Aus dem Robert Koch-Institut
Abteilung für Infektionsepidemiologie

DISSERTATION

**Socio-behavioural determinants for
Antimicrobial prescribing and antimicrobial resistance in
Hospital and outpatient care practice in Germany**

zur Erlangung des akademischen Grades
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1. Summary of the doctoral research

1.1. Abstract

Purpose: To provide scientific evidence on determinant factors of physicians' prescribing of antibiotics, and also factors that influence physicians' opinions about interventions to ameliorate the problem of antimicrobial resistance in Germany.

Methods: A mixed-methods quantitative-qualitative research approach consisting of: focus group discussions within outpatient care and hospital care practice in the Berlin region, Germany; a national, cross-sectional survey of outpatient care and hospital care physicians and a nationally representative online survey of the general population in Germany.

Results: The qualitative investigation indicated that outpatient care physicians believed the most important factors associated with antibiotic prescribing and antimicrobial resistance to be the ability to diagnose and prescribe precisely, patient demand and noncompliance. For hospital care physicians, this was found to be challenges associated with the spread of multi-resistant pathogens; challenges associated with hygiene and the limited time they have to consult patients. In the survey of physicians the following factors were found to be statistically significant in logistic regression analyses: status as a hospital physician, male physician, age 50-59, and place of practice in states in the former East Germany. Bivariate analysis in the survey of the general population suggested that the prevalence of self-reported expectations of antibiotics for the common cold is related to level of education, but the majority of participants showed a basic understanding that antibiotics are effective against bacteria but not viruses and knew about antibiotics resistance.

Conclusions: The general population appears to be well informed about antibiotics, therefore the research evidence suggests that the factors influencing antibiotic prescribing and resistance are more in the domain of physicians and quality of clinical treatment. While previous research in other countries has focused on improving patient education or increasing public awareness, this research suggests that a focus on factors influencing physicians' decisions to prescribe antibiotics, the quality of their prescribing and their realisation of antimicrobial resistance could be more appropriate for Germany.

1.1.1. Zusammenfassung in deutscher Sprache

Zielsetzung: Die Erhebung von möglichen Determinanten von Antibiotika-Verschreibung durch Ärzte sowie Einflussfaktoren auf deren Einstellungen zu Maßnahmen, die das Problem der Antibiotika-Resistenzen verringern.

Methodik: Eine sowohl quantitative als auch qualitative Forschungsmethodik bestehend aus: Fokusgruppendiskussionen geführt mit ambulanten und stationären Ärzten in der Berliner Region; eine repräsentative Querschnittsbefragung unter ambulanten und stationären Ärzten in Deutschland; und eine repräsentative online-Querschnittsbefragung der Bevölkerung in Deutschland.

Ergebnisse: Die qualitative Untersuchung zeigte, dass es den ambulanten Ärzten eher wichtig war, korrekt diagnostizieren und verschreiben zu können. Zudem waren für sie der von den Patienten ausgehende Druck sowie die *Noncompliance* von Relevanz. Stationäre Ärzte betonten besonders Aspekte der Ausbreitung multiresistenter Erreger, Hygiene-assoziierte Herausforderungen sowie die Problematik eingeschränkter Beratungszeiten mit Patienten. In einer logistischen Regressionsanalyse der Ergebnisse der Querschnittsbefragung unter Ärzten zeigten sich folgende Faktoren als statistisch signifikant: Status als Krankenhausarzt, männlich, Alter 50-59 Jahre, Praxis in den neuen Bundesländern. Aus der Befragung der Bevölkerung lieferte eine bivariate Analyse Hinweise, dass das Vorherrschen der selbstberichteten Erwartung, für eine Erkältung ein Antibiotika verschrieben zu bekommen, in Bezug zum Bildungsgrad steht. Die Mehrheit der Befragten zeigte aber ein Grundverständnis dafür, dass Antibiotika effektiv sind gegen Bakterien aber nicht Viren, und wusste von Antibiotikaresistenz.

Schlussfolgerungen: Die Bevölkerung scheint gut über Antibiotika informiert zu sein. Damit legen die Forschungsergebnisse nahe, dass die Einflussfaktoren auf Antibiotikaverschreibung und -resistenz eher im Bereich der Ärzte und der Qualität der klinischen Behandlung liegen. Während die bisherige Forschung in anderen Ländern sich auf die Verbesserung der Patienten-Aufklärung oder die Sensibilisierung der Bevölkerung konzentriert, könnte für Deutschland ein Fokus auf Einflussfaktoren auf die Entscheidungen von Ärzten, Antibiotika zu verschreiben, sowie die Qualität ihrer Verschreibung und deren Auswirkungen auf Antibiotikaresistenz angezeigt sein.

1.2. Introduction

1.2.1. Background

Antimicrobial-resistant bacteria have remained a persistent challenge in medicine. Resistant and multi-resistant pathogens can prevent the successful uptake of antimicrobial therapy, leading to potentially fatal consequences for some patients. Antimicrobial resistance can often be traced to clinical causes, like too much and uncontrolled use and applications for the wrong conditions (e.g. viral infections on which antimicrobials have no affect). Physicians make clinical assessments, consider appropriate therapies, and decide whether or not, and when to prescribe antimicrobials. The challenges for prescribing are diverse, but it comes down to the following key problems: 1. The physician must weigh many decisions in a risk assessment that could have potential consequences that are harmful to the patient, and 2. Prescribing is difficult, since once a viral diagnosis is ruled out, it is often unclear what the underlying bacteria is and whether it will be susceptible to the antimicrobial of choice.[1]

From an epidemiological perspective, the problem is of as much concern in the community care setting as it is in the hospital care setting, where resistant pathogens can cause severe outbreaks that are more difficult to bring under control, posing a threat to the larger population. Combating antimicrobial resistance is now widely considered a priority area in public health, and several surveillance campaigns across Europe [2,3,4,5,6,7] and within Germany[8,9,10] have been developed to follow antimicrobial consumption and usage patterns to present evolving resistance trends over time and comparisons between countries and regions.

In 2007 the Robert Koch Institute (RKI), the federal public health institution in Germany, initiated research to investigate factors to be considered when designing a national strategy to prevent rising antimicrobial resistance. Efforts to combat resistance in other countries have focused on limiting antimicrobial use and boosting public awareness and patient education about appropriate use. Many factors affect the issue differentially, from patient demand and expectations, to geographic region, individual infectious diseases treated and the availability of clinical support and diagnostics.[11, 12, 13] The aim of the research initiated by RKI was thus to uncover the most relevant factors of influence for antibiotic prescribing and antimicrobial resistance in Germany.

1.2.2. Research goals and scientific questions

The goal of the doctoral research was to provide scientific evidence on factors of physicians' prescribing of antimicrobials, and also factors that influence physicians' opinions about interventions to ameliorate the problem of resistance in Germany. The scientific questions addressed in the publications representing this research are as follows:

1. What are physicians' perceptions of antimicrobial resistance, about their role as prescribers of antibiotics and their opinions about potential interventions? [Publication 1, page 19]
2. Which physician-related characteristics are associated with the decision to prescribe antibiotics? [Publication 2, page 30]
3. What are the expectations of the general population in Germany concerning prescriptions of antibiotics? [Publication 3, page 40]

1.3. Methods

1.3.1. Study design

This doctoral research is submitted as a cumulative dissertation (*Publikationspromotion*), which comprised various published studies (Section 3). The studies cover a triangulated, mixed-methods, quantitative-qualitative research approach as follows:

1.3.2. Qualitative study of physicians (focus group discussions)

A literature review was first conducted to identify previous research on factors of influence for antimicrobial prescribing. The results were used to develop a socio-behavioural model for antimicrobial prescribing in hospital and outpatient care that links various factors (demographics, diagnosis patterns, physician knowledge and expectations, and opinions) to antimicrobial prescribing. A resulting conceptual structure served as the basis for this study component. [Publication 1, page 19] We conducted four focus group sessions of 5-7 physicians each: 1. Outpatient setting, less experience; 2. Outpatient setting, more experience; and 3. Hospital setting, less experience; 4. Hospital setting, more experience. [Table 1 and 2, Publication 1, page 19]

A semi-quantitative approach was used to analyse the results of the focus group discussions. Discussions were transcribed into text, which was labelled based on emerging themes related to antimicrobial prescribing and resistance. The transcripts were subjected to constant comparative analysis—an iterative method of content analysis where a category is assigned to textual statements and constantly revised during categorisation. The method is popularly used to allow so called "emergent codes" to be applied at all points in the analysis.[14,15] The frequencies of codes were used as a measure of significance of emergent themes. All data making and content analyses were done using TAMS Analyzer for Macintosh OS X (version 4.13), an open-source, computer-assisted qualitative research tool.[16] We extracted relevant quotes from each focus group interview in order to further establish an in-depth look at each topic. Video footage was also later reviewed in greater detail to provide further descriptive evidence on focus group dynamics between the participating physicians.

1.3.3. Representative, national cross-sectional study of physicians (physician survey)

A clinical-style survey instrument was developed from the aforementioned focus group study. A pilot test was conducted among scientists at the Robert Koch Institute (RKI), and a short article describing the study was placed prominently in the German medical journal, *Deutsche Ärzteblatt*.[17]

Proportionate stratified sampling methods were applied based on the known registries of all practicing physicians provided by each state medical association in Germany. We first allocated physicians to one of four regions: *north, south, west and east.* We included both hospital and outpatient care physicians belonging to practice specialties that are known to more frequently prescribe antimicrobials: general practice (GP), internal medicine, surgery, gynaecology, paediatrics, ear, nose and throat specialists (ENT), dermatologists and urologists. We excluded any respondent who reported not belonging to our targeted specialties or not prescribing antimicrobials within the last year. We treated the total population of registered physicians in each of four regions separately in two groups based on care setting. Using STATA, we calculated a final sample size of 10,600 physicians.

The survey collected information on factors of influence (demographics, diagnosis patterns, physician knowledge and expectations, and opinions) related to physicians' antimicrobial prescribing. It also collected information about the frequency within the last year of deciding to begin any antimicrobial therapy in their field of practice; and opinions about statements on experience with antimicrobials and surveillance of antimicrobial resistance in their practice. Data was stored in a Structured Query Language-database (SQL) and exported to STATA software (Release 10, 2007) for descriptive and regression analyses.

Multiple statistical analyses were done using STATA. In a first analysis, we calculated frequencies for demographic information, and for consideration to prescribe daily and weekly. The frequency of prescribing was explored in greater detail by identifying statistically significant factors for "considering daily to make a decision to prescribe antimicrobials," using the likelihood-ratio test (80% CI; $P \leq 0.20$). Because we explored 74 potential influence factors, we did not define a model a-priori. Instead, we first conducted univariate regression analyses on all factors and included only those found to be significant into a stepwise multivariate regression model to test predictors for "deciding daily to start an antimicrobial therapy in a patient" (95% CI; $P \leq 0.05$). We performed a second analysis, in which we took predictors found to be significant in our regression model and performed chi-square or Fisher's exact tests (95% CI; $P \leq 0.05$), using demographic variables to assess significance levels. [Publication 2, page 30]

1.3.4. A representative cross-sectional study of the general population (public survey)

A representative sample of 1778 persons was drawn by a large market research company. An online survey instrument covered expectations concerning prescriptions of antibiotics and

on knowledge and attitudes regarding effectiveness and use of antibiotics in the context of upper respiratory tract infections only. We calculated relative frequencies of answers (total and stratified by demographic characteristics). The chi-square, t-test or Cuzick test for trend was applied to test for significant differences between subgroups. Logistic regression analysis was used to find determinants (demographics, knowledge, attitudes) for expecting a prescription of antibiotics when suffering from a common cold. Variables associated with these expectations in the bivariate analysis (80% CI; $P \leq 0.20$) were entered into the model and retained if the adjusted p value was less than 0.10 (stepwise backward elimination). We used logistic regression analysis to identify determinants for expecting a prescription of antibiotics when suffering from a common cold. [Publication 3, page 40]

1.4. Results

1.4.1. Qualitative study of physicians (focus group discussions)

Overall, results showed that physicians exhibited differential interest in topics related to antibiotic prescribing and antibiotic resistance. This was related to various factors, including to whether a physician practices in either outpatient or hospital care. Major factors associated with prescribing antimicrobials in the outpatient care setting were being able to diagnose and prescribe more precisely, patient demand and noncompliance and the perception of the influence of the pharmaceutical industry. For hospital care physicians, major factors associated with prescribing antimicrobials were first and foremost interested in challenges with hygiene and the prevalence of multi-resistant pathogens, the often limited time to consult patients and their use of clinical guidelines.

Table 3 [Publication 1, page 19] provides a detailed overview of the highest incident emergent codes and code categories from constant comparison analysis for all focus groups combined. Emergent codes served as a way to begin further critical analysis of the main insights reflected in this group of physicians, which we stratified by each focus group. Additional in depth-responses on several determinants of antibiotic prescribing and antibiotic resistance that cut across all focus groups, such as non-patient factors, hygiene, the pharmaceutical industry and antibiotic costs are presented. [Table 4, Publication 1, page 19] The topic of UTIs arose as a specific concern driving resistance – one that was also shown as statistically significant in the physician survey. (Results 1.4.2)

1.4.2. Representative, national cross-sectional study of physicians (physician survey)

A total of 3,492 physicians answered the questionnaire (response rate = 33%; 3,492/10,600). We verified the representativeness of our responders by performing a non-response bias analysis using the complete medical registries of all German physicians and the normal distribution of registered physicians in Germany. We compared individual response rates, and performed chi-square goodness of fit tests, which showed no significant differences between the observed proportions from our responders and from proportions in the original representative sample. Overall differences in response rates were low; but paediatricians—while only 6.7% of the original sample population—were overrepresented by over 10% compared to the originally calculated proportionate stratified sample. Responders from states in the former East Germany, though 22% of the original sample, were also overrepresented by approximately 10%.

Among respondents, 90% indicated that they decide to start an antimicrobial therapy in a patient at least weekly, and 66% reported that they decide daily. Overall, respondents indicated the most frequent diagnoses to be for uncomplicated urinary tract infections (UTI). For deciding to start an antimicrobial therapy in a patient, statistically significant factors that are not directly related to the physician-patient relationship were: status as a hospital physician [odds ratio (OR) 1.29 (95% confidence interval (CI) 1.00-1.68)], male physician [OR 1.81 (95% CI 1.42-2.31)], being age 50-59 [OR 1.56 (95% CI 1.10-2.21)], and practicing in states in the former East Germany [OR 1.60 (95% CI 1.15-2.21)]. Each specialist was significantly less likely to decide to start a course of antimicrobial therapy than ENTs and urologists. Other predictors were agreeing to prescribe to be on the safe side [OR 1.34 (95% CI 1.03-1.76)], believing that the quality of prescribing practice improves after receiving continuing education from pharmaceutical companies [OR 1.43 (95% CI 1.11-1.84)] and having experience with failed therapies for resistant pathogens [OR 2.42 (95% CI 1.83-3.19)].

Results from our frequency analyses show that the older a physician is, the less they were inclined to prescribe to be on the safe side. Outpatient care physicians indicated that they prescribe to be on the safe side more so than hospital physicians. [Table 5, Publication 2, page 30] Hospital physicians in the sample were more likely to find it either important or very important that they receive data on regional antimicrobial resistance and appropriate feedback for prescribing. Hospital physicians also found it either important or very important that they receive intervention that would provide them with consulting, audits and feedback on their own antimicrobials use. Physicians in each practice setting equally found important or very important increased antimicrobial surveillance activities.

1.4.3. Representative cross-sectional study of the general population (public survey)

In total, 1076 persons aged 15-78 years participated (response: 61%). Compared to Germany's general population, there was no considerable difference in our sample concerning the distribution of persons through Germany's sixteen states and different sizes of places of residence but higher age groups, women and persons with a lower level of education were underrepresented.

The majority of participants knew that "antibiotics are effective against bacteria" (72.3%) but not viruses (52.6%), knew about antibiotics resistance (89.0%) and acknowledged it to be a problem in German hospitals (72.6%). Of all participants in the public survey, 445/1076

(41.4%) knew that antibiotics are not effective against the common cold or flu, and 91.8% reported using antibiotics “only if absolutely necessary”. A prescription of antibiotics was expected by 113/1076 (10.5%) for the common cold and by 92.7% for pneumonia. Among those expecting a prescription, 70.8% reported to trust their physician when he/she deems a prescription unnecessary, further 7.1% would be unsatisfied but accept the decision.

For the common cold, the prevalence of self-reported expectations depended on level of education in the bivariate analysis (19.9%, 12.0%, and 7.6% for low, medium and high level of education, respectively). No other significant associations with demographic data (age group, sex, places of residence, migration background, household income, type of health insurance, occupational group) were seen after stratification by level of education.

In the multivariate analysis, the strongest predictors for expecting an antibiotic prescription for the common cold were the following opinions: “common cold or flu can effectively be treated with antibiotics” [prevalence: 37.6% OR 9.60 (95%CI 3.8-24.3)] and “antibiotics should be taken when having a sore throat to prevent more serious illness.” [prevalence 8.6%, OR 7.6 (95%CI 3.9-14.5)].

1.5. Discussion

The research featured a methodology that incorporated both qualitative and quantitative approaches to uncover socio-behavioural determinants of antimicrobial prescribing and resistance. Qualitative focus group discussions were used to identify issues of antibiotics and resistance as expressed by physicians themselves. The use of a nationally representative survey of hospital and outpatient physicians provided statistically significant evidence that can be generalized for Germany. For the general population, an additional survey provided a clearer picture of patient expectations for antibiotics in Germany when faced with a cold or flu, which offers important findings for an issue that still causes confusion for patients and physicians alike. The combined results provide a basis to explain the influences on antibiotic prescribing and resistance, the possible impact on medical activities, as well as physicians' and patients' attitudes towards possible intervention measures in Germany.

Overuse of antibiotics remains a driving force for antibiotic resistance. This is consistent with other findings that antimicrobials belong to the 10 most prescribed groups of drugs in Germany. [18, 19] Yet, on the whole, overall consumption of antimicrobials within Germany is low in comparison to other European countries.[20,21, 22] Historically, patient expectations, misuse and noncompliance have been shown to influence resistance.[23, 24, 25] But our study on the general population indicated that patients in Germany are generally well informed about some of the most common diagnoses, only a minority expect antibiotics often and most trust their physician's decision to prescribe or not. [Publication 3, page 40] Overall, this research suggested that physicians are aware of this, and that they believe factors not associated with patients to also have a large influence on their prescribing and the resistance situation.

The physician survey identified that status as a hospital physician was a statistically significant factor for deciding to start antimicrobial therapy on a patient, and significantly more hospital than outpatient physicians in our sample thought their practice has an influence on antimicrobial resistance. [Publication 2, page 30] This could be attributed to the fact that hospital physicians attend more acute cases than their outpatient care counterparts. The increasing prevalence of multi-resistant pathogens is of particular concern in hospital, where more patients with complex indications are often seen during shorter consult times.[19] [Publication 2, page 30] Hospital care physicians are aware of the problem of antimicrobial resistance, but they demonstrate varying knowledge about antimicrobials.[12, 26, 27] In both the physician survey and focus group discussions, hospital care physicians found surveillance

data on regional resistance, improved hygiene, better access to microbiologists and more consulting, audits and feedback to be important influence factors.

Aside from patient diagnosis, symptoms and discomfort, factors that influence the decision whether or not physicians decide to prescribe antimicrobials in outpatient care can range from perceived patient-expectations to whether or not the physician feels well informed or has access to guidelines.[28, 29] Physicians are more likely to prescribe to be on the safe side in outpatient care settings, where they often rely on common empirical therapy, where it may be harder to ask colleagues for advice or where setting-specific guidelines are less prevalent.[30] Unlike physicians in the hospital setting, where there is access to an array of in-house developed guidelines,[31] physicians in the outpatient care setting indicated that guidelines are differentially updated. Physicians increasingly encounter difficult diagnoses that are complicated by resistance patterns. The increasing prevalence of antibiotic resistant uncomplicated urinary tract infections (UTI) exemplifies this problem. Newly resistant pathogens leading to UTIs, such as *Escherichia coli*, *Proteus mirabilis* and *Klebsiella pneumoniae*, complicate antibiotic treatment choices, and first line treatments that must be adapted to patterns often may be an influence factor for resistance, but problems associated with various diagnoses lead to differential prescribing outcomes among hospital and outpatient care physicians.[32, 33] [Publications 1 and 4, pages 19 and 48]

Physicians who belong to certain practice specialties that are known to prescribe more antimicrobials, like urology, ear-nose-throat and paediatrics might share similar attitudes on use and resistance. Children receive more daily doses of antimicrobials than adults in Germany,[34, 35] and paediatricians were also more likely to respond to our physician survey, a self-selection that may arise out of more concern about antimicrobials use and resistance in their practice.

Cultural variance related to differences in age and in region of practice may also affect attitudes when it comes to factors of influence for prescribing antimicrobials. A factor associated with older respondents in the physician survey was finding formal education to be important. For younger physicians, the associated factor was finding consulting, audits and feedback, as well as hands-on, on-the-job training to be important. Preferences for continuing medical education on antibiotic resistance may be another influence factor that is experienced differentially by physicians belonging to different age groups.[36]

The physician survey indicated that physicians in the former East Germany are more likely to decide daily to start an antimicrobial therapy in a patient, even though most evidence shows that significantly less antimicrobials are consumed in the eastern parts of Germany.[18] While we are unsure of the direct cause, physicians practicing in the former East Germany may demonstrate a protective factor for prescribing that predisposes them to more prudent use of antimicrobials: being aware of rational prescribing and associated surveillance efforts.[37] They are more aware, but use less. Awareness is an important factor that has been illustrated in recent studies that aim to look at the motivations for prescribing or not.[29, 32, 38]

Though the exact influence remains unclear, this research indicates that, despite some caution about the persistence of the pharmaceutical industry, it enjoys a largely positive presence among outpatient care physicians in Germany. [Publication 1, page 19]

1.6. Conclusions

Despite some indication of disparity based on level of education and the persistent challenge of clinical noncompliance, patients appear to be well informed about antibiotics and they trust their physicians' decisions. While previous research in other countries has focused on improving patient care or increasing public awareness in order to improve antibiotic resistance, this research suggests that the situation in Germany requires a different focus – on physician-oriented factors. While previous research in other countries has focused on improving patient education or increasing public awareness, this research suggests that a focus on factors influencing physicians' decisions to prescribe antibiotics, the quality of their antibiotic prescribing and their realisation of antibiotic resistance could be more appropriate for Germany.

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2. Declaration of personal contribution to the publications

Velasco E, Ziegelmann A, Eckmanns T, Krause G. Eliciting views on antibiotic prescribing and resistance from hospital and outpatient care physicians in Berlin, Germany: a qualitative research study. *BMJ Open* 2012. doi: 10.1136/bmjopen-2011-000398.

Contribution to the publication: 60%

- Conception of the study design and article
- Completed literature reviews and selection of relevant research articles and information to collect and create qualitative data
- Leadership of data preparation, data analysis and quality checks
- Created concept for data presentation (tables and graphic)
- Interpretation of results in collaboration with co-authors
- Drafted the manuscript and completed revisions in collaboration with co-authors

Velasco E, Espelage W, Noll I, Ziegelmann A, Krause G, Eckmanns T. A national cross-sectional study on socio-behavioural factors that influence physicians' decisions to begin antimicrobial therapy. *Infection* 2011 Aug; 39(4): 289-97. Epub 2011: Jun 30.

Contribution to the publication: 75%

- Conception of the study design
- Completed literature reviews and selection of relevant research articles and information to collect and create cross-sectional survey data
- Sole responsibility for all data preparation, data analysis and quality checks
- Created concept for data presentation (tables and graphic)
- Interpretation of results and presentation (tables and graphic) in collaboration with co-authors
- Drafted the manuscript and completed revisions in collaboration with co-authors

Faber M, Heckenbach K, **Velasco E**, Eckmanns T. Antibiotics for the common cold. What are the expectations of Germany's general population? *Euro Surveill.* 2010 Sep 2;15(35). pii: 19655.

Contribution to the publication: 20%

- Interpretation of results in collaboration with co-authors
- Completed revisions in collaboration with first author

Schweickert B, Noll I, Feig M, Claus H, Krause G, **Velasco E**, Eckmanns T. MRSA-surveillance in Germany: data from the Antibiotic Resistance Surveillance System (ARS) and the mandatory surveillance of MRSA in blood. *Eur J Clin Microbiol Infect Dis* 2011 Dec 31.

Contribution to the publication: 10%

- Interpretation of results in collaboration with co-authors
- Completed revisions in collaboration with first author

Date Signature

3. Original work, published for the doctorate

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Eliciting views on antibiotic prescribing and resistance among hospital and outpatient care physicians in Berlin, Germany: results of a qualitative study

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Data access All authors had full access to all the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. The authors assure that all authors included on this paper fulfil the criteria of authorship. In addition, we assure that there is no one else who fulfils the criteria but has not been included as an author.

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ABSTRACT

Objective: To better understand physicians' views on factors of influence for the prescribing of antibiotics and on antibiotic resistance in the Berlin region, Germany.

Design: Qualitative study with focus groups.

Setting: Outpatient care and hospital care practice in the Berlin region, Germany.

Participants: 7 General practitioners, two urologists, one paediatrician from outpatient care and eight internists, two paediatricians, two ear, nose and throat specialists and two urologists from hospital care.

Results: Physicians showed differential interest in topics related to antibiotic prescribing and antibiotic resistance. Outpatient care physicians were interested in topics around their own prescribing, such as being able to diagnose and prescribe precisely, and topics about patient demand and non-compliance. Hospital care physicians were interested in hygiene challenges, limited consult time and multi-resistant pathogens.

Conclusions: Physicians considered the development of resistance to be more in the domain of clinical treatment than that of the patient. Major challenges related to antibiotic resistance for this group of physicians are access to and clarity of treatment recommendations, implementation of hygienic measures, as well as increased outsourcing of laboratory services. Results raise questions about whether meeting physicians' expectations should be a focus when developing intervention that aims to influence antibiotic resistance in this and other areas of Germany.

ARTICLE SUMMARY

Article focus

- Overuse of antibiotics across many specialities and in some of the most common diagnoses remains a driving force for antibiotic resistance.
- While much attention has focused on limiting use and addressing clinical concerns like improving point-of-care diagnostic tests, prior literature has largely left out the consideration of socio-behavioural factors that influence physicians' decisions to prescribe antibiotics.
- Focus group discussions were used to show physicians' views on factors that influence their prescribing of antibiotics and antibiotic resistance.

Key messages

- Berlin area physicians are interested in receiving help to make informed decisions on the appropriate measures for mitigating patient discomfort and risk.
- In this group, well-informed prescribing practice appears to be influenced by non-patient-oriented factors that are both structural (eg, overcrowding in hospitals) as well as non-structural in nature (eg, access to feedback from microbiologists or time allowed for patient consult).
- Physicians desire intervention activities that address their own skills, like assessment of patient needs, time management for consult and navigation of pharmaceutical consulting.

Strengths and limitations of this study

- Modern methodologies for focus group data analysis, including a comprehensive plan for ensuring validity in data-making and data reduction were used in the study.
- Presented study methodology allows replication by other research groups.
- The number of participating physicians was limited; however, they were recruited from diverse backgrounds with respect to age, sex, size of practice, care setting and number of years in practice.

INTRODUCTION

Antimicrobial use has remained a major concern in medicine and epidemiology over the last years. Surveillance initiatives have been implemented in order to monitor antimicrobial consumption and usage patterns and resistance data for selected pathogens in order to present trends over time and comparisons between countries and regions.[1 2] The results provide evidence that antimicrobial resistance has continued to

persist across all specialities and in some of the most common diagnoses. Efforts to combat resistance have focused on limiting antimicrobial use, providing patient education about appropriate use and developing better point-of-care tests. There are also other socio-behavioural factors of antibiotic use and resistance, which should also be a core part of campaigns that attempt to monitor resistance in both hospital and outpatient care settings.[3–6]

In 2007, the Robert Koch Institute, the federal public health institution in Germany, initiated a number of different studies to investigate factors to be considered when designing a national strategy to prevent the spread of antimicrobial resistance. The aim was to use different methodological approaches to describe factors of influence for antibiotic prescribing and antibiotic resistance in Germany. As a preliminary study, a literature review was conducted to identify previous work on factors of influence for antimicrobial prescribing and to guide further research. The aim of this study using focus groups was to elicit physicians' views on factors that influence their prescribing of antibiotics and antibiotic resistance. As a mixed-methods research approach can help to explore research findings in greater detail,[7 8] a further aim was to generate exploratory information as the basis to develop a nationally representative cross-sectional survey on the same topic, conducted in 2008.[9]

METHODS

Focus group conceptual structure

A conceptual structure was created to serve as the basis for the focus group discussions. Five conceptual areas encompassed influence factors for the following: (1) general impressions of antibiotic resistance (eg, How is the development of antibiotic-resistance perceived? How generally relevant is the topic of rising antibiotic resistance?), (2) prescribing in outpatient care (eg, Which influence factors are relevant for prescribing antibiotics? Which factors are relevant for prescribing in outpatient care?), (3) Prescribing in hospital care (eg, Which influence factors are relevant for prescribing antibiotics? Which factors are relevant for prescribing in hospital care?), (4) Information and knowledge about antibiotic treatment (eg, what are sources of knowledge about antibiotics? How are physicians generally informed about medical areas related to antibiotics?) and (5) Impressions on problematic areas of concern (eg, How are problem areas in antibiotics and antibiotic resistance addressed? Which factors should be addressed by potential interventions to combat antibiotic resistance?).

Focus group participants

We recruited physicians from the Berlin region, Germany, with diverse backgrounds with respect to age, sex, specialty, practice type, the number of patients seen quarterly and location of practice. Physicians were offered monetary compensation of €200. We conducted four focus group sessions of five to seven physicians each: (1) outpatient setting, less experience; (2) outpatient setting, more experience and (3) hospital setting, less experience; (4) hospital setting, more experience (tables 1 and 2). A qualitative research agency drew the sample of physicians, and moderated and transcribed all focus group discussion sessions.[10]

Interview methodology

The focus groups were held between 4 and 6 December 2007 in Berlin and were facilitated in four sessions of 2 h each. All sessions were held separately and conducted by a trained moderator. Moderators used a semistructured framework, a method which has been found to enable participants to share and confirm their views, or construct new views based on interactions in a peer

Table 1 Focus group participant details: outpatient care

Focus group	Participant ID	Sex	Age	Specialty	Practice type	Years in practice	Location	Patients per quarter
1	1	Female	46	Paediatrics	Group	12	East	~900
	2	Female	35	General practitioner	Group	5	West	~200
	3	Male	48	General practitioner	Single	9	East	~1000
	4	Male	54	Urology	Single	11	West	~1200
	5	Male	40	General practitioner	Group	10	West	~800
2	1	Male	62	General practitioner	Group	25	West	~2000
	2	Female	53	Urology	Group	15	West	~800–900
	3	Female	55	General practitioner	Group	16	East	~150
	4	Female	42	General practitioner	Group	15	East	~180
	5	Male	57	General practitioner	Single	15	East	~800–900

Table 2 Focus group participant details: hospital care

Focus group	Participant ID	Sex	Age	Specialty/position	Beds (n)	Years in practice	Location	Patients per quarter
3	1	Female	40	Paediatrics/consultant	1200	8	West	~600–700
	2	Male	34	Internal/resident	620	5	West	~400
	3	Male	43	Internal/consultant	538	9	East	~500
	4	Male	42	Internal/resident	626	4	West	~300–400
	5	Female	34	Internal/resident	363	3.5	West	~400
	6	Male	30	ENT/resident	1200	3	East	~350
	7	Male	43	Urology/consultant	220	12	West	~500
4	1	Male	51	Internal/consultant	538	16	West	~500
	2	Female	40	Internal/consultant	1200	14	East	~1000
	3	Male	56	Internal/consultant	276	31	West	~500
	4	Male	48	ENT/consultant	1000	10	West	~1400
	5	Male	41	Internal/consultant	1200	10	West	~1000
	6	Male	44	Paediatrics/consultant	542	16	West	~300–500
	7	Female	63	Urology/consultant	1200	37	East	~4000

context, and build knowledge together.[11] For each discussion, the framework was based on the topics from the five conceptual areas but allowed participants in each group to explore topics differentially. Interviews were transcribed in real time, and each session was video recorded for later in-depth review. To check for accuracy of the text in each transcription, six random samples of 5–7 min were chosen from the video footage of each focus group and then checked against the corresponding text. Video footage was also later reviewed in greater detail in order to explore group dynamics.

Data analysis

A semiquantitative approach was used to analyse the results of the focus group discussions. This first consisted of examining the data based on the five conceptual areas and the respective study questions. We were able to draw key relationships between conceptual areas, so called 'code-categories' under which were assigned individual topics arising from the content of the focus group discussions. The resulting framework was used to guide all subsequent data-making and analysis tasks.

A preanalysis code map was developed from the framework, showing a hierarchy from the five code categories to each topic and subtopic. (online supplementary data table) The code map was then created, to be used later for constant comparative analysis—an iterative method of content analysis where each category is searched and constantly revised, popularly used to allow so called 'emergent codes' to be applied at all points in the analysis.[12 13] Before beginning the analysis, we validated our code map by performing a code check, looking for duplicates and comparing codes to the topics within the aforementioned framework. Revisions were made and a resulting code map was used for subsequent data-making (figure 1).

All text from transcripts was subjected to constant comparative analysis, and the frequencies of codes were used as a measure of significance. All data-making and content analyses were done using TAMS Analyser for Macintosh OS X (version 4.13), an open-source computer-assisted qualitative research tool.[14]

We extracted quotes from all transcripts when a specific topic involved multiple sentences, when the comment provided was observed to be provocative and/or when it generated lively discussion among more than two individuals. We extracted relevant quotes from each focus group interview in order to further establish an in-depth look at each topic. An epidemiologist who is fluent in German and a native English speaker completed German–English translations. We assigned each participant a quote identifier based on the focus group in which they belonged and their demographic information (shown in tables 1 and 2). The identifier is presented in the Results section as a two numbers (focus group number—ID number).

RESULTS

Table 3 provides a detailed overview of the highest incident emergent codes and code categories from constant comparison analysis for all focus groups combined. Emergent codes served as a way to begin further critical analysis of the main insights reflected in this group of physicians, which we present in the following segments stratified by each focus group. Additional in-depth responses on several determinants of antibiotic prescribing and antibiotic resistance that cut across all focus groups, such as non-patient factors, hygiene, the pharmaceutical industry and antibiotic costs are also presented (table 4).

Focus group 1: outpatient care physicians with fewer years of practice experience

Physicians focused on themes that are related to prescribing in the outpatient care setting (*frequency*: 146). Discussion focused on general impressions of rising resistance (115), sources of information on

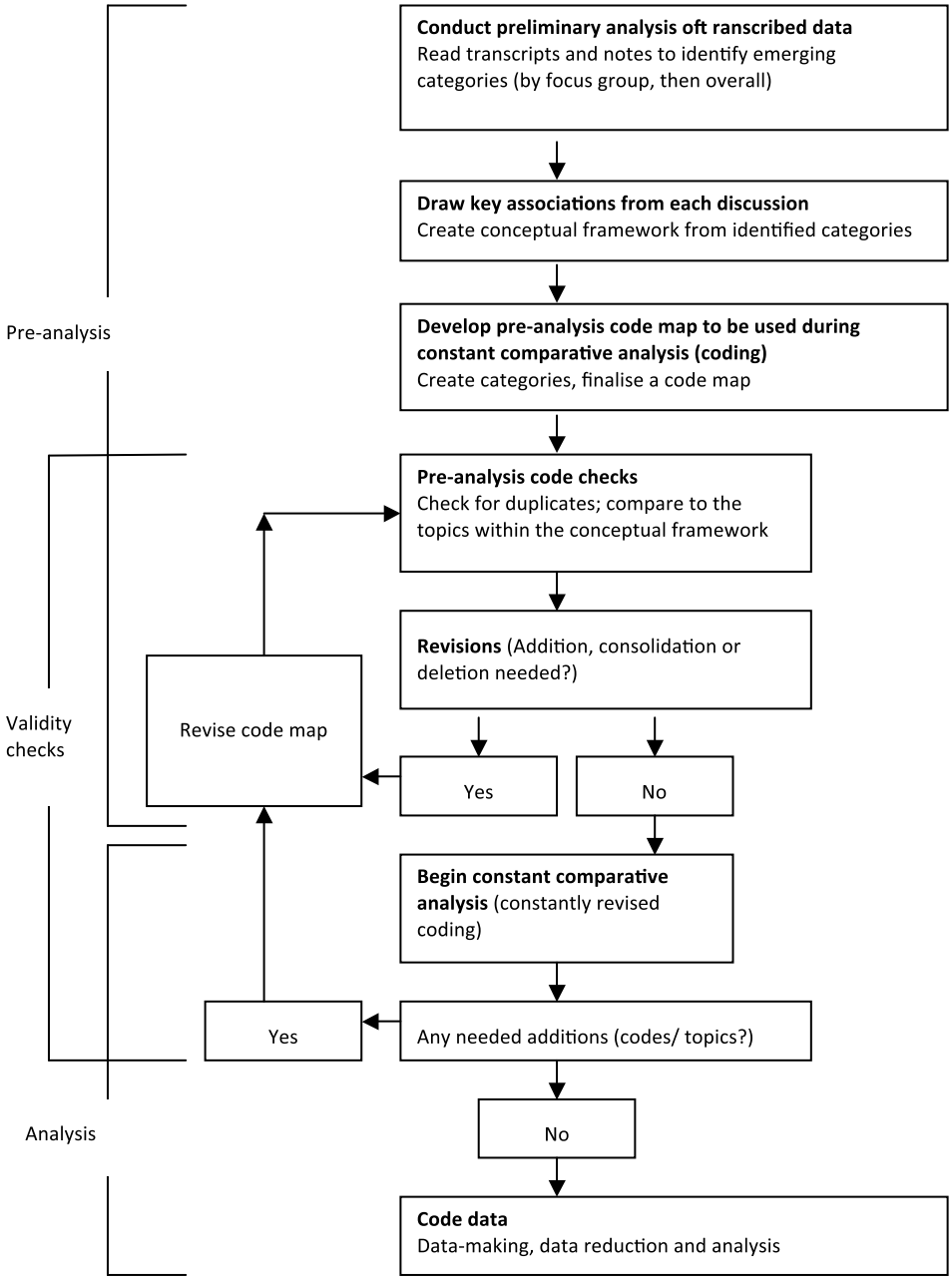

Figure 1 Plan for data-making, data reduction and analysis.

antibiotics (64) and physician-oriented interventions (17). They expressed concern about difficulties dealing with complicated patient histories (12), patient compliance (9) and patient perception of treatment (8). Participants frequently discussed the development of antibiotic substances (11) and about responsibility in their own practice (4). Participants also focused on specific diagnoses that are perceived to be driving resistance, with major discussion occurring around the topic of uncomplicated urinary tract infections (UTIs) (5). Cost was also discussed as a factor influencing antimicrobial prescribing, specifically, the effects of health regulations on the accessibility of medications.

Conferences (9) and pharmaceutical companies (4) were discussed most when it came to common sources of information on antibiotics. A large amount of time was spent discussing pharmaceutical representatives, whom participants found to be persistent and aggressive:

> "They come often and always have antibiotics on hand. You get a bag of them every day. And high doses of drugs. It all stacks up in the cabinet. For me there are 4 to 5 representatives each day" (*Participant* 1–3: tables 1 and 2).

> "I notice that they approach me, too. But I do not accept them all. I would estimate that there are about 5–7 every day, and they do bring whole bags full (of giveaways)." (1-2)

> "The representatives come into my practice. And you do listen to them. You even take the information they offer, even if with a critical eye. But you do learn something as well." (1-5)

Table 3 Top five highest incident emergent codes and categories from constant comparison analysis (all groups combined; total codes n=1035)

Code-category	Five most frequent code topics	Frequency
General impressions on rising resistance		401
	Patient non-compliance	15
	Antibiotics development	13
	Hospital-specific issues, eg, hygiene, laboratories	11
	Antibiotic dosing	10
	Urinary tract infections	10
Outpatient-specific influences on prescribing		251
	Patient history	18
	Patient demand	18
	Physician experience	14
	Patient self-education	11
	Patient compliance	11
Sources of information on antibiotics		234
	Practice guidelines	10
	Continuing medical education	8
	Specialty journals	8
	Internet	8
	Quality of conferences	7
Physician-oriented interventions		84
	Surveillance	9
	Laboratory feedback	7
	Information on local resistance situation	7
	Hospital	4
	Hygiene	4
Hospital-specific influences on prescribing		65
	Up-to-date internal guidelines	4
	Laboratory/microbiologists exchange	4
	Specificity of internal guidelines	4
	Experience with infectious diseases	3
	Problematic diagnoses	3

> "The pharmaceutical industry is very aggressive." (1-3)

> "For urology I cannot remember in recent months receiving a visit on this issue. But that is certainly very different than in the primary care sector." (1-4)

There was no single participant dominating the discussion, and comments readily came from each; however, the paediatrician did mention that there is less pharmaceutical presence in her practice. This group most frequently saw feedback on their resistance situation and cooperation with laboratories (5) as ways to address the problem of rising antibiotic resistance.

Focus group 2: outpatient care physicians with more years of practice experience

Unlike the first outpatient group, this group veered away from a dominant focus on outpatient-specific topics and discussed most frequently those topics within the category of general impressions on rising resistance (150). The group was also concerned with having adequate sources of information on antibiotics (126), outpatient-specific influences on prescribing (105) and other physician-oriented interventions (28).

Physicians frequently discussed the effectiveness of antibiotic substances and drug development (6). As in the previous outpatient care group, cost was seen as a factor of influence on antimicrobial prescribing. In this group, participants agreed that they are less wary of the cost of antibiotics because the nature of predominantly short treatments makes it affordable compared with longer-term treatments, like those prescribed for high blood pressure. This group also talked about social factors that may be driving the situation, like increased foreign travel (6), over-the-counter availability of drugs abroad (4) and migration (4). The topic of UTIs arose as a specific concern driving resistance.

This group discussed the category of hospital-specific influences on prescribing (8), like multi-resistant pathogens (6). The topic of hospital hygiene arose in each of the two outpatient focus groups, which agreed that antibiotic resistance was largely a problem of the hospital setting, "In hospitals resistance plays a bigger role because there one finds hospital specific germs." (1−4) Incidentally, the topic of resistance was often quickly averted when brought up, instead being commented as a problem specific to the hospital care setting:

Table 4 Selected in-depth responses from focus group discussions

Category	Quotes
Hygiene	Have a look what is happening in the operating rooms. Time for cleaning up is getting shorter every day. Before we had around 100 beds in a normal ward, now its cut down to 40–50 beds, but we are still treating as many patients as they were 10 years ago. Get in and get out. A bed is never empty. And I have my doubts as to whether these disinfectant wipes are an ideal solution. I think the time pressure is there and already a problem. (4-7). The highest infection rates are in intensive care units, but it is certainly always clean. In the OR smears are made at regular intervals. I think this is still the safest. Unless they have very septic cases and those cases where the pus runs from the abdomen. On the hospital ward that is where I think it is not very hygienic. In intensive care so they can get almost all antibiotics, and that is where the transmission of nosocomial infections at the highest, and where there are more immunosuppressed patients. (4-1) From our end in the clinic, it is the hospital-acquired infections that are acquired in the hospital and last for 2–3 days, possibly even later. They are often preventable through effective hygiene measures and can be much better than they would be with antibiotics. (4-3)
Laboratory and resistance data	Our laboratory is outsourced, but once we had also invited a microbiologist to provide training, and he made a comparison of the germs in hospital with those generally presented in the other hospitals. It was good information. (4-3) Many things change as well over the years, procedures change. Too often, there is a deficit in this information. (4-3) Guidelines vary and are specific to each hospital. We have a very committed leader in this area, who takes a lot of trouble to log and actually follow information from each recommending commission, which often revise their information. We have a commission that discusses and revises information which is then put online for reference and so that all staff can gain insight. We also have disclosure on which department prescribe show much and how expensive it is. This is useful in individual cases, and to follow the development of resistance and hygiene. So, it is all kept very transparent. (3-3)
Pharmaceutical industry	Pharmaceutical advertising is very important. There are at least two variants. There are those that visually present with more or less exciting images and colours. And these accordingly make you curious so that you might read some fine print and look more closely to find out what the stuff is. I find this to be the more pleasant variant. Because you immediately recognize it as such and may or may have to look closer. Medical journals on the other hand may contain interesting content, but there it's hard for you to determine what the content is. Is it a short conference report? Is it a topic that interests me? A professor on a topic I am interested in? Is it really is objective? And that's the annoying thing, because then it is difficult to distinguish. (3-7) They also know as who is receptive. Then they just leave the bag there and just want a signature and a seal. Much is given at each and every day, many just want a short word. I've been doing this at the reception counter. Very rarely do I give them an appointment. For me there are 4 to 5 representatives each day. (1-1) Pharmaceutical representatives give me bags full (of antibiotic samples)! (1-1) In the moment when the pressure in the outpatient setting is relatively high, even from marketing, then certain things are pushed. Something has changed in prescribing in the outpatient setting; this is what will notice from practice in the clinic. Prescribing practice, what is underlying it, this is often not transparent. (4-6)
Cost	Until three years ago, I was still prescribing Cotrim in the urology setting. It was still cheap, at about €3. Back then, gyrase-inhibitors had a starting price of about €12. Then health regulations led to compulsory levies, which introduced a fixed fee of €8. Since then, Cotrim increased from €3 to €12—the same as the gyrase-inhibitors. Until then, the threshold for prescribing gyrase-inhibitors for UTIs was relatively high, and I prefered to prescribe Cotrim. But since the price drop, I prescribe Cotrim less and more quickly look to prescribing gyrase-inhibitors. (1-4) Yes, I would think that costs are different for antibiotics than for other treatments. Simply because the duration of (antibiotic) treatment is short. When I prescribe an antibiotic, and even if it is an expensive one, then I know it takes 10 days or 2 weeks, so the treatment is limited from the outset. When I prescribe someone a drug for high blood pressure, which in the quarter costs 150€, then I am affected each quarter. Thus, the antibiotics—treatment when it comes to price, is certainly not as problematic as the high blood pressure treatment or other therapies I am prescribing. (2-1)
Other non-patient determinants	We have experienced changes: like short stays in hospital. Hospitals are simply the most dangerous places for patients. The sooner the patient is out of the hospital the better. The more minimal invasive interventions are, the lower the probability for wound infections. (3-7) Recent medical interventions are indeed more complex and daring; cardio-haematology, oncology. We are also treating acute myelogenous leukaemia, which accounts for a lot of consumption of antibiotics. You also can't ignore that in certain areas treatments are simply too complex. The result is also that inappropriate consumption is higher. This is the price for medical progress. Bypasses for 80 year olds, do an ACVB and then they still catch pneumonia, lie for weeks in intensive care. This is the reality now. We believe in all sorts of advances; but we'll see the resulting effects soon enough. (4-1)

> "I think the development of resistance is more the domain of clinical treatment and not the patient." (2-5)
>
> "Exactly." (2-3)
>
> "Yeah, especially in intensive care." (2-4)

Participants discussed most frequently that patient demand (11) is a major driver for prescribing in the outpatient setting, followed by doctor experience (9) and specific diagnoses (6). The role of the patient, including patient non-compliance and self-medication, also emerged. Physicians discussed two types of patients: those concerned with getting an antibiotic and those concerned with avoiding what they think is harmful:

> "Pressure from patients is not insignificant…the worst are the mothers where the children are really very sick and the mothers say: I don't want any chemotherapy. The lymph nodes are thick with pus, almost hanging out, and then the mother says no, no antibiotics for us. That's bad." (2-1)

Physicians in this group valued information that is concise and available to them in a way that complements their work without taking up too much time:

> "Is there a new antibiotic? What is the resistance situation? Which organisms are being affected? What are the indications, what are the side effects? The interactions with other drugs? Are there alternatives? If this information could be given to us in a short and sweet way, then we would be happy. Something like this is not currently available to us." (2-1)

Participants in focus group 2 found treatment guidelines (8), pharmaceutical-based materials (5) and conferences (4) to be main sources of information on antibiotics. This group found information from pharmaceuticals to be concise and readily available:

> "There's been a big change from the expertise of representatives who come in. These are all clinicians and they do not give a bad impression at all. They bring me a lot of information although, of course, you have to make sense of it all. But I do admit that I feel as though I am getting good consulting. Because I don't have the time to do my own research nor to sit down on the Internet every evening. I am very grateful for the very specific information they offer me." (2-2)

As evidenced above, most other comments about the pharmaceutical industry also remained positive in this group. There were comments that patient outreach is not needed in Germany (2), and this focused largely on the belief that the patient population is well informed and, if at all, opposed to antibiotics, sometimes opting for alternative therapies.

They discussed the need to have more access to surveillance of their local resistance situation: "I think we need what there was in (the former) East Germany, a short, independent information sheet that shows the current epidemiological situation in the country or the region where I live." (2-5) The group seems to have agreed since they mostly discussed interest the following intervention options: increased surveillance (9), including information on their regional resistance situation (5), constraints on their patient consult time (3) and consulting (2).

Focus group 3: hospital physicians with fewer years of experience

Physicians most frequently discussed their general impressions on rising resistance (70), hospital-specific influences on prescribing (40), sources of information on antibiotics (15) and physician-oriented interventions (12). Patient non-compliance (8), correct prescribing and antibiotic dosing (5), hospital care (3) and hygiene (3) were the most frequently addressed topics.

The internet (3), pharmaceutical advertising (2) and conferences (2) were listed as the most frequent physician-oriented interventions mentioned by this group. The visibility of pharmaceutical advertising was also discussed, and this group found it easy to access and useful for learning. Participants were in agreement about how pharmaceutical advertising is more accessible than other traditional forms of information dissemination, such as medical journals.

Participants overwhelmingly stayed with the topic of hospital workplace concerns, like hygiene (7) and time for patient consult (4) as the most needed intervention to combat resistance in their setting. They discussed non-structural demands on the hospital, such as advances in treatment possibilities for more complex indications, which might necessitate more antibiotics consumption in the hospital setting, which may in turn itself be a driver for resistance.

The hospital itself was viewed as having structural aspects that might contribute to increased antibiotic use and resistance (7). One such aspect, maintaining hygiene, was a perceived danger of interrelated issues of increased patient load (3), patient–patient contact (1) and infectiousness (2). One physician noted that the pressure to treat more patients has led to a related need for a faster consult time, which may put strain on the thoroughness of hospital hygiene measures. Hospital physicians also pointed out that they would prefer to pursue intervention through new programmes for hygiene, although they also recognise it to be a challenging method of improvement. Participants also discussed the benefits of transparency and feedback on antibiotic consumption, costs and trends in the hospital setting.

Focus group 4: hospital physicians with more years of experience

Participants discussed most frequently about their general impressions on rising resistance (66), followed by hospital-specific influences on prescribing (29), sources of information on antibiotics (27) and physician-oriented interventions (21). The most frequent topics

brought up by this group were diagnostics possibilities (5), patient history/epidemiology (increasingly acute cases in care) (4) and social factors like ageing (4). When talking about the influence on prescribing in hospital care, the following topics were most frequent: indication and disease (2), risk assessment in acute cases (2), specificity of guidelines (2) and time constraints during patient consultation (2). This group of physicians made relatively long commentaries at a higher level of detail than was observed in participants during the other focus group sessions. The group spoke at such detail about non-patient factors of antibiotic prescribing and antibiotic resistance, including patient stays in non-intensive wards of hospitals as increasing risk and minimised hygiene routines in hospital due to increased patient intake.

Physicians frequently consulted specialty journals (9), clinical handbooks (3) and the internet (3) as sources of information on antibiotics. Discussion points on hospital feedback on the resistance situation (5) and continuing education (2), especially in the area of hygiene (2) and infectious diseases (2) emerged most frequently in discussions regarding intervention for antibiotic resistance.

Collegial exchange with microbiologists/laboratories (5) emerged as the most frequent topic under the category of hospital-specific influences on prescribing, something that was also observed in focus group 3. Physicians in this group spoke about opportunities to closely collaborate with laboratories and microbiologists, which they saw as helpful in navigating antibiotic treatments:

> The microbiologists that we have are top. We mostly get reports via the doctor calling us before anything is published on our intranet. It is then also discussed, what underlying disease does the patient have, which antibiotic was given, and the provisional findings will be communicated first. Short, quick ways; you have to communicate well with people. (4-1)

The topic of outsourcing of laboratories arose throughout this discussion. Physicians perceived this as prohibiting close communication and producing too much bureaucracy, "For us, it is unfortunately not the case. The laboratory has been outsourced. A service provider is at the other end of town; they can't communicate with us much." (4-5) Other emerging themes were the role of the hospital pharmacist in influencing prescribing choices (4), followed by how often and appropriately internal/hospital antibiotic treatment guidelines are updated (4) and subsequently by multi-resistant pathogens (3).

DISCUSSION

Past research has underlined the importance of patient-oriented factors of influence for prescribing, and the focus has primarily been on patient demand and non-compliance.[15–17] This is consistent with the historical data on the subject showing that antibiotics are more likely to be prescribed when the patient expects them and that they may be even more likely to be prescribed when the doctor may perceive that the patient wants a prescription, when in fact the demands of patient are unclear.[18] Responses from physicians in these groups indicated something different: an overwhelming interest in non-patient factors that influence antibiotic prescribing and resistance.

A major topic in both groups of participating physicians from outpatient care was their experience of increasingly difficult diagnoses that are complicated by resistance patterns. A good example is the increasing prevalence of antibiotic-resistant UTIs. Many participants are involved in the management of UTIs, a finding supported by the cross-sectional study component of this research (survey).[9] Indeed, the trends in many European studies of antimicrobial resistance show UTIs to be accountable for a large amount of antibiotics consumption.[1] Many of the common pathogens leading to UTIs, such as *Escherichia coli*, *Proteus mirabilis* and *Klebsiella pneumoniae*, are increasingly becoming resistant to standard treatments, which affects antibiotic treatment choices[19 20]; however, physicians showed differential interest topics related to their antibiotics prescribing and resistance, based on their care setting.

Outpatient care physicians found resistance primarily a problem of the hospital care setting, related to the presence of different multi-resistant pathogens and challenges with hygiene. This was also a major topic discussed by hospital physicians. The increasing prevalence of multiresistant pathogens is of particular concern, especially given the views that the hospital ward is increasingly faced with more patients at any single time and that patients—many of whom are carrying more complex indications—are also seen during shorter consult times.[21 22] In fact, data from the survey identified that status as a hospital physician was a predictor for deciding to start antimicrobial therapy on a patient.[9] This could be attributed to the fact that, generally, hospital physicians attend more acute cases than their outpatient care counterparts.

Hospital care physicians were accustomed to regular and easy collaboration with microbiologists when discussing indications and possibilities for therapy. This was also found in the study sample of the survey, which showed that hospital physicians found it either important or very important that they receive data on regional antimicrobial resistance and appropriate feedback for prescribing.[9] This opinion was also shared in the focus group discussions among physicians, who want laboratories to provide feedback on the resistance situation for their hospitals. Participants expressed frustration and concern around outsourcing of laboratories. It was a matter of having less contact with helpful microbiologists and described a need: that even in a hospital setting with outsourced laboratory services, it is important to offer chances to dialogue with microbiologists. While

this finding does seem to match the views shown by the national survey, more qualitative research on other groups could help to show whether or not there is a need to enhance access to their local resistance situation in the hospital setting in other areas of Germany.

There was differential discussion about treatment guidelines, which may also be an important influence factor on physician prescribing practice. Participants from the outpatient care setting found clinical recommendations to be difficult to access quickly and use. For the hospital setting, this was significantly different. There was more discussion about whether guidelines are up to date and about their relevance, specificity and availability in clinical practice. There are many guidelines with varying degrees of quality available to physicians. Hospital care physicians have an array of inhouse developed guidelines, differentially taking into account local resistance data.[23] But, as also evidenced by other studies, availability is differential and may warrant addressing this separately for each practice setting.[4 24]

The pharmaceutical industry was often a major topic of discussion, but it remains unclear how large the current influence of the pharmaceutical industry is on physicians in Germany. Physicians indicated that the pharmaceutical industry plays a large role in outpatient care practice. Visits to doctors' offices by the industry and free samples of antibiotics are ubiquitous; their informational materials are generally perceived as attractive. This may have to do with the fact that information from the industry presents information in ways that are more convenient than scientific literature on the same topics.[25] These important findings about the presence of the pharmaceutical industry also showed up among the participants of the survey: despite some caution about the persistence of the industry, most outpatient care physicians welcome their assistance and view them as another resource among many other sources of information on antibiotics. Results from these focus groups and the survey indicate that the pharmaceutical industry has a large presence among physicians in Germany.

CONCLUSIONS

Our findings suggest that physicians in Berlin are interested in topics around their own prescribing, like physician sensitivity to patient need, time management for patient consult, access to guidelines and their perception of the pharmaceutical industry. These non-patient determinants, when coupled with intervention ideas for the hospital care setting (eg, improving hygiene measures, easing diagnostics and cooperation with laboratories), are different from factors of antibiotic prescribing and resistance that have been previously observed in similar contexts: they are physician oriented. Furthermore, focus group discussions provided more details about some of the determinants that were also found relevant by physicians participating in the survey component of this research. Together, these study components raise questions about whether targeting other physicians may be a better approach for intervention that aims to influence antibiotic resistance in this and other areas of Germany. This could be a remarkable finding for Germany: in other countries, intervention to reduce antimicrobial resistance has often been targeted at the patient directly, but more qualitative research and similar focus groups in other areas of Germany could show whether or not this trend is nationally relevant.

STUDY LIMITATIONS

Participants were all from the Berlin region and included physicians from diverse backgrounds with respect to age, sex, size of practice, care setting and number of years in practice. Additionally, we recruited physicians from the former east and west areas of Berlin and from outer city areas to reflect greater diversity specific to this setting in Germany. We used a relatively small, purposive convenience sample of physicians from specialties known to prescribe most often; thus, there may have been some degree of representational bias. Although many findings from the focus groups align well with findings from our nationally representative survey, which was conducted to further explore influence factors on this topic, other focus groups in other regions or large metropolitan areas in Germany could strengthen these results and are critical before determining national relevance.

The same moderator conducted all focus group discussions based on a conceptual framework drawn before the sessions, so there could be issues of reliability due to its application to four different groups of physicians. But, since we intended for the moderator to allow for participants in each group to explore topics differentially around this framework, so that any new or previously unanticipated topics could come up, we believe that this provided a strength that is unique to this qualitative approach.

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Patient consent Obtained.

Ethics approval This study was approved by the institutional commission for data protection of the Robert Koch Institute. All participants gave informed consent before taking part in focus group discussions.

Contributors EV completed all analysis and drafted the manuscript. AZ, TE and GK conceived of the study and obtained funding. All authors contributed to the study design, the carrying out of the study and provided critical feedback to the manuscript.

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A national cross-sectional study on socio-behavioural factors that influence physicians' decisions to begin antimicrobial therapy

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Abstract

Purpose: Current efforts to prevent antimicrobial resistance include limiting antimicrobial use, providing education about appropriate use, and developing better point of care tests, but what do physicians actually think of rational prescribing and potential interventions? We tried to ascertain which factors can influence a physician's decision to start an antimicrobial therapy in a patient, and their opinions on measures to promote rational prescribing.

Methods: We conducted a nationwide, cross-sectional survey of 10,600 physicians from medical registries of all known board-certified physicians in Germany.

Results: Among respondents (n = 3,492; response rate = 33%, detailed non-response bias analysis included), 90% indicated that they decide to start an antimicrobial therapy in a patient at least weekly, and 66% reported that they decide daily. We identified correlates for deciding to start an antimicrobial therapy in a patient. Predictors were status as a hospital physician [odds ratio (OR) 1.29 (95% confidence interval (CI) 1.00-1.68)], male physician [OR 1.81 (95% CI 1.42-2.31)], being age 50-59 [OR 1.56 (95% CI 1.10-2.21)], and practicing in states in the former East Germany [OR 1.60 (95% CI 1.15-2.21)]. Each specialist was significantly less likely to decide to start a course of antimicrobial therapy than ENTs and urologists. Other predictors were agreeing to prescribe to be on the safe side [OR 1.34 (95% CI 1.03-1.76)], believing that the quality of prescribing practice improves after receiving continuing education from pharmaceutical companies [OR 1.43 (95% CI 1.11-1.84)] and having experience with failed therapies for resistant pathogens [OR 2.42 (95% CI 1.83-3.19)].

Conclusions: Physicians in our sample decide to start an antimicrobial therapy in a patient, and they value interventions to support prudent use, such as continuing education, practice guidelines and implementation of surveillance measures. Socio-behavioural factors, regional variation, gender and age merit further research to promote rational antimicrobial prescribing and explore related influence factors.

Keywords: antimicrobials, prescribing, surveillance, cross-sectional studies, interventions

Running Title: Socio-behavioural factors and antimicrobial prescribing in Germany

Introduction

Combating antimicrobial resistance is now widely considered a priority area in public health, and several surveillance campaigns across Europe have been developed in response.[1,2] Antimicrobial surveillance systems collect information on evolving resistance trends, and follow antimicrobial consumption and usage patterns.[3-6] Germany takes part in European Surveillance of Antimicrobial Consumption (ESAC),[7] and the European Antimicrobial Resistance Surveillance System (EARSS)[8] that collects validated resistance data for selected pathogens in order to present trends over time and comparisons between countries and regions in Europe. The Antimicrobial Resistance Surveillance (ARS) project,[9] which monitors antimicrobial consumption and captures resistance data from routine diagnostics of the whole spectrum of clinically relevant pathogens in both hospitals and from the outpatient care setting, serves to complement European resistance surveillance. ESAC, EARSS and ARS serve as core components of the German Antibiotic Resistance Strategy (DART).[10]

Looking to socio-behavioural factors of physicians' antimicrobial use and acceptance of interventions for resistance has newly been recognized as an area of interest in campaigns to monitor resistance.[11,12, 13] Physicians make clinical assessments, consider appropriate therapies, and decide whether or not and when to prescribe antimicrobials. Such decisions are facilitated by what physicians know and what attitudes they have toward treatment. However, little evidence exists on these factors. We aimed to measure factors of influence among board-certified physicians in Germany when they consider making a decision to prescribe antimicrobials. A further objective was to ascertain physicians' opinions on potential measures that can promote rational use of antimicrobials.

Methods

Development of the survey

During 2007 we conducted an extensive literature review to identify previous work on socio-behavioural factors of influence for antimicrobial prescribing. Additionally, a series of representative focus groups involving German hospital and outpatient care physicians was conducted to provide qualitative insight into general concerns about antimicrobials resistance. The results were used to develop a socio-behavioural model for antimicrobial prescribing in hospital and outpatient care physicians that links various factors (demographics, diagnosis patterns, physician knowledge and expectations, and opinions) to consideration of antimicrobial prescribing. A survey instrument was developed from the model.

The survey instrument solicited the following information in sections: 1. Demographic information on age, gender, practice speciality and regional population size, using multiple choice questions; 2. The frequency within the last year of deciding to start an antimicrobial therapy in a patient, and of any provision of consultations to peers, using multiple choice questions; 3. Information about the most frequent diagnosis within the last year in any of our surveyed fields of clinical practice, whether or not an empirical therapy was chosen for that diagnosis, whether or not a diagnostic test was implemented, and whether there was change of antimicrobial therapy after a first line therapy failed, using Likert scales; 4. Opinions about statements on experience with antimicrobials, antimicrobial resistance surveillance and limited use in clinic or practice, using 'agree/disagree statements;' and, 5. Evaluation of potential interventions to aide in improved antimicrobial usage, using a Likert scale. A copy of the survey instrument can be viewed on the ARS homepage.[14] The results of section 3 do not fall within the context of this analysis and will be presented in another paper. We used two survey forms, one for hospital and one for outpatient care setting. Each form contained 45 questions, and in sections 2, 3, and 4 the language was adjusted to be appropriate for hospital and outpatient care physicians where appropriate. The survey form was designed to have a clear and clinically-friendly format, and a pilot test was conducted among scientists at the Robert Koch Institute (RKI). A short article describing the study was placed prominently in the German Medical Journal.[15]

Criteria for inclusion and exclusion

Recruiting was done from a complete population of known board-certified physicians registered in each of 17 state medical associations in Germany. We included both hospital and outpatient care physicians belonging to practice specialties that are known to more frequently prescribe antimicrobials: general practice (GP), internal medicine, surgery, gynaecology, paediatrics, ear, nose and throat specialists (ENT), dermatologists and urologists. We excluded any respondent who reported not belonging to our targeted specialties or not prescribing antimicrobials within the last year.

Sample estimation

This is study is based on the known population of registered physicians in Germany, and proportionate stratified sampling methods were applied. Using known registries of all practicing physicians provided by each state medical association in Germany, we first allocated physicians to one of four regions: *north: Schleswig Holstein, Lower Saxony, Hamburg, Bremen; south: Baden-Wuerttemberg, Bavaria; west: North Rhein, Westphalia-Lippe, Hessen, Rheinland-Palatinate, Saarland*; and *east: Mecklenburg-Lower Pomerania,*

Brandenburg, Berlin, Saxony-Anhalt, Saxony, Thuringia. We treated the total population of registered physicians in each of four regions separately in two groups based on care setting. For the hospital setting the size of the smallest region was north at 7,231 physicians, and the largest region was west with 17,720 physicians. For the outpatient care setting, the smallest was also north at 14,669 physicians and the largest was west at 32,031 physicians.

We then used STATA software (Release 10, 2007) to calculate a sample estimate for each group. We set our level of significance at .10, and estimated that approximately 544 physicians per group (each care setting, per 4 regions) were needed in order to allow for a statistically significant comparison of proportions at 45-55%. We thus calculated a needed number of 1,360 survey forms per care setting and region in order to receive an expected response rate of 40%. The response rate was based on previous experience with similar response rates at the RKI, where difficulties reaching physicians are a result of strict data protection laws preventing direct follow-up with non-responders. The methods enabled us to predict a sample size of 10,998. Due to political and administrative barriers, the medical association of Saxony chose not to participate, our sample was reduced by 398 to 10,600, and our stratification was adjusted accordingly.

Ethics and informed consent

Due to the nature of data protection laws for the federal collection and distribution of medical data within Germany, anonymous survey forms were sent first to state medical associations and then distributed to physicians based on our stratified sample. Anonymous postage-paid return-envelopes were provided. The commissioner for data protection at the RKI approved the survey instrument and the study methods.

Statistical Analysis

A two-part analysis was conducted using STATA. In a first analysis, we calculated relative frequencies for demographic information, and for consideration to prescribe daily and weekly. The frequency of prescribing was explored in greater detail by identifying significant factors related to “considering daily to make a decision to prescribe antimicrobials,” using the likelihood-ratio test (80% CI; $P \leq 0.20$). Because we explored 74 potential influence factors, we did not define a model a-priori. Instead, we first conducted univariate analyses on all factors and included only those found to be significant into a stepwise multivariate regression model to test predictors for "deciding daily to start an antimicrobial therapy in a patient” (95% CI; $P \leq 0.05$). We chose to use a combined reference group of ENT and urologists, because they are known to be frequent prescribers and resulted in significantly higher odds ratios in univariate analyses. Once we found predictors to be significant, we

performed a second analysis, in which we took predictors found to be significant in our regression model and performed chi-squared or Fisher's exact tests (95% CI; P≤0.05), using demographic variables to assess significance levels.

Results

A total of 3,492 physicians answered the questionnaire (response rate = 33%; 3,492/10,600). Despite our response rate, we were able to verify the representativeness of our responders by performing a non-response bias analysis using the complete medical registries of all German physicians and the normal distribution of registered physicians in Germany. We compared individual response rates, and performed chi-square goodness of fit tests, which showed no significant differences between the observed proportions from our responders and from proportions in the original representative sample. Overall differences in response rates were low; but paediatricians—while only 6.7% of the original sample population—were overrepresented by over 10%. Responders from states in the former East Germany, though 22% of the original sample, also deviated from the general response rate by approximately 10%. Please see table 1 for results of a non-response bias analysis.

Table 2 shows the demographic characteristics of our sample of physicians. Nearly 90% of all responding physicians reported that they decided at least weekly to start an antimicrobial therapy in a patient, and 66% considered at least daily. Physicians in hospital settings (69%) responded that they decided daily to start an antimicrobial therapy in a patient more frequently than those in outpatient care settings (63%)(*P<0.004*). The number of physicians who decided daily to start an antimicrobial therapy in a patient was highest compared to all other specialities among urologists, ENT, and paediatricians (92%, 90%, and 72% respectively; *P<0.001*). Gender showed to be consistently significant across many variables in our study: of all surveyed male physicians, 72% decided daily to make a decision to start an antimicrobial therapy in a patient vs. 56% of all female physicians. Two intriguing findings from the multivariate regression were that each specialty was considerably less associated with deciding to start an antimicrobial therapy in a patient than ENTs and urologists. Physicians from states in the former East Germany were also more likely to start an antibiotic therapy in a patient daily [OR 1.60 (95% CI 1.15-2.21)], and thinking own work has an influence on antimicrobial resistance [OR 1.55 (95% CI 1.23-1.95)]. Table 3 shows complete results from the multivariate regression.

Physicians responded to selected questions about their attitudes toward prescribing antimicrobials. (Selected results are shown in table 4) Results from our frequency analyses show that the older a physician is, the less they were inclined to prescribe to be on the safe side. More outpatient care physicians indicated that they prescribe to be on the safe side than did those in hospitals. Dermatologists in our sample were almost two times more likely to indicate that they prescribe to be on the safe side than other specialties (45% vs. 24% combined

average). More hospital (70%) than outpatient care physicians (52%) agreed that "their own work has an influence on antimicrobial resistance," and older physicians were less likely to agree with the statement. More male (86%) than female physicians (76%) indicated that they "have experience with failed therapies for resistant pathogens." Among all physicians, the older they were the more they agreed that "the quality of prescribing practice improves after receiving continuing education from pharmaceutical companies." More descriptive results can be viewed on the ARS project homepage.[14]

Table 5 shows complete respondent evaluations of potential interventions for improving antimicrobials use to minimise resistance. More hospital physicians in our sample found it either important or very important that they receive data on regional antimicrobial resistance and appropriate feedback for prescribing. More hospital physicians also found either important or very important an intervention providing consulting audits and feedback on their antimicrobials use. Physicians in each practice setting equally found important or very important increased antimicrobial surveillance activities, the availability of federal guidelines for making diagnoses and prescribing antimicrobials, and improvement of educational opportunities at university.

Discussion

Physicians responding to our study decide often to start an antimicrobial therapy in a patient. This is consistent with other findings that antimicrobials belong to the 10 most prescribed groups of drugs in Germany. There is no other medicine that is used so widely across all physician specialties.[16,17] Yet, on the whole, overall consumption of antimicrobials within Germany is low in comparison to other European countries.[18] This is true for both outpatient care and hospital settings. As an example, Germany's outpatient antimicrobial consumption in 2007 was in the lower third of the range observed across Europe, at 13-15 defined daily doses (DDD) per 1000 inhabitants. In higher range countries of Greece, Cyprus, France, Italy and Belgium the amount is more than double.[16] Additionally, other studies on European national consumption in hospital care show that consumption in Germany is only 5-10% of total exposure to antimicrobials in many European countries, even if some regional differences within Germany indicate that there is room to improve.[19,20]

Looking more closely at differences between hospital and outpatient care physicians may inform about the influences behind their motivations for antimicrobial prescribing. Over 80% of all antimicrobial prescriptions occur in the outpatient care setting. Actual data shows that in 2007, 56% of all antimicrobial prescriptions were made in outpatient care settings by GPs.[16]

Given that outpatient care physicians prescribe more, why did significantly more hospital than outpatient physicians in our sample think their practice has an influence on antimicrobial resistance? It might

have to do with differing cultures within each practice setting. For example, hospitals tend toward increased use of surveillance data, enabling physicians to have greater knowledge of the relationship between their practice and the resistance situation. Thinking that own work has an influence on resistance—also found in our analysis to be a significant factor for more frequent decisions to start an antibiotic therapy in a patient —might be because physicians who prescribe more may also have increased awareness about antimicrobial use. Collection of regional antimicrobial resistance data with appropriate feedback and within practice settings could be a step to create a culture of utilising resistance data for increased awareness and responsible antimicrobial use.

The nature of antimicrobial prescribing and diagnoses in hospital versus outpatient care settings may also play a role. Hospital physicians attend fewer but more acute cases than their outpatient care counterparts. Hospital settings also require special attention because of the increasing prevalence of antimicrobial resistant emerging infections like MRSA.[21] As such, physicians in hospital settings have been shown to be aware of the problem of antimicrobial resistance, but they demonstrate varying knowledge about antimicrobials.[22,12] Physician attitudes about antimicrobials use and resistance might thus vary based on available knowledge.[23] Provision of 'antimicrobial experts' in hospitals who give on-site consulting, audits and feedback may offer knowledge and help to regulate variation in antimicrobials use.

Physicians are more likely to prescribe to be on the safe side in outpatient care settings, where it may be harder to ask colleagues for advice, or where setting-specific guidelines are less prevalent. That antimicrobials may be prescribed out of insecurity is also shown indirectly: younger physicians in this sample consider prescribing most often, indicating that more years of experience could increase security with antimicrobials use. Physicians' characteristics, like age, should be accounted for in intervention options, such as ways to offer information and guidance, and university education in the area of antimicrobials.

Physicians who belong to certain practice specialties that are known to prescribe more antimicrobials, like urology, ENT and paediatrics might share similar attitudes on use and resistance. A look at paediatric diagnoses in Germany shows that between 1998 and 2005 children received 20-50% more daily doses of antimicrobials than adults.[24,25] Paediatricians were also more likely to respond to our survey, a self-selection that may arise out of more concern about antimicrobials use and resistance in their practice. In general, ENT and urinary tract diagnoses are often treated in outpatient care settings and often rely on common empirical therapies.[26] While this may be due to the nature of diagnoses, physicians in some specialties might be more autonomous, and individual professional characteristics may carry influence over deciding when and how to prescribe.[27] Interventions such as improved guidelines, continuing education and audits should be tailored to

account for professional characteristics that clearly relate to the specific nature of diagnoses and clinical situations in certain specialities.

Our sample indicated that physicians in the former East Germany are more likely to decide daily to start an antimicrobial therapy in a patient, even though most evidence shows that significantly less antimicrobials are consumed in the eastern parts of Germany. [16] This may be true and also consistent: physicians practicing in the former East Germany might exhibit cultural differences that predispose them to more rational use of antimicrobials. This trend has been explored before. It has been speculated that poor economic status and bureaucratic barriers in the former socialist East Germany presented constraints to prescribing. Others refer to a general scepticism among East Germans, although this has been discounted due to different patterns of consumption in other countries within the former Eastern Bloc. A third explanation argues that a strong state interest in public health - including authoritative surveillance- made physicians cautious to the use of clinical guidelines, versions of which were still in use until after the fall of the Berlin wall.[28] Physicians practicing in the former East Germany may demonstrate a protective factor for prescribing: being aware of rational prescribing and associated surveillance efforts. Awareness is an important factor that has been illustrated in recent studies which aim to look at the motivations for prescribing.[23,26,29]

Cultural variance related to differences in region of practice, gender and age may also affect attitudes when it comes to factors of influence for prescribing antimicrobials. Related intervention requirements vary accordingly. For example, different age groups that indicate varied preferences for information gathering and continuing education about antimicrobials resistance have unique needs. In a comparison of two surveys about influences on prescribing practice within the same generation of GPs in the former East Germany in 1979 and again in the same reunited states in 1998, Sturm found that among older physicians, university education had become more important.[30] Indeed, formal education was also valued by older respondents in our survey, and younger physicians more often valued consulting, audits and feedback, indicating that hands-on, on-the-job training may better suit their needs. Current efforts in Germany to develop training possibilities on infectious disease, antimicrobial use and resistance at university can be enhanced by taking into account different needs in regions and among age groups.

Limitations

Given the response rate of 33%, we recognize that potential biases may be caused by self-selection based on respondent interest in the subject and by non-response. Survey responses are also from self-report, and

respondents may be prone to social desirability about their experience with antimicrobials. We also recognize that patient and public opinion is important and have thus collaborated in other studies of patients in Germany.[31]

We considered measures to increase the response rate considering the associated potential for bias. It was not possible, however, to survey non-responders due to the nature of data protection laws for federal data collection within Germany, which meant that contact details for follow up with non-responders were unavailable. Additionally, the use of institutional infrastructure at the state medical associations to process more than one mailing of questionnaires was not possible. We also considered the use of proxy respondents to compare our results, but we believe that proxies are unsuitable for measuring knowledge, attitudes or opinions. Since our survey was not based on a random sample but was stratified to account for the complete population of known registered physicians in Germany by performing a non response bias analysis, we were able to show representativeness of our stratified sample using a non-response bias analysis, already presented in the results section of this paper. The results of the non-response bias analysis show a close match of proportions and distribution of physician attributes, thus helping to rule out the chance for selection bias. We are thus confident about our ability to make comparisons among the following 5 attributes in our results: hospital and outpatient setting, practice specialty, region, age and sex. We have also included in our multivariate regression 4 factors related to attitudes, since these were repeatedly found to be significant in our univariate analyses. As these were not included in the non-response bias analysis, these factors may be interpreted as a property of our group of responders only, not necessarily all physicians.

Conclusions

The prioritisation of interventions to support physicians in rational antimicrobial prescribing and to minimise resistance is a major task facing public health authorities. Working to promote rational antimicrobials use, to provide education for physicians and patients on rational use, and to develop better point of care tests remain important measures for intervention. This work can be complemented by measures that address socio-behavioural factors affecting behaviour for prescribing—such as awareness of practice impact and availability of individualised clinical support—and the acceptance of related interventions.[13, 32] The results of this national cross-sectional survey provide much needed quantitative research evidence on socio-behavioural factors, like attitudes and individual professional characteristics that affect antimicrobial use and potential interventions for resistance.

Competing Interests

The author(s) declare that they have no competing interests.

Author Contributions

EV carried out the data management, data analysis, and drafted the manuscript. WE, MF, IN and AR participated in the coordination of the study and in the analysis design. GK and TE participated in the coordination of the study, contributed to data interpretation and revised the manuscript critically. All authors read and approved the final manuscript.

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Tables

Table 1: Results of a non-response bias analysis, comparing percent of the original sample from known medical registries to actual received response rates, with respective results of chi-square goodness of fit analyses (*P≤0.05)*. The overall response rate in the study was 33% (N=3492/10600).

Physicians characteristics	% of Sample	Response Rate, %	Chi-square goodness of fit
Hospital	50.0	31.8	*P=0.03*
Outpatient care	50.0	34.1	
GP	30.2	30.2	*P=0.00*
Internal	20.1	28.1	
Surgery	22.4	30.7	
Ear Nose Throat	3.6	33.3	
Paediatrics	6.7	47.6	
Urology	3.6	35.6	
Gynaecology	10.4	34.1	
Dermatology	3.0	33.5	
State in the Former East Germany	22.3	23.2	*P=0.04*
State in the Former West Germany	77.7	35.7	

Table 2: Demographic and professional characteristics of responding physicians

		Total		Hospital physicians		Outpatient care physicians	
Variable		n	%	n	%	n	%
		3492	100	1,682	48	1,810	52
Sex	Male	2222	65	1093	66	1129	64
	Female	1200	35	564	34	636	36
Age group	< 30	15	0.4	13	1	2	0.1
	30-39	583	17	459	28	124	7
	40-49	1396	40	723	43	673	37
	50-59	1049	39	385	23	664	37
	> 59	422	12	89	5	333	19
Population of site of hospital/practice	< 19,999	900	26	333	20	567	32
	20,000-100,000	1,142	33	583	35	559	32
	>100,000	1,377	40	642	36	735	45
Specialty	GPs	914	27	183	11	731	41
	Internal	652	19	416	25	236	13
	Surgery	729	21	536	32	193	11
	Ear Nose Throat	126	4	48	3	78	4
	Paediatrics	340	10	163	10	177	10
	Urology	134	4	76	5	58	3
	Gynaecology	377	11	154	9	223	13
	Dermatology	111	3	34	2	77	4
	No specialty	51	1	42	3	9	0.5
Region	State in the Former East Germany	548	16	257	15	291	16
	State in the Former West Germany	2944	84	1425	85	1519	84

Table 3: Multivariate analysis: factors associated with deciding daily to start antimicrobial therapy in a patient

Variables: Demographics, determinants ($p \leq 0.05$)	Odds Ratio	95% CI
Setting: Hospital	1.29	1.00 - 1.68
Sex: Male	1.81	1.42 - 2.31
Practice specialty: ENT and Urologist (reference)		
GP	0.14	0.07 - 0.29
Internist	0.14	0.10 - 0.31
Surgeon	0.15	0.09 0.28
Paediatrician	0.24	0.11 - 0.53
Gynaecologist	0.11	0.05 - 0.24
Dermatologist	0.10	0.04 - 0.23
No specialty	0.04	0.13 - 0.14
Region: State in the Former East Germany	1.60	1.15 - 2.21
Age Group: 20-29 (reference)		
50-59	1.56	1.10 - 2.21
"Yes, I prescribe to be on the safe side"	1.34	1.03 - 1.76
"Yes, I think my own work has an influence on antimicrobial resistance"	1.55	1.23 - 1.95
"Yes, I have experience with failed therapies for resistant pathogens "	2.42	1.83 - 3.19
"Yes, the quality of my prescribing practice has improved after consulting and continuing education from pharmaceutical companies "	1.43	1.11 - 1.84

Table 4. Attitudes concerning antimicrobial prescribing: approval of selected items, demographic and professional characteristics

	I prescribe to be on the safe side	I think my own work has an influence on antimicrobial resistance	I have experience with failed therapies	The quality of my prescribing practice has improved after consulting and continuing education from pharmaceutical companies
Setting	Yes/All (% Yes)	Yes/All (% Yes)	Yes/All (% Yes)	Yes/All (% Yes)
Hospital	353/1654 (21)	1136/1619 (70)	1393/1619 (83)	315/1390 (23)
Outpatient care	474/1762 (27)	880/1698 (52)	1356/1711 (86)	453/1544 (29)
Total	827/3416 (24)	2016/3317 (61)	2749/3330 (83)	768/2934 (26)
Specialty				
GP	258/895 (29)	502/847 (60)	696/858 (81)	243/780 (31)
Internal	123/644 (19)	463/631 (73)	566/632 (90)	142/552 (26)
Surgery	156/715 (22)	445/703 (63)	607/702 (86)	153/607 (25)
Ear Nose Throat	30/125 (24)	60/119 (50)	97/120 (81)	20/102 (20)
Paediatrics	45/331 (14)	211/324 (65)	253/324 (78)	68/291 (23)
Urology	32/134 (24)	83/132 (63)	123/130 (95)	34/113 (30)
Gynaecology	106/367 (29)	149/357 (42)	245/358 (68)	65/315 (21)
Dermatology	49/109 (45)	39/108 (36)	86/107 (80)	24/92 (26)
No specialty	15/49 (31)	35/48 (75)	38/51 (75)	10/40 (25)
Total	814/3369 (24)	1989/3269 (61)	2711/3282 (83)	759/2892 (26)
Age Group				
< 30	5/14 (35)	8/13 (62)	11/15 (73)	1/11 (9)
30-39	151/577 (26)	411/559 (74)	488/563(87)	99/491 (20)
40-49	329/1370 (24)	871/1337(65)	1127/1335 (84)	290/1189 (24)
50-59	237/1027 (23)	543/988 (55)	819/1001 (82)	251/881 (28)
> 59	99/408 (24)	170/401 (42)	287/396 (72)	122/346 (35)
Total	821/3396 (24)	2003/3298 (61)	2732/3310 (83)	763/2918 (26)
Sex				
Male	514/2188 (23)	1359/2131 (64)	1835/2144 (86)	500/1880 (27)
Female	300/1165 (26)	618/1125 (55)	853/1127 (76)	254/1002 (25)
Total	814/3353 (24)	1987/3256 (61)	2699/3271 (82)	754/2882(26)
Region				
State in the Former East Germany	125/540 (23)	306/526 (58)	421/527 (80)	164/459 (36)
State in the Former West Germany	702/2876 (24)	1710/2791 (61)	2328/2803 (83)	604/2475 (24)
Total	827/3416 (24)	2016/3317 (61)	2749/3330 (82)	768/2934 (26)

Table 5: Opinions on interventions to improve appropriate antimicrobial use: importance of selected items, demographic and professional characteristics

	Collection of regional antimicrobials resistance data with appropriate feedback for prescribing physicians important or very important	Federal guidelines-independent from the pharmaceutical industry-for diagnostics and antimicrobials therapy important or very important	Availability of 'antimicrobial experts' (consulting, audits and feedback) important or very important	Improvement of training possibilities at universities important or very important
Setting	Yes/All (% Yes)	Yes/All (% Yes)	Yes/All (% Yes)	Yes/All (% Yes)
Hospital	1581/1650 (96)	1463/1641 (89)	1441/1658 (87)	1502/1650 (91)
Outpatient care	1648/1766 (93)	1587/1768 (90)	1393/1765 (79)	1563/1766 (89)
Total	2259/3416 (95)	3050/3409 (89)	2834/3423 (83)	3065/3416 (88)
Specialty				
GP	856/894 (96)	799/894 (89)	721/895 (81)	788/894 (88)
Internal	616/637 (97)	579/643 (90)	538/644 (84)	567/637 (89)
Surgery	659/716 (92)	631/708 (89)	615/720 (85)	641/716 (90)
Ear Nose Throat	115/124 (93)	115/125 (92)	100/123 (81)	108/124 (87)
Paediatrics	323/331 (98)	294/333 (82)	279/330 (75)	313/331 (95)
Urology	125/134 (93)	108132 (82)	101/134 (75)	123/134 (92)
Gynaecology	335/372 (90)	334/367 (91)	310/371 (84)	333/372 (90)
Dermatology	104/110 (95)	107/110 (97)	94/110 (85)	103/110 (94)
No specialty	49/51 (96)	43/50 (86)	42/50 (84)	46/51 (90)
Total	3182/3369 (95)	3010/3362 (90)	2800/3377 (83)	3022/3369 (90)
Age Group				
< 30	13/15 (87)	15/15 (100)	14/15 (93)	14/15 (93)
30-39	556/577 (96)	510/570 (89)	501/577(87)	511/577 (88)
40-49	1312/1375 (95)	1257/1370 (92)	1157/1370 (84)	1225/1375 (89)
50-59	957/1024 (93)	888/1024 (87)	830/1032 (79)	930/1024 (91)
> 59	374/405 (92)	362/419 (88)	316/411 (77)	369/405 (91)
Total	3212/3396 (95)	3032/3389 (89)	2818/3405 (83)	3049/3396 (90)
Sex				
Male	2060/2182 (94)	1918/2184 (88)	1782/2192 (81)	650/2187 (29)
Female	1115/1174 (95)	1076/1163 (93)	1002/1169 (86)	399/1172 (34)
Total	3175/3356 (95)	2994/3347 (89)	2784/3361(83)	1049/3359(31)
Region				
State in the Former East Germany	511/543 (94)	501/545 (92)	451/542 (83)	498/543 (92)
State in the Former West Germany	2718/2873 (95)	2549/2864 (89)	2383/2881 (83)	2567/2873 (89)
Total	3229/3416 (94)	3050/3409 (89)	2834/3423 (83)	3065/3416 (90)

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Antibiotics for the common cold: expectations of Germany's general population

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Physicians mention patients' expectations as a reason for prescribing antibiotics for common (viral) upper respiratory tract infections despite clinical evidence against their use and the physicians' better judgement. We aimed to assess the prevalence of such expectations and factors of influence (knowledge and attitudes) in Germany's general population. In November 2008, 1,778 persons registered with a large market research company were invited to complete an online questionnaire on expectations concerning prescription of antibiotics and on knowledge and attitudes regarding the effectiveness and use of antibiotics for upper respiratory tract infections. A total of 1,076 persons aged 15–78 years participated (response: 61%), of whom 91.8% reported using antibiotics 'only if absolutely necessary'. Prescription of antibiotics was expected by 113 (10.5%) of the 1,076 respondents for the common cold and by 997 (92.7%) for pneumonia. In a logistic regression analysis, predictors for expecting a prescription for antibiotics for the common cold included the following opinions: 'common cold or flu can effectively be treated with antibiotics' (prevalence: 37.6%; odds ratio (OR): 9.6; 95% confidence interval (CI): 3.8 to 24.3) and 'antibiotics should be taken when having a sore throat to prevent more serious illness' (prevalence 8.6%; OR: 7.6; 95% CI: 3.9 to 14.5). Among those expecting a prescription (n=113), 80 (71%) reported that they would trust their physician when he or she deems a prescription unnecessary; a further eight (7%) would be unsatisfied, but would accept the decision. Our results suggest that only a minority expects antibiotics for the treatment of cold symptoms. Physicians should be educated that their decisions not to prescribe antibiotics for the common cold, even when against patients' expectations, are apparently accepted by the majority.

Introduction

Most respiratory tract infections (e.g. common cold, influenza and sinusitis) are self-limiting and viral in origin. Thus, antibiotics are rarely necessary or effective [1-3]. While overall figures of outpatient antibiotic use in Germany fall within the lower third of those of European countries [4], 28% of German respondents in the recently published Eurobarometer on antimicrobial resistance had taken antibiotics in the past year and more than a third had taken them for a viral infection such as a cold or influenza [5]. In a direct observation study conducted in general practices in Germany, 18% and 64% of patients with common cold and sinusitis respectively were prescribed antibiotics [6]. These unnecessary prescriptions are thought to largely contribute to the development of antimicrobial resistance and increasing numbers of infections without treatment options [4].

As a reason for these prescriptions against their better judgment, physicians mention pressure exerted by their patients to receive antibiotics even for minor ailments or diseases of viral origin (such as influenza or the common cold) [7]. Doctors feel the need to give in to this pressure due to time constraints or to avoid losing the patient to another practice.

Public knowledge and attitudes concerning antibiotic use and action differ greatly between countries in Europe and between groups of different socio-economic background. People in northern European countries and those with a higher level of education are among the best informed about the effects and sensible use of antibiotics, whereas there are generally higher levels of misconceptions in southern and eastern European countries and among those with a lower level of education. These geographical and socio-economic differences in knowledge and attitudes can in part explain differences in observed use of antibiotics [5,8].

Large campaigns, educating the public about antibiotic action and responsible antibiotic use, have therefore been conducted in various countries including Australia, Belgium, Canada, the United Kingdom and the United States [9,10] as well as at the European level [11], aiming at decreasing unnecessary antibiotic use and thus slowing down the development of antibiotic resistance.

Little is known about the prevalence of expectations regarding the prescription of antibiotics for upper respiratory tract infections in Germany and possible determinants of these expectations. With this survey, we try to explore knowledge, attitude and expectations of Germany's general public in order to guide decisions on further preventive measures such as public awareness campaigns.

Methods

Design, sample size, questionnaire design

We conducted a cross-sectional study among a sample of the German general population using an Internet-based questionnaire. A sample size of 1,000 was calculated to yield a precision of 3.1 on a confidence level of 95%, which was judged to be sufficient for the purposes of this study.

In total, 1,778 individuals were selected from a panel of approximately 30,000 Internet users, who registered with a large market research company and had given their consent to be contacted for purposes of (market-) research-oriented studies. Upon invitation via email, participants were able to log on to a website and complete the online questionnaire during a 10-day period in November 2008. They received a small remuneration for their efforts in completing the survey.

The questionnaire consisted of closed questions (multiple-choice, Likert scale) on expectations of prescription of antibiotics from physicians and knowledge and attitudes regarding effectiveness of antibiotics and antibiotic use for upper respiratory tract infections. Questions were mostly selected from published studies with similar objectives (e.g. [8,10,12]) and slightly rephrased according to the objectives of this study. Detailed demographic data had been recorded at the time of the participant's registration and kept in a separate database with the market research company. The definition of levels of education, as used in this study, was as follows:

- low – maximum of nine years of basic school education;
- medium – 10 years of extended school education;
- high – 12 or 13 years of extended school education, including persons who went on to university.

Participants' answers were directly recorded into a database, merged with demographic data and exported

Table 1

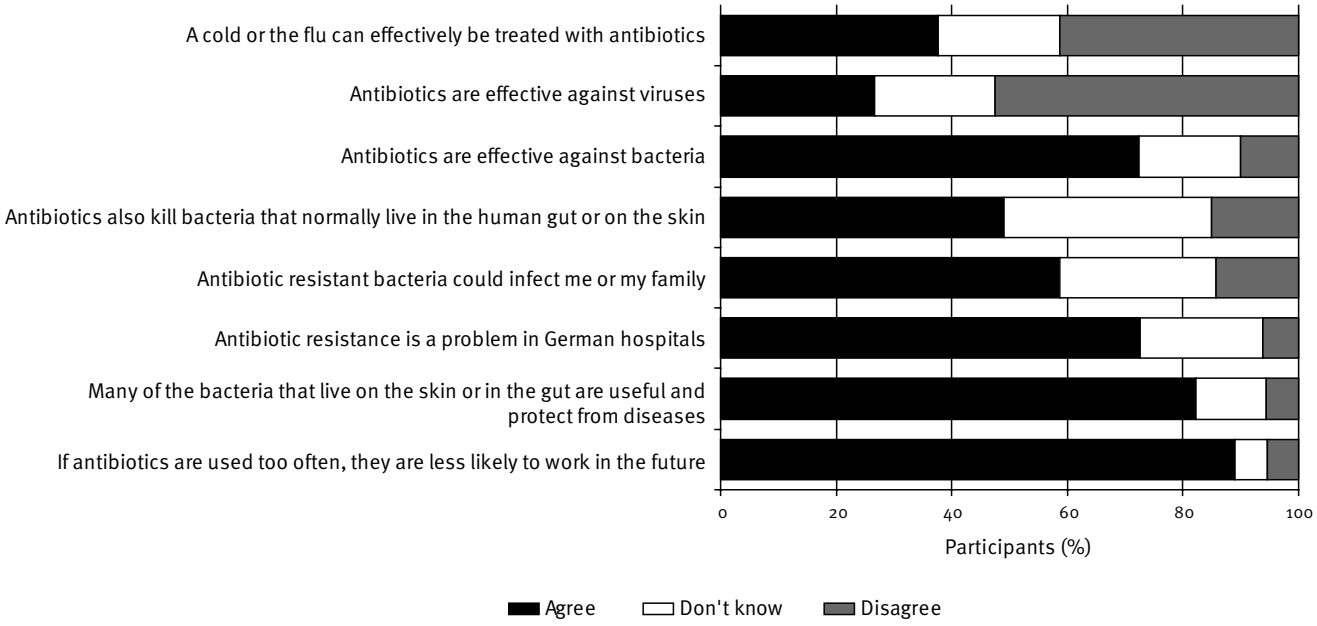
Demographic characteristics of the study participants in 2008 (n=1,076) and general public, Germany

Characteristics	Number (percentage) of study participants	Percentage of general public aged ≥15 years[a]
Male	589 (54.7)	48.9
Age (years)		
15–19	95 (8.8)	7.4
20–29	213 (19.8)	13.8
30–39	251 (23.3)	14.5
40–49	271 (25.2)	19.5
50–59	164 (15.2)	15.7
≥60	82 (7.6)	29.1
Level of school education		
Low	156 (14.5)	48.7
Medium	276 (25.7)	27.6
High	644 (59.9)	23.7

[a] Data for 2007 according to the German Federal Statistical Office [14].

Figure 1

Relative frequency of participants' responses to statements concerning knowledge of antibiotic action and resistance and normal flora, Germany, 2008 (n=1,076)



to a single database that was then checked for missing data and monotonous answers (e.g. yes/no only). Variables were dichotomised if needed for the analysis (e.g. 'agree fully' and 'agree somewhat' = 'agree', 'disagree fully' and 'disagree somewhat' = 'disagree').

Table 2

Number of correct responses (to eight knowledge statements)[a] and number of responses indicating responsible antibiotics use (to eight attitude statements)[b], by participants' demographic characteristics, Germany, 2008 (n=1,076)

Characteristics	Knowledge		Attitudes	
	Mean	95% CI	Mean	95% CI
Sex				
Male	5.12	4.94–5.29	6.20	6.06–6.34
Female	5.25	5.07–5.44	6.39	6.26–6.52
Age (years)				
15–19	4.17	3.74–4.59	5.77	5.43–6.12
20–29	4.94	4.65–5.23	6.21	6.00–6.42
30–39	5.35	5.11–5.60	6.34	6.15–6.54
40–49	5.62	5.38–5.86	6.50	6.32–6.68
50–59	5.48	5.16–5.79	6.26	6.00–6.51
≥60	4.35	3.85–4.86	6.26	5.96–6.55
Level of education				
Low	4.38	4.06–4.71	5.88	5.59–6.17
Medium	5.00	4.73–5.26	6.24	6.04–6.43
High	5.45	5.29–5.60	6.41	6.29–6.52
Total	**5.18**	**5.05–5.30**	**6.29**	**6.19–6.38**

CI: confidence interval.

[a] See Figure 1.

[b] See Figure 2.

Statistical analysis

We calculated relative frequencies of responses (total and stratified by demographic characteristics or particular items in the questionnaire). Scores were calculated for: (i) knowledge of antibiotics and (ii) responsible antibiotic use, summing up the number of correct responses to statements or answers indicating responsible views of antibiotic use, respectively. The chi-square test, t-test or Cuzick's test for trend was applied to test for significant differences between subgroups.

Determinants (demographics, knowledge and attitudes) for expecting a prescription of antibiotics for the common cold were sought using logistic regression analysis. Variables associated with these expectations in the bivariate analysis ($p<0.2$) were entered into the model and retained if the adjusted p value was less than 0.1 (stepwise backward elimination). Logistic regression analysis was conducted with a separate set of variables using mean substitution of missing values (separately for the outcomes 'respondent expects antibiotics' versus 'respondent does not expect antibiotics') [13].

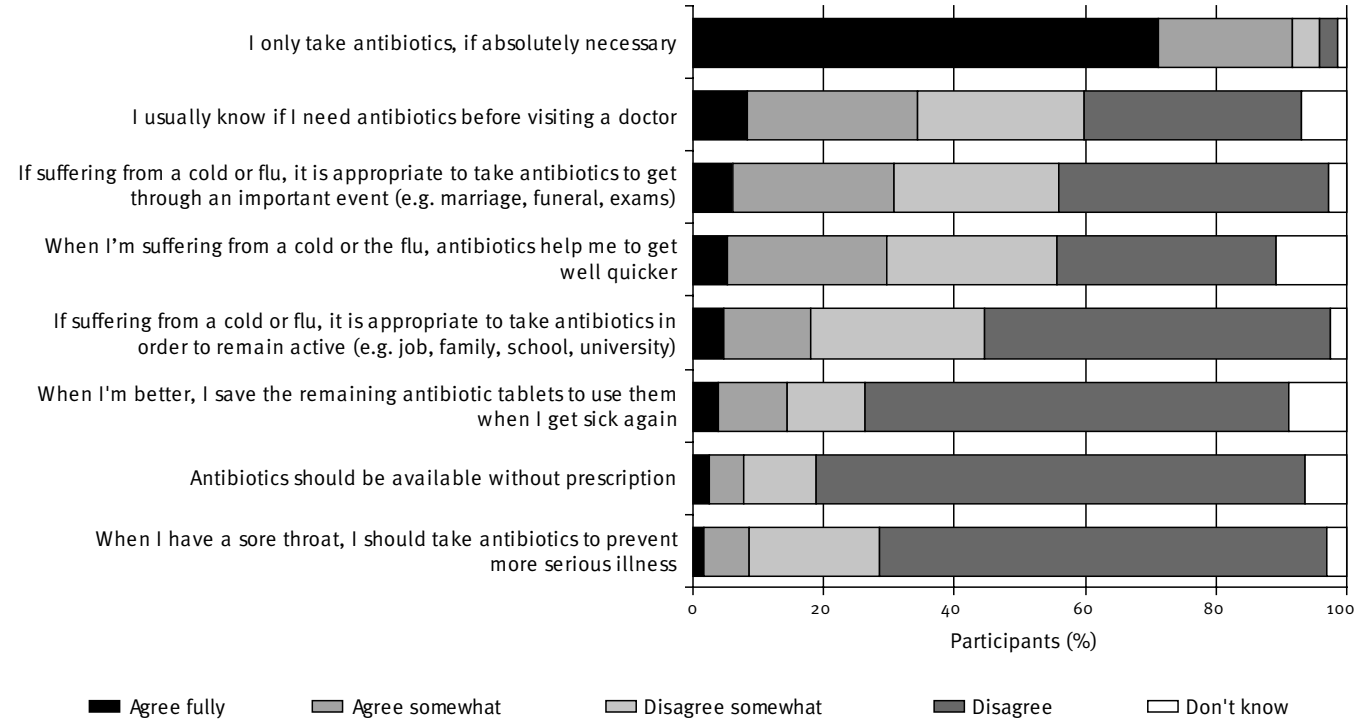
All statistics were conducted using STATA 10.1.

Results

Of 1,778 invited, 1,076 persons between the age of 15 and 78 years (54.7% male) participated, resulting in an overall response of 61%. Compared with Germany's general population, there was no considerable difference in our sample concerning the distribution of persons across Germany's 16 Laender and the size of places of residence (scale of five ranks), but higher

Figure 2

Relative frequency of participants' responses to statements concerning attitudes towards antibiotics and antibiotic use, Germany, 2008 (n=1,076)



age groups, women and persons with a lower level of education were under-represented (Table 1).

Knowledge and attitudes concerning antibiotics and respiratory tract infections

The majority of participants knew that antibiotics are effective against bacteria (72.3%) but not viruses (52.6%), knew about antibiotic resistance (89%) and acknowledged it to be a problem in German hospitals (72.6%). However, only 445 (41.4%) knew that antibiotics are not effective against the common cold or influenza (Figure 1).

The mean number of correct responses to eight statements on antibiotic knowledge was 5.2 of eight (65%). Participants with a high level of education responded to more statements correctly than those with a medium or low level of education (Cuzick's test for trend: p<0.001). Persons of younger (15–29 years) or older (≥60 years) age had lower scores in the questions on antibiotic knowledge (Table 2), also after stratification by level of education (data not shown).

When asked about views on antibiotics and antibiotic use, most participants (91.8%) reported that they use antibiotics 'only if absolutely necessary', and disagreed with the statement 'antibiotics should be available without prescription' (86.0%). However, 34.4% thought they knew if they needed antibiotics before visiting a doctor and 30.8% considered it appropriate to take antibiotics to get through an important event when suffering from a cold or influenza (Figure 2). Overall, self-reported views on antibiotics were more sensible or responsible in persons with higher levels of education and least in participants less than 20 years of age (Table 2).

Prevalence of expectations

Participants were asked on two occasions during the survey whether they expect their physician to prescribe antibiotics for the common cold: the first question dealt with general expectations when consulting their physician because of the common cold or influenza. Most respondents reported that they consult in order to 'be examined, receive advice or a sick certificate' (47.3%) or for symptomatic treatment (44.4%). A wish for antibiotics was mentioned by 83 (7.7%) respondents. In the second question, participants were asked whether they would expect a prescription of antibiotics for certain common respiratory infections (along with their typical symptoms). In this question, 113 (10.5%) reported to expect antibiotics for the common cold (sore throat, blocked nose, cough), while 46.9% and 92.7% did so for influenza (fever, fatigue, head- and muscle aches, cough) and pneumonia, respectively. For the common cold, the prevalence of self-reported expectations of receiving a prescription of antibiotics depended on level of education in the bivariate analysis (19.9%, 12.0% and 7.6% for low, medium and high level of education, respectively, p<0.01). No other significant associations with demographic data (age group, sex, place of residence, migration background, household income, type of health insurance, occupational group) were seen after stratification by level of education (data not shown).

Association of expectations and knowledge and attitudes

In the multivariable analysis, the strongest predictors for expecting a prescription of antibiotics for the common cold were holding the following opinions: 'a cold or the flu can effectively be treated with antibiotics' (prevalence: 37.6%; odds ratio (OR): 9.6; 95% confidence interval (CI): 3.8 to 24.3) and 'when I have a sore throat, I should take antibiotics to prevent more

Table 3

Multivariable analysis: factors associated with self-reported expectations for antibiotic prescription for the common cold, Germany, 2008 (n=1,076)

Factors	Odds ratio	95% CI
Knowledge and beliefs		
A cold or the flu can effectively be treated with antibiotics	9.58	3.77–24.31
When I have a sore throat, I should take antibiotics to prevent more serious illness	7.56	3.94–14.51
Many of the bacteria that live on the skin or in the gut are useful and protect from diseases	0.21	0.08–0.55
I only take antibiotics if absolutely necessary	0.26	0.11–0.62
When suffering from a cold or flu, it is appropriate to take antibiotics to get through an important event	2.26	1.28–4.00
Antibiotics should be available without prescription	2.65	1.25–5.59
Antibiotic resistant bacteria could infect me or my family	3.25	1.28–8.21
When I'm suffering from a cold or the flu, antibiotics help me to get well quicker	2.18	1.15–4.15
Antibiotics are effective against viruses	2.01	1.07–3.79
If antibiotics are used too often, they are less likely to work in the future	0.31	0.10–0.94
Characteristics		
Antibiotic use during the last year	1.86	1.07–3.22
Reported suffering from cough, cold, sore throat or fever at the time of the investigation	1.77	1.03–3.06
Level of school education: high	0.55	0.32–0.94

CI: confidence interval.

serious illness' (prevalence 8.6%; OR: 7.6; 95% CI: 3.9 to 14.5). The full results are shown in Table 3.

Confidence in the physicians' decisions

Among those expecting a prescription of antibiotics for the common cold (n=113), 80 (71%) reported that they trust their physician when he or she deems a prescription unnecessary. A further eight (7%) would be unsatisfied but accept the decision, whereas 14 (12%) reported that they would win over the doctor to prescribe and three (3%) would consult another doctor. In a more general question, 99 of 1076 (9.2%) reported that they felt they were not taken seriously or were not receiving proper treatment if they were not prescribed antibiotics for a cold or influenza.

Discussion

We found that 10.5% of respondents expected a prescription of antibiotics for the common cold and that such expectation was associated with a lack of knowledge of correct indications for antibiotic use and antibiotic resistance. Of those expecting antibiotics from a consultation, 77.9% reported that they trusted their physician when he or she deemed a prescription unnecessary or would at least accept such a decision.

Strengths and limitations

This is, to our knowledge, the largest study specifically investigating public views and knowledge of common respiratory tract infections and antibiotic use in Germany. The use of an online access panel allowed us to achieve a high response and to gain insight into the views and expectations of a wide range of population groups before they visit a doctor. Our study has limitations: firstly, the shortage of participants with a lower education level might bias the overall results towards better knowledge and more responsible views than actually present in the general population. We therefore presented stratified results whenever appropriate. Secondly, asking the general public might introduce a bias towards a lower prevalence of expectations of receiving a prescription of antibiotics when compared with asking patients. We therefore included a question on the presence of common cold or influenza symptoms at the time of investigation, which allowed us to partially compensate for this effect. Finally, as with all questionnaire studies, participants may give answers that they consider are socially desirable, which might introduce a bias towards more responsible use of antibiotics.

Patients' expectations

The existence of patients' expectations regarding the prescription of antibiotics and their influence on the decisions of doctors to prescribe is unequivocal [7,15,16]; however, the prevalence of such expectations varies considerably depending on the setting or type of study. It can be as high as 50% in United States adults consulting for cold symptoms [17] or as low as 1.2% in the Dutch general population [12].

Overall, our results indicate a sensible approach to antibiotics among Germany's public. Only a minority reported that they expected a prescription of antibiotics for cold symptoms and most reported to be taking antibiotics 'only if absolutely necessary'.

This is remarkable in light of the overprescription of antibiotics and the common belief that patient expectations at least partly drive it. However, our findings are in line with several studies that show that most patients seek information, reassurance or a diagnosis rather than a prescription of any kind [18] or a prescription of antibiotics in particular [19,20]. Real expectations of patients regarding the prescription of medication seem to be much less prevalent than expectations perceived by the doctor and furthermore their presence less predictive of the decision to prescribe [21-23]. Cockburn *et al*. found that when a patient expected a prescription he was three times more likely to receive it, but when the general practitioner thought the patient expected medication, the patient was 10 times more likely to receive it [22]. A study conducted in general practices in Germany showed that nearly all patients who, in their doctor's opinion, expected a drug left the surgery with a prescription. However, doctors accurately perceived the patient's wish for a drug prescription in only 41% of cases [24].

Furthermore, if patients do expect a prescription for cold symptoms, they do not necessarily expect a prescription of antibiotics. Van Driel *et al*. suggested that patients with acute sore throat and who hope for antibiotics are actually seeking treatment for pain [19]. This corresponds well to results of our survey, where 44% of respondents reported to expect symptomatic treatment for cold symptoms (e.g. lozenges, painkiller, cough medication) while only 7.7% reported to expect antibiotics for these symptoms.

In contrast to the observed low prevalence of expecting antibiotics for the common cold, nearly half of the participants in our study reported to expect a prescription of antibiotics for influenza. Given the existence of antiviral medication used for the treatment of influenza, it is unclear whether this question was not specific enough or whether influenza is much more frequently expected to be treated with antibiotics. But even if an individual patient has such expectations and the physician denies an actual wish for a prescription of antibiotics, he or she must not necessarily worry about losing the patient to another practice. The results of our study indicate a high level of confidence towards physicians and their decisions among Germany's general public. Less than 3% of those reporting to expect an antibiotic for cold symptoms stated that they would consult another doctor if their request were denied. Studies conducted in general practice settings showed similar results and concluded that a medically justified refusal to prescribe antibiotics had, in most cases, no negative effect on the consultation or its assessment by the patient [15,24,25].

Misconceptions and their implications

Misconceptions concerning the appropriateness and effectiveness of antibiotics for different indications seem to be quite common among Germany's public, comparable with results found in similar studies conducted in the United Kingdom [10] or the Netherlands [12]. In our multivariable analysis, these misconceptions were clearly associated with the expectation of receiving antibiotics for the common cold. The two 'items' most strongly associated were both related to the plain beliefs that antibiotics can be used to effectively treat the common cold or influenza and if they are used for a sore throat they could prevent more serious illness. It therefore seems to make sense to educate the public on antibiotic effectiveness, correct indications and risks of antibiotic mis- or overuse. If this is considered, efforts should be focused on the group where relevant expectations are most prevalent: those with a lower level of education. However, simply educating the public may not be effective in reducing the level of prescribing. A large household survey conducted in the United Kingdom demonstrated that those with a greater knowledge of antibiotics were no less likely to be prescribed an antibiotic [10]. According to a systematic review of 39 studies focusing on interventions to improve antibiotic prescription practices in ambulatory care, multifaceted interventions involving informing patients, communication training of physicians and educating the public were more successful [26]. In a cluster-randomised study conducted in more than 100 general practices in Germany, an intervention focusing on doctor–patient communication and patient empowerment even reduced antibiotic prescription rates for acute cough by 40% after 12 months [23].

Conclusions and recommendations

Our study suggests that there may be several opportunities to reduce unwarranted use of antibiotics and thus ultimately reduce further development of antibiotic resistance. Expectations that antibiotics will be prescribed for the common cold are generally not widespread and are most likely less prevalent than believed by general practitioners.

Physicians should therefore carefully explore if a perceived wish for antibiotics really exists in an individual patient. It may turn out that the consulting patient actually seeks symptomatic relief, reassurance or just a sick certificate.

Existing erroneous expectations might be caused by misconceptions of what can be achieved by taking antibiotics for cold symptoms and what risks are involved (e.g. adverse effects or development of resistance). With the high level of confidence physicians enjoy among the public, they may often be able to convince patients of alternative strategies and should not overly worry that they may displease their patients by not yielding to their requests. Change, however, does not come easily and multifaceted approaches are needed to tackle the problem of overprescribing and antibiotic resistance.

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MRSA surveillance in Germany: data from the Antibiotic Resistance Surveillance System (ARS) and the mandatory surveillance of MRSA in blood.

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Introduction

Surveillance is an indispensible part of most strategies for prevention and control of Methicillin-resistant *Staphylococcus aureus* (MRSA) in healthcare and community settings. It provides a scientific basis for public health activities and political decisions, gives indications for research and identifies needs for infection control measures thereby enabling a targeted allocation of financial resources.

In Germany, the surveillance of MRSA is shouldered by several institutions that use different methodological approaches and complement each other by covering different aspects of the MRSA-problem. Besides nation-wide surveillance-systems such as the German Krankenhaus-Infektions-Surveillance System (KISS), which has been supplemented with an MRSA-specific module (MRSA-KISS), and SARI (Surveillance of Antibiotic-usage and bacterial Resistance on Intensive Care Units), local surveillance systems at regional and hospital level are implemented, e.g. regional MRSA-networks comprising different healthcare facilities and primary care providers in a specific region [1,2,3]. The National Reference Centre (NRZ) for Staphylococci investigates molecularbiological characteristics of *S. aureus*-isolates originating from all over the country [4]. Furthermore, German laboratories take part in international surveillance systems such as EARS-Net with varying participation rates.

Within the framework of DART (German Antibiotic Resistance strategy), initiated by the ministery of health, a national Antibiotic Resistance Surveillance System (ARS) has been established in 2007. It aims to collect and analyse regionally and nationally representative antimicrobial resistance data from hospital and ambulatory care [5].

In order to enabling quantification of the burden of invasive MRSA-infections, the ministery of health has enacted mandatory notification of MRSA that is detected in blood cultures and cerebrospinal fluid (CSF). The law is effective since the 1st July 2009. We present data from ARS and mandatory surveillance in order to provide insight into current epidemiological features of MRSA in Germany.

Material and methods

ARS (Antibiotic Resistance Surveillance)

ARS is a voluntary laboratory-based sentinel, which relies on the electronic transfer of resistance data originating from routine laboratory testing of all clinical pathogens and sample types. Data are transmitted from the laboratory information system (LIS) via a standardised interface to the central database at the Robert Koch Institute (RKI), the national public health institution.

The transmitted data comprise: resistance data implying Minimal Inhibitory Concentration (MIC)-interpretations (susceptible, intermediate, resistant) and optionally MIC-raw data (mg/l), species-identification, gender and age (month, year) of the patient, sample type (blood, urinary tract, respiratory samples, punctures of sterile body fluids, samples from surgical sites and skin and soft tissues), date of sampling, type of medical supply (hospital or ambulatory care), hospital-type (tertiary care hospitals, other general acute hospitals, single speciality hospitals) and ward-type (Intensive Care Unit (ICU), general ward), medical department and speciality and region (federal state). Patients and healthcare providers are uniquely identified by a pseudonym, in order to warrant confidentiality.

Feed back is performed via an interactive database on the ARS-website (https:\\ars.rki.de). It offers free public access to general statistics and password-protected access for participating laboratories enabling them to retrieve resistance data from their specific client hospitals and to compare them to reference data from hospitals e.g. of the same type or from the same geographic region. ARS is linked to EARS-Net (European Antimicrobial Resistance Surveillance Network) via the European data-base of TESSy (The European Surveillance System). Hence, all ARS-laboratories take part in the annual external quality assessment exercise organized by EARS-Net and UK NEQAS (United Kingdom National External

Quality Assessment Service). In addition, ARS-laboratories are accredited, which implies the obligation for continuous quality control in routine laboratory testing.

Analysis is based on data from 2008-2010 from laboratories and hospitals with continuous participation in ARS within this time period (8 laboratories, 100 hospitals). The number of ambulatory health care providers was 2003 in 2008, 1913 in 2009 and 1763 for 2010. Isolates came from health care providers in 9 federal states (out of 16 federal states in Germany). Data analysis was performed separately for hospital and outpatient care. Copy-strains have been eliminated according to two different rules:

Copy-strain-rule 1 used for general queries: first *S. aureus* -isolate/patient/year

Copy-strain-rule 2 used for queries referring to sample type: first *S. aureus* - isolate/patient/sample type/year.

Resistance-Testing was performed by Vitek II (Biomerieux) and MIC-interpretations were done according to CLSI (M100-S17)-breakpoints. Generally, ARS is open for laboratories using any automated system for resistance testing or any current standard of breakpoint criteria. Strata with sample-sizes of less than 50 isolates have not been considered for analysis. Screening samples have been excluded.

Statutory MRSA-notification:

Statutory notification implies that all microbiological laboratories receiving patient samples from hospitals, other health care facilities and the ambulatory care sector are obliged to notify MRSA detected in blood cultures and CSF. The data flow works as follows: The microbiological laboratories report MRSA-cases to the local public health authority from where it is conveyed electronically to the RKI via the state health department. A case is defined as the initial MRSA isolate from blood or CSF from one patient for a time period of 14 days. An isolate detected more than 14 days after the first isolate is counted as a second episode. The basic data set comprises age and gender of the patient, sample type, method and

result of laboratory testing, type of health care supply (hospital- and outpatient care), federal state and governmental district. Provision of information on the clinical relevance of blood cultures positive for MRSA is not legally scheduled. In order to preserve comparability with international data, the presented analysis is restricted to MRSA-isolates from blood, which have been notified for the year 2010.

Statistical analysis:

Descriptive analysis of the data comprises the presentation of absolute numbers and calculated frequencies. Incidences of MRSA-bacteraemia were calculated by using denominators based on the German population 2009 (Deutschland, Land und Leute 2010, Statistisches Bundesamt Deutschland, Wiesbaden, 2010 Destatis). Extrapolation to the annual incidence of *S. aureus*-bacteremia was performed by using ARS data and application of a simple rule of proportion: (MRSA-incidence/100,000/year x 100)/ MRSA-Proportion in blood culture samples (ARS-database). In order to analyse the relationship of regional MRSA-incidences and proportions of MRSA from hospital care generated in ARS, Spearman Rank correlation was performed. Comparisons of proportions of MRSA yielded in 2008 and 2010 were done by using the chi squared-test or the Fisher's exact test where appropriate. A two-sided p-value of <0.05 was considered as significant.

Results

ARS:

From 2008 to 2010, resistance data from 70,935 *S. aureus*-strains were transferred to the central RKI-database with 39,655 isolates coming from hospitalised patients and 31,280 isolates from outpatients.

Characteristics of patients with *S. aureus*-isolates

Pooled data from the years 2008-2010 show that in-hospital *S. aureus*-isolates stem from patients of all hospital types with the majority of samples coming from conservative medical departments (46.2%). In community outpatient care most of the isolates originate from general/internal practices (44.1%) followed by isolates from ear nose and throat medicine (11.4%), dermatology (10.3%) and general surgery (9.2%). Swaps from surgical sites (hospital care: 25.7% and outpatient care: 26.2%) and skin and soft tissue (33.9% and 59.4%, respectively) account for the most frequent sample types. Demographic data show that in hospital care *S. aureus* predominantly has been isolated from patients >= 60 years (62.1%; average age: 66.0 years), whereas community outpatients were younger (average age: 45.7 years) and *S. aureus* was evenly frequent in the age groups >= 60 (42.0%) and 16-59 (42.9%). In both health care settings the average age of MRSA-patients was higher than in MSSA-patients (hospital care: 71.9 versus 57.8 years; outpatient care: 69.1 versus 46.1 years). *S. aureus* was isolated more frequently in males than in females (54.9% versus 45.1%).

Proportions of MRSA

If not indicated otherwise, in the following joined data from 2008 to 2010 are used to describe epidemiologic features of MRSA-occurrence.

Hospital care

Proportions of MRSA in hospital care stratified by hospital level, ward type, medical department, medical speciality, sample type, age, sex and region are presented in table 1.

The overall proportions of MRSA account for 19.2%. Stratification by ward-type reveals that ICUs yield higher proportions of MRSA as compared to general wards (21.7% versus 18.8%), which is mainly reflected in the differences of the proportions of MRSA in surgical

departments (27.0% on surgical ICUs versus 16.4% on surgical general wards, p<0.001), whereas no significant discrepancies between the medical departments of both ward types can be seen (19.0% on medical ICUs versus 21.0% on medical general wards, p=0.12). Within ICUs, surgical disciplines exhibit higher oxacillin-resistance-rates than conservative and interdisciplinary disciplines, whereas a reciprocal relationship is seen on general wards. Looking at single specialties (general ward) separately, shows that the highest proportions of MRSA were found in nephrology (49.4%), geriatrics (45.8%) and neurology (34.2%), which present with rates above 30%.

Considering overall proportions of MRSA over time, we see an increase from 2008 (18.7%) to 2009 (20.2%) followed by a return to 2008 –values in 2010 (18.6%). The proportions of MRSA produced by urological wards showed a significant difference between 2008 and 2010 (33.0% versus 22.8%, p=0.02), which was accompanied by a decline in urine samples (34.9% versus 31.0%, p=0.09). A significant difference of the proportions of MRSA between 2008 and 2010 was observed in skin and soft tissue samples (21.0% versus 18.7%, p=0.01). Further stratification of the proportions of MRSA of skin and soft tissue samples reveals a significant decrease in patients, who were >= 60 years old (p=0.006) and with stay on internal general wards (p=0.005). As in the individual years the sample size of *S. aureus*-isolates coming from nephrological wards was <50, data have not been used to estimate differences of proportions of MRSA over time.

Community outpatient care:

Proportions of MRSA in hospital care stratified by medical speciality, sample type, age, sex and region are presented in Table 2. The overall proportions of MRSA in outpatient care (10.6%) achieved more than half the height of the values generated in hospital care. Stratification by medical speciality reveals that the highest proportions of MRSA were found

in samples from urological practices (29.2%), which after a wide gap were followed by internal medicine (14.2%) and nephrological practices (14.9%). Blood and urinary tract samples present with high proportions of MRSA (25.0% and 20.5%, respectively). More than two thirds (72.6%) of the blood culture samples came from nephrological practices. Comparing overall proportions of MRSA between 2008 and 2010 revealed a steady course. Nevertheless, looking at the data in more detail showed a significant increase of proportions of MRSA in gynaecological practices from 3.3% to 5.7%, p=0.03, while proportions of MRSA in samples from ambulatory nephrological practices sank significantly (from 17.5% to 12.5%, p=0.02). A non-significant rise could be observed in respiratory samples. As in the individual years the sample size of *S. aureus*-isolates from blood was <50, data have not been used to estimate differences of proportions of MRSA over time.

Statutory MRSA-notification:

From 01.01.2010 to 12.31.2010 3900 cases of MRSA-bacteremia have been reported, which corresponds to a nationwide annual incidence of 4.8/100,000 inhabitants. Information about age and sex is available for 3111 (88.8%) patients. The average age was 71 years. The extrapolated annual incidence increases continuously with patient age from 0.1/100,000 inhabitants in children <= 15 years to 20.5/100,000 in patients >70 years and is generally markedly higher in males than in females (6.1 versus 3.5/100,000 inhabitants). A more detailed view on the age group of children revealed that neonates <1 year of age presented with a higher incidence (1.2/100,000/year) as compared to infants 1-15 years of age (0.05/100,000/year). In contrast to the pattern of the other age groups, girls were affected more frequently. Notable regional differences were seen on all administration levels. The incidences on federal state-level range from 1.0/100,000 inhabitants/year to 8.3/100,000 inhabitants/year (Figure 1). Further subdivision in 38 governmental districts reveals

underlying heterogeneities e.g. the federal state Rhineland-Palatinate consists of 3 governmental districts with annual incidences ranging from 2.3-6.2/100,000 inhabitants/year. 88.9% of MRSA-positive blood cultures stem from hospital care accounting for an incidence of 4.24/100,000 inhabitants/year and of 0.53/100,000 inhabitants/year. No significant differences concerning average age (71.1 versus 71.2 years) or sex (males: 63.1% versus 63.0%) were observed between hospitalised patient and outpatients.

Analyses using data from both surveillance systems:

Regional proportions of MRSA (hospital care, 16 governmental districts from 38) and MRSA-bacteraemia incidences on the level of governmental districts are positively correlated (Spearman correlation coefficient: 0.64; p=0.01). Extrapolation of the annual MRSA-incidence-values by using the proportions of MRSA in blood-cultures from ARS yields a nationwide MSSA-incidence of 16.8/100,000 inhabitants/year and a total *S. aureus*-bacteraemia-incidence of 21.6/100,000 inhabitants/year.

Discussion

In order to describe current epidemiological features of MRSA in Germany, we presented incidence rates and proportions of MRSA from two recently implemented nationwide surveillance systems. While incidence rates best describe the burden of MRSA-infections, proportions of MRSA may also give an impression of the magnitude of the MRSA-problem and are an important metric for guiding empirical antibiotic therapy. Both measures might show differing trends over time, but they might be used complementary for the estimation of the actual MRSA-situation.

In the nineties and in the beginning of the first decade 2000, Germany experienced a steep increase of proportions of MRSA in *S. aureus* isolates, which appears to have stabilised in the

last years [6,7,8]. Ranking of the proportions of MRSA of European countries participating in EARS-Net, shows that in 2009 Germany took a position in the second third exhibiting stabile values as compared to 2008 [8].

Current nationwide population-based incidence-data from other countries are scarce. The annual German MRSA-bacteraemia-incidence (4.8/100,000) is higher than the reported incidences from Scandinavia (e.g. Denmark: 0.4/100,000, Sweden: 0/100,000), the United Kingdom after realising the 50% target (2.9/100,000) and Canada (2.2/100,000), but lower than in the United States (29.3/100,000) and Australia (41/100,000) [9,10,11,12,13,14,15]. ARS-Data served to extend the MRSA-bacteraemia-incidence to an overall *S. aureus*-bacteraemia (SAB)-incidence (21.6/100,000/year), which is in line with the values of other European countries (range: 14-26/100,000 inhabitants) and lower than in the US, Australia and New Zealand [16]. But it should be considered that the validity of the extrapolated data is compromised, because national representativity of ARS-data for the period considered can not be assumed. Nevertheless, SAB-incidences represent an important parameter for the estimation of nosocomial infections [17,18].

Except Newborns <1 year showing the highest MRSA-bacteraemia incidences within the <=15 years age group, rising incidences with increasing age and predominance of male gender conform to widely known distribution patterns [19,20]. Likewise in other countries, intra-country regional differences (federal state- and/or district-level) of MRSA-bacteraemia-incidences and of proportions of MRSA generated from ARS have been ascertained [21,22,23]. The positive correlation of both parameters on the level of governmental districts appears to be plausible by indicating that high proportions of MRSA generate high MRSA-incidences. Furthermore, it might be interpreted as a strengthening of the validity the data. Nevertheless, comparisons of unadjusted regional incidence values and MRSA-proportions should be considered with caution. Thus, different sampling policies might influence national and regional MRSA-bacteraemia figures and might affect the magnitude of the proportions of

MRSA as well [21,24, 25].These and other potentially influencing factors such as varying case-mix-characteristics in regional hospital populations and differences in surveillance policies indicate that without adjustment for these variables interpretations are difficult to make and that under the suspicion of constant external conditions longitudinal analyses should be preferred [26].

The available data do not allow a differentiation of hospital-acquired, health-care-associated and community acquired MRSA-bacteremia-cases according to internationally recognised definitions. However, similar demographic characteristics of patients with MRSA-bacteremia diagnosed in hospital and outpatient care might indicate that the majority of cases in the outpatient-setting were healthcare-related, which is in accordance with the results of several studies inquiring the characteristics of outpatients with MRSA-bacteremia [27,28,29,30]. Despite low sample size, further support might be provided by ARS-data, which show high proportions of MRSA in blood cultures from community outpatients (25.0%), of which more than two thirds attended nephrological practices providing hemodialysis, a well known risk factor for the acquisition of invasive MRSA-infections [31]. In a recent study, assessing the genetic background of invasive MRSA-isolates on a European level, only 0.5% of the isolates could be classified as typical Community-acquired (CA)-MRSA [32].

Several limitations of MRSA-bacteremia incidence values should be considered. Thus, the magnitude of MRSA-bacteremia-incidences might be underestimated, because an uncertain number of patients with invasive infection under effective antibiotic therapy did not yield positive blood cultures. Additionally, it can be assumed that diagnostic blood culture sampling has not been performed in every case. Data from EARS-Net show, that in comparison to many other countries the blood culture sampling rate in Germany lies below the 50th percentile [8]. An overestimation is also possible, since merely contaminated blood cultures cannot be excluded. This appears not to be of great concern, as blood cultures tetsted positive for *S. aureus* are generally considered to be indicative of systemic infection [33].

However, performing enhanced surveillance of MRSA-bacteremias Jeyaratnam et al. found that 12% of the isolates were contaminants [34].

While MRSA-BSI-reporting is primarily a marker for the burden of hospital MRSA-infections, ARS offers the opportunity to provide resistance-data in equal measure from hospital and outpatient care and moreover allows a deeper insight into specific clinical settings in which MRSA occurs.

Data from EARS-Net show a relatively stable course in the years 2008/2009, while the overall proportions of MRSA from ARS increased, which was primarily due to a rise in general wards of tertiary care hospitals. However in 2010 the proportions of MRSA returned to the level of 2008. The reasons for the rise in 2009 are unclear. It cannot be excluded that samples from outbreak investigations, which have not been declared as screening samples might have biased the results. The proportions of MRSA on ICUs are higher than on general wards, which is sufficiently explained by the high selective antibiotic pressure, extended device-application and severity of patient disease, which are known risk factors for MRSA-acquisition [35,36,37]. The overall constant course over time is consistent with the results of two other German surveillance systems, KISS and SARI [38, 39].The fact that patients treated in surgical ICUs are at higher risk to acquire MRSA-infections as compared to medical ICUs, has already been confirmed by other studies [36,40]. On general wards the specialities geriatrics, nephrology, urology and neurology present with particular high MRSA-rates, which might be due to the presence of well known risk factors such as hemodialysis, surgical interventions, urinary tract catheterisation and the application of other indwelling devices [35].

While the majority of MRSA-isolates originate from wounds and other skin or soft tissue samples, thus marking the body surface as the main reservoir, the proportion of MRSA in relation to all *S. aureus*-isolates is highest in urine samples (>30%). This may be due to the

fact that in hospitals most of the urinary tract infections or colonisations are associated with urinary tract catheterisation and surgical interventions, known precursors of MRSA-manifestation [41]. The decrease of the proportions of MRSA of urinary tract samples and on urological wards in the recent 3 years might be due to an increased attention to this problematic area inducing the introduction of specific surveillance-activities, the improvement of the implementation of infection control measures and modification of antibiotic policies [42]. Similar reasons may serve as explanation of the significant decrease of the proportions of MRSA in skin and soft tissue samples of internal general wards in tertiary care hospitals. However, as this category also includes unspecified swaps, misclassification can not be excluded. Furthermore, the increase of the sample size (22.7%) from 2008 to 2010 might also indicate a change of sampling policies.

The proportions of MRSA in outpatient care account for more than half the estimates found in hospital care. A similar relation was found in a Spanish study, which, in contrast to ARS, considered solely *S. aureus*- infections [23]. Keeping in mind that the MRSA-proportion in the German general population is estimated around 1%, this relatively high percentage of MRSA indicates that besides pure community acquired infections a considerable portion of MRSA-isolates stem from patients with recent health care contact [43]. Furthermore, it can be assumed that a portion of the medical practices serves nursing homes. Nevertheless, epidemiological data about place and time of MRSA acquisition in community outpatient care are not available. Indeed, the fact that the high proportions of MRSA on urological wards and in urinary tract samples in hospital care were reflected in the outpatient setting on a lower level, where urological practices and urine samples stand out with particular high proportions of MRSA as well, might indicate that at least part of the infections were hospital-related. However, these results are also an expression of routine diagnostic strategies in the outpatient setting, where it is standard practice to initiate microbiological investigations of urine samples

only in complicated urinary tract infections, but not in simple cystitis of young women [44]. In turn, this is surely also true for other clinical entities such as respiratory tract infections. Proportions of MRSA from samples of nephrological practices sank between 2008 and 2010. From the United Kingdom, Fluck et al. also reported a decline in MRSA-bacteraemias in centers providing renal replacement therapy [31]. This might be due to increased awareness of high risk constellations (old persons, hemodialysis, frequent health care contact) prompting the improvement of infection control measures in ambulatory and hospital care as well. Furthermore, changing diagnostic procedures or -strategies might have played a role. In contrast, gynaecological practices show an increase of the proportions of MRSA over time. Comparable data from gynaecology and obstetrics in outpatient care are rare as the available point prevalence studies focussed quite specific settings (45). One reason for the observed increase might be the transmission of treatment options from hospital to community care, on the other hand a rising prevalence of MRSA in the general population can not be excluded. These considerations remain speculative as information about potential underlying factors was not available.

Currently, detailed data about the occurrence of antibiotic resistant pathogens and avoidable infections in outpatient settings in Germany are scarce [43, 46, 47]. With respect to current developments in medical delivery with the transfer of medical interventions from hospital care into the ambulatory sector, further investigations in this field are urgently needed. This is underscored by the fact that on the other hand the amount of hospital-acquired MRSA-infections is significantly triggered by the burden of MRSA in the institution, which in turn is mainly determined by MRSA imported from outside the hospital [48].

Besides infection control purposes, resistance data should support correct antibiotic prescriptions on an individual basis and serve as a guide for empirical therapy as well. The pooled ARS-Data, despite being a precious source for the estimation of the occurrence of MRSA in outpatient samples, do not allow an appreciation of the role of MRSA in strictly

community-acquired infections and consequently cannot be used to guide recommendations for empirical therapy in community-acquired infections.

The presented ARS-data suffer from several additional limitations. The voluntary character of ARS causes an unequal distribution of the participating laboratories resulting in a clustering in certain regions and in the missing of data particularly from eastern regions in Germany. Thus, the generalisability of the results can not be assumed. A differentiation of colonisation and infection is not possible. Though, from an infection control perspective the inclusion of colonising strains in surveillance efforts is crucial. Molecular-epidemiological data are not available, which would be desirable in order to allocate specific genotypes to different clinical settings and to monitor their geographical spread. Despite the restriction of analysis on laboratories and hospitals continuously participating in ARS for the last three years, we cannot exclude that changes in hospital structure and case mix and a varying composition of medical practitioners might have biased the results of longitudinal observations.

Conclusion: Surgical ICUs, geriatric, neurological, nephrological, and urological general wards and nephrological, urological and gynaecological practices have been pointed out as problematic areas requiring further in depth investigations in order to identify the most vulnerable points concerning MRSA-transmission in these setting and to focus infection control measures more efficiently.

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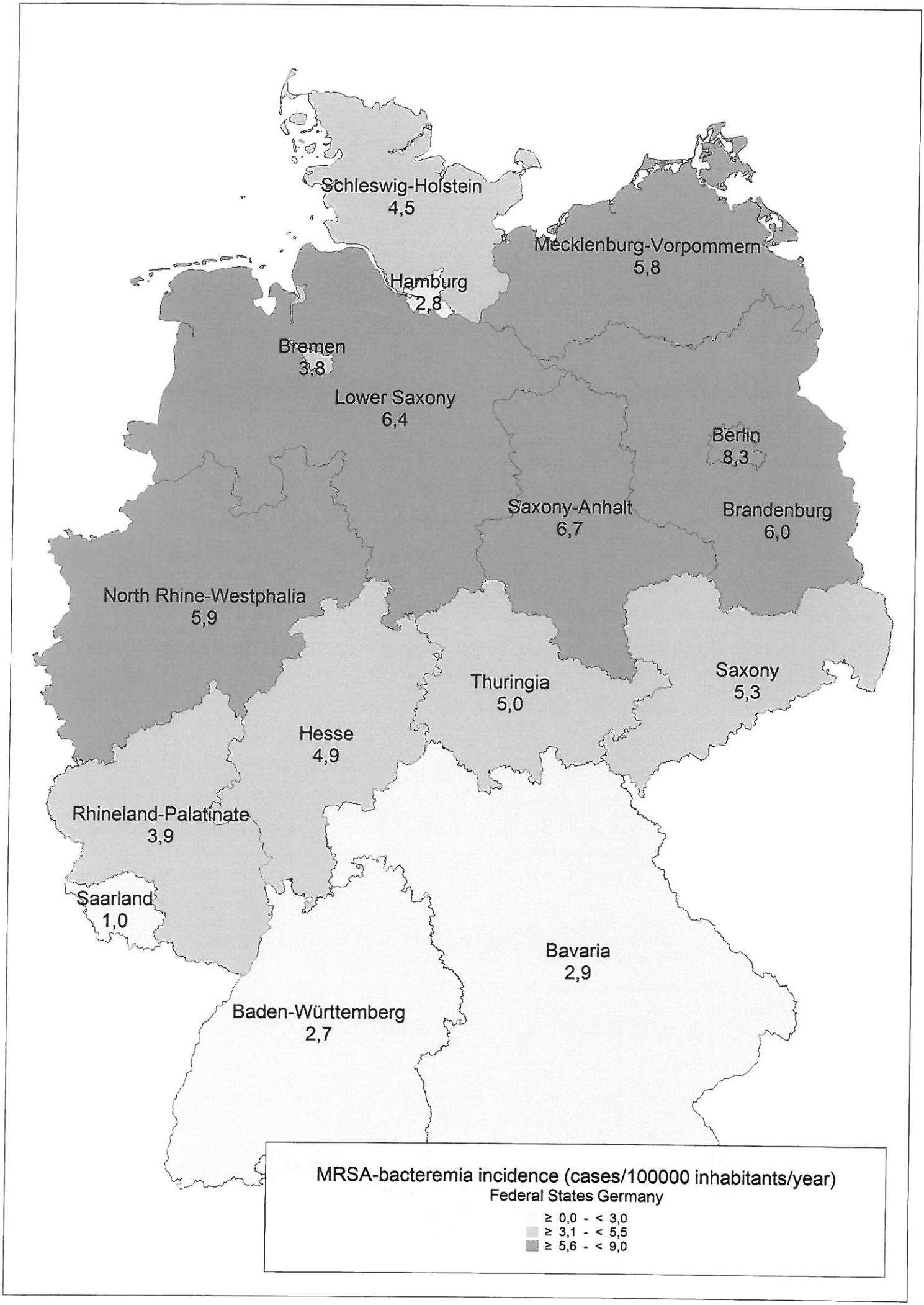
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Saxony
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Hesse
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Rhineland-Palatinate
3,9
Saarland
1,0
Bavaria
2,9
Baden-Württemberg
2,7
MRSA-bacteremia incidence (cases/100000 inhabitants/year)
Federal States Germany
≥ 0,0 - < 3,0
≥ 3,1 - < 5,5
≥ 5,6 - < 9,0

Figure caption:

Figure 1 Regional incidences (federal states) of MRSA-bacteraemia in 2010 in Germany.

Northrhine-Westphalia	16102	11.8	10.9	12.7	11.9
Hessen	452	15.0	12.3	20.0	12.0
Rhineland Palatinate	787	17.5	17.6	17.0	18.0
Baden-Württemberg	2267	7.8	9.1	8.6	5.6
Bavaria	740	15.1	16.1	14.3	14.8
Berlin	6527	8.9	9.1	8.8	8.7
Brandenburg	291	7.9	9.1	6.0	8.0
unknown	329	11.6	16.1	12.8	6.9

[a]chi squared-test, Fisher's exact test, respectively for estimating the difference of the MRSA-proportions between 2008 and 2010

[b]as in the individual years the sample size was < 50 no calculations have been performed

[c]n.d., not done

[d]*p=0.02; **p=0.03

Table 1 Overall MRSA-proportions from 2008-2010 and MRSA-proportions per year in hospital care (100 hospitals) stratified by hospital level, ward type, medical department and speciality, sample type, age, gender and region

Hospital care	2008-2010		2008	2009	2010	
	S. aureus	MRSA	MRSA	MRSA	MRSA	p-value[a]
	n	%	%	%	%	
Total	**39655**	**19.2**	**18.7**	**20.2**	**18.6**	
Hospital level						
Tertiary care	13938	22.0	20.6	23.6	21.9	
General acute care	21427	18.9	18.9	20.0	17.9	
Single speciality	3837	11.6	12.1	12.5	9.6	
Not classified	453	8.2	11.2	6.5	6.1	
Ward type						
Intensive care unit	4714	21.7	20.6	22.6	21.9	
General ward	34941	18.8	18.4	19.9	18.1	
Medical department						
Intensive Care Unit						
Surgical	730	27.0	25.0	30.0	25.8	
Medical	1632	19.0	19.0	18.9	19.1	
Interdisciplinary	2352	22.0	20.5	22.8	22.7	
General ward						
Surgical	10914	16.4	15.9	17.1	16.1	
Medical	16679	21.0	20.4	22.1	20.3	
Other	7348	17.7	17.5	19.2	16.2	
Single Specialities[b]						
Nephrology	176	49.4	42.9	55.1	47.7	
Geriatrics	354	45.8	48.2	46.6	41.2	
Neurology	351	34.2	37.7	34.1	32.6	
Urology	1190	28.6	33.0	31.6	22.8	*[c]
Internal medicine	11460	25.4	25.1	26.3	24.7	
Surgery other	3104	19.4	18.5	21.2	18.5	
General surgery	7752	15.3	15	15.7	15.2	
Gynaecology and obstetrics	1294	6.2	6.4	5.4	6.7	
Dermatology	879	5.9	4.6	7.8	5.4	
Pediatrics	3191	3.8	3.2	5.0	3.1	
Other	3174	16.6	15.4	17.7	16.6	
Unknown	2016	19.8	20.4	21.2	17.6	

Sample type						
Urinary tract	4919	32.9	34.9	32.9	31.0	
Respiratory samples	7252	25.0	25.4	26.3	23.2	
Blood	2430	22.7	22.6	20.7	24.6	
Surgical site	12255	21.3	20.9	21.4	21.7	
Skin and Soft tissue	16178	20.2	21.0	21.3	18.7	**[c]
Invasive punctures	1121	15.6	14.2	16.6	15.8	
Other	3529	36.6	31.1	39.2	39.7	
Unknown	16	31.3	n.d.	n.d.	31.3	
Age						
<15	4381	3.8	3.7	4.9	2.6	
16-59	10654	11.6	11.2	12.2	11.4	
>=60	24620	25.2	24.9	26.4	24.2	
Sex						
Male	16832	17.0	16.6	17.8	16.6	
Female	12741	15.1	14.9	15.8	16.6	
Unknown	10082	27.9	26.1	30.4	27.3	
Region						
Schleswig Holstein	3893	14.6	14.7	14.2	14.8	
Northrhine-Westphalia	15413	24.8	23.2	26.6	24.2	
Hessen	2097	16.7	16.8	18.9	14.6	
Rhineland Palatinate	7437	15.2	15.6	15.6	14.5	
Baden-Württemberg	7837	16.3	16.8	17.1	15.1	
Bavaria	2037	9.9	10.1	9.4	10.2	
Berlin	941	26.8	29.1	25.2	26.2	

[a] chi squared-test, Fisher's exact test, respectively for estimating the difference of the MRSA-proportions between 2008 and 2010

[b] general wards only

[c] *p=0.02, **p=0.01

Table 2 Overall MRSA-proportions from 2008-2010 and MRSA-proportions per year in community outpatient care (2003, 1913, 1763 medical practices, respectively) stratified by medical speciality, sample type, age, gender and region

Community outpatient care	**2008-2010**		**2008**	**2009**	**2010**	
	S. aureus	**MRSA**	**MRSA**	**MRSA**	**MRSA**	**p-value**[a]
	n	%	%	%	%	
total	**31280**	**10.6**	**10.3**	**11.0**	**10.3**	
Medical speciality						
Urology	559	29.2	27.4	31.1	29.3	
Nephrology	2174	14.9	17.5	14.9	12.5	*[d]
Internal /general medicine	13807	14.2	13.9	14.6	14.1	
General surgery	2885	11.4	11.9	11.6	10.7	
Surgery, other	249	6.8	6.6	9.0	4.6	
Throat neck ear	3570	5.1	3.8	6.4	5.0	
Dermatology	3218	4.3	4.5	4.1	4.2	
Gynecology and obstetrics	2102	4.2	3.3	3.9	5.7	**[d]
Pediatrics	2319	3.4	3.1	3.9	3.3	
other	397	5.0	3.0	4.8	7.2	
Sample type						
Blood[b]	84	25.0	n.d.[c]	n.d.	n.d.	
Urinary tract	2930	20.5	20.5	22.4	18.8	
Surgical site	8534	15.0	15.1	15.4	14.6	
Respiratory samples	1175	13.2	12.0	13.2	14.4	
Skin and soft tissue	19285	8.9	9.1	8.9	8.5	
Invasive punctures	278	7.2	7.4	8.0	6.0	
Other	193	15.0	17.1	12.1	15.4	
Unknown	12	n.d.	n.d.	n.d.	n.d.	
Age						
<15	4749	2.7	2.3	2.9	2.8	
16-59	13404	5.5	5.7	5.3	5.4	
>=60	13127	18.6	18.2	19.7	17.8	
Sex						
Male	13566	11.6	11.7	12.1	11.1	
Female	12278	9.6	9.1	9.6	9.9	
Unknown	5436	10.0	9.5	11.5	9.2	
Region						
Schleswig Holstein	3785	6.9	6.6	6.7	7.5	

4. Curriculum vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Due to data protection reasons, my curriculum vitae are not published in the electronic version of this work.

5. Complete list of scientific publications

Publications in scientific journals with peer-review:

1. **E Velasco**, A Ziegelmann, T Eckmanns, G Krause. Eliciting views on antibiotic prescribing and resistance from hospital and outpatient care physicians in Berlin, Germany: a qualitative research study. *BMJ Open* 2012. doi: 10.1136/bmjopen-2011-000398.
2. B Schweickert, I Noll, M Feig, H Claus, G Krause, **E Velasco,** T Eckmanns. MRSA-Surveillance in Germany: data from the Antibiotic Resistance Surveillance System (ARS) and the mandatory surveillance of MRSA in blood. *Eur J Clin Microbiol Infect Dis* 2011 Dec 31.
3. **E Velasco**, W Espelage, M Faber, I Noll, A Ziegelmann, G Krause and T Eckmanns. A national cross-sectional study on socio-behavioural factors that influence physicians' decisions to begin antimicrobial therapy. *Infection* 2011 Aug;39(4):289-97.
4. M Faber, **Velasco E**, Heckenbach M and T Eckmanns. Antibiotic prescriptions for the common cold. What are the expectations of Germany's general population? *Euro Surveill* 2010 Sep 2;15(35).
5. Mohr O, **Velasco E**, Fell G, Burckhardt F, Poggensee G and T. Eckmanns. Using teleconferences for national surveillance of infectious diseases in Germany: Evaluation after three quarters in 2009. *Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz.* 2010; 53:903–909.

Publications currently under review:

6. **E Velasco**, I Noll, W Espelage, A Ziegelmann, G Krause and T Eckmanns. First line treatment for uncomplicated urinary tract infections in outpatient practice: results of a national cross-sectional survey. *In revision after peer review and conditional acceptance by Deutsches Ärzteblatt International*.

Institutional collaborations in scientific journals with peer-review

7. Wadl M, Rieck T, Nachtnebel M, Greutélaers B, an der Heiden M, Altmann D, Hellenbrand W, Faber M, Frank C, Schweickert B, Krause G, Benzler J, Eckmanns T; HUS surveillance and laboratory team. Enhanced surveillance during a large outbreak of bloody diarrhoea and haemolytic uraemic syndrome caused by Shiga toxin/verotoxin-producing Escherichia coli in Germany, May to June 2011. *Euro Surveill.* 2011 Jun 16;16(24). pii: 19893.
8. Frank C, Werber D, Cramer JP, Askar M, Faber M, an der Heiden M, Bernard H, Fruth A, Prager R, Spode A, Wadl M, Zoufaly A, Jordan S, Kemper MJ, Follin P, Müller L, King LA, Rosner B, Buchholz U, Stark K, Krause G; HUS Investigation Team. Epidemic profile of Shiga-toxin-producing Escherichia coli O104:H4 outbreak in Germany. *N Engl J Med.* 2011 Nov 10;365(19):1771-80. Epub 2011 Jun 22.
9. Poggensee G, Gilsdorf A, Buda S, Eckmanns T, Claus H, Altmann D; RKI Working Group Pandemic Influenza, Krause G, Haas W. The first wave of pandemic influenza (H1N1) 2009 in Germany: from initiation to acceleration. *BMC Infect Dis.* 2010 Jun 7;10:155.

10. Gilsdorf A, Poggensee G; Working Group Pandemic Influenza A(H1N1)v. Influenza A(H1N1)v in Germany: the first 10,000 cases. *Euro Surveill.* 2009 Aug 27;14(34). pii: 19318.
11. Description of the early stage of pandemic (H1N1) 2009 in Germany, 27 April-16 June 2009. Novel influenza A(H1N1) investigation team. *Euro Surveill.* 2009 Aug 6;14(31). pii: 19295.

Other publications:

12. **E Velasco**, I Schöneberg, J Benzler, T Eckmanns. [Evaluation of the Infectious disease epidemiological yearbook of reportable diseases for 2009: a user survey] Robert Koch-Institut, *Epid Bull* Nr. 47 29. November 2010.

Scientific works with citations (conferences with proceedings):

13. **E Velasco**, Espelage W, Noll I, Barger A, Krause G and T Eckmanns. Physicians' prescribing practices and antibiotic resistance in Germany. Oral presentation at EuroEpi (European Society for Epidemiology), Warsaw, Poland. Juli 2009.
14. **E Velasco**, Espelage W, Noll I, Barger A, Krause G and T Eckmanns. Antibiotic therapy and resistance in Germany, influence and intervention. Oral presentation at ECCMID (European Congress Clinical Microbiology and Infectious Diseases), Helsinki, Finland. May 2009.

Other scientific works:

15. **E Velasco**, M Krieck, L Otrusina, F Bazoche, J Linge, T Eckmanns, J Dreesman. Social media and epidemiology: tweets indicate Norovirus outbreak at a university. Poster presentation at the IMED (International Meeting on Emerging Diseases and Surveillance). Vienna, Austria. Feb 2011.
16. **E Velasco**, W Espelage, M Faber, I Noll, A Barger, G Krause and T Eckmanns. Outpatient care prescribing practice and antimicrobial resistance for urogenital infections in German hospitals and outpatient settings. Oral presentation at the 3rd Joint Conference of the German Society for Infectious Diseases and the Association for General and Applied Microbiology. Hannover, Germany. March 2010.
17. **E Velasco**, Espelage W, Noll I, Barger A, Krause G and T Eckmanns. German physicians' role in antibiotic therapy and resistance in Germany, influence and intervention. Oral presentation at DGHM (German Society for Hygiene and Medicine), Göttingen, Germany. September 2009
18. **E Velasco**, Espelage W, Noll I, Barger A, Krause G and T Eckmanns. Einflüsse auf die ärztliche Verschreibung von Antibiotika in Deutschland (EVA-Studie). Poster at DGEpi (German Society for Epidemiology), Münster, Germany. September 2009

6. Statement of authorship

„Ich, Edward Velasco, erkläre, dass ich die vorgelegte Dissertation mit dem Thema *Socio-behavioural determinants for antimicrobial prescribing and antimicrobial resistance in hospital and outpatient care practice in Germany* selbst verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt, ohne die (unzulässige) Hilfe Dritter verfasst und auch in Teilen keine Kopien anderer Arbeiten dargestellt habe."

Datum Unterschrift

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