested in each study. The prevalence of resistance to the tested antimicrobials varied between 0.8% and 1% for nitrofurantoin and was approx. 43% for amoxicillin (Fig. 4.1.5.1.5). The rate of isolates with the ESBL phenotype was 8% in 2010 and dropped to 4.7% in 2013. At the same time, the prevalence

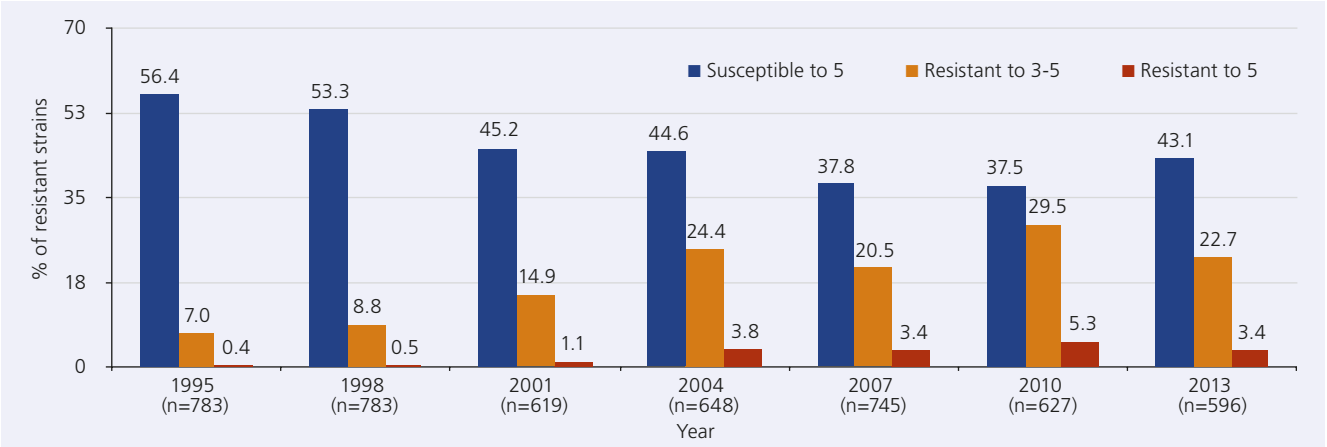


Fig. 4.1.5.1.4: Percentage of susceptible *E. coli* strains and those resistant to at least three or five antimicrobial agents of various antimicrobial classes* from hospital care, 1995-2013 (Source: PEG resistance study)
*Ampicillin (penicillins), cefuroxime (cephalosporins), ciprofloxacin (fluoroquinolones), co-trimoxazole (trimethoprim/sulfamethoxazole), gentamicin (aminoglycosides) were taken into account

of resistance to not only the broad-spectrum oral cephalosporins of the second (cefuroxime) and the third generation (cefixime, cefpodoxime) but also fluoroquinolones and co-trimoxazole decreased.[6,7]

Antimicrobial Resistance Surveillance System (ARS)

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.[8]

Under these circumstances, the resistance situation for 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; 2014 data).

As already demonstrated in the 2008 GERMAP report, the resistance situation may vary greatly between hospitals and regions.[9] 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 antimicrobial resistance is just as widespread in *E. coli* isolates from patients at primary-care hospitals as it is in isolates from patients at secondary- and tertiary-care hospitals (Fig. 4.1.5.1.7; 2014 data).

By contrast, the data from outpatient care reveals some significant differences in resistance rates between isolates from patients in various care sectors (Fig. 4.1.5.1.8; 2014 data). It is remarkable to see that isolates resistant to certain antimicrobials (ampicillin, co-trimoxazole, ciprofloxacin, gentamicin) are found in patients treated in specialist outpatient general/internal and urology clinics just as often as in patients on general hospital wards. This also includes first-line antimicrobials recommended for the empiric parenteral initial treatment of nosocomial infections (e.g. second- and third-generation (group 2 and 3) cephalosporins, piperacillin/tazobactam, fluoroquinolones).

Surveillance of Antimicrobial Use and Bacterial Resistance in Intensive Care Units (SARI)

The number of bacterial strains isolated from patients in the participating intensive care units during the period 2000-2014 was 248,138[10], 42,159 of which were *E. coli* isolates. Even if the presence of copy strains cannot be ruled out completely, the results of the SARI study are significant. The rate of resistance to fluoroquinolones (ciprofloxacin) increased from 7.4% in 2000 to

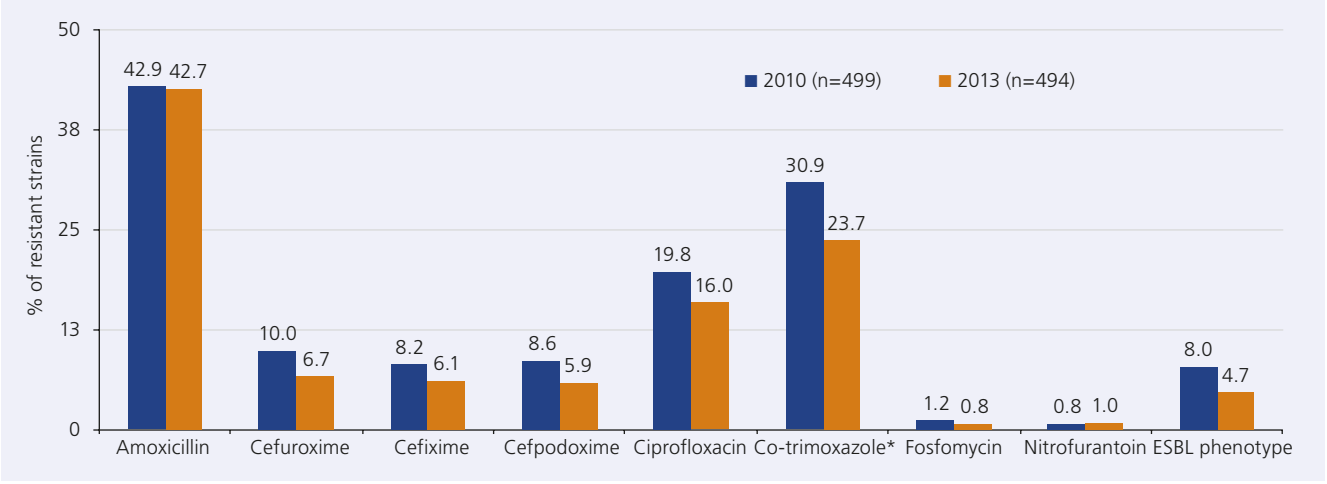


Fig. 4.1.5.1.5: Percentage of resistant *E. coli* urine isolates from outpatient care, 2010 and 2013 (Source: PEG resistance study)
*Trimethoprim/Sulfamethoxazole

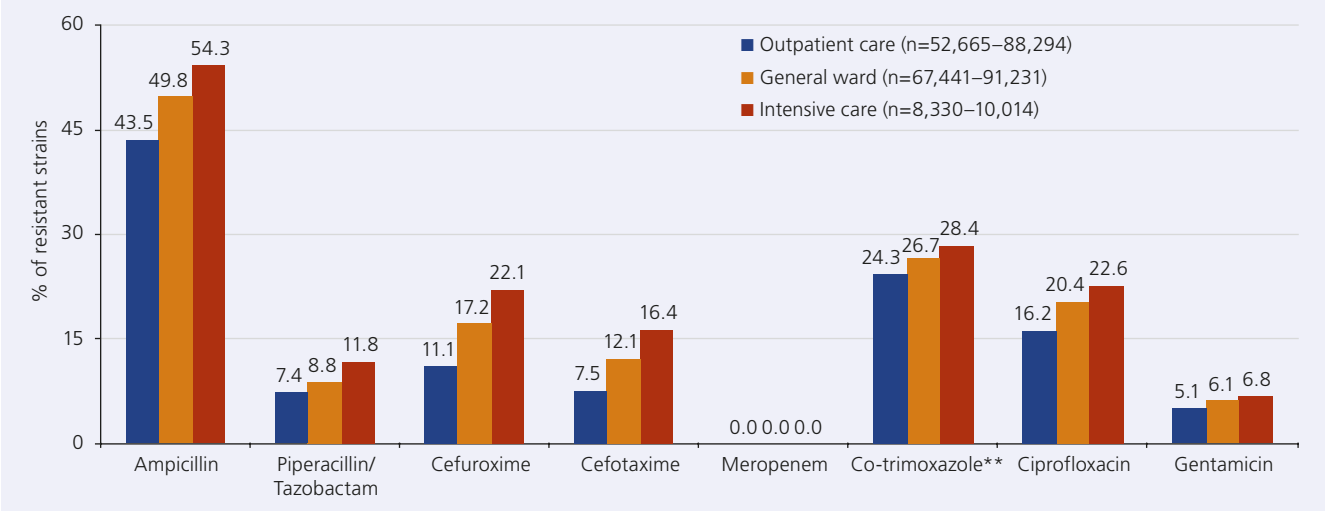


Fig. 4.1.5.1.6: Percentage of resistant *E. coli* strains from outpatient care, on general wards and in intensive care units (Source: ARS, 2014 data*)
*Data as of: 01/07/2015; ** Trimethoprim/Sulfamethoxazole

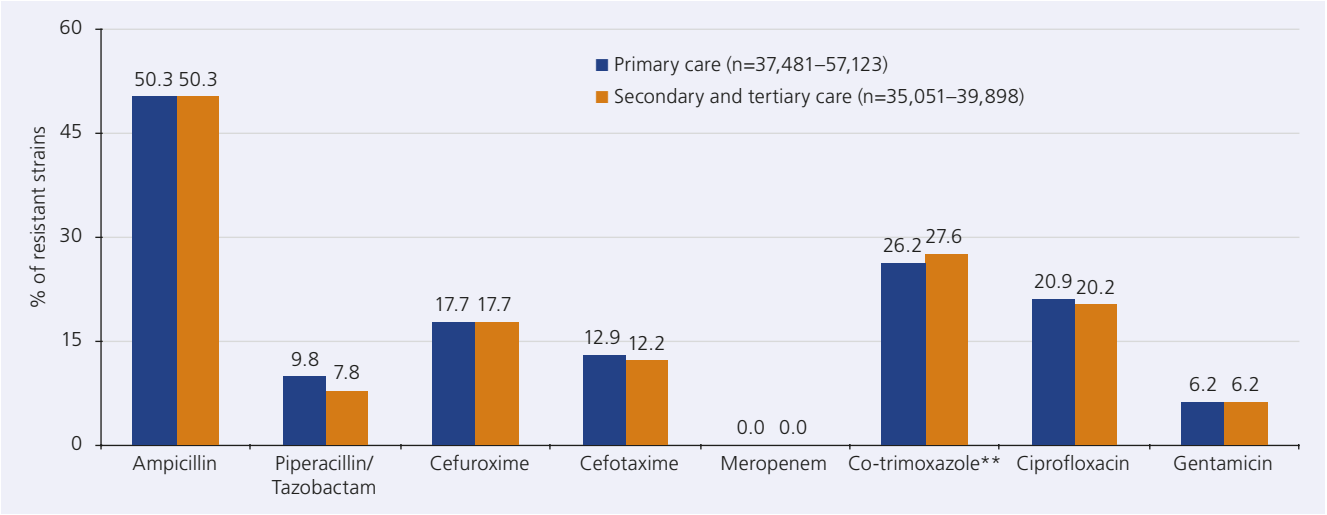


Fig. 4.1.5.1.7: Percentage of resistant *E. coli* strains from hospitals of various levels of care (Source: ARS, 2014 data*)
*Data as of: 01/07/2015; ** Trimethoprim/Sulfamethoxazole

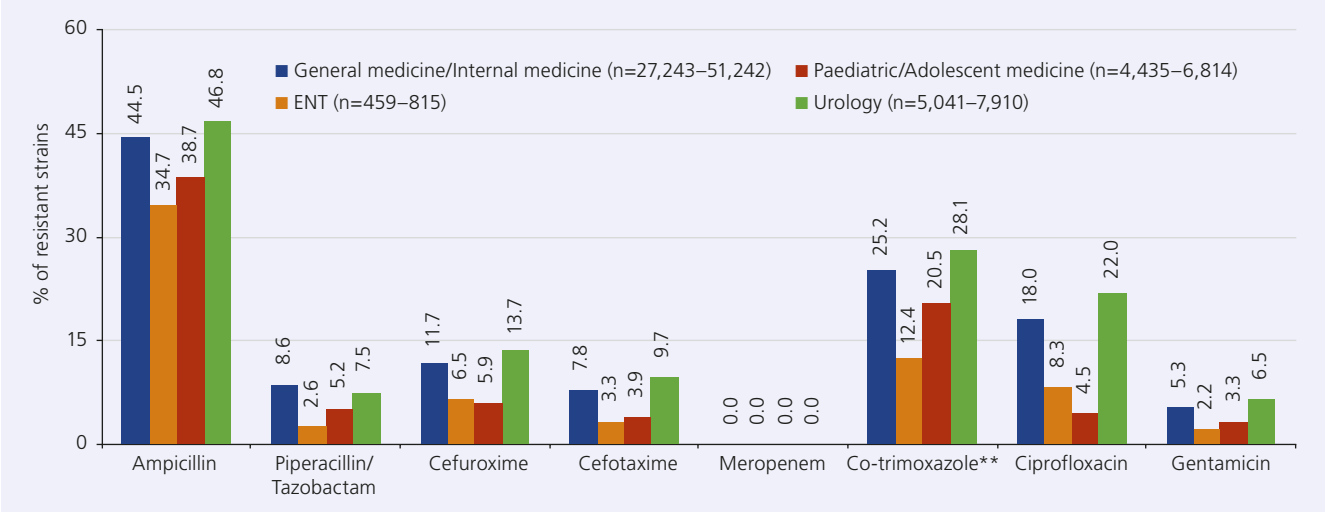


Fig. 4.1.5.1.8: Percentage of resistant *E. coli* strains in various specialities of outpatient care (Source: ARS, 2014 data*)
*Data as of: 01/07/2015; ** Trimethoprim/Sulfamethoxazole

27.8% in 2011 and remained almost constant after this period. In 2014, the percentage of fluoroquinolone-resistant strains was 25.5%. The prevalence of resistance to third-generation (group 3) cephalosporins rose from 1.3% in 2000 to 17% in 2011, ranging at 17.6% in 2014.[10]

The incidence density of isolates resistant to third-generation (group 3) cephalosporins increased on average (mean value) from 0.16 per 1,000 patient days in 2001 to 1.39 in 2008[11], with another increase to 2.6% being observed in 2011.[12] In 2014, the rate already ranged well above 3 per 1,000 patient days.[10] The increase in the rates of resistance to fluoroquinolones and third-generation (group 3) cephalosporins led to a significant increase in the use density of carbapenems between 2001 and 2012. After this period, however, consumption did not increase further and was even observed to decrease in 2014.[10] The percentage of isolates resistant to carbapenems (imipenem) was below 1% during the entire study period.[10]

European Antimicrobial Resistance Surveillance Network (EARS-Net)

During the period 2003-2014, the resistance data of 850 to 6,251 blood culture isolates was reported each year by 12-22 participating German laboratories.[13] The rate of aminopenicillin resistance was 47% at the beginning and 52% at the end of the study period. The highest rate observed was 60% (in 2006). The rate of fluoroquinolone resistance initially rose from 14% to 30% (in 2007), ranged between 23% and 25% in the following four years and was 21% at the end of the study period. The percentage of strains resistant to third-generation (group 3) cephalosporins initially increased from < 1% in 2003 to 8% in 2007, then remained almost constant until 2011 and subsequently rose to 11% in 2014. Until 2007, the prevalence of resistance to aminoglycosides was 4-6% throughout the entire study period; in 2006, however, a resistance rate of 10% was recorded. After 2007, the rate ranged between 7% and 9%.[13] The rate of carbapenem resistance did not exceed 0.7% in any of the study years.

German Tigecycline Evaluation Surveillance Trial (G-TEST)

The study ended in 2009. The rates of resistance ascertained in 2005, 2007 and 2009 were presented in the 2012 GERMAP report.[14]

Remarks

The results of the PEG resistance study and the data provided by ARS may only allow for a rough estimation of the resistance level of *E. coli* in outpatient care, because a disproportionately large number of specimens submitted to microbiology laboratories are obtained from patients with risk factors for carriage of resistant pathogens, for example from patients who have undergone antimicrobial treatment before.[15]

In view of this, the results of the ARESC study on the resistance situation of *E. coli* isolates from patients with acute uncomplicated cystisis are interesting. Less than 5% of the 243 strains isolated in Germany from September 2003 to June 2006, showed resistance to amoxicillin/clavulanic acid, cefuroxime, ciprofloxacin, fosfomycin or nitrofurantoin. The percentage of isolates resistant to cefuroxime or fosfomycin was even below 1%, whereas the rates of resistance to ampicillin and co-trimoxazole were 34.9% and 25.9%, respectively.[16,17]

ESBL-producing *E. coli*

Nearly all epidemiological studies conducted in recent years reveal an increase in the prevalence of ESBL-producing isolates in Germany. In the 2013 PEG resistance study, however, the ESBL rate was observed to decrease in both outpatient and inpatient isolates (see above).[3,7]

Molecular characterisation of a total of 198 strains with an ESBL phenotype isolated from inpatients as part of the 2010 and 2013 PEG resistance studies demonstrated that more than 90% of the strains produce a CTX-M ESBL (Fig. 4.1.5.1.9). In both study years, the CTX-M-15 enzyme was detected most frequently (50%), followed by CTX-M-1 (approx. 24%) and CTX-M-14 (7-9%). A similar distribution pattern was observed for the total of 63 outpatient urine isolates with an ESBL phenotype (Fig. 4.1.5.1.10).

Accounting for more than 50%, CTX-M-15 was also the predominant ESBL variant in numerous other studies on human *E. coli* isolates from hospitals, outpatient care, nursing homes and the general population.[18,19,20] Especially in inpatient and outpatient care, but also in nursing homes, the prevalence of CTX-M-15 is closely associated with the pandemic spread of the clone O25b-ST131, the proportion of which is > 30% of all ESBL-positive *E. coli* in the studies.[18,19,21,22] Whereas *E. coli* ST131 has only been sporadically detected in animals, the CTX-M-15-producing clone *E. coli* ST410 is found in both humans and livestock. Initial evidence of the transmission of the clone *E. coli* ST410 between humans and animals has recently been provided by whole genome analyses.[18,23,24]

Unlike CTX-M-15-producing strains, CTX-M-1-producing strains are also often isolated from veterinary specimens and detected in food.[25,26] 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.[27,28] The results of the study suggest that ESBL-producing *E. coli* can be transmitted from poultry to humans. However, to what extent CTX-M-1-producing clones or $bla_{CTX\text{-}M\text{-}}$

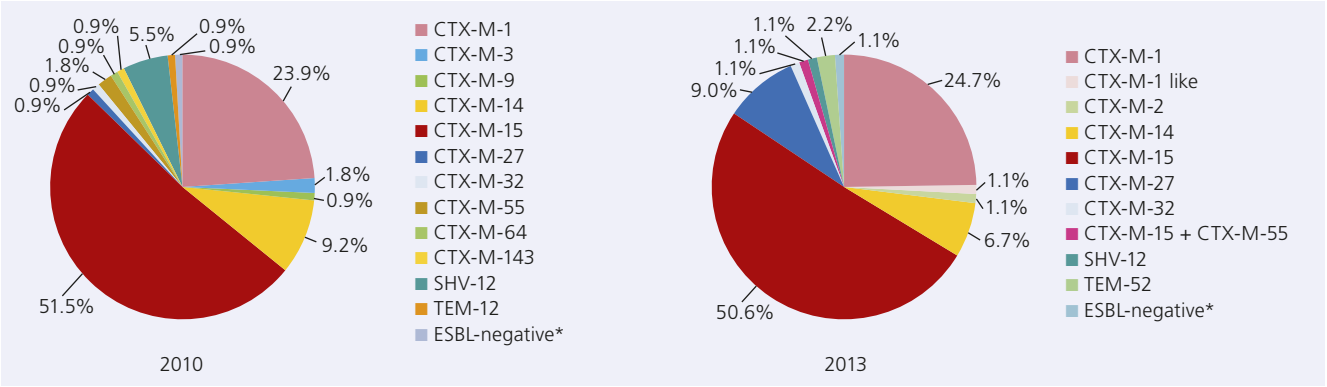


Fig. 4.1.5.1.9: Percentage of ESBL variants of *E. coli* isolates with the ESBL phenotype from hospital care, 2010 (n=109) and 2013 (n=89).
(Source: PEG resistance study)
*No CTX-M, SHV or TEM ESBL according to the Bush classification was detected.

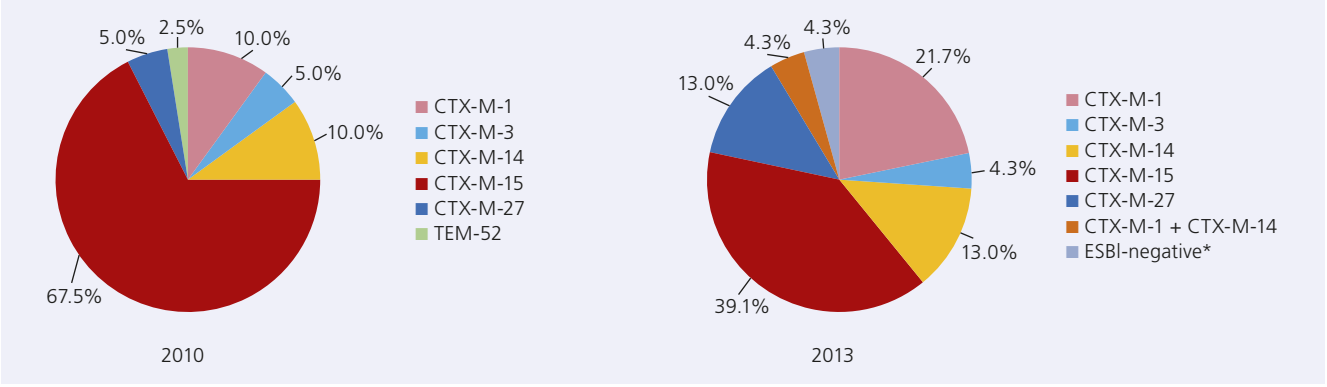


Fig. 4.1.5.1.10: Percentage of ESBL variants of *E. coli* isolates with the ESBL phenotype from outpatient care, 2010 (n=40) and 2013 (n=23).
(Source: PEG resistance study)
*No CTX-M, SHV or TEM ESBL according to the Bush classification was detected .

$_1$-carrying plasmids are transmitted from animals or animal products to humans has so far been unknown. In the future, extensive whole genome analyses will make it possible to more accurately determine the routes of transmission of ESBL-producing *E. coli*.

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 2014, the NRZ performed molecular characterisation of the carbapenemase types of 177 *E. coli* isolates.[29] In most cases, OXA-48 carbapenemases were detected (n=56), followed by KPC-2 (n=39, thereof 29 in the postcode area 6), VIM-1 (n=20), OXA-181 (n=16) and NDM-1 (n=9). In 2014, the number of KPC-2-producing *E. coli* was high compared to other years, which is attributed to an outbreak at a single location where KPC-2 plasmids were detected in several species.

Conclusion

According to the results of the PEG resistance study, the prevalence of resistance to antimicrobial classes widely used at hospitals (broad-spectrum penicillins, cephalosporins, fluoroquinolones) in isolates from the hospital sector was not observed to rise further in 2013 after 15 years of continuous increase. By contrast, the prevalence of carbapenem resistance never exceeded 0.1%.

Despite the decline in the resistance level to approx. 25%, fluoroquinolones are still only recommended to a limited extent 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 stabilise or even decrease in the long term, the carbapenem consumption could be reduced further in the next few years. The SARI network already reports a decrease in the use density of carbapenems in intensive care units for 2014.[10] The reduced consumption is also expected to reduce the risk of emergence and spread of carbapenem-resistant *E. coli* strains.

Except for outpatient general/internal and urology clinics, the resistance level in outpatient care is significantly lower than in inpatient care, although ESBL-producing and/or fluoroquinolone-resistant *E. coli* are widespread. Isolates from patients in outpatient general/internal and 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 internal and urological diseases, who are predisposed to recurrent 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 acquiring resistant pathogens. The example also points to the fundamental problem of interpreting outpatient resistance data, because 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 such laboratory statistics.[15]

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], the resistance situation also worsened in this patient group in the first half of the last decade, 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%.[30] A more careful use of antimicrobials is therefore also urgently needed in the outpatient sector in order to avoid the selection of (multidrug-)-resistant *E. coli*.

Fortunately, the rate of colistin-resistant *E. coli* has so far been very low. Since strains with a plasmid-mediated resistance mechanism to colistin have now been reported – also in Germany – for the first time, it is essential to monitor colistin resistance and especially the new mechanism MCR-1 to be able to recognise increasing rates of resistance to this second-line antimicrobial.[31,32]

The decline in the rates of resistance to cephalosporins and fluoroquinolones observed in the PEG resistance study between 2010 and 2013 was not observed in other surveillance studies, which is why further efforts in the form of rational antimicrobial use and prevention of transmission are required to reduce the prevalence of resistance to these two therapeutically relevant antimicrobial classes.

➤ M. Kresken, B. Körber-Irrgang, M. Kaase, Y. Pfeifer
Reviewer: E. Straube

1. Becker A, Rosenthal JK, Studiengruppe. Antibiotika-Empfindlichkeit von Sepsis-Erregern 2006-2007. Vierte Blutkulturstudie der Arbeitsgemeinschaft „Blutkulturstudie" der Paul-Ehrlich-Gesellschaft für Chemotherapie e.V. Chemother J 2010;19:28-39.
2. Kresken M, Hafner D, Körber-Irrgang B für die Studiengruppe. Epidemiologie und Resistenzsituation bei klinisch wichtigen Infektionserregern aus dem Hospitalbereich gegenüber Antibiotika. Bericht über die Ergebnisse einer multizentrischen Studie der Paul-Ehrlich-Gesellschaft für Chemotherapie e.V. aus dem Jahre 2010. Antiinfectives Intelligence, Rheinbach, 2013. Verfügbar unter http://www.p-e-g.org/econtext/Berichte%20der%20Studien.
3. Kresken M, Hafner D, Körber-Irrgang B für die Studiengruppe. Epidemiologie und Resistenzsituation bei klinisch wichtigen Infektionserregern aus dem Hospitalbereich gegenüber Antibiotika. Bericht über die Ergebnisse einer multizentrischen Studie der Paul-Ehrlich-Gesellschaft für Chemotherapie e.V. aus dem Jahre 2013. Antiinfectives Intelligence, Rheinbach, 2016. Verfügbar unter http://www.p-e-g.org/econtext/Berichte%20der%20Studien.
4. Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility testing; Twenty Second Informational Supplement, M100-S25, Wayne, PA, 2015.
5. Empfehlung der Kommission für Krankenhaushygiene und Infektionsprävention (KRINKO) beim Robert Koch-Institut (RKI). Hygienemaßnahmen bei Infektionen oder Besiedlung mit multiresistenten gramnegativen Stäbchen. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2012;55:1311-54.
6. Kresken M, Hafner D, Körber-Irrgang B für die Studiengruppe. Resistenzsituation bei klinisch wichtigen Infektionserregern aus dem ambulanten Versorgungsbereich gegenüber Antibiotika. Bericht über die Ergebnisse einer multizentrischen Studie der Paul-Ehrlich-Gesellschaft für Chemotherapie e.V. aus dem Jahre 2010. Antiinfectives Intelligence, Rheinbach, 2013. Verfügbar unter http://www.p-e-g.org/econtext/Berichte%20der%20Studien.

7. Kresken M, Hafner D, Körber-Irrgang B für die Studiengruppe. Resistenzsituation bei klinisch wichtigen Infektionserregern aus dem ambulanten Versorgungsbereich gegenüber Antibiotika. Bericht über die Ergebnisse einer multizentrischen Studie der Paul-Ehrlich-Gesellschaft für Chemotherapie e.V. aus dem Jahre 2013. Antiinfectives Intelligence, Rheinbach, 2016. Verfügbar unter http://www.p-e-g.org/econtext/Berichte%20der%20Studien.
8. ARS - Antibiotika-Resistenz-Surveillance in Deutschland. Verfügbar unter https://ars.rki.de.
9. GERMAP 2008. Bericht über den Antibiotikaverbrauch und die Verbreitung von Antibiotikaresistenzen in der Human- und Veterinärmedizin. Antiinfectives Intelligence, Rheinbach, 2008. Verfügbar unter http://www.p-e-g.de/econtext/germap.
10. SARI – Surveillance der Antibiotika-Anwendung und der bakteriellen Resistenzen auf Intensivstationen. Verfügbar unter http://sari.eu-burden.info/.
11. Meyer E, Schwab F, Schroeren-Boersch B, Gastmeier P. Dramatic increase of third-generation cephalosporin-resistant *E. coli* in German intensive care units: secular trends in antibiotic drug use and bacterial resistance, 2001 to 2008. Crit Care 2010;14:R113.
12. Meyer E, Gastmeier P, Deja M, Schwab F. Antibiotic consumption and resistance: data from Europe and Germany. Int J Med Microbiol 2013;303:388-95.
13. European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2014. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net).Stockholm: ECDC; 2015. http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-europe-2014.pdf.
14. GERMAP 2012. Bericht über den Antibiotikaverbrauch und die Verbreitung von Antibiotikaresistenzen in der Human- und Veterinärmedizin. Antiinfectives Intelligence, Rheinbach, 2014. Verfügbar unter http://www.p-e-g.de/econtext/germap.
15. Kronenberg A, Koenig S, Droz S, Mühlemann K. Active surveillance of antibiotic resistance prevalence in urinary tract and skin infections in the outpatient setting. Clin Microbiol Infect 2011;17:1845-51.
16. Schito GC, Naber KG, Botto H, Palou J, et al. The ARESC study: an international survey on the antimicrobial resistance of pathogens involved in uncomplicated urinary tract infections. Int J Antimicrob Agents 2009;34:407-13.
17. Cagnacci S, Gualco L, Debbia E, Schito GC, et al. European emergence of ciprofloxacin-resistant *Escherichia coli* clonal groups O25:H4-ST131 and O15:K52:H1 causing community-acquired uncomplicated cystitis. J Clin Microbiol 2008;46:2605-12.
18. Pietsch M, Eller C, Wendt C, Holfelder M, et al. Molecular characterisation of extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* isolates from hospital and ambulatory patients in Germany. Vet Microbiol 2015 Nov 24. pii: S0378-1135(15)30097-3. doi: 10.1016/j.vetmic.2015.11.028. [Epub ahead of print] PMID: 26654217.
19. Valenza G, Nickel S, Pfeifer Y, Pietsch M, et al. Prevalence and genetic diversity of extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* in nursing homes in Bavaria, Germany. Vet Microbiol 2015 Oct 19. pii: S0378-1135(15)30048-1. doi: 10.1016/j.vetmic.2015.10.008. [Epub ahead of print] PMID: 26494113.
20. Valenza G, Nickel S, Pfeifer Y, Eller C, et al. Extended-spectrum-β-lactamase-producing *Escherichia coli* as intestinal colonizers in the German community. Antimicrob Agents Chemother 2014;58:1228-30.
21. Rogers BA, Sidjabat HE, Paterson DL. *Escherichia coli* O25b-ST131: a pandemic, multiresistant, community-associated strain. J Antimicrob Chemother 2011;66:1-14.
22. Arvand M, Moser V, Pfeifer Y. Prevalence of extended-spectrum-β-lactamase-producing *Escherichia coli* and spread of the epidemic clonal lineage ST131 in nursing homes in Hesse, Germany. J Antimicrob Chemother 2013;68:2686-8.
23. Fischer J, Rodríguez I, Baumann B, Guiral E, et al. $bla_{CTX-M-15}$-carrying *Escherichia coli* and *Salmonella* isolates from livestock and food in Germany. J Antimicrob Chemother 2014;69:2951-8.
24. Schaufler K, Semmler T, Wieler LH, Wöhrmann M, et al. Clonal spread and interspecies transmission of clinically relevant ESBL-producing *Escherichia coli* of ST410 – another successful pandemic clone? FEMS Microbiol Ecol 2016;92(1).
25. Valentin L, Sharp H, Hille K, Seibt U, et al. Subgrouping of ESBL-producing *Escherichia coli* from animal and human sources: an approach to quantify the distribution of ESBL types between different reservoirs. Int J Med Microbiol 2014;304:805-16.
26. Kola A, Kohler C, Pfeifer Y, Schwab F, et al. High prevalence of extended-spectrum-β-lactamase-producing Enterobacteriaceae in organic and conventional retail chicken meat, Germany. J Antimicrob Chemother 2012;67:2631-4.
27. Overdevest I, Willemsen I, Rijnsburger M, Eustace A, et al. Extended-spectrum β-lactamase genes of *Escherichia coli* in chicken meat and humans, the Netherlands. Emerg Infect Dis 2011;17:1216-21.
28. Kluytmans JA, Overdevest IT, Willemsen I, Kluytmans-van den Bergh MF, et al. Extended-spectrum β-lactamase-producing *Escherichia coli* from retail chicken meat and humans: comparison of strains, plasmids, resistance genes, and virulence factors. Clin Infect Dis 2013;56:478-87.
29. Robert Koch-Institut. Bericht des Nationalen Referenzzentrums (NRZ) für gramnegative Krankenhauserreger - Zeitraum 1. Januar 2014 bis 31. Dezember 2014. Epid Bull 2016(2),11-4.
30. Kahlmeter G, Poulsen HO. Antimicrobial susceptibility of *Escherichia coli* from community-acquired urinary tract infections in Europe: the ECO·SENS study revisited. Int J Antimicrob Agents 2012;39:45-51.
31. Liu YY, Wang Y, Walsh TR, Yi LX, et al. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. Lancet Infect Dis 2016;16:161-8.
32. Falgenhauer L, Waezsada SE, Yao Y, Imirzalioglu C, et al. Colistin resistance gene *mcr-1* in extended-spectrum β-lactamase-producing and carbapenemase-producing Gram-negative bacteria in Germany. Lancet Infect Dis 2016;16:282-3.

ESBL prevalence in Africa and Asia – a selective literature search regarding recently published colonisation and infection rates

In addition to the published data from industrialised countries, an increasing amount of data on the epidemiology of resistant Gram-negative bacteria in Africa[1,2] and Asia has now been available. Among Gram-negative bacteria, extended-spectrum beta-lactamase (ESBL)-producing bacteria are of particular clinical and hygienic significance. They frequently affect *Escherichia coli* and *Klebsiella pneumoniae*, i.e. Gram-negative bacteria that are typically pathogenic in humans. Since co-resistance to antimicrobials such as quinolones, co-trimoxazole and aminoglycosides is present in many cases, the antimicrobial treatment options are often limited. In some African countries, the relatively new spread of carbapenemase-producing bacteria has become a relevant clinical threat. Individual and short series of cases have now also been reported for this continent, while the development and spread of carbapenemases in Asia has been a cause of concern for many years. However, the spread of carbapenemases cannot be shown here.

The two tables below show the results of a selective and comprehensive literature search. In each case, the most recently published and PubMed-listed data (as of 1 May 2015) on colonisation and infection with ESBL producers was evaluated. The evaluation included only data that did not originate from clusters or outbreak events and did not concern imported infections or colonisations. An increasing amount of more reliable prevalence data has now been available for both Africa and Asia. The countries were categorised based on the classification of the United Nations (UN).

However, it must be noted that both the quality and the representativeness of the available studies cannot be fully evaluated in many cases and therefore must be critically examined. In most countries, no national surveillance data is available, but only selective regional studies; for some countries, no data is available at all. Moreover, there is no sufficient information available to evaluate the microbiological standards in the individual countries, i.e. the technical resources and the related validation processes used for reproducible in-vitro susceptibility testing and molecular or phenotypic characterisation of resistance mechanisms are unknown.

➤ A. Mischnik, I. Bekeredjian-Ding, F. Schaumburg, C. Lübbert
Reviewer: W.V. Kern, Y. Pfeifer

1. Manenzhe RI, Zar HJ, Nicol MP, Kaba M. The spread of carbapenemase-producing bacteria in Africa: a systematic review. J Antimicrob Chemother 2015;70:23-40.
2. Tansarli GS, Poulikakos P, Kapaskelis A, Falagas ME. Proportion of extended-spectrum beta-lactamase (ESBL)-producing isolates among Enterobacteriaceae in Africa: evaluation of the evidence-systematic review. J Antimicrob Chemother 2014;69:1177-84.
3. Bouzenoune F, Boudersa F, Bensaad A, Harkat F, et al. Urinary tract infections in Ain M'lila (Algeria). Antibiotic resistance of 239 strains isolated between 2006 and 2007. Med Mal Infect 2009;39:142-3.
4. Iabadene H, Messai Y, Ammari H, Alouache S, et al. Prevalence of plasmid-mediated AmpC beta-lactamases among Enterobacteriaceae in Algiers hospitals. Int J Antimicrob Agents 2009;34:340-2.
5. Nedjai S, Barguigua A, Djahmi N, Jamali L, et al. Prevalence and characterization of extended spectrum beta-lactamases in *Klebsiella-Enterobacter-Serratia* group bacteria, in Algeria. Med Mal Infect 2012;42:20-9.
6. Metwally L, Gomaa N, Attallah M, Kamel N. High prevalence of *Klebsiella pneumoniae* carbapenemase-mediated resistance in *K. pneumoniae* isolates from Egypt. East Mediterr Health J 2013;19:947-52.
7. Fam N, Leflon-Guibout V, Fouad S, Aboul-Fadl L, et al. CTX-M-15-producing *Escherichia coli* clinical isolates in Cairo (Egypt), including isolates of clonal complex ST10 and clones ST131, ST73, and ST405 in both community and hospital settings. Microb Drug Resist 2011;17:67-73.
8. Saied T, Elkholy A, Hafez SF, Basim H, et al. Antimicrobial resistance in pathogens causing nosocomial bloodstream infections in university hospitals in Egypt. Am J Infect Control 2011;39:61-5.
9. Girlich D, Bouihat N, Poirel L, Benouda A, et al. High rate of faecal carriage of extended-spectrum beta-lactamase and OXA-48 carbapenemase-producing Enterobacteriaceae at a university hospital in Morocco. Clin Microbiol Infect 2014;20:350-4.
10. Zohoun A, Ngoh E, Bajjou T, Sekhsokh Y, et al. Epidemiological features of multidrug resistant bacteria isolated from urine samples at the Mohammed V Military Teaching Hospital in Rabat, Morocco. Med Trop (Mars) 2010;70:412-3.
11. Barguigua A, El Otmani F, Talmi M, Zerouali K, et al. Prevalence and types of extended spectrum beta-lactamases among urinary *Escherichia coli* isolates in Moroccan community. Microb Pathog 2013;61-62:16-22.
12. Thabet L, Messadi A, Mbarek M, Turki A, et al. Surveillance of multidrug resistant bacteria in a Tunisian hospital. Tunis Med 2008;86:992-5.
13. Ben Haj Khalifa A, Khedher M. Epidemiological study of *Klebsiella* spp. uropathogenic strains producing extended-spectrum beta-lactamase in a Tunisian university hospital, 2009. Pathol Biol (Paris). 2012;60:1-5.
14. Hammami S, Boutiba-Ben Boubaker I, Saidani M, Lakhal E, et al. Characterization and molecular epidemiology of extended spectrum beta-lactamase producing *Enterobacter cloacae* isolated from a Tunisian hospital. Microb Drug Resist 2012;18:59-65.
15. Brink A, Moolman J, da Silva MC, Botha M, National Antibiotic Surveillance Forum. Antimicrobial susceptibility profile of selected bacteraemic pathogens from private institutions in South Africa. S Afr Med J 2007;97:273-9.
16. Habte TM, Dube S, Ismail N, Hoosen AA. Hospital and community isolates of uropathogens at a tertiary hospital in South Africa. S Afr Med J 2009;99:584-7.
17. Brink AJ, Botha RF, Poswa X, Senekal M, et al. Antimicrobial susceptibility of gram-negative pathogens isolated from patients with complicated intra-abdominal infections in South African hospitals (SMART Study 2004-2009): impact of the new carbapenem breakpoints. Surg Infect (Larchmt) 2012;13:43-9.
18. Ahoyo AT, Baba-Moussa L, Anago AE, Avogbe P, et al. Incidence of infections dues to *Escherichia coli* strains producing extended spectrum betalactamase, in the Zou/Collines Hospital Centre (CHDZ/C) in Benin. Med Mal Infect 2007;37:746-52.
19. Obeng-Nkrumah N, Twum-Danso K, Krogfelt KA, Newman MJ. High levels of extended-spectrum beta-lactamases in a major teaching hospital in Ghana: the need for regular monitoring and evaluation of antibiotic resistance. Am J Trop Med Hyg 2013;89:960-4.
20. Isendahl J, Turlej-Rogacka A, Manjuba C, Rodrigues A, et al. Fecal carriage of ESBL-producing *E. coli* and *K. pneumoniae* in children in Guinea-Bissau: a hospital-based cross-sectional study. PLoS One 2012;7:51981.
21. Ahmed SF, Ali MM, Mohamed ZK, Moussa TA, et al. Fecal carriage of extended-spectrum beta-lactamases and AmpC-producing *Escherichia coli* in a Libyan community. Ann Clin Microbiol Antimicrob 2014;13:22.
22. Olowe OA, Grobbel M, Buchter B, Lubke-Becker A, et al. Detection of bla(CTX-M-15) extended-spectrum beta-lactamase genes in *Escherichia coli* from hospital patients in Nigeria. Int J Antimicrob Agents 2010;35:206-7.

Tab. 1: Most recently published ESBL colonisation and infection rates in Africa by UN region

UN region	Country	Colonisation				Infection			
		ESBL rate	Place of detection	Survey period	Source	ESBL rate	Place of detection	Survey period	Source
North Africa	Algeria	No data				4% 16% 31%	Urine cultures Various Wound swabs	2006–2007 2003–2007 2009	3 4 5
	Egypt	31%	Various	2011–2012	6	16% 76%	Urine cultures Blood cultures	2007–2008 2006–2007	7 8
	Libya	No data				No data			
	Morocco	3%	Rectal swabs Rectal swabs	2009–2010 2012	N/A 9	5% 8%	Urine cultures Urine cultures	2008 2010–2011	10 11
	Sudan	43%				No data			
	Tunisia	No data				47% 20% 66%	Various Urine cultures Urine cultures	2005–2006 2009 2009	12 13 14
	Western Sahara	No data				No data			
South Africa	Botswana	No data				No data			
	Lesotho	No data				No data			
	Namibia	No data				No data			
	Republic of South Africa	No data				10% 15% 8% 41%	Various Urine cultures Urine cultures Peritoneal swabs	2006 2005–2006 2007–2011 2004–2009	15 16 N/A 17
	Swaziland	No data				No data			
West Africa	Benin	No data				22%	Various	2005	18
	Burkina Faso	No data				No data			
	Ivory Coast	No data				No data			
	Gambia	No data				No data			
	Ghana	No data				49%	Various	2011–2012	19
	Guinea-Conakry	No data				No data			
	Guinea-Bissau	33%	Rectal swabs	2010	20	No data			
	Cabo Verde	No data				No data			
	Liberia	13%	Rectal swabs	2001–2007	21	No data			
	Mali	No data				No data			
	Mauritania	No data				No data			
	Niger	No data				No data			
	Nigeria	No data				10% 21% 13% 22% 37%	Various Various Various Various Various	2006–2007 2005–2007 2008–2009 2012 2013	22 23 24 25 26
	St. Helena	No data				No data			
	Senegal	No data				6% 4%	Urine cultures Urine cultures	2001–2003 2004–2006	27 28
	Sierra Leone	No data				No data			
	Togo	No data				No data			

23. Ogbolu DO, Daini OA, Ogunledun A, Alli AO, et al. High levels of multidrug resistance in clinical isolates of Gram-negative pathogens from Nigeria. Int J Antimicrob Agents 2011;37:62-6.
24. Aibinu I, Odugbemi T, Koenig W, Ghebremedhin B. Sequence type ST131 and ST10 complex (ST617) predominant among CTX-M-15-producing *Escherichia coli* isolates from Nigeria. Clin Microbiol Infect 2012;18:49-51.
25. Motayo BO, Akinduti PA, Adeyakinu FA, Okerentugba PO, et al. Antibiogram and plasmid profiling of carbapenemase and extended spectrum Beta-lactamase (ESBL) producing *Escherichia coli* and *Klebsiella pneumoniae* in Abeokuta, South western, Nigeria. Afr Health Sci 2013;13:1091-7.
26. Raji MA, Jamal W, Ojemhen O, Rotimi VO. Point-surveillance of antibiotic resistance in Enterobacteriaceae isolates from patients in a Lagos Teaching Hospital, Nigeria. J Infect Public Health 2013;6:431-7.
27. Dromigny JA, Nabeth P, Juergens-Behr A, Perrier-Gros-Claude JD. Risk factors for antibiotic-resistant *Escherichia coli* isolated from community-acquired urinary tract infections in Dakar, Senegal. J Antimicrob Chemother 2005;56:236-9.
28. Sire JM, Nabeth P, Perrier-Gros-Claude JD, Bahsoun I, et al. Antimicrobial resistance in outpatient *Escherichia coli* urinary isolates in Dakar, Senegal. J Infect Dev Ctries 2007;1:263-8.
29. Schaumburg F, Alabi A, Kokou C, Grobusch MP, et al. High burden of extended-spectrum beta-lactamase-producing Enterobacteriaceae in Gabon. J Antimicrob Chemother 2013;68:2140-3.
30. Alabi AS, Frielinghaus L, Kaba H, Kosters K, et al. Retrospective analysis of antimicrobial resistance and bacterial spectrum of infection in Gabon, Central Africa. BMC Infect Dis 2013;13:455.
31. Lonchel CM, Melin P, Gangoue-Pieboji J, Assoumou MC, et al. Extended-spectrum beta-lactamase-producing Enterobacteriaceae in Cameroonian hospitals. Eur J Clin Microbiol Infect Dis 2013;32:79-87.
32. Magoue CL, Melin P, Gangoue-Pieboji J, Okomo Assoumou MC, et al. Prevalence and spread of extended-spectrum beta-lactamase-producing Enterobacteriaceae in Ngaoundere, Cameroon. Clin Microbiol Infect 2013;19:416-20.
33. Frank T, Arlet G, Gautier V, Talarmin A, et al. Extended-spectrum beta-lactamase-producing Enterobacteriaceae, Central African Republic. Emerg Infect Dis 2006;12:863-5.
34. Bercion R, Mossoro-Kpinde D, Manirakiza A, Le Faou A. Increasing prevalence of antimicrobial resistance among Enterobacteriaceae uropathogens in Bangui, Central African Republic. J Infect Dev Ctries 2009;3:187-90.
35. Seid J, Asrat D. Occurrence of extended spectrum beta-lactamase enzymes in clinical isolates of *Klebsiella* species from Harar region, eastern Ethiopia. Acta Trop 2005;95:143-8.
36. Kohli R, Omuse G, Revathi G. Antibacterial susceptibility patterns of blood stream isolates in patients investigated at the Aga Khan University Hospital, Nairobi. Afr Med J 2010;87:74-80.

Tab. 1: Most recently published ESBL colonisation and infection rates in Africa by UN region

UN region	Country	Colonisation				Infection			
		ESBL rate	Place of detection	Survey period	Source	ESBL rate	Place of detection	Survey period	Source
Central Africa	Angola	No data				No data			
	Equatorial Guinea	No data				No data			
	Democratic Republic of Congo	No data				No data			
	Gabon	45%	Rectal swabs	2012	29	15%	Various	2009–2012	30
	Cameroon	55% 54%	Rectal swabs Rectal swabs	2009 2010	31 32	No data			
	Republic of Congo	No data				No data			
	São Tomé and Príncipe	No data				No data			
	Chad	No data				No data			
	Republic of Central Africa	No data				4% 12%	Various Urine cultures	2003–2005 2004–2006	33 34
East Africa	Ethiopia	No data				33%	Various	2003–2004	35
	Burundi	No data				No data			
	Djibouti	No data				No data			
	Eritrea	No data				No data			
	Kenya	No data				14% 27%	Blood cultures Various	2003–2008 1992–2010	36 37
	Comoros	No data				No data			
	Madagascar	No data				No data			
	Malawi	No data				1%	Blood cultures	2004–2005	38
	Mauritius	No data				No data			
	Mayotte	No data				No data			
	Mozambique	No data				No data			
	Réunion	No data				No data			
	Rwanda	No data				23%	Urine cultures	2009	39
	Zambia	No data				No data			
	Seychelles	No data				No data			
	Zimbabwe	No data				No data			
	Somalia	No data				No data			
	South Sudan	No data				No data			
	Tanzania	No data				15% 79%	Blood cultures Wound swabs	2001–2002 2011–2012	40 41
	Uganda	No data				79%	Wound swabs	2011–2012	42

37. Kiiru J, Kariuki S, Goddeeris BM, Butaye P. Analysis of beta-lactamase phenotypes and carriage of selected beta-lactamase genes among *Escherichia coli* strains obtained from Kenyan patients during an 18-year period. BMC Microbiol 2012;12:155.
38. Gray KJ, Wilson LK, Phiri A, Corkill JE, et al. Identification and characterization of ceftriaxone resistance and extended-spectrum beta-lactamases in Malawian bacteraemic Enterobacteriaceae. J Antimicrob Chemother 2006;57:661-5.
39. Muvunyi CM, Masaisa F, Bayingana C, Mutesa L, et al. Decreased susceptibility to commonly used antimicrobial agents in bacterial pathogens isolated from urinary tract infections in Rwanda: need for new antimicrobial guidelines. Am J Trop Med Hyg 2011;84:923-8.
40. Blomberg B, Olsen BE, Hinderaker SG, Langeland N, et al. Antimicrobial resistance in urinary bacterial isolates from pregnant women in rural Tanzania: implications for public health. Scand J Infect Dis 2005;37:262-8.
41. Manyahi J, Matee MI, Majigo M, Moyo S, et al. Predominance of multidrug resistant bacterial pathogens causing surgical site infections in Muhimbili National Hospital, Tanzania. BMC Res Notes 2014;7:500.
42. Seni J, Najjuka CF, Kateete DP, Makobore P, et al. Antimicrobial resistance in hospitalized surgical patients: a silently emerging public health concern in Uganda. BMC Res Notes 2013;6:298.
43. Tsu JH, Ma WK, Chan WK, Lam BH, et al. Prevalence and predictive factors of harboring fluoroquinolone-resistant and extended-spectrum beta-lactamase-producing rectal flora in Hong Kong Chinese men undergoing transrectal ultrasound-guided prostate biopsy. Urology 2015;85:15-21.
44. Zhang H, Yang Q, Xiao M, Chen M, et al. Antimicrobial susceptibility of Gram-negative bacteria causing intra-abdominal infections in China: SMART China 2011. Chinese Med J 2014;127:2429-33.
45. Yang Q, Zhang H, Wang Y, Xu Y, et al. A 10 year surveillance for antimicrobial susceptibility of *Escherichia coli* and *Klebsiella pneumoniae* in community- and hospital-associated intra-abdominal infections in China. J Med Microbiol 2013;62:1343-9.
46. Kim J, Lee JY, Kim SI, Song W, et al. Rates of fecal transmission of extended-spectrum beta-lactamase-producing and carbapenem-resistant Enterobacteriaceae among patients in intensive care units in Korea. An Lab Med 2014;34:20-5.
47. Kwon JS, Han J, Kim TW, Oh JH, et al. Changes in causative pathogens of acute cholangitis and their antimicrobial susceptibility over a period of 6 years. Korean J Gastroenterol 2014;63:299-307.
48. Kim SH, Kwon JC, Choi SM, Lee DG, et al. *Escherichia coli* and *Klebsiella pneumoniae* bacteremia in patients with neutropenic fever: factors associated with extended-spectrum beta-lactamase production and its impact on outcome. Ann Hematol 2013;92:533-41.
49. Sato T, Hara T, Horiyama T, Kanazawa S, et al. Mechanism of resistance and antibacterial susceptibility in ESBL-phenotype *Klebsiella pneumoniae* and *Klebsiella oxytoca* isolated between 2000 and 2010 in Japan. J Med Microbiol 2015;64:538-43.
50. Nakamura T, Komatsu M, Yamasaki K, Fukuda S, et al. Epidemiology of *Escherichia coli*, *Klebsiella* species, and *Proteus mirabilis* strains producing extended-spectrum beta-lactamases from clinical samples in the Kinki Region of Japan. Am J Clin Pathol 2012;137:620-6.
51. Jean SS, Ko WC, Xie Y, Pawar V, et al. Clinical characteristics of patients with community-acquired complicated intra-abdominal infections: a prospective, multicentre, observational study. Int J Antimicrob Agents 2014;44:222-8.
52. Hsieh CJ, Shen YH, Hwang KP. Clinical implications, risk factors and mortality following community-onset bacteremia caused by extended-spectrum beta-lactamase (ESBL) and non-ESBL producing *Escherichia coli*. J Microbiol Immunol Infect 2010;43:240-8.
53. Shu JC, Chia JH, Kuo AJ, Su LH, et al. A 7-year surveillance for ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* at a university hospital in Taiwan: the increase of CTX-M-15 in the ICU. Epidemiol Infect 2010;138:253-63.

Tab. 2: Most recently published ESBL colonisation and infection rates in Asia by UN region

UN region	Country	Colonisation				Infection			
		ESBL rate	Place of detection	Survey period	Source	ESBL rate	Place of detection	Survey period	Source
East Asia	China	41%	Rectal swabs	2011–2012	43	38-69% 70%	Various Intraabdominal specimens	2011 2002–2011	44 45
	Mongolia	No data				No data			
	Korea	28%	Rectal swabs	2012	46	37% 26%	Bile cultures Blood cultures	2006–2008 2007–2008	47 48
	Japan	No data				2-5% 7%	Various Various	2000–2010 2000–2009	49 50
	Taiwan	No data				16% 5% 10-23%	Abdominal Blood cultures Various	2010–2011 2005–2006 2001–2008	51 52 53
Southeast Asia	Myanmar	No data				21%	Various	2013–2014	54
	Laos	No data				9%	Various	2000–2006	55
	Thailand	No data				12% 66%	Blood cultures Various	2004–2010 2005–2007	56 57
	Cambodia	No data				50% 17%	Blood cultures Respiratory specimens	2007–2010 2007–2009	58 59
	Vietnam	No data				40-49%	*Escherichia coli* and *Klebsiella pneumoniae* isolates	2009–2011	60
	Indonesia	10%	Stool cultures	2001–2002	61	36%	Various	2005	62
	East Timor	No data				No data			
	Singapore	12%	Screening swabs	2006–2007	63	33%	Urine cultures	2009	64
	Malaysia	No data				11%	*Klebsiella* isolates	2003–2004	65
	Philippines	No data				22%	Various	1998–2002	66
South Asia	India	41%	Screening swabs	2001		64% 37%	Urine cultures Urine cultures	2013 2013	67 68
	Nepal	No data				14-17%	Urine cultures	2011–2012	69
	Pakistan	No data				34% (2005) 60% (2009) 52%	Urine cultures, Cultures from pus Various	2005–2009 2002	70 71
	Bangladesh	No data				12% 67-82% 25%	Urine cultures, wound swabs Urine cultures Urine cultures, wound swabs	2003–2007 No data No data	72 73 74
	Bhutan	No data				No data			
Central Asia	Kazakhstan	No data				No data			
	Uzbekistan	No data				No data			
	Turkmenistan	No data				No data			
	Afghanistan	No data				No data			
	Kirgizstan	No data				No data			
	Tajikistan	No data				No data			
Russia and Caucasus	Russia					0.2% 16% 61%	*Salmonella* stool cultures *Escherichia coli* isolates *Klebsiella pneumoniae* isolates	2002–2005 1997–1998	75 76

54. Chalmers L, Cross J, Chu CS, Phyo AP, et al. The role of point of care tests in antibiotic stewardship for urinary tract infections in a resource limited setting on the Thailand-Myanmar border. Trop Med Int Health 2015;20:1281-9.

55. Stoesser N, Crook DW, Moore CE, Phetsouvanh R, et al. Characteristics of CTX-M ESBL-producing *Escherichia coli* isolates from the Lao People's Democratic Republic, 2004-09. J Antimicrob Chemother 2012;67:240-2.

56. Kanoksil M, Jatapai A, Peacock SJ, Limmathurotsakul D. Epidemiology, microbiology and mortality associated with community-acquired bacteremia in northeast Thailand: a multicenter surveillance study. PLoS One 2013;8:54714.

57. Kiratisin P, Chattammanat S, Sa-Nguansai S, Dansubutra B, et al. A 2-year trend of extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in Thailand: an alert for infection control. Trans R Soc Trop Med Hyg 2008;102:460-4.

58. Vlieghe ER, Huang TD, Phe T, Bogaerts P, et al. Prevalence and distribution of beta-lactamase coding genes in third-generation cephalosporin-resistant Enterobacteriaceae from bloodstream infections in Cambodia. Eur J Clin Microbiol Infect Dis 2015;34:1223-9.

59. Rammaert B, Goyet S, Beaute J, Hem S, et al. *Klebsiella pneumoniae* related community-acquired acute lower respiratory infections in Cambodia: clinical characteristics and treatment. BMC Infect Dis 2012;12:3.

60. Jones SL, Nguyen VK, Nguyen TM, Athan E. Prevalence of multiresistant Gram-negative organisms in a surgical hospital in Ho Chi Minh City, Vietnam. Trop Med Int Health 2006;11:1725-30.
61. Severin JA, Lestari ES, Kloezen W, Lemmens-den Toom N, et al. Faecal carriage of extended-spectrum beta-lactamase-producing Enterobacteriaceae among humans in Java, Indonesia, in 2001-2002. Trop Med Int Health 2012;17:455-61.
62. Severin JA, Mertaniasih NM, Kuntaman K, Lestari ES, et al. Molecular characterization of extended-spectrum beta-lactamases in clinical *Escherichia coli* and *Klebsiella pneumoniae* isolates from Surabaya, Indonesia. J Antimicrob Chemother 2010;65:465-9.
63. Young BE, Lye DC, Krishnan P, Chan SP, et al. A prospective observational study of the prevalence and risk factors for colonization by antibiotic resistant bacteria in patients at admission to hospital in Singapore. BMC Infect Dis 2014;14:298.
64. Hsueh PR, Hoban DJ, Carmeli Y, Chen SY, et al. Consensus review of the epidemiology and appropriate antimicrobial therapy of complicated urinary tract infections in Asia-Pacific region. J Infect 2011;63:114-23.
65. Loh LC, Nor Izran Hanim Bt Abdul S, Rosdara Masayuni Bt Mohd S, Raman S, et al. Hospital Outcomes of Adult Respiratory Tract Infections with Extended-Spectrum B-Lactamase (ESBL) Producing *Klebsiella Pneumoniae*. Malays J Med Sci 2007;14:36-40.
66. Hirakata Y, Matsuda J, Miyazaki Y, Kamihira S, et al. Regional variation in the prevalence of extended-spectrum beta-lactamase-producing clinical isolates in the Asia-Pacific region (SENTRY 1998-2002). Diagn Microbiol Infect Dis 2005;52:323-9.
67. Nandagopal B, Sankar S, Sagadevan K, Arumugam H, et al. Frequency of extended spectrum beta-lactamase producing urinary isolates of Gram-negative bacilli among patients seen in a multispecialty hospital in Vellore district, India. Indian J Med Microbiol 2015;33:282-5.
68. Bajpai T, Pandey M, Varma M, Bhatambare GS. Prevalence of extended spectrum beta-lactamase producing uropathogens and their antibiotic resistance profile in patients visiting a tertiary care hospital in central India: Implications on empiric therapy. Indian J Pathol Microbiol 2014;57:407-12.
69. Chander A, Shrestha CD. Prevalence of extended spectrum beta lactamase producing *Escherichia coli* and *Klebsiella pneumoniae* urinary isolates in a tertiary care hospital in Kathmandu, Nepal. BMC Res Notes 2013;6:487.
70. Habeeb MA, Sarwar Y, Ali A, Salman M, et al. Rapid emergence of ESBL producers in *E. coli* causing urinary and wound infections in Pakistan. Pakistan J Med Sci 2013;29:540-4.
71. Jabeen K, Zafar A, Hasan R. Frequency and sensitivity pattern of Extended Spectrum beta Lactamase producing isolates in a tertiary care hospital laboratory of Pakistan. J Pak Med Assoc 2005;55:436-9.
72. Lina TT, Khajanchi BK, Azmi IJ, Islam MA, et al. Phenotypic and molecular characterization of extended-spectrum beta-lactamase-producing *Escherichia coli* in Bangladesh. PLoS One 2014;9:108735.
73. Yesmin T, Hossain MA, Paul SK, Mahmud C, et al. Prevalence and antimicrobial susceptibility pattern of ESBL producing isolates. Mymensingh Med J 2013;22:625-31.
74. Farzana R, Shamsuzzaman SM, Mamun KZ, Shears P. Antimicrobial susceptibility pattern of extended spectrum beta-lactamase producing gram-negative bacteria isolated from wound and urine in a tertiary care hospital, Dhaka City, Bangladesh. South Asian J Trop Med Public Health 2013;44:96-103.
75. Egorova S, Kaftyreva L, Grimont PA, Weill FX. Prevalence and characterization of extended-spectrum cephalosporin-resistant nontyphoidal *Salmonella* isolates in adults in Saint Petersburg, Russia (2002-2005). Microbial Drug Resist 2007;13:102-7.
76. Edelstein M, Pimkin M, Palagin I, Edelstein I, et al. Prevalence and molecular epidemiology of CTX-M extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in Russian hospitals. Antimicrob Agents Chemother 2003;47:3724-32.

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 show the temporal development of resistance rates of the four above-mentioned Enterobacteriaceae species 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 extended-spectrum β-lactamase (ESBL)-producing isolates (not for *E. cloacae*).[1,2]

Over the period 1995-2013, the percentage of *E. cloacae* strains resistant to cefotaxime initially increased from 30.7% to 43.5% in 2007, then dropped to 28.4% in 2010, most recently ranging at 34% (Fig. 4.1.5.2.1). 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. Cefepime shows in vitro activity against AmpC β-lactamase-producing strains, which is why cefepime-resistant strains are very likely to produce an ESBL. In 2013, 7.1% of the isolates were resistant to cefepime. The rate of ciprofloxacin resistance increased from 2.2% in 1995 to 10.3% in 2001, most recently being 8.1%. The rate of co-trimoxazole resistance also rose initially, namely from < 5% in the 1990s to 17% in 2007, and was 13.7% in the last study year. The rate of meropenem resistance was < 1% in all study years.

Over the study period, the prevalence of resistance to some antimicrobials in *K. pneumoniae* increased significantly, e.g. to cefuroxime from 8% to 25.3%, to cefotaxime from 2.3% to 17.8%, to piperacillin/tazobactam from 3.3% to 13.5% and to gentamicin from 4.6% to 10.5% (Fig. 4.1.5.2.2). The rate of resistance to ciprofloxacin also increased significantly; however, the highest resistance rate of 19.1% was reached in 2010. 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 increased from 4.1% in 1995 to 17.4% in 2013. The rate of resis-

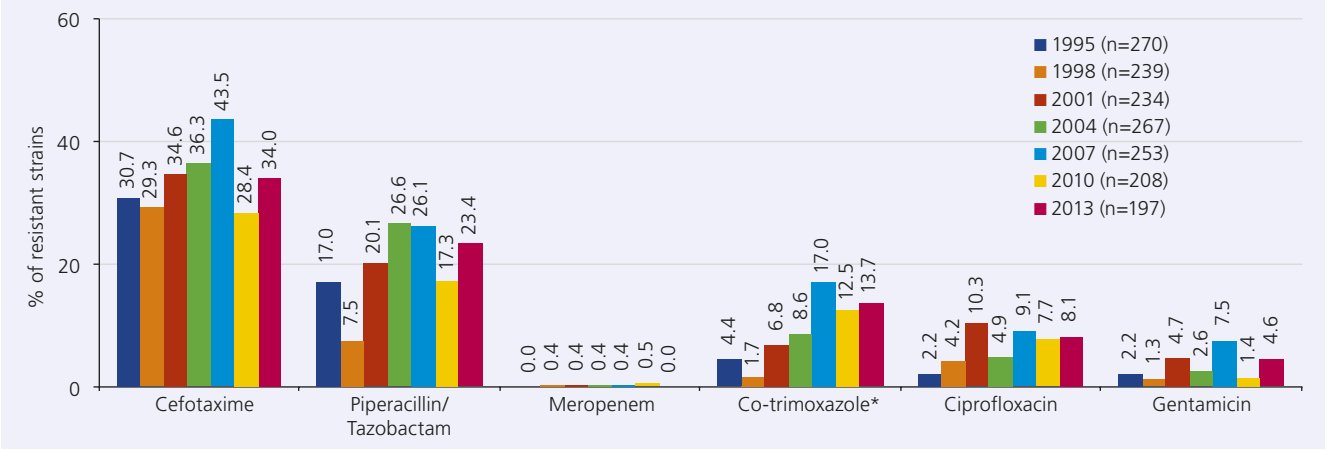


Fig. 4.1.5.2.1: Percentage of resistant *E. cloacae* strains from hospital care (Source: PEG resistance study)
* Trimethoprim/Sulfamethoxazole

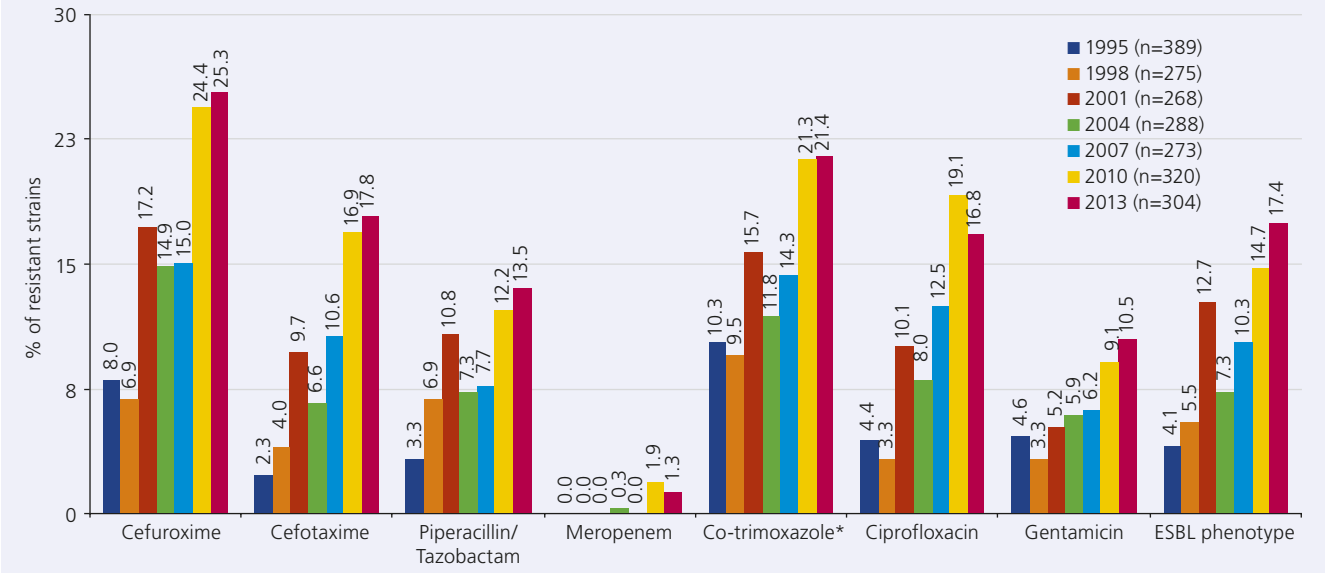


Fig. 4.1.5.2.2: Percentage of resistant *K. pneumoniae* strains from hospital care (Source: PEG resistance study)
* Trimethoprim/Sulfamethoxazole

tance to first-generation (group 1) carbapenems (test substance meropenem) was 1-2% in the last two study years.

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 20% in 2010 (Fig. 4.1.5.2.3). In 2013, the resistance rate reached a comparable level (18.2%). A corresponding trend in resistance development was also observed for co-trimoxazole, ciprofloxacin and piperacillin/tazobactam. The percentage of cefotaxime-resistant strains initially rose from 2.1% to 11% in 2007 and subsequently dropped to 5.3%. The percentage of strains with an ESBL phenotype was subject to the same trend. No change in the resistance situation was apparent for gentamicin and meropenem.

The prevalence of resistance to β-lactam antimicrobials in *P. mirabilis* saw hardly any change (Fig. 4.1.5.2.4). By contrast, an upward trend in the rates of resistance to ciprofloxacin and co-trimoxazole was observed. The percentage of ESBL-producing isolates ranged between 0% and 3.1%.

The percentage of 3MRGN multidrug-resistant strains (as defined by the KRINKO[4]) in all *K. pneumoniae* isolates during the period 1995-2013 increased from 1.0% to 13.2%, in *E. cloacae from* 1.1% to 9.1% in 2007, most recently being 7.6%, in *K. oxytoca* from 0% to 7.1% in 2010, most recently being 6.1% and in *P. mirabilis* from 0.4% in 1995 to 2.3%. Five strains of *K. pneumoniae* (1.6%) as well as one strain of *E. cloacae* (0.5%) were classified as 4MRGN in 2013.

Possible alternatives for the treatment of infections caused by multidrug-resistant *Enterobacteriaceae* include colistin, fosfomycin and tigecycline. *P. mirabilis* exhibits intrinsic resistance to colistin and tigecycline. In 2013, the prevalence of colistin resistance in *E. cloacae* was 4.6% (7.2% in 2010), in *K. pneumoniae* 3.9% (1.3% in 2010) and in *K. oxytoca* 0.8% (0% in 2010). The percentage of strains resistant to fosfomycin varied between species,

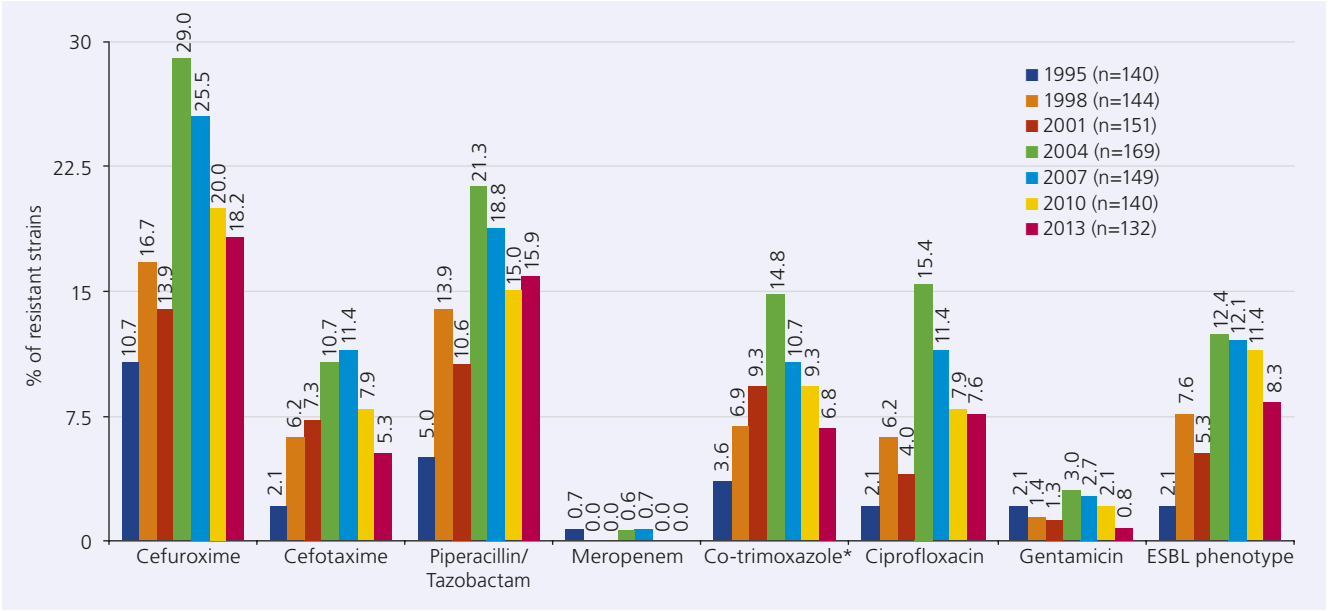


Fig. 4.1.5.2.3: Percentage of resistant *K. oxytoca* strains from hospital care (Source: PEG resistance study)
* Trimethoprim/Sulfamethoxazole

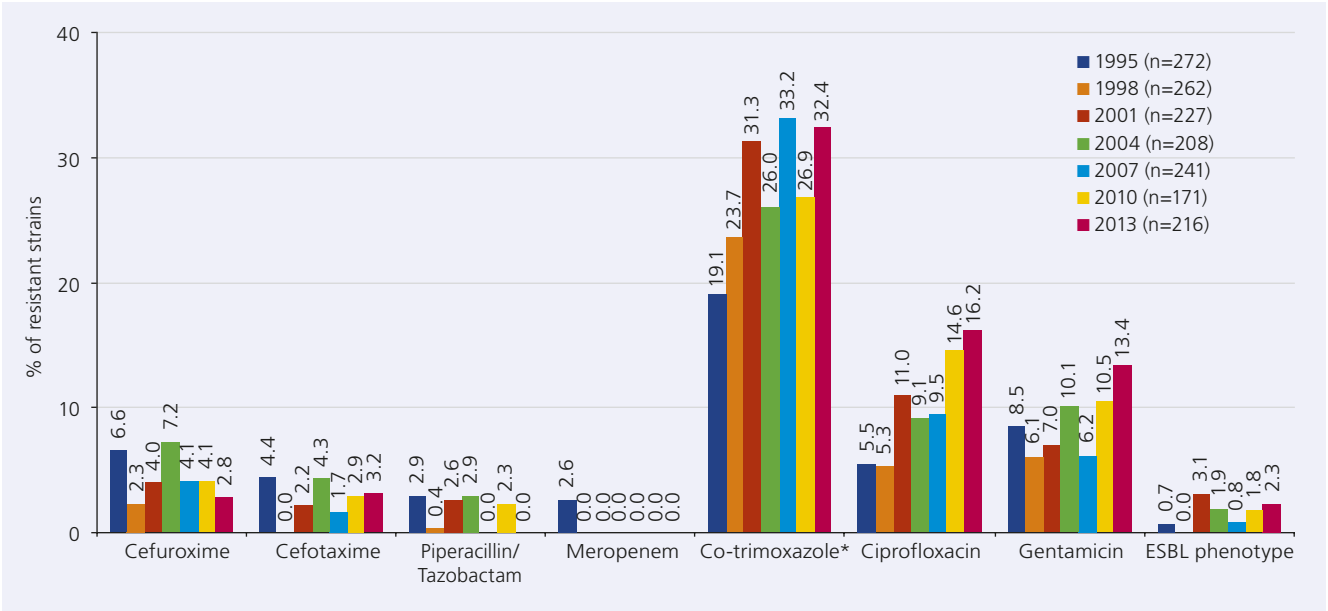


Fig. 4.1.5.2.4: Percentage of resistant *P. mirabilis* strains from hospital care (Source: PEG resistance study)
* Trimethoprim/Sulfamethoxazole

amounting in 2013 to 35.5% in *E. cloacae*, 22.7% in *K. oxytoca*, 20.1% in *K. pneumoniae* and 15.7% in *P. mirabilis*. The testing of *Klebsiella* strains with an ESBL phenotype for susceptibility to tigecycline revealed that all tested *K. oxytoca* isolates and 94.3% of the *K. pneumoniae* isolates were susceptible.[1]

Antimicrobial Resistance Surveillance System (ARS)

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 than that of isolates 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* (Fig. 4.1.5.2.5-4.1.5.2.8).[5]

Surveillance of Antimicrobial Use and Bacterial Resistance in Intensive Care Units (SARI)

The number of bacterial strains isolated from patients in intensive care units during the period 2000-2011 was 248,138[6], 15,979 of which were *K. pneumoniae* isolates and 12,512 *E. cloacae* isolates.

The prevalence of resistance to third-generation (group 3) cephalosporins in *K. pneumoniae* rose from 2.2% in 2000 to 20.1% in 2010, ranging at 16.5% in 2014.[6] The incidence density of isolates resistant to third-generation (group 3) cephalosporins increased from 0.25 per 1,000 patient days in 2001 to 0.82 in 2008[7], reaching 1.19 in 2011[8] and finally approx. 1.3 per 1,000 patient days in 2014.[6] The increase in the rates of resistance to third-generation (group 3) cephalosporins went hand in hand with an increase in carbapenem consumption between 2001 and 2012. After this period, however, consumption did not increase further and was even observed to decrease in 2014.[8] With one exception, the percentage of imipenem-resistant strains in all *K. pneumoniae* isolates up to and including 2010 was always below 1%, increasing to 1.2% (meropenem) and 1.5% (imipenem) in 2011 and to 2.1% (meropenem) and 1.7% (imipenem) in 2014.[6] At the beginning of the study period, the rate of fluoroquinolone resistance (test substance ciprofloxacin) was 2.2%, than ranged between 4.2% and 9.3% until 2007, reached 16.7% in 2011, most recently being 15.3%.[6]

The percentage of *E. cloacae* strains resistant to third-generation (group 3) 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%.[6]

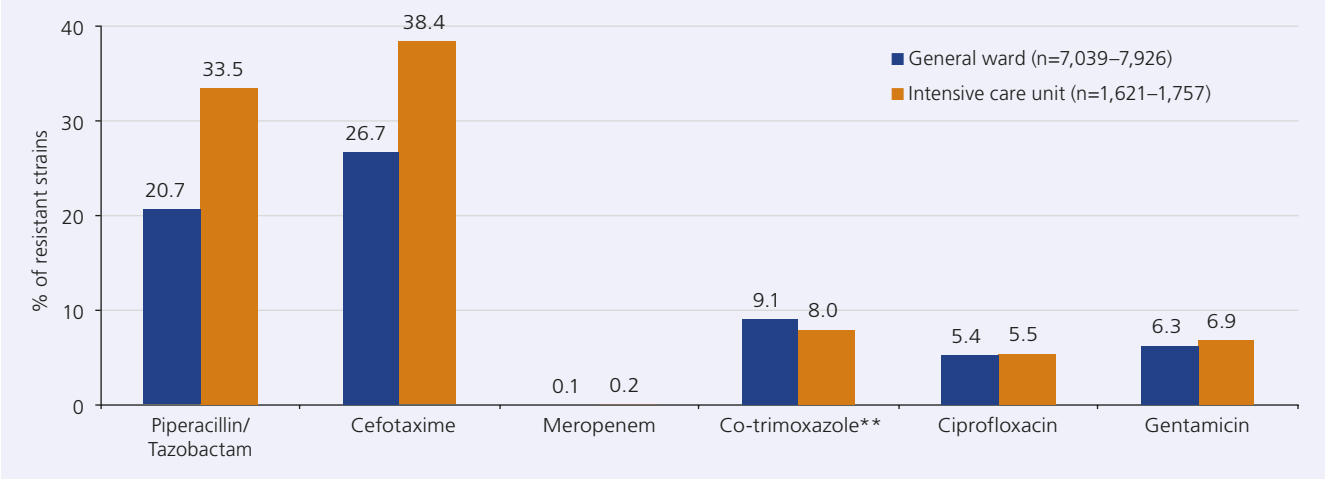


Fig. 4.1.5.2.5: Percentage of resistant *E. cloacae* strains on general wards and in intensive care units (Source: ARS, 2014 data*)
*Data as of: 01/07/2015; **Trimethoprim/Sulfamethoxazole

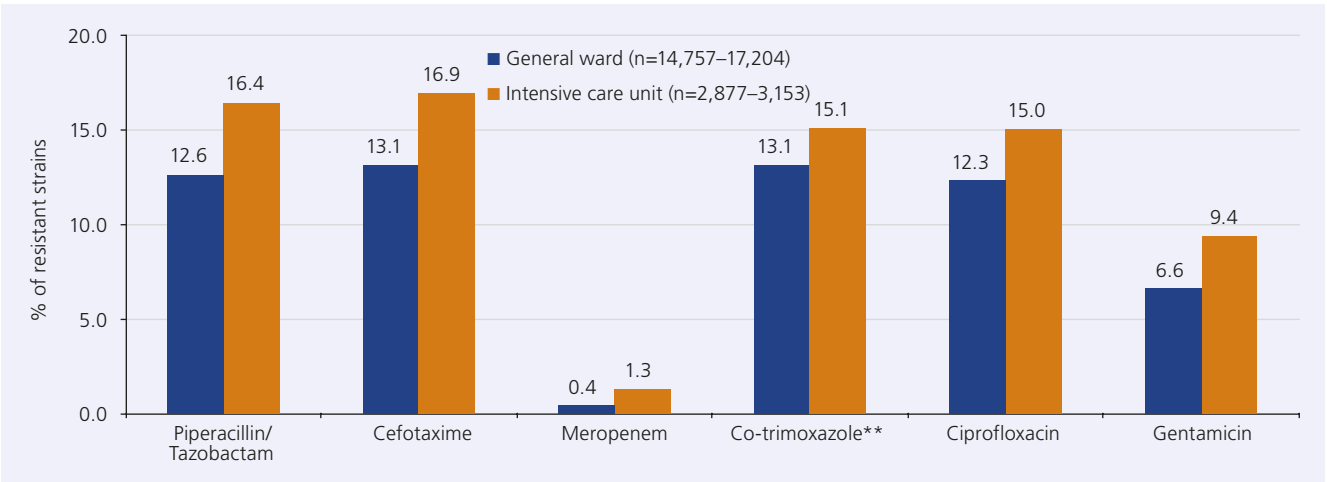


Fig. 4.1.5.2.6: Percentage of resistant *K. pneumoniae* strains on general wards and in intensive care units (Source: ARS, 2014 data*)
*Data as of: 01/07/2015; **Trimethoprim/Sulfamethoxazole

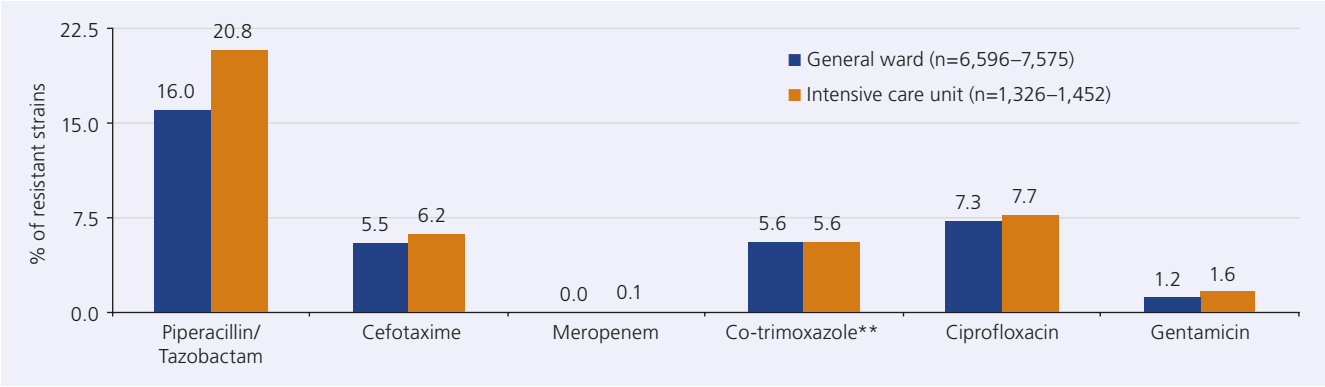


Fig. 4.1.5.2.7: Percentage of resistant *K. oxytoca* strains on general wards and in intensive care units (Source: ARS, 2014 data*)
*Data as of: 01/07/2015; **Trimethoprim/Sulfamethoxazole

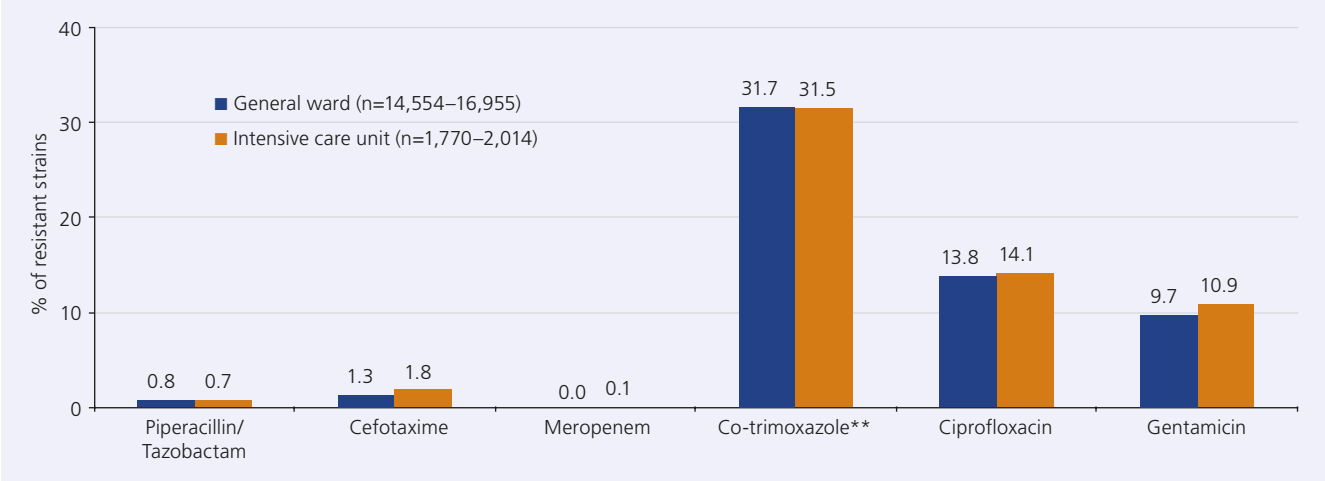


Fig. 4.1.5.2.8: Percentage of resistant *P. mirabilis* strains on general wards and in intensive care units (Source: ARS, 2014 data*)
*Data as of: 01/07/2015; **Trimethoprim/Sulfamethoxazole

European Antimicrobial Resistance Surveillance Network (EARS-Net)

During the period 2005-2014, the resistance data of 105 to 1,008 *K. pneumoniae* blood culture isolates was reported each year by 10-21 participating German laboratories.[9] 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 2009-2014, the prevalence of resistance to aminoglycosides was 7-10%, to fluoroquinolones 13-15%, to third-generation (group 3) cephalosporins 13-16% and to carbapenems < 1%.

German Tigecycline Evaluation Surveillance Trial (G-TEST)

The study ended in 2009. The rates of resistance ascertained in 2005, 2007 and 2009 were presented in the 2012 GERMAP report.[10]

ESBL-producing Enterobacteriaceae

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

Molecular characterisation of 100 *K. pneumoniae* isolates with an ESBL phenotype isolated from inpatients as part of the 2010 and 2013 PEG resistance studies demonstrated that more than 85% of the isolates produce a CTX-M ESBL (Fig. 4.1.5.2.9). The CTX-M-15 enzyme was detected most frequently (71-75%). An SHV ESBL was identified in 6-10% of the isolates. One isolate was found to produce the VEB-1 enzyme and one the TEM-92 enzyme. In some isolates with an ESBL phenotype, no CTX-M, SHV, TEM or VEB ESBL was detected.

Merely one strain of the 11 *K. oxytoca* isolates with an ESBL phenotype from 2013 was found to produce an ESBL (CTX-M-1). In the remaining 10 isolates classified as expressing the ESBL phenotype, this was associated with the overexpression of the chromosomal OXY-2 β-lactamase (older designation K1 or KOXY), which can simulate the presence of a plasmid-mediated ESBL phenotype.[11]

At least one ESBL type was detected in 12 of the 14 cefepime-resistant *E. cloacae* isolates, namely CTX-M-15 in four cases, CTX-M-9 plus SHV-12 in five cases, SHV-12 alone in two cases and CTX-M-9 alone in one case. In the five *P. mirabilis* isolates with an ESBL phenotype in 2013, the ESBL types CTX-M-65 (n=2), CTX-M-9, TEM-94-like and VEB-5-like were detected.

K. pneumoniae and *E. cloacae* isolates submitted to the Robert Koch Institute for routine molecular characterisation show that smaller outbreak events (clonal transmission of an ESBL-producing strain to 2-10 patients) occur every year on several, in particular neonatal, wards (Pfeifer Y., personal communication). 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-

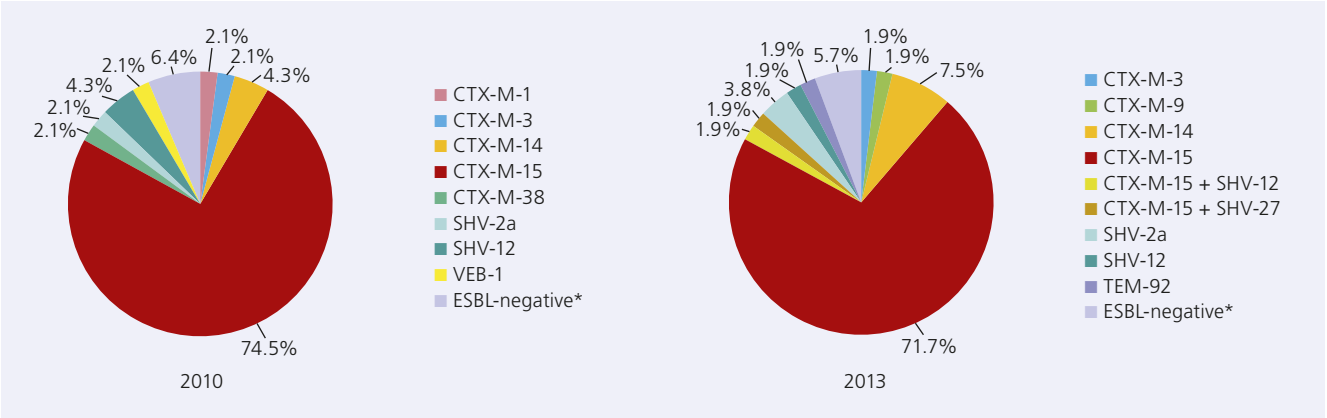


Fig. 4.1.5.2.9: Percentage of ESBL variants of *K. pneumoniae* isolates with the ESBL phenotype from hospital care, 2010 (n=47) and 2013 (n=53).
(Source: PEG resistance study)
* No CTX-M, SHV, TEM or VEB ESBL according to the Bush classification was detected.

M-15-producing *K. pneumoniae* strain caused several deaths in the neonatal intensive care unit of a hospital in Bremen.[12]

Carbapenemase-producing strains

Resistance or intermediate susceptibility to second-generation (group 2) carbapenems (ertapenem) was observed in 2.5% of the *E. cloacae* isolates and 2% of the *K. pneumoniae* isolates obtained from inpatients within the 2013 PEG resistance study. Four (1.3%) of the *K. pneumoniae* strains were additionally found to be resistant to first-generation (group 1) carbapenems (imipenem, meropenem, see Fig. 4.1.5.2.2). In these strains as well as in one *E. cloacae* strain, the resistance was found to be associated with the production of a carbapenemase.[1] Molecular characterisation of the five strains revealed the presence of the metallo-β-lactamase GIM-1 in *E. cloacae* and the serine β-lactamases KPC-3 (n=3) and KPC-2 in *K. pneumoniae*.

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 Bacteria in Bochum. In 2014, the NRZ performed molecular characterisation of the carbapenemases of 672 *K. pneumoniae*, 98 *E. cloacae* and 57 *K. oxytoca* strains. Among all Enterobacteriaceae species, carbapenemases were detected by far most frequently in *K. pneumoniae*. OXA-48 (n=241) was most prevalent in *K. pneumoniae*, followed by NDM-1 (n=141), KPC-2 (n=110), KPC-3 (n=42) and VIM-1 (n=20), whereas VIM-1 was predominant in *E. cloacae* (n=61) and KPC-2 in *K. oxytoca* (n=27) (Kaase M., personal communication).[13] The fact that KPC-2 was the most common carbapenemase in *K. oxytoca* in 2012 was attributable to an outbreak at a single facility, in which KPC-2 plasmids were involved in multiple species. When seen in the long term, however, the most common carbapenemase in *K. oxytoca* is VIM-1, which was detected in this bacterial species in 22 cases in 2014.

Conclusion

The treatment of *Klebsiella* infections with third- and fourth-generation (group 3 and 4) cephalosporins has been limited by the emergence of strains with an ESBL phenotype for several years. The average rate of ESBL-producing strains in all *K. pneumoniae* isolates is estimated at 15-18%. Isolates that constitutively produce AmpC β-lactamases are commonly found in *Enterobacter* spp., causing resistance to third-generation (group 3) cephalosporins (cefotaxime, ceftazidime, ceftriaxone) and other antimicrobial agents. Third-generation (group 3) cephalosporins are also not indicated for treatment 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 mutants with constitutive (derepressed) expression of AmpC β-lactamase being selected 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 is still below that of *Escherichia coli*. The resistance situation for carbapenems is still favourable. Since the carbapenem consumption did not increase further during the last two years, there is reason to hope that the feared significant increase in the prevalence of carbapenem-resistant strains, in particular among *K. pneumoniae* isolates, will not take place in Germany in the next few years.

➤ M. Kresken, B. Körber-Irrgang, M. Kaase, Y. Pfeifer
Reviewer: E. Straube

1. Kresken M, Hafner D, Körber-Irrgang B für die Studiengruppe. Epidemiologie und Resistenzsituation bei klinisch wichtigen Infektionserregern aus dem Hospitalbereich gegenüber Antibiotika. Bericht über die Ergebnisse einer multizentrischen Studie der Paul-Ehrlich-Gesellschaft für Chemotherapie e.V. aus dem Jahre 2013. Antiinfectives Intelligence, Rheinbach, 2016. Verfügbar unter http://www.p-e-g.org/econtext/Berichte%20der%20Studien.
2. Paul-Ehrlich-Gesellschaft für Chemotherapie. Individuelle Datenbankabfrage der Arbeitsgemeinschaft *Empfindlichkeitsprüfung und Resistenz*. Verfügbar unter http://www.p-e-g.org/resistenz/database/index.php.
3. Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility testing; Twenty Second Informational Supplement, M100-S25, Wayne, PA, 2015.
4. Empfehlung der Kommission für Krankenhaushygiene und Infektionsprävention (KRINKO) beim Robert Koch-Institut (RKI). Hygienemaßnahmen bei Infektionen oder Besiedlung mit multiresistenten gramnegativen Stäbchen. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2012;55:1311-54.
5. ARS - Antibiotika-Resistenz-Surveillance in Deutschland. Verfügbar unter https://ars.rki.de.
6. SARI – Surveillance der Antibiotika-Anwendung und der bakteriellen Resistenzen auf Intensivstationen. Verfügbar unter http://sari.eu-burden.info/
7. Meyer E, Schwab F, Schroeren-Boersch B, Gastmeier P. Dramatic increase of third-generation cephalosporin-resistant *E. coli* in German intensive care units: secular trends in antibiotic drug use and bacterial resistance, 2001 to 2008. Crit Care 2010;14:R113.
8. Meyer E, Gastmeier P, Deja M, Schwab F. Antibiotic consumption and resistance: data from Europe and Germany. Int J Med Microbiol 2013:303:388-95.

9. European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2014. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net).Stockholm: ECDC; 2015. http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-europe-2014.pdf.
10. GERMAP 2012. Bericht über den Antibiotikaverbrauch und die Verbreitung von Antibiotikaresistenzen in der Human- und Veterinärmedizin. Antiinfectives Intelligence, Rheinbach, 2014. Verfügbar unter http://www.p-e-g.de/econtext/germap.
11. Potz NA, Colman M, Warner M, Reynolds R, et al. False-positive extended-spectrum beta-lactamase tests for *Klebsiella oxytoca* strains hyperproducing K1 beta-lactamase. J Antimicrob Chemother 2004;53:545-7.
12. Haller S, Eller C, Hermes J, Kaase M, et al. What caused the outbreak of ESBL-producing *Klebsiella pneumoniae* in a neonatal intensive care unit, Germany 2009 to 2012? Reconstructing transmission with epidemiological analysis and whole-genome sequencing. BMJ Open 2015;5:e007397.
13. Robert Koch-Institut. Bericht des Nationalen Referenzzentrums (NRZ) für gramnegative Krankenhauserreger - Zeitraum 1. Januar 2014 bis 31. Dezember 2014. Epid Bull 2016;2:11-4.

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 2013 saw an upward trend in the prevalence of 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] However, the level of resistance in 2013 was below that in 2010. The percentage of strains resistant to antipseudomonal cephalosporins (ceftazidime, cefepime) as well as piperacillin (± tazobactam) was well below 10% until 2008, varied between 10% and 15% from 2001 to 2007 and reached a level of 15-20% in 2010. In 2013, less than 15% of the strains showed resistance to ceftazidime and cefepime and 16-20% to piperacillin (± tazobactam). The rate of resistance to first-generation (group 1) carbapenems was most recently 8.6% (imipenem) and 8% (meropenem). In 2013, the percentage of strains susceptible to imipenem and meropenem was 82.5% and 81.9%, respectively.

The prevalence of resistance to ciprofloxacin and levofloxacin varied between 14% and 23% during the study period, with the resistance level in the last study year being 16.6% and 20.9%, respectively. 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 1.4% for amikacin and 5.5% for gentamicin (Fig. 4.1.6.1.1).

The percentage of 3MRGN multidrug-resistant strains, as defined by the KRINKO[3], in all isolates was initially 3.3% in 1995 and 1.5 % in 1998, increasing to 4.2% in 2001 and then further to 6% in 2010. In the last study year, the rate was 4.6%. The percentage of 4MRGN strains was initially 1.6%, increased to 3.5% in 2001, to 6.8% in 2010 and was most recently 5.0%.

All isolates from patients in intensive care units showed higher resistance rates than isolates from patients on general wards. For the second time, the 2013 PEG resistance study also investigated the antimicrobial resistance situation of clinically relevant bacterial species in private practices. A total of 246 isolates from non-CF patients were included in the study. The level of resistance to the tested antimicrobials reached a maximum rate of 10.6% (levofloxacin).[3] Colistin-resistant strains were not detected in any of the care sectors (Fig. 4.1.6.1.2).

Antimicrobial Resistance Surveillance System (ARS)

The resistance data so far recorded in the laboratories participating in ARS allows its evaluation not only by care sector (outpatient care, general ward, intensive care unit) but also by level of

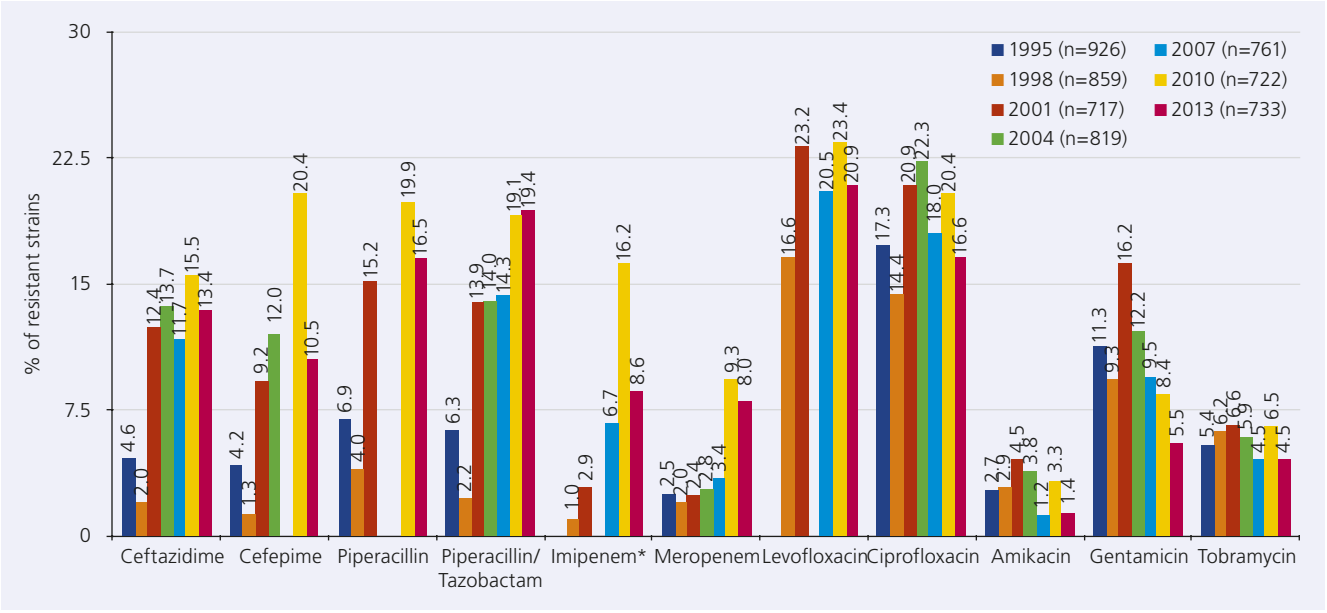


Fig. 4.1.6.1.1: Percentage of resistant *P. aeruginosa* strains from hospital care, 1995-2013 (Source: PEG resistance study)
*Imipenem was not taken into account in 2004.

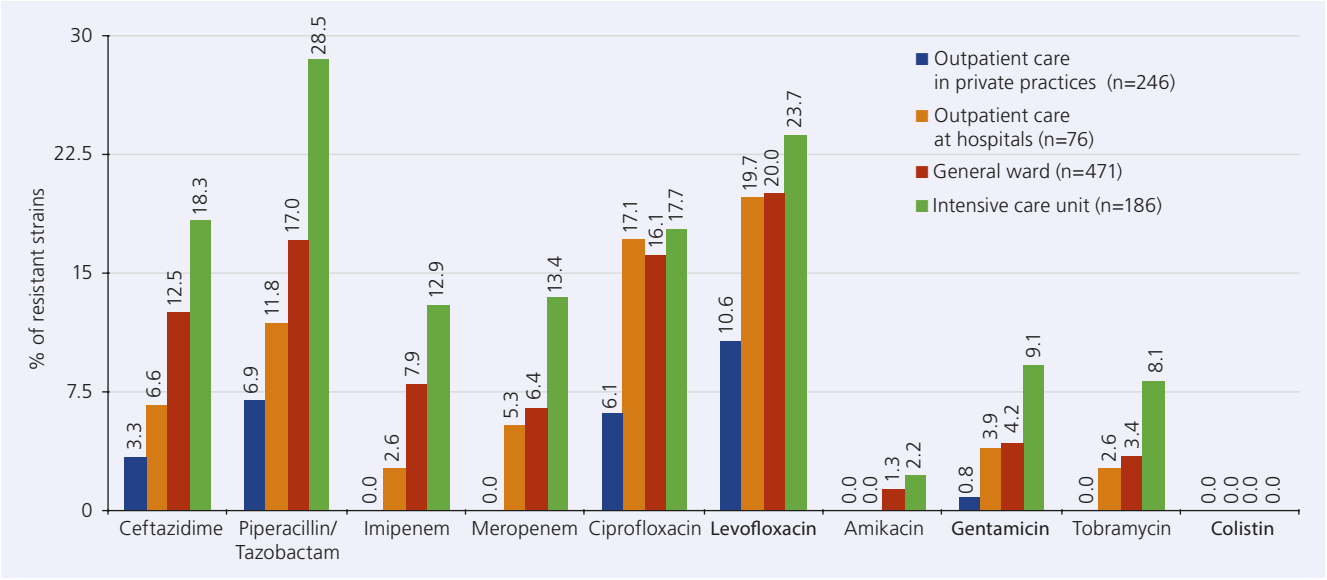


Fig. 4.1.6.1.2: Percentage of resistant *P. aeruginosa* strains from outpatient care, on general wards and in intensive care units (Source: PEG resistance study 2013)

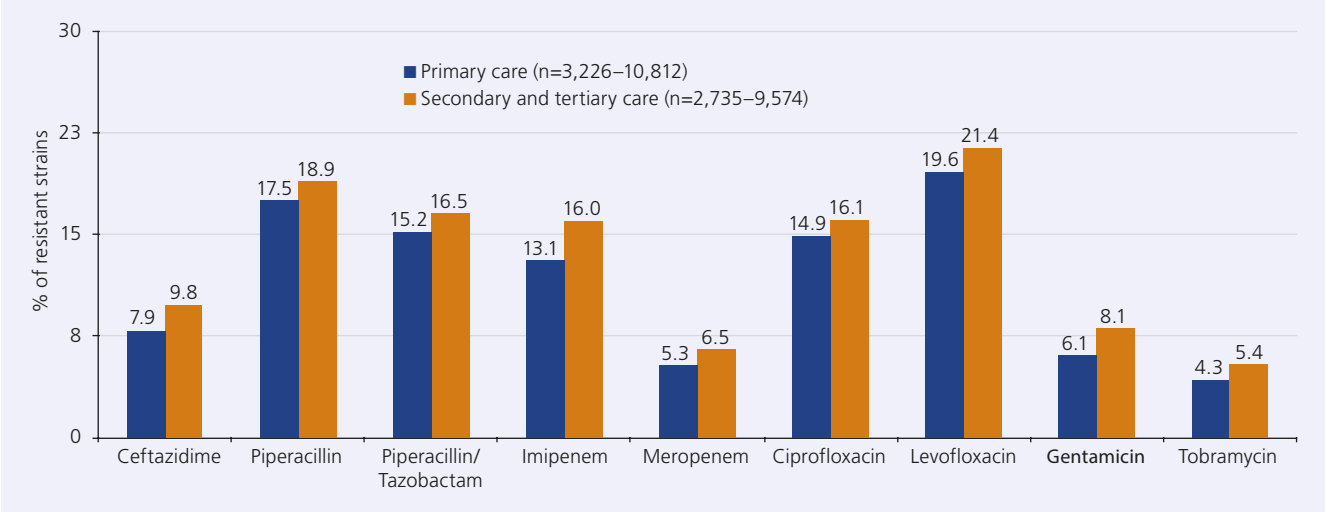


Fig. 4.1.6.1.3: Percentage of resistant *P. aeruginosa* strains from hospitals of various levels of care (Source: ARS, 2014 data*)
*Data as of 01/07/2015

hospital care. However, the reliability of the data is limited by the fact that the susceptibility to various antimicrobials was tested in different strain collectives.[5]

Under these circumstances, large differences in the resistance situation between isolates from patients at primary-care hospitals and those from patients at secondary/tertiary-care hospitals were not observed (Fig. 4.1.6.1.3; 2014 data).

Surveillance of Antimicrobial Use and Bacterial Resistance in Intensive Care Units (SARI)

The number of bacterial strains isolated from patients in the participating intensive care units during the period 2000-2014 was 248,138[6], 25,691 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% in 2001, 16.5% in 2008 and 21.2% in 2014. The level of resistance to imipenem was stable until 2008 (25%) and then rose to approx. 30%. The rate of meropenem resistance was 8.9% in 2001, 16.9% in 2008 and most recently 18.6%. The average incidence density (mean value) of isolates resistant to imipenem was mostly < 2 until 2005 and then consistently > 2.5 per 1,000 patient days.

European Antimicrobial Resistance Surveillance Network (EARS-Net)

During the period 2012-2014, 438 to 643 blood culture isolates were tested each year in 20-21 laboratories. The rate of resistance to aminoglycosides was 6-11%, to fluoroquinolones 13-20%, to piperacillin/tazobactam 16-18%, to ceftazidime 10% and to carbapenems 11-17%.[7] A downward trend in resistance rates was observed for aminoglycosides and fluoroquinolones and an upward trend for carbapenems.

Carbapenemase-producing strains

As part of the 2013 resistance study, a metallo-β-lactamase (MBL), in most cases a VIM β-lactamase (5x VIM-1, 7x VIM-2), was confirmed to cause carbapenem resistance in 16/30 (53.3%) strains resistant to imipenem, meropenem and ceftazidime. The other four strains produced an IMP MBL.[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 2014, the NRZ performed molecular characterisation of the carbapenemases of 279 strains. In most of the cases, VIM-2 MBL (n=223) were detected, although other MBL, mainly IMP and VIM, were found as well.[8]

Conclusion

The level of resistance to antipseudomonal β-lactams and fluoroquinolones has seen an upward trend over the last two decades, but it has recently stabilised. By contrast, a stable or downward trend has been observed for aminoglycosides since 2001. In view of this, aminoglycosides can again be increasingly recommended for the empiric therapy of infections with suspected involvement of *P. aeruginosa*. The prevalence of resistance in 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.

➤ M. Kresken, B. Körber-Irrgang, M. Kaase, M. Trautmann
Reviewer: E. Straube

1. Kresken M, Hafner D, Körber-Irrgang B für die Studiengruppe. Epidemiologie und Resistenzsituation bei klinisch wichtigen Infektionserregern aus dem Hospitalbereich gegenüber Antibiotika. Bericht über die Ergebnisse einer multizentrischen Studie der Paul-Ehrlich-Gesellschaft für Chemotherapie e.V. aus dem Jahre 2013. Antiinfectives Intelligence, Rheinbach, 201. Verfügbar unter http://www.p-e-g.org/econtext/Berichte%20der%20Studien.
2. Paul-Ehrlich-Gesellschaft für Chemotherapie. Individuelle Datenbankabfrage der Arbeitsgemeinschaft *Empfindlichkeitsprüfung und Resistenz*. Verfügbar unter http://www.p-e-g.org/resistenz/database/index.php.
3. Empfehlung der Kommission für Krankenhaushygiene und Infektionsprävention (KRINKO) beim Robert Koch-Institut (RKI). Hygienemaßnahmen bei Infektionen oder Besiedlung mit multiresistenten gramnegativen Stäbchen. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2012;55:1311-54.
4. Kresken M, Hafner D, Körber-Irrgang B für die Studiengruppe. Resistenzsituation bei klinisch wichtigen Infektionserregern aus dem ambulanten Versorgungsbereich gegenüber Antibiotika. Bericht über die Ergebnisse einer multizentrischen Studie der Paul-Ehrlich-Gesellschaft für Chemotherapie e.V. aus dem Jahre 2013. Antiinfectives Intelligence, Rheinbach, 2016. Verfügbar unter http://www.p-e-g.org/econtext/Berichte%20der%20Studien.
5. ARS - Antibiotika-Resistenz-Surveillance in Deutschland. Verfügbar unter https://ars.rki.de.
6. SARI – Surveillance der Antibiotika-Anwendung und der bakteriellen Resistenzen auf Intensivstationen. Verfügbar unter http://sari.eu-burden.info/.
7. European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2014. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net).Stockholm: ECDC; 2015. http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-europe-2014.pdf.
8. Robert Koch-Institut. Bericht des Nationalen Referenzzentrums (NRZ) für gramnegative Krankenhauserreger - Zeitraum 1. Januar 2014 bis 31. Dezember 2014. Epid Bull 2016;2:11-4.

4.1.6.2 *Pseudomonas aeruginosa* in CF patients

Resistance situation in CF patients

Mucoviscidosis (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 exocrine 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 typical in the chronic stage of infection.

The resistance situation for the periods 2000-2008 and 2009-2011 regarding both adults and children was addressed in the previous GERMAP reports. Due to the reduction to only one Consultant Laboratory for CF Bacteriology, the data presented herein stem from the Consultant Laboratory at the Hannover Medical School only. We would like to present the colonisation status of CF patients over a 14-year period and the current resistance situation observed during the last three years.

Colonisation status of CF patients at the Consultant Laboratory with *Pseudomonas aeruginosa*

To ascertain the colonisation rate of CF patients, the percentage of patients with *P. aeruginosa*-positive cultures was determined and examined separately by age group.

As shown in Fig. 4.1.6.2.1 a steady increase in the rate of CF patients colonised with *Pseudomonas* over the first 16 years of life takes place. *Pseudomonas* is often acquired from the environment or *P. aeruginosa* isolates are transmitted within a patient population despite careful hygiene measures. The evaluation was carried out over the 3-year periods shown in the chart in order to be able to recognise any changes in the colonisation dynamics over time that may have been achieved as a result of progress in patient management. Fortunately, the proportion of patients colonised with *Pseudomonas* decreased steadily in all age groups over the last 15 years. This may be attributable to successful hygiene measures, early eradication therapies and more effectively applied therapy regimens (see Fig. 4.1.6.2.1).

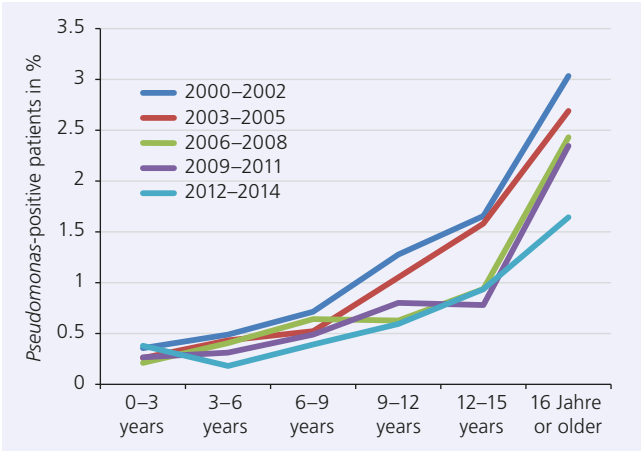


Fig. 4.1.6.2.1: Percentage of *P. aeruginosa*-positive CF patients of various age groups over a 15-year period

Resistance situation of CF: Trends in recent years (patients aged 18 years or older)

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 for lifetime. The numerous interval treatments performed in the course of chronic *P. aeruginosa* pulmonary infections gradually lead to the selection of ever more resistant *P. aeruginosa* isolates. Moreover, despite careful hygiene measures, there is a risk for transmission of *P. aeruginosa* strains within the CF population. Today, 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, and recently aztreonam) substances. In the case of acute exacerbation, combination therapy is used in order to cover several resistance variants of a *Pseudomonas* clone and to minimise early resistance development.

During the previous study period 2009-2011, a slight increase in the rates of resistance to antipseudomonal substances was observed in adult CF patients (18 years or older) compared to the period 2000-2008. Compared to previous years, the resistance rates during the period 2012-2014 were identical for ceftazidime (43.4-45.0% vs. 41.4-48.7% in 2009-2011) and ciprofloxacin (51.3-59% vs. 52.9-56.4%), but increased for meropenem (38.5-44.3% vs. 35.5-40.3% in 2009-2011) and colistin (5.3-8.8% vs. 3.3-6.2% in 2009-2011). The rates of tobramycin resistance were nearly unchanged in 2012 (56.4% vs. 57.6-62.5% in 2009-2011), whereas this rate was only 23.6% and 19.6% in 2013 and 2014, respectively. The remarkable decline in resistance rates to the aminoglycoside tobramycin is in contrast to its continued extensive use in both systemic and inhalation CF therapy and the in-

crease in resistance rates until 2011. The rapid drop in resistance rates observed in 2013/2014 is based on two effects: Firstly, other therapeutic agents for inhalation therapy are now available and used increasingly, which reduces the selection pressure for tobramycin resistance. Secondly, the EUCAST breakpoints are now used instead of the DIN standard for susceptibility testing in our laboratories. As a result of the change in breakpoints, the proportion of isolates classified as resistant has decreased. Based on the MIC results, which yield slightly different values due to the lack of exclusion of copy strains, the resistance rates based on our classification scheme (intermediate susceptibility equated to resistance) were 53.5% (DIN) vs. 21.6% (EUCAST) in 2012, 40.2% vs. 15.2% in 2013 and 32.7% vs. 12.8% in 2014. Hence, a significant drop in tobramycin resistance becomes apparent, regardless of the classification scheme (see Fig. 4.1.6.2.2).

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, with a slight increase in resistance rates having become apparent over the last three years. The by far lowest (but also slightly increasing) 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. Data on the rates of resistance to aztreonam will be published in the next GERMAP report.

Prevalence of resistance in CF patients aged below 18 years

Unlike in adult CF patients, no significant differences have been observed in recent years (2012-2014) in patients aged below 18 years compared to the period 2009-2011. Resistant *P. aeruginosa* strains are already relatively common in children and adolescents. 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 (19.8-29.8%; 2009-2011:18.2-30.1%). 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 (25% vs. 56% on average) (see Fig. 4.1.6.2.3).

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 (< 9% in adults, < 5% in children). Previously, the treatment of mucoviscidosis exclusively involved colistin inhalation therapy and colistin was only used systemically in the exceptional cases as a last option in respiratory diseases. Since 2012, colistin has been approved in Germany for systemic use as well. To what extent this will be reflected in an increase in resistance remains to be seen (see Fig. 4.1.6.2.3).

Multidrug resistance (MDR)

At present, there is no uniform international definition of MDR ("multidrug resistance"). The definition by the KRINKO (Hygiene measures for infection or colonisation with multidrug-resistant gram-negative bacilli, Federal Health Gazette, October 2012) makes a distinction between 3MRGN and 4MRGN (MRGN=multi-resistant gram-negative bacteria). This definition only partly reflects the characteristics of *P. aeruginosa* strains from CF patients, which is why we use the term MDR to refer to *P. aeruginosa* CF strains which are only susceptible to one or none of the antimicrobials ceftazidime, ciprofloxacin and meropenem. Since testing of piperacillin alone is not available for all isolates, but the test is often performed in combination with tazobactam, an evaluation based strictly on the KRINKO definition is only possible to a limited extent. The authors will also determine the prevalence of 3MRGN/4MRGN strains based on the KRINKO definition in the next GERMAP report.

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* have been found in a nearly constant rate of approx. 43% over the last three years. This rate of MDR *P. aeruginosa* is the result of the lifelong persistence of individual clones in the respiratory tract of CF patients (see Fig. 4.1.6.2.4).

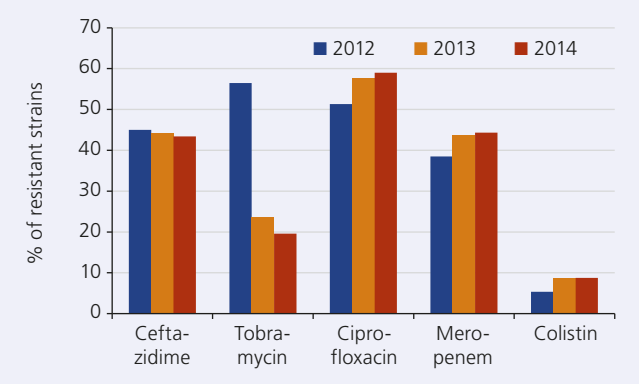


Fig. 4.1.6.2.2: Percentage of *P. aeruginosa* isolates resistant to ceftazidime, tobramycin, ciprofloxacin, meropenem and colistin in CF patients aged 18 years or older

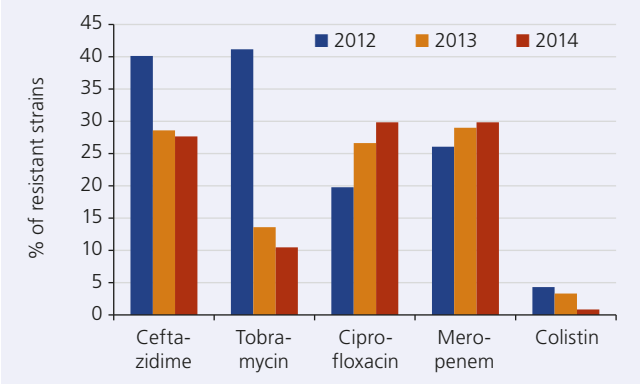


Fig. 4.1.6.2.3: Percentage of *P. aeruginosa* isolates resistant to ceftazidime, tobramycin, ciprofloxacin, meropenem and colistin in CF patients aged below 18 years

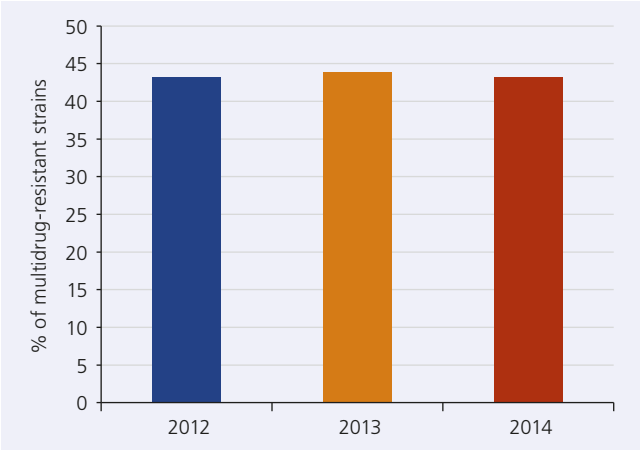


Fig. 4.1.6.2.4: Percentage of multidrug-resistant *P. aeruginosa* isolates (susceptible to only one or none of the antimicrobials ceftazidime, ciprofloxacin and meropenem). Isolates from CF patients aged > 18 years are shown. Every phenotype was counted only once per patient and year.

Compared to previous studies (GERMAP 2012), the rate has remained constant when looking only at the data reported by the Consultant Laboratory in Hannover and has increased when evaluating all data reported by both former consultant laboratories (37%). The increase in resistance rate compared to that ascertained previously on the basis of the cumulative data can probably be explained by the facts that the isolates were obtained from final-stage pulmonary infections. The Hannover Medical School has a focus on lung transplantation in CF patients, so these patients have previously been repeatedly exposed to antipseudomonal substances.

Conclusion

According to the data reported by the former Consultant Laboratories for CF Bacteriology (Northern Germany: Institute of Medical Microbiology and Hospital Hygiene of the Hannover Medical School [MHH], Southern Germany: Max von Pettenkofer Institute of Hygiene and Medical Microbiology of the Ludwig Maximilian University Munich [MvP]), the resistance situation for the antipseudomonal antimicrobials used most commonly for the treatment of CF remained stable over the period 2000-2011 and only a slight increase in the resistance rates of *Pseudomonas* isolates from adult CF patients was observed.

In the new study period 2012-2014, only the data reported by the current Consultant Laboratory for CF Bacteriology (Hannover) can be evaluated. The level of resistance continues to increase slowly, although not for all antimicrobials, while the overall *P. aeruginosa* colonisation rate (age adjusted) in CF patients in Germany is decreasing.

Overall, the resistance rates of *P. aeruginosa* in CF patients are at a high level. The further development needs to be monitored as part of continuous surveillance, in particular to recognise any changes in the prevalence and spread of resistance timely 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. In view of these numerous specific factors, microbiological CF testing should be performed in specialised laboratories.

➤ L. Sedlacek, S. Suerbaum and S. Ziesing
Reviewer: N. Schnitzler

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 (occasionally also referred to as *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex).[1] 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 mutations. 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 two other 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.[2] β-lactamases most commonly causing carbapenem resistance are the oxacillinases OXA-23, OXA-40, OXA-58 and OXA-143.[2] Outbreaks are almost exclusively limited to intensive care units. Outside intensive care units, *A. baumannii* usually causes no clinical or hygiene-related problems.

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), 2010 (n=200) and 2013 (n=173). When applying the EUCAST breakpoints (version 5.0), a significant increase in the rate of carbapenem resistance was observed during the study period (Fig. 4.1.6.3.1). To some extent, this resistance development is attributable to the fact that the identification of *Acinetobacter* species using conventional methods was previously less reliable, which is why species outside the *A. baumannii* group in which carbapenem resistance virtually never occurs were also included. In 2013, approx. 25% of the isolates were resistant to fluoroquinolones (ciprofloxacin, levofloxacin) and approx. 15% to carbapenems. The rates of resistance to amikacin and tobramycin were 10-15% and to gentamicin above 15%.[3]

Among the 173 isolates tested in 2013, 88 were identified as *A. baumannii* and 85 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). Of the 28 isolates that showed intermediate susceptibility or resistance to imipenem and/or meropenem, 27 belonged to the *A. baumannii* species and one to the *A. pittii* species. Eight of the 88 (9.1%) *A. baumannii isolates* and 9 of the 85 (10.6%) *A. pittii* isolates additionally showed intrinsic resistance to penicillins and cephalosporins and non-susceptibility to fluoroquinolones, but were susceptible to carbapenems (formally 3MRGN according to the KRINKO definition).[4] Non-susceptibility to carbapenems (4MRGN according to the KRINKO definition) was found in 27 of the 88 (30.7%) *A. baumannii* isolates and in one *A. pittii* isolate.

Colistin represents a therapeutic alternative for the treatment of infections caused by carbapenem-resistant isolates of the *A. baumannii* group. All isolates tested in the 2013 study were found to be susceptible to colistin. In the presence of a concentration

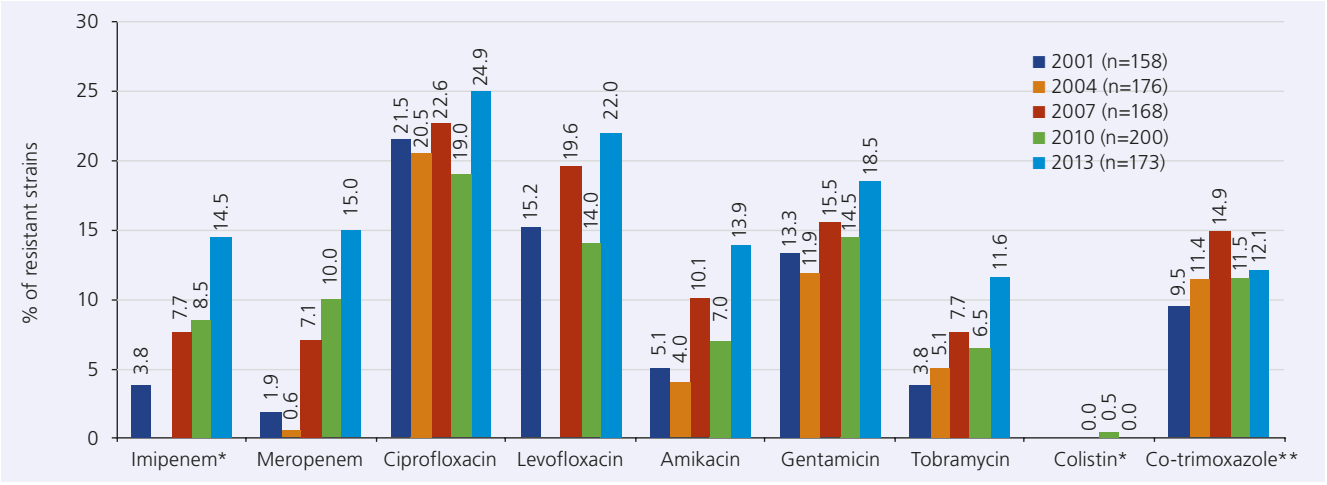


Fig. 4.1.6.3.1: Percentage of resistant strains of the *A. baumannii* group, 2001-2013 (Source: PEG resistance study, hospital care)
* Imipenem and levofloxacin were not tested in 2004 and colistin was tested from 2007 on; ** Trimethoprim/Sulfamethoxazole

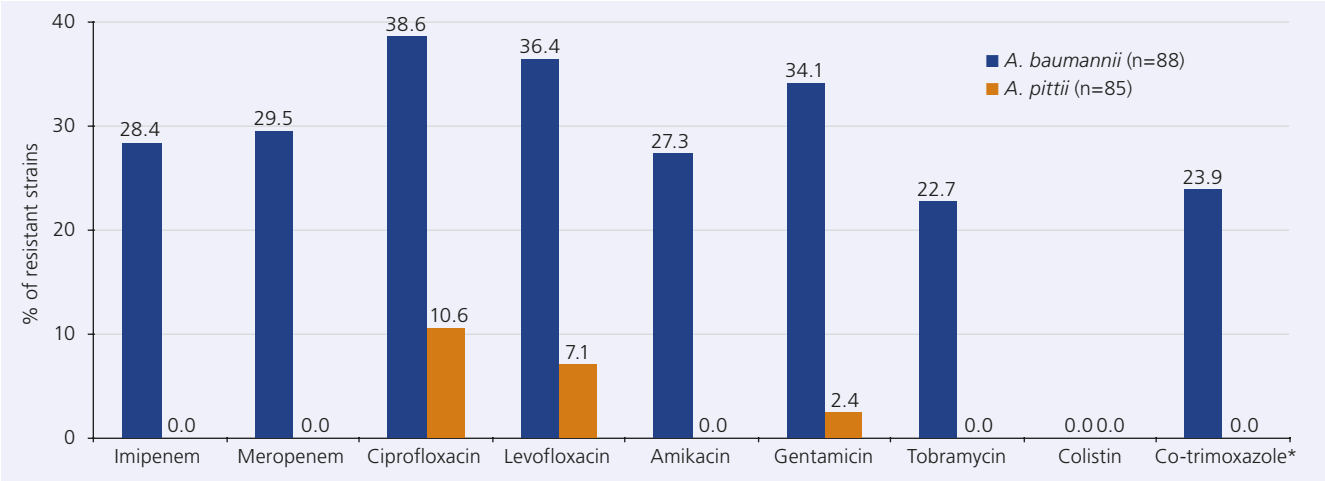


Fig. 4.1.6.3.2: Percentage of resistant *A. baumannii* and *A. pittii* strains in 2013 (Source: PEG resistance study, hospital care)
** Trimethoprim/Sulfamethoxazole

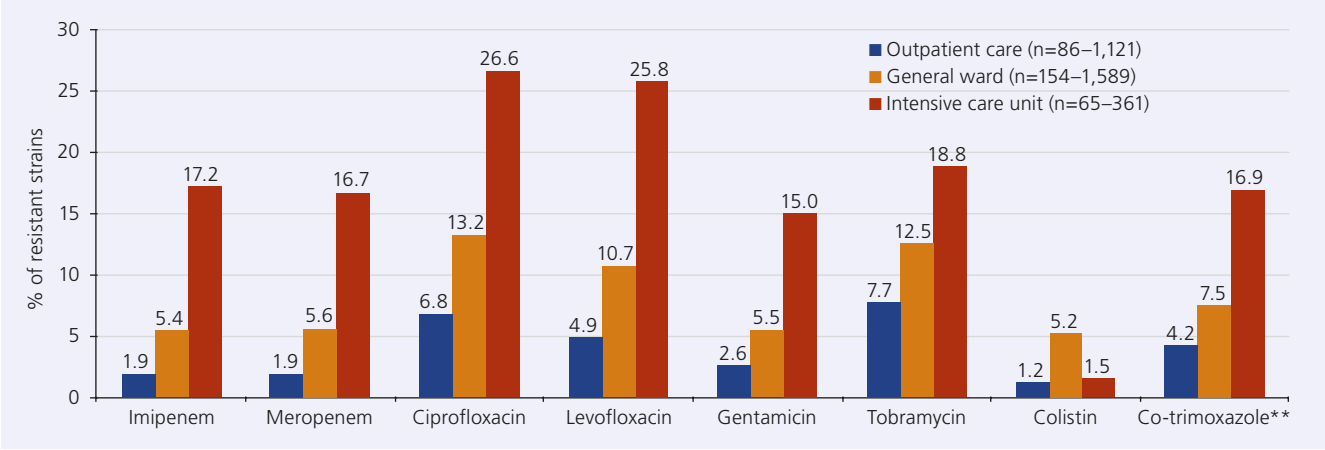


Fig. 4.1.6.3.3: Percentage of resistant strains of the *A. baumannii* group from outpatient care, on general wards and in intensive care units (Source: ARS, 2014 data*)
* Data as of: 01/07/2015; ** Trimethoprim/Sulfamethoxazole

of 1 mg/l, tigecycline exhibited in vitro activity against 23 and in the presence of a concentration of 2 mg/l to 27 of the 28 isolates with intermediate susceptibility or resistance to carbapenems.[3]

Antimicrobial Resistance Surveillance System (ARS)

The ARS project provides data for the period 2008-2014 for the inpatient and outpatient care sectors.[5] However, the reliability of the data is limited by the fact that the susceptibility to various antimicrobials was tested in different strain collectives. Fig. 4.1.6.3.3 shows based on the 2014 data that the level of resistance to the relevant antimicrobials in isolates from patients in intensive care units is about three times as high as in isolates from patients on general wards and from outpatients.

The data on the resistance development in isolates of the *A. baumannii* group in inpatient care is presented below. The rate of carbapenem resistance (imipenem, meropenem) initially increased from < 5% in 2008 to approx. 14% in 2012 and then dropped to 7-8% in 2014 (data as of 01/07/2015). Aminoglycosides showed a comparable trend; the prevalence of resistance to gentamicin and tobramycin was 8.6% and 1.6% in 2008, 14.9% and 16.3% in 2012 and 7.1% and 14.4% in 2014, respectively. By contrast, fluoroquinolones and co-trimoxazole were subject to a downward trend in resistance between 2008 and 2014 (decrease from 29.9% to 15.5% for ciprofloxacin, from 22.8% to 13.2% for levofloxacin and from 19.7% to 9.1% for co-trimoxazole). The observed trends in resistance are thus only partly consistent with the results of the PEG resistance study, which indicates a continued increase in the prevalence of resistance to the relevant antimicrobial classes for 2013.

However, it should be mentioned that the routine laboratory methods often do not allow a clear identification of *Acinetobacter* spp. at species level, which is why the indicated resistance rates of *A. baumannii* can be regarded as being too low.

German Tigecycline Evaluation Surveillance Trial (G-TEST)

The study ended in 2009. The rates of resistance ascertained in 2005, 2007 and 2009 were presented in the 2012 GERMAP report.[6]

Characterisation of carbapenem-resistant strains

Molecular characterisation of the above-mentioned 28 isolates showing intermediate susceptibility or resistance to imipenem and meropenem tested within the 2013 PEG resistance study demonstrated that 21 *A. baumannii* isolates expressed an OXA-23-like carbapenemase and four *A. baumannii* isolates as well as the one single *A. pittii* isolate with reduced susceptibility to carbapenems expressed an OXA-24-like carbapenemase. One

A. baumannii isolate expressed an OXA-58-like carbapenemase and another isolate an NDM-1 carbapenemase.[3] 24 of the 27 carbapenem-resistant *A. baumannii* isolates were classified as belonging to the clonal lineage IC 2 predominant in Europe.[2]

The predominance of OXA-23 also became apparent in the test specimens of *A. baumannii* isolates with suspected presence of carbapenemases submitted to the National Reference Centre for Gram-Negative Hospital Pathogens in 2014. An OXA-24 carbapenemase was detected in 346 of the 467 strains. The second and third most common carbapenemases were OXA-72 (n=63) and OXA-58 (n=37), respectively.[7] The 30 carbapenemase-positive *A. pittii* isolates show a greater diversity of carbapenemases, with the metallo-β-lactamase GIM-1 being observed most frequently (n=12), followed by VIM-4 (n=6), VIM-2 (n=5) and OXA-72 (n=4).

Conclusion

According to the results of the 2013 PEG resistance study, the average prevalence of resistance to carbapenems in strains of the *A. baumannii* group is approx. 15%, with the rate of non-susceptible strains in *A. baumannii* isolates (approx. 30%) being significantly higher than in *A. pittii* isolates (1.2%). Based on the data reported by the ARS project, 7.6% of the *A. baumannii* isolates were resistant to carbapenems in 2014, with the rates of resistance varying greatly between intensive care units and general wards (approx. 17% vs. 5-6%). To some extent, this difference is attributable to the fact that in the past semi-automated systems such as VITEK, Phoenix and Microscan did not allow for a clear identification of *A. baumannii*, and the inclusion of *A. pittii*, a species which is more common outside intensive care units and rarely exhibits resistance to carbapenems, contributes to a low carbapenem resistance rate. Overall, this entails considerable inaccuracies in the assessment of the resistance development.

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. Second-generation (group 2) carbapenems (imipenem, meropenem) are still recommended for the treatment of severe infections. In the event of resistance to carbapenems and fluoroquinolones, colistin can be used. Tigecycline is occasionally also considered to be an alternative for the treatment of *Acinetobacter* infections.

➤ M. Kresken, B. Körber-Irrgang, M. Kaase, H. Seifert
Reviewer: E. Straube

1. Peleg AY, Seifert H, Paterson DL. *Acinetobacter baumannii*: emergence of a successful pathogen. Clin Microbiol Rev 2008;21:538-82.
2. Higgins PG, Dammhayn C, Hackel M, Seifert H. Global spread of carbapenem-resistant *Acinetobacter baumannii.* J Antimicrob Chemother 2010;65:233-8.
3. Kresken M, Hafner D, Körber-Irrgang B für die Studiengruppe. Epidemiologie und Resistenzsituation bei klinisch wichtigen Infektionserregern aus dem Hospitalbereich gegenüber Antibiotika. Bericht über die Ergebnisse einer multizentrischen Studie der Paul-Ehrlich-Gesellschaft für Chemotherapie e.V. aus dem Jahre 2013. Antiinfectives Intelligence, Rheinbach, 2016. Verfügbar unter http://www.p-e-g.org/econtext/Berichte%20der%20Studien.
4. Empfehlung der Kommission für Krankenhaushygiene und Infektionsprävention (KRINKO) beim Robert Koch-Institut (RKI). Hygienemaßnahmen bei Infektionen oder Besiedlung mit multiresistenten gramnegativen Stäbchen. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2012; 55: 1311-54.
5. ARS – Antibiotika-Resistenz-Surveillance in Deutschland. Verfügbar unter https://ars.rki.de.
6. GERMAP 2012. Bericht über den Antibiotikaverbrauch und die Verbreitung von Antibiotikaresistenzen in der Human- und Veterinärmedizin. Antiinfectives Intelligence, Rheinbach, 2014. Verfügbar unter http://www.p-e-g.de/econtext/germap.
7. Robert Koch-Institut. Bericht des Nationalen Referenzzentrums (NRZ) für gramnegative Krankenhauserreger - Zeitraum 1. Januar 2014 bis 31. Dezember 2014. Epid Bull 2016;2:11-4.

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 (see review: Brooke 2012[1]; Looney et al. 2009[2]). Although it is not considered highly virulent, it exhibits intrinsic resistance to multiple antimicrobials. It is frequently associated with biofilm and device-associated infections. It primarily causes pneumonia, in particular late-onset ventilator-associated pneumonia, since it is capable of growing in biofilms on respiratory epithelial cells.[3] However, this potentially 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 greatly in intensive care units compared to other pathogens or per 1,000 patient days, and, according to a multivariate analysis, correlates with the use 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 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] 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 effective than 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 15/05/2015).

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 than 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 prediction of the clinical efficacy of antimicrobials.

The first-line antimicrobial agent used for the treatment of *S. maltophilia* infections is trimethoprim/sulfamethoxazole (co-trimoxazole). Fluoroquinolones available on the German market and, where 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, which can be discussed on a case-by-case basis once MIC values are available. A small number of individual case reports suggest that ceftazidime could also be effective (see review: Samonis et al. 2012[11]; Falagas et al. 2008[12]; Nicodemo and Paez 2007[13]).

Initial reports of trimethoprim/sulfamethoxazole resistance and its molecular basis were given particular attention.[14,15] Resistance is conferred by mobile genetic elements, which may lead to rapid spread of resistance.

In vitro resistance situation

A number of resistance studies in Germany provide a relatively up-to-date picture of the resistance situation (Tab. 4.1.6.4.1). These include the 2013 resistance study on clinical infection isolates conducted by the Paul Ehrlich Society, the Antimicrobial Resistance Surveillance project of the Robert Koch Institute (ARS, https://ars.rki.de, data as of 15/05/2015), which provides information on isolates from inpatient care, as well as the "Surveillance of Antimicrobial Use and Bacterial Resistance in Intensive Care Units" project (SARI). They classify pathogens according to clinical categories based on the various antimicrobial testing

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)	Antimicrobial	Number of isolates tested	Resistance rate (%)
PEG V/2013 (EUCAST)	Co-trimoxazole	286	2.4
SARI 01/2009–12/2014 (DIN, CLSI, EUCAST)	Co-trimoxazole	2,161	4.2
	Ceftazidime	2,276	48.2
	Ciprofloxacin	2,067	28.8
	Levofloxacin	943	18.7
ARS 2013 (DIN, CLSI, EUCAST)	Co-trimoxazole	3,405	4.9
	Ceftazidime	2,259	62.1
	Moxifloxacin	1,545	16.0
	Tigecyclin	1,432	20.0
	Colistin	798	45.6
ARS 2008 (DIN, CLSI)	Co-trimoxazole	829	5.3
	Ceftazidime	792	40.7
	Moxifloxacin	583	9.3
	Tigecyclin	120	14.2
	Colistin	41	17.1

standards used by the microbiology laboratories (DIN, CLSI or EUCAST). They all agree that the rates of resistance to co-trimoxazole are at 5%. When comparing the last few years, the ARS results reveal a trend towards increasing rates of resistance to moxifloxacin, ceftazidime and tigecycline.

Except for co-trimoxazole, the rates of resistance to all other antimicrobials have been observed to increase considerably in Germany over the past years. In isolates from CF patients or in other regions of the world, however, the rates of resistance to co-trimoxazole may be significantly higher.[16,17]

Conclusion

EUCAST breakpoints have so far only been available for co-trimoxazole. 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, co-trimoxazole seems to be the first-line antimicrobial agent currently used for the (empiric) treatment of infections in Germany. The potential spread of various 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 mechanism being known. Combinations, e.g. with a colistin inhalation therapy, represent a clinically effective alternative.

➤ D. Jonas
Review: W.V. Kern

1. Brooke JS. *Stenotrophomonas maltophilia*: an emerging global opportunistic pathogen. Clin Microbiol Rev 2012;25:2-41.
2. Looney WJ, Narita M, Muhlemann K. *Stenotrophomonas maltophilia*: an emerging opportunist human pathogen. Lancet Infect Dis 2009;9:312-23.
3. Pompilio A, Crocetta V, Confalone P, Nicoletti M, et al. Adhesion to and biofilm formation on IB3-1 bronchial cells by *Stenotrophomonas maltophilia* isolates from cystic fibrosis patients. BMC Microbiol 2010;10:102.
4. Meyer E, Schwab F, Gastmeier P, Rueden H, et al. *Stenotrophomonas maltophilia* and antibiotic use in German intensive care units: data from project SARI (Surveillance of Antimicrobial Use and Antimicrobial Resistance in German Intensive Care Units). Journal of Hospital Infection 2006;64:238-43.
5. Kaiser S, Biehler K, Jonas D. A *Stenotrophomonas maltophilia* multilocus sequence typing scheme for inferring population structure. J Bacteriol 2009;191:2934-43.
6. Crossman LC, Gould VC, Dow JM, Vernikos GS, et al. The complete genome, comparative and functional analysis of *Stenotrophomonas maltophilia* reveals an organism heavily shielded by drug resistance determinants. Genome Biol 2008;9:R74.
7. Ryan RP, Monchy S, Cardinale M, Taghavi S, et al. The versatility and adaptation of bacteria from the genus *Stenotrophomonas*. Nat Rev Microbiol 2009;7:514-25.
8. Carroll KC, Cohen S, Nelson R, Campbell DM, et al. Comparison of various in vitro susceptibility methods for testing *Stenotrophomonas maltophilia*. Diagn Microbiol Infect Dis 1998;32:229-35.
9. Tatman-Otkun M, Gurcan S, Ozer B, Aydoslu B, et al. The antimicrobial susceptibility of *Stenotrophomonas maltophilia* isolates using three different methods and their genetic relatedness. BMC Microbiol 2005;5:24.
10. Wu K, Yau YC, Matukas L, Waters V. Biofilm compared to conventional antimicrobial susceptibility of *Stenotrophomonas maltophilia* Isolates from cystic fibrosis patients. Antimicrob Agents Chemother 2013;57:1546-8.
11. Samonis G, Karageorgopoulos DE, Maraki S, Levis P, et al. *Stenotrophomonas maltophilia* infections in a general hospital: patient characteristics, antimicrobial susceptibility, and treatment outcome. PLoS One 2012; 7:e37375.
12. Falagas ME, Valkimadi PE, Huang YT, Matthaiou DK, et al. Therapeutic options for *Stenotrophomonas maltophilia* infections beyond co-trimoxazole: a systematic review. J Antimicrob Chemother 2008;62:889-94.
13. Nicodemo AC, Paez JI. Antimicrobial therapy for *Stenotrophomonas maltophilia* infections. Eur J Clin Microbiol Infect Dis 2007;26:229-37.
14. Toleman MA, Bennett PM, Bennett DM, Jones RN, et al. Global emergence of trimethoprim/sulfamethoxazole resistance in *Stenotrophomonas maltophilia* mediated by acquisition of *sul* genes. Emerg Infect Dis 2007;13:559-65.
15. Barbolla R, Catalano M, Orman BE, Famiglietti A, et al. Class 1 integrons increase trimethoprim-sulfamethoxazole MICs against epidemiologically unrelated *Stenotrophomonas maltophilia* isolates. Antimicrob Agents Chemother 2004;48:666-9.
16. Milne KE, Gould IM. Combination antimicrobial susceptibility testing of multidrug-resistant *Stenotrophomonas maltophilia* from cystic fibrosis patients. Antimicrob Agents Chemother 2012;56:4071-7.
17. Farrell DJ, Sader HS, Jones RN. Antimicrobial Susceptibilities of a Worldwide Collection of *Stenotrophomonas maltophilia* Isolates Tested against Tigecycline and Agents Commonly Used for *S. maltophilia* Infections. Antimicrob Agents and Chemother 2010;54:2735-7.

4.1.7 *Neisseria meningitidis*

Neisseria meningitidis is a pathogen causing bloodstream infections and meningitis, especially in infants, young children and adolescents. Meningococcal disease, which is a notifiable disease in Germany, 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 annual incidence in Germany is currently below 0.5 infections per 100,000 inhabitants and can thus be classified as low, even if slight under-reporting has to be assumed. By contrast, outbreaks, some of which affected more than 10,000 people, have been observed for decades in the African Meningitis Belt, but have now been reduced significantly as a result of the introduction of a serogroup-A vaccine (MenAfriVac™) specifically developed for Africa.[1]

Hence, the most important measure to prevent invasive meningococcal disease is vaccination. In addition to the so-far available vaccines against the serogroups A, C, W and Y, most of which are based on conjugated capsular polysaccharides, a vaccine against serogroup B meningococci based on outer membrane proteins (Bexsero®), which is approved for use from the second month of life and has been available in Germany since the end of 2013, was introduced in Europe in 2012. Since 2014, another serogroup B vaccine, which is also based on an outer membrane protein, has been approved in the U.S.[2] However, the protein-based vaccines are not active against all serogroup B strains.[3] Since 2006, there has been a recommendation of the Standing Committee on Vaccination (STIKO) in Germany for the use of meningococcal C conjugate vaccines from the second year of life. If indicated, tetravalent conjugate vaccines (ACWY) are available to travellers, high-risk individuals, close contacts of patients as well as microbiology laboratory staff. The use of the serogroup B vaccine has so far not been generally recommended by the STIKO. However, the use of the serogroup B vaccine for high-risk individuals, close contacts of patients and microbiology laboratory staff has been newly added to the current STIKO recommendations (Epidemiological Bulletin, No. 34/2015).

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-contacts of patients (e.g. household members) (cf. current STIKO recommendations, Epidemiological Bulletin, No. 34/2015). The use of azithromycin as an alternative is being discussed at European level.[4]

In contrast to the situation of the related species *Neisseria gonorrhoeae* (gonococci), the resistance situation of meningococci is not alarming. The failure of the antimicrobial therapy rarely results in lethal infections, in which the rapid progression usually cannot be stopped despite therapy and effective eradication of the bacteria. There is experimental evidence that both penicillin resistance[5] and rifampicin resistance[6] have a negative influence on the fitness of the bacteria. The secondary cases of an outbreak with rifampicin-resistant isolates in patients who had received rifampicin prophylaxis, which were processed in 2015 by the National reference centre for meningococci and Haemophilus influenzae (NRZMHi), the Robert Koch Institute (RKI) and the local health authorities, nevertheless demonstrated that the development of rifampicin resistance needs to be monitored carefully (unpublished). This is also confirmed by previous reports from other countries.[7]

The molecular mechanisms of antimicrobial resistances in meningococci have been identified. 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 PBP2 circulate in meningococci.[8] 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.[9] Resistance to gyrase inhibitors is attributed to mutations in the *gyrA* and *parC* genes.[10] An international *Neisseria* sequence database comprising resistance genes has been established and is now used at reference laboratory level (http://pubmlst.org/ neisseria/).

The Reference Centre tests all submitted meningococcal isolates for susceptibility to penicillin G, rifampicin, ciprofloxacin and cefotaxime by means of agar diffusion tests using E-test strips. Since 2011, the EUCAST breakpoints have been used for the interpretation of the test results. Resistance to rifampicin, ciprofloxacin and cefotaxime is extremely rare in Germany. Since 2002, more than 99% of all tested strains were susceptible to rifampicin and ciprofloxacin. During the period 2013/2014, one single invasive strain was found to be resistant to rifampicin. Cefotaxime has been tested since 2010. Resistance to cefotaxime has so far not been observed at the NRZMHi.

Trends in the development of penicillin resistance

According to EUCAST, a MIC of more than 0.06 mg/l indicates reduced susceptibility to penicillin. Meningococcal strains with a MIC value of more than 0.25 mg/l are classified as resistant. During the period 2002-2012, the average percentage of strains with reduced susceptibility to penicillin was 17%. In 2013, a peak value of 40% was observed, which dropped again to 22% in 2014 (Fig. 4.1.7.1). The percentage of penicillin-resistant strains in 2013 (2.4%) and 2014 (2.9%) remained at a similar level as in 2012 (2.2%). This trend is monitored carefully by the NRZ for Meningococci. Temporal variations may be associated with the variable occurrence of meningococcal clones or clonal complexes which comprise genetically related meningococci. 23% of all 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%

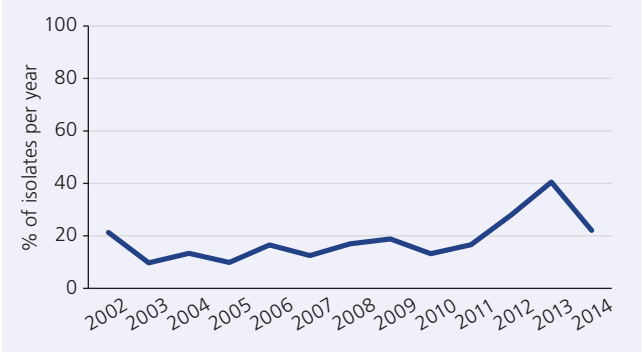


Fig. 4.1.7.1: Meningococcal strains with reduced susceptibility to penicillin (MIC values above 0.06 mg/l; 2002–2014)

in meningococci belonging to the ST-41/44 complex. This clonal complex is responsible for a large number of serogroup B infections in Germany.

Conclusion

The resistance situation of meningococci continues to be relative uncritical, so treatment and post-exposure prophylaxis can be conducted using the approved regimens, as published in an ECDC *Guidance*[4]. Rifampicin-resistant isolates are observed as part of outbreaks following rifampicin prophylaxis. The increase in the prevalence of strains showing intermediate susceptibility to penicillin observed since 2011 did not continue in 2014; the percentage of susceptible strains again approximates 80%. The development nevertheless needs to be monitored further.

➤ H. Claus, U. Vogel
Reviewer: R. Berner, W. Hellenbrand

1. Daugla DM, Gami JP, Gamougam K, Naibei N, et al. Effect of a serogroup A meningococcal conjugate vaccine (PsA–TT) on serogroup A meningococcal meningitis and carriage in Chad: a community study. The Lancet 2014;383:40-7.
2. Oviedo-Orta E, Ahmed S, Rappuoli R, Black S. Prevention and control of meningococcal outbreaks: The emerging role of serogroup B meningococcal vaccines. Vaccine 2015;33:3628–35.
3. Vogel U, Taha MK, Vazquez JA, Findlow J, et al. Predicted strain coverage of a meningococcal multicomponent vaccine (4CMenB) in Europe: a qualitative and quantitative assessment. Lancet Infect Dis 2013;13:416-25.
4. ECDC Guidance. Public health management of sporadic cases of invasive meningococcal disease and their contacts. October 2010.
5. Zarantonelli ML, Skoczynska A, Antignac A, El Ghachi M, et al. Penicillin resistance compromises Nod1-dependent proinflammatory activity and virulence fitness of *Neisseria meningitidis*. Cell Host Microbe 2013;13:735-45.
6. Taha MK, Zarantonelli ML, Ruckly C, Giorgini D, et al. Rifampin-resistant *Neisseria meningitidis*. Emerg Infect Dis 2006;12:859-60.
7. Dawson SJ, Fey RE, McNulty CA. Meningococcal disease in siblings caused by rifampicin sensitive and rifampicin resistant strains. Commun Dis Public Health 1999;2:215-6.
8. Taha MK, Vazquez JA, Hong E, Bennett DE, et al. Target gene sequencing to characterize the penicillin G susceptibility of *Neisseria meningitidis*. Antimicrob Agents Chemother 2007;51:2784-92.
9. Taha MK, Hedberg ST, Szatanik M, Hong E, et al. Multicenter study for defining the breakpoint for rifampin resistance in *Neisseria meningitidis* by *rpoB* sequencing. Antimicrob Agents Chemother 2010;54:3651-8.
10. Hong E, Thulin Hedberg S, Abad R, Fazio C, et al. Target gene sequencing to define the susceptibility of *Neisseria meningitidis* to ciprofloxacin. Antimicrob Agents Chemother 2013;57:1961-4.

4.1.8 *Neisseria gonorrhoeae*

Neisseria gonorrhoeae (gonococci) is a pathogen 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 pelvic inflammatory disease (PID) 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 general in Germany. Based on estimates, an incidence of 25-40 cases/100,000 inhabitants is assumed, which is equivalent to approx. 21,000-33,000 new infections per year in Germany.[1] In 2010, incidence rates of 0.6-30/100,000[1] were estimated in other European countries and 100.8/100,000 in the U.S.[3]

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[4-6] 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

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

Antimicrobial	Breakpoints (MIC in 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

Tab. 4.1.8.2: Breakpoints for interpreting the antimicrobial susceptibility of *N. gonorrhoea* (Source: EUCAST Version 5.0, 2015)

Antimicrobial	Breakpoints (MIC in 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

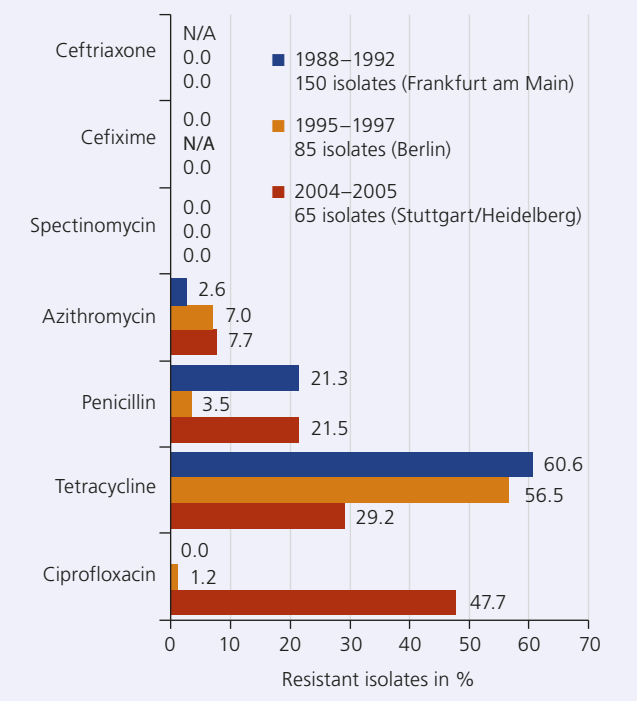


Fig. 4.1.8.1: Temporal and regional development of antimicrobial resistance in *N. gonorrhoea* (Source: References[4-6])

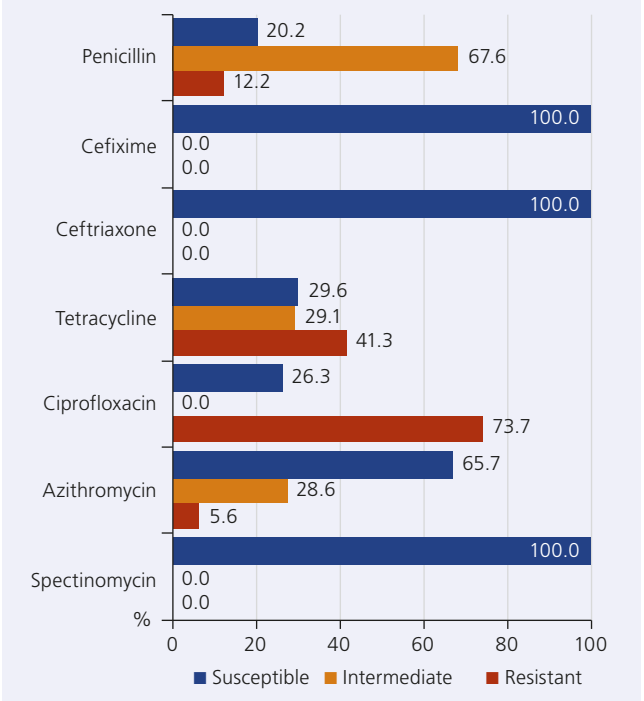


Fig. 4.1.8.2: Antimicrobial susceptibility of *N. gonorrhoeae* (n=213) in Germany; PEG resistance study, 01/10/2010-31/12/2011[9]

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 for 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 confirmed in Northern German surveys, revealing a 34% ciprofloxacin resistance rate in 1999[7] and in the Rhine-Main region and a 64% ciprofloxacin resistance rate in 2008[8]. 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 (group 3) cephalosporins (ceftriaxone and cefixime) as well as the aminoglycoside spectinomycin exhibited 100% in vitro activity.

The antimicrobial susceptibility and molecular epidemiology of gonococci were recorded for the first time throughout Germany as part of the 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 Infection Control at the Hospital of Goethe-University in Frankfurt am Main, for the purpose of antimicrobial susceptibility testing and pathogen identification. The 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).

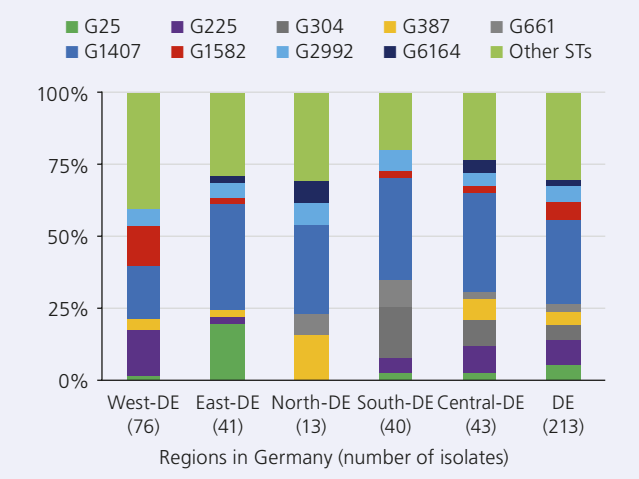


Fig. 4.1.8.3: Percentage of various *N. gonorrhoeae* genotypes in various regions in Germany[9]

Molecular characterisation of the 213 gonococcal isolates from Germany demonstrated the predominance of the worldwide most common genotype G1407 as well as an overall high level of heterogeneity with 99 different sequence types (ST) (Fig. 4.1.8.3).

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 based on the voluntary submission of isolates. According to the data reported by the consultant laboratory, gonococcal isolates with reduced susceptibility to third-generation (group 3) cephalosporins have been detected in Germany.[10-12] The data for the first half of 2014 confirms 75% non-susceptibility to penicillin, 1% to cefixime, 0% to ceftriaxone, 70% to ciprofloxacin, 39% to azithromycin and 0% to spectinomycin (Fig. 4.1.8.4). The Gonococcal Resistance Network (GORENET) was established in 2014 at the RKI in collaboration with the Consultant Laboratory for Gonococci with the aim to improve the availability of gonococcal resistance data.

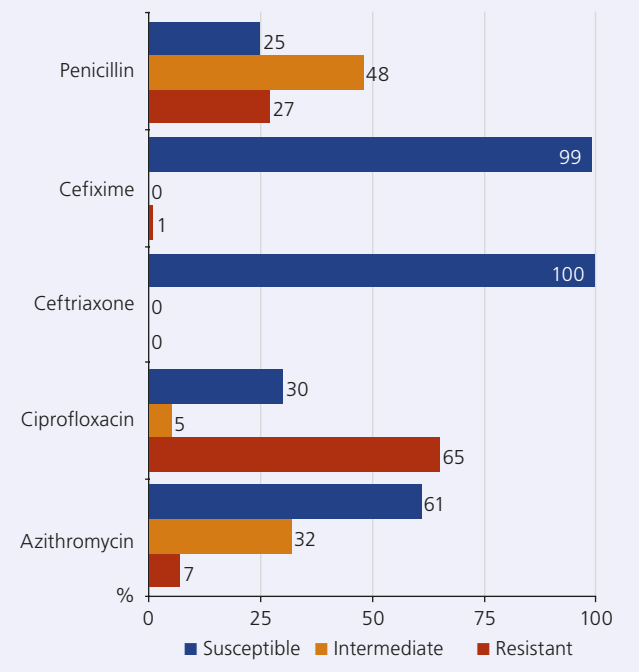


Fig. 4.1.8.4: Antimicrobial susceptibility of *N. gonorrhoeae* (n=100) in Germany; data reported by the Consultant Laboratory for Gonococci, 1st half of 2014[10]

Antimicrobial resistance knows no geographical limits. Reports from the Netherlands on the increasing rate of *N. 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.[13,14]

Conclusion

The antimicrobial susceptibility of *N. gonorrhoeae* was recorded systematically in Germany for the first time as part of the PEG resistance study. Continuous surveillance of the antimicrobial susceptibility of *N. gonorrhoeae* has been ensured by the Consultant Laboratory/GORENET since 2010. The maintenance and advancement of a surveillance system is ensured by the establishment of the Consultant Laboratory for Gonococci as well as GORENET. The WHO demands that empiric therapy of gonorrhoea yield a therapeutic success of ≥ 95%. In view of the present resistance data of *N. gonorrhoeae*, third-generation (group 3) cephalosporins and spectinomycin seem to be the only options to achieve this goal. The efficacy of a combination therapy (ceftriaxone + azithromycin) requires evaluation regarding clinical evidence and resistance selection.

➤ T.A. Wichelhaus
Reviewer: V. Bremer, S. Buder, S. Dudareva-Vizule, K. Jansen

1. RKI: Gonorrhoe und Syphilis in Deutschland bis zum Jahr 2000. Epid Bull 2001;38:287-91.
2. ECDC: Annual epidemiological report Reporting on 2010 surveillance data and 2011 epidemic intelligence data 2012, ISBN 978-92-9193-443-0.
3. http://www.cdc.gov/std/stats10/gonorrhea.htm
4. Schäfer V, Enzensberger R, Schneider C, Rickmann J, et al. Epidemiology of penicillin-resistant *Neisseria gonorrhoeae* in Frankfurt, Germany. Eur J Clin Microbiol Infect Dis 1995;14:914-8.
5. Wagner J, Tebbe B, Hornle R, Chahin M, et al. Antibiotic susceptibility of *Neisseria gonorrhoeae* isolates in Berlin. Hautarzt 2000;51:666-9.
6. Enders M, Turnwald-Maschler A, Regnath T. Antimicrobial resistance of *Neisseria gonorrhoeae* isolates from the Stuttgart and Heidelberg areas of southern Germany. Eur J Clin Microbiol Infect Dis 2006;25:318-22.
7. Ungeheuer J, Michalewski-Zietz I. Stark zunehmende Resistenz von *Neisseria gonorrhoeae* gegen Ciprofloxacin in Norddeutschland. Chemother J 2001;10:35-6.
8. Rosenthal EJK, Lemberg U, Riegel H. Zum Auftreten von Resistenzen bei *Neisseria gonorrhoeae* im Rhein-Main-Gebiet. Epid Bull 2009;13:122-3.
9. Horn NN, Kresken M, Körber-Irrgang B, Göttig S, et al. Antimicrobial susceptibility and molecular epidemiology of *Neisseria gonorrhoeae* in Germany. Int J Med Microbiol 2014;304:586-91.
10. http://www.vivantes.de/uploads/GORENET_1_Hlbj_2014_Zahlen_und_Diagramme.pdf
11. ECDC: Gonococcal antimicrobial susceptibility surveillance in Europe 2010, ISBN 978-92-9193-343-3.
12. ECDC: Gonococcal antimicrobial susceptibility surveillance in Europe 2011, ISBN 978-92-9193-450-8.
13. de Vries HJ, van der Helm JJ, Schim van der Loeff MF, van Dam AP, et al. Multidrug-resistant *Neisseria gonorrhoeae* with reduced cefotaxime susceptibility is increasingly common in men who have sex with men, Amsterdam, The Netherlands. Eurosurveillance 2009;14:19330.
14. Unemo M, Golparian D, Nicholas R, Ohnishi M, et al. High-level cefixime- and ceftriaxone-resistant *Neisseria gonorrhoeae* in France: novel penA mosaic allele in a successful international clone causes treatment failure. Antimicrob Agents Chemother 2012;56:1273-80.

4.1.9 *Legionella* spp.

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. This most important representative of *Legionella* is 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.[1] 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.[2]

Specific patients are predisposed to acquiring a *Legionella* infection. These include in particular immunosuppressed patients after organ transplantation, a tumour disease and extended therapy with corticosteroids or TNF antagonists. 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. This means that the cases confirmed by laboratory testing and reported under the Infection Protection Act, most recently 922 cases in 2013, only represent a small fraction of the actually occurring infections. According to the findings of CAPNETZ, about 4% of all community-acquired pneumonia infections in Germany are caused by *Legionella*[3]. The severity of the clinical condition may vary greatly. In 2013, the mortality rate in the cases reported in Germany was 5.2%.[1]

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 was determined using cell cultures or animal experiments. Fluoroquinolones and newer macrolides such as clarithromycin or azithromycin exhibited the highest activity. Bruin et al. determined the 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.[4] According to in vitro studies, a new fluoroketolide exhibits an even higher activity against intracellular *Legionella*. However, the results of clinical studies are currently not yet available.[5]

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 reported a clinical wild-type isolate with elevated MIC values for both ciprofloxacin and azithromycin[6], resistance to the therapeutic agents of the classes of fluoroquinolones, macrolides, tetracyclines or rifampicin has so far not been found among clinical isolates. In this one isolate, a typical mutation in the QRDR region of the *gyrA* gene was detected, which explains the elevated MIC values. Studies conducted by the Consultant Laboratory for *Legionella* on 94 *L. pneumophila* strains isolated in Germany between 2002 and 2006 showed no elevated MIC values for these substances either (Lück et al., unpublished).

However, mutants resistant to erythromycin, rifampicin or fluoroquinolones can be easily cultured under laboratory conditions. These mutants also exhibit the typical mutations in the corresponding genes (*gyrA*, *gyrB*, *rpo*B, 23srRNA, ribosomal proteins). 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. The few published clinical observational studies found that levofloxacin was slightly superior to newer macrolides as regards the length of hospital stay.[7]

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 caused side effects, which is why it cannot be recommended without reservations. 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, as 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 suitable fluoroquinolone administered in the maximum dosage. Newer macrolides are also effective. 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.[8]

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

1. Robert-Koch-Institut: Legionärskrankheit in Deutschland (2001 bis 2013) Epid Bull 2015(13),95-106.
2. Lück C, Steinert M. Pathogenese, Diagnostik und Therapie der Legionella-Infektion. Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz 2006;49:439-49.

3. von Baum H, Ewig S, Marre R, Suttorp N, et al. Community acquired *Legionella pneumonia*. New insights from the German competence network CAPNETZ. Clin Inf Dis 2008;46:1356-64.
4. Bruin JP, Ijzerman EPF, den Boer JW, Mouton JW, et al. Wild-type MIC distribution and epidemiological cut-off values in clinical *Legionella pneumophila* serogroup 1 isolates. Diagn Microbiol Infect Dis 2012;72:103-8.
5. Mallegol J, Fernandes P, Melano RG, Guyard C. Antimicrobial activity of solithromycin against clinical isolates of *Legionella pneumophila* serogroup 1. Antimicrob Agents Chemother 2014;58:909-15.
6. Bruin JP, Koshkolda T, Ijzerman EP, Lück C, et al. Isolation of ciprofloxacin-resistant *Legionella pneumophila* in a patient with severe pneumonia. J Antimicrob Chemother 2014;69:2869-71.
7. Burdet C, Lepeule R, Duval X, Caseris M, et al. Quinolones versus macrolides in the treatment of legionellosis: a systematic review and meta-analysis. J Antimicrob Chemother 2014;69:2354-60.
8. Höffken, Lorenz J, Kern WV, Welte T, et al. S 3 Leitlinie - Epidemiologie, Diagnostik, antimikrobielle Therapie und Management von erwachsenen Patienten mit ambulant erworbenen tiefen Atemwegsinfektionen (akute Bronchitis, akute Exazerbation einer chronischen Bronchitis, Influenza und andere respiratorische Virusinfektionen) sowie ambulant erworbener Pneumonie – online version http://www.p-e-g.org/econtext/leitlinien.

4.1.10 *Mycobacterium tuberculosis*

Tuberculosis is one of the major causes of diseases and deaths worldwide. According to estimates of the World Health Organisation (WHO), about nine million people were diagnosed with tuberculosis and 1.5 million people died of the consequences of the disease in 2013. 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 patients. 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. Based on their efficacy and tolerability, the following antimicrobials are used for first-line therapy: isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E). Because of the necessity of parenteral administration, streptomycin (S) is used only rarely. 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 for the development of drug resistance 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 intrinsically resistant pathogens can multiply unimpeded, causing the susceptible pathogens eradicated by the antituberculous agent to be superseded by resistant bacteria after a short period of time. In particular in regions with high resistance rates, these resistant bacterial strains are transmitted and the patients are predominantly diagnosed with resistant tuberculosis.

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. For this reason, there is an urgent need for new, well-tolerated and highly effective anti-TB drugs, which must be prescribed carefully and specifically to prevent the development of further resistance. For the treatment of multidrug-resistant and extensively drug-resistant tuberculosis delamanid and bedaquiline are available.

With the introduction of the Infection Protection Act in 2001, resistance against the above-mentioned first-line antimicrobials (HREZS) in TB cases has to be notified nationwide and transmitted to the Robert Koch Institute (RKI). In addition, since 2011 the registration of resistance to second-line antimicrobials has also been implemented .

The resistance situation described in this chapter is based on the tuberculosis reporting data transmitted to the RKI by the deadline of 01/03/2014.

Tuberculosis and resistance situation in Germany in 2013

In 2013, a total of 4,318 new tuberculosis cases were notified in Germany, which is equivalent to an incidence rate of 5.3 TB cases per 100,000 inhabitants. Compared to the previous year, the number of cases increased by 2.4% (2012: 4,217 cases, incidence rate 5.2), which is comparable to that in 2011 (4,307 cases, incidence rate 5.3). This means that the downward trend in the number of cases observed for many years has now reached a plateau with a more or less consistent incidence rate.

The result of the susceptibility testing was available for 2,982 of the 4,318 cases (69.1%) – 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 2013, resistance to at least one of the five first-line antimicrobials ("any resistance" [HRZES]) was observed in 427 cases (14.3%). Multidrug-resistant tuberculosis (MDR-TB), defined as resistance to at least isoniazid and rifampicin, was found in 102 cases (3.4%).

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. The registration of resistance data for second-line antimicrobials was introduced in 2011 as part of the general reporting obligation. However, the software for recording this data has not yet been adapted in all health authorities, which is why the availability of data is currently limited and a reliable statement on the prevalence of XDR-tuberculosis in Germany cannot yet be made based on the present data.

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. The situation appears to be particularly problematic in the countries of the former Soviet Union. According to the findings of a multicentre, prospective cohort study among eight participating countries conducted by Dalton et al.[1], the average percentage of XDR-TB in all MDR-TB was 6.7%.

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. Based on the reporting data, the results of the susceptibility testing to at least one of eleven second-line antimicrobials (moxifloxacin, ofloxacin, levofloxacin, amikacin, capreomycin, kanamycin, cycloserine, linezolid, para-aminosalicylic acid (PAS), protionamide and rifabutin) were available for 32 (31.4%) of the total of 102 multidrug-resistant tuberculoses (MDR-TB) notified in Germany in 2013. Among the 32 MDR patients tested, resistance to at least one of the 11 second-line antimicrobials was detected in a total of 30 cases (93.7%). In 12 of the 30 cases, resistance to three or more second-line antimicrobials was found, with three cases being identified as XDR-tuberculosis. Four other patients also showed

very complex resistance patterns. However, the case definition of an XDR-TB was not yet met here, because no resistance to a fluoroquinolone was present in these cases. Such cases are referred to as pre-XDR-TB as per definition.

Results of susceptibility tests and molecular-epidemiological studies conducted by the NRZ for Mycobacteria at the Borstel Research Centre

The National Reference Centre for Mycobacteria at the Borstel Research Centre performed susceptibility testing as well as detailed molecular typing (24-loci MIRU-VNTR typing and spoligotyping) for 1,237 MDR-TB strains isolated from patients living in Germany during the period 1995-2013. A relevant number of MDR-TB strains was found to be resistant to further antituberculous drugs, e.g. to ethambutol (59%), pyrazinamide (42%), ethionamide (40%), amikacin (18%) and capreomycin (13%).

By means of genotyping, a large number of the strains were classified as the Beijing genotype (54%), followed by the genotypes LAM (13%), Haarlem (5%) and Ural (5%). In addition, 9% of all MDR strains were classified as belonging to a subgroup which has so far not been described in detail. The total rate of clustered isolates was 70%, with the clustering rate in Beijing strains (88%) being significantly higher than in strains not belonging to the Beijing family (50%). Moreover, more than 30% of all isolates were classified as belonging to the two largest clusters (Beijing 94-32, 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, 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. Information on a history of tuberculosis was available for 3,754 (86.9%) of the total of 4,318 cases reported. About one in eight of these patients (446 of 3,754; 11.9%) 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 tuberculosis and therapy is significantly higher than in patients without a previous tuberculosis and therapy (new cases).

For people with an immigration background, the epidemiological tuberculosis situation and the associated risk of infection in the country of origin play a crucial role in the respective risk of developing active tuberculosis (including resistant tuberculosis), since a latent *M. tuberculosis* infection may become active even many years later. The resistance characteristics of the pathogen usually also reflect the situation in the country of origin. This is confirmed by the evaluation of the data reported for 2013. The analysis of the resistance situation by country of birth reveals a significantly higher percentage of drug-resistant strains in patients born abroad (Tab. 4.1.10.2). Thus, the percentage of multidrug-resistant tuberculosis in patients born abroad is approximately eight times higher than in those born in Germany (Tab 4.1.10.2).

Among patients who were born in one of the successor states of the former Soviet Union (NIS; New Independent States), the prevalence of drug resistance is particularly high, although the absolute numbers are lower than those found in patients born in Germany. Approximately one-third of the pathogens (36.3%, 106 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 nearly four times higher than in patients born in Germany (9.4%, 113 cases) and nearly three times higher than in patients from all other native countries (13.6%, 183 cases; Fig. 4.1.10.1).

This difference is even more pronounced regarding multidrug-resistant tuberculosis: The proportion of MDR-TB in patients from the NIS (18.2%, 53 cases) was 26 times higher than in patients born in Germany (0.7%, 8 cases) and seven times higher than in patients born in other countries (2.5%, 33 cases; Fig. 4.1.10.1). The three XDR patients mentioned above were also born in an NIS country and had a history of tuberculosis.

A further risk factor for the development of resistant tuberculosis is non-adherence to treatment. Thus, homeless persons, persons with a history of imprisonment or addictive diseases (alcoholism, drug addiction) are not only at increased risk of developing tuberculosis, but also at increased risk of developing resistant

Tab. 4.1.10.1: Number and percentage of resistant tuberculosis by status of previous TB-diagnosis and previous treatment (Source: Robert Koch Institute, 2013 Report on Tuberculosis Epidemiology in Germany)

Resistance phenotype	Previous TB-diagnosis with previous treatment (n=146)		New cases (n=2,359)		Factor previous TB-diagnosis/ new cases
	Number	Percentage	Number	Percentage	
Isoniazid (H)*	34	23.3%	190	8.1%	2.9
Rifampicin (R)*	29	19.9%	63	2.7%	7.4
Pyrazinamide (P)*	20	13.7%	72	3.1%	4.5
Ethambutol (E)*	16	11.0%	31	1.3%	8.3
Streptomycin (S)*	28	19.2%	184	7.8%	2.5
Multi-drug resistance*	27	18.5%	56	2.4%	7.8
Any resistance excl. PZA (HRES)*	38	26.0%	276	11.7%	2.2
Any resistance incl. PZA (HRESZ)*	39	26.7%	308	13.1%	2.0
Poly-resistance excl. PZA (HRES)	3	2.1%	62	2.6%	0.8

*Significantly higher percentage of resistant pathogens in patients with a previous TB-diagnosis 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 country of birth: Germany vs. abroad, cases incl. resistance data, 2013 (Source: Robert Koch Institute, 2013 Report on Tuberculosis Epidemiology in Germany)

Resistance phenotype	Germany (n=1,202)		Other countries (n=1,650)		Total (n=2,982)	
	Number	Percentage	Number	Percentage	Number	Percentage
Isoniazid (H)*	60	5.0%	192	11.6%	265	8.9%
Rifampicin (R)*	12	1.0%	95	5.8%	114	3.8%
Pyrazinamide (P)	30	2.5%	81	4.9%	120	4.0%
Ethambutol (E)*	10	0.8%	49	3.0%	63	2.1%
Streptomycin (S)*	54	4.5%	191	11.6%	256	8.6%
Multi-drug resistance*	8	0.7%	87	5.3%	102	3.4%
Any resistance (HRES)*	92	7.7%	266	16.1%	375	12.6%
Any resistance (HRESZ)*	113	9.4%	287	17.4%	421	14.1%
Poly-resistance (HRES)*	23	1.9%	52	3.2%	77	2.6%

* Significantly higher percentage of resistant pathogens in patients born abroad ($p < 0.001$)

Note: No information on country of birth was available in 130 of the 2,982 tuberculosis cases tested for resistance, which is why these cases were not taken into account in the analysis by country of birth.

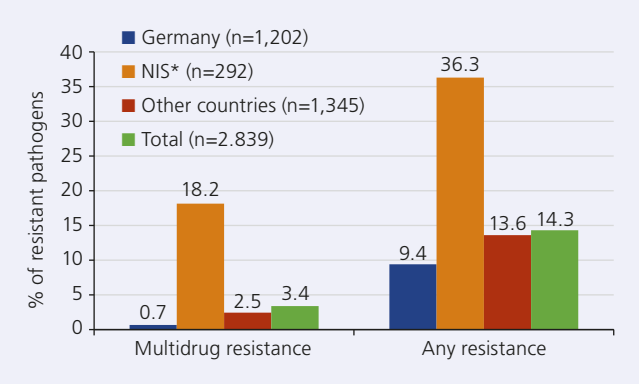


Fig. 4.1.10.1: Percentage of resistant tuberculosis by country of birth: Germany, NIS, other countries, Germany 2013

tuberculosis. However, corresponding data is not transmitted as part of the statutory reporting obligation.

Trends in drug resistance development between 2002 and 2013

The nationwide registration of resistance data as part of the statutory notification obligation allows the analysis of the epidemiological resistance situation regarding the five first-line drugs over several years.

In 2013, the proportion of multidrug-resistant tuberculosis (MDR-TB) was 3.4% (102 cases), which represents a significant increase ($p<0.01$) compared to the previous year (2.1%; 64 cases). This is the highest proportion that has been documented for Germany since registration of resistant tuberculosis was implemented in 2001. A comparable number of cases was observed in 2005 (106 MDR cases; 2.7%), whereas 50-64 MDR-TB cases per year were reported during the last 5 years. Thus the current case numbers and rates of resistant tuberculosis are higher than in many other low-incidence countries. It should be monitored carefully whether the increase of MDR-TB will continue or whether it is just a one-time upward deviation (Fig. 4.1.10.2).

A similar trend is seen regarding "any resistance". The proportion of pathogens resistant to at least one of the five first-line drugs was 14.3% (427 cases) in 2013, which is higher than in the previous year (12.7%; 380 cases) and even exceeds the so far highest rate observed in 2004 (13.9%; 566 cases) (Fig. 4.1.10.2). "Any resistance" is based predominantly on resistance to isoniazid or streptomycin (Fig. 4.1.10.2).

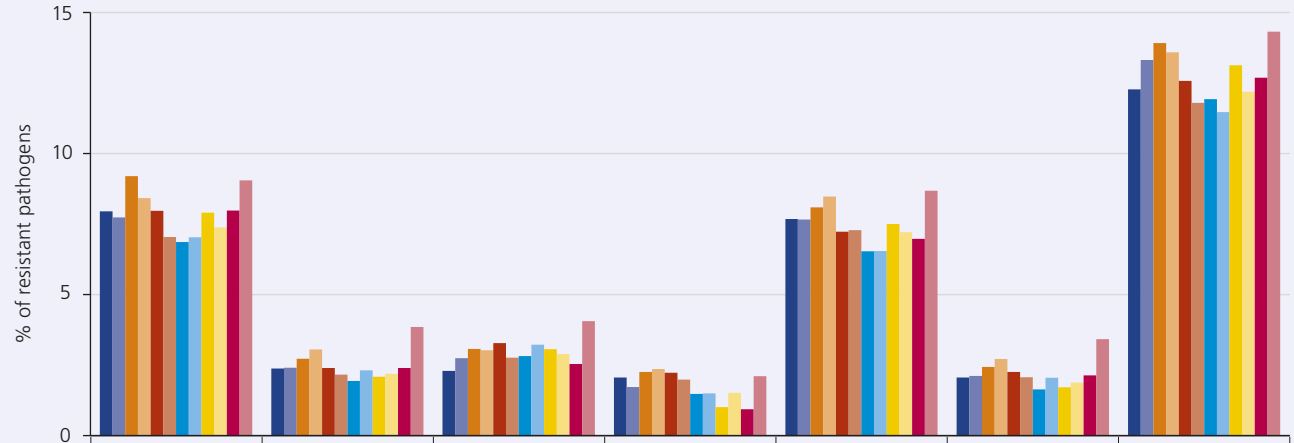
Conclusion

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

Stagnant case numbers and the current grow of resistant and multidrug-resistant tuberculosis indicate that this disease still remains a relevant public health problem in Germany. 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 monitoring are required to anticipate the effects of the global situation as quickly as possible and to adapt the control strategies, if necessary. The increase in resistance rates in patients born outside Germany as well as the significantly increased risk of resistance in patients with a history of previous TB treatment have direct consequences for planning an effective therapy. The occurrence – even of small numbers – of XDR-TB cases presents particular challenges for public health in terms of the protection of the general population against further spread and also of cost-intensive treatment. The registration of resistance against second-line drugs will help to assess the situation and trends in the future even better.

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

1. Dalton T, Cegielski P, Akksilp S, Asencios L, et al. Prevalence of and risk factors for resistance to second-line drugs in people with multidrug-resistant tuberculosis in eight countries: a prospective cohort study. Lancet 2012;380:1406-17.



	Isoniazid	Rifampicin	Pyrazinamide	Ethambutol	Streptomycin	Multidrug resistance	Any resistance
2002	8.0%	2.4%	2.3%	2.1%	7.7%	2.1%	12.3%
2003	7.7%	2.4%	2.7%	1.7%	7.7%	2.1%	13.3%
2004	9.2%	2.7%	3.1%	2.3%	8.1%	2.4%	13.9%
2005	8.4%	3.1%	3.0%	2.4%	8.5%	2.7%	13.6%
2006	8.0%	2.4%	3.3%	2.2%	7.2%	2.3%	12.6%
2007	7.0%	2.2%	2.8%	2.0%	7.3%	2.1%	11.8%
2008	6.9%	1.9%	2.8%	1.5%	6.5%	1.6%	11.9%
2009	7.0%	2.3%	3.2%	1.5%	6.5%	2.1%	11.5%
2010	7.9%	2.1%	3.1%	1.0%	7.5%	1.7%	13.1%
2011	7.4%	2.2%	2.9%	1.5%	7.2%	1.9%	12.2%
2012	8.0%	2.4%	2.5%	0.9%	7.0%	2.1%	12.7%
2013	9.1%	3.9%	4.1%	2.1%	8.7%	3.4%	14.3%

Fig. 4.1.10.2: Percentage of tuberculosis resistant to isoniazid, rifampicin, pyrazinamide, ethambutol, streptomycin as well as multidrug resistance and any resistance, Germany 2013 (n=2,982) compared to the previous years 2012 (n=2,994), 2011 (n=2,968), 2010 (n=2,971), 2009 (n=3,069), 2008 (n=3,044), 2007 (n=3,323), 2006 (n=3,625), 2005 (n=3,893), 2004 (n=4,066), 2003 (n=4,474) and 2002 (n=4,700)

4.1.11 *Candida* spp.

Introduction

Candida species are the most common causative agents of invasive mycoses in Germany and Europe. The major high-risk groups for invasive *Candida* infections include post-transplant patients, leukaemia patients and intensive care patients.[1] According to a study[2] based on data provided by the Hospital Infection Surveillance System (KISS), *Candida* species take fourth place as the causative agents of nosocomial bloodstream infections in intensive care units, where they are responsible for 6.5% of all bloodstream infections, equivalent to about 465 cases of primary nosocomial candidaemia per year in German intensive care units.[2] When extrapolated to the total population, a French study revealed a candidaemia incidence of about 2.5/100,000.[3] With 15-50%, the mortality rate of invasive *Candida* infections is higher than that of comparable bacterial infections.[4]

Range of species

In recent years, three multicentre studies were conducted to investigate the epidemiology and resistance of *Candida* spp. in Germany: the MykoLabNet-D study[5] (study period 2004-2005), a study conducted by the Antifungal Susceptibility Testing (AFST) Study Group[6] (study period 2008-2009) and the 2010 resistance study conducted by the Paul Ehrlich Society (PEG) for Chemotherapy[7] (study period 2010-2011). Although these studies differ in terms of the test specimens, they come to similar results with regard to the frequency distribution of the individual *Candida* spp. Based on these results, the following species distribution can be expected in Germany: *C. albicans* (54%-62.5%), *C. glabrata* (19.1%-22%), *C. parapsilosis* (5%-8%), *C. tropicalis* (5%-7.5%), *C. krusei* (1.4%-4.3%) and *C. kefyr* (0%-2%). Another study, investigating exclusively nosocomial bloodstream infections in intensive care units[2] revealed a more significant predominance of *C. albicans* (74%).

Intrinsic resistance

Various non-*albicans* species show intrinsically reduced susceptibility to antifungals. *C. glabrata* shows a significantly reduced susceptibility to fluconazole and *C. krusei* is intrinsically resistant to fluconazole. Intrinsic fluconazole resistance was also found in *C. inconspicua* and *C. norvegensis*, two species which are rarely detected in clinical specimens.[8] *C. parapsilosis* was reported to exhibit reduced susceptibility to echinocandins, which is why echinocandin therapy for *C. parapsilosis* infections is not recommended in practice guidelines.[9] A French monocentre study additionally revealed an association between the increased use of echinocandins and the rising number of *C. parapsilosis* infections.[10] Reduced susceptibility to echinocandins was also reported for *C. rugosa* and *C. guilliermondii*.[8]

Acquired resistance

Amphotericin B resistance

Acquired polyene resistance in *Candida* spp. occurs rarely and is poorly characterised at molecular level. To some extent, it correlates with changes in the sterol composition of the cellular membrane.[8]

Azole resistance

Acquired azole resistance in *Candida* spp. can be caused by a multitude of different mechanisms. These include efflux pumps, the overexpression of the target enzyme *Erg11*, mutations in *ERG11* and changes in the chromosomal structure.[8] In a large-scale study, which analysed more than 250,000 strains from 41 countries, the susceptibility of *C. albicans* to fluconazole was 98%.[12]

Echinocandin resistance

The susceptibility testing to echinocandins by means of microdilution is technically challenging and produces – in particular for caspofungin – varying results.[13] At present, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) only recommends susceptibility testing to anidulafungin and micafungin. Acquired echinocandin resistance in *Candida* spp. is mostly caused by mutations in the FKS genes: FKS1 in *Candida* spp. and FKS1 and FKS2 in *C. glabrata*. Within the FKS genes, there are two hotspot regions (HS1 and HS2) in which resistance mutations occur predominantly.[8] FKS mutations have so far been detected in nearly all clinically relevant species and acquired echinocandin resistance in *Candida* spp. is increasingly reported worldwide.[8]

Resistance situation in Germany

Concerning the susceptibility rates of *Candida* spp., the rates ascertained in the three multicentre studies conducted in recent years (MykoLabNet-D study, AFST study, PEG study) are difficult to compare, because the microdilution tests were performed based on different protocols and breakpoints. Compared to the two other studies, the AFST study[6] used a ten times higher inoculum and in some cases non-species-specific breakpoints, which results in high resistance rates that are hardly comparable to those stated in international literature references. Therefore, this data is not addressed in the following. The MykoLabNet-D study[5] used the CLSI protocol to measure the minimum inhibitory concentration (MIC). The study reveals an overall high level of susceptibility of the 561 tested *Candida* spp. isolates from normally sterile test specimens. However, the resistance distribution was not itemised by species in the study. The PEG study[7] examined 542 yeast isolates from normally sterile test specimens (Germany, Austria and Switzerland), which were tested by means

Tab. 4.1.11.1: Susceptibility rates (%) of *Candida* spp. from normally sterile isolates (PEG study[7])

Species	Fluconazole		Voriconazole	Amphotericin B		Anidulafungin
	405nm	450nm	405/450nm	405nm	450nm	405/450nm
C. albicans (n=339)	0.29%	0.29%	0	0.29%	0.59%	0
C. glabrata (n=116)	6%	6.9%	n.g.	0	0.86%	0.86%
C. parapsilosis (n=27)	0	0	0	0	0	0
C. tropicalis (n=27)	0	0	0	0	0	0
C. krusei (n=13)	nt	nt	nt	7.7%	30.8%	0

nt, not testet

of the microdilution method according to the recommendations given by EUCAST. The minimum inhibitory concentrations (MIC values) were interpreted on the basis of the species-specific EUCAST breakpoints.[14] The photometric measurement was performed at two different wavelengths (405 nm and 450 nm; wavelength currently recommended by EUCAST: 530 nm, alternative wavelengths recommended by EUCAST: 450 nm and 405 nm) and it turned out that the wavelength has an influence on the MIC values.

Resistance to amphotericin B was detected in less than 1.5% of all tested *Candida* spp. from clinical specimens (Tab. 4.1.11.1[5,7]). The PEG study revealed a great influence of the wavelength used, in particular as regards the amphotericin B resistance in *C. krusei*.[7]

In the PEG study, the rate of fluconazole resistance in *C. albicans* was 0.3%. Isolates of *C. parapsilosis* and *C. tropicalis* were fully susceptible. Resistance to posaconazole or voriconazole was not detected (Tab. 4.1.11.1[7]). The MykoLabNet-D study[5] classified 3.7% of all *Candida* strains as resistant to fluconazole based on the CLSI breakpoints. The rate was 0.4% for voriconazole; in this case, a breakpoint of 4 µg/ml recommended by Pfaller et al. was taken as a basis for the definition of resistance.[11]

The rates of resistance to echinocandins are very low in the available studies on the resistance situation in Germany. The PEG study classified one (*C. glabrata*) of the 522 isolates as resistant to anidulafungin (Tab. 4.1.11.1[7]). However, it should be noted that the available studies may not reflect the present situation, because most of the tested isolates were obtained before 2012. The NRZMyk in Jena performs susceptibility testing on request by means of the microdilution tests based on the EUCAST protocol. In 2015, a total of 37 *Candida* strains were submitted which were found to be resistant to one or more antifungals, among them 15 *C. albicans* strains (7 azole-resistant, 7 echinocandin-resistant, 1 combined echinocandin/azole resistance), 9 *C. glabrata* strains (4 echinocandin-resistant, 5 combined echinocandin/azole resistance), 1 azole-resistant *C. parapsilosis* strain, 4 *C. tropicalis* strains (1 azole-resistant, 1 echinocandin-resistant, 2 combined echinocandin/azole resistance), 7 echinocandin-resistant *C. krusei* strains and 1 multidrug-resistant *C. dubliniensis* strain showing resistance to echinocandins and azoles. In 17 echinocandin-resistant strains, mutations in the FKS genes were detected, which led to amino acid substitutions (unpublished data).

Conclusion

Among the pathogenic *Candida* species in Germany, *C. albicans*, which causes more than 50% of all infections, continues to be predominant, followed by *C. glabrata*, *C. parapsilosis*, *C. tropicalis* and *C. krusei*. The resistance situation is still favourable and is particularly characterised by intrinsic resistance mechanisms with therapeutic relevance (*C. glabrata*, *C. krusei*). Case-by-case analyses at the NRZMyk may suggest that the trend towards increasing prevalence of echinocandin-resistant strains observed worldwide also affects Germany. However, reference figures from previous years and systematic analyses are not available.

➤ G. Walther, O. Kurzai
Reviewer: A. Groll

1. Quindós G. Epidemiology of candidaemia and invasive candidiasis. A changing face. Rev Iberoam Micol 2014;31:42-8.
2. Meyer E, Geffers C, Gastmeier P, Schwab F. No increase in primary nosocomial candidemia in 682 German intensive care units during 2006 to 2011. Euro Surveill 2013;13;18(24).
3. Bitar D, Lortholary O, Le Strat Y, Nicolau J, et al. Population-based analysis of invasive fungal infections, France, 2001-2010. Emerg Infect Dis 2014;20:1149-55.
4. Pfaller MA, Diekema DJ. Epidemiology of invasive candidiasis: a persistent public health problem. Clin Microbiol Rev 2007;20:133-63.
5. Borg-von Zepelin M, Kunz L, Rüchel R, Reichard U, et al. Epidemiology and antifungal susceptibilities of *Candida* spp. to six antifungal agents: results from a surveillance study on fungaemia in Germany from July 2004 to August 2005. J Antimicrob Chemother 2007;60:424-8.
6. Schmalreck AF, Willinger B, Haase G, Blum G, et al. Antifungal Susceptibility Testing-AFST Study Group. Species and susceptibility distribution of 1062 clinical yeast isolates to azoles, echinocandins, flucytosine and amphotericin B from a multi-centre study. Mycoses 2012;55:124-37.
7. Kresken M, Körber-Irrgang B, Lass-Flörl C, Groll AH for the Working Group Antimicrobial Resistance of the Paul Ehrlich Society for Chemotherapy. Epidemiology of *Candida* species from sterile specimens in Germany and susceptibility to antifungal agents in vitro using the EUCAST method. http://www.paul-ehrlich-gesellschaft.de/econtext/Poster%20Publikation-enAntiinfectives Intelligence, Rheinbach, 2013.
8. Maubon D, Garnaud C, Calandra T, Sanglard D, et al. Resistance of *Candida* spp. to antifungal drugs in the ICU: where are we now? Intensive Care Med 2014;40:1241-55.
9. Koehler P, Tacke D, Cornely OA. Our 2014 approach to candidaemia. Mycoses 2014;57:581-3.
10. Fournier P, Schwebel C, Maubon D, Vesin A, et al. Antifungal use influences *Candida* species distribution and susceptibility in the intensive care unit. J Antimicrob Chemother 2011;66:2880-6.
11. Pfaller MA, Diekema DJ, Rex JH, Espinel-Ingroff A, et al. Correlation of MIC with outcome for *Candida* species tested against voriconazole: analysis and proposal for interpretive breakpoints. J Clin Microbiol 2006;44:819-26.
12. Pfaller MA, Boyken L, Hollis RJ, Kroeger J, et al. Wild-type MIC distributions and epidemiological cutoff values for posaconazole and voriconazole and *Candida* spp. as determined by 24-hour CLSI broth microdilution. J Clin Microbiol 2011;49:630-7.
13. Kurzai O. Stellungnahme des Nationalen Referenzzentrums für Invasive Pilzinfektionen zu den EUCAST Breakpoints für Echinocandine. (2014) http://www.nrz-myk.de/newsticker/eucast-breakpoints-fuer-echinocandine-stellungnahme-des-nrzmyk.html.
14. EUCAST, European Committee on Antimicrobial Susceptibility Testing, Antifungal Clinical Breakpoints, table v 4.1, 14.03.2012.

4.1.12 *Aspergillus* spp.

Several species of the genus *Aspergillus* can cause invasive infections – in particular in patients with a limited immune function. Limitation of the cellular immune function is of particular relevance for the individual risk. In addition to patients with an underlying haematological/oncological disease (in particular acute myeloic leukaemia) and patients with granulocytopenia and/or dysfunction of the granulocytes, other patient populations, such as post-lung transplant patients or intensive care patients, are affected as well. The disease manifests itself mainly as invasive pulmonary aspergillosis and can also disseminate into other organs. With 40-60%, the mortality rate remains to be high.[1]

Range of species

Within the *Aspergillus* genus, *Aspergillus fumigatus* is by far the most common causative agent of invasive mycoses. *A. flavus, A. terreus*, *A. niger*, *A. nidulans* and *A. versicolor* as well as other rarer species are detected significantly less commonly, with strong local variations in the individual distribution. As a result of the increased use of DNA-based species identification, numerous other *Aspergillus* species have been identified in recent years as the causative agents of mycoses. These included some morphologically indistinguishable sister species of the common pathogens, which is why only their affiliation to sections can be morphologically determined today. Some species, such as *A. lentulus*[2] or *A. calidoustus*[3], were recognised as independent species in the course of this development. In the U.S., the following prevalence of species complexes and species was found: section *Fumigati* (67.4%) with *A. fumigatus* (93.9%), *A. lentulus* (2.7%), *A. udagawae* (2.0%) and *A. thermomutatus (Neosartorya pseudofischeri)* (0.8%); *A. flavus* (13.2%); section *Nigri* (8.7%) with *A. niger* (68%) and *A. tubingensis* (32%); *A. terreus* (7.4%), *A. calidoustus* (2.7%), section *Versicolores* (2.3%) with *A. versicolor* (60%) and *A. sydowii* (40%); section *Nidulantes* (0.5%) with *Aspergillus quadrilineatus (Emericella quadrilineata)* (100%).[4]

Since few centres in Germany perform routine sequencing of fungal pathogens and in most cases these closely related sister species are not differentiated by means of MALDI-TOF-based identification, there is very limited data to estimate the spread of the rarer types in Germany. Symoens et al.[6] identified *A. thermomutatus (Neosartorya pseudofischeri)* (section *Fumigati*) as the coloniser of the lungs of a CF patient in Germany. The National Reference Centre for Invasive Mycoses (NRZMyk) performs routine molecular identification of the submitted isolates. Among the 21 strains of the section *Fumigati* submitted in 2014/2015, 20 strains were identified as *A. fumigatus* sensu stricto and one strain as *A. udagawae*. Among the 2 strains of the section *Nigri* submitted so far, one strain was identified as *A. niger* sensu stricto and another one as *A. tubingensis*. So far, 3 strains of the section *Nidulantes* have been examined, 2 of which were identified as *A. nidulans* sensu stricto and one as *A. quadrilineatus* (*Emericella quadrilineata*).

Intrinsic resistance

Clinically relevant *Aspergillus* species differ as regards their in vitro resistance profiles (Tab. 4.1.12.1). For this reason, correct species identification is important for selecting the treatment for aspergillosis.[7] Wild-type isolates of *A. fumigatus* are susceptible to amphotericin B, anti-*Aspergillus* azoles (e.g. itraconazole, voriconazole and posaconazole) and echinocandins. Other potentially pathogenic species of the section *Fumigati*, such as *A. lentulus*, *A. udagawae* and *A. thermomutatus (Neosartorya pseudofischeri),* are intrinsically resistant to one or more antifungals (cf. Tab. 4.1.12.1). Intrinsic resistance mechanisms have also been reported in other sections. The potential amphotericin B resistance of *A. terreus* and *A. flavus* is of special therapeutic relevance.[7] The literature references provide inconsistent information on the resistance characteristics of the section *Nigri*. Alcazar-Fuoli et al.[8] measured elevated MIC values mainly in *A. tubingensis,* whereas Arendrup et al.[9] reported itraconazole resistance in *A. niger*, however, without any statements on the molecular species identification.

Acquired resistance in *Aspergillus fumigatus*

Azole resistance

Itraconazole-resistant *A. fumigatus* isolates, which have also led to a failure of aspergillosis therapy, have occurred since the mid-1990s.[10] Azoles are competitive inhibitors of the lanosterol 14α demethylase (Cyp51A), an enzyme that plays a central role in ergosterol biosynthesis. The majority of resistance mechanisms to azoles so far investigated are attributable to mutations in the target gene CYP51A.[7] The most common mutation is TR34/L98H, which consists of a 34-bp tandem repeat (TR34) in the promoter region of the CYP51A gene and a point muta-

Tab. 4.1.12.1: Intrinsic resistance (R) and variable susceptibility (V) of invasive *Aspergillus* species assumed on the basis of elevated MIC values (acc. to van der Linden et al.[28] and Arendrup[7], modified)

Species	Section	Amphotericin B	Azoles	Echinocandins
A. fumigatus	Fumigati	S	S	S
A. lentulus	Fumigati	R	R	V
A. udagawae	Fumigati	R	R (VOR)	S
A. thermomutatus (Neosartorya pseudofischeri)	Fumigati	V	R	S
A. viridinutans	Fumigati	R	R	S
A. flavus	Flavi	R	V	S
A. nidulans	Nidulantes	R	S	S
A. quadrilineatus (E. quadrilineata)	Nidulantes	S	S	R
A. terreus	Terrei	R	S	S
A. niger	Nigri	S	V	S
A. tubingensis	Nigri	S	V	S
A. calidoustus	Usti	S	R	V
A. versicolor	Versicolores	R	V	S
A. sydowii	Versicolores	R	V	S

S=susceptible, R=resistant, V=variable, VOR=voriconazole, ITR-itraconazole

tion in the gene itself, causing the substitution of leucine (L) for histidine (H) at position 98, the consequence being a pan-azole resistance, with the MIC values for itraconazole being elevated most strongly. In Germany, the TR34/L98H mutation was first reported in 2012.[11,12] In the literature, numerous other mutations in the CYP51 gene were described which were associated with a higher level of azole resistance. The in vitro resistance development affects azoles to a varying extent. The TR46/Y121F/T289A mutation[13], a 46-bp tandem repeat in the promoter region of the CYP51A gene in combination with amino acid substitutions in codon 121 and 289, manifests itself in high-level voriconazole resistance and moderately elevated MIC values for itraconazole and posaconazole. Some mutations have also been detected in *A. fumigatus* strains from azole-naive patients.[7-14] Since the agricultural use of azoles coincided with the emergence of the TR34/L98H mutation, a connection is assumed, which has, however, not been confirmed to date.[15,16] Besides mutations in the CYP51A gene, other mechanisms, such as efflux pumps[17], the expression of the Cdr1B efflux transporter[18], the up-regulation of the target gene as a result of mutations in the HapE gene[19] and a CYP51B expression[20], have been reported. Moreover, there are azole-resistant *A. fumigatus* isolates in which the molecular mechanism has so far not been clarified. Acquired azole resistance has also been detected in *A. terreus*[21] and *A. flavus*[22].

Echinocandin resistance

To date, only one case of acquired echinocandin resistance in *A. fumigatus* has been reported worldwide.[23] However, the evaluation of microdilution tests for echinocandins is difficult with filamentous fungi and echinocandins are usually not used for the first-line therapy of invasive aspergillosis, which is why such cases may be underdiagnosed.[7] Breakthrough infections under echinocandin therapy have been reported[24,25], but are not necessarily associated with resistance characterised at molecular level.

Resistance situation in Germany

To date, there have only been few studies investigating the resistance situation in Germany. A study conducted by the MykoLabNet-D network[10] during the period 2011-2012 tested 527 clinical *A. fumigatus* isolates (353 from pulmonary/oropharyngeal specimens, 30 from the skin, 39 from invasive infections; 163 from CF patients). Among the 17 *A. fumigatus* isolates (3.2%) that showed elevated MIC values to at least one of the three tested azoles (itraconazole, voriconazole and posaconazole) in microdilution tests according to the EUCAST protocol, nine exhibited a mutation of the CYP51A gene. The highest rate of resistant isolates (5.2%) was observed in CF patients. Among the resistant isolates, the TR34/L98H mutation of the CYP51A gene was most common (35.3%), but isolates with G54W, M220I and F219C substitutions were detected as well. According to the information provided by the authors, the isolate with the G54W substitution additionally exhibited a duplication of the CYP51A gene as well as high-level resistance to itraconazole and posaconazole. The isolates with the other substitutions showed selective resistance to itraconazole. No mutations of the CYP51A gene were found in eight isolates with elevated MIC values for azoles (47.1%), which suggests the presence of different resistance mechanisms.

During the period 2010-2013, Fischer et al.[26] tested 2,677 respiratory specimens of 221 CF patients for azole-resistant *Aspergillus* strains. Among the 573 tested *Aspergillus* isolates, six *A. fumigatus* isolates (from 4 patients) were found to show high-level resistance to itraconazole. Five of the isolates were pan-azole-resistant. The TR34/L98H mutation was again most common (n=4); the M220L mutation and the TR46/Y121F/T289A mutation were each detected in only one isolate.

A study conducted by the haematology centres of Cologne and Essen[27] during the period 2012-2013 collected specimens from 762 patients who had undergone stem cell transplantation to detect *A. fumigatus* in the culture. Eight of the total of 27 isolates were resistant to azoles. The infections caused by these azole-resistant strains had a fatal outcome in seven cases. With one exception, these patients received antifungal prophylaxis (in five cases triazoles). The most common mutation in this study was again TR34/L98H (n=5), followed by TR46/Y121F/T289A (n=2). No CYP51A mutation was detected in one isolate. Genotyping by means of microsatellites revealed a genetic diversity within the azole-resistant *A. fumigatus* isolates. Interestingly, the German isolates with a TR34/L98H mutation did not form a group with the Dutch, Indian or French isolates with the same mutation.

Conclusion

Primary antifungal resistance plays an important role in numerous *Aspergillus* species, which is why accurate species identification is important. Since DNA-based routine identification is only performed at few centres and surveillance studies are lacking, the prevalence of rarer, morphologically indistinguishable, invasive *Aspergillus* species showing intrinsic resistance to one or more antifungals cannot be estimated at present.

To date, little data on secondary resistance development in the *Aspergillus* genus is available in Germany. Azole-resistant *A. fumigatus* have so far been rare (according to the study by the MykoLabNet-D network about 3%). Acquired resistance in *A. fumigatus* occurs in both patients treated with antifungals and antifungal-naive patients. CF patients exhibit a higher rate of resistant strains in studies. In Germany, the azole resistance of *A. fumigatus* is also caused predominantly by mutations of the CYP51A gene. Strains from Germany that exhibit these mutations are not related closely to such mutated strains from other countries.

➤ G. Walther, O. Kurzai
Reviewer: A. Groll

1. Bignell E. *Aspergillus fumigatus*: Saprotroph to Pathogen. In: The Mycota: Vol. XII Human Fungal Pathogens (Ed. O. Kurzai), Springer, Heidelberg, 2014;ISBN 978-3-642-39431-7,19-44.
2. Balajee SA, Gribskov JL, Hanley E, Nickle D, et al. *Aspergillus lentulus* sp. nov., a new sibling species of *A. fumigatus*. Eukaryot Cell. 2005;4:625-32.
3. Varga J, Houbraken J, Van Der Lee HA, Verweij PE, et al. *Aspergillus calidoustus* sp. nov., causative agent of human infections previously assigned to *Aspergillus ustus*. Eukaryot Cell. 2008;7:630-8.
4. Balajee SA, Kano R, Baddley JW, Moser SA, et al. Molecular identification of *Aspergillus* species collected for the Transplant-Associated Infection Surveillance Network. J Clin Microbiol 2009;47:3138-41.
5. Baddley JW, Marr KA, Andes DR, Walsh TJ, et al. Patterns of susceptibility of *Aspergillus* isolates recovered from patients enrolled in the Transplant-Associated Infection Surveillance Network. J Clin Microbiol 2009;47:3271-5.
6. Symoens F, Haase G, Pihet M, Carrere J, et al. Unusual *Aspergillus* species in patients with cystic fibrosis. Med Mycol 2010;48:10-6.

7. Arendrup MC. Update on antifungal resistance in *Aspergillus* and *Candida*. Clin Microbiol Infect 2014;20:42-8.
8. Alcazar-Fuoli L, Mellado E, Alastruey-Izquierdo A, Cuenca-Estrella M, et al. Species identification and antifungal susceptibility patterns of species belonging to *Aspergillus* section Nigri. Antimicrob Agents Chemother 2009;53:4514-7.
9. Arendrup MC, Cuenca-Estrella M, Lass-Flörl C, Hope WW. EUCAST Technical Note on *Aspergillus* and amphotericin B, itraconazole, and posaconazole. Clin Microbiol Infect 2012;18:248-50.
10. Bader O, Weig M, Reichard U, Lugert R, et al. MykoLabNet-D Partners. Cyp51A-based mechanisms of *Aspergillus fumigatus* azole drug resistance present in clinical samples from Germany. Antimicrob Agents Chemother 2013;57:3513-7.
11. Hamprecht A, Buchheidt D, Vehreschild JJ, Cornely OA, et al. Azole-resistant invasive aspergillosis in a patient with acute myeloid leukaemia in Germany. Euro Surveill 2012;17:20262.
12. Rath PM, Buchheidt D, Spiess B, Arfanis E, et al. First reported case of azole-resistant *Aspergillus fumigatus* due to the TR/L98H mutation in Germany. The first clinical case of TR34/L98H resistance in Germany. Antimicrob Agents Chemother 2012;56:6060-1.
13. Kuipers S, Bruggemann RJ, de Sevaux RG, Heesakkers JP, et al. Failure of posaconazole therapy in a renal transplant patient with invasive aspergillosis due to *Aspergillus fumigatus* with attenuated susceptibility to posaconazole. Antimicrob Agents Chemother 2011;55:3564-6.
14. Alanio A, Sitterle E, Liance M, Farrugia C, et al. Low prevalence of resistance to azoles in *Aspergillus fumigatus* in a French cohort of patients treated for haematological malignancies. J Antimicrob Chemother 2011;66:371-4.
15. Verweij PE, Snelders E, Kema GHJ, Mellado E, et al. Azole resistance in *Aspergillus fumigatus*: a side-effect of environmental fungicide use? Lancet Infect Dis 2009;9:789-95.
16. Bericht des BgVV zur Problematik der Resistenzen humaner Mykosen gegenüber Azolantimykotika und eventueller Wechselwirkungen mit den als Fungizid eingesetzten Pflanzenschutzmitteln vom 7.6.2001 (http://www.bfr.bund.de/cm/343/problematik_der_entwicklung_von_resistenzen_humaner_mykosen_gegenueber_azol_antimykotika.pdf).
17. Slaven JW, Anderson MJ, Sanglard D, Dixon GK, et al. Increased expression of a novel *Aspergillus fumigatus* ABC transporter gene, atrF, in the presence of itraconazole in an itraconazole resistant clinical isolate. Fungal Genet Biol 2002;36:199-206.
18. Fraczek MG, Bromley M, Buied A, Moore CB, et al. The cdr1B efflux transporter is associated with noncyp51a-mediated itraconazole resistance in *Aspergillus fumigatus*. A new non-CYP51A-mediated resistance mechanism is proposed. J Antimicrob Chemother 2013;68:1486-96.
19. Camps SM, Dutilh BE, Arendrup MC, Rijs AJ, et al. Discovery of a HapE mutation that causes azole resistance in *Aspergillus fumigatus* through whole genome sequencing and sexual crossing. A new method for identification of azole resistance mechanisms in *A. fumigatus* is described as well as a new non-CYP51A-mediated resistance mechanism. PLoS One 2012;7:50034.
20. Buied A, Moore CB, Denning DW, Bowyer P. High-level expression of cyp51B in azole-resistant clinical *Aspergillus fumigatus* isolates. J Antimicrob Chemother 2013;68:512-4.
21. Arendrup MC, Jensen RH, Grif K, Skov M, et al. In vivo emergence of *Aspergillus terreus* with reduced azole susceptibility and a Cyp51a M217I alteration. J Infect Dis 2012;206:981-5.
22. Liu W, Sun Y, Chen W, Liu W, et al. The T788G mutation in the cyp51C gene confers voriconazole resistance in *Aspergillus flavus* causing aspergillosis. Antimicrob Agents Chemother 2012;56:2598-603.
23. Arendrup MC, Perkhofer S, Howard SJ, Garcia-Effron G, et al. Establishing in vitro-in vivo correlations for *Aspergillus fumigatus*: the challenge of azoles versus echinocandins. Antimicrob Agents Chemother 2008;52:3504-11.
24. Arendrup MC, Garcia-Effron G, Buzina W, Mortensen KL, et al. Breakthrough *Aspergillus fumigatus* and *Candida albicans* double infection during caspofungin treatment: laboratory characteristics and implication for susceptibility testing. Antimicrob Agents Chemother 2009;53:1185-93.
25. Madureira A, Bergeron A, Lacroix C, Robin M, et al. Breakthrough invasive aspergillosis in allogeneic haematopoietic stem cell transplant recipients treated with caspofungin. Int J Antimicrob Agents 2007;30:551-4.
26. Fischer J, van Koningsbruggen-Rietschel S, Rietschel E, Vehreschild MJGT, et al. Prevalence and molecular characterization of azole resistance in *Aspergillus* spp. isolates from German cystic fibrosis patients. J Antimicrob Chemother 2014;69:1533-6.
27. Steinmann J, Hamprecht A, Vehreschild MJGT, Cornely OA, et al. Emergence of azole-resistant invasive aspergillosis in HSCT recipients in Germany. J Antimicrob Chemother 2015;doi:10.1093/jac/dku566.
28. Van der Linden JWM, Warris A, Verweij PE. *Aspergillus* species intrinsically resistant to antifungal agents. Med Mycol 2011;49:82-9.

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 is estimated at 5% in children and at 25% in adults, and is significantly higher in patients with an immigration background (86%).[1] Approx. 20% of all patients with an *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 a large number of 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] This therapy is to be adapted to the regional clarithromycin resistance level: In regions where the clarithromycin resistance level is assumed to be below 20%, a combination of a proton pump inhibitor (PPI), clarithromycin and amoxicillin or metronidazole for at least 7 days can be used as the first-line therapy[1]; this therapy has a success rate of 79%-95%.[4] If the regional clarithromycin resistance level is above 20%, an alternative bismuth-based quadruple therapy consisting of PPI, metronidazole, tetracycline and bismuth subcitrate should be prescribed.[5]

If eradication cannot be achieved using the above-mentioned first-line antimicrobials, treatment with amoxicillin, levofloxacin and rifabutin or a bismuth-based quadruple therapy is considered.[1,5]

Besides a lack of patient compliance, one of the major causes of the failure of eradication therapy is resistance to the antimicrobials used. The most important risk factor for the development of resistance is previous unsuccessful eradication therapies: The chance of carrying clarithromycin-resistant or clarithromycin- and metronidazole-resistant *H. pylori* is increased by a factor of 20 after a previous unsuccessful therapy.[6] Resistance in *H. pylori* can develop quickly and is usually based on the acquisition of point mutations.[7]

Resistance situation

The susceptibility of *H. pylori* to antimicrobials which are commonly used in eradication, such as amoxicillin, metronidazole, clarithromycin, levofloxacin, tetracycline and rifabutin, is determined after culturing the bacteria by means of agar diffusion testing (E-test®). The respective susceptibility is determined based on the breakpoints published by EUCAST (http://www.eucast.org/clinical_breakpoints/).

Based on 2013 and 2014 routine data, the primary resistance rates of *H. pylori* in Germany are 44.9% for metronidazole (MTZ), 9% for clarithromycin (CLR) and 10.3% for levofloxacin (LVX). Strains with double resistance (resistant to MTZ and CLR) are found in 3.8% and isolates with triple resistance (resistant to MTZ, CLR and LVX) in 1.3% of the patients without a history of antimicrobial therapy (unpublished NRZ data). Based on this data and the specifications of the Maastricht IV Consensus Report[5], a combination of a PPI, clarithromycin and amoxicillin can still be recommended as the first-line therapy.

After one single unsuccessful therapy, the rates of resistance to MTZ, CLR and LVX increase to 63.4%, 70.8% and 19.7%, respectively. After two unsuccessful eradication therapies, the resistance rates are as high as 79.1% for MTZ, 78.7% for CLR and 30.3% for LVX (Fig. 4.2.1.1). At the same time, the rates of double resistance (to MTZ and CLR) rise to 35.5% and 41.4%, respectively, and the rates of triple resistance (to MTZ, CLR and LVX) to 12% and 23.9%, respectively (Fig. 4.2.1.1). After three or more therapies, the rates of resistance increase further, although less dramatically.

Resistance to amoxicillin has so far not been observed in Germany. The resistance situation for rifampicin/rifabutin is also still very favourable (< 1%). Resistance or reduced susceptibility to tetracyclines has so far only been reported in individual cases.[8-10] Resistance to rifabutin or tetracycline has been observed almost exclusively in patients who have undergone multiple previous treatments.

In addition to phenotypic susceptibility testing, genotypic susceptibility testing can also be performed to detect resistance-associated mutations, with the detection of these mutations correlating well with the results of the phenotype testing.[7] In

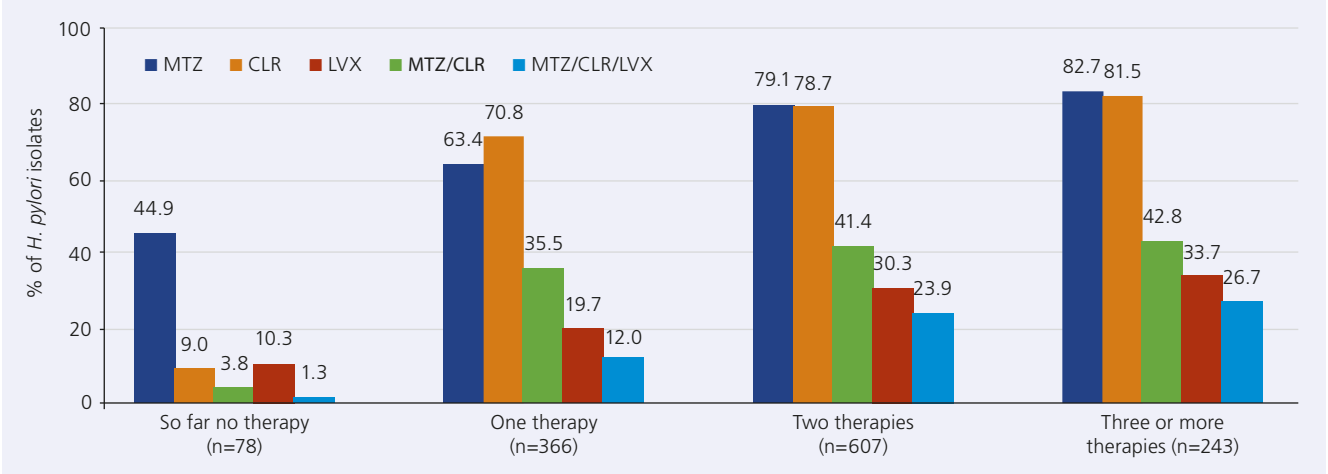


Fig. 4.2.1.1: Resistance rates of *Helicobacter pylori* in dependence on the number of previous treatments (2013 and 2014 routine data reported by the NRZ)

routine testing, methods of identifying clarithromycin and/or levofloxacin resistance are available (real-time PCR or reverse hybridisation).[11,12] These methods are used primarily if the pathogen cannot be cultured.

Conclusion

The introduction of the EUCAST breakpoints marks the first time that standardised breakpoints are available for all antimicrobials used to eradicate *H. pylori*. 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 resistance 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.

➤ E. O. Glocker
Reviewer: G. Werner

1. Fischbach W, Malfertheiner P, Hoffmann JC, Bolten W, et al. S3-Leitlinie "*Helicobacter pylori* und gastroduodenale Ulkuskrankheit". Z Gastroenterol 2009;47:68-102.
2. Malaty HM. Epidemiology of *Helicobacter pylori* infection. Best Pract Res Clin Gastroenterol 2007;21:205-14.
3. Fischbach W, Chan AO, Wong BC. *Helicobacter pylori* and Gastric Malignancy. Helicobacter 2005;10:34-9.
4. Lind T, Veldhuyzen van Zanten S, Unge P, Spiller R, et al. Eradication of *Helicobacter pylori* using one-week triple therapies combining omeprazole with two antimicrobials: the MACH I Study. *Helicobacter* 1996;3:138-44.
5. Malfertheiner P, Megraud F, O'Morain CA, Atherton J, et al. European *Helicobacter* Study Group. Management of *Helicobacter pylori* infection – the Maastricht IV/ Florence Consensus Report. Gut 2012;61:646-64.
6. Wüppenhorst N, Draeger S, Stüger HP, Hobmaier B, et al. Prospective multicentre study on antimicrobial resistance of *Helicobacter pylori* in Germany. J Antimicrob Chemother 2014;69:3127-33.
7. Mégraud F, Lehours P. *Helicobacter pylori* detection and antimicrobial susceptibility testing. Clin Microbiol Rev 2007;20:280-322.
8. Glocker E, Kist M. Emergence of a *Helicobacter pylori* isolate with reduced susceptibility to tetracycline in Germany. J Antimicrob Chemother 2006;58:1103-4.
9. Wüppenhorst N, Stueger HP, Kist M, Glocker E. Identification and molecular characterisation of triple- and quadruple-resistant *Helicobacter pylori* clinical isolates in Germany. J Antimicrob Chemother 2009;63:648-53.
10. Wüppenhorst N, Lenze F, Ross M, Kist M. Isolation and eradication of a clinical isolate of *Helicobacter pylori* resistant to five antimicrobials in Germany. J Antimicrob Chemother 2011; 66:222-3.
11. Oleastro M, Menard A, Santos A, Lamouliatte H, et al. Real-time PCR assay for rapid and accurate detection of point mutations conferring resistance to clarithromycin in *Helicobacter pylori*. J Clin Microbiol 2003;41:397-402.
12. Cambau E, Allerheiligen V, Coulon C, Corbel C, et al. Evaluation of a new test, genotype HelicoDR, for molecular detection of antibiotic resistance in *Helicobacter pylori*. J Clin Microbiol 2009;47:3600-7.

4.2.2 *Shigella* spp.

The number of *Shigella* infections reported in Germany has been declining for years (https://survstat.rki.de). 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 68 in 2014. More than half of these isolates obtained from human diarrhoeal diseases were confirmed to have been caused by travel-associated infections abroad. Each year, 60-70% of the tested *Shigella* strains were *Shigella sonnei*, about 20% *Shigella flexneri* and less than 5% each *Shigella dysenteriae* or *Shigella boydii*. Between 1998 and 2014, a total of 1,904 *Shigella* strains were tested for susceptibility to 16 antimicrobials. Within the National Reference Centre's scope of tasks, 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 6% during the period 2012-2014. The rates of resistance to streptomycin, co-trimoxazole and tetracycline were consistently very high in all *Shigella* spp. over the years (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 8-12 other antimicrobials. Since 2005, multidrug-resistant *S. sonnei*, *S. flexneri* and *S. dysenteriae* isolates, exhibiting resistance

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; 2001-2014)

Antimicrobial	Breakpoint [mg/l] Resistant (>)	2001–2003 n=380	2004–2006 n=354	2007–2011 n=289	2012–2014 n=194
		% of resistant strains			
Streptomycin	16	82	83	88	83
Co-trimoxazole	16	81	87	93	77
Tetracycline	4	65	80	69	70
Ampicillin	8	33 *sonnei* 24 *flexneri* 63	33 *sonnei* 25 *flexneri* 75	29 *sonnei* 21 *flexneri* 69	39 *sonnei* 22 *flexneri* 67
Mezlocillin	16	27	23	18	27
Mezlocillin/Sulbactam	16	7	16	2	2
Chloramphenicol	8	17 *sonnei* 5 *flexneri* 56	20 *sonnei* 5 *flexneri* 75	11 *sonnei* 2 *flexneri* 64	21 *sonnei* 3 *flexneri* 57
Nalidixic acid	16	7	10	19	28
Ciprofloxacin	2	0,3	0,6	5	12,4
Gentamicin	4	0,8	0,9	0,3	2,6
Kanamycin	16	1,0	0	0	1,5
Amikacin	16	0,5	0	0	0
Cefotiam	4	1,3	3,4	6	9
Cefoxitin	16	0	1,7	0	1,5
Cefotaxime	8	1,1	1,6	6	7
Ceftazidime	16	0,5	1,1	1,0	1,5

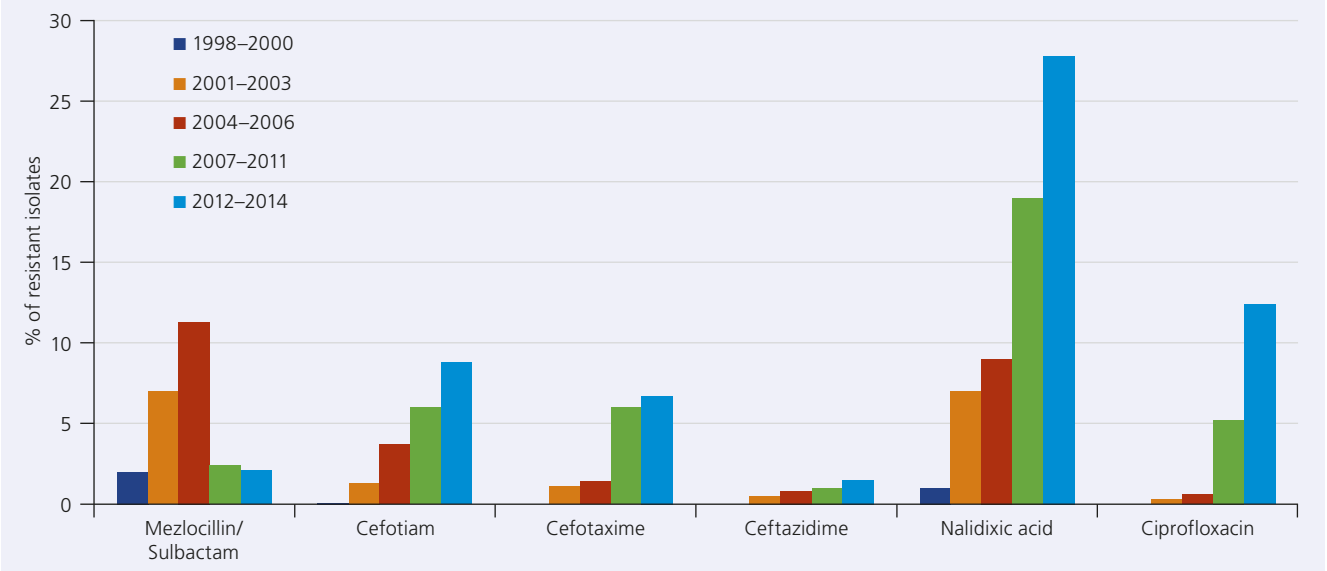


Fig. 4.2.2.1: Temporal development of resistance to some antimicrobials in *Shigella* spp., 1998-2014 (Source: National Reference Centre for *Salmonellae* and Other Bacterial Enterics at the Robert Koch Institute, Wernigerode Branch)

to the therapeutically relevant antimicrobial classes of acylureidopenicillins, cephalosporins and fluoroquinolones (3MRGN), have also occurred in isolated cases. The susceptibility to carbapenems (meropenem) was included in the testing for the first time in 2014. All tested isolates showed an MIC value of ≤ 0.06 mg/l – which is significantly below the breakpoint R > 2 mg/l.

Trends in resistance development

Whereas the percentage of fully susceptible strains has continuously decreased over the years and the percentage of strains resistant to one or two antimicrobials ranged around 15%, the percentage of multidrug-resistant (resistant to more than two of the tested antimicrobials) strains increased to more than 80% during the period 2012-2014. The resistance rates to 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 all mezlocillin-resistant *Shigella* were still susceptible to the combination with the β-lactamase inhibitor. By 2005, this rate dropped to about 30%. In the following years, however, *Shigella* species resistant to mezlocillin/sulbactam were found far less commonly, and more than 80% of all mezlocillin-resistant *Shigella* were again susceptible to the combination with the β-lactamase inhibitor during the period 2012-2014. Resistance to cephalosporins was first observed in 2001. Since then, the rate of resistance to third-generation (group 3) 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 28% during the period 2012-2014 is observed in resistance to nalidixic acid. The rate of ciprofloxacin resistance follows this trend at a somewhat lower level (Fig. 4.2.2.1).

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. Based on the available data, *Shigella* isolated in Germany was 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.

➤ E. Tietze
Reviewer: M. Kist

4.2.3 *Salmonella enterica* subspecies *enterica*

Despite the downward trend in the number of reported infections from 72,450 in 2002 to 16,168 in 2014, *Salmonella* infections are still among the most common causes of bacterial gastroenteritis in Germany. In addition to individual infections, *Salmonella enterica* subspecies *enterica* causes a great number of food-associated outbreaks every year, with the serovars Typhimurium and Enteritidis being most predominant (https://survstat.rki.de). The two most common serovars together accounted for 60-70% of the test specimens at the National Reference Centre (NRZ) for Salmonellae and Other Bacterial Enterics at the Robert Koch Institute, Wernigerode Branch, with their percentage being nearly constant over the years until 2011. During the period 2012-2014, however, the percentage of these serovars dropped to 52% (Tab. 4.2.3.1). The number of *Salmonella* isolates tested annually at the NRZ always accounted for about 10% of the *Salmonella* infections reported. During the period 1999-2014, a total of 62,407 *Salmonella* isolates obtained from diarrhoeal diseases in Germany 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

As has been the case since 1999, about 90% of the serovar Enteritidis isolates were tested susceptible, whereas a continuous downward trend from 32% susceptible isolates in 1999 to 11% during the period 2012-2014 was observed for the serovar Typhimurium. The percentage of susceptible strains in the other serovars remained more or less constant (65-75%; 69% in 2014). 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

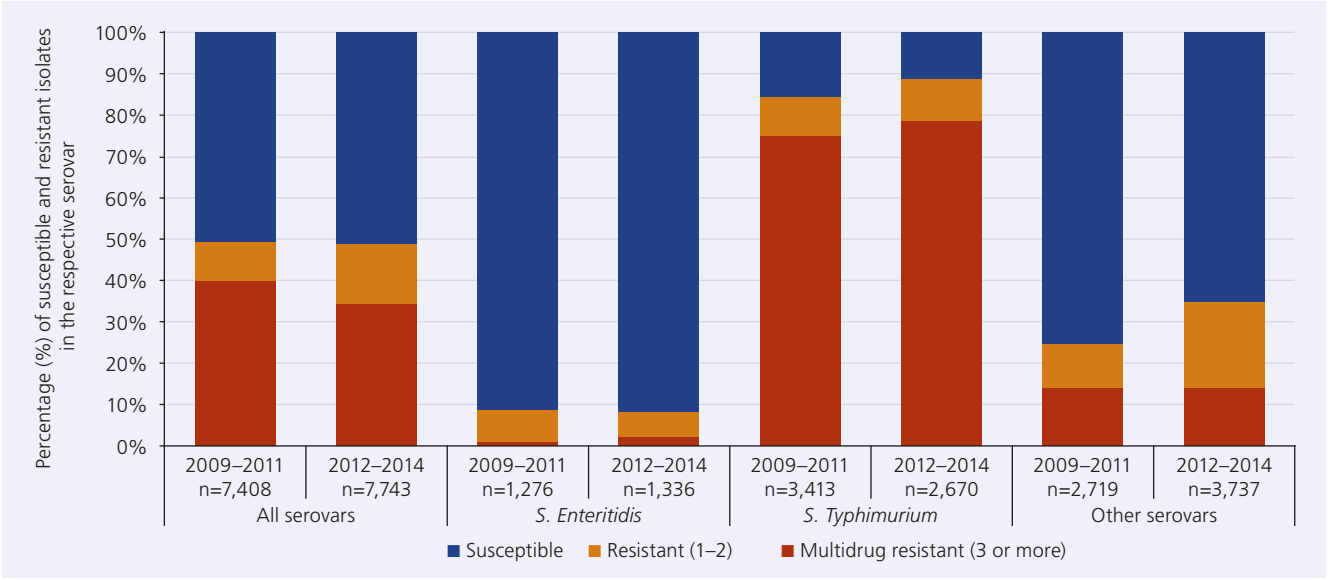


Fig. 4.2.3.1: Percentage of susceptible and (multidrug-) resistant strains in all *S. enterica* isolates, itemised by the most common serovars Typhimurium and Enteritidis: Comparison of the periods 2009-2011 and 2012-2014 (Source: National Reference Centre for *Salmonellae* and Other Bacterial Enterics 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; 2002-2014)

Serovar		2002–2004 n=13,658			2005–2007 n=10,348			2008–2011 n=10,490			2012–2014 n=7,743		
		Typhimurium	Enteritidis	Other	Typhimurium	Enteritidis	Other	Typhimurium	Enteritidis	Other	Typhimurium	Enteritidis	Other
Percentage (%) during the period		31	52	17	31	42	28	43	22	35	35	17	48
Antimicrobial	Breakpoint [mg/l] Resistant (>)	% of resistant strains of the respective serovars											
Streptomycin	16	69	1	24	74	1	24	77	0.3	22	81	0.7	24
Tetracycline	4	65	1	13	73	2	22	75	1	15	75	1	11
Ampicillin	8	61	1	8	71	2	16	77	4	13	80	2	10
Mezlocillin	16	61	1	7	71	1	16	77	4	13	79	2	10
Mezlocillin/Sulbactam	16	14	0.3	4	11	0.2	5	10	0.4	5	12	0.4	5
Chloramphenicol	8	35	1	16	30	1	6	20	0.3	5	13	0.5	5
Co-trimoxazole	16	11	1	5	17	1	7	10	0.5	9	10	0.4	7
Nalidixic acid	16	4	4	10	4	3	10	6	3	11	5	6	9
Ciprofloxacin	2	0	0	0.2	0	0	0.7	0.1	0	2	0.1	0	2
Kanamycin	16	4	0.2	3	6	0.3	2	3	0.1	2	3	0	1
Gentamicin	4	2	0.2	2	1	1	2	1	0.1	2	1	0.1	2

about 85% (81% in 2014) 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% (50% in 2014). This suggests an unequal spread of different β-lactam resistance determinants in the various serovars, since nearly 70% of the ampicillin-resistant serovar Typhimurium isolates are attributable to a small number of predominant clones (phage types DT193, DT120) with a chromosomally encoded inhibitor-susceptible TEM-1 β-lactamase. The rates of resistance to chloramphenicol dropped steadily from about one-third of all serovar Typhimurium isolates during the period 2002-2004 to only 13% in 2014 and in other serovars (excl. Enteritidis) from 16% to 2% in 2014. The level of resistance to co-trimoxazole and nalidixic acid was more or less constant in all serovars throughout the reference periods. Resistance to fluoroquinolones was not detected in the serovar Enteritidis. Overall, 95% of the fluoroquinolone-resistant salmonellae were classified as serovar Kentucky; however, independent serovar Typhimurium isolates resistant to ciprofloxacin have also emerged sporadically since 2010. When applying the epidemiological cut-off (ECOFF) value (WT ≤ 0.06 mg/l) of the European Committee on Antimicrobial Susceptibility Testing (EUCAST, http://mic.eucast.org/Eucast2/) to ciprofloxacin instead of the NRZ breakpoint used in Tab. 4.2.3.1, a resistance rate of 7.9% would be ascertained for the period 2012-2014. Under this condition, all strains resistant to nalidixic acid would also be resistant to ciprofloxacin, which would lead to a lack of differentiation between strains that are only resistant to nalidixic acid but not to ciprofloxacin and thus to a loss of a useful epidemiological marker. Apart from the widespread resistance to streptomycin, resistance to other aminoglycosides (kanamycin, gentamicin, amikacin) occurred only rarely. Cephalosporin-resistant salmonellae still represent exceptions. In 2014, 0.9% of the tested *Salmonella* strains showed resistance to cefotaxime and 0.4% were additionally resistant to ceftazidime (2 multidrug-resistant serovar Typhimurium isolates and 1 Newport, Haifa, Choleraesuis, Munich, Uganda, Poona and Paratyphi B/Java isolate each). Multidrug-resistant isolates of various serovars (Kentucky, Haifa, Rissen, Paratyphi-B/Java) exhibiting resistance to the therapeutically relevant antimicrobial classes of acylureidopenicillins, cephalosporins and fluoroquinolones (3MRGN) were also observed in isolated cases. The susceptibility to carbapenems (meropenem) was included in the testing for the first time in 2014. All tested isolates showed an MIC value of ≤ 0.06 mg/l – which is significantly below the breakpoint R > 2 mg/l.

Trends in resistance development

Multidrug resistance (resistance to three or more antimicrobials) in serovar Typhimurium strains increased continuously from 44% in 1999 to 79% in 2014 (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 13% during the period 2012-2014 (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 (2% in 2014). The percentage of multidrug-resistant isolates in the other serovars ranged between 10% and 20% (14% in 2014), 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 (excl. 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.

Conclusion

Based on the pathogen isolates tested by the NRZ, 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 all 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: M. Kist

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 (https://survstat.rki.de). Between 2005 and 2014, the National Reference Centre for Salmonellae and Other Bacterial Enterics at the Robert Koch Institute, Wernigerode Branch, identified and tested nearly 2,000 *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 2 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 nearly 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 intrinsic 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. About 20% of the isolates showed resistance to chloramphenicol. 10-20% 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 co-trimoxazole were also low (< 5%). Whereas the level of resistance to cefotiam, a second-generation (group 2) cephalosporin, slightly dropped over the years, the level of resistance to the cephamycin cefoxitin remained between 5% and 13% over the reference periods. Resistance to third-generation (group 3) 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 nearly 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. The susceptibility to carbapenems (meropenem) was included in the testing for the first time in 2014. All tested isolates showed an MIC value of ≤ 0.06 mg/l – which is significantly below the breakpoint R > 2 mg/l.

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 2009-2014 were significantly lower than in 2005/2008, 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. The continuous evaluation of data from a largely consistent population over a period as long as nine years yet allows an assessment of trends, at least to some extent.

Tab. 4.2.4.1: Resistance rates of *Yersinia enterocolitica* (Source: National Reference Centre for Salmonellae and Other Bacterial Enterics at the Robert Koch Institute, Wernigerode Branch; 2005-2014)

Antimicrobial	Breakpoint [mg/l] Resistant (>)	2005–2006 n=365	2007–2008 n=350	2009–2011 n=806	2012–2014 n=468
		% of resistant strains			
Ampicillin	8	98	99	100	99
Mezlocillin	16	15	8	3	2
Mezlocillin/Sulbactam	16	0	0	0.2	0
Chloramphenicol	8	14	20	26	23
Streptomycin	16	14	20	18	10
Kanamycin	16	1.1	0.9	0.6	0.1
Amikacin	16	0.5	0.9	0.7	0
Gentamicin	4	0.5	0.6	0.6	0.3
Tetracycline	4	3	5	4	1.8
Co-trimoxazole	16	2	1.4	1.2	1.0
Cefotiam	4	12	9	3	1.7
Cefoxitin	16	10	5	7	13
Cefotaxime	8	0	0.3	0.4	0
Ceftazidime	16	0.3	0.6	0.2	0
Nalidixic acid	16	1.4	2	3	2
Ciprofloxacin	2	0	0	0.1	0

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 (group 3) 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: M. Kist

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 (https://survstat.rki.de). Between 2005 and 2014, the National Reference Centre (NRZ) for Salmonellae and Other Bacterial Enterics at the Robert Koch Institute, Wernigerode Branch, tested 1,566 *Campylobacter jejuni* and 827 *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 2 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 a consensus on breakpoints for *Campylobacter* spp. as epidemiological cut-off (ECOFF) values or clinical breakpoints of the European Committee on Antimicrobial Susceptibility Testing (EUCAST, http://mic.eucast.org/Eucast2/) has been available since 2013 for only some of the tested substances, the isolates were still classified as "resistant" based on the DIN values for *Enterobacteriaceae* used since 2005 and, for some antimicrobials, based on the preliminary MIC_{90} values for all *Campylobacter* spp. isolates tested so far at the NRZ (Tab. 4.2.5.1). Where applicable, more significant differences to a classification based on the ECOFF breakpoints for the period 2012-2014 are pointed out to facilitate the comparison with data from other international sources (e.g. Fig. 4.2.5.2).

Resistance situation

The percentage of fully susceptible strains in all tested *C. jejuni* isolates dropped to below 10%; in 2014, this rate was only 2% 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 until 2012 (Tab. 4.2.5.1). The significant increase in the rates of resistance to erythromycin and gentamicin in both *C. coli* and *C. jejuni* during the period 2012-2014 compared to the previous reference periods is notable.

The rates of resistance shown in Tab. 4.2.5.1 separately for *C. jejuni* and for *C. coli* demonstrate that, when using a uniform MIC breakpoint for both species, the resistance situation as regards ampicillin, nalidixic acid, ciprofloxacin and chloramphenicol was similar in the two *Campylobacter* species. By contrast, the rates of resistance to tetracycline, erythromycin, clindamycin and the aminoglycosides in *C. coli* were two to ten times higher than in *C. jejuni*. The species-specific differences in the rates of streptomycin and tetracycline resistance remain unchanged

Tab. 4.2.5.1: Resistance rates of *Campylobacter* spp.: Comparison of the periods 2005-2008, 2009-2011 and 2012-2014 (Source: National Reference Centre for *Salmonellae* and Other Bacterial Enterics at the Robert Koch Institute, Wernigerode Branch)

		2005–2008		2009–2011		2012–2014	
		C. jejuni n=570	*C. coli* n=342	*C. jejuni* n=532	*C. coli* n=250	*C. jejuni* n=464	*C. coli* n=235
Antimicrobial	**Breakpoint [mg/l] Resistant (>)**	**% of resistant strains of the respective species**					
Ampicillin	8	75	67	90	96	89	89
Nalidixic acid	16	43	47	55	60	50	58
Ciprofloxacin	2	39	43	51	54	45	55
Tetracycline	4	19	49	11	44	19	56
Erythromycin	4	9	22	5	16	39	69
Clindamycin	4	3	9	3	8	5	15
Streptomycin	16	5	47	5	50	7	56
Kanamycin	16	4	9	4	28	6	20
Gentamicin	4	3	5	2	3	17	37
Amikacin	16	3	6	2	4	6	7
Chloramphenicol	8	4	4	2	4	3	5

Fig. 4.2.5.1: Change in the prevalence of fully susceptible and resistant (to 1-2 or 3 or more of the tested antimicrobials) strains in all tested *C. jejuni* (n=1,566) and *C. coli* (n=827) strains, comparison of the periods 2005-2008, 2009-2011 and 2012-2014 (Source: National Reference Centre for *Salmonellae* and Other Bacterial Enterics at the Robert Koch Institute, Wernigerode Branch)

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 in the resistance situation of the two species are assumed in this case. By contrast, a corresponding correction of the MIC breakpoints for the other aminoglycosides as well as for erythromycin and clindamycin would result in more or less equal rates of resistance to these substances in *C. coli* and *C. jejuni*. As regards erythromycin, this phenomenon of varying intrinsic susceptibility was taken into account by specifying different ECOFF values for *C. coli* (wild-type WT ≤8 mg/l) and C. jejuni (WT ≤4 mg/l) (http://mic.eucast.org/Eucast2/). When applying the species-specific ECOFF breakpoint, the percentage of erythromycin-resistant *C. coli* during the period 2012-2014 would drop from 69%, as stated in Tab. 4.2.5.1, to 38% and would thus correspond to the percentage of erythromycin-resistant *C. jejuni* during this period (39%).

The vast majority of the tested *Campylobacter* strains were multidrug-resistant (Fig. 4.2.5.1). 68% of the *C. jejuni* and 96% of the *C. coli* isolates tested in 2014 were resistant to at least three antimicrobials; individual *C. jejuni* and *C. coli* strains were resistant to all tested substances. The prevalence of co-resistance to ciprofloxacin and erythromycin, to ciprofloxacin and gentamicin as well as to erythromycin and gentamicin was observed to increase, but even co-resistance to all three of these therapeutically relevant antimicrobials was observed in both species (Fig. 4.2.5.2).

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 in resistance development in *Campylobacter* spp. The percentage of ciprofloxacin-resistant isolates of both species (about 25% in 2005) increased, but seems to have stabilised around 50% during the period 2012-2014 (Tab. 4.2.5.1). The rate of ampicillin resistance also rose from about 30% in 2005 to about 90% in 2014. The significant increase in the rates of resistance to erythromycin and gentamicin in both *C. coli* and *C. jejuni* during the period 2012-2014 compared to previous reference periods is remarkable. Whereas in 2012 the corresponding resistance rates were still at a level comparable to the previous reference periods, a significant increase was observed in 2013, culminating in erythromycin resistance rates of 70% in *C. jejuni* and 82% in *C. coli* and gentamicin resistance rates of 38% in *C. jejuni* and 86% in *C. coli*. This change is also clearly reflected in the rising number of isolates of both *Campylobacter* species showing co-resistance to ciprofloxacin and erythromycin, to ciprofloxacin and gentamicin as well as to erythromycin and gentamicin, in addition to co-resistance to all three of these therapeutically relevant antimicrobials (see Fig. 4.2.5.2). This figure also shows that although there are minor differences in the absolute rates when applying the ECOFF values instead of the NRZ breakpoints stated in Tab. 4.2.5.1, the general trend is the same.

Conclusion

It remains uncertain to what extent the above-described resistance situation of *Campylobacter* isolates, nearly all of which came from a single large region covering several adjacent Länder, reflects the situation in Germany. Regional differences, for example between rural regions with large-scale livestock farming and big cities, cannot be excluded. The continuous evaluation of data from a largely consistent population over a period as long as nine years yet allows an assessment of trends, at least to some extent.

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). Whether the rapid increase in resistance rates to erythromycin and gentamicin in both *Campylobacter* species started in 2013 will continue and what its causes may be still needs to be clarified as part of extensive future studies.

The definition and standardisation of breakpoints for the susceptibility testing of *Campylobacter* spp. is desirable not only for therapeutically relevant antimicrobials but also in general. The development of further standardised breakpoints – separately

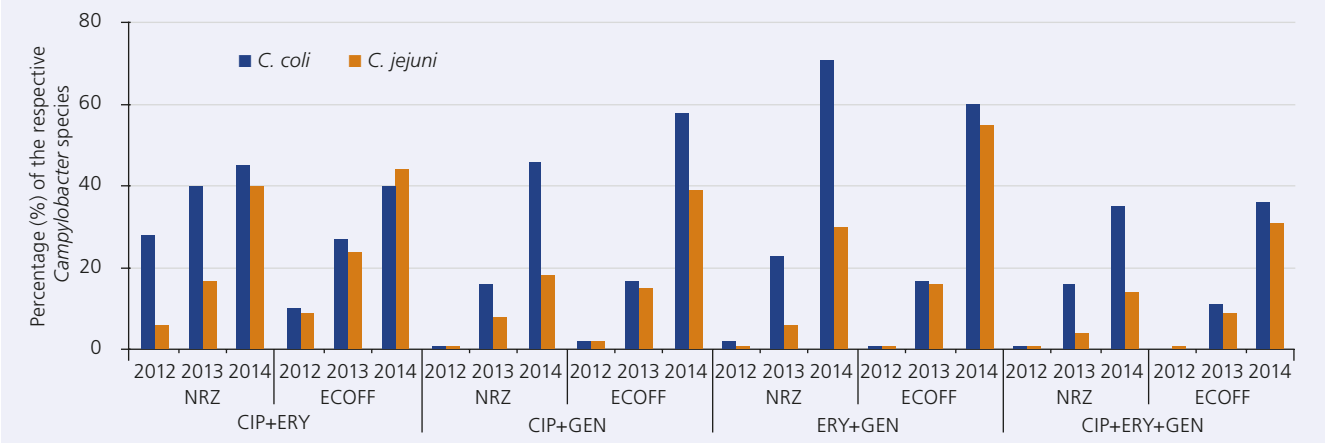


Fig. 4.2.5.2: Prevalence of co-resistance to ciprofloxacin (CIP), erythromycin (ERY) and gentamicin (GEN) in all *C. jejuni* (n=464) and *C. coli* (n=235) strains tested during the period 2012-2014 (Source: National Reference Centre for *Salmonellae* and Other Bacterial Enterics at the Robert Koch Institute, Wernigerode Branch)

NRZ: based on the breakpoints used at the NRZ (Tab. 4.2.5.1), ECOFF: based on the epidemiological cut-off values of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) http://mic.eucast.org/Eucast2/ for *C. coli*: CIP WT ≤ 0.5 mg/l, ERY WT ≤ 8 mg/l, GEN ≤ 2 mg/l and for *C. jejuni*: CIP WT ≤ 0.5 mg/l, ERY WT ≤ 4 mg/l, GEN ≤ 2 mg/l

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: M. Kist

4.2.6 Enteropathogenic *Escherichia coli*

The species *Escherichia coli* is commonly found in the physiological intestinal microbiota. 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* are of special significance due to the infection's potential life-threatening complications. During the period 1999-2014, the National Reference Centre for Salmonellae and Other Bacterial Enterics at the Robert Koch Institute, Wernigerode Branch, tested a total of more than 12,000 enteropathogenic *E. coli* isolates from diarrhoeal diseases in Germany for susceptibility to 16 antimicrobials. These were mainly EHEC (each year 70-80% of the tested *E. coli* strains), 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 all *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 three antimicrobials). Streptomycin (around 20%) and tetracycline (around 15%) were most frequently affected by resistance (Tab. 4.2.6.1), followed by amino- and ureidopenicillins (10-17%). About 75% of the mezlocillin-resistant strains were still susceptible to the combination of mezlocillin and the β-lactamase inhibitor sulbactam. The rates of resistance to chloramphenicol and co-trimoxazole (around 10%) were at a more or less constant level over the years. Resistance to the aminoglycosides kanamycin (below 4%), gentamicin (below 2%) and amikacin (below 0.5%) occurred less commonly. Up to and including 2014, the rates of quinolone and cephalosporin resistance were also at a very low level. When applying the epidemiological cut-off (ECOFF) value (WT ≤ 0.06 mg/l) of the European Committee on Antimicrobial Susceptibility Testing (EUCAST, http://mic.eucast.org/Eucast2/) to ciprofloxacin instead of the NRZ breakpoint used in Tab. 4.2.6.1, a resistance rate of 4.9% would be ascertained for the period 2012-2014. Under this condition, all strains resistant to nalidixic acid would also be resistant to ciprofloxacin, which would lead to a lack of differentiation between strains that are only resistant to nalidixic acid but not to ciprofloxacin and thus to a loss of a useful epidemiological marker.

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, 2009-2011 and 2012-2014 (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. The overall percentage of resistant isolates – dominated by the five most common EHEC serovars (Fig. 4.2.6.2) – remained constant over the years. *E. coli* isolates resistant to 10 or more of the tested antimicrobials occurred repeatedly, among them sporadic cases of isolates showing resistance to the therapeutically relevant antimicrobial classes of acylureidopenicillins, cephalosporins and fluoroquinolones (3MRGN). The susceptibility to carbapenems (meropenem) was included in the testing for the first time in 2014. All tested isolates showed an MIC value of ≤ 0.06 mg/l – which is significantly below the breakpoint R > 2 mg/l.

Conclusion

The comparatively moderate resistance situation of enteropathogenic *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 regarded as problematic and is usually not recommended, at least not during the acute diarrhoeal phase. However, the resis-

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; 2002-2014)

		2002–2004 n = 2,982	2005–2007 n = 2,161	2008–2011 n = 2,647 *)	2012–2014 n = 2,092
Antimicrobial	Breakpoint [mg/l] Resistant (>)	% of resistant strains			
Streptomycin	16	21	19	17	15
Tetracycline	4	17	16	15	13
Ampicillin	8	12	12	17	13
Mezlocillin	16	10	11	11	10
Mezlocillin/Sulbactam	16	2	2	3	2.8
Chloramphenicol	8	14	5	10	6
Co-trimoxazole	16	8	10	10	10
Kanamycin	16	4	3	4	3
Gentamicin	4	1.1	1.1	1.3	1.6
Amikacin	16	0.2	0.2	<0.1	0.1
Nalidixic acid	16	2.0	3.4	3.4	5
Ciprofloxacin	2	0.2	0.8	0.4	0.3
Cefotiam	4	0.4	1.2	2.4	2.5
Cefoxitin	16	0.3	0.5	0.5	0.4
Cefotaxime	8	0.2	1.1	1.4	2.0
Ceftazidime	16	0.1	0.7	0.6	0.6

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

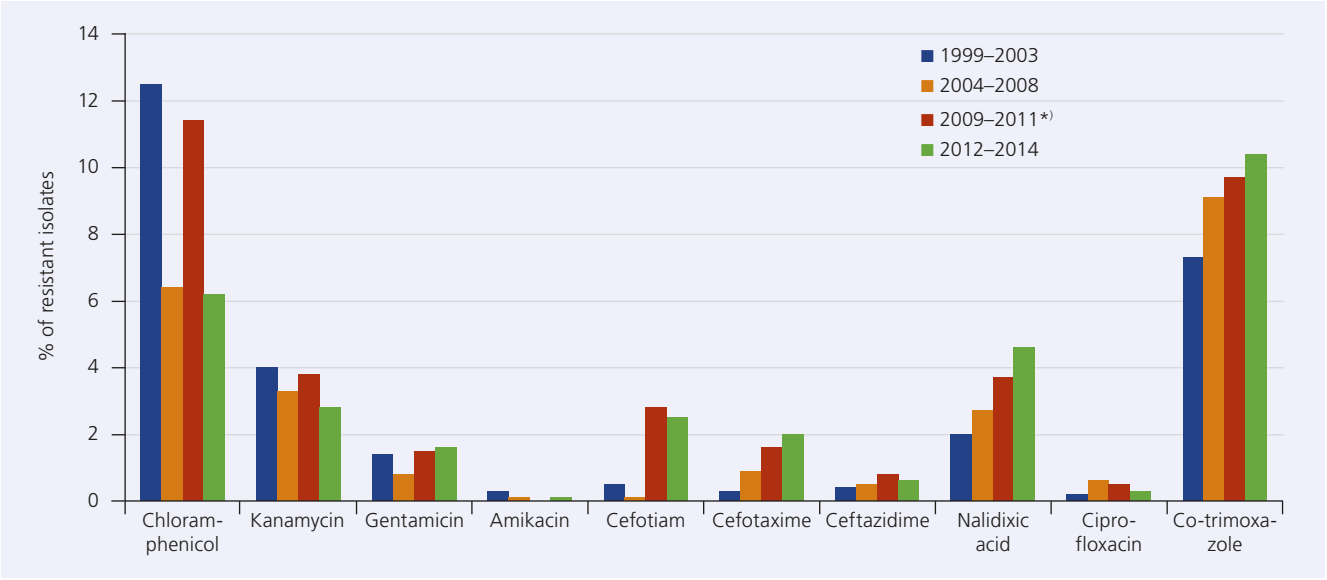


Fig. 4.2.6.1: Resistance rates of enteropathogenic *E. coli* to some selected antimicrobials, comparison of the periods 1999-2003, 2004-2008, 2009-2011 and 2012-2014 (Source: National Reference Centre for *Salmonellae* and Other Bacterial Enterics at the Robert Koch Institute, Wernigerode Branch)
*) The figures for 2011 were corrected to exclude the multidrug-resistant EHEC O104:H4 outbreak isolates.

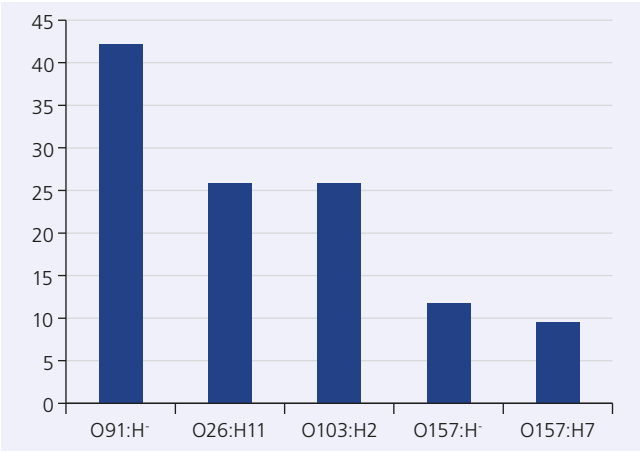


Fig. 4.2.6.2: Percentage of not fully susceptible EHEC isolates among the 5 most common serovars during the period 2009-2014 (Source: National Reference Centre for *Salmonellae* and Other Bacterial Enterics at the Robert Koch Institute, Wernigerode Branch)
For the tested substances, see Tab. 4.2.6.1; number of tested isolates: O91:H n=365, O26:H11 n=216, O103:H2 n=209, O157:H n= 186, O157:H7 n=105

tance situation shows that these pathogens are also exposed to the ecological selection process of antimicrobial-resistant strains in their reservoirs.

➤ E. Tietze, A. Fruth
Reviewer: M. Kist

5 Antimicrobial 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 pathogens 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 2013 GE*RM*-Vet study included a total of 48 *Pasteurella multocida* isolates, 41 of which were obtained from cattle and 7 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 below 10%. The 2013 study found no resistant isolates in the majority of the tested bacterial strains (amoxicillin/clavulanic acid, ceftiofur, enrofloxacin and florfenicol), while one florfenicol-resistant isolate was still detected in the previous year. The rate of resistance to tetracycline was 10.4% in 2013 (Fig. 5.1.1.1.1).

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 MIC_{90} values remain in the lower test range, except for tilmicosin with an MIC_{90} value of 16 mg/l in 2013 as well as co-trimoxazole, where the MIC_{90} value increased from 0.25 to 2 mg/l.

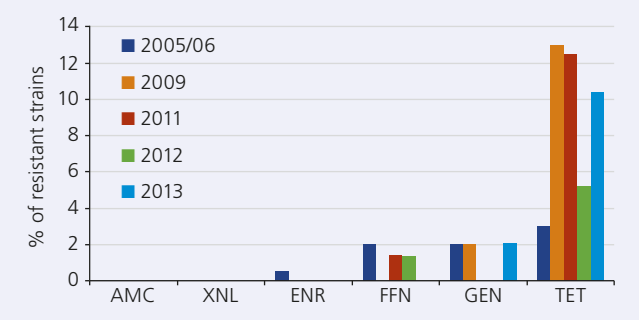


Fig. 5.1.1.1.1: Resistance rates of *P. multocida* from cattle, Germany 2005-2013 (2005/2006 n=188; 2009 n=68; 2011 n=73; 2012 n=77; 2013 n=48)

Tab. 5.1.1.1.1: 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	2012	2013
Ampicillin	0.25	0.5	1	0.25	0.25
Cefoperazone	0.06	0.06	0.06	0.015	0.06
Cefotaxime	–	0.015	0.015	0.015	0.015
Cefquinome	0.06	0.06	0.06	0.015	0.06
Colistin	4	4	4	2	4
Penicillin	0.25	0.25	0.5	0.5	0.25
Tilmicosin	0.25	8	8	8	16
Co-trimoxazole	0.12	0.25	0.25	0.25	2

Conclusion

All isolates from the various types of production were generally characterised by low resistance levels. Resistance rates of approx. 10% are only expected for tetracycline. The antimicrobial agent florfenicol must continue to be monitored carefully; it has been exclusively approved in veterinary medicine for the treatment of respiratory diseases since the middle of the 1990s. Since then, sporadic cases of resistant isolates have been reported in various countries, with Europe having so far been affected rarely. The GE*RM*-Vet studies of the past years only detected resistant isolates in individual cases.

➤ H. Kaspar
Reviewer: A. Römer

5.1.1.2 *Mannheimia haemolytica*

Trends in resistance development

The 2013 GE*RM*-Vet study tested 63 isolates of the *Mannheimia haemolytica* species; these were obtained from cattle in various types of production (calf, young cattle and adult cattle).

For many antimicrobials for which a CLSI breakpoint was available, no resistant isolates were detected in this study, except for tetracycline with 14.1% and penicillin with 12.7% resistant isolates (Fig. 5.1.1.2.1). One isolate turned out to be resistant to florfenicol (resistance rate 1.7%). Although none of the isolates was resistant to enrofloxacin by definition, 12% and 19% of the isolates showed intermediate resistance in the 2012 and 2013 study years, respectively. Accounting for 128 mg/l, the MIC_{90} values for nalidixic acid were also in the higher range.

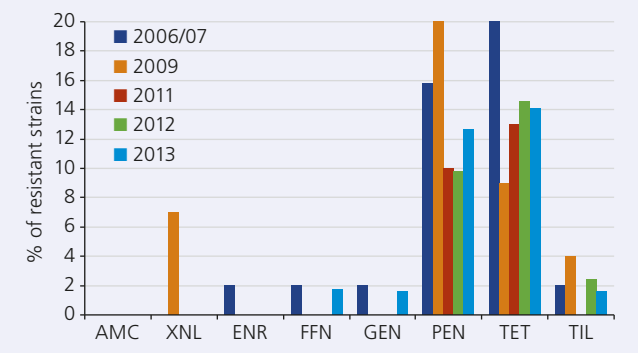


Fig. 5.1.1.2.1: Resistance rates of *M. haemolytica* from cattle, Germany 2006-2013 (2006/2007 n=55; 2009 n=45; 2011 n=33; 2012 n=41; 2013 n=63)

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	MHK_{90} (mg/l)				
	2006/2007	2009	2011	2012	2013
Ampicillin	> 64	16	0.5	0.25	0.25
Cefoperazone	0.25	0.25	0.25	0.06	0.06
Cefotaxime	0.015	0.06	0.015	0.015	0.015
Cefquinome	0.06	0.12	0.06	0.03	0.03
Colistin	0.25	0.5	1	0.5	1
Co-trimoxazole	0.25	0.12	0.12	0.25	0.25

Conclusion

On the whole, noteworthy resistance rates are not expected in *M. haemolytica*. A resistance rate of approx. 14% is to be expected for tetracycline. No resistant isolates were identified for most antimicrobial agents. 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. The statement on the antimicrobial agent florfenicol in the section about *P. multocida* also applies to *M. haemolytica*.

➤ H. Kaspar
Reviewer: A. Römer

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. Financial losses occur due to both reduced milk yields and production shortfalls in milk processing. As a result of milk production and potential direct introduction into the food chain, this disease is of special significance for human health. As a rule, mastitis is by nature a multifactorial disease, which is caused by bacteria, but is additionally strongly influenced by stable, feed and health management. 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 2013 GE*RM*-Vet study measured the MIC values of 205 *S. aureus* isolates obtained from dairy cattle with mastitis. The overall resistance level was low. The highest resistance rates were found for ampicillin and penicillin (16.1% each) (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 (Tab. 5.1.2.1.1). A 5.9% rate of resistance was recorded for oxacillin; the MRSA rate was thus low, but has been subject to an overall slight upward trend since the first MRSA-positive isolates were detected in the 2008 study year (Fig. 5.1.2.1.2).

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	2013
Cefoperazone	2	2	2	1	2
Cefotaxime	n.g.	n.g.	2	2	4
Cefquinome	n.g.	0.5	1	1	1
Clindamycin	n.g.	0.12	0.25	0.25	0.25
Enrofloxacin	0.25	0.25	0.25	0.25	0.25
Tylosin	n.g.	0.5	1	2	2

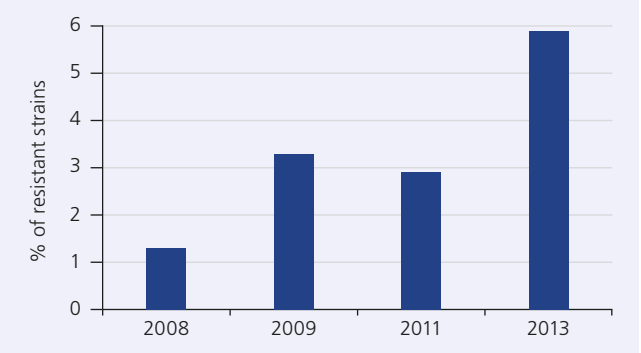


Fig. 5.1.2.1.2: MRSA rates in dairy cattle, Germany 2008-2013

Conclusion

S. aureus isolated from clinical mastitis samples showed high-level susceptibility to most of the tested antimicrobials, in particular to all tested cephalosporins. Although the rates of ampicillin and penicillin G resistance were observed to fluctuate over the study years, there were overall hardly any noteworthy changes. These stable values are remarkable in view of the fact that penicillins (chapter 3) are used in particularly large quantities in intramammary therapy. The MRSA rate was consistently approx. 6%, with the first MRSA in clinical mastitis samples being detected in the 2008 study year.

➤ H. Kaspar
Reviewer: A. Römer

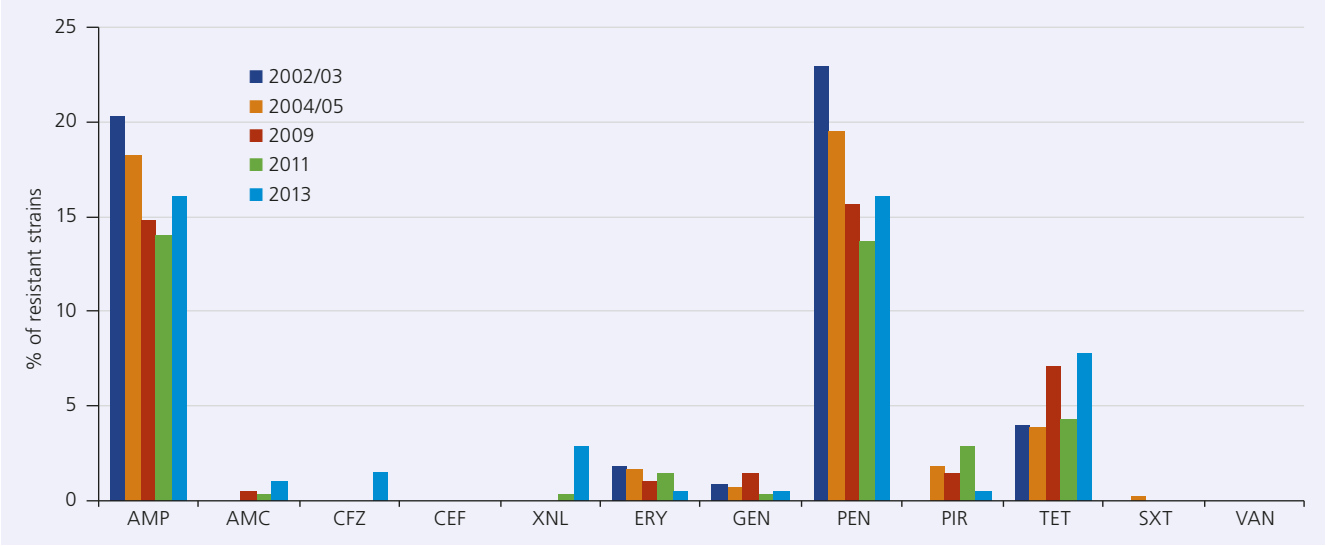


Fig. 5.1.2.1.1: Resistance rates of *S. aureus* from dairy cattle, Germany 2002-2013 (2002/2003 n=227; 2004/2005 n=411; 2009 n=201; 2011 n=350; 2013 n=205)

5.1.2.2 *Enterococcus* spp.

Enterococcus spp. usually enter the udders 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 antimicrobial resistance to other species.

Trends in resistance development

The 2013 GE*RM*-Vet study tested 29 *Enterococcus faecium* isolates and 23 *Enterococcus faecalis* isolates. Resistance rates of more than 10% were detected for some antimicrobials (Fig. 5.1.2.2.1 and 5.1.2.2.2) and the MIC_{90} values were also frequently elevated (Tab. 5.1.2.2.1). As expected, this predominantly concerned cephalosporins (data not shown) and lincosamides, since *Enterococcus* spp. exhibit an intrinsic resistance to these antimicrobials.

E. faecalis

Isolates resistant to ampicillin/clavulanic acid, penicillin, ciprofloxacin and vancomycin were not found. By contrast, the rates of resistance to erythromycin (26.1%) and gentamicin (60.9%) were well above 10%. As was the case in the 2006/2007 and 2010 study years, one isolate with high-level gentamicin resistance was detected in the 2013 study. The rate of resistance to gentamicin was significantly higher than in the previous year and well above that of human clinical isolates. With a rate of 30.4%, an unusually large number of isolates showed intermediate resistance to gentamicin. Concerning this species, it should be noted that only a small number of isolates were included in the study.

E. faecium

Isolates resistant to ampicillin, amoxicillin/clavulanic acid and vancomycin were not found. The rates of resistance to penicillin G and erythromycin were low (6.9% each). Similarly to *E. faecalis*, *E. faecium* showed the highest rate of resistance to gentamicin (17.2%), followed by ciprofloxacin (13.8%). Overall, the rate of resistance to gentamicin was significantly lower than in *E. faecalis*. However, the rate of isolates showing intermediate resistance to gentamicin (41.4%) was at a similarly high level as in *E. faecalis*.

The 2013 study also found differences between E. faecalis and E. faecium isolates in terms of the MIC_{90} values (Tab. 5.1.2.2.1 and 5.1.2.2.2). Regarding the tested isolates, the macrolide MIC values measured for *E. faecium* isolates were somewhat lower than those for *E. faecalis*. The enrofloxacin MIC_{90} values of *E. faecium* isolates ranged at 8 mg/l and those of *E. faecalis* isolates one to three titre steps lower.

Conclusion

Enterococcus spp. isolates from dairy cattle have so far not shown resistance to vancomycin. As was the case in the 2010 and 2006/2007 study years, the 2013 study provided indications of high-level resistance to aminoglycosides, which may signalise a change in the resistance situation. In particular, the resistance rates of *E. faecium* isolates are well below those reported for human isolates (ampicillin, erythromycin, gentamicin and ciprofloxacin). To some extent, this also applies to the tested *E. faecalis* isolates (erythromycin and ciprofloxacin).

➤ H. Kaspar
Reviewer: A. Römer

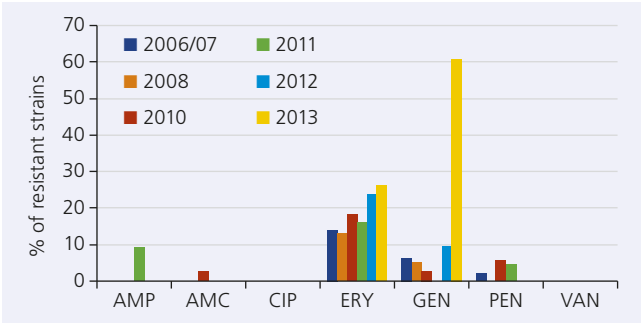


Fig. 5.1.2.2.1: Resistance rates of *E. faecalis* from dairy cattle, Germany 2006-2013 (2006/2007 n=50; 2009 n=39; 2010 n=36; 2011 n=25; 2012 n=21; 2013 n=23)

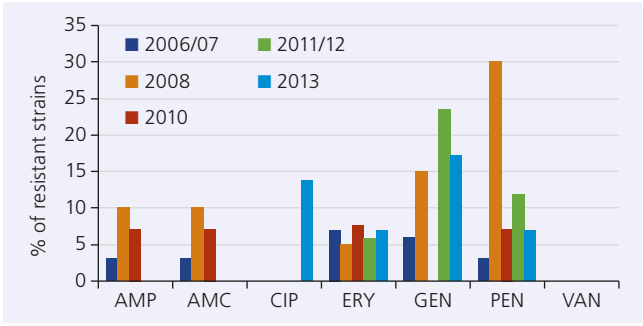


Fig. 5.1.2.2.2: Resistance rates of *E. faecium* from dairy cattle, Germany 2006-2013 (2006/2007 n=30; 2009 n=20; 2011/2012 n=17; 2013 n=29)

Tab. 5.1.2.2.1: Dairy cattle – MIC_{90} values of *E. faecalis* for antimicrobials for which no CLSI-approved breakpoints are available

Antimicrobial	MIC_{90} (mg/l)					
	2006/2007	2008	2010	2011	2012	2013
Tetracycline	128	128	128	128	128	128
Enrofloxacin	1	1	1	1	4	1
Tilmicosin	> 64	> 64	> 64	> 64	> 64	> 64
Co-trimoxazole	0.25	0.25	0.12	8	8	0.06

Tab. 5.1.2.2.2: Dairy cattle – MIC_{90} values of *E. faecium* for antimicrobials for which no CLSI-approved breakpoints are available

Antimicrobial	MIC_{90} (mg/l)				
	2006/2007	2008	2010	2011/2012	2013
Tetracycline	1	64	256	4	0.5
Enrofloxacin	8	8	8	8	8
Tilmicosin	16	16	16	16	16
Co-trimoxazole	0.5	1	0.12	0.12	0.5

5.1.2.3 *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 2002, the BVL has been testing E. coli isolates from dairy cattle with this indication; the 2012 monitoring study included 323 isolates.

Resistance rates of more than 10% were found for ampicillin (17%) and tetracycline (10.5%) (Fig. 5.1.2.3.1). The rates of resistance to the combinations of amoxicillin/clavulanic acid (2.5%) and trimethoprim/sulphamethoxazole (co-trimoxazole) (7.4%) as well as to ceftiofur (8.7%) and gentamicin (1.5%) were significantly below 10%.

A comparison of the five study years revealed an increase in both resistance rates and MIC_{90} values for newer cephalosporins from 0.12 mg/l to 8 mg/l (Tab. 5.1.2.3.1). The rate of resistance to ceftiofur rose from 3% in the 2010 study year to nearly 9% in the 2012 study year, although the resistance rates had not exceeded 3% during the previous 10 year-period. The MIC_{90} values for the fluoroquinolone enrofloxacin and the indicator substance nalidixic acid were in the lower range throughout the entire study period (0.06 mg/l and 4 mg/l, respectively).

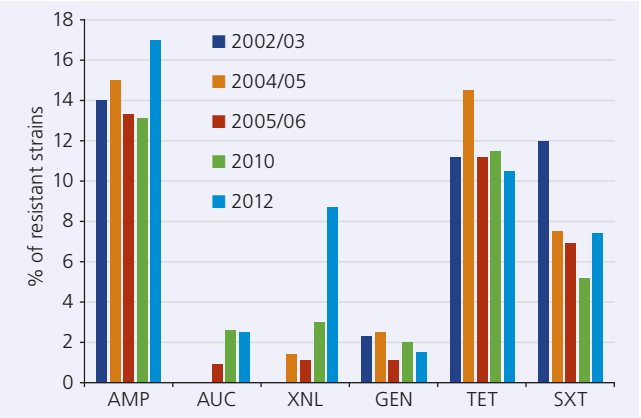


Fig. 5.1.2.3.1: Resistance rates of *E. coli* from dairy cattle, Germany 2002–2012 (2002/2003 n=258, 2004/2005 n=353; 2005/2006 n=534; 2010 n=305, 2012 n=323)

Conclusion

When comparing the resistance rates of mastitis pathogens, *E. coli* shows somewhat lower resistance rates than *S. aureus.* At present, the resistance situation of *E. coli* isolated from mastitis samples of dairy cattle is still favourable, but a change in trend is becoming apparent in newer cephalosporins, which are also approved for intramammary therapy.

➤ H. Kaspar
Reviewer: A. Römer

Tab. 5.1.2.3.1: Dairy cattle – MIC_{90} values of *E. coli* for antimicrobials for which no CLSI-approved breakpoints are available

Antimicrobial	MIC_{90} (mg/l)				
	2002/2003	2004/2005	2005/2006	2010	2012
Cefoperazone	0.5	2	1	0.5	16
Cefotaxime	0.06	1	0.12	0.12	8
Cefquinome	n.g.	0.12	0.06	0.12	8
Nalidixic acid	4	4	4	4	4
Enrofloxacin	0.03	0.06	0.06	0.06	0.06
Florfenicol	8	8	8	16	8

5.1.2.4 *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 2013 study year included 39 isolates.

As expected, high resistance rates and high MIC_{90} values were measured for ampicillin and penicillin, since *Klebsiella* spp. exhibit an intrinsic resistance to aminopenicillins and benzylpenicillins. The rate of resistance to tetracycline was 15.4%. Resistance rates of less than 10% were found for cephalothin (5.1%); isolates resistant to gentamicin and to the combination of amoxicillin/clavulanic acid were not detected. The MIC_{90} values for newer cephalosporins and for enrofloxacin were consistently in the lower range, which is why reduced susceptibility is not yet expected in this case (Tab. 5.1.2.4.1).

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 newer 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 (Tab. 5.1.2.4.1). Since the 2011 study year, ESBL-positive *Klebsiella* spp. isolates have been detected in isolated cases (Fig. 5.1.2.4.2); however, the MIC_{90} values for the individual cephalosporins tested were still at the same level as in the previous study years.

Conclusion

When comparing the results of the study years, it became apparent that the resistance rates and MIC_{90} values of *Klebsiella* spp. were in a favourable range. The further development of ESBLs in both *E. coli* and *Klebsiella* spp. requires particular monitoring in order to be able to anticipate the trend in resistance development. At least the bacterial isolates from the "udder" compartment in dairy cattle still showed significantly more favourable susceptibility levels than human isolates.

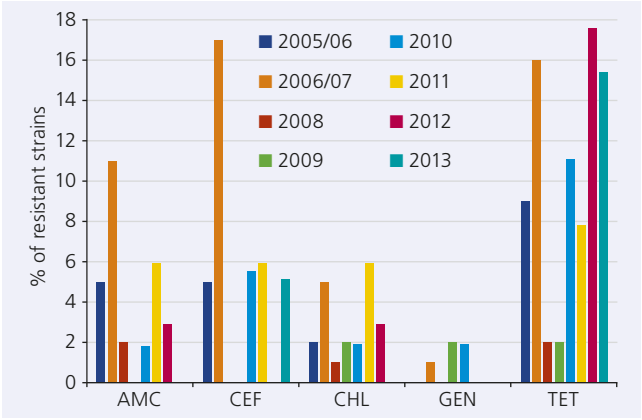
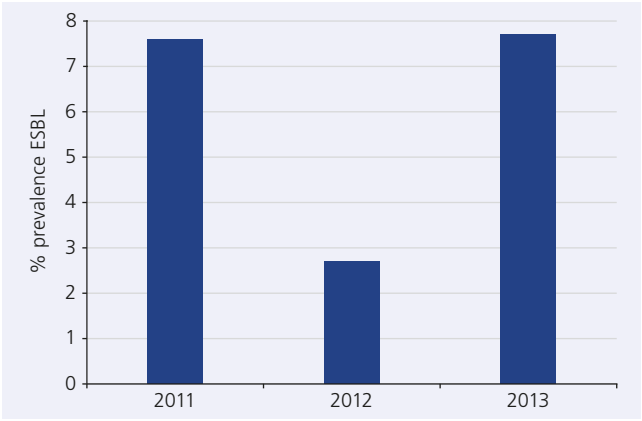


Fig. 5.1.2.4.1: Resistance rates of *Klebsiella* spp. from dairy cattle, Germany 2005–2013 (2005/2006 n=141, 2006/2007 n=76; 2008 n=95, 2009 n=49; 2011 n=51, 2012 n=68, 2013 n=39)



Fgi. 5.1.2.4.2: Phenotypic ESBL-producers in *Klebsiella* spp. from dairy cattle

➤ H. Kaspar
Reviewer: A. Römer

Tab. 5.1.2.4.1: Dairy cattle – MIC_{90} values of *Klebsiella* spp. for antimicrobials for which no CLSI-approved breakpoints are available

Antimicrobial	MIC_{90} (mg/l)							
	2005/2006	2006/2007	2008	2009	2010	2011	2012	2013
Cefoperazone	2	2	2	2	2	1	1	1
Cefotaxime	–	0.25	0.06	0.06	0.06	0.06	0.06	0.12
Cefquinome	0.06	0.12	0.06	0.06	0.06	0.06	0.06	0.12
Ceftiofur	0.5	0.5	0.5	0.5	0.5	0.5	0.5	1
Colistin	0.5	0.5	0.5	0.5	2	1	1	1
Enrofloxacin	0.06	0.12	0.06	0.12	0.12	0.06	0.06	0.06
Nalidixic acid	4	4	4	4	4	4	4	4
Ciprofloxacin	–	–	–	–	–	–	–	0.06
Doxycycline	4	16	4	4	4	4	16	32

5.1.3 Enteritis

Enteritis caused by infections with *Escherichia coli* and *Salmonella* spp. 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 antimicrobials is part of routine practice.

5.1.3.1 *Escherichia coli*

Trends in resistance development

The GE*RM*-Vet studies have provided data for *Escherichia coli* isolates from calves with "enteritis" since 2004. 250 isolates were tested in 2013, 287 isolates in 2012 and 163 isolates in 2011. MIC values of seven antimicrobials were classified on the basis of the CLSI standard. Ciprofloxacin, which is only approved for use in human medicine, was tested and evaluated based on the EUCAST breakpoints (human-specific clinical breakpoints) for the first time in the 2013 study year.

As was the case in previous study years, the highest resistance rates in the 2013 study were observed for ampicillin (78%), tetracycline (74%) and trimethoprim/sulphamethoxazole (co-trimoxazole) (56%, Fig. 5.1.3.1.1). The high rate of isolates showing intermediate resistance (25%) detected for the combination of amoxicillin/clavulanic acid also suggests a shift in the bacterial population towards increased prevalence of resistance characteristics.

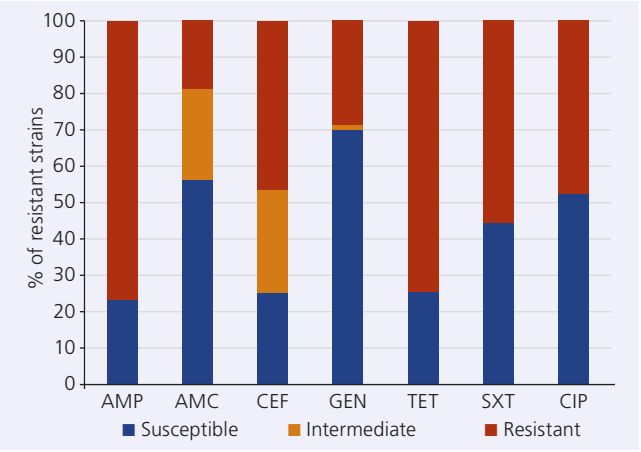


Fig. 5.1.3.1.1: Resistance rates of *E. coli* from calves, Germany 2013 (n=250)

The tested aminoglycosides showed reduced efficacy: The rate of gentamicin resistance has ranged at approx. 30% for two years now; the apramycin MIC_{90} value was 8 mg/l in 2012. This antimicrobial was not tested in the 2013 study year (Fig. 5.1.3.1.2).

The consistently high enrofloxacin MIC_{90} value (> 16 mg/l) also suggests reduced efficacy. Evaluated on the basis of the human-specific clinical breakpoints (EUCAST), a resistance rate of 48% was observed for the fluoroquinolone ciprofloxacin. Moreover, high MIC_{90} values (Tab. 5.1.3.1.1) have been observed for some newer cephalosporins since 2009: ≥ 32 mg/l for cefotaxime and cefquinome as well as ≥ 64 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).

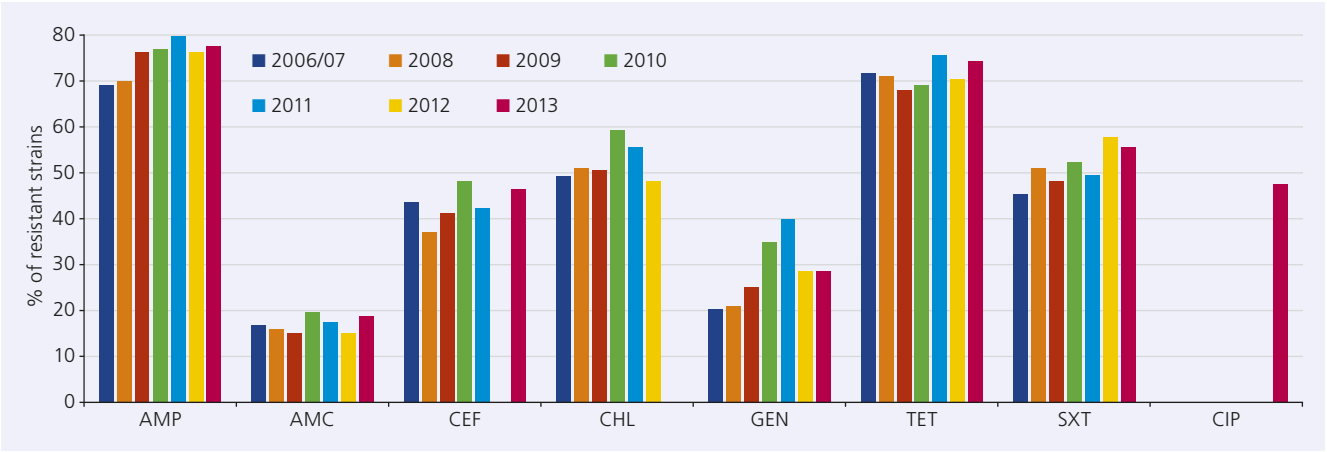


Fig. 5.1.3.1.2: Resistance rates of *E. coli* from calves, Germany 2008-2013 (2006/2007 n=154; 2008 n=166; 2009 n=160; 2010 n=140; 2011 n=161; 2012 n=287 (CEF not tested); 2013 n=250 (CHL not tested, CIP tested for the first time)

Tab. 5.1.3.1.1: Calf – MIC_{90} values of *E. coli* for antimicrobials for which no CLSI-approved breakpoints are available

Antimicrobial	MIC_{90} (mg/l)						
	2006/2007	2008	2009	2010	2011	2012	2013
Apramycin	16	> 32	8	8	> 128	8	n.g.
Cefoperazone	> 32	> 32	32	> 32	> 32	> 32	> 32
Cefotaxime	1	16	32	> 32	> 32	> 32	> 32
Cefquinome	8	16	> 32	> 32	> 32	> 32	> 32
Ceftiofur	2	64	> 64	>64	> 64	> 64	> 64
Colistin	0.5	0.5	0.5	1	2	1	1
Enrofloxacin	> 16	> 16	> 16	> 16	> 16	> 16	> 16
Nalidixic acid	> 128	> 128	> 128	> 128	> 128	> 128	> 128

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%, 2013: 19%; up to 25% 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, which increased from 7% in 2006 to 29% in 2013 (Fig. 5.1.3.1.3).

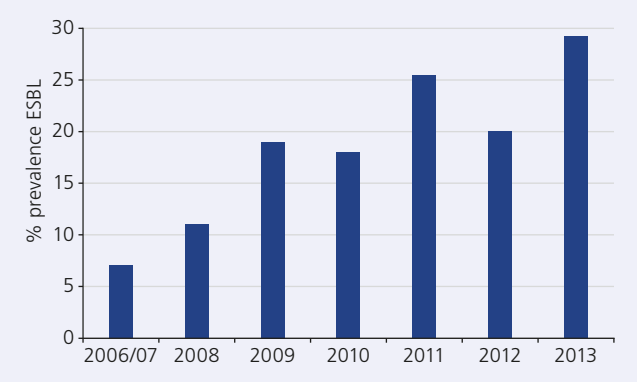


Fig. 5.1.3.1.3: Phenotypic ESBL-producers in *E. coli* from calves

Conclusion

Overall, the resistance rates of *E. coli* isolates from calves with enteritis are still 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 further efficacy of colistin.

➤ H. Kaspar
Reviewer: A. Römer

Antibiotics of last resort – an established term? Considerations on the responsible use of antimicrobials in human and veterinary medicine

Introduction

This article gives a brief overview of the term "antibiotics of last resort" and their consumption in human and veterinary medicine. Several correlations between antimicrobial use and antimicrobial resistance will be discussed to stimulate ideas on generally applicable rules for the responsible use of all antimicrobials in both human and veterinary medicine. These considerations are based on the principle that bacterial infections in both humans and animals should be treated with the antimicrobial that is the most suitable based on scientific criteria.

The term "second-line antimicrobials"

Although the term "antibiotics of last resort" is frequently used in the media, there is no generally accepted definition for it. However, publications of the Research Institute of the AOK (WIdO)[1,2] make a distinction between first-line antimicrobials and antibiotics of last resort for outpatient use in human medicine. Antibiotics of last resort should only be used if first-line antimicrobials are no longer effective or life-threatening diseases are present.[1] Tab. 1 shows a comparison of first-line antimicrobials and antibiotics of last resort according to this classification.

On an international scale, the WHO AGISAR list is generally used to determine the significance of antimicrobial classes for the treatment of human bacterial infections.[3] The classification of antimicrobials into the three categories of critically important antimicrobials, highly important antimicrobials and important antimicrobials is based on the two criteria listed below.

Criterion 1: An antimicrobial agent which is the sole, or one of limited available therapy, to treat serious human disease.

Tab. 1: First-line antimicrobials and antibiotics of last resort in outpatient therapy in Germany according to the WIdO

First-line antimicrobial	Antibiotics of last resort
Tetracyclines	Antistaphylococcal penicillins
Basic penicillins	Aminopenicillins + β-lactam antimicrobials
Folic acid antagonists	Oral cephalosporins
Nitroimidazoles	Newer macrolides
Erythromycin and older macrolides	Fluoroquinolones
	Lincosamides
	Fusidic acid
	Streptogramins

Criterion 2: Antimicrobial agent is used to treat diseases caused by either: (1) organisms that may be transmitted to humans from non-human sources or, (2) human diseases causes by organisms that may acquire resistance genes from non-human sources.

Antimicrobials that meet both criteria are deemed critically important, those that meet one criterion highly important, and those that meet neither of the two criteria important. The category of the highest importance contains 15, the second category 13 and the last category 4 antimicrobial classes. The WHO AGISAR document also lists examples of substances from the various classes that are used exclusively in veterinary medicine. Tab. 2 gives an overview of the WHO AGISAR classification.

The critically important antimicrobials have been prioritised by WHO AGISAR based on three sub-criteria.

Criterion 1.1: High absolute number of people affected by diseases for which the antimicrobial is the sole or one of few alternatives to treat serious human disease.

Tab. 2: Classification of antimicrobial classes based on their significance for human medicine according to the 2012 WHO-AGISAR List

Critically Important	Highly Important	Important
Aminoglycosides	Amdinopenicillins*	Aminocyclitols
Carbapenems and other penems*	Amphenicols	Cyclic polypeptides
Cephalosporins (3rd and 4th generation)	Cephalosporins (1st and 2nd generation)	Nitrofurantoins*
Cyclic esters (fosfomycin)*	Lincosamides	Nitroimidazoles
Fluoro- and other quinolones	Antistaphylococcal penicillins	
Glycopeptides*	Pleuromutilins	
Glycylcyclines*	Pseudomonic acid A (mupirocin)*	
Lipopeptides*	Riminofenazines*	
Macrolides and ketolides	Steroid antimicrobials	
Monobactams*	Streptogramins*	
Oxazolidinones*	Sulphonamides and combinations with DHFR inhibitors	
Penicillins (natural, aminopenicillins and antipseudomonal penicillins)	Sulphones*	
Polymyxins	Tetracyclines	
Rifamycins*		
Drugs used solely to treat tuberculosis*		

* Not approved for use in veterinary medicine in Germany (ketolides are not approved either)

Criterion 1.2: High frequency of use of the antimicrobial for any indication in human medicine, since usage may favour selection of resistance.

Criterion 2.1: Greater degree of confidence that there are non-human sources that result in transmission of resistant bacteria (Campylobacter spp.), or their resistance genes, to humans (high for Salmonella spp., Escherichia coli and Enterococcus spp.).

Four antimicrobial classes meet all three sub-criteria and thus have the highest priority for risk management. These are fluoroquinolones, third- and fourth-generation cephalosporins, macrolides and glycopeptides.

The OIE (World Organisation for Animal Health) created a corresponding classification into veterinary critically important, veterinary highly important and veterinary important antimicrobials for veterinary antimicrobials used in food-producing animals.[4] This list was last revised in May 2015 and is shown in Tab. 3.

In late 2014, upon request of the European Commission, the European Medicines Agency (EMA) classified the critically important antimicrobials and several highly important antimicrobials from the WHO list according to the risk for humans posed by resistance selection in veterinary medicine.[5] The following three categories were created:

Category 1: Antimicrobials used in veterinary medicine where the risk to public health is estimated as low or limited.

Category 2: Antimicrobials used in veterinary medicine where the risk is estimated higher.

Category 3: Antimicrobials not approved for use in veterinary medicine.

For category 1 substances, it is recommended that any inappropriate use should be avoided. Treatment of animal groups should be limited as much as possible.

For category 2 substances, it is recommended that they should only be used if there are no alternative antimicrobials authorized for the respective target species and indication.

Category 3 substances are not approved for use in veterinary medicine and therefore have no MRL (Maximum Residue Level) and hence, may only be used by way of exception in non-food-producing animals. Tab. 4 summarises the EMA's classification.

In summary, it is concluded

- that there is no clear definition of the term "antibiotics of last resort" and that in Germany this specific term refers to a classification by the WIdO,
- that the WHO AGISAR classification of the importance of antimicrobial classes for treatment in humans is used internationally,
- that there is a corresponding classification by the OIE for the use of antimicrobials in food-producing animals,
- that aminoglycosides, third- and fourth-generation cephalosporins, macrolides, penicillins and fluoroquinolones are classified as critically important for both human and veterinary medicine and
- that especially the modern classes of the critically important antimicrobials are not approved for use in veterinary medicine (cf. Tab. 2).

Tab. 3: Classification of antimicrobial classes based on their significance for veterinary medicine according to OIE 2014

Veterinary Critically Important	Veterinary Highly Important	Veterinary Important
Aminoglycosides	Ansamycins, rifamycins	Aminocoumarins
Amphenicols	N/A	N/A
Cephalosporins (3rd and 4th generation)	Cephalosporins (1st and 2nd generation)	Organic arsenic compounds
Macrolides	Ionophore antimicrobials	Bicyclomycines
Penicillins	Lincosamides	Fusidic acid
	Cyclic esters (fosfomycin)	Orthosomycins
Fluoroquinolones	Pleuromutilins	Quinoxalines
Sulphonamides and combinations with diaminopyrimidines	Polypeptides incl. cyclic polypeptides	Streptogramins
Tetracyclines	Quinolones (1st generation)	Thiostreptons

* N/A, no information

Tab. 4: Classification of antimicrobial classes according to EMA/381884/2014[5]

Category 1	Category 2	Category 3
Macrolides incl. ketolides	Fluoroquinolones and quinolones	Carbapenems and other penems
Penicillins: natural and narrow-spectrum	Cephalosporins (3rd and 4th generation)	Ceftaroline and ceftobiprole
Polymyxins	Aminoglycosides*	Cyclic esters (fosfomycin)
Rifamycins	Aminopenicillins and combinations with β-lactamase inhibitors*	Glycopeptides
Tetracyclines		Glycylcyclines
		Lipopeptides
		Monobactams
		Oxazolidinones
		Penicillins: carboxypenicillins, ureidopenicillins incl. β-lactamase inhibitors
		Riminofenazines
		Sulphones
		Antituberculous drugs

* Risks not yet conclusively assessed and classification still to be reviewed

Use of antibiotics of last resort in human and veterinary medicine

In Germany, there has been a trend for many years towards the increased use of so-called antibiotics of last resort (Tab. 1) in outpatient treatment of infectious diseases. Whereas antibiotics of last resort accounted for about 11% of all prescriptions in 1991, their share rose from 35% in 2004 to 48% in 2010.[6] According to the WIdO's latest figures on antimicrobial consumption in 2013, which are discussed in detail elsewhere in GERMAP 2015, the share of antibiotics of last resort has now increased to about 52%. The share of those antimicrobials classified by the WHO AGISAR as critically important antimicrobials of the highest priority is about 25% of all prescriptions.

The 2013 data on antimicrobial sales in veterinary medicine was published by the BVL.[7] According to the WIdO's definition of antibiotics of last resort (Tab. 1), merely 3% of all antimicrobials sold to veterinarians fell into this category, and only about 10% belonged to the four most important antimicrobial classes specified by the WHO AGISAR. Of this 10%, 89% were macrolides, 8% quinolones and 3% third- and fourth-generation cephalosporins. The data of the first joint report of the ECDC, EFSA and EMA on antimicrobial consumption and antimicrobial resistance in humans and food-producing animals also indicates a low consumption of fluoroquinolones and third- and fourth-generation cephalosporins in veterinary medicine.[8] Based on standardised patient and livestock populations, the consumption (in mg/kg of estimated biomass) of third- and fourth-generation cephalosporins in humans in 2015 was more than twice as high, and the consumption of fluoroquinolones even more than five times as high, as in veterinary medicine.

The causes that led to a high level of antimicrobial use and an increasing share of prescriptions of antibiotics of last resort in human medicine were summarised by Schröder (2011)[6]. There is great need for education and training among physicians and patients. Up to 50% of all antimicrobial prescriptions are inappropriate, for example in terms of dosage and duration of therapy. The need for improvement in well reflected diagnoses is equally great. For example, even though 80% of all respiratory tract infections are of viral origin and therefore constitute no indication for antimicrobial therapy, they are treated with antimicrobials in about 80% of all cases due to a lack of knowledge among physicians and patients, diagnostic uncertainty and the patients' strong expectation to be prescribed medication. This unreflective use of antimicrobials has been increasingly criticised in recent years.

Of course, antimicrobial use in veterinary medicine must also be limited to confirmed diagnoses of bacterial infections for which no alternative therapies are available based on the current state of scientific knowledge. Antimicrobials should by no means be used to compensate for shortcomings in hygiene and husbandry conditions.

In German veterinary medicine, comprehensive documentation requirements have been in place since 2001 regarding the sale and use of antimicrobials in livestock farming for both livestock owners (livestock population register) and veterinarians (record of sale and use). Another improvement in the registration and monitoring of antimicrobial use in food-producing animals was introduced on July 1st, 2014, with the reporting of antimicrobial consumption data for livestock populations to the central HIT database. The aim is to identify farms on whichh antimicrobial consumption is comparatively high and to take measures to reduce the need for antimicrobials on these farms.

The overall aim must be to establish intelligent practices for antimicrobial use in line with the principles of using "as much as necessary but as little as possible".

Correlations between antimicrobial use and antimicrobial resistance in humans and food-producing animals

A recently published report by the ECDC/EFSA/EMA[8] not only indicates the antimicrobial consumption data reported by the European member states, but also correlates the consumption data of selected antimicrobials and the resistance data of indicator bacteria collected during the same period as part of the European antimicrobial resistance monitoring. Major findings of the report are listed below.

- There is a correlation between antimicrobial use in human medicine and resistance in bacteria isolated from humans.
- There is a correlation between antimicrobial use in food-producing animals and resistance in bacteria isolated from these animals.
- In food-producing animals, this correlation applies primarily to E. coli, but also to Salmonella and Campylobacter.
- In human medicine, correlations have been found between the use of fluoroquinolones and third- and fourth-generation cephalosporins and corresponding bacterial resistance in humans.
- There is a correlation between the use of both cephalosporins and fluoroquinolones in food-producing animals and resistance in *E. coli* isolated from humans.
- Regarding the correlation between the use of fluoroquinolones in livestock and resistance in human *E. coli*, the report states that this result should be interpreted with caution because only a small portion of the resistant *E. coli* may actually be of animal origin. Other important sources of these bacteria include human-to-human transmission, travel and consumption of foreign meat products.
- Further correlations between use in food-producing animals and resistance in humans were found for macrolides and Campylobacter as well as well for tetracyclines and Salmonella and Campylobacter.
- No correlations were found for the use of fluoroquinolones in livestock and resistance of Salmonella and Campylobacter in humans.
- This also applies to the use of third- and fourth-generation cephalosporins in livestock.
- Clonal expansion of resistant bacteria in humans and animals may occur without detectable selection pressure through

antimicrobial use, thereby strongly influencing conclusions on correlations between antimicrobial use and resistance.

- Antimicrobial use in humans is regarded as the most likely cause of the occurrence of antimicrobial resistance in bacteria isolated from humans.

In conclusion, the report states that the epidemiology of antimicrobial resistance is complex and influenced by numerous factors other than antimicrobial use. Furthermore, it recommends that the described correlations should be interpreted with caution because the underlying data is difficult to compare.

Since the report by the ECDC/EFSA/EMA[8] did not identify any clear correlations between antimicrobial use in food-producing animals and resistance of indicator bacteria in humans, it is the author's opinion that unilateral restrictions of antimicrobial use in veterinary medicine are not the right approach without having been able to provide a clear scientific understanding of the risk that antimicrobial use in animals presents to public health and the routes through which antimicrobial resistance is transferred from animals to humans and vice versa.

Recommendation of generally applicable guidelines for responsible antimicrobial use in human and veterinary medicine

Like all other medicinal products for humans and animals, antimicrobials are subject to an extensive approval procedure to scientifically prove their quality, safety and efficacy in order to have these properties confirmed by the regulatory authorities together with a positive benefit-risk balance. The general requirements for the approval of veterinary medicinal products are set forth in Directive 2001/82/EC[9] (incl. amendments). In addition, there are specific guidelines for antimicrobials, namely EMEA/CVMP/627/2001-FINAL[10], the revision of which is currently being prepared (EMA/CVMP/261180/2012)[11], CVMP/VICH/644/2001[12], EMEA/CVMP/SAGAM/383441/2005[13] and EMEA/CVMP/344/99-FINAL-Rev.1[14]. The guideline on the summary of product characteristics for antimicrobial products (EMEA/CVMP/SAGAM/383441/2005)[13] states in its introduction that all necessary information must be included in order to use an antimicrobial product safely and effectively while minimising the risk of the development of antimicrobial resistance. The CVMP/VICH/644/2001[12] guideline specifies the requirements for studies aimed at characterising potential resistance due to use in food-producing animals and, in accordance with the EMEA/CVMP/627/2001-FINAL[10] guideline, resistance rates as well as cross- and co-resistance must be taken into account in evaluating efficacy. The approval process thereby ensures to only approve those substances that are effective, safe and tested regarding minimisation of resistance development. Consequently, antimicrobials that are administered as specified in the package leaflet pose no immediate risk and there is no reason to restrict their use without any scientific evidence of concrete risks.

For the use of antimicrobials in veterinary medicine, the guidelines of the German Federal Chamber of Veterinarians[15] have been issued, listing basic principles of responsible antimicrobial use. In human medicine, there is also a wide range of recommendations on the responsible use of antimicrobials in various infectious diseases, such as the guidelines of the Infectious Diseases Society of America (IDSA)[16]. In order to ensure the efficacy of antimicrobials on a long-term basis while minimising resistance selection, it is indispensable to observe both the rules set forth in these documents and additional generally accepted rules for the responsible use of antimicrobials in human and veterinary medicine.

The elements of such general guidelines for responsible use of antimicrobials in human and veterinary medicine are briefly outlined below.

Improved training and continuing education

Extensive training and continuing education are essential prerequisites to avoid future unreflected and inappropriate use of antimicrobials in veterinary and human medicine. Although universities increasingly offer lecture contents and voluntary courses on this subject, there are no compulsory lectures focusing on antimicrobial use, antimicrobial resistance and its prevention.

To ensure a comparable and solid level of education, students of veterinary and human medicine should be required to attend hands-on lectures on the subject of antimicrobial resistance, including a final exam. The areas to be covered should include the spectrum of activity and the pharmacological and pharmacokinetic characteristics of all approved antimicrobials, naturally occurring resistance, cross-resistance, selection and control of resistance, bacterial sampling, interpretation of susceptibility test results and the principles of responsible use of antimicrobials. Additionally, it would be desirable to introduce mandatory continuing education including the corresponding certificates in these areas for practitioners of veterinary and human medicine.

This is the only way for the general principles of responsible antimicrobial use, which are outlined below but still need to be defined more precisely, to become permanently established in daily practice.

Use only in bacterial infections

Antimicrobials are apparently still used far too often to treat viral infections such as common cold.[6] The training of future generations of students therefore needs to focus on establishing a clear catalogue of diseases in which the use of antimicrobials is appropriate in the first place. Such a therapy guideline for antimicrobials in human and veterinary medicine must be a mandatory part of study programmes and be included in exams.

Use only after diagnosis

Furthermore, antimicrobials may only be used after a bacterial infection has been diagnosed. Differential diagnostic decision trees should be developed for both human and veterinary medicine, including the severity of the respective symptoms as a criterion for a treatment decision. There must also be a clear guideline stating which symptoms of primary viral infections indicate that a bacterial secondary infection requiring antimicrobial treatment can be expected.

Not for use in minor infections

There is a general consensus among scientists that antimicrobials should not be used to treat mild infections. However, antimicro-

bials are often prescribed for the prevention of any risks. This applies to both human and veterinary medicine. Minor infections with a high rate of spontaneous recovery would also be covered by clear practice guidelines and differential diagnostic decision trees, strongly reducing their use for such indications.

Use only for approved indications

After making a diagnosis and reaching a responsible decision on antimicrobial use, a suitable drug must be selected. This must be done based on the principle of using only those antimicrobials that are approved for the diagnosed indication and the involved bacteria. Only in exceptional cases deviations from this principle are acceptable, for instance if no approved therapies are available. In veterinary medicine, the provisions of the therapy cascade set forth in the Directive 2001/82/EC[9], Article 10 and 11, must be observed.

Combinations of different approved medicinal products should only be used in exceptional cases and only if their benefits have been scientifically proven.

Disease-specific susceptibility testing

Prior to antimicrobial treatment, the bacterial pathogens causing the disease should, whenever possible, be isolated and tested for their susceptibility to the antimicrobial classes that may be used for treatment. The therapy guidelines for antimicrobials in human and veterinary medicine should specify exactly for which diseases susceptibility testing must be performed, depending on the severity and risk of infection. For this purpose, diseases should be defined for which an antibiogram is to be prepared before starting therapy, either in any case or depending on severity, and for which antimicrobial treatment must be initiated immediately due to a life-threatening situation or high risk of infection.

When there are symptoms of disease in individual animals on livestock farms, metaphylactic group treatments are often performed to prevent the spread of infectious diseases to other animals in the herd. In many cases, action must be taken at an early stage to avoid economic losses. Sampling for susceptibility testing in individual animals without immediately starting therapy is not practical due to the resulting delays and is questionable in terms of animal welfare. This is why it is necessary to perform regular – e.g. quarterly – susceptibility testing at farm level in order to have a continuously updated susceptibility profile of the stable-specific bacterial flora and thereby minimise the risk of incorrect empiric antimicrobial treatment. This approach should be part of good veterinary practice.

Use in accordance with the package leaflet

The package leaflet indicates the scientifically proven stage of knowledge regarding the efficacy and safety of the antimicrobial medicinal product that has been confirmed by the regulatory authorities. The instructions in package leaflets should therefore be strictly followed. This particularly applies to the therapeutic indications, dosage, route of administration, duration of treatment, warnings and contraindications. Deviations from these instructions are only permissible in exceptional cases in line with the therapy cascade.

Selection of the best antimicrobial on the basis of available data

Once the infectious disease and the susceptibility of the involved bacterial pathogens is known, the approved antimicrobial that is the most suitable for the indication according to the available scientific data should be selected and used. To maintain the greatest possible variety of therapeutic alternatives, no a priori limitations should apply to individual antimicrobial classes. Once the most suitable antimicrobial class has been identified based on the available scientific data, the antimicrobial agent within that class that has the best characteristics in terms of resistance selection and efficacy should be selected, known as the "best in class" agent. If several antimicrobial classes are equally well suited, the principle of preferably using a "less modern" class should apply.

Regular susceptibility testing

An important prerequisite for selecting a suitable antimicrobial for the therapy is to know the current susceptibility situation of the relevant bacterial populations, both within the livestock population and at regional or national level. To obtain a comprehensive and reliable body of data, it would be desirable to initiate joint resistance monitoring programmes of antimicrobial manufacturers and government institutions conducted in accordance with scientifically established and standardised testing protocols. The collaboration of the German Federal Office of Consumer Protection and Food Safety (BVL) and the Federal Association for Animal Health (BfT) from 2004 to 2006 could serve as an example.[17]

No approval without clinical breakpoints

The susceptibility status of bacterial populations can only be determined on the basis of breakpoints that define minimum inhibitory concentrations or inhibition zone diameters at which bacteria are classified as susceptible or resistant to an antimicrobial agent. There are still numerous substances for which no specific clinical breakpoints have been defined, especially in veterinary medicine. This is why it is indispensable to make the establishment of such breakpoints based on approved regulations a prerequisite for all future approvals of antimicrobials.

Increased research into the epidemiology of antimicrobial resistance

One element of responsible and intelligent antimicrobial use is the recommendation for therapeutic use on the basis of reliable data on the susceptibility and risk potential of an antimicrobial agent. Over the last few years and decades, there have been countless publications on the prevalence of antimicrobial resistance in humans and animals, the genetic basis of such resistance and the prevalence of resistance genes. Our knowledge about the prevalence of resistance mechanisms and resistance genes has become very extensive, but it remains difficult to transfer this knowledge to the epidemiology of antimicrobial resistance, and even more so to understand it in its full complexity. In this context, there are two notable publications by Sommer et al. (2009[18], 2010[19]). The authors examined the human microbiome using culture-independent functional metagenomic methods and identified a multitude of new resistance genes in intestinal

bacterial flora that had previously not been detectable in cultures of human pathogenic bacteria. One of the authors' major conclusions was that there appear to be barriers for the lateral transfer of these resistance genes to bacteria that are pathogenic in humans. One way to achieve a better understanding of the transfer of resistance genes and its significance for the epidemiology of resistance mechanisms would be to shift the focus of research from laboratory-based studies of pure cultures to the actual situation in the target organism and its complex communities of bacterial populations. If close collaboration between human and veterinary medicine provides deeper insights into the development, spread and persistence of antimicrobial resistance, specific measures and generally applicable principles for the intelligent use of antimicrobials can be defined to maintain these essential therapies for both fields on a long-term basis.

Conclusion

There is no uniform definition of the term "antimicrobials of last resort", neither in Germany nor internationally. Since every antimicrobial treatment can lead to the selection of resistant bacteria, all substances, including antibiotics of last resort, must be used appropriately and responsibly. This article provides some food for thought on the subject. Increased collaborative research efforts of human and veterinary medicine are recommended to gain a comprehensive understanding of the epidemiology of antimicrobial resistance and to define suitable measures.

➤ B. Stephan
Reviewer: S. Klee, J. Wallmann

1. Schröder H, Nink K, Günther J, Kern WV. Antibiotika: Solange sie noch wirken... Revisited: 2001-2004. WIdO Wissenschaftliches Institut der AOK, 2005.
2. Schröder H. Einsatz von Antibiotika in Deutschland. Vortrag MRE-Fachtagung am 27.09.2011.
3. WHO (2012). Tackling foodborne antimicrobial resistance globally through integrated surveillance. Report of the 3rd meeting of the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance, 14-17 June 2011, Oslo, Norway.
4. OIE (2015). OIE list of antimicrobial agents of veterinary importance. OIE (World Organisation for Animal Health).
5. EMA (2014). Answers to the requests for scientific advice on the impact on public health and animal health of the use of antibiotics in animals. EMA/381884/2014.
6. Schröder H. Hände weg von der eisernen Reserve. Gesundheit und Gesellschaft 2011;14:21-6.
7. BVL, Dritte Datenerhebung zur Antibiotikaabgabe in der Tiermedizin http://www.bvl.bund.de/DE/08_PresseInfothek/01_FuerJournalisten/01_Presse_und_Hintergrundinformationen/05_Tierarzneimittel/2014/2014_08_01_pi_Abgabemengen_korrigiert_29_08_2014.html.
8. ECDC/EFSA/EMA (2015). ECDC/EFSA/EMA first joint report on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals. ECDC/EFSA/EMA 636088/2013.
9. Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products.
10. EMEA/CVMP/627/2001: Demonstration of efficacy for veterinary medicinal products containing antimicrobial substances.
11. Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances – Draft.
12. CVMP/VICH/644/2001. VICH GL27. Guidance on the pre-approval information for registration of new veterinary medicinal products for food-producing animals with respect to antimicrobial resistance.
13. EMEA/CVMP/SAGAM/383441/2005. Revised guideline on the SPC for antimicrobial products.
14. EMEA/CVMP/344/99-FINAL-Rev.1. Conduct of efficacy studies for intramammary products for use in cattle.
15. Bundestierärztekammer (BTK). Leitlinien für den sorgfältigen Umgang mit antibakteriell wirksamen Tierarzneimitteln – mit Erläuterungen. Überarbeitete Fassung (Stand Januar 2015). http://www.bundestieraerztekammer.de/downloads/btk/leitlinien/Antibiotika-Leitlinien_01-2015.pdf.
16. Infectious Diseases Society of America, IDSA Practice Guidelines. http://www.idsociety.org/Organ_System/.
17. Schwarz S, Alesík E, Grobbel M, Lübke-Becker A, Wallmann J, Werckenthin C, et al. The BfT-GermVet monitoring program-aims and basics. Berl Münch Tierarztl Wochenschr. 2007 Sep-Oct;120(9-10):357-62.
18. Sommer MOA, Dantas G, Church GM. Functional characterization of the antibiotic resistance reservoir in the human microflora. Science 2009;325:1128-31.
19. Sommer MOA, Church GM, Dantas G. The human microbiome harbors a diverse reservoir of antibiotic resistance genes. Virulence 2010;1:299-303.

5.2 Swine (piglet/weaning pig/fattening pig/ breeding pig)

5.2.1 Respiratory tract infections

Due to the intensification of pig farming, respiratory tract infections have gained in significance. Respiratory tract infections are usually promoted by unfavourable husbandry conditions such as draught, high ammonia and dust content in the air or temperature variations. Other immunosuppressive factors such as transport, change of stable or dominance fights are also of relevance in connection with respiratory tract infections.

Clinical symptoms of such infections include coughing, sneezing, increased secretion and changed respiratory rates as well as respiratory sounds, in addition to degeneration of the nasal septum and the nasal concha. Where therapeutic relevance was given, the data was evaluated separately for the individual types 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 2013 study, a total of 150 *P. multocida* isolates obtained from swine in the individual types 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 and/ or MALDI-TOF mass spectrometry.

The resistance level was classified as low in all three types of production. With the exception of tetracycline with a resistance rate of 15%, the rates of resistance to the tested antimicrobials were below 5% in all types of production. When comparing the types of production, a significant difference was observed for tetracycline. The respective rate of tetracycline resistance was 17% in isolates from piglets, 8% in those from weaning pigs and 16% in those from fattening pigs. The susceptibility of *P. multocida* isolates from fattening pigs to a total of six of the tested antimicrobials (amoxicillin/clavulanic acid, ceftiofur, enrofloxacin, florfenicol, tilmicosin, tulathromycin) was not limited at all (no figure).

The MIC_{90} values for the tested antimicrobials were virtually identical in all three types of production (Tab. 5.2.1.1.1).

Tab. 5.2.1.1.1: Swine – MIC_{90} values of *P. multocida* for antimicrobials (2013 study) for which no CLSI-approved breakpoints are available

Antimicrobial	MIC_{90} (mg/l)		
	Piglet	Weaning pig	Fattening pig
Cefoperazone	0.06	0.06	0.06
Cefquinome	0.06	0.06	0.06
Colistin	8	8	8
Doxycycline	0.5	0.5	1
Marbofloxacin	0.03	0.03	0.03
Nalidixic acid	2	1	1
Neomycin	16	8	8
Penicillin	0.25	0.25	0.24
Spectinomycin	32	32	32
Tiamulin	32	32	32
Trimethoprim/ Sulphamethoxazole	16	8	16

Compared to the results of the previous study years, no increase but a slight decline in resistance rates was observed.

Conclusion

Most of the tested antimicrobials continue to show good efficacy against *P. multocida*. Compared to the results of the previous study years, an overall moderate decline in resistance rates is observed. The 2013 study did not find resistance rates of more than 5% (except for tetracycline) in any type of production. The repeated detection of an isolate non-susceptible to florfenicol following the 2008 and 2010 studies should be viewed critically. In order to be able to recognise future resistance developments within the types of production at an early point, the data needs to be evaluated using the classification selected here.

➤ J. Wallmann
Reviewer: A.-K. Karaalp

5.2.1.2 *Actinobacillus pleuropneumoniae*

Pleuropneumoniae 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. The disease caused by APP often occurs between the 9th and 16th week of life. APP occurs in two biovars. By now, 15 different serotypes have been detected, of which the serotypes 1, 2, 3, 5, 6, 7 and 9 have been identified in Germany.

Trends in resistance development

In the 2013 study, a total of 102 APP isolates obtained from swine in the individual types of production (piglet, weaning pig, fattening pig) were tested for susceptibility. Eleven antimicrobials were classified on the basis of the CLSI standard. The tested collective was not evaluated separately for the individual types of production, since the number of isolates was not sufficient for this purpose.

Resistance to tetracycline (14%) and sulphamethoxazole (12%) as well as a significant percentage of isolates (22%) showing intermediate resistance to tetracycline were observed. Isolates resistant to ceftiofur were not detected, unlike in the 2011 study year, when they were identified for the first time (Fig. 5.2.1.2.1).

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, cefquinome, enrofloxacin, florfenicol and penicillin G, which suggests good efficacy (Tab. 5.2.1.2.1).

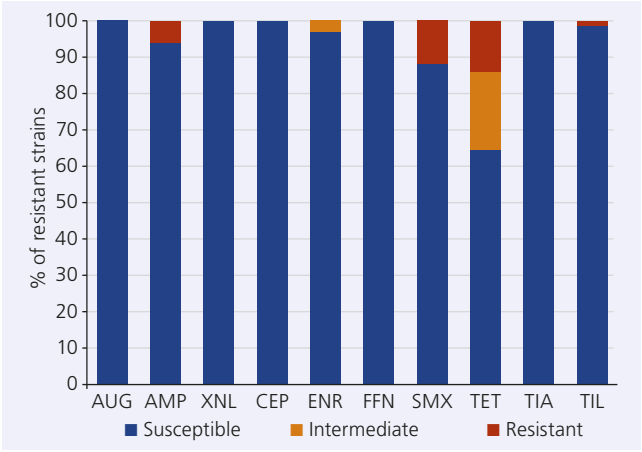


Fig. 5.2.1.2.1: Resistance rates of APP from swine, Germany 2013 (n=102)

Conclusion

The low level of resistance to most antimicrobials has remained nearly unchanged over the years.

➤ J. Wallmann
Reviewer: A.-K. Karaalp

Tab. 5.2.1.2.1: Swine – MIC_{90} values of *A. pleuropneumoniae* for antimicrobials (2008-2013 studies) for which no CLSI-approved breakpoints are available

Antimicrobial	MIC_{90} (mg/l)					
	2008	2009	2010	2011	2012	2013
Cefotaxime	0.015	0.015	0.015	0.25	0.015	0.015
Cefquinome	0.03	0.03	0.03	0.5	0.03	0.03
Doxycycline	1	2	2	8	2	2
Enrofloxacin	0.12	0.12	0.06	0.06	0.06	0.06
Nalidixic acid	4	4	4	4	4	4
Penicillin G	1	1	0.5	4	0.5	1
Spiramycin	64	64	64	64	64	64
Trimethoprim/Sulphamethoxazole	0.12	0.25	0.12	0.12	0.12	0.12

5.2.1.3 *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 2012 GERM-Vet study, a total of 90 *B. bronchiseptica* strains from swine with respiratory tract infections were tested, with high MIC values being measured for most of the tested β-lactam antimicrobials. The results were not evaluated separately for piglets, weaning pigs and fattening pigs, since the susceptibility test results were very similar.

In general, the MIC distribution determined in the 2012 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. 5.2.1.3.1). The rates of florfenicol, gentamicin and tetracycline resistance were below 10%, with 88% of the isolates showing intermediate susceptibility to florfenicol.

Tab. 5.2.1.3.1: Swine – MIC_{90} values of *B. bronchiseptica* for antimicrobials (2008-2012 studies) for which no CLSI-approved breakpoints are available

Antimicrobial	MIC_{90} (mg/l)				
	2008	2009	2010	2011	2012
Cefotaxime	> 32	8	> 32	> 32	> 32
Cefquinome	32	32	32	32	32
Ceftiofur	> 64	> 64	> 64	> 64	> 64
Enrofloxacin	0,5	0,5	0,5	0,5	0,5
Nalidixic acid	8	8	16	16	16
Tetracycline	0,5	1	1	1	2
Tiamulin	> 64	> 64	> 64	> 64	> 64
Tilmicosin	32	32	32	32	32
Trimethoprim/ Sulphamethoxazole	4	4	8	8	2
Tulathromycin	16	8	16	16	n.g.

Figures 5.2.1.3.1 to 5.2.1.3.3 compare the percentages of susceptible, intermediate and resistant strains in three study years (2010-2012). Cephalothin was not tested in the 2012 study.

Conclusion

B. bronchiseptica strains isolated from swine showed good susceptibility to most antimicrobials, in particular to tetracycline and enrofloxacin. Treatment with β-lactam antimicrobials as well as pleuromutilins is not recommended and the high percentage of isolates showing intermediate resistance to florfenicol also leads to the above assessment.

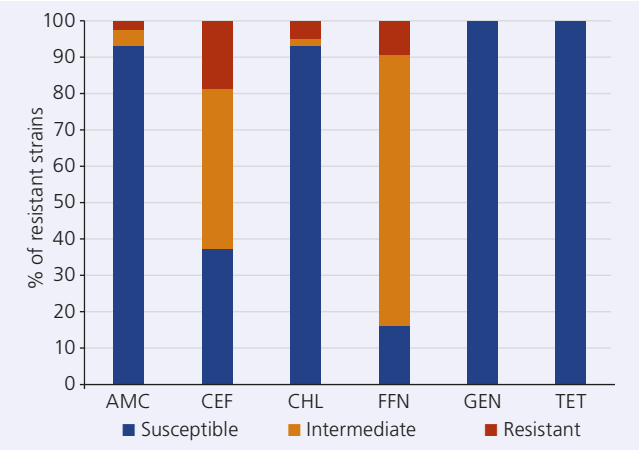


Fig. 5.2.1.3.1: Resistance rates of *B. bronchiseptica* from swine, Germany 2010 (n=43)

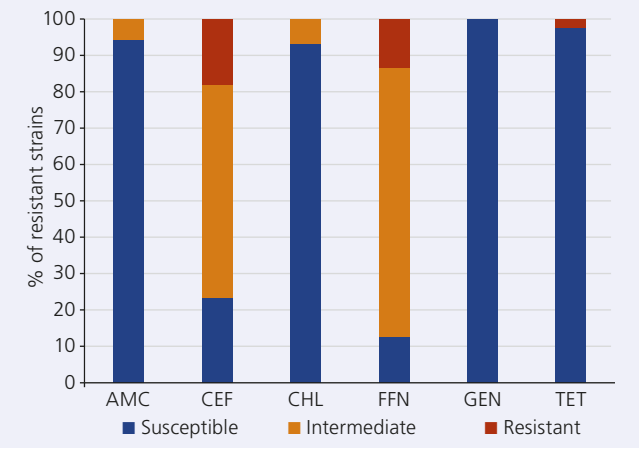


Fig. 5.2.1.3.2: Resistance rates of *B. bronchiseptica* from swine, Germany 2011 (n=89)

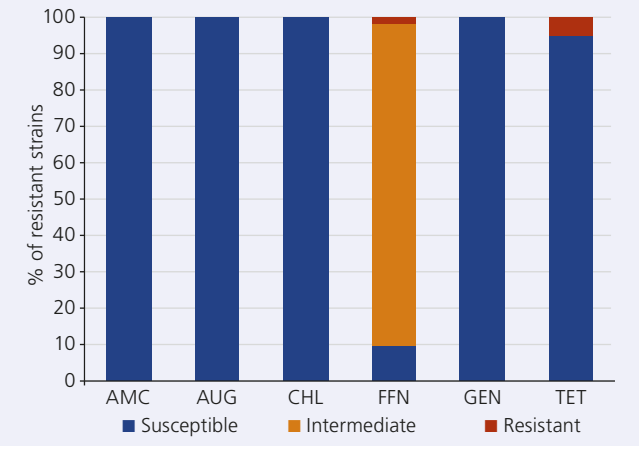


Fig. 5.2.1.3.3: Resistance rates of *B. bronchiseptica* from swine, Germany 2012 (n=90)

➤ J. Wallmann
Reviewer: A.-K. Karaalp

5.2.2 Enteritis

Enteritis caused by infections with *Escherichia coli* or *Salmonella* spp. plays a major role in pig farming, in particular in the 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 2012 GERM-Vet study, a total of 252 *E. coli* isolates from swine with the indication of "gastritis/enteritis" were tested and the data was evaluated separately for the three types of production: piglet (n=150), weaning pig (n=42) and fattening pig (n=60).

Piglet/Weaning pig/Fattening pig

High resistance rates in *E. coli* isolates were observed for tetracycline (69-73%), ampicillin (67-74%), sulphamethoxazole (56-73%) and trimethoprim/sulphamethoxazole (co-trimoxazole) (38-56%). The rates of chloramphenicol resistance (not approved for use in food-producing animals) ranged between 12% and 23% and those of gentamicin between 5% and 12%. Overall, isolates from piglets (Fig. 5.2.2.1.1) exhibited the highest and those from weaning pigs (Fig. 5.2.2.1.2) the lowest resistance rates. Compared to previous studies, another increase in resistance rates is not observed.

Colistin (8 mg/l in piglets and weaning pigs) 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 (2006/2007, 2010 and 2012: 128 mg/l) are remarkable, with the enrofloxacin MIC_{90} values being stable and significantly lower in dependence on the type of production. In 2012, enrofloxacin MIC_{90} values of 8 mg/l were measured in piglets, 0.25 mg/l in weaning pigs and 0.06 mg/l in fattening pigs. Cephalosporins still have a good efficacy, with MIC_{90} values ranging between 0.12 mg/l and 1 mg/l. Compared to the results of previous studies, a slight upward trend yet becomes apparent. The MIC_{90} reference values (mg/l) for piglets for the period 2006-2012 are listed in Tab. 5.2.2.1.1.

Conclusion

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 weaning pigs.

➤ J. Wallmann
Reviewer: A.-K. Karaalp

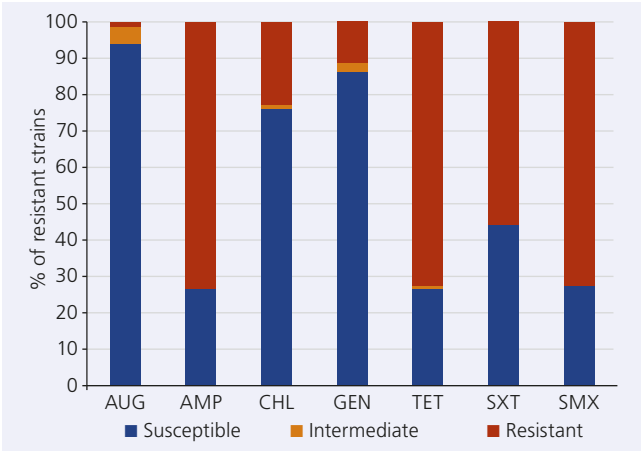


Fig. 5.2.2.1.1: Resistance rates of *E. coli* from piglets with enteritis, Germany 2012 (n=151)

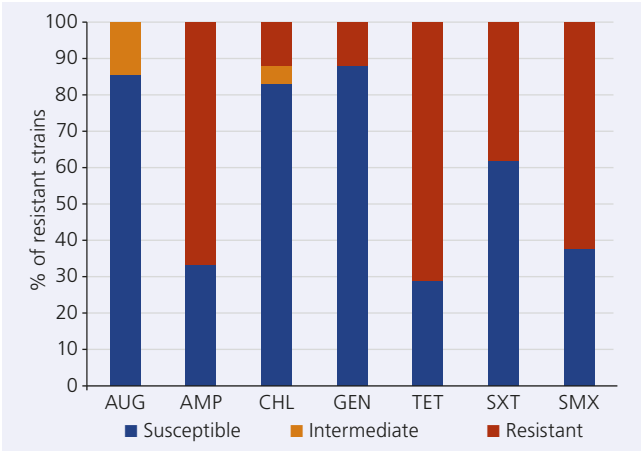


Fig. 5.2.2.1.2: Resistance rates of *E. coli* from weaning pigs with enteritis, Germany 2012 (n=43)

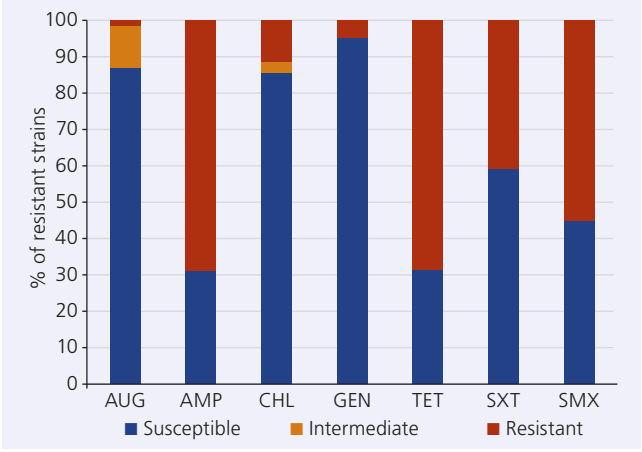


Fig. 5.2.2.1.3: Resistance rates of *E. coli* from fattening pigs with enteritis, Germany 2012 (n=62)

Tab. 5.2.2.1.1: Piglet – MIC_{90} values of *E. coli* for antimicrobials (2006/2007-2012 studies) for which no CLSI-approved breakpoints are available

Antimicrobial	MIC_{90} (mg/l)					
	2006/ 2007	2008	2009	2010	2011	2012
Apramycin	32	8	> 64	> 64	16	16
Cefoperazone	32	16	16	> 32	16	> 64
Cefotaxime	0.12	0.12	0.12	0.12	0.12	0.5
Cefquinome	0.12	0.12	0.12	0.12	0.12	0.5
Ceftiofur	0.5	0.5	0.5	0.5	0.5	0.5
Colistin	4	0.5	4	8	8	8
Doxycycline	32	64	32	32	32	64
Enrofloxacin	0.5	1	1	0.5	0.5	8
Florfenicol	8	16	16	16	8	8
Nalidixic acid	128	> 128	> 128	128	128	64
Penicillin	> 32	> 32	> 32	> 32	> 32	> 64
Trimethoprim	> 128	> 128	> 128	> 128	n.g.	n.g.

5.2.3 Skin infections

Bacteria of the *Staphylococcus* species are commonly found on the skin and on mucous membranes. In certain cases, the otherwise harmless *Staphylococcus aureus* can cause wound infections or chronic skin and mucosal infections. Skin changes are warning signs of other diseases and pathogens and suggest shortcomings in animal husbandry. In the past, antimicrobials were quite effective in the treatment of such diseases.

5.2.3.1 *Staphylococcus aureus*

Trends in resistance development

In the 2012 and 2013 monitoring studies, a total of 28 porcine *Staphylococcus aureus* isolates were submitted for testing.

The highest rates of resistance were observed for penicillins (ampicillin and penicillin 89% each) as well as for tetracyclines (82%) and for erythromycin with a somewhat lower rate (46%). The rates of resistance to the other antimicrobials for which clinical breakpoints were available were below 15%, with the exception of oxacillin, for which a resistance rate of 61% was found. High MIC_{90} values (128 mg/l) were measured for clindamycin, lincomycin, tylosin, tulathromycin, tilmicosin and pirlimycin. Vancomycin-resistant isolates were not detected.

Conclusion

Given the small number of porcine isolates submitted, conclusive statements on the current resistance development cannot be made here.

➤ J. Wallmann
Reviewer: A.-K. Karaalp

5.3 Poultry (chicken, turkey)

5.3.1 *Escherichia coli*

Trends in resistance development

The 2013 study within the GERM-Vet monitoring programme included 342 *Escherichia coli* isolates from diseased poultry, 195 of which were obtained from pullets and laying hens, 109 from turkeys (2 of them from turkey chicks) and 38 from broilers (6 of them from day-old chicks [despite the designation, "day-old chicks" include all animals aged up to 72 hours]).

The primary indication among pullets and laying hens was "cases of death", among turkeys "bloodstream infections" (88 cases, respiratory diseases 21 cases) and among broilers also "bloodstream infections".

Broilers

The (better) technical term for fattening chicken is "broiler", because it is gender-neutral. This is of relevance because only cocks from broiler lines are fattened, whereas all male animals from layer lines are culled for economic reasons.

E. coli isolates from both day-old chicks and broilers with the indication of "bloodstream infections" showed higher rates of resistance only to ampicillin (31%), tetracycline (24%), trimethoprim/sulphamethoxazole (18%) and cephalothin (16%). The rates of resistance to the other tested antimicrobials were below 10%. 5.3% of the strains showed resistance and 23.7% of the isolates intermediate resistance to enrofloxacin (Fig. 5.3.1.1). The results for enrofloxacin suggest that a therapeutic success with enrofloxacin is no longer guaranteed in each case.

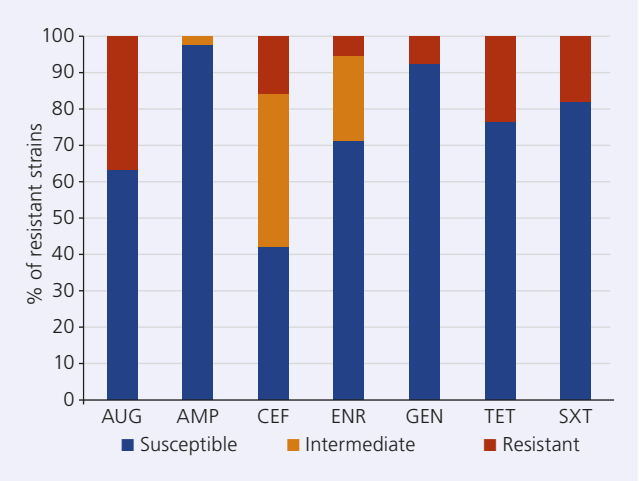


Fig. 5.3.1.1: Resistance rates of *E. coli* from broilers and day-old chicks with bloodstream infections, Germany 2013 (n=38)

A comparison of the study years revealed that the resistance rates of the isolates from broilers and day-old chicks ranged at a similar level over the years. Given the small number of isolates, differentiated evaluations cannot be made.

Laying hens

E. coli isolates from pullets and laying hens with the indication of "bloodstream infections" showed an overall significantly lower resistance level compared to other types of chicken and turkey use. Resistance to ampicillin was detected in 15% and to tetracycline in 14% of the cases. In turkeys, however, the rate of resistance to ampicillin was 33% and to tetracycline 17%. The resistance rates in pullets and laying hens were below those ascertained in 2011 (ampicillin 24%, tetracycline 22%). The rates of resistance to all other antimicrobials were below 10% resistant isolates. 4% of the submitted *E. coli* isolates from pullets and laying hens were non-susceptible to enrofloxacin and 11% of the isolates were classified as "intermediate" (Fig. 5.3.1.2). About 5 years ago, 1% of the *E. coli* isolates from pullets and laying hens showed non-susceptibility and 5% of the isolates "intermediate" susceptibility to enrofloxacin. This result indicates an upward trend in resistance development.

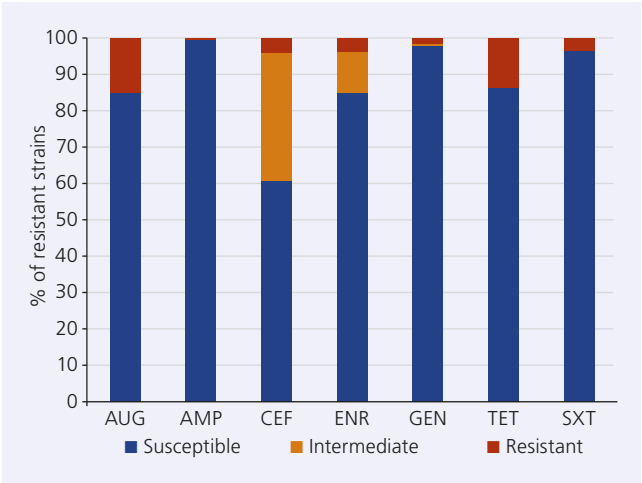


Fig. 5.3.1.2: Resistance rates of *E. coli* from pullets and laying hens with bloodstream infections, Germany 2013 (n=195)

Turkeys

The resistance rate in turkeys with the indication of respiratory tract infections was 43% to ampicillin and 14% to tetracycline. The level of resistance to enrofloxacin was 10%. 5% of the isolates were classified as "intermediate". The resistance rates in turkeys with the indication of bloodstream infections were somewhat lower. 31% of the isolates were classified as clinically resistant to ampicillin, 17% to tetracycline and 5% to enrofloxacin.

Conclusion

The resistance rates recorded for avian isolates were observed to strongly depend on the type of production. In relation to each other, isolates from turkey flocks showed higher resistance rates (Fig. 5.3.1.3) than strains isolated from broiler flocks (Fig. 5.3.1.4); the resistance rates found in laying hens were by far the lowest. Overall, the ascertained MIC frequency distributions demonstrated that the resistance level of avian isolates exceeded the level determined by the BVL for other veterinary pathogens in other animal species.

The ascertained data cannot completely reflect the resistance situation 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 poultry, the poultry industry's private laboratories, which are mainly in charge of laboratory testing of poultry in Germany, would have to intensify their participation. It should again be noted that cephalosporins are not approved for use in poultry in the EU.

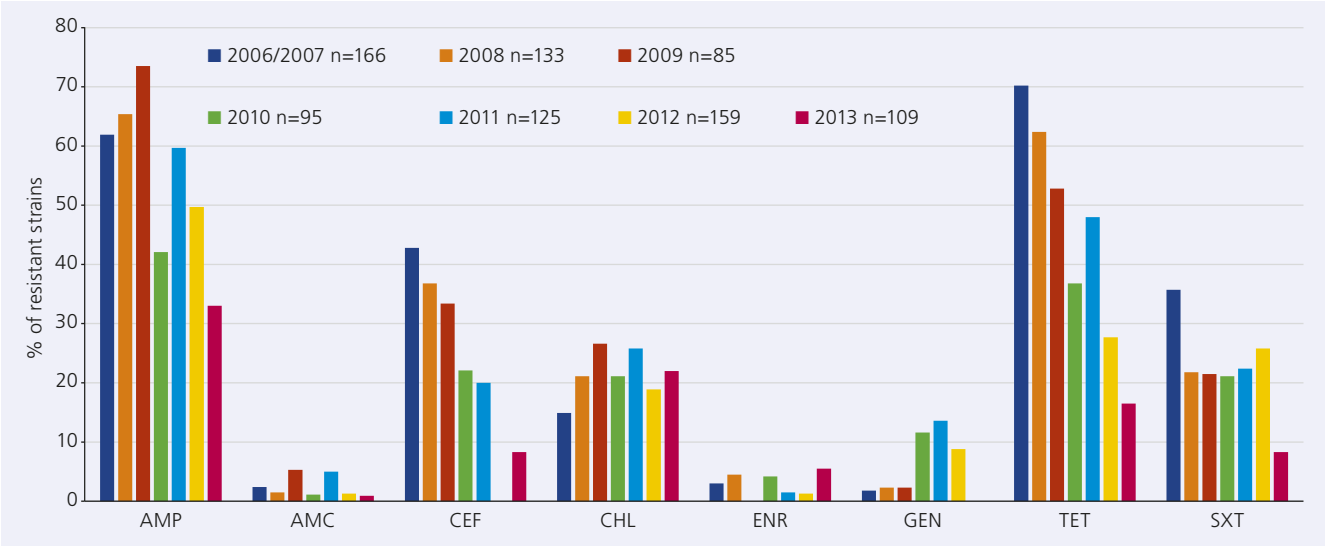


Fig. 5.3.1.3: Resistance rates of *E. coli* from turkeys, various indications (2006/2007-2013)

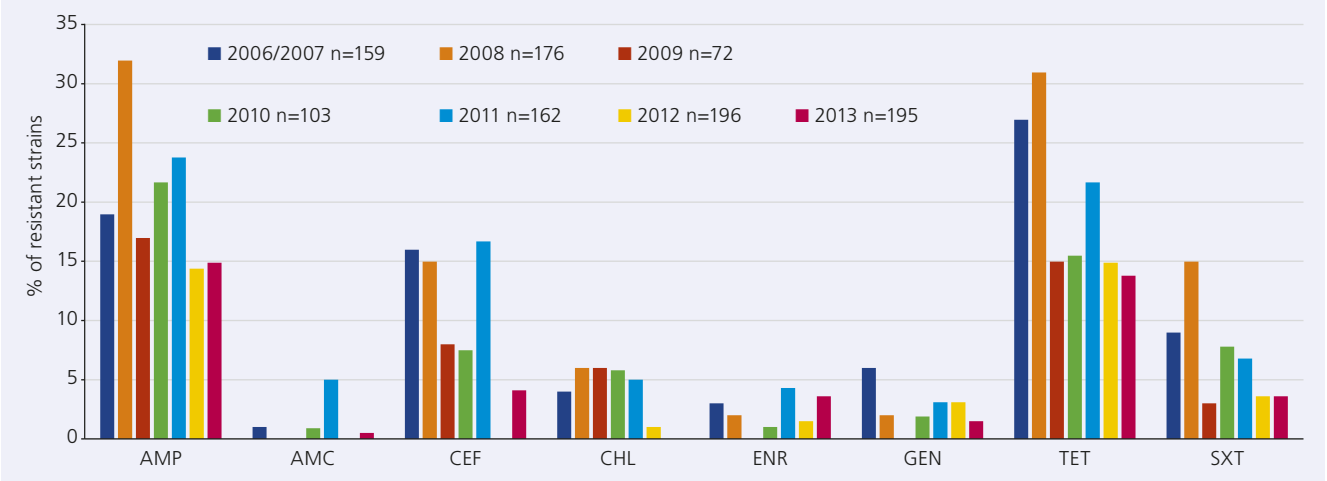


Fig. 5.3.1.4: Resistance rates of *E. coli* from broiler flocks, indication bloodstream infections (2006/2007-2013)

➤ J. Wallmann
Reviewer: R. Hauck

5.3.2 *Staphylococcus aureus*

Trends in resistance development

Poultry

The avian *Staphylococcus aureus* isolates (n=63) tested within the GERM-Vet study were obtained from turkeys (n=43), broilers (n=13) as well as from pullets and laying hens (n=7) 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 (70%), tetracycline (62%) and the macrolide erythromycin (52%) (Fig. 5.3.2.1). Furthermore, 4 oxacillin-resistant isolates (6.3%) were detected, which were confirmed as being mecA-positive.

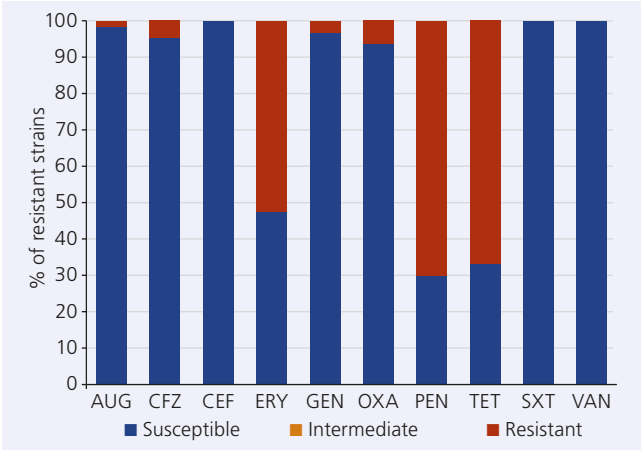


Fig. 5.3.2.1: Resistance rates of *S. aureus* (n=63) from poultry (turkeys, broilers, pullets and laying hens), various indications, Germany 2013

Conclusion

A comparison of the study years revealed that the resistance level of avian *S. aureus* isolates has not really increased compared to previous years (Fig. 5.3.2.2). The rate of erythromycin resistance is somewhat lower than in the previous year, but has increased by approx. 20% over the course of about 10 years (2006/2007 32%, currently 52%). A decrease in resistance rates over the past 10 years has only been observed for oxacillin and trimethoprim/sulphamethoxazole (co-trimoxazole) (oxacillin currently approx. 6%, 2006/2007 19%; trimethoprim/sulphamethoxazole currently 0%, 2006/2007 11%). Given the small number of isolates tested in the 2009, 2010 and 2012 studies, however, conclusive statements on trends are not possible. A significantly larger number of isolates need to be tested to verify the results. However, this is only possible if poultry producers participate in resistance monitoring by submitting bacterial isolates. So far, this has not been done to a sufficient extent.

➤ J. Wallmann
Reviewer: R. Hauck

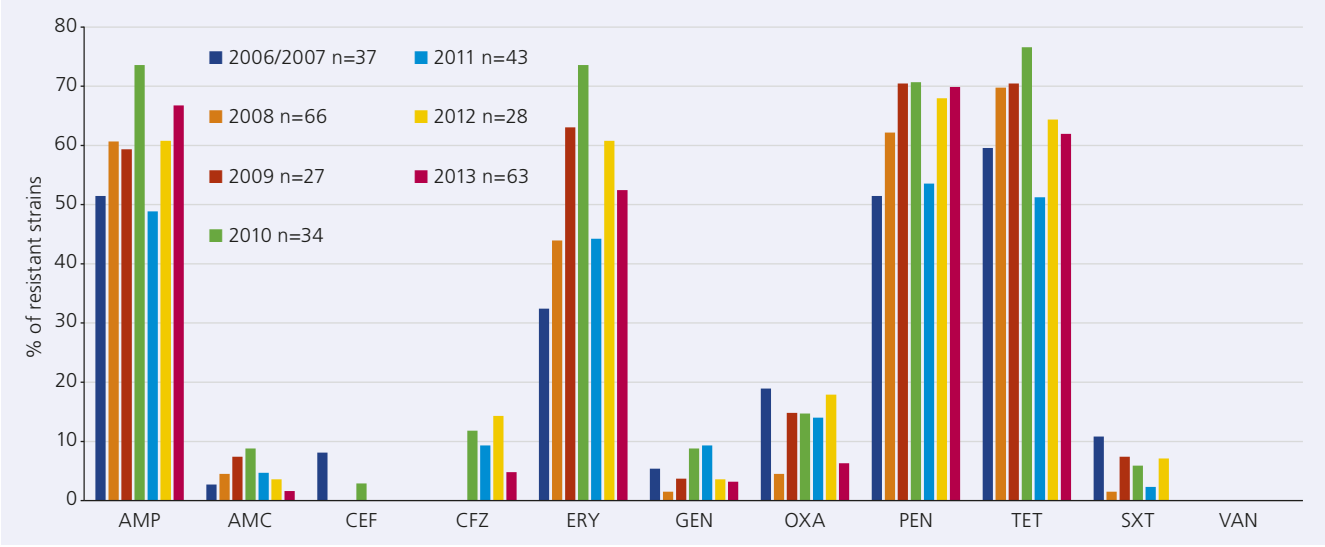


Fig. 5.3.2.2: Resistance rates of *S. aureus* from poultry, various indications (2006/2007-2013)

5.3.3 *Pseudomonas* spp.

Trends in resistance development

Poultry

The avian *Pseudomonas* spp. isolates (n=32) tested within the 2012 and 2013 GERM-Vet studies were obtained mainly from turkeys (n=25), broilers (n=3) as well as pullets and laying hens (n=4) with the indication of "bloodstream infections" and "respiratory tract infections". Given the very small number of isolates, the results were not differentiated by indication, type of production or study year.

High resistance rates (100% each) were observed for the therapeutic combination of amoxicillin/clavulanic acid as well as for cephalothin. Since clinical breakpoints were only available for 4 antimicrobials/therapeutic combinations, the susceptibility to the other tested antimicrobials was determined on the basis of the MIC_{90} values. Given the high MIC_{90} values measured (> 64 mg/l), non-susceptibility has to be expected to ampicillin, penicillin, tiamulin, tilmicosin and tulathromycin.

Conclusion

Given the small number of isolates tested in the 2012 and 2013 studies, reliable statements on the susceptibility of *Pseudomonas* spp. cannot be made. A significantly larger number of isolates need to be tested to verify the results. Irrespective of this, the available data demonstrates that the therapeutic options for poultry affected by *Pseudomonas* spp. are strongly limited.

➤ J. Wallmann
Reviewer: R. Hauck

5.4 *Escherichia coli* strains from Northwestern Lower Saxony obtained as part of the zoonosis monitoring (General Administrative Regulation on Zoonoses in the Food Chain)

Broiler breeders/broilers 2013 broilers/meat turkeys 2014

In 2013, 90 strains from broiler farms and 52 strains from broiler breeder farms were tested. In 2014, 91 strains from broiler farms and 109 strains from meat turkey farms were included in the evaluation. All strains were isolated as part of the studies under the General Administrative Regulation on Zoonoses in the Food Chain[1].

Overall, *Escherichia coli* strains from broiler breeder farms exhibited lower resistance rates than strains isolated from broilers (Fig. 5.4.1). When comparing the 2013 and 2014 study years, only minor changes are observed for broilers. Compared to strains from broilers, meat turkeys showed significantly higher rates of resistance to some antimicrobials (tetracycline, chloramphenicol). An overall higher rate of resistance to fluoroquinolones (ciprofloxacin) was also ascertained in strains from turkeys, with a shift in strains with only slightly elevated minimum inhibitory concentrations (MIC values) in 2013 towards a higher proportion of strains with significantly elevated MIC values in 2014 being observed for these antimicrobials in broilers as well (Fig. 5.4.1).

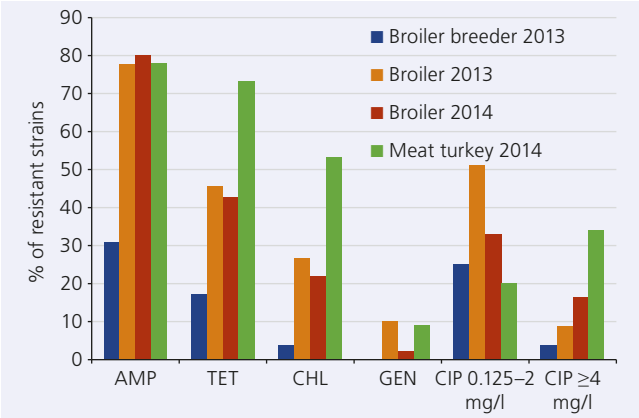


Fig. 5.4.1: Resistance rates of commensal *E. coli* from broiler breeders (n=52) and broilers (n=90) in 2013 as well as from broilers (n=91) and meat turkeys (n=109) in 2014 in Northwestern Lower Saxony

Strains with elevated MIC values for cephalosporins (cefotaxime ≥ 0.5 mg/l) were only observed in few cases in all tested animal groups in both years (highest rate in broilers in 2013 6.7%).

By contrast, strains with elevated trimethoprim values (MIC ≥ 8 mg/l) were observed frequently in 2013, except for breeder stocks (58.9% and 63.7% of the strains from broilers in 2013 and 2014, respectively, and 47.7% of the strains from meat turkeys).

Colistin MIC values of ≥ 2 mg/l were not detected in broiler breeders, but were detected sporadically in broilers and in 25.7% of the strains from meat turkeys.

Layer breeders/Laying hens 2014

In addition to broiler farms, laying hen farms and layer breeder farms were also tested in 2014 as part of the General Administrative Regulation on Zoonoses in the Food Chain. 44 strains were isolated from laying hens and 34 strains from layer breeders. Given the small number of tested strains, the ascertained data should be interpreted carefully. The resistance rates of strains from layer breeders in 2014 were at a similar (comparatively low) range as those from broiler breeders in 2013. Unlike in strains from broilers, the resistance rates of strains from laying hens were lower than those from layer breeders (Fig. 5.4.2). Elevated cefotaxime and colistin MIC values were not observed; only one strain from a layer breeder farm exhibited elevated trimethoprim MIC values.

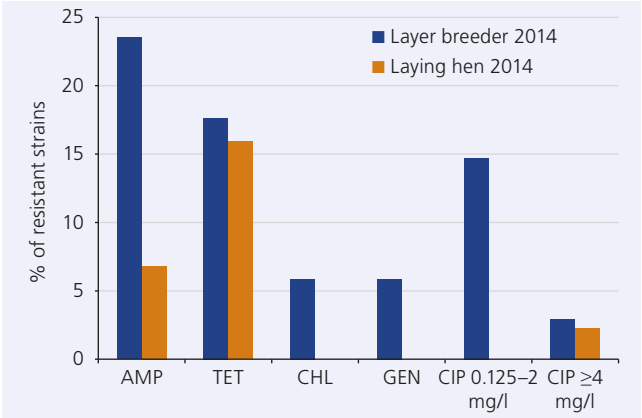


Fig. 5.4.2: Resistance rates of commensal *E. coli* from layer breeders (n=34) and laying hens (n=44) in 2014 in Northwestern Lower Saxony

Beef cattle 2013

As part of the General Administrative Regulation on Zoonoses in the Food Chain, strains from beef cattle aged 1-2 years were also tested in 2013. The farm had to comprise at least 50 animals and various farm sizes had to be tested. Pooled samples from at least 10 animals were tested; 76 strains were included in the evaluation.

In strains from beef cattle, resistance rates of more than 5% were only observed for ampicillin and tetracycline (Fig. 5.4.3).

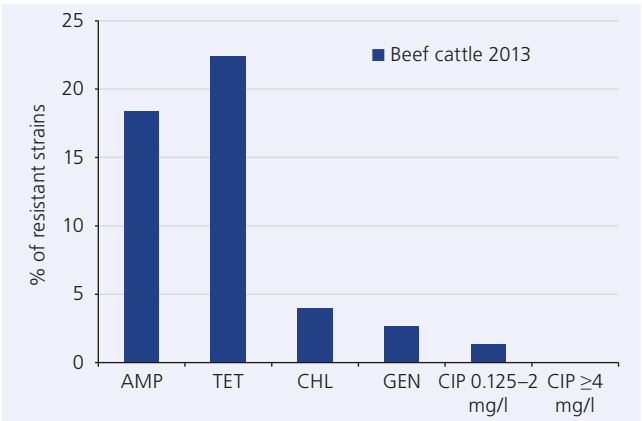


Fig. 5.4.3: Resistance rates of commensal *E. coli* from beef cattle (n=76) in 2013 in Northwestern Lower Saxony

Elevated colistin MIC values (≥ 2 mg/l) were not detected. A single strain showed an elevated cefotaxime MIC value (1 mg/l); 7 strains (9.2%) exhibited high trimethoprim MIC values (≥ 128 mg/l).

➤ C. Werckenthin
Reviewer: J. Wallmann

1. Allgemeine Verwaltungsvorschrift über die Verfassung, 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.verwaltungs-vorschriften-im-internet.de/bsvwvbund_10022012_3289026230009.htm.

Resistance situation of *Campylobacter* spp. in the food chain

During the period 2012-2014, the National Reference Laboratory (NRL) for *Campylobacter* at the Federal Institute for Risk Assessment (BfR), Department of Biological Safety, tested 994 isolates obtained from the chicken food chain (689 C. jejuni, 303 *C. coli*, 2 *C. lari*) and 1,045 isolates obtained from the turkey food chain (509 *C. jejuni*, 534 *C. coli*, 2 *C. lari*) for susceptibility to six antimicrobials. In addition, the veal calf food chain (100 isolates, among them 74 *C. jejuni*, 23 *C. coli*, 3 *C. hyointestinalis*) and the cattle food chain (78 isolates, among them 66 *C. jejuni*, 2 *C. coli*, 9 *C. hyointestinalis*, 1 *C. fetus*) were analysed. The prevalence of *Campylobacter* in beef and veal calf meat has been low for years, whereas *Campylobacter* is often detected in the faeces of cattle and calves (BfR Science, issues of 02/2014 and 02/2015). Since the number of isolates from food produced from these animal species is small, the resistance data for cattle and calves is limited to isolates from faecal samples.

The isolates were obtained as part of the zoonosis monitoring. The pertinent zoonoses sampling plan is prepared by the BfR and stipulates that the competent authorities take samples and that the laboratories of the individual Länder culture isolates from the various samples (animal, food) according to a predefined testing procedure and submit them to the NRL. The NRL measured the minimum inhibitory concentrations using the broth microdilution method and the European plate format EUCAMP (or EUCAMP2 from 2014) (Tab. 1). For years, resistance to chloramphenicol has only been detected in Germany in individual isolates of *Campylobacter* spp.

The interpretation criteria of the European resistance platform EUCAST (www.eucast.org) were used for the definition of resistance (Tab. 1). These have remained constant for the corresponding substances for *Campylobacter* spp. since 2012. The epidemiological breakpoints, which may deviate from the clinically relevant breakpoints, but reveal changes in the bacterial physiology as regards adaptation to antimicrobials at the early stage, were used for the classification. The ascertained resistance data is submitted to the European Food Safety Authority (EFSA) on an annual basis. Since EUCAST breakpoints for the definition of resistance do not yet exist for the species *C. lari, C. fetus* and *C. hyointestinalis*, only *C. jejuni* and *C. coli,* which are considered to be the main causative agents of campylobacteriosis, are addressed below.

Resistance situation

The isolates from the various matrices showed species-specific differences in resistance to antimicrobial agents. Whereas the isolates from cattle were largely susceptible or exhibited only single resistance, nearly 50% of the isolates from the chicken food chain and even more than half of the isolates from veal calves (58%) and the turkey food chain (66%) were resistant to at least two antimicrobial classes (Fig. 1). It was remarkable that the resistance level of *C. coli* isolates was significantly higher than that of *C. jejuni* isolates (Fig. 2, Fig. 3). *C. coli* from the chicken food chain and from calves showed resistance to at least two antimicrobial classes about two times more frequently as *C. jejuni* (factor 1.94 for the chicken food chain and factor 2.08 for veal calves). In the turkey food chain, the percentage of multidrug-resistant *C. coli* was 1.69 times higher than that of *C. jejuni*. Direct comparisons between *C. jejuni* and *C. coli* obtained from the same sample confirmed the observation that the resistance rate of *C. coli* is significantly higher than that of *C. jejuni*, despite the "same history". *C. coli* thus seem to either acquire resistance mechanisms more readily (e.g. as a result of a higher spontaneous mutation rate or enhanced horizontal gene transfer) and/or express them more stably. At present, this difference cannot yet be explained by physiological factors. *C. coli* thus represent a sensitive "biomarker" for the assessment of antimicrobial resistance in the food chain.

In the chicken and poultry food chains, the contents of the animal's caecum and skin samples from the slaughterhouse as well as fresh meat from retailers were tested. Overall, the isolates from poultry showed particularly high rates of resistance to (fluoro-)quinolones and tetracycline (Fig. 3, Fig. 4). The similar prevalences of resistant isolates from the various stages of the food chain suggest that *Campylobacter* with a specific resistance profile are transmitted from animals to the food product via the slaughtering process and do not change significantly along the food chain.

The resistance rate of *C. jejuni* was 38.8-59.2% to tetracycline and 60.5-71% to ciprofloxacin, with isolates of both species from the turkey food chain showing somewhat higher resistance rates. Only one isolate from turkeys and chickens each was resistant to

Tab. 1: Antimicrobial agents used, concentration ranges and breakpoints (ECOFF values)

Antimicrobial class	Antimicrobial agent	Breakpoint (mg/l)	Concentration range	
			Minimum (mg/l)	Maximum (mg/l)
Aminoglycosides	Gentamicin	2	0.125	16
	Streptomycin	4	1/0.25#	16
(Fluoro)quinolones	Nalidixic acid	16	2/1#	64
	Ciprofloxacin	0.5	0.06/0.125#	4/16#
Tetracyclines	Tetracycline	1/2*	0.25/0.5#	16/64#
Macrolides	Erythromycin	4/8*	0.5/1#	32/128#

Broth microdilution test using the plate formats EUCAMP (2012-2013) and EUCAMP2 (2014); breakpoints acc. to EUCAST (www.eucast.org);
*deviating for *C. coli*; # deviating in EUCAMP2

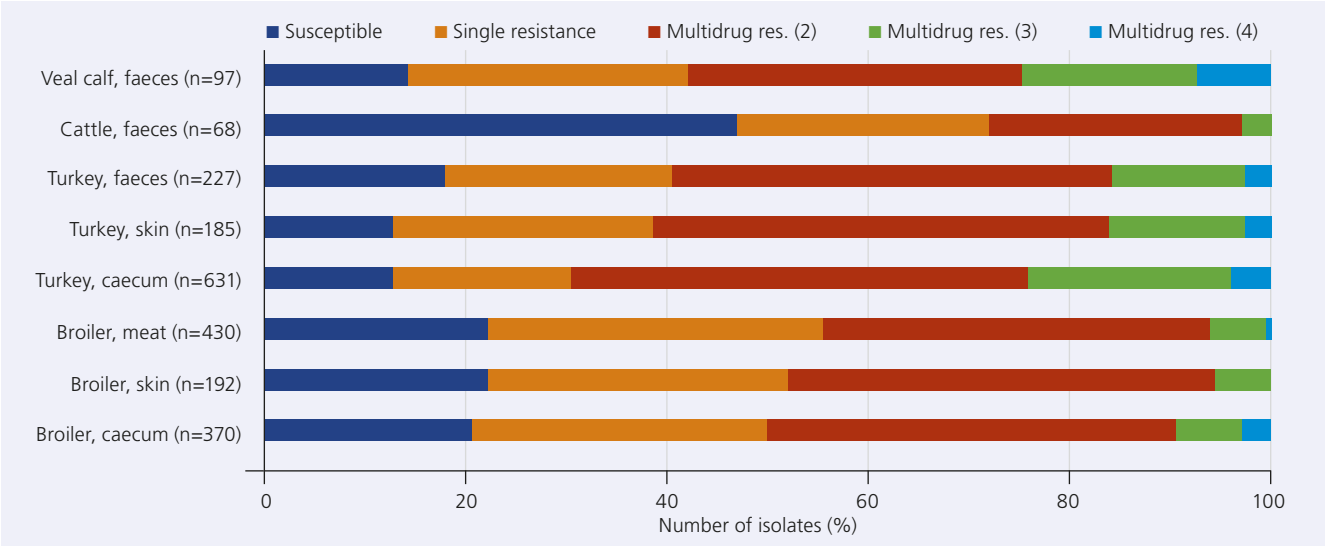


Fig. 1: Percentage of resistant *C. jejuni* and *C. coli* isolates from various matrices tested during the period 2012-2014

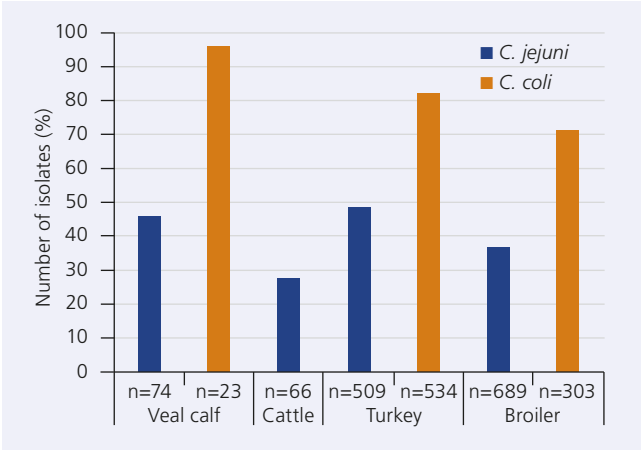


Fig. 2: Percentage of *C. jejuni* and *C. coli* isolates (2012-2014) from various matrices which showed resistance to at least two antimicrobial classes

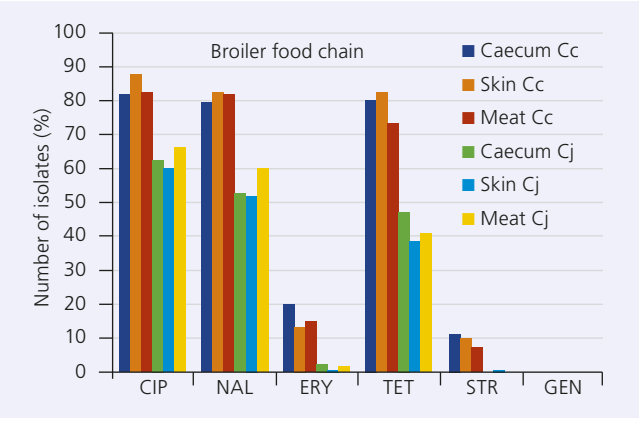


Fig. 3: Percentage of resistant *C. jejuni* (Cj) and *C. coli* (Cc) isolates from the broiler food chain itemised by antimicrobial agents; CIP, ciprofloxacin; NAL, nalidixic acid; ERY, erythromycin; TET, tetracycline; STR, streptomycin; GEN, gentamicin

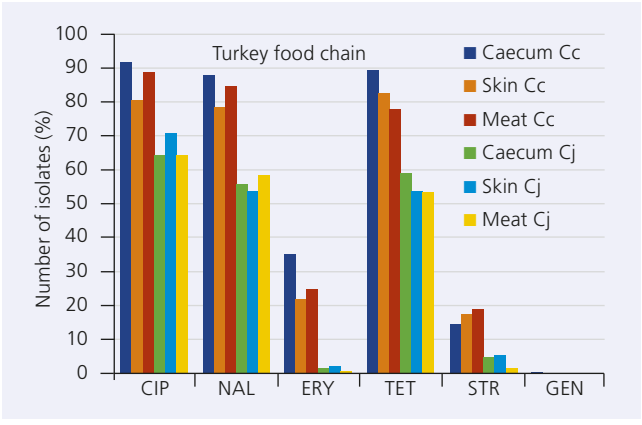


Fig. 4: Percentage of resistant *C. jejuni* (Cj) and *C. coli* (Cc) isolates from the turkey food chain itemised by antimicrobial agents; CIP, ciprofloxacin; NAL, nalidixic acid; ERY, erythromycin; TET, tetracycline; STR, streptomycin; GEN, gentamicin

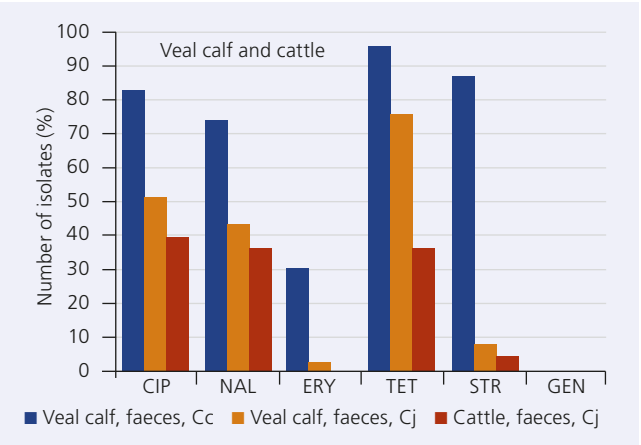


Fig. 5: Percentage of resistant *C. jejuni* (Cj) and *C. coli* (Cc) isolates from the faeces of veal calves and cattle itemised by antimicrobial agents; CIP, ciprofloxacin; NAL, nalidixic acid; ERY, erythromycin; TET, tetracycline; STR, streptomycin; GEN, gentamicin; due to the small number of isolates, C. coli from cattle (n=2) is not shown

gentamicin. The erythromycin resistance rate of *C. coli* was 13.8-20.3% in isolates from the chicken food chain and 21.7-35.1% in isolates from the turkey food chain, whereas a maximum of 2.2-2.9% of the *C. jejuni* isolates from the two poultry food chains exhibited this resistance. The situation was similar with streptomycin resistance, which was present in 7.7-11.7% of the *C. coli* isolates from the chicken food chain and in 14.6-19% of those from the turkey food chain. Resistance to streptomycin in *C. jejuni* isolates from the chicken and turkey food chains was only detected in a maximum of 0.8% and 5.4% of the cases, respectively. It is all the more remarkable that 87% of the *C. coli* isolates from veal calves were resistant to streptomycin (Fig. 5).

In this case, the highest resistance rate in *C. jejuni* was significantly lower, accounting for 8.1%. Significant differences in erythromycin resistance rates in calves were also observed between *C. coli* and *C. jejuni* (30.4% vs. 2.7%). As much as 95.7% of the *C. coli* isolates and 75.7% of the *C. jejuni* isolates from veal calves were resistant to tetracycline, rates which are well above those of isolates from the turkey food chain. The (fluro-) quinolone resistance rates of *C. jejuni* isolates from veal calves were slightly lower (maximum 51.4%), but were at a similarly high level in *C. coli* as in isolates from poultry (82.6%).

The (fluoro-)quinolone and tetracycline resistance rates of *C. jejuni* isolates from cattle were below 40%. None of the isolates were resistant to erythromycin. The streptomycin resistance was low, accounting for 4.6%.

Conclusion

During the period 2012-2014, *C. jejuni* and *C. coli* isolates from the poultry and veal calf food chains exhibited very high rates of resistance to (fluoro-)quinolones and tetracycline. *C. coli,* which caused approx. 10.7% of all human campylobacteriosis cases between 2012 and 2014, could serve as a sensitive "biomarker" for species-specific antimicrobial resistance of *Campylobacter* isolates in food production[1]. The results of the zoonosis monitoring have demonstrated that *C. coli* isolates from the poultry and veal calves food chains showed significance rates of resistance to erythromycin, reaching maximum rates of 30.4% in isolates from calves and 35.1% in those from turkeys. In addition, *C. coli* isolates from veal calves were exceptionally often resistant to streptomycin, showing a resistance rate of 87%. However, it should be noted, that the overall number of *C. coli* isolates from calves was relatively small (n=23).

How can the German data be seen in a European context? In the chicken food chain, which is considered to be the main cause of human campylobacteriosis[2], the (fluoro-)quinolone resistance rates of German *C. jejuni* isolates are in the upper middle range, below those of isolates from Spain and Hungary and significantly higher than in Norway, Finland and Denmark[3]. The erythromycin resistance rate of *C. jejuni* isolates from chickens is relative low throughout Europe (in 2013 below 1% on average). As regards the *C. coli* isolates, Germany is ranking in the mid-range, with significantly lower resistance rates compared to isolates from Spain and Portugal.

The differences in the resistance rates of Campylobacter isolates from various matrices in Germany and the comparison with other EU member states suggest that the species-specific use of antimicrobials may in some cases lead to very high rates of resistance to (fluro-)quinolones, tetracycline and, in the case of *C. coli* from veal calves, additionally to streptomycin, as observed in the food chain. By contrast, the erythromycin resistance rates are low in *C. jejuni* and moderate in *C. coli.* Resistance to (fluro-)quinolones can particularly increase the risk of severe courses of human campylobacteriosis that may require antimicrobial treatment.

➤ P. Vogt, U. Lenski, A. Weiser, L. Ellerbroek, A. Käsbohrer, K. Stingl
Reviewer: T. Alter

1. SurvStat@RKI 2.0; Web-basierte Abfrage der Meldedaten gemäß Infektionsschutzgesetz (IfSG), Abfrage 03.08.2015
2. Scientific Opinion on Campylobacter in broiler meat production: control options and performance objectives and/or targets at different stages of the food chain. EFSA Journal 2011;9(4):2105 [141 pp.].
3. EU Summary Report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2013. EFSA Journal 2015;13(2):4036 [178 pp.].

Acknowledgement
We would like to express our thanks to the laboratories of the individual Länder for the excellent collaboration, in particular for the isolation and submission of Campylobacter isolates to the National Reference Laboratory as part of the zoonoses sampling plan.

6 Antimicrobial 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* spp. of the intermedius group

Representatives of the coagulase-positive *Staphylococcus* spp., *Staphylococcus aureus* and *Staphylococcus* spp. of the intermedius group, play an important role in dogs and cats as both natural inhabitants of the outer skin layer and pathogens. Coagulase-positive staphylococci are commonly isolated in connection with surgical site infections, otitis externa and canine pyoderma. These species are also understood to be responsible for post-surgical complications in the form of surgical site infections in veterinary practice. In this respect, methicillin-resistant S. aureus (MRSA) and S. *pseudintermedius* (MRSP) strains are of particular significance, firstly because the therapeutic options in these cases are strongly limited and secondly due to their zoonotic potential. They also cause infections in humans, with transmissions of the corresponding strains having been observed from humans to dogs/cats and vice versa.

Trends in resistance development

As part of the 2012 GE*RM*-Vet study, 58 *S. aureus* isolates from dogs and cats with the indication of "skin/mucosal infections" and "otitis externa" were tested, among them 35 canine and 23 feline isolates. In the 2013 study year, 11 isolates were tested (6 canine and 5 feline isolates). The two study years were evaluated together.

High or increased resistance rates were found for ampicillin (65%), penicillin (66%), amoxicillin/clavulanic acid (48%), oxacillin (25%) as well as for the fluoroquinolones enrofloxacin, ciprofloxacin and marbofloxacin (28% each). As was the case in previous study years, vancomycin-resistant isolates were not detected (Fig. 6.1.1.1.1).

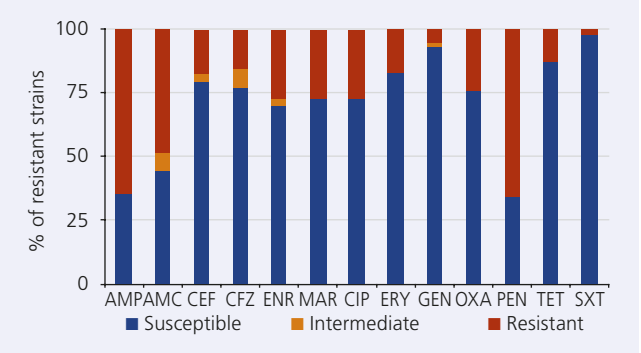


Fig. 6.1.1.1.1: Resistance rates of *S. aureus* from dogs and cats, indication skin infections, Germany 2012/2013 (n=69)

566 and 38 *Staphylococcus* spp. isolates of the intermedius group from dogs with the indication of "skin/mucosal infections" and "otitis externa" were tested in the 2012 and 2013 study years, respectively.

The highest resistance rates were observed for penicillin (67% and 71%), ampicillin (42% and 53%), tetracycline (38% and 45%) as well as for erythromycin and clindamycin (31% and 45%). 12-18% of the isolates were resistant to the tested fluoroquinolones. Resistance rates of up to 21% were found for the other tested antimicrobials. One vancomycin-resistant isolate was identified in the 2012 study.

The MIC_{90} values of methicillin-susceptible *Staphylococcus aureus* for newer cephalosporins are not in a low range, also over the course of the study years (Tab. 6.1.1.1.1).

Tab. 6.1.1.1.1: Small animals – MIC_{90} values of methicillin-susceptible *S. aureus* for antimicrobials for which no CLSI-approved breakpoints are available

Antimicrobial	MIC_{90} (mg/l)		
	2010	2011	2012/2013
Cefoperazone	4	8	4
Cefotaxime	2	4	4
Cefquinome	0.5	1	1
Ceftiofur	1	2	1
No. of isolates (n)	35	14	51

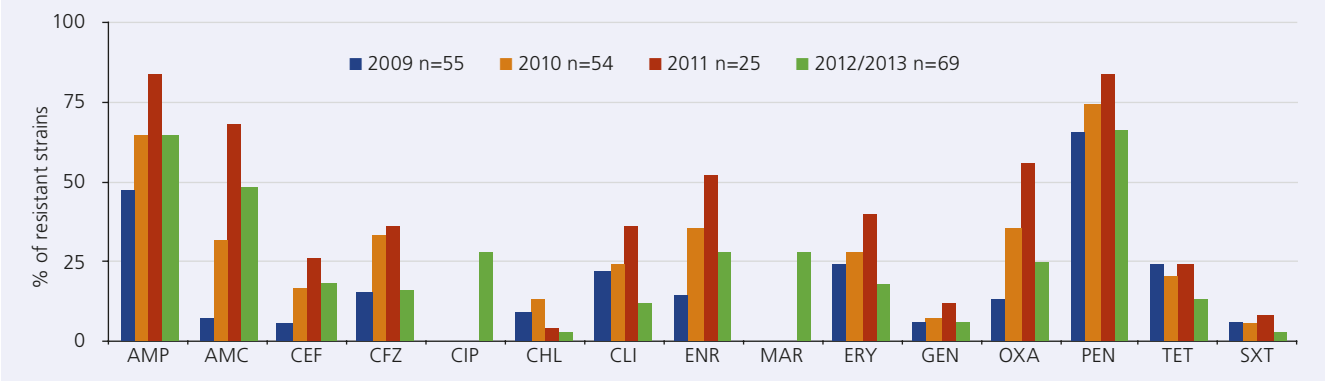


Fig. 6.1.1.1.2: Resistance rates of *S. aureus* from dogs and cats, indication skin infections/otitis externa, Germany 2009-2013

In particular, the majority of oxacillin- and methicillin-resistant *Staphylococcus* spp. of the intermedius group (usually MRSP) were multidrug-resistant, for example to erythromycin, gentamicin, trimethoprim/sulphamethoxazole, enrofloxacin and marbofloxacin (Fig. 6.1.1.1.3). In the 2012 and 2013 study years, 8% and 10% methicillin-resistant *Staphylococcus* spp. of the intermedius group were detected, respectively.

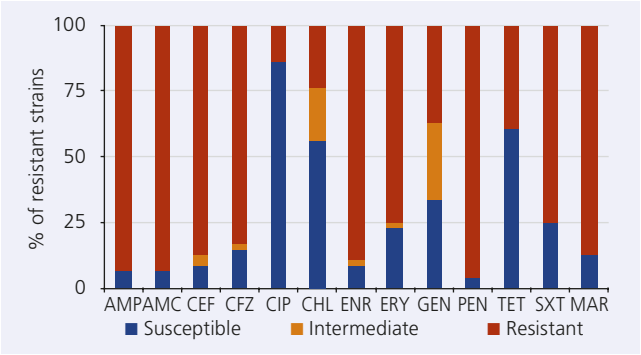


Fig. 6.1.1.1.3: Resistance rates of methicillin-resistant *Staphylococcus* spp. of the intermedius group from dogs, indication skin infections/otitis externa, Germany 2012 (n=48)

The MIC_{90} values of methicillin-susceptible *Staphylococcus* spp. of the intermedius group for newer cephalosporins are in the low range, also over the course of the study years (Tab. 6.1.1.1.2).

Tab. 6.1.1.1.2: Small animals – MIC_{90} values of methicillin-susceptible *Staphylococcus* spp. of the intermedius group for antimicrobials for which no CLSI-approved breakpoints are available

Antimicrobial	MIC_{90} (mg/l)		
	2011	2012	2013
Cefoperazone	0.5	0.5	0.5
Cefotaxime	0.5	0.5	0.5
Cefquinome	0.5	0.25	0.25
Ceftiofur	0.25	0.25	0.25
No. of isolates (n)	46	518	34

Conclusion

Over the course of the study years, the trend has been inconsistent as regards both *S. aureus* and *Staphylococcus* spp. of the intermedius group (Fig. 6.1.1.1.2 and 6.1.1.1.4). However, the overall resistance situation is rather unfavourable. Susceptibility testing prior to starting a therapy should be performed whenever possible.

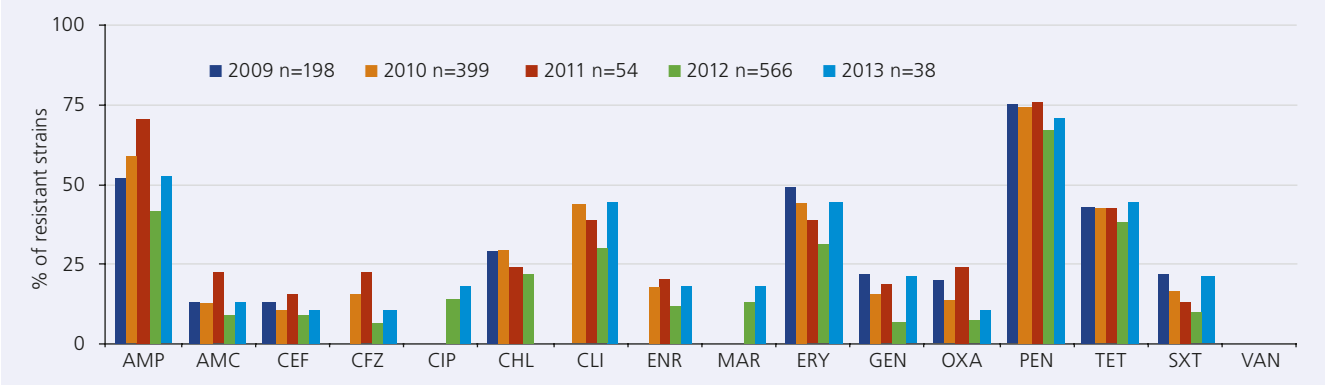


Fig. 6.1.1.1.4: Resistance rates of *Staphylococcus* spp. of the intermedius group from dogs, indication skin infections/otitis externa, Germany 2009-2013

➤ Author: U. Steinacker
Reviewer: A. Lübke-Becker

6.1.1.2 *Bordetella bronchiseptica*

Bordetella bronchiseptica is a gram-negative pathogen of the respiratory tract. Transmission occurs mainly 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

Given the small number of specimens, the results of the 2012 (n=9) and 2013 (n=7) studies were evaluated collectively.

None of the isolates were found to be resistant to amoxicillin/clavulanic acid, cephalothin and gentamicin. One isolate was resistant to chloramphenicol. The high MIC_{90} values for β-lactam antimicrobials suggest that these antimicrobials are expected to have reduced efficacy, as was the case in previous study years.

Fairly high MIC_{90} values (8 mg/l and 16 mg/l) were observed for nalidixic acid, which is considered to be an indicator of an incipient fluoroquinolone resistance. Enrofloxacin is nonetheless expected to be effective (MIC_{90} 0.5-1 mg/l). By contrast, the MIC_{90} value for marbofloxacin, which was tested in the 2012/2013 study years for the first time, is quite high (16 mg/l) (Tab. 6.1.1.2.1).

Tab. 6.1.1.2.1: Small animals – MIC_{90} values of *B. bronchiseptica* for antimicrobials for which no CLSI-approved breakpoints are available

Antimicrobial	MIC_{90} (mg/l)		
	2008/2009	2010/2011	2012/2013
Ampicillin	32	32	32
Cefoperazone	8	8	8
Cefotaxime	≥ 32	≥ 32	≥ 32
Cefquinome	32	32	32
Ceftiofur	≥ 64	≥ 128	≥ 64
Ciprofloxacin	–	–	1
Colistin	0.25	0,5	1
Doxycycline	0.5	1	1
Enrofloxacin	1	0,5	1
Florfenicol	4	4	8
Marbofloxacin	–	–	16
Nalidixic acid	16	8	16
Neomycin	–	–	8
Penicillin	≥ 32	≥ 32	≥ 32
Streptomycin	–	–	128
Tetracycline	1	2	4
Trimethoprim/ Sulphamethoxazole	4	8	4
No. of isolates (n)	26	30	16

Conclusion

B. bronchiseptica isolates showed reduced susceptibility to many β-lactam antimicrobials. Compared to previous studies, the results for most of the tested antimicrobial agents were in the same range. The small number of tested isolates should be considered while evaluating the data.

➤ Author: U. Steinacker
Reviewer: A. Lübke-Becker

6.1.2 Enteritis

6.1.2.1 *Escherichia coli*

Escherichia coli is 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 2013 GE*RM*-Vet study tested 17 *E. coli* isolates from dogs and cats with gastrointestinal tract infections. In each of the two previous study years (2012 and 2011), 18 isolates were tested.

Given the small number of isolates, the data can only provide indications of the resistance situation and does not reflect the situation in the entire population.

Canine-specific CLSI breakpoints were available to interpret the ampicillin and gentamicin MIC values of canine isolates. The feline isolates were classified on the basis of non-species-specific breakpoints. The highest resistance rates in 2013 were observed for ampicillin (altogether 71%: canine 100%, feline 38%), tetracycline and trimethoprim/sulphamethoxazole (24% each) (Fig. 6.1.2.1.1). Two isolates, which were phenotypically classified as suspected of producing ESBL, showed high MIC_{90} values for newer cephalosporins. None of the isolates were resistant to amoxicillin/clavulanic acid.

Conclusion

Over the course of the study years, the trend in the development of resistance rates of canine and feline *E. coli* isolates from gastrointestinal tract infections appears to be inconsistent. Given the small number of isolates, a conclusive assessment is not possible.

➤ Author: U. Steinacker
Reviewer: A. Lübke-Becker

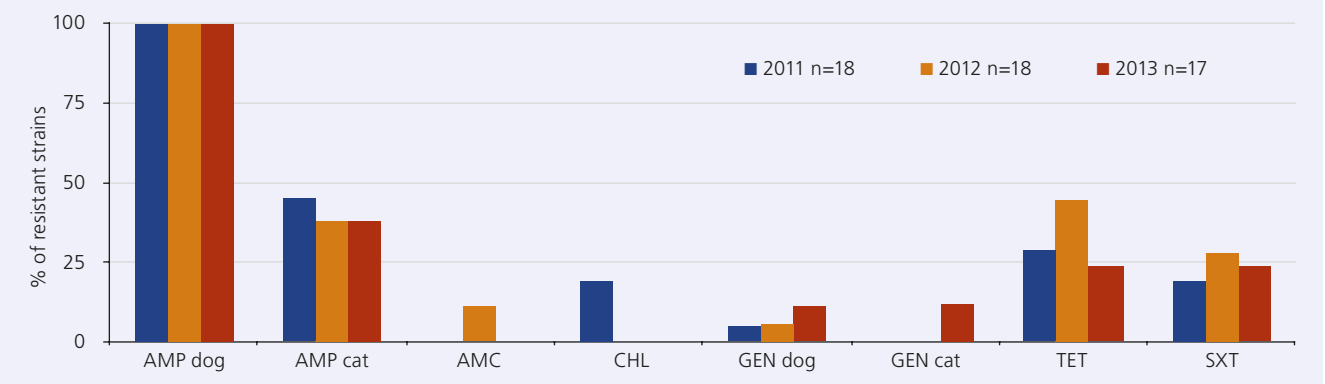


Fig. 6.1.2.1.1: Resistance rates of *E. coli* from dogs and cats, indication gastrointestinal tract infections, Germany 2011-2013

OXA-48 carbapenemase in *Klebsiella* species and *Escherichia coli* in animals

Introduction

Carbapenem resistance in Enterobacteriaceae poses a growing problem in infection medicine and is attributable mainly to the worldwide spread of various carbapenem-hydrolysing β-lactamases. These carbapenemases belong to the Ambler class A (e.g. KPC), B (e.g. VIM, IMP and NDM) and D (e.g. OXA-48 and variants, characterised by weaker but still significant carbapenemase activity).[1,2] At present, ≤ 1% of the isolated Enterobacteriaceae species in Germany produce carbapenemases. According to the latest report of the National Reference Centre (NRZ) for Gram-Negative Hospital Pathogens, however, there has been a continuous upward trend since it started its operations in 2009.[3] The Enterobacteriaceae species in which carbapenemase genes are found most commonly is *Klebsiella* (*K.*) *pneumoniae*. In Germany, OXA-48 is predominant among carbapenemases detected in Enterobacteriaceae, but other types, such as VIM-1, KPC-2, KPC-3 and NDM-1 have also been frequently found in Enterobacteriaceae during the past years. Since the carbapenemase gene is almost always located on plasmids, it is readily transferred both within isolates of a bacterial species and between different species and isolates, which contributes to rapid spread within a population.

To date, little has been known about the occurrence of carbapenemases in *Enterobacteriaceae* in animals. In addition to VIM-1-producing *Escherichia (E.) coli* and *Salmonella enterica* isolates on pig and poultry farms in Germany as well as in samples from the surroundings of the farms (fly, manure, mouse faeces)[4,6], the reports on the detection of carbapenemases in food-producing animals worldwide are limited to bacterial species outside the family of *Enterobacteriaceae,* such as *Acinetobacter* (*A.*) *baumannii,*[7,8] *A. lwoffii,*[9] *Acinetobacter* spp.[10] and *Pseudomonas aeruginosa*.[8] In the U.S., a carbapenemase in companion animals was reported for the first time with the detection of NDM-1-producing *E. coli* isolates in dogs and cats[11], and *Acinetobacter* spp. expressing an OXA-23 carbapenemase were also found in a cat in Portugal and in horses in Belgium.[12,13]

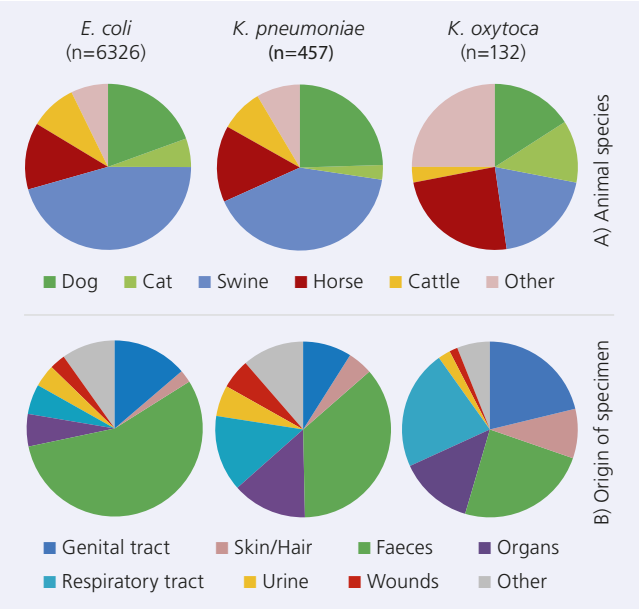


Fig. 1: Origin of *Klebsiella* spp. and *E. coli* isolates tested for reduced susceptibility to carbapenems

Most of the data currently available in veterinary medicine on the occurrence of carbapenemases is based on non-systematic studies. Rather, carbapenemases are often detected by chance, for example as part of surveys investigating the occurrence of ESBL- or AmpC-producing bacteria. A similar incidental finding also formed the basis for a systematic study investigating the occurrence and the molecular characteristics of carbapenemase-producing *K. pneumoniae* and *E. coli* isolates in animals, which is presented below.[14]

Klebsiella spp. and *E. coli* isolates with reduced susceptibility to carbapenems detected in clinical test specimens of animals

During the period from June 2012 to January 2014, the microbiology laboratory of the Institute of Hygiene and Infectious Diseases of Animals, Justus Liebig University of Gießen, successively cultured 457 *K. pneumoniae*, 132 *K. oxytoca* and 6,326 *E. coli* isolates from clinical test specimens submitted during this period by more than 400 German veterinary practices and veterinary hospitals. The origin of the isolates as regards host species and test specimens is shown in Fig. 1.

All isolates were tested for reduced susceptibility to carbapenems in a liquid growth medium [1 ml Mueller-Hinton agar with a meropenem disc (10 µg)].[14] A total of 42 isolates grew in this medium, among them 36 *K. pneumoniae* isolates (7.9% based on the total number of tested isolates of this species), one *K. oxytoca* isolate (0.8%) and five *E. coli* isolates (0.4%). These isolates were tested based on the standards of the Clinical and Laboratory Standards Institute (CLSI) by means of the modified Hodge test and were phenotypically confirmed to produce carbapenemases.[16]

Origin of carbapenemase-producing *Klebsiella* spp. and *E. coli* isolates as regards host species, test specimens and reporting facilities

Carbapenemase-producing *Klebsiella* spp. and *E. coli* isolates were obtained exclusively from specimens of small animals. None of the 2,692 *E. coli* isolates and the 427 *Klebsiella* spp. isolates from swine, cattle, horses and other animals were identified by means of the liquid medium screening test to exhibit reduced susceptibility to carbapenems. The 37 carbapenemase-producing *Klebsiella* spp. isolates were obtained from various test specimens of 29 dogs and two cats, in particular from urine (37.8%), wounds and skin injuries (30.6%), central venous catheters (8.1%) as well as from various other test specimens (23.5%), among them irrigation solutions of tracheal tubes as well as abdominal drainages. In six of the 29 dogs, two *Klebsiella* spp. isolates each were obtained at different test points. The five *E. coli* isolates were obtained from five dogs and were of different

origins as regards the test specimens (wound, abscess, faeces, blood and bronchoalveolar lavage fluid).

Besides veterinary practices, the reporting facilities included 67 veterinary hospitals, among them 46 specialising in "small animals/small companion animals". All carbapenemase-producing isolates were obtained from the departments of internal medicine (n=19) and surgery (n=23) of a single hospital for small animals.

Clinical resistance of carbapenemase-producing *Klebsiella* spp. and *E. coli* isolates

In cases where specific CLSI breakpoints for Enterobacteriaceae isolated from animals were available to interpret the measured MIC values (ampicillin, cefpodoxime, ceftiofur, amikacin, gentamicin, marbofloxacin, tetracycline, nitrofurantoin, chloramphenicol, trimethoprim/sulphamethoxazole, imipenem, enrofloxacin, amoxicillin/clavulanic acid), they were taken as a basis for the susceptibility testing.[15] The susceptibility to the other antimicrobials was determined on the basis of human-specific CLSI breakpoints.[16] Based on these interpretation criteria, all 37 *Klebsiella* spp. isolates turned out to be resistant to ampicillin, amoxicillin/clavulanic acid and to all tested fluoroquinolones (Fig. 2). Resistance rates ranging from 24.3% to 43.2% were ascertained for gentamicin, tobramycin, trimethoprim/sulphamethoxazole, chloramphenicol, nitrofurantoin and tetracycline. 20 isolates (54.1%) were resistant to imipenem, 13 other isolates were characterised by reduced susceptibility, whereas four isolates were susceptible despite carbapenemase production having been detected. The susceptibility of these four isolates was confirmed by means of the epsilometer test (E-test).

The evaluation of the MIC values measured for the carbapenemase-producing *E. coli* showed that all five isolates were resistant to ampicillin, amoxicillin/clavulanic acid, piperacillin and to all tested fluoroquinolones. A resistance rate of 80% each was ascertained for cefalexin, cefpodoxime, trimethoprim/sulphamethoxazole, tetracycline and chloramphenicol. Unlike most *Klebsiella* spp. isolates, all carbapenemase-producing *E. coli* isolates were susceptible to imipenem, showing a MIC value of ≤ 1 mg/l; this was also confirmed by means of the E-test.

ESBL and AmpC β-lactamases in carbapenemase-producing *Klebsiella* spp. and *E. coli* isolates

To confirm the presence of the ESBL phenotype, the susceptibility of isolates with cefpodoxime MIC values of > 4 mg/l to cefotaxime ± clavulanic acid and ceftazidime ± clavulanic acid was tested based on the CLSI standards.[16]

Among the 37 carbapenemase-producing *Klebsiella* spp. isolates, the ESBL confirmatory test confirmed the presence of an ESBL phenotype in 17 *K. pneumoniae* isolates. Nine other isolates as well as the *K. oxytoca* isolate were suspected of producing AmpC β-lactamase. Among *E. coli*, two isolates were phenotypically confirmed to produce ESBL. Three isolates were suspected of producing AmpC β-lactamase in the ESBL confirmatory test.

Genotypic characterisation of β-lactamase and detection of PMQR genes

An OXA-48 β-lactamase was detected by means of PCR and sequence analysis in all *Klebsiella* spp. and E. coli isolates that had been phenotypically confirmed to produce carbapenemases. All *K. pneumoniae* and *E. coli* isolates additionally expressed β-lactamases, which were not found to be located on the OXA-48 plasmid. Furthermore, various plasmid-mediated (fluoro) quinolone resistance (PMQR) genes, which were also not located on the OXA-48 plasmid, were identified in all *K. pneumoniae* isolates and in four of the *E. coli* isolates.

Apart from the OXA-48 carbapenemase, the *K. oxytoca* isolate did not express any of the tested β-lactamases or PMQR genes (Tab. 1).

OXA-48 carbapenemases and genotypic characteristics of the plasmids in animal isolates

The OXA-48 carbapenemase was first detected in 2001 in a clinical *K. pneumoniae* isolate in Turkey. Over many years, detections of OXA-48 β-lactamases have been confirmed exclusively in patients from Turkey or in those with a connection to this country. This is also from where they started to spread to Europe in 2008 via countries of the Middle East as well as North Africa, which are considered to be reservoirs of the OXA-48 carbapenemase.[1,2,17,18] In addition to sporadic cases, a rising number of outbreaks caused by OXA-48-producing *K. pneumoniae* is being observed at hospitals in various countries, such as Turkey, Belgium, France, Greece, Spain and the Netherlands.[2] In Germany, an OXA-48 β-lactamase was first identified in a carbapenem-resistant *K. pneumoniae* isolate from 2004 as part of a retrospective study.[19] Since then, the number of detections has been rising continuously and there are sporadic reports of a nosocomial spread of these pathogens at German hospitals.[3,18]

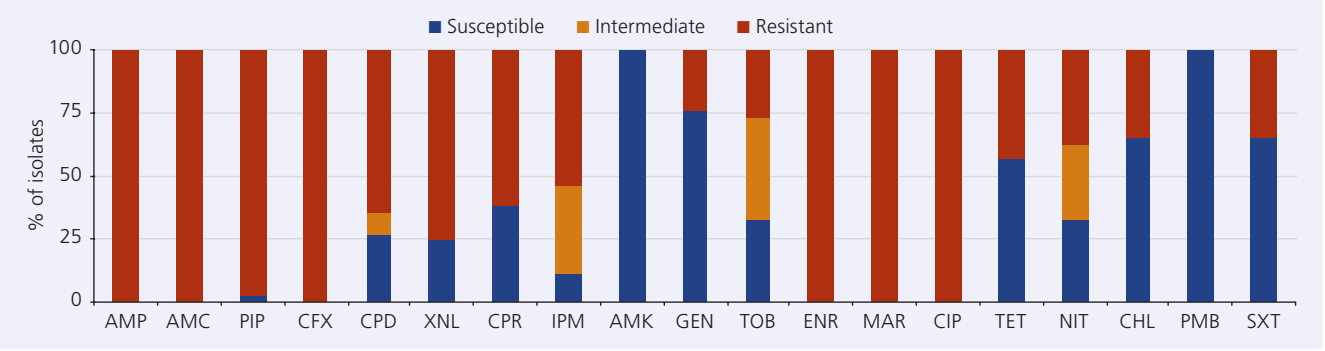


Fig. 2: Resistance rates of carbapenem-producing *Klebsiella* spp. isolates (n=37) from dogs and cats (AMP=ampicillin, AMC=amoxicillin/clavulanic acid, PIP=piperacillin, CFX=cefalexin, CPD=cefpodoxime, XNL=ceftiofur, CPR=cefpirome, IPM=imipenem, AMK=amikacin, GEN=gentamicin, TOB=tobramycin, ENR=enrofloxacin, CIP=ciprofloxacin, MAR=marbofloxacin, TET=tetracycline, NIT=nitrofurantoin, CHL=chloramphenicol, PMB=polymyxin, B, SXT=trimethoprim/sulphamethoxazole)

OXA-48 is one of the few plasmid-encoded variants of OXA carbapenemases. The great genetic similarity among the plasmids carrying the bla_{OXA-48} gene detected worldwide in various Enterobacteriaceae species and in various clonal groups of individual species has led to the assumption that the one single plasmid was responsible for the spread of OXA-48. A plasmid similar to the pOXA-48a reference plasmid (isolated from a patient in Turkey in 2004) has also been detected multiple times in isolates from patients in Germany.[18,20]

In line with the characteristics described for pOXA-48a[20], all OXA-48 plasmids of animal origin detected in the present study had a size of approx. 62 kb, were classified as belonging to the IncL plasmid replicon type and were transferable to an *E. coli* recipient strain by conjugation. The detection of the Tn*1999.2* transposon directly upstream of the bla_{OXA-48} gene also suggests a great similarity between the plasmid found in small animals and the pOXA-48a occurring in humans.

Clonal relationship of OXA-48 carbapenemase-producing *K. pneumoniae* and *E. coli* isolates and indications of nosocomial spread

The high detection rate of *Klebsiella* spp. and *E. coli* isolates with reduced susceptibility to carbapenems at a veterinary hospital suggests the nosocomial spread of these pathogens within this hospital. First, multilocus sequence typing (MLST) was performed to assess the relationship of the carbapenemase-producing isolates. The evaluation was carried out on the basis of the *K. pneumoniae* MLST database of the Pasteur Institute, France (http://bigsdb.web.pasteur.fr/klebsiella/klebsiella.html) and the *E. coli* MLST database of the University of Warwick, Great Britain (http://mlst.warwick.ac.uk/mlst/dbs/Ecoli). Among the *K. pneumoniae* isolates producing OXA-48 carbapenemase, the ST15 sequence type was predominant with 25 isolates, followed by ST11 (n=10) and ST895 (n=1), which differs from the ST11 by merely one allele (Tab. 1). *K. pneumoniae* isolates with the ST15 sequence type play a major role in the spread of ESBL and carbapenemase genes worldwide. In combination with the CTX-M-15 ESBL, this sequence type has been described as an epidemic clone in both human and veterinary medicine.[21-26] A previous study already found evidence of the nosocomial spread of ST15 CTX-M-15 *K. pneumoniae* isolates from small animals at 5 of the 45 veterinary hospitals included in the study. *K. pneumoniae* isolates of the ST15 and ST11 sequence types have been repeatedly identified in human clinical isolates as carriers of various carbapenemases, including OXA-48.[27-30]

Using pulsed-field gel electrophoresis (PFGE), further subgroups were differentiated for the veterinary isolates of identical sequence types, among them three subgroups for ST15 (Kp-I, Kp-III and Kp-IV) and two subgroups for ST11 (Kp-II and Kp-V) with a similarity of > 90% each within the individual clusters (Tab. 1). The ST895 isolate showed a 94.1% similarity to the ST11 PFGE group. Among *E. coli*, three isolates belonged to the ST1196 sequence type and two other isolates to the ST410 and ST1431 sequence types, respectively. The PFGE analysis confirmed this classification, identifying the three ST1196 isolates as clones (Ec-I) and the two other isolates as singletons (Ec-II and Ec-III) (Tab. 1).

The classification of OXA-48-producing *K. pneumoniae* and *E. coli* isolates of identical sequence type and resistance profile into common PFGE groups suggests an epidemiological correlation and nosocomial spread within this veterinary hospital. Even if the chain of events was not revealed completely, spatial and temporal points of contact were identified in many cases, suggesting transmission of the pathogens or transfer of the plasmid either directly between animals or via the environment. Over the entire study period, OXA-48-producing isolates were detected almost equally often in animals treated in the veterinary hospital's department of internal medicine and in those treated in the department of surgery. The length of inpatient stay of the animals ranged from two days to several weeks and many of the altogether 31 affected animals were treated on the same days in the examination and operating rooms used collectively by the two departments as well as in the veterinary hospital's intensive care unit.

As regards isolates from clinical facilities, it must be taken into account that some of the animals may have already undergone antimicrobial treatment at a veterinary practice before admission to the veterinary hospital[16] and a selection of resistant variants

Tab. 1: Chronology of occurrence of OXA-48 carbapenemase-producing *Klebsiella* spp. and *E. coli* isolates as well as genotypic characteristics

Klebsiella/ *E. coli* type	No. of isolates	Origin of specimens (no.)	Period of isolation	Animal species and animal no.	ST	ESBL/AmpC	β-lactamases	PMQR determinants
Kp-I	10	U(4), W(1), H(1), L(2), ZVK(1), shunt(1)	11.06.–11.12.12	Dog 1-6, 8-10	15	CTX-M-15	SHV-28, TEM-1, OXA-1	OqxA, AAC(6')-Ib-cr
Ec-I	3	W(1), blood culture(1), L(1)	11.06.–30.10.12	Dog 1, 2, 4	1196	SHV-12, CMY-2	TEM-1	QnrB2
Ec-II	1	Kot(1)	25.09.12	Dog 5	1431	CTX-M-15	TEM-1, OXA-1	OqxA
Kp-II	3	U(2), cyst prostate (1)	10.10.12–14.01.13	Dog 6, 11	11	DHA-1	SHV-11, OXA-1	QnrB4
Ec-III	1	Abscess abdominal(1)	29.10.12	Dog 10	410	–	SHV-1, TEM-1	–
Kox	1	U(1)	26.11.12	Dog 7	nt	–	–	–
Kp-III	10	W(1), H(2), ZVK(2), fistula(1), abdominal cavity(2), cyst(1), TT(1)	17.05.13–15.01.14	Dog 12-14, 16, 17, 19-21, 23, 29	15	–	SHV-1	OqxA
Kp-IV	3	U(1), W(1), fat necrosis(1)	01.1.–23.12.13	Cat 1, 2, Dog 27	15	CTX-M-15	SHV-1, OXA-1	OqxA/B, AAC(6')-Ib-cr
Kp-V	7	U(5), abdominal cavity(2)	26.06.–14.01.14	Dog 15, 18, 22, 26, 28	11	DHA-1	SHV-11, OXA-1	OqxA/B, QnrB4, AAC(6')-Ib-cr
Kp-VI	2	W(1), drainage leg(1)	11.10.–14.10.13	Dog 24	15	CTX-M-15	SHV-1, OXA-1	OqxA, AAC(6')-Ib-cr
Kp-VII	1	U(1)	05.11.13	Dog 25	895	DHA-1	SHV-11	OqxA/B, QnrB4,

Kp = *K. pneumoniae*, Kox = *K. oxytoca*, Ec = *E. coli*, ST = sequence type, nt = not tested, PMQR = plasmid-mediated (fluoro)quinolone resistance, U = urine, W = wound, S = skin, L = lavage (bronchoalveolar/tracheal), CVC = central venous catheter, N = necrosis, TT = tracheal tube

(such as OXA, ESBL, AmpC) may have already taken place in the animals. In the present case, it was merely determined that many of the animals at the veterinary hospital have undergone antimicrobial treatment prior to the detection of the OXA-48 carbapenemase-producing isolates. The antimicrobial agents used included ampicillin, amoxicillin/clavulanic acid, enrofloxacin and marbofloxacin. Cephalosporins were only used in isolated cases. Carbapenems, which are approved for off-label use in dogs and cats exclusively under certain circumstances, are not used at this hospital at all. Whether the animals have already been colonised with the pathogens on admission to the veterinary hospital is not known, since an admission screening for multidrug-resistant bacteria is not performed at veterinary facilities.

Conclusion

Over a period of 20 months, 42 OXA-48 carbapenemase-producing *Klebsiella* spp. and *E. coli* were detected in test specimens from dogs and cats at a veterinary hospital. The detection of identical sequence types, PFGE types as well as resistance profiles in the repeatedly isolated species *K. pneumoniae* and *E. coli* as well as the great genetic similarity among the OXA-48 plasmids suggest a nosocomial spread of the pathogens and/or the OXA-48 plasmid within this veterinary hospital. The question of the original source of the OXA-48 plasmid in animals and humans remains unanswered and requires further epidemiological studies, including the persons who have direct contact with the animals as well as the surroundings of the veterinary hospital. To what extent there is a causal relationship between the occurrence of the detected isolates and the respective disease of the animals also remains unclear in many cases because of the simultaneous detection of other bacterial species.

The study results nevertheless demonstrate the urgent need for the implementation of systematic studies on the surveillance of carbapenemase-producing bacteria in small animals. Susceptibility testing for carbapenems usually does not take place at veterinary testing facilities, because the therapeutic application of antimicrobial agents of this class is restricted exclusively to off-label use. The phenotypic detection of acquired carbapenemases is often difficult and can only be ensured by using standardised methods within surveillance studies. It must be noted that the prevalence of these enzymes, in particular that of the OXA-48 oxacillinase, may be underestimated due to their weak carbapenemase activity.

➤ C. Ewers, I. Stolle
Reviewer: G. Brenner Michael

1. Nordmann P, Dortet L, Poirel L. Carbapenem resistance in Enterobacteriaceae: here is the storm! Trends Mol Med 2012;18:263-72.
2. Poirel L, Potron A, Nordmann P. OXA-48-like carbapenemases: the phantom menace. J Antimicrob Chemother 2012; 67:1597-606.
3. Robert-Koch-Institut, Bericht des Nationalen Referenzzentrums für gramnegative Krankenhauserreger. Epid Bull 2014;43:421-8.
4. Fischer J, Rodriguez I, Schmoger S, Friese A, et al. *Escherichia coli* producing VIM-1 carbapenemase isolated on a pig farm. J Antimicrob Chemother 2012;67:1793-5.
5. Fischer, J, Rodriguez I, Schmoger S, Friese A, et al. *Salmonella enterica* subsp. *enterica* producing VIM-1 carbapenemase isolated from livestock farms. J Antimicrob Chemother 2013;68:478-80.
6. Guerra B, Fischer J, Helmuth R. An emerging public health problem: acquired carbapenemase-producing microorganisms are present in food-producing animals, their environment, companion animals and wild birds. Vet Microbiol 2014;171:290-7.
7. Zhang WJ, Lu Z, Schwarz S, Zhang RM, et al. Complete sequence of the bla(NDM-1)-carrying plasmid pNDM-AB from *Acinetobacter baumannii* of food animal origin. J Antimicrob Chemother 2013;68:1681-2.
8. Al Bayssari C, Dabboussi F, Hamze M, Rolain, JM. Emergence of carbapenemase-producing *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in livestock animals in Lebanon. J Antimicrob Chemother, 2015;70:950-1.
9. Wang Y, Wu C, Zhang Q, Qi J, et al. Identification of New Delhi metallo-beta-lactamase 1 in *Acinetobacter lwoffii* of food animal origin. PLoS One 2012;7:e37152.
10. Poirel L, Bercot B, Millenamm Y, Bonnin RA, et al. Carbapenemase-producing *Acinetobacter* spp. in Cattle, France. Emerg Infect Dis 2012;18:523-5.
11. Shaheen BW, Nayak R, Boothe DM. Emergence of a New Delhi metallo-beta-lactamase (NDM-1)-encoding gene in clinical *Escherichia coli* isolates recovered from companion animals in the United States. Antimicrob Agents Chemother 2013;57:2902-3.
12. Pomba C, Endimiani A, Rossano A, Saial D, et al. First report of OXA-23-mediated carbapenem resistance in sequence type 2 multidrug-resistant *Acinetobacter baumannii* associated with urinary tract infection in a cat. Antimicrob Agents Chemother 2014;58:1267-8.
13. Smet A, Boyen F, Pasmans F, Butaye P, et al. OXA-23-producing *Acinetobacter* species from horses: a public health hazard? J Antimicrob Chemother 2012;67:3009-10.
14. Stolle I, Prenger-Berninghoff E, Stamm I, Scheufen S, et al. Emergence of OXA-48 carbapenemase-producing *Escherichia coli* and *Klebsiella pneumoniae* in dogs. J Antimicrob Chemother 2013;68:2802-8.
15. Clinical and Laboratory Standards Institute (CLSI), Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacterial Isolated from Animals. CLSI document VET01-A4 and VET01-S2. Wayne, PA: Clinical and Laboratory Standards Institute.
16. Clinical and Laboratory Standards Institute (CLSI), Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fifth Informational Supplement, M100-S25, 2015: Wayne, PA, 2015.
17. Dimou V, Dhanji H, Pike R, Livermore DM, et al. Characterization of Enterobacteriaceae producing OXA-48-like carbapenemases in the UK. J Antimicrob Chemother 2012;67:1660-5.
18. Pfeifer Y, Schlatterer K, Engelmann E, Schiller RA, et al. Emergence of OXA-48-type carbapenemase-producing Enterobacteriaceae in German hospitals. Antimicrob Agents Chemother 2012;56:2125-8.
19. Weinberg J, Heisig A, Heisig P. Molecular characterisation of the first carbapenem resistant isolate Va22038 expressing blaOXA-48 β-lactamase in Germany. 20th Europ Congr of Clin Microbiol Infect Dis, Basel, Switzerland, 2010;16(suppl. 2):S186-7.
20. Poirel L, Bonnin RA, Nordmann P. Genetic features of the widespread plasmid coding for the carbapenemase OXA-48. Antimicrob Agents Chemother 2012;56:559-62.
21. Damjanova I, Toth A, Paszti J, Hajbel-Vekony G, et al. Expansion and countrywide dissemination of ST11, ST15 and ST147 ciprofloxacin-resistant CTX-M-15-type beta-lactamase-producing *Klebsiella pneumoniae* epidemic clones in Hungary in 2005-the new 'MRSAs'? J Antimicrob Chemother 2008;62:978-85.
22. Lee MY, Ko KS, Kang CI,Chung DR, et al. High prevalence of CTX-M-15-producing *Klebsiella pneumoniae* isolates in Asian countries: diverse clones and clonal dissemination. Int J Antimicrob Agents 2011;38:160-3.
23. Breurec S, Guessennd N, Timinouni M, Le TA, et al. *Klebsiella pneumoniae* resistant to third-generation cephalosporins in five African and two Vietnamese major towns: multiclonal population structure with two major international clonal groups, CG15 and CG258. Clin Microbiol Infect 2013;19:349-55.
24. Nielsen JB, Skov MN, Jorgensen RL, Heltberg O, et al. Identification of CTX-M15-, SHV-28-producing *Klebsiella pneumoniae* ST15 as an epidemic clone in the Copenhagen area using a semi-automated Rep-PCR typing assay. Eur J Clin Microbiol Infect Dis 2011;30:773-8.
25. Ewers C, Bethe A, Stamm I, Pfeifer Y, et al. Clonal spread of highly successful ST15-CTX-M-15 *Klebsiella pneumoniae* in companion animals and horses. J Antimicrob Chemother 2014;69:2676-80.
26. Haenni M, Ponsin C, Metayer V, Medaille C, et al. Veterinary hospital-acquired infections in pets with a ciprofloxacin-resistant CTX-M-15-producing *Klebsiella pneumoniae* ST15 clone. J Antimicrob Chemother 2012;67:770-1.
27. Osterblad M, Kirveskari J, Hakanen AJ, Tissari P, et al. Carbapenemase-producing Enterobacteriaceae in Finland: the first years (2008-11). J Antimicrob Chemother 2012;67:2860-4.
28. Lascols C, Peirano G, Hackel M, Laupland KB, et al. Surveillance and molecular epidemiology of *Klebsiella pneumoniae* isolates that produce

carbapenemases: first report of OXA-48-like enzymes in North America. Antimicrob Agents Chemother 2013;57:130-6.

29. Oteo J, Hernandez JM, Espasa M, Fleites A, et al. Emergence of OXA-48-producing *Klebsiella pneumoniae* and the novel carbapenemases OXA-244 and OXA-245 in Spain. J Antimicrob Chemother 2013;68:317-21.
30. Voulgari E, Zarkotou O, Ranellou K, Karageorgopoulos DE, et al. Outbreak of OXA-48 carbapenemase-producing *Klebsiella pneumoniae* in Greece involving an ST11 clone. J Antimicrob Chemother 2013;68:84-8.

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 1995-2013 (in some cases also in 2014). 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. The establishment of the Antimicrobial Resistance Surveillance System (ARS) at the RKI has ensured continuous surveillance.

Studies conducted by the Paul Ehrlich Society for Chemotherapy (PEG)

Resistance study

The Susceptibility Testing and Resistance Working Group of the 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 2013 (to some extent also in 2014). 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 using harmonised and standardised methods. The use of standardised 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 2010 and 2013/14 studies in one reference laboratory.

The results of the study can be seen on the website of the PEG, 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 trends in resistance development, while also contributing to understanding the respective prevalent mechanisms that play a role in the spread of resistant bacteria.

In the last two study years, the study was conducted in four subprojects with the participation of more than 50 laboratories. A total of approx. 9,000 pathogen 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),

in 2010 additionally:

3. Project with *Candida* isolates from blood and other sterile sites (subproject C),
4. Project with gonococci (subproject G),

in 2013 additionally:

5. Project with *Clostridium difficile* isolates from patients with *C. difficile*-associated diarrhoea (subproject Cdiff),
6. Project with blood culture isolates (subproject Bk) – in 2014

The reports on the Cdiff and Bk subprojects are not available yet.

The pathogens 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) as well as by the National Antimicrobial Susceptibility Testing Committee in Germany (NAK) are applied. A change in breakpoints has the consequence that the resistance rates for the years up to and including 2007 stated in this report may deviate from the data provided in the 2008, 2010 and 2012 GERMAP reports.

Subproject H – Project with isolates from hospitalised patients

The studies conducted as part of this subproject focus mainly on typical causative agents of nosocomial infections. These include *Enterobacteriaceae* species, *Pseudomonas aeruginosa* and other non-fermenting bacteria as well as staphylococci and enterococci. In addition, the resistance situation of pneumococci is examined. The 2010 and 2013 study protocols are consistent with those of previous resistance surveys, which is why the results of subproject H can be compared with those of previous years without any limitations. 58-65% of the bacterial strains tested during the period 1995-2013 were obtained from patients on general wards, 22-26% from patients in intensive care units and 10-18% from outpatients. The pathogens were cultured mainly from wound specimens (23-29%), respiratory tract specimens (18-23%), urinary tract specimens (11-26%) and blood cultures (7-15%). During the period under review, the percentage of isolates from urinary tract specimens decreased continuously, whereas the percentage of isolates from other specimens increased. The percentage of male patients increased

from 53% to 59% and the average age (median) of patients from 57 to 65 years.

Subproject N – Project with isolates from ambulatory care patients (outpatients)

In 2010 and 2013, the prevalence of resistance in various bacterial pathogens from outpatient care submitted to the microbiology laboratories was also investigated. These included *E. coli* (only urine isolates), *Haemophilus influenzae*, *Moraxella catarrhalis*, *P. 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 study 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) and presented in the 2008 and 2010 GERMAP reports. In 2014, the study was resumed as part of the Bk subproject within the PEG resistance study. However, the study has not yet been concluded.

Antimicrobial Resistance Surveillance (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 indicated samples/specimens submitted to the participating laboratories and the relevant bacterial pathogens isolated from them. ARS is based on the results of the susceptibility tests performed by the participating laboratories as part of laboratory routine. 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 2014, 18 laboratories participated actively in ARS, transmitting data of approx. 1,307,173 clinical specimens from 386 hospitals as well as of approx. 409,316 clinical specimens from 6,905 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/

European Antimicrobial Resistance Surveillance Network (EARS-Net)

EARS-Net (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: *S. pneumoniae*, *S. aureus*, *Enterococcus faecalis*, *Enterococcus faecium*, *E. coli*, *Klebsiella pneumoniae*, *P. aeruginosa* and *Acinetobacter* spp. (since 2012). In the 2014 reporting year, resistance data from 21 microbiology laboratories, which cover 242 hospitals, was transmitted to EARS-Net for Germany. The vast majority of the data is obtained from the Antimicrobial Resistance Surveillance (ARS), a continuously declining number of laboratories transmitting exclusively resistance data of invasive isolates for EARS-Net to the RKI. The German laboratories apply the guidelines of EUCAST (predominantly) and the Clinical and Laboratory Standards Institute (CLSI) as methods of susceptibility testing. 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.

› http://ecdc.europa.eu/en/healthtopics/antimicrobial-resistance-and-consumption/antimicrobial_resistance/EARS-Net/Pages/EARS-Net.aspx

Surveillance of Antimicrobial Use and Bacterial Resistance in Intensive Care Units (SARI)

SARI 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 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 102 intensive care units in Germany (102 wards take part in SARI light and 63 wards in SARI). The susceptibility tests are performed based on the EUCAST, CLSI or DIN standard. Reference data of altogether 83,420 clinical isolates is available (2010-2014).

› 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 for Helicobacter pylori and has since then been carried forward as one of the essential tasks of the NRC funded by the RKI.

The study is aimed at identifying risk factors for the development of resistance in H. pylori, 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 by means of E-test®.

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

German Tigecycline Evaluation Surveillance Trial (G-TEST)

G-TEST was 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.

National Reference Centres (NRZ) and Consultant Laboratories

In the course of restructuring the sector of infection epidemiology in Germany, National Reference Centres (NRZ) entrusted 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 the RKI based on the statements of external experts and the advice provided by the Scientific Advisory Board for Public Health Microbiology at the RKI (http://www.rki.de/DE/Content/Kommissionen/WissBeirat_PH/WissBeirat_PH_node.html).

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 and Haemophilus influenzae
  › www.meningococcus.de
- National Reference Centre for Mycobacteria
  › www.fz-borstel.de/cms/forschungszentrum/nationales-referenzzentrum-fuer-mykobakterien.html
- National Reference Centre for Salmonellae and Other Bacterial Enterics
  › www.rki.de/DE/Content/Infekt/NRZ/Salmonellen/salmo_node.html

- National Reference Centre for Staphylococci and Enterococci
  › www.rki.de/DE/Content/Infekt/NRZ/Staphylokokken/staphylo_node.html

- National Reference Centre for Streptococci
  › www.streptococcus.de

- National Reference Centre for Invasive Mycoses
  › www.nrz-myk.de (formerly: www.nrz-mykosen.de)

- National Reference Centre for the Surveillance of Nosocomial Infections
  › www.nrz-hygiene.de

Resistance data is also collected by the following Consultant Laboratories:

- Consultant Laboratory for Gonococci
  › www.vivantes.de/gonokokken

- Consultant Laboratory for Legionella
  › www.konsiliarlabor-legionella.de

- Consultant Laboratory for Listeria
  › www.listeriose.eu

- Consultant Laboratory for Anaerobic Bacteria
  › Email: acr@medizin.uni-leipzig.de

- Consultant Laboratory for *Clostridium difficile*
  › www.uniklinikumsaarland.de/de/einrichtungen/kliniken_institute/infektionsmedizin/medizinische_mikrobiologie_und_hygiene/konsiliarlabor_clostridium_difficile/

The list of general tasks of NRZ comprises (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. Meyer
Reviewer: M. Mielke

7.2 Resistance surveillance studies in veterinary medicine

System of susceptibility testing of veterinary pathogens

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 (dogs and cats) 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 2006, comprehensive and evidence-based resistance data has been available in Germany for all important animal species and clinically relevant bacterial pathogens.[1]

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 diagnostic laboratories) in accordance with a detailed sampling plan. Bacterial strains from animals that received antimicrobial treatment in the last four weeks before the sample collection are not taken into account in the tests. 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. 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.

Method of susceptibility testing

The susceptibility of the tested bacterial strains to the various antimicrobials is determined using the broth microdilution method in accordance with the information provided in the VET01-A4 and VET01S performance standards of the Clinical and Laboratory Standards Institute (CLSI, 2013[2], 2015[3]).

As part of the GE*RM*-Vet programme, a total of 22 individual antimicrobials and 2 therapeutic combinations are tested 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. That 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*).

Interpretation of susceptibility test results

The measured MIC values are classified into the categories "susceptible", "intermediate" or "resistant" using clinical breakpoints, as stated in the VET01 S document (CLSI, 2015[2]). At the time of the evaluation, the CLSI document VET01 S 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 antimicrobial 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 above-mentioned CLSI document defines 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 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 in growth by the corresponding antimicrobial agent.[4]

System of susceptibility testing of zoonotic agents

The recording of resistance of zoonotic agents is governed by the Directive 2003/99/EC and the General Administrative Regulation on Zoonoses in the Food Chain based on it.[5] The General Administrative Regulation on Zoonoses in the Food Chain regulates the planning, coordination and performance of studies for zoonosis monitoring. The zoonosis monitoring is taken care of by the Länder as part of the official food and veterinary monitoring.

Test design

The nationwide applicable zoonoses sampling plan is created and discussed in collaboration between the Federal Institute for Risk Assessment and the Länder and approved by the Committee on Zoonoses. The sampling plan contains specifications concerning the species of zoonotic agents to be tested, the stages of food chain to be monitored, the number of specimens to be tested, etc.

Method of susceptibility testing

The susceptibility of the tested bacterial strains to the various antimicrobials is determined using the broth microdilution method in accordance with the information provided in the M31-A3 document of the CLSI (CLSI, 2008[6]) as well as in accordance with ISO 20776-1:2006 using commercially available microtitre plate formats.

Interpretation of susceptibility test results

The collected susceptibility data is interpreted on the basis of the Implementing Decision 2013/652/EU[7], which specifies both the antimicrobial agents to be tested and the interpretation criteria. This interpretation is usually based on epidemiological cut-off values, which are usually not identical to the clinical breakpoints.

➤ H. Kaspar
Reviewer: J. Wallmann

Tab. 7.2.1: Antimicrobial agents/antimicrobial combinations, test ranges and breakpoints (acc. to VET01 S2, CLSI 2013) for antimicrobials tested in the BVL resistance monitoring studies

Antimicrobial 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] ≥ 1[h]
Aminopenicillins	Ampicillin	AMP	0.03–64	≥ 32[d] ≥ 0,5[a, q, r] ≥ 8[b] ≥ 16[d] ≥ 1[e] ≥ 2[s]
β-lactam/β-lactamase inhibitors	Amoxicillin/Clavulanicacid (ratio 2:1)	AMC	0.03/0.015–64/32	≥ 8/4[a] ≥ 32/16[f] ≥ 1/0,5[a, e, r, t]
Isoxazolylpenicillins	Oxacillin +2% NaCl	OXA	0.015–8	≥ 4[g] ≥ 0,5[a, q]
Cephalosporins	Cephalothin	CEF	0.06–128	≥ 32 ≥ 8
	Cefazolin	CFZ	0.03 – 64	≥ 8
	Cefoperazone	CPZ	0.06–32	
	Cefotaxime	CTX	0.015–32	
	Ceftiofur	XNL	0.03–64	≥ 8[h, l, j]
	Cefquinome	CQN	0.015–32	
Tetracyclines	Tetracycline	TET	0.12–256	≥ 8[b, h] ≥ 16[a, d] ≥ 2[i]
	Doxycycline	DOX	0.06–128	
Macrolides	Erythromycin	ERY	0.015–32	≥ 8[a, c] ≥ 1[b]
	Tilmicosin	TIL	0.06–128	≥ 32[k]
	Tulathromycin	TUL	0.03–64	≥ 64[h, v]
	Tylosin	TYL	0.06–128	
Lincosamides	Pirlimycin	PIR	0.03–64	≥ 4[j]
	Clindamycin	CLI	0.03–64	
	Lincomycin	LIN	0.03–64	
Aminoglycosides	Gentamicin	GEN	0.12–256	≥ 16[f] (apart from APP) ≥ 8[l]
Phenicols	Florfenicol	FFN	0.12–256	≥ 8[h, m]
	Chloramphenicol	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] ≥ 1[w] ≥ 4[a, e, t]
	Ciprofloxacin	CIP	0.008–16	
	Marbofloxacin	MAR	0.008–16	
	Nalidixic acid	NAL	0.06–128	
Glycopeptides	Vancomycin	VAN	0.015–32	≥ 32[a, b, c]
Polypeptides	Colistin	COL	0.03–16	
Carbapenems	Imipenem	IPM	0.015 – 32	
Combinations of diaminopyrimidine/ sulphonamide	Trimethoprim/Sulphamethoxazole (1:19)	SXT	0.015/0.29–32/608	≥ 4/76[a, c]

[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.* (pseud)*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); [m] Applies to APP, *P. multocida, B. bronchiseptica* (swine); [n] Applies to APP (swine); [o] Applies to *P. multocida* and *E. coli* (dog and turkey); [p] human-medical breakpoint; [q] Applies *S. pseudintermedius*; [r] Applies to skin and soft tissue infections; [s] Applies to APP, *P. multocida* and *S. suis* (swine); [t] Applies to cat; [u] Applies to *S. aureus*; [v] Applies to APP, *P. multocida* and *P. haemolytica* (swine); [w] Applies to APP, *P. multocida* (swine)

1. http://www.bvl.bund.de/SharedDocs/Downloads/09_Untersuchungen/Archiv_berichte_Resistenzmonitoring/Bericht_Resistenzmonitoring_2012_2013.pdf?__blob=publicationFile&v=5.
2. Clinical and Laboratory Standards Institute, CLSI: Performance standards for antimicrobial disk and dilution susceptibility tests for bacteria isolated from animals; approved standard-fourth edition. CLSI document VET01-A4. Wayne, PA, USA, 2013.
3. Clinical and Laboratory Standards Institute, CLSI Performance standards for antimicrobial disk and dilution susceptibility tests for bacteria isolated from animals; second informational supplement. CLSI document VET01-S2. Wayne, PA, USA, 2015.
4. Schwarz S, Böttner A., Hafez HM, Kehrenberg C, et al. Antimicrobial susceptibility testing of bacteria isolated from animals: methods for *in-vitro* susceptibility testing and their suitability with regard to the generation of the most useful data for therapeutic applications. Berl Münch Tierärztl Wochenschr 2003:116;353–61.
5. Allgemeine Verwaltungsvorschrift über die Verfassung, 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.

6. Clinical and Laboratory Standards Institute (CLSI): Performance standards for antimicrobial disk and dilution susceptibility tests for bacteria isolated from animals; approved standard. 3rd Edition. CLSI document M31-A3. National Committee for Clinical Laboratory Standards, Wayne, PA, USA, 2008.

7. 2013/652/EU: Durchführungsbeschluss der Kommission vom 12. November 2013 zur Überwachung und Meldung von Antibiotikaresistenzen bei zoonotischen und kommensalen Bakterien (Bekanntgegeben unter Aktenzeichen C(2013) 7145) Text von Bedeutung für den EWR, http://eur-lex.europa.eu/legal-content/DE/ALL/?uri=CELEX%3A32013D0652.

Acknowledgement

We would like to express our special thanks to the state veterinary investigation offices, the animal health services of the federal countries, the private laboratories and the university laboratories that have enabled the results of our work in the first place through their constructive collaboration on a voluntary and honorary basis.

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 Hannover, Field Station for Epidemiology	Bakum
Berlin-Brandenburg State Laboratory	Berlin
Institute of Veterinary Diagnostics	Berlin
State Health Office for Chemistry, Hygiene and Veterinary Medicine	Bremen
Saxony State Investigation Bureau, Veterinary Diagnostics, Chemnitz	Chemnitz
Chemical and Veterinary Investigation Office East Westphalia-Lippe	Detmold
LVL GmbH	Ernstek
Bavarian Health and Food Safety Authority (LGL)	Erlangen
Brandenburg State Laboratory, Frankfurt/Oder	Frankfurt/Oder
State Office Laboratory Hesse (LHL)	Gießen
Veterinärlabor Heidemark Mästerkreis GmbH	Haldensleben
LAVES Veterinary Institute Hannover	Hannover
IVD GmbH	Hannover
University of Veterinary Medicine Hannover, 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
IDEXX	Ludwigsburg
Ludwig Maximilian University, Faculty of Veterinary Medicine, Institute of Infection Medicine and Zoonoses	Munich
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
Chemical and Veterinary Investigation Office	Stuttgart/Fellbach

7.3 Antimicrobial consumption data – Methodology and sources

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 or the general population). 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 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 up to 30%. In recent years, the official adaptation of the DDDs to the doses commonly prescribed in the inpatient sector has been sporadic. Besides DDD, the inpatient use density is often also expressed as prescribed daily doses (PDD) or recommended daily doses (RDD).

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). Alternatively or additionally, prescription figures can be used, for example expressed as number of prescriptions per 100 or 1,000 insured and year. The benefit in this case is the independence of dose definitions, which is advantageous when the usually prescribed doses strongly deviate from the DDD definition; this is often important when examining age-dependent prescriptions, for example.

For the hospital sector, we now used RDD per 100 days of care (RDD/100), in addition to stating (WHO-ATC) DDD per 100 days of care (DDD/100) at some points – which permits better usability of international comparative figures in particular. 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 based on 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 data

The most important sources for outpatient consumption include the healthcare research projects of the health insurance funds, most notably the SHI Drug Index project.

SHI Drug Index – 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 are the prescriptions under statutory health insurance within one calendar year that are filled in public pharmacies. Until 2001, a 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 Infectious Diseases 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.

The SHI data also forms the basis for present use density surveys in the outpatient sector conducted by the European health authority ECDC (*European Centre for Disease Prevention and Control*, Stockholm). After the third EU funding phase from 2007 to 2010, a project originally launched in 2001 and initially co-funded using EU research funds (ESAC, *European Surveillance of Antimicrobial Consumption*) was ultimately taken over by the ECDC and continued as ESAC-Net. One of the most important publications of the former ESAC was the compilation and analysis of outpatient consumption data for the period 1997-2002. On Germany's part, Winfried V. Kern and Katja de With, Freiburg, as well as Helmut Schröder, Bonn, were National Representatives of the former ESAC project group. Winfried Kern was additionally a member of the Scientific Advisory Board.

ESAC-Net collects up-to-date national data on antimicrobial use in the EU and analyses it at European level. Overall, the data sources have remained quite heterogeneous; over-the-counter

antimicrobials are not included in the analyses in countries where such antimicrobials are available. However, the quality of data in the outpatient sector can now be regarded as very good.

Rapid Prescription Feedback System of the SHI (GAmSi)

This 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 Sec. 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. A focus is therefore placed on presenting pharmaceutical sales data. 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, now merged with BEK) for several years, is processed by the Bremen Centre for Social Policy Research and contains analyses of the pharmaceutical consumption of its members.

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.

Health Care Atlas

Organised and funded by the Central Research Institute of Ambulatory Health Care (ZI), the Health Care Atlas is the scientific equivalent of the WIdO for panel physicians. It places a focus on regionalised analyses, especially prescribing rate, and to a lesser extent on sales data and market analyses. On its website (www.versorgungsatlas.de), the ZI also provides an option for interactive regionalised analysis. In the field of antimicrobial prescriptions (as well as vaccinations), both longitudinal and cross-sectional analyses, including an overview of some indication-specific prescriptions, have now been presented. Potential quality indicators of antimicrobial prescribing for Germany proposed by ESAC have also been issued for the first time.

Sources in human medicine – Inpatient care

In the past, the availability of non-commercial data on antimicrobial use density at German hospitals was very limited. One of the studies at that time (Janknegt et al.[1]) compared 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 was 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 point 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.

More recent data for Germany was analysed by the University Hospital Freiburg as part of the former MABUSE network ("*Medical Antimicrobial Use Surveillance and Evaluation*"), collected from intensive care units within the SARI project ("*Surveillance of Antimicrobial Use and Bacterial Resistance in Intensive Care Units*") as part of a long-term survey (now carried forward by the Charité) and is now being collected continuously for a great number of acute care hospitals within the ADKA-if-DGI project (until 2015 ADKA-if-RKI project).

In addition to the two current systems ADKA-if-DGI and AVS (RKI-Charité), there are still numerous other systems, some of which featuring purely local solutions (hospital associations), via IMS (commercial use of data) and via laboratory software (some offered in connection with private laboratories). The responsibility for the establishment of reliable reference data with benchmarking options will lie mainly with the scientific/official systems.

Formerly: MABUSE Network & SARI

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 results of the 2004 study have been considered important previous reference figures to this day.

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 and www.adka.de). In 2010, the so-called ADKA-if project entered into collaboration with the Robert Koch Institute (ADKA-if-RKI project) and was renamed ADKA-if-DGI project in 2016.

SARI was an initiative focussing on intensive care units, which was started in Freiburg and was later on carried forward by the Charité as a specialised KISS module including resistance data from the same wards.

Today: ADKA-if-RKI and ADKA-if-DGI Surveillance and AVS (RKI-Charité)

ADKA-if-DGI Surveillance – The surveillance of hospital use densities has been further developed with substantial support by the ADKA (Association of German Hospital Pharmacists) as well as (2010-2015) by the RKI. The plan was to establish continuous national hospital antimicrobial surveillance at about 150-250 representative hospitals as part of the German Antimicrobial Resistance Strategy (DART). The amendment of the Infection Protection Act, which requires the recording and assessment of antimicrobial consumption, has greatly supported the establishment and the willingness to participate. A very large number of departments and wards, differentiated by type and discipline as well as bed capacity, are now participating in the ADKA-if project. For the present report, hospitals were evaluated that supplied verified consumption data for at least 4 consecutive quarters during the 2013/2014 period. The annual use density was calculated on the basis of the most recent quarters.

The benefits of the project, which is now supported by the DGI (German Society for Infectious Diseases) and the German ABS expert network, are the considerable number of participants, the strong participation of stakeholders (ABS teams, infectious disease physicians and pharmacists) and the focus on users.

AVS (RKI-Charité) – Because of the great demand for improved, rapid electronic upload and download functions, the RKI has decided to establish further systems for the surveillance of antimicrobial use density in the hospital sector by introducing AVS (Antimicrobial Consumption Surveillance] by analogy with ARS [Antimicrobial Resistance Surveillance] and simultaneously to KISS [Hospital Infection Surveillance]). The system has been in use since 2016 and currently has > 100 participants from Germany and Austria.

The medium-term goal of the participants is to optimise, coordinate and later on merge the two systems – ADKA-if-DGI and AVS (RKI-Charité). On the one hand, this will make it possible to achieve the goal of secure data hosting and a sufficiently representative number of acute-care hospitals continuously supplying verified data, enabling to better utilise the future possibilities of Big Data analyses in the fields of infection epidemiology, consumption and resistance. On the other hand, the focus on users and the interdisciplinary approach are maintained. A corresponding panel of experts have already been established at the RKI.

➤ W.V. Kern
Reviewer: K. de With, M. Kresken

1. Janknegt R, Wijnands WJ, Caprasse M, Brandenburg W, et al. Antimicrobial drug use in hospitals in The Netherlands, Germany and Belgium. Eur J Clin Microbiol Infect Dis 1993 Nov;12:832-8.

7.4 Basic key figures of inpatient hospital care in Germany with particular reference to nosocomial infections (2013)

In 2013, about 18.8 million inpatients on approx. 141 million days of care were treated at 1,996 hospitals in Germany, in addition to medical treatments as part of outpatient medical care 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.

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.

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 assessment 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 (Sec. 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.

Multidrug-resistant pathogens that spread within 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), and especially Escherichia coli and Klebsiella strains producing extended-spectrum β-lactamases (ESBLs). However, multidrug-resistant strains of Pseudomonas spp. and Acinetobacter spp. as well as the increasing rate of infections with toxin-producing Clostridium difficile also 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 classification of isolates with certain resistance and multidrug resistance mechanisms in accordance with Sec. 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. 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 (Sec. 7 Cl. 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 (see below).

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 (STATIONS-KISS) on ventilator-associated pneumonia and catheter-associated bloodstream infections is not representative of all peripheral wards to the same extent. The number 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 2009-2013).

Surgical site infections

The surgical site infection rate for 2013, calculated on the basis of the OP-KISS (surgical site infection surveillance) 2009-2013 reference data, amounted to 1.5432 surgical site infections/100 surgeries. This surgical site infection rate relates to 15,818,274 surgical procedures/OPS 5 (German Procedure Classification System) performed in Germany in 2013. This yields an estimated (extrapolated) number of 244,108 surgical site infections in Germany in 2013. 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. KISS specifically monitors surgeries

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 (as of: 2013)

		Datenquelle	Berechnungsformel	Beispiel
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 2013** A: 141.339.992
1.1	**Patient days in intensive care units per year (A_1)**		Available directly in the data source	**for 2013** A_1: 7.756.268
1.2	**Patient days on peripheral wards per year (A_2)**	Lines 1 and 1.1 of this table	$A–A_1$	**for 2013** A_2: 133.583.724 (141.339.992-7.756.268)
2	**Incidence of device-associated NI (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 primary bloodstream infections based on the 2011-2013 reference data** **For lower respiratory tract infections based on the 2009-2013 reference data**
2.1	**Incidence of NI in intensive care units (B_1)**			**For urinary tract infections** B_1: 0,000758 (4.525/ 5.973.507) **For lower respiratory tract infections** B_1: 0,002046 (18.417/ 9.003.299) **For primary bloodstream infections** B_1: 0,000728 (4.346/ 5.973.507)
2.2	**Incidence of NI on peripheral wards (B_2)**			**For urinary tract infections** B_2: 0,000553 (1.085/ 1.963.649)
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	**$(A_1 \times B_1) + (A_2 \times B_2)$**	**or urinary tract infections** 79.721 (7.756.268x0, 000758+ 133.583.724x0,000553)

which are associated with a higher risk of infections and/or in which the anticipated postoperative inpatient stay for the type of surgery is not too short to enable surveillance of surgical site infections in the first place. However, the total number of surgical procedures also includes procedures associated with a lower risk.

MRSA prevalence

Extrapolations in respect of MRSA prevalence can be made as follows: hospital patients (treatment cases; number of cases) in Germany in 2013: 18,787,168, patient days in Germany in 2013: 141,339,992.

Given an average MRSA prevalence of 1.00% (MRSA cases /100 patients) at hospitals in 2013 (source: MRSA-KISS; 62,004 MRSA cases in 6,228,023 patients), the extrapolation yields 187,872 hospital patients (cases) with MRSA (mostly colonisations) (readmissions are counted again).

The MRSA incidence density of nosocomial cases in 2013 amounted to 0.17 MRSA/1,000 patient days (source: MRSA-KISS; 7,149 nosocomial MRSA cases on 43,154,496 patient days). When extrapolating this figure, this yields 24,027 MRSA cases in 2013 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 all 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 2013).

Detection of MRSA in blood cultures and cerebrospinal fluid

According to the "Regulation to adapt the reporting obligation pursuant to Sec. 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 2014, 3,841 cases that met the reference definition were reported, which is equivalent to an incidence of 4.8 cases per 100,000 inhabitants. Compared to the previous year (5.3), the incidence dropped significantly for the first time since this reporting obligation was introduced.

The regional, state-specific incidence of MRSA cases in 2014 ranged between 1.8 and 8.4 cases per 100,000 inhabitants, 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 unclear and cannot be explained by the collected surveillance data alone. They may be caused by differences in diagnostic techniques, the treatment of colonised and infected patients, reporting behaviour, hospital hygiene and other measures of infection control.

Except for infants, the incidence increases with age. The age-specific incidence of reported invasive MRSA infections reached its peak in the group of patients aged > 79 years (23.2 cases/100,000 inhabitants); in the age group of 70-79 years, the incidence was 16.6. More than four-fifths (82.8%) of the affected patients are 60 years or older. Within the age group of < 15 years, infants in the first year of life exhibit the highest incidence rate (1.3). With an incidence of 6.3, men were affected much more often than women (3.3), with the reasons for this difference again being unclear.

89% of the patients were hospitalised. Information on the onset of the disease and admission to the hospital is available for 2,282 cases. Only 915 (40%) of these patients acquired the infection during the first two days of the current inpatient stay, which

means that the remaining 60% of the patients were already infected with MRSA on admission. However, it can be assumed that a large number of these patients have previously come into contact with a care facility (e.g. previous inpatient hospital stay, treatment at a dialysis facility).

The data provided as part of the MRSA reporting obligation allows an estimation of the population-specific burden posed by severe invasive MRSA infections, which decreased considerably in 2014 for the first time since the MRSA reporting obligation was introduced. Since the presence of MRSA in blood is considered to be an indicator of the overall burden posed by all MRSA infections, this data suggests that the prevalence of other MRSA infections has also dropped in Germany.

Summary

In summary, based on the above-stated extrapolations for over 18 million inpatient hospital stays, this results for 2013 in

- approx. 80,000 catheter-associated urinary tract infections
- approx. 244,000 surgical site infections.

Based on the above extrapolations, the MRSA prevalence at German hospitals in 2013 amounted to approx. 188,000 cases (colonisation and infection; readmissions are counted again). MRSA infections were detected in approx. 39,000 MRSA cases.

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
- **www.destatis.de**
- **www.nrz-hygiene.de**
  > Surveillance
- **https://ars.rki.de/**

➤ M. Mielke, U. Bölt, J. Walter, J. Hermes, C. Geffers

1. Demografischer Wandel in Deutschland, Heft 2 „Auswirkungen auf Krankenhausbehandlungen und Pflegebedürftige im Bund und in den Ländern“, Hrsg.: Statistische Ämter des Bundes und der Länder, Ausgabe 2008.
2. Gastmeier P, Geffers C: Nosocomial infections in Germany. What are the numbers, based on the estimates for 2006? Dtsch Med Wochenschr 2008;133:1111-5.

Basic key figures of inpatient hospital care in Germany

Tab. 7.4.2: Inpatient care between 1991 and 2013 – 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
2011	2,045	502,029	626	18,344,156	22,870	141,676	7.7	77.3
2012	2,017	501,475	624	18,620,442	23,152	142,024	7.6	77.4
2013	**1,996**	**500,671**	**621**	**18,787,168**	**23,296**	**141,340**	**7.5**	**77.3**
Of which (2013):								
Baden-Württemberg	272	56,726	535	2,090,033	19,717	15,892	7.6	76.8
Bavaria	366	75,675	602	2,883,438	22,954	21,218	7.4	76.8
Berlin	81	20,070	591	794,009	23,363	6,022	7.6	82.2
Brandenburg	55	15,191	620	556,606	22,725	4,386	7.9	79.1
Bremen	14	5,111	779	205,721	31,356	1,463	7.1	78.4
Hamburg	52	12,163	699	474,802	27,283	3,715	7.8	83.7
Hesse	172	36,158	600	1,331,355	22,075	10,164	7.6	77.0
Mecklenburg-Western Pom.	39	10,385	650	404,226	25,289	2,887	7.1	76.2
Lower Saxony	197	42,302	543	1,655,203	21,262	12,263	7.4	79.4
North Rhine-Westphalia	370	120,247	685	4,420,386	25,169	33,475	7.6	76.3
Rhineland-Palatinate	91	25,360	635	921,358	23,078	6,779	7.4	73.2
Saarland	21	6,405	645	274,842	27,692	2,060	7.5	88.1
Saxony	79	26,340	651	1,003,215	24,781	7,550	7.5	78.5
Saxony-Anhalt	48	16,332	725	606,332	26,924	4,443	7.3	74.5
Schleswig-Holstein	95	15,969	568	588,147	20,921	4,500	7.7	77.2
Thuringia	44	16,237	750	577,497	26,666	4,523	7.8	76.3
Change compared to the previous year (in %):								
Germany	**-1.0**	**-0.2**	**-0.4**	**0.9**	**0.6**	**-0.5**	**-1.4**	**0.0**
Baden-Württemberg	-1.4	0.1	-0.5	0.8	0.2	-0.2	-1.0	0.0
Bavaria	-0.8	-0.4	-1.0	1.0	0.3	0.0	-1.0	0.6
Berlin	–	-0.3	-1.8	1.4	-0.1	-0.2	-1.6	0.4
Brandenburg	1.9	-0.6	-0.5	1.5	1.6	-0.7	-2.1	0.2
Bremen	–	-0.6	-1.1	1.0	0.5	-0.8	-1.8	0.1
Hamburg	2.0	0.3	-0.6	0.8	0.0	-0.7	-1.5	-0.7
Hesse	–	-0.2	-0.6	1.0	0.5	-0.2	-1.1	0.3
Mecklenburg-Western Pom.	2.6	–	0.3	-1.0	-0.7	-2.4	-1.4	-2.1
Lower Saxony	-0.5	0.5	0.4	1.0	1.0	-0.9	-1.9	-1.1
North Rhine-Westphalia	-3.9	-0.6	-0.7	0.9	0.8	-0.6	-1.5	0.3
Rhineland-Palatinate	–	-0.1	-0.1	1.4	1.4	-0.3	-1.7	0.0
Saarland	–	-0.9	-0.6	2.2	2.6	0.1	-2.1	1.3
Saxony	1.3	0.6	0.6	0.4	0.5	-0.9	-1.3	-1.2
Saxony-Anhalt	-2.0	0.2	0.9	0.6	1.3	-1.1	-1.7	-1.1
Schleswig-Holstein	–	–	-0.2	0.1	-0.2	-0.7	-0.8	-0.4
Thuringia	-2.2	0.1	0.5	0.7	1.1	-0.1	-0.8	0.1

[1] Number of cases and billing/occupancy days including hour cases, [2] From 2011, calculated for the general population on the basis of preliminary results of the 2011 census, census data as of 10/04/2014. Until 2010, calculated for the general population on the basis of previous censuses.

Source: Basic Data of Hospitals, © Federal Statistical Office (Destatis), Wiesbaden, 2015

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 departments[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							
Of which:							
Total number of general departments							
Ophthalmology	**311**	**4,666**	**–**	**63.5**	**–**	**1,082,004**	**583**
Surgery	**1,181**	**103,847**	**6.665**	**72.6**	**78.5**	**27,533,599**	**1,908,554**
Of which: Vascular surgery	258	7,884	475	75.7	76.7	2,177,590	133,008
Thoracic surgery	65	2,296	279	73.4	81.9	615,052	83,445
Trauma surgery	420	24,092	1.054	80.3	75.1	7,058,153	288,797
Visceral surgery	179	9,035	801	71.2	85.4	2,346,783	249,643
Gynaecology and obstetrics	**863**	**32,226**	**280**	**58.5**	**57.9**	**6,877,274**	**59,152**
Of which: Gynaecology	497	10,848	130	51.1	59.8	2,021,704	28,393
Obstetrics	411	8,175	12	65.0	123.2	1,940,962	5,396
Otorhinolaryngology	**690**	**10,456**	**153**	**61.4**	**76.4**	**2,344,235**	**42,644**
Skin and venereal diseases	**116**	**4,711**	**3**	**78.3**	**93.7**	**1,346,442**	**1,026**
Cardiac surgery	**74**	**4,827**	**1.344**	**83.2**	**85.3**	**1,465,281**	**418,612**
Of which: Thoracic surgery	7	324	106	70.8	74.6	83,674	28,844
Internal medicine	**1,218**	**152,692**	**9.764**	**80.1**	**83.6**	**44,632,459**	**2,980,258**
Of which: Angiology	34	745	31	76.7	80.8	208,467	9,142
Endocrinology	29	882	10	78.1	104.3	251,564	3,806
Gastroenterology	253	14,454	494	80.7	80.6	4,260,093	145,301
Haematology andinternal oncology	163	7,909	317	79.9	80.2	2,307,906	92,743
Cardiology	308	23,023	2.577	86.1	88.6	7,236,653	833,832
Nephrology	111	3,942	265	83.6	90.7	1,202,915	87,721
Pneumology	110	6,992	576	80.7	84.5	2,058,464	177,747
Rheumatology	61	2,274	6	72.3	47.7	599,849	1,045
Geriatric medicine	**277**	**14,182**	**111**	**92.3**	**79.5**	**4,779,092**	**32,215**
Paediatric surgery	**82**	**1,842**	**131**	**59.7**	**52.8**	**401,646**	**25,237**
Paediatric medicine	**360**	**18,979**	**2.668**	**65.4**	**72.8**	**4,527,475**	**709,077**
Of which: Paediatric cardiology	30	610	153	64.6	77.4	143,760	43,207
Neonatology	148	885		76.4	79.4	693,672	256,403
Oral and maxillofacial surgery	**183**	**2,161**	**64**	**64.6**	**68.4**	**509,586**	**15,969**
Neurosurgery	**186**	**7,106**	**984**	**77.4**	**85.3**	**2,007,189**	**306,449**
Neurology	**427**	**23,922**	**2.074**	**85.5**	**82.7**	**7,466,000**	**625,843**
Nuclear medicine	**110**	**877**	**2**	**49.6**	**74.9**	**158,680**	**547**
Orthopaedics	**421**	**24,197**	**538**	**68.8**	**63.4**	**6,077,680**	**124,569**
Of which: Rheumatology	15	545	11	61.6	77.0	122,589	3,092
Plastic surgery	**134**	**1,954**	**78**	**66.5**	**83.7**	**474,478**	**23,829**
Radiotherapy	**162**	**2,997**	**4**	**68.0**	**147.8**	**743,952**	**2,158**
Urology	**522**	**14,682**	**407**	**71.6**	**75.2**	**3,836,702**	**111,724**
Other specialist departments/general beds	**217**	**4,294**	**1.288**	**75.5**	**77.1**	**1,183,525**	**362,385**
Total number of psychiatric departments							
Of which:							
Paediatric/Adolescent psychiatry and psychotherapy	**142**	**5,941**	**–**	**92.8**	**–**	**2,011,564**	**37**
Psychiatry and psychotherapy	**405**	**54,433**	**21**	**93.9**	**70.3**	**18,656,644**	**5,389**
Of which: Addiction	97	-4,524	–	86.3	–	1,425,653	9
Psychotherapeutic medicine	**220**	**9,679**	**–**	**91.3**	**–**	**3,224,485**	**11**

[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, 2015

Tab. 7.4.4: Types of treatment at hospitals 2002-2013

Year	Treatment cases[1]				Outpatient surgeries
	Inpatient	Semi-inpatient	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
2011	18,344,156	686,364	3,820,969	958,163	1,865,319
2012	18,620,442	734,263	4,092,333	988,307	1,867,934
2013	18,787,168	724,685	4,336,205	993,593	1,897,483

[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, 2015

Tab. 7.4.5: Selected key figures of hospitals differentiated by bed capacity and type of funding body, 2013

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	1,996	500,671	621
Hospital with 0 beds[1]	60	–	–
Hospital with 1 to 49 beds	377	7,762	10
Hospital with 50 to 99 beds	256	18,670	23
Hospital with 100 to 149 beds	250	30,598	38
Hospital with 150 to 199 beds	182	31,466	39
Hospital with 200 to 299 beds	273	66,924	83
Hospital with 300 to 399 beds	200	68,504	85
Hospital with 400 to 499 beds	137	61,407	76
Hospital with 500 to 599 beds	92	49,958	62
Hospital with 600 to 799 beds	75	51,287	64
Hospital with 800 and more beds	94	114,095	141
Public hospitals	**596**	**236,179**	**298**
Under private law	353	133,657	170
Under public law	243	102,522	128
Legally dependent	106	33,718	42
Legally independent	137	68,804	86
Non-profit hospitals	**706**	**167,480**	**211**
Private hospitals	**694**	**78,378**	**112**

[1] Day or night hospitals exclusively offering semi-inpatient care

Source: Basic Data of Hospitals, Federal Statistical Office (Destatis), Wiesbaden, 2015

Tab. 7.4.6: General hospitals by bed capacity, 2013

Allgemeine Krankenhäuser	In total 1,668	beds 456,784
> 100 beds	516	20,985
100 to < 200 beds	365	52,853
200 to < 500 beds	534	172,803
500 to < 800 beds	160	97,167
≥ 800 beds	93	112,976

Source: Basic Data of Hospitals, Federal Statistical Office (Destatis), Wiesbaden, 2015

Tab. 7.4.7: Distribution of age and sex of inpatients in Germany (2004-2013)
Key patient figures at a glance

Subject of proof	Reporting year									
	2013	2012	2011	2010	2009	2008[a]	2007[a]	2006[a]	2005[a]	2004[a]
	Number									
Total number of treatment cases[b]	**19,249,313**	**19,082,321**	**18,797,989**	**18,489,998**	**18,231,569**	**17,937,101**	**17,568,576**	**17,142,476**	**17,033,775**	**17,233,624**
- Men	9,120,687	9,029,838	8,885,990	8,705,679	8,569,023	8,392,426	8,188,483	7,995,913	7,923,621	7,968,271
- Women	10,128,610	10,052,395	9,911,945	9,784,155	9,662,423	9,544,617	9,379,967	9,146,276	9,110,081	9,265,287
Treatment cases excl. patients with foreign/unknown place of residence, of unknown sex and age	**19,152,535**	**18,991,497**	**18,714,863**	**18,412,117**	**18,161,404**	**17,869,372**	**17,497,527**	**17,078,512**	**16,970,819**	**17,159,213**
- Men	9,066,164	8,978,837	8,839,431	8,662,490	8,530,096	8,354,296	8,149,525	7,960,327	7,889,241	7,929,456
- Women	10,086,371	10,012,660	9,875,432	9,749,627	9,631,308	9,515,076	9,348,002	9,118,185	9,081,578	9,229,757
Treatment cases per 100,000 inhabitants[d]	**23,749**	**23,614**	**23,332**	**22,520**	**22,182**	**21,760**	**21,270**	**20,735**	**20,580**	**20,799**
- Men	22,970	22,844	22,584	21,602	21,254	20,762	20,228	19,744,	19,553	19,652
- Women	24,495	24,350	24,045	23,404	23,074	22,719	22,270	21,685	21,564	21,897
Treatment cases per 100,000 inhabitants (standardised)[c, d]	**–**	**–**	**–**	**20,684**	**20,513**	**20,291**	**20,003**	**19,651**	**19,629**	**19,962**
- Men	–	–	–	18,618	18,496	18,263	17,990	17,753	17,744	17,992
- Women	–	–	–	22,287	22,082	21,883	21,589	21,144	21,122	21,549
Average age of patients (in years)	**54.6**	**54.0**	**54.1**	**53.8**	**53.6**	**53.2**	**52.8**	**52.5**	**52.1**	**51.9**
- Men	54.2	53.9	53.5	53.1	52.4	52.4	52.0	51.6	51.2	51.0
- Women	54.9	54.8	54.6	54.3	54.2	53.9	53.5	53.2	52.9	52.7
Age-specific rate per 100,000 inhabitants[d]										
- Below 15 years	16,489	16,346	16,206	16,171	15,867	16,052	15,810	15,427	15,284	14,678
- 15 to less than 45 years	14,260	14,174	13,980	13,395	13,197	12,891	12,634	12,361	12,348	12,783
- 45 to less than 65 years	20,512	20,555	20,561	19,872	19,710	19,544	19,339	19,319	19,498	20,319
- 65 to less than 85 years	46,140	46,151	45,712	44,458	44,033	43,336	42,622	41,772	41,971	42,775
- 85 years or older	73,735	72,613	71,410	66,364	66,124	65,415	63,964,	61,604	61,171	59,913
Average length of stay (in days)	**7.6**	**7.6**	**7.7**	**7.9**	**8.0**	**8.1**	**8.3**	**8.4**	**8.6**	**8.6**
Hour cases within one day	**546,052**	**549,046**	**540,722**	**528,461**	**516,298**	**504,116**	**493,400**	**493,861**	**506,891**	**606,418**
Short-stay patients (1 to 3 days)	**7,649,540**	**7,429,866**	**7,149,083**	**6,828,023**	**6,568,703**	**6,279,504**	**5,944,592**	**5,631,308**	**5,401,207**	**5,406,254**
Number of deaths	**417,290**	**404,842**	**401,865**	**407,473**	**408,310**	**400,943**	**395,169**	**389,339**	**392,715**	**384,805**
Coverage (%)	**99.8**	**99.9**	**99.9**	**99.8**	**99.7**	**99.6**	**99.4**	**98.9**	**100.9**	**100.0**

[a] Including healthy newborns [b] Treatment cases including patients of unknown sex [c] Until 2010, calculated for the average population on the basis of previous censuses. 2011: Population as of 09/05/2011. Preliminary results of the 2011 census, census data as of 10/04/2014. 2012 and 2013: Preliminary results on the basis of the 2011 census, census data as of 10/04/2014. Reporting years 1994-2010 standardised with the standard population "Germany 1987". [d] Excl. patients domiciled abroad, of unknown sex and unknown age.

Source: Basic Data of Hospitals, Federal Statistical Office (Destatis), Wiesbaden, 2015

Tab. 7.4.8: Most common surgeries[1)] differentiated by type of procedure (2013; four-digit level)

Rank	OPS code	Surgery	Number	Percentage
	5	**Surgeries [1) 2)]**	**15,818,274**	**100**
1	5-469	Other surgeries of intestines	367,185	2.3
2	5-812	Arthroscopic surgeries of articular cartilage and menisci	289,462	1.8
3	5-758	Reconstruction of female genitals after rupture, postpartum [perineal rupture]	275,367	1.7
4	5-032	Access to lumbar vertebral column, sacrum and coccyx	275,290	1.7
5	5-513	Endoscopic surgeries of bile ducts	247,057	1.6
6	5-896	Surgical wound toilet [wound debridement] and excision of diseased dermal or hypodermal tissue	223,906	1.4
7	5-820	Hip joint replacement	210,384	1.3
8	5-749	Other caesarean sections	210,035	1.3
9	5-794	Open reposition of multi-fragment fractures near the joint of a long tubular bone incl. osteosynthesis	203,817	1.3
10	5-811	Arthroscopic surgeries of synovial membrane	201,414	1.3
11	5-511	Cholecystectomy	197,253	1.2
12	5-787	Removal of osteosynthesis material	180,031	1.1
13	5-530	Closure of inguinal hernia	177,758	1.1
14	5-839	Other surgeries of vertebral column	171,942	1.1
15	5-800	Open-surgical joint revision	167,326	1.1
16	5-814	Arthroscopic refixation and reconstruction of the capsuloligamentous structures of the shoulder joint	167,220	1.1
17	5-810	Arthroscopic joint revision	159,373	1.0
18	5-452	Local excision and destruction of diseased colon tissue	155,720	1.0
19	5-831	Excision of diseased intervertebral disc	155,244	1.0
20	5-916	Temporary coverage of soft tissue	154,672	1.0
21	5-790	Closed reposition of fractures or separation of epiphysis incl. osteosynthesis	153,368	1.0
22	5-788	Surgeries of the metatarsus and phalanx of the feet	151,160	1.0
23	5-215	Surgeries of nasal concha [Concha nasalis]	147,962	0.9
24	5-900	Simple restoration of dermal and hypodermal surface continuity	147,948	0.9
25	5-895	Radical and extended excision of diseased dermal and hypodermal tissue	144,461	0.9
26	5-822	Knee joint replacement	143,024	0.9
27	5-892	Other dermal and hypodermal incisions	141,069	0.9
28	5-385	Elimination, excision and stripping of varices	139,975	0.9
29	5-399	Other surgeries of blood vessels	135,175	0.9
30	5-793	Open reposition of simple fractures near the joint of a long tubular bone	124,744	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, 2015

Tab. 7.4.9: Most common surgeries[1)] differentiated by body area (2013; three-digit level)

Rank	OPS code	Surgery	Number	Percentage
	5	**Surgeries [1) 2)]**	**15,818,274**	**100**
1	5-81	Arthroscopic joint surgeries	884,798	5.6
2	5-78	Surgeries of other bones	812,857	5.1
3	5-83	Surgeries of the vertebral column	751,954	4.8
4	5-89	Surgeries of the dermis and hypodermis	662,848	4.2
5	5-79	Reposition of fractures and luxations	618,084	3.9
6	5-82	Endoprosthetic joint and bone replacement	516,720	3.3
7	5-51	Surgeries of the gall bladder and bile ducts	464,376	2.9
8	5-46	Other surgeries of small intestines and colon	454,920	2.9
9	5-38	Incision, excision and closure of blood vessels	445,917	2.8
10	5-03	Surgeries of the medulla, meninx and spinal cord	421,749	2.7
11	5-80	Open joint surgeries	347,476	2.2
12	5-90	Surgical restoration and reconstruction of dermis and hypodermis	328,480	2.1
13	5-21	Surgeries of the nose	313,536	2.0
14	5-75	Other obstetric surgeries	310,489	2.0
15	5-45	Incision, excision, resection and anastomosis of small intestines and colon	309,805	2.0
16	5-53	Closure of abdominal hernia	307,119	1.9
17	5-85	Surgeries of muscles tendons, fascia and bursa	292,466	1.8
18	5-39	Other surgeries of blood vessels	287,636	1.8
19	5-74	Caesarean section and child development	278,173	1.8
20	5-57	Surgeries of the urinary bladder	256,601	1.6
21	5-37	Arrhythmia surgeries and other surgeries of the heart and pericardium	221,999	1.4
22	5-37	Surgeries of the retina, choroid and vitreous body	209,506	1.3
23	5-91	Other surgeries of the dermis and hypodermis	209,134	1.3
24	5-54	Other surgeries in the abdominal area	188,740	1.2
25	5-40	Surgeries of the lymphatic tissue	183,173	1.2
26	5-68	Incision, excision and extirpation of the uterus	173,089	1.1
27	5-65	Surgeries of the ovary	168,966	1.1
28	5-49	Surgeries of the anus	168,403	1.1
29	5-06	Surgeries of the thyroid and parathyroid	166,223	1.1
30	5-28	Surgeries in the nasopharyngeal and oropharyngeal area	162,909	1.0

[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, 2015

Authors and reviewers

Prof. Dr. Thomas Alter
Free University of Berlin
Institute of Food Hygiene, Department of Veterinary Medicine
Königsweg 69, 14163 Berlin
Tel.: 030-838 62560
Fax: 030-8384 62550
Email: thomas.alter@fu-berlin.de

Doris Altmann
Robert Koch Institute
Department of Infectious Disease Epidemiology
Seestraße 10, 13353 Berlin
Tel.: 030-18 754 3454
Fax: 030-18 754 3533
Email: altmannd@rki.de

PD Dr. Isabelle Bekeredjian-Ding
Paul Ehrlich Institute
Division of Microbiology
Paul-Ehrlich-Straße 51-59, 63225 Langen
Tel.: 06103-77 3700
Email: isabelle.bekeredjian-ding@pei.de

Dr. Alice Bender
Federal Office of Consumer Protection and Food Safety (BVL)
Unit 304: Post-Marketing
Department 3 Veterinary Drugs
Mauerstraße 39-42, 10117 Berlin
Tel.: 03018-445 7418
Fax: 03018-445 7499
Email: alice.bender@bvl.bund.de

Prof. Dr. Reinhard Berner
University Hospital Carl Gustav Carus
Technische Universtität Dresden
Department of Paediatrics
Fetscherstraße 74, 01307 Dresden
Tel.: 0351-458 2508
Fax: 0351-458 4384
Email: reinhard.berner@uniklinikum-dresden.de

Ute Bölt
Federal Statistical Office, Bonn Branch
H101 – Hospital Statistics, Causes of Death Statistics
PO box 17 03 77, 53029 Bonn
Tel.: 0228-99 643-8107
Fax: 0228-99 10643-8107
Email: ute.boelt@destatis.de

Dr. Viviane Bremer
Robert Koch Institute
Department of Infectious Disease Epidemiology
Seestraße 10, 13353 Berlin
Tel.: 030-18754 3487
Fax: 030-18754 3533
Email: bremerv@rki.de

Dr. Bonita Brodhun
Robert Koch Institute
Department of Infectious Disease Epidemiology
Seestraße 10, 13353 Berlin
Tel.: 030-18754 3445
Fax: 030-18754 3341
Email: brodhunb@rki.de

Dr. Susanne Buder
Vivantes Clinic of Dermatology and Venereology
Consultant Laboratory for Gonococci of the RKI
Rudower Straße 48, 12351 Berlin
Tel.: 030-130 14 3601
Fax: 030-130 14 3542
Email: konsiliarlabor-gonokokken@googlemail.com

PD Dr. Heike Claus
University of Würzburg
National Reference Centre for Meningococci and Haemophilus influenzae
Institute of Hygiene and Microbiology
Josef-Schneider-Straße 2, Bldg. E1, 97080 Würzburg
Tel.: 0931-31 46936
Fax: 0931-31 46445
Email: hclaus@hygiene.uni-wuerzburg.de

Dr. Christiane Cuny
Robert Koch Institute, Wernigerode Branch
National Reference Centre for Staphylococci and Enterococci
Department of Infectious Diseases
Burgstraße 37, 38855 Wernigerode
Tel.: 03943-679 346
Fax: 03943-679 317
Email: cunych@rki.de

Dr. Dr. Katja de With
University Hospital Carl Gustav Carus Dresden
Clinical Infectiology
Fetscherstraße 74, 01307 Dresden
Tel.: 0351-458 2851
Fax: 0351-458 5729
Email: katja.dewith@uniklinikum-dresden.de

Sandra Dudareva-Vizule
Robert Koch Institute
Department of Infectious Disease Epidemiology
Seestraße 10, 13353 Berlin
Tel.: 030-18754 3427
Fax: 030-18754 3533
Email: dudareva-vizules@rki.de

PD Dr. Lüppo Ellerbroek
Federal Institute for Risk Assessment
Food Hygiene and Virology
Department of Biological Safety
Diedersdorfer Weg 1, 12277 Berlin
Tel.: 030-18412 2121
Fax: 030-18412 2966
Email: lueppo.ellerbroek@bfr.bund.de

Prof. Dr. Christa Ewers
Justus Liebig University of Gießen
Institute of Hygiene and Infectious Diseases of Animals
Frankfurter Straße 85-89, 35392 Gießen
Tel.: 0641-9938301
Fax: 0641-9938309
Email: christa.ewers@vetmed.uni-giessen.de

Dr. Matthias Fellhauer
Schwarzwald-Baar Hospital
Pharmacy
Klinikstraße 11, 78052 Villingen-Schwenningen
Tel.: 07721-933901
Fax: 07721-9393909
Email: matthias.fellhauer@sbk-vs.de

Dr. Angelika Fruth
Robert Koch Institute, Wernigerode Branch
Burgstraße 37, 38855 Wernigerode
Tel.: 030-187544241
Fax: 030-18754-4207
Email: frutha@rki.de

PD Dr. Christine Geffers
Charité – University Hospital Berlin
National Reference Centre for the Surveillance of Nosocomial Infections
Institute of Hygiene and Environmental Medicine
Hindenburgdamm 27, 12203 Berlin
Tel.: 030-8445 3680
Fax: 030-8445 4486
Email: christine.geffers@charite.de

PD Dr. Erik-Oliver Glocker
Municipal Hospital Brandenburg
Institute of Laboratory Medicine
Hochstr. 29, 14770 Brandenburg an der Havel

Prof. Dr. Andreas H. Groll
University Hospital Münster
Infectious Disease Research Programme
Clinic of Paediatric and Adolescent Medicine –
Paediatric Haematology and Oncology and Centre for Bone Marrow Transplantation
Albert-Schweitzer-Campus 1, Bldg. A1, 48149 Münster
Tel.: 0251-834 7742
Fax: 0251-834 7828
Email: grollan@ukmuenster.de

Professor Dr. Walter Haas
Robert Koch Institute
Department of Infectious Disease Epidemiology
Seestraße 10, 13353 Berlin
Tel: 030-18754 3431
Fax: 030-18754 3341
Email: haasw@rki.de

PD Dr. Rüdiger Hauck
Auburn University
302J Poultry Science Building
260 Lem Morrison Drive, Auburn, Alabama 36849, USA
Tel.: +1 334 844 4152
Email: ruediger.hauck@auburn.edu

Dr. Barbara Hauer
Robert Koch Institute
Department of Infectious Disease Epidemiology
Seestraße 10, 13353 Berlin
Tel.: 030-18 754 3910
Fax: 030-18 754 3341
Email: hauerb@rki.de

Dr. Wiebke Hellenbrand
Robert Koch Institute
Department of Infectious Disease Epidemiology
Seestraße 10, 13353 Berlin
Tel.: 030-18754 3408
Fax: 030-18754 3533
Email: hellenbrandw@rki.de

Dr. Julia Hermes
Robert Koch Institute
Department of Infectious Disease Epidemiology
Seestraße 10, 13353 Berlin
Tel.: 030-187540

Dr. Torsten Hoppe-Tichy
University Hospital Heidelberg
Pharmacy
Im Neuenheimer Feld 670, 69120 Heidelberg
Tel.: 06221-56 6761
Fax: 06221-56 33570
Email: torsten.hoppe-tichy@med.uni-heidelberg.de

Prof. Dr. Johannes Hübner
University Hospital of Ludwig Maximilian University
Hauner Clinic and Outpatient Clinic of Paediatric Medicine
Department of Paediatric Infectiology
Lindwurmstraße 4, 80337 Munich
Tel.: 089-5160 7970
Fax: 089-5160 3155
Email: johannes.huebner@med.uni-muenchen.de

PD Dr. Matthias Imöhl
University Hospital RWTH Aachen
National Reference Centre for Streptococci
Institute of Med. Microbiology
Pauwelsstraße 30, 52074 Aachen
Tel.: 0241-80 36610
Email: mimoehl@ukaachen.de

Dr. Klaus Jansen
Robert Koch Institute
Department of Infectious Disease Epidemiology
Seestraße 10, 13353 Berlin
Tel.: 030-18754 3754
Fax: 030-18754 3533
Email: jansenk@rki.de

Prof. Dr. Daniel Jonas
University Hospital Freiburg
Infection Prevention and Hospital Hygiene
Central Institution of the University Hospital
Breisacher Straße 115 B, 79106 Freiburg
Tel.: 0761-270 82730
Fax: 0761-270 82030
Email: daniel.jonas@uniklinik-freiburg.de

Dr. Martin Kaase
University Medical Centre Göttingen
Central Department of Hospital Hygiene and Infectiology
Robert-Koch-Straße 40, 37075 Göttingen
Tel.: 0551-39 19914
Email: martin.kaase@med.uni-goettingen.de

Prof. Dr. Annemarie Käsbohrer
Federal Institute for Risk Assessment
Epidemiology, Zoonoses and Antimicrobial Resistance
Department of Biological Safety
Diedersdorfer Weg 1, 12277 Berlin
Tel.: 030-18412 2202
Fax: 030-18412 2952
Email: annemarie.kaesbohrer@bfr.bund.de

Dr. Anne-Kathrin Karaalp
Federal Office of Consumer Protection and Food Safety
Unit 505: Monitoring of Resistance to Antibiotics
Department 5 Reference Laboratories, Method Standardisation, Resistance to Antibiotics
Mauerstraße 39-42, 10117 Berlin
Tel.: 030-18445 8510
Fax: 030-18445 8399
Email: anne-kathrin.karaalp@bvl.bund.de

Dr. Heike Kaspar
Federal Office of Consumer Protection and Food Safety
Unit 505: Monitoring of Resistance to Antibiotics
Department 5 Reference Laboratories, Method Standardisation, Resistance to Antibiotics
Mauerstraße 39-42, 10117 Berlin
Tel.: 030-18445 8500
Fax: 030-18445 8399
Email: heike.kaspar@bvl.bund.de

Prof. Dr. Winfried V. Kern
University Hospital and Medical Center Freiburg
Division of Infectious Diseases
Hugstetter Straße 55, 79106 Freiburg
Tel.: 0761-270 181 90
Fax: 0761-270 182 00
Email: kern@if-freiburg.de

Prof. Dr. Manfred Kist
University Hospital Freiburg
Institute of Med. Microbiology and Hygiene
Hermann-Herder-Straße 11, 79104 Freiburg
Email: manfred.kist@uniklinik-freiburg.de

Dr. Ingo Klare
Robert Koch Institute, Wernigerode Branch
National Reference Centre for Staphylococci and Enterococci
Burgstraße 37, 38855 Wernigerode
Tel.: 03943-679 247
Fax: 03943-679 207
Email: klarei@rki.de

Dr. Sabine Klee
Federal Office of Consumer Protection and Food Safety
Unit 304: Post-Marketing
Department 3 Veterinary Drugs
Mauerstraße 39-42, 10117 Berlin
Tel.: 030-18445 7415
Fax: 030-18445 7499
Email: sabine.klee@bvl.bund.de

Dr. Barbara Körber-Irrgang
Antiinfectives Intelligence GmbH
Campus of Bonn-Rhine-Sieg University of Applied Sciences
Von-Liebig-Straße 20, 53359 Rheinbach
Tel.: 02226-908 921
Fax: 02226-908 919
Email: barbara.koerber-irrgang@antiinfectives-intelligence.de

Dr. Evelyn Kramme
Clinic of Infectiology and Microbiology
Campus Lübeck
Ratzeburger Allee 160, 23538 Lübeck
Tel.: 0451-500 3970
Fax: 0451-500 3351
Email: evelyn.kramme@uksh.de

Prof. Dr. Michael Kresken[1,2]
[1] Antiinfectives Intelligence GmbH
Campus of Bonn-Rhine-Sieg University of Applied Sciences
Von-Liebig-Straße 20, 53359 Rheinbach
Tel.: 02226-908 912
Fax: 02226-908 918
Email: michael.kresken@antiinfectives-intelligence.de
[2] Rheinische Fachhochschule Köln gGmbH
Department of Medical Economics
Schaevenstraße 1 a/b
50676 Cologne

Prof. Dr. Oliver Kurzai
Leibniz Institute for Natural Product Research and Infection Biology – Hans Knöll Institute
National Reference Centre for Invasive Mycoses
Beutenbergstraße 11A, 07745 Jena
Tel.: 03641-5321347
Fax: 03641-5320816
Email: oliver.kurzai@leibniz-hki.de

Dr. Thiên-Trí Lâm
University of Würzburg
National Reference Centre for Meningococci and Haemophilus influenzae
Institute of Hygiene and Microbiology
Josef-Schneider-Straße 2, E1, 97080 Würzburg
Tel: 0931-31 46737
Fax: 0931-31 46445
Email: ttlam@hygiene.uni-wuerzburg.de

Fabian Lander
University Hospital Carl Gustav Carus
Department of Paediatrics
Fetscherstraße 74, 01307 Dresden
Tel.: 0351-458 18025
Fax: 0351-458 4384
Email: fabian.lander@uniklinikum-dresden.de

Dr. Franziska Layer
Robert Koch Institute, Wernigerode Branch
National Reference Centre for Staphylococci and Enterococci
Department of Infectious Diseases
Burgstraße 37, 38855 Wernigerode
Tel.: 030-18754 4249
Fax: 030-18754 4317
Email: layerf@rki.de

Dr. Ulf Lenski
Federal Institute for Risk Assessment
GLP Federal Bureau and Quality Management
Department Exposure
Diedersdorfer Weg 1, 12277 Berlin
Tel.: 030-18412 2265
Fax: 030-18412 4741
Email: ulf.lenski@bfr.bund.de

PD Dr. Christoph Lübbert
University Hospital Leipzig
Clinic of Gastroenterology and Rheumatology
Department of Infectiology and Tropical Medicine
Liebigstraße 20, 04103 Leipzig
Tel.: 0341-97 24970
Fax: 0341-97 24979
Email: christoph.luebbert@medizin.uni-leipzig.de

Dr. Antina Lübke-Becker
Free University of Berlin
Institute of Microbiology and Epizootics
Robert von Ostertag-Straße 7-13, 14163 Berlin
Tel.: 030-838 51836
Fax: 030-838 451854
Email: antina.luebke-becker@fu-berlin.de

Dr. Christian Lück
University Hospital of TU Dresden
Consultant Laboratory for Legionella
Institute of Med. Microbiology and Hygiene
Fiedlerstraße 42, 01307 Dresden
Tel.: 0351-458 6580
Fax: 0351-458 6310
Email: christian.lueck@tu-dresden.de

Dr. Matthias Merker
Borstel Research Centre
Leibniz Centre for Medicine and Biosciences
Molecular and Experimental Mycobacteriology
Parkallee 1, 23845 Borstel
Tel.: 04537-188 2750
Fax: 04537-188 3110
Email: mmerker@fz-borstel.de

PD. Dr. Elisabeth Meyer
Charité – University Hospital Berlin
Institute of Hygiene and Environmental Medicine
Hindenburgdamm 27, 12203 Berlin
Tel.: 030-8445 4883
Fax: 030-8445 3682
Email: elisabeth.meyer@charite.de

Dr. Geovana Brenner Michael
Free University of Berlin
Institute of Microbiology and Epizootics
Robert von Ostertag-Strase 7-13, 14163 Berlin
Tel.: 030-838 51791
Fax: 030-838 451851
Email: g.brenner.michael@fu-berlin.de

Prof. Dr. Martin Mielke
Robert Koch Institute
Department of Infectious Diseases
Nordufer 20, 13353 Berlin
Tel.: 030-18754 2233
Fax: 030-1810754-2191
Email: mielkem@rki.de

Dr. Alexander Mischnik
University Hospital and Medical Center Freiburg
Division of Infectious Diseases and Department of Medicine
Hugstetter Straße 55, 79106 Freiburg
Tel.: 0761-270 18190
Fax: 0761-270 18200
Email: alexander.mischnik@uniklinik-freiburg.de

Prof. Dr. Stephan Niemann
Borstel Research Centre
National Reference Centre for Mycobacteria
Molecular and Experimental Mycobacteriology
Parkallee 1, 23845 Borstel
Tel.: 04537-188 7620
Fax: 04537-188 2091
Email: sniemann@fz-borstel.de

Dr. Yvonne Pfeifer
Robert Koch Institute, Wernigerode Branch
Department of Infectious Diseases
Burgstraße 37, 38855 Wernigerode
Tel.: 030-187544337
Email: pfeifery@rki.de

Prof. Dr. Mathias W. Pletz
University Hospital Jena
Centre of Infectiology and Hospital Hygiene
Erlanger Allee 101, 07740 Jena
Tel.: 03641-932 4650
Fax: 03641-932 4652
Email: mathias.pletz@med.uni-jena.de

Inke Reimer
Federal Office of Consumer Protection and Food Safety
Unit 304: Post-Marketing
Department 3 Veterinary Drugs
Mauerstraße 39-42, 10117 Berlin
Tel.: 030-18445 7423
Fax: 030-18445 7499
Email: inke.reimer@bvl.bund.de

Prof. Dr. Ralf René Reinert
University Hospital RWTH Aachen
National Reference Centre for Streptococci
Institute of Med. Microbiology
Pauwelsstraße 30, 52074 Aachen
Email: ralfrene.reinert@pfizer.com

Dr. Antje Römer
Federal Office of Consumer Protection and Food Safety
Unit 505: Monitoring of Resistance to Antibiotics
Department 5 Reference Laboratories, Method Standardisation, Resistance to Antibiotics
Mauerstraße 39-42, 10117 Berlin
Tel.: 030-18445 8511
Fax: 030-18445 8399
Email: antje.roemer@bvl.bund.de

Dr. Sabine Rüsch-Gerdes
Lindensteg 10, 21465 Reinbek
Tel.: 040-7279966
Email: srueschg@t-online.de

Julia Schaufler
Research Institute of the AOK
Rosenthaler Straße 31, 10178 Berlin
Tel.: 030-34646 2152
Email: julia.schaufler@wido.bv.aok.de

PD Dr. Frieder Schaumburg
University Hospital Münster
Institute of Med. Microbiology
Domagkstraße 10, 48149 Münster
Tel.: 0251-83 52752
Email: frieder.schaumburg@ukmuenster.de

PD Dr. Norbert Schnitzler
Public Health Department, District Düren
Bismarckstraße 16, 52351 Düren
Tel.: 02421-222410
Fax: 02421-222409
Email: n.schnitzler@kreis-dueren.de

Dr. Ludwig Sedlacek
Hannover Medical School
Institute for Medical Microbiology and Hospital Epidemiology
Carl-Neuberg-Straße 1, 30625 Hannover
Tel.: 0511-532 4431
Fax: 0511-532 4366
Email: sedlacek.ludwig@mh-hannover.de

Prof. Dr. Harald Seifert
University Hospital Cologne
Institute of Med. Microbiology, Immunology and Hygiene
Goldenfelsstraße 19-21, 50935 Cologne
Tel.: 0221-478 32009
Fax: 0221-478 32035
Email: harald.seifert@uni-koeln.de

Prof. Dr. Dr. Bhanu Sinha
University Medical Centre Groningen
Medical Microbiology, HPC: EB80
Hanzeplein 1, 9713 GZ Groningen
The Netherlands
Tel: + 31-50-361-3480
Email: b.sinha@umcg.nl

Prof. Dr. Barbara Spellerberg
University Hospital Ulm
Institute of Med. Microbiology and Hygiene
Albert-Einstein-Allee 11, 89081 Ulm
Tel.: 0731-500 65 333
Fax: 0731-500 65 302
Email: barbara.spellerberg@uniklinik-ulm.de

Michaela Steib-Bauert
University Hospital Freiburg
Centre of Infectiology and Travel Medicine
Hugstetter Straße 55, 79106 Freiburg
Tel.: 0761-270 182 50
Fax: 0761-270 182 00
Email: michaela.steib-bauert@uniklinik-freiburg.de

Dr. Ulrike Steinacker
Federal Office of Consumer Protection and Food Safety
Unit 505: Monitoring of Resistance to Antibiotics
Department 5 Reference Laboratories, Method Standardisation, Resistance to Antibiotics
Mauerstraße 39-42, 10117 Berlin
Tel.: 030-18445 8512
Fax: 030-18445 8399
Email: ulrike.steinacker@bvl.bund.de

Dr. Bernd Stephan
Bayer Animal Health GmbH
Antimicrobial Development Department
Kaiser-Wilhelm-Allee 10, 51373 Leverkusen
Tel.: 02173-382182
Email: bernd.stephan@bayer.com

Dr. Kerstin Stingl
Federal Institute for Risk Assessment
National Reference Laboratory for Campylobacter
Department of Biological Safety
Diedersdorfer Weg 1, 12277 Berlin
Tel.: 030-18412 2135
Fax: 030-18412 2951
Email: kerstin.stingl@bfr.bund.de

Inka Stolle
Justus Liebig University of Gießen
Institute of Hygiene and Infectious Diseases of Animals
Frankfurter Straße 85-89, 35392 Gießen
Tel.: 0641-9938 442
Fax: 0641-9938 309
Email: inka.stolle@vetmed.uni-giessen.de

Prof. Dr. Eberhard Straube
Hermann-Löns-Straße 58
07745 Jena
Tel.: 03641-609087
Email: eberhard.straube@med.uni-jena.de

Dr. Birgit Strommenger
Robert Koch Institute, Wernigerode Branch
National Reference Centre for Staphylococci and Enterococci
Department of Infectious Diseases
Burgstraße 37, 38855 Wernigerode
Tel.: 03943-679 260
Fax: 03943-679 317
Email: strommengerb@rki.de

Prof. Dr. Sebastian Suerbaum
Hannover Medical School
Institute for Medical Microbiology and Hospital Epidemiology
Carl-Neuberg-Straße 1, 30625 Hannover
Tel.: 0511-532 6769
Fax: 0511-532 4355
Email: suerbaum.sebastian@mh-hannover.de

Dr. Carsten Telschow
Research Institute of the AOK
Rosenthaler Straße 31, 10178 Berlin
Tel.: 030-34646 2111
Fax: 030-34646 2144
Email: carsten.telschow@wido.bv.aok.de

Dr. Erhard Tietze
Robert Koch Institute, Wernigerode Branch
Burgstraße 37, 38855 Wernigerode
Tel.: 030-18754 4238
Fax: 030-18754 4207
Email: tietzee@rki.de

Prof. Dr. Matthias Trautmann
Clinical Centre Stuttgart
Institute of Hospital Hygiene
Kriegsbergstr. 60, 70174 Stuttgart
Tel.: 0711-278 32801
Fax: 0711-278 32804
Email: m.trautmann@klinikum-stuttgart.de

Prof. Dr. Andrew J. Ullmann
University Hospital Würzburg
Medical Clinic and Outpatient Clinic II
Department of Clinical Infectiology
Oberdürrbacher Straße 6, 97080 Würzburg
Tel.: 0931-201 40166
Fax: 0931-201 9 40115
Email: ullmann_a@ukw.de

Prof. Dr. Dr. Timo Ulrichs[1,2]
[1] Akkon University of Human Sciences
Colditzstraße 34-36, 10179 Berlin
Tel.: 030-809 233 215
Fax: 030-809 233 230
Email: timo.ulrichs@akkon-hochschule.de
[2] Koch Metschnikow Forum
Langenbeck-Virchow-Haus
Luisenstraße 59, 10117 Berlin

Dr. Mark van der Linden
University Hospital RWTH Aachen
National Reference Centre for Streptococci
Institute of Med. Microbiology
Pauwelsstraße 30, 52074 Aachen
Tel: 0241-8089946
Fax: 0241-8082483
Email: mlinden@ukaachen.de

Prof. Dr. Ulrich Vogel
University of Würzburg
National Reference Centre Meningococci and Haemophilus influenzae
Institute of Hygiene and Microbiology
Josef-Schneider-Straße 2 / E1, 97080 Würzburg
Tel: 0931-31 467802
Fax: 0931-31 46445
Email: vogel_u@ukw.de

Petra Vogt
Federal Institute for Risk Assessment
Food Hygiene and Virology
Department of Biological Safety
Diedersdorfer Weg 1, 12277 Berlin
Tel.: 030-18412 2175
Fax: 030-18412 2966
Email: petra.vogt@bfr.bund.de

Prof. Dr. Heike von Baum
University Hospital Ulm
Institute of Med. Microbiology and Hygiene
Albert-Einstein-Allee 23, 89081 Ulm
Tel.: 0731-500 65350
Fax: 0731-500 65349
Email: heike.von-baum@uniklinik-ulm.de

Dr. Jürgen Wallmann
Federal Office of Consumer Protection and Food Safety
Unit 306 Drug Resistance
Department 3 Veterinary Drugs
Mauerstraße 39-42, 10117 Berlin
Tel.: 030-18445 7600
Fax: 030-18445 7098
Email: juergen.wallmann@bvl.bund.de

Dr. Jan Walter
Robert Koch Institute
Department of Infectious Disease Epidemiology
Seestraße 10, 13353 Berlin
Tel.: 030-18754 3212
Fax: 030-18754 3533
Email: walterj@rki.de

Dr. Grit Walther
Leibniz Institute for Natural Product Research and Infection Biology – Hans Knöll Institute
National Reference Centre for Invasive Mycoses
Beutenbergstraße 11A, 07745 Jena
Tel.: 03641-532 1038
Fax: 03641-532 2038
Email: grit.walther@leibniz-hki.de

Dr. Armin Weiser
Federal Institute for Risk Assessment
Epidemiology, Zoonoses and Antimicrobial Resistance
Department of Biological Safety
Diedersdorfer Weg 1, 12277 Berlin
Tel.: 030-18412 2118
Fax: 030-18412 2952
Email: armin.weiser@bfr.bund.de

Prof. Dr. Tobias Welte
Hannover Medical School
Clinic of Pneumology
Carl-Neuberg-Straße 1, 30625 Hannover
Tel.: 0511-532 3531
Fax: 0511-532 3353
Email: welte.tobias@mh-hannover.de

Prof. Dr. Constanze Wendt
Medical Care Centre Laboratory Dr. Limbach & Kollegen GbR
Im Breitspiel 15, 69126 Heidelberg
Tel.: 06221-3432 344
Fax: 06221-3432 8344
Email: constanze.wendt@labor-limbach.de

PD Dr. Christiane Werckenthin
Lower Saxony State Office of Consumer Protection and Food Safety
Food and Veterinary Institute Oldenburg
Philosophenweg 38, 26121 Oldenburg
Tel.: 0441-9713 820
Fax: 0441-9713 814
Email: christiane.werckenthin@laves.niedersachsen.de

Prof. Dr. Guido Werner
Robert Koch Institute, Wernigerode Branch
National Reference Centre for Staphylococci and Enterococci
Department of Infectious Diseases
Burgstraße 37, 38855 Wernigerode
Tel.: 030-18754 4210
Fax: 030-18754 4317
Email: wernerg@rki.de

Prof. Dr. Dr. Thomas A. Wichelhaus
University Hospital Frankfurt, Goethe University
Institute of Med. Microbiology and Infection Control
Paul-Ehrlich-Straße 40, 60596 Frankfurt am Main
Tel.: 069-6301 64 38
Fax: 069-6301 57 67
Email: wichelhaus@em.uni-frankfurt.de

Dr. Stefan Ziesing
Hannover Medical School
Institute for Medical Microbiology and Hospital Epidemiology
Carl-Neuberg-Straße 1, 30625 Hannover
Tel.: 0511-532 4844
Fax: 0511-532 4366
Email: ziesing.stefan@mh-hannover.de

List of abbreviations

ABS	Antibiotic Stewardship
ADKA	Association of German Hospital Pharmacists
AFST	Antifungal Susceptibility Testing
AmB	Amphotericin B
AMC	Amoxicillin/Clavulanic acid
AMG	German Medicinal Products Act
AMIS	Drug Information System
AMK	Amikacin
AMP	Ampicillin
AOK	General local health insurance fund
APP	*Actinobacillus pleuropneumoniae*
ARESC	Antimicrobial Resistance Epidemiological Survey on Cystitis
ARS	Antimicrobial Resistance Surveillance
AT	Austria
ATC	Anatomical Therapeutic Chemical Classification
ATI	Animal Treatment Index
AVS	Antimicrobial Consumption Surveillance
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
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
CC	Clonal complex
CDC	Centers for Disease Control
CDI	*Clostridium difficile* infection
CEF	Ceftiofur
CF	Cystic fibrosis
CFZ	Cefazolin
CHL	Choramphenicol
CIP	Ciprofloxacin
CLI	Clindamycin
CLSI	Clinical and Laboratory Standards Institute
COL	Colistin
CPR	Cefpirome
CPZ	Cefoperazone
CQN	Cefquinome
CTX	Cefotaxime
CY	Cyprus
CZ	Czech Republic
DART	German Antimicrobial Resistance Strategy
DDD	Defined daily doses
DE	Germany
DGHM	German Society for Hygiene and Microbiology
DGI	German Society for Infectious Diseases
DHFR	Dihydrofolate reductase
DIMDI	German Institute of Medical Documentation and Information
DIN	German Institute for Standardisation
DK	Denmark
DOX	Doxycycline
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*
EMA	European Medicines Agency
ENR	Enrofloxacin
ENT	Ear-nose-throat
EOD	Early-onset disease
EPEC	Enteropathogenic *E. coli*
ERY	Erythromycin
ES	Spain
ESAC	European Surveillance of Antimicrobial Consumption
ESBL	Extended-spectrum β-lactamases
ESVAC	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
FPA	Food-producing animals
FR	France
FUS	Fusidic acid
GAmSi	Rapid Prescription Feedback System of the SHI
GB	Great Britain
GBS	Group-B streptococci
GEK	Gmünder ErsatzKasse
GEN	Gentamicin
GENARS	German Network for Antimicrobial Resistance Surveillance
GERM-Vet	National Resistance Monitoring of Veterinary Pathogens
GORENET	Gonococcal Resistance Network
GR	Greece
G-TEST	German Tigecycline Evaluation Surveillance Trial
HA-MRSA	Hospital-acquired MRSA
HCA-MRSA	Hospital-associated community onset MRSA
Hib	*H. influenzae* of serotype b
HI-Tier	Origin and Information System for Livestock
HR	Croatia
HU	Hungary
IAP	Intrapartum antimicrobial prophylaxis
IDSA	Infectious Diseases Society of America
IE	Ireland
if	Infectiology Freiburg
IfSG	German Infection Protection Act
IGES	Institute for Health and Social Research
IPM	Imipenem
IS	Iceland
IT	Italy
ITR	Itraconazole
KG	Kilogram of body weight
KISS	Hospital Infection Surveillance System
KNS	Coagulase-negative *Staphylococcus* spp.
KRINKO	Commission for Hospital Hygiene and Infection Prevention
KV	Regional Associations of Panel Physicians
L-AMB	Liposomal amphotericin B
LA-MRSA	Livestock-associated MRSA
LFL	Levofloxacin
LIN	Lincomycin
LOD	Late-onset disease
LT	Lithuania
LU	Luxembourg
LV	Latvia
MABUSE	Medical Antimicrobial Use Surveillance and Evaluation
MALT lymphoma	Mucosa-associated lymphatic tissue lymphoma
MDR	Multi-drug resistance
MDR-TB	Multi-drug-resistant tuberculosis
MENEC	Meningitis-associated *E. coli*
MIC	Minimum inhibitory concentration
MLST	Multilocus sequence typing
MOX	Moxifloxacin
MRA	Macrorestriction analysis

MRGN	Multi-resistant gram-negative bacteria
MRL	Maximum residue level
MRSA	Methicillin-resistant *S. aureus*
MRSP	Methicillin-resistant *S. pseudintermedius*
MUP	Mupirocin
NAK	National Antimicrobial Susceptibility Testing Committee
NAL	Nalidixic acid
NI	Nosocomial infections
NIDEP	Nosocomial Infections in Germany – Assessment and Prevention
NIS	Newly Independent States
NIT	Nitrofurantoin
NL	Netherlands
NO	Norway
NRZ	National Reference Centre
NRZMHi	National Reference Centre for Meningococci and *Haemophilus influenzae*
NRZMyk	National Reference Centre for Invasive Mycoses
NSBL	Narrow-spectrum beta-lactamase
nt	Not tested
NTHi	Non-typable *H. influenzae*
OIE	World Organisation for Animal Health
OXA	Oxacillin
PAS	Para-aminosalicylic acid
PBP	Penicillin-binding protein
PCR	Polymerase chain reaction
PCU	Population correction unit; number of FPA 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
PHO	Fosfomycin
PID	Pelvic inflammatory disease
PIR	Pirlimycin
PL	Poland
PPI	Proton-pump inhibitor
PT	Portugal
Q/D	Quinupristin/Dalfopristin
RAM	Rifampicin
RDD	Recommended daily doses
ResiNet	Study for monitoring the resistance situation and identifying risk factors for the resistance development of *H.pylori*
RKI	Robert Koch Institute
RNA	Ribonucleic acid
RO	Romania
rRNA	Ribosomal RNA
SARI	Surveillance of Antimicrobial Use and Bacterial Resistance in Intensive Care Units
SE	Sweden
SEPEC	Septicaemic *E. coli*
SHI	Statutory health insurance
SI	Slovenia
SK	Slovakia
spa	Gene coding for the protein A in *S. aureus* (*S. aureus* protein A)
ST	Sequence type
STEC	Shiga toxin-producing *E. coli*
STIKO	Standing Committee on Vaccination
STR	Streptomycin
SXT	Trimethoprim/Sulphamethoxazole (co-trimoxazole)
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
TNF	Tumour necrosis factor
TPL	Teicoplanin
TUL	Tulathromycin
TYL	Tylosin
UK	United Kingdom
UK NEQAS	United Kingdom National External Quality Assessment Service
UN	United Nations
UPEC	Uropathogenic *E. coli*

VAN	Vancomycin
VOR	Voriconazole
VRE	Vancomycin-resistant enterococci
WHO	World Health Organisation
WIdO	Research Institute of the AOK
XDR-TB	Extensively drug-resistant tuberculosis
XNL	Ceftiofur
ZI	Central Research Institute of Ambulatory Health Care in Germany
ZI	Zentralinstitut für die kassenärztliche Versorgung

ISBN 978-3-9818383-0-5