ORIGINAL ARTICLE

Outpatient Antibiotic Prescription

A Population-Based Study on Regional Age-Related Use of Cephalosporins and Fluoroquinolones in Germany

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SUMMARY

Background: In view of the rise in antibiotic resistance and *Clostridium difficile* superinfection, close monitoring of antibiotic prescribing practices is essential so that targeted quality assurance measures can be taken.

Methods: We analyzed nationwide data from multiple statutory health insurance carriers on prescriptions of systemic antibiotics in the years 2008–2014, with special attention to cephalosporins and fluoroquinolones. Prescribing rates were characterized in terms of defined daily doses (DDD) per 1000 statutory insureds per year and were analyzed separately for each age group and each federal state in Germany. Trends were analyzed with joinpoint regression.

Results: Antibiotic prescribing rates for persons aged 15 to 69 increased slightly overall during the period of observation. On the other hand, there was a significant decline in antibiotic prescribing rates for persons under age 15 in all of the German states, with a mean annual decrease of 6.8%. There was also a slight decline in antibiotic prescribing rates for persons aged 70 and above, mainly accounted for by fluoroquinolones. Cephalosporin prescribing rates rose significantly in all states, by an overall average of 7.6% per annum. Cephalosporin prescribing rates rose significantly in all age groups except persons under age 15, for whom there was a decline that did not reach statistical significance.

Conclusion: This study revealed an overall decline in outpatient antibiotic prescriptions for persons under age 15 as well as other major changes in prescribing practices for the types of antibiotics studied. The observed marked rise in cephalosporin prescribing rates in all German states demands special attention because of the associated danger of increased antibiotic resistance and *C. difficile* superinfection. Oral cephalosporins are not recommended as drugs of first choice in current guidelines.

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The relationship between antibiotic use and the development of antibiotic resistance for human medicine has been well documented, both at the individual level and the community level, by numerous publications (1–3). From the perspective of the World Health Organization (WHO) Regional Office for Europe, the following factors in human medicine are primarily responsible for the emergence of resistance: “... overuse, particularly to treat minor or non-bacterial infections [...]; misuse due to faulty diagnosis or lack of information about alternative appropriate treatments; and underuse as a result of lack of access [...] or simply insufficient compliance with the prescribed course” (e1).

In 2008, Germany adopted a first national Antibiotic Resistance Strategy (DART, *Deutsche Antibiotika-Resistenzstrategie*) (4), with a revised version published in 2015 (5). An important goal given by DART is to establish a representative surveillance of antibiotic resistance in both inpatient and outpatient sectors. Data on antibiotic consumption should serve as a basis for future strategies and interventions to minimize resistance problems.

The outpatient care sector, with its estimated 500–600 tons of annual overall use, accounts for some 85% of total human antibiotic consumption in Germany (e2). Outpatient consumption density of total antibiotics in 2012 was 14.9 defined daily doses (DDD) per 1000 inhabitants per day in Germany, which is relatively low in comparison to Europe (with a population-weighted European Union/European Economic Area [EU/EEA] mean consumption from 30 countries of 21.5 DDD per 1000 inhabitants per day) (e3). However, it is noteworthy that, since 2009, outpatient cephalosporin in Germany lies above the EU average. Trend analysis shows that the cephalosporin consumption density between 2008 and 2012 increased significantly only in Germany and Estonia. Indeed, in some EU countries, outpatient cephalosporin consumption is almost negligible (in 2012, the DDD per 1000 inhabitants per day was 0.03 for Denmark, 0.04 for the Netherlands, and 2.82 for Germany) (e3). The current release of DART summarizes it as follows: „Compared to other European countries, however, reserve

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antibiotics and broad-spectrum antibiotics are prescribed more frequently in the outpatient sector in Germany.”

Antibiotic-associated *Clostridium difficile* infections (CDI) are the most common nosocomial-acquired gastrointestinal infections (6). Data from the nationwide surveillance of *Clostridium difficile*-associated diarrhea (CDAD) in the framework of the Hospital Infection Surveillance System (*Krankenhaus-Infektions-Surveillance-System*; CDAD-KISS) revealed that 73% cases were hospital-acquired; by implication, therefore, up to a quarter of cases were acquired in the outpatient sector (7). Clindamycin, quinolones, cephalosporins, and amoxicillin/clavulanic acid are antibiotics with high colitogenic potential (8). The risk factor associated with older age can explain the accumulation of CDI in long-term care residences in the outpatient sector (9).

Analyses of outpatient antibiotic consumption in Germany have been available for some time, and these reveal regional differences (10–13). Similarly, other countries have evidence of significantly different regional consumption densities (14–17). The related issue of quality assurance was noted in the current report from the Advisory Council on the Assessment of Developments in the Health Care System (18).

Special attention needs to be paid to both the development of cephalosporin consumption density in Germany as compared to that for Europe, and to preliminary studies showing a high prescription density of fluoroquinolones in the age group over 70 years old, which is particularly susceptible to CDAD (e4). This prompted us to examine in-depth the development of consumption density for both drug classes, taking into account drug subclasses, regions, and age.

This investigation spanned the period of 2008 to 2014. The obtained results can be used for instance to derive a best-practice approach for appropriate region-based recommendations for implementation of quantitative and qualitative improvements in outpatient antibiotic use. This investigation therefore provides an important complement to data available from surveillance of inpatient antibiotic consumption, which indicate a steady increase in prescribing, in particular for cephalosporins (10, 19, e3, e5).

To better classify these two specific drug classes within the total consumption development, we also present the overall prescription density, and the development of prescription densities, of important drug classes.

Methods

The database was provided by the nationwide Drug Prescriptions Data (AVD, *Arzneiverordnungsdaten*), which includes all statutory health insurers, in accordance with §300 paragraph 2 SGB V (e4). These data are based on all drug prescriptions (except for dental prescriptions) that were redeemed at pharmacies by persons insured through the statutory health insurance (SHI). No data were available from the private health insurance (PHI).

FIGURE 1

Nationwide development of annual antibiotic prescription density in SHI-physician outpatient care. Numbers are defined daily doses (DDD) per 1000 SHI-insured persons, given as total and for three age groups, over the period 2008 to 2014. SHI, statutory health insurance

The investigated cephalosporins and fluoroquinolones were divided into three groups based on their pharmacotherapeutic properties (*eTable 1*). As an indicator of antibiotic consumption, defined daily doses (e6, e7) were calculated with respect to the population of SHI-insured persons (e8). Trends were analyzed using the Joinpoint Trend Analysis Software (e9, e10) (see *eBox* for further information).

Results

Development of total antibiotic prescription density

Outpatient antibiotic consumption density remained relatively stable from 2008 to 2014 (*Figure 1*). An overarching trend of a minimal annual decrease of –0.5% was observed across all age groups, which was however not statistically significant.

A significant decline in the annual total prescription density was observed for the group under 15 years old. The previous peak level of 2009, of nearly 6000 DDD per 1000 SHI-insured persons, fell by 2014 to just under 4000 DDD per 1000 SHI insured persons (*Figure 1*). This represents an annual decline of 6.7% nationwide, which ranged from 4.4% in Bremen to 9.8% in Thuringia. Results of the trend analysis for all federal states were statistically significant, regardless of outset values (*eTable 2*).

A weaker, statistically non-significant declining trend was observed nationwide for the group 70 years old and older, although the annual decline in Saxony–Anhalt and Thuringia of –3.7% and –13.3%, respectively, was more pronounced and significant.

In the age range from 15 to 69 years, the overall consumption density was slightly increased (by 0.6%); however, this trend was only significant for the federal states of Bremen and Thuringia (*eTable 2a*).

FIGURE 2

Nationwide development of the proportional use of the 9 antibiotic active groups in the SHI-physician total prescription density of antibiotics. Proportions in percent based on defined daily doses (DDD) per 1000 SHI-insured persons, given as total and for three age groups, in the first and last years of the study period (2008 and 2014). SHI, statutory health insurance

Prescription trends for the proportional use of different antibiotic groups

The proportional use of the different antibiotic drug groups prescribed (as DDD per 1000 SHI-insured persons) differed significantly in the three age groups (Figure 2). Basic penicillins and cephalosporins accounted for over three-quarters of antibiotic prescriptions for the group under 15 years old. Hereby, the proportional use of cephalosporins continued to increase from 2008 to 2014, at the expense of basic penicillins and macrolides (Figure 2). In the other age groups, the proportion of cephalosporins was also significantly increased, yet it still was less than that for the <15-years-old group. For the ≥70-years-old group, the increase in the proportional use of cephalosporins did not influence that of the basic penicillins. Despite a slight decrease in prescription proportion, fluoroquinolones still play an important role for this age group (Figure 2).

It should be noted that there was an increase in the percentage of the cephalosporin proportion in the <15-years-old group. However, the total number of cephalosporin prescriptions was slightly lower, due to the significant reduction in overall antibiotic prescription density.

Regional characteristics in prescribing fluoroquinolones and cephalosporins

The fluoroquinolone consumption density in 2008 was especially higher for the group of 15- to 69-year-olds in southwest Germany as compared to most of the new federal states (Figure 3). Up to 2014, fluoroquinolone consumption showed regional trends of slightly decreasing, but it is only significant for Baden-Württemberg, which had an annual percent change (APC) of 1.7% (eTable 2c). However, these trends were significant for the ≥70-years-old group in almost all federal states, with the exception of Schleswig-Holstein, Hamburg, and Bremen; APC values ranged from -1.1% in Hamburg to -10.3% in Thuringia (eTable 2c).

The proportional use of fluoroquinolones from group 3, which is mainly norfloxacin, was very low over the entire observation period and decreased even further by 2014. In contrast, the proportional use of ciprofloxacin (group 1) increased in most regions (Figure 3 and eFigure 1).

A somewhat different picture emerged for the cephalosporins (eFigure 2 and eTable 2b). Prescription density increased in all federal states, with the annual trend values ranging from +5.6% in Saxony to +9.1% in Rhineland-Palatinate (eTable 2b). A similar trend is observed for the groups of 15- to 69-year-olds and 70 years old and older, with both showing significant increases in all federal states with average annual APC values of +10.7% and +8.1%, respectively (eTable 2b). In contrast, a negative trend was observed for the group of under-15s in almost all federal states; however, this was only significant in Saxony and Mecklenburg-West Pomerania (with an APC of -8.5% and -5.5%, respectively). Nonetheless, the relative importance of cephalosporins has increased in this age group, considering the overall trend of significant decreases in antibiotic consumption density in all federal states (eTables 2a and 2b).

The consumption density of first-generation cephalosporins continued to decline, as shown by a comparison between 2008 and 2014 (eFigure 2). Currently, they only still play a (minor) role in pediatrics and adolescent medicine. The proportional use of second-generation cephalosporins (and primarily, cefuroxime axetil) largely increased as compared to that of first- and third-generation cephalosporins during the study period, for all age groups and nationwide. Third-generation cephalosporins were also partially replaced by the second-generation ones in the new federal states. In Mecklenburg-West Pomerania and Saxony-Anhalt, for example, third-generation cephalosporins still made up more than 50% of cephalosporin consumption in 2008 (eFigure 2).

Discussion

The cause for the observed increase in cephalosporin prescriptions in all regions cannot be explained by the data currently available to us and the methods used. This trend is expected to predominantly affect respiratory infections (e11, e12), for which the use of

penicillins, macrolides, and tetracyclines has been correspondingly lower—even though these antibiotics are especially indicated for respiratory infections (e13). Prescribing substitutions of penicillin, however, is not observed for the ≥ 70 -years-old group. Nonetheless, based on our own preliminary investigations, we can rule out that DDD increased only due to higher dosages—that is, a pseudo-increase with a similar number of prescriptions (e4). Analyses by season for 2009 and 2013, years with striking numbers of reported influenza cases (e14), indicate a similar variability in prescription incidence of oral cephalosporins in these years. However, the trend analysis over the entire period is only slightly affected by prescription fluctuations.

Oral cephalosporins are not considered the drug of choice for respiratory infections or pneumonia in any current practice guidelines. Indeed, they are at the most mentioned as amoxicillin alternatives in cases of intolerance by the national Pneumonia Guideline from 2009 (20), the European Pneumonia Guidelines from 2011 (21), and the Treatment Recommendations of the Drug Commission of the German Medical Association from 2013 (e15). In the guidelines of the German College of General Practitioners and Family Physicians (DEGAM), they are given as alternatives to patients with incompatibility in individual cases for “cough” in 2008 and 2014 (e16, e17) and for “rhinosinusitis” in 2008 (e18). Problems of incompatibility while treating respiratory infections with amoxicillin are often cited in Germany as a reason for prescribing oral cephalosporins rather than penicillin derivatives. However, the side-effect incidence is only about 10%, and only about 10–20% of these patients can be classified as being allergic to amoxicillin (22).

Denmark, the Netherlands, Sweden, and Norway use almost no oral cephalosporins in their outpatient sectors (e3). Perhaps the guideline content and data for antibiotic intolerance and allergies have to be more intensely communicated and discussed in the medical community working with outpatient services in Germany. The preferred single compound cefuroxime was approved as an oral drug in the late 1980s. The daily treatment costs for cefuroxime are not more favorable than those for amoxicillin. Cefuroxime axetil has 40–60% systemic availability, with widely varying levels of active compound (23), which could be responsible for its negative effects of resistance development. The potentially adverse consequences of increased prescriptions of cephalosporins rather than oral penicillin and amoxicillin are sufficiently demonstrated for the outpatient sector in our view, especially with regard to antibiotic-associated *Clostridium difficile* infections (24–27). Data for selection of gram-negative bacteria that are extended-spectrum beta-lactamase (ESBL)-positive or otherwise resistant to cephalosporins are less certain but still plausible (28–31).

The declining antibiotic consumption density for children is interesting. Here, the pneumococcal conjugate vaccines introduced in 2006 might be playing a

Cartographic representation of outpatient SHI medical prescription levels of fluoroquinolones by federal state, in 2014. Numbers are given as defined daily doses (DDD) per 1000 SHI-insured persons between 15 and 69 years of age. Pie charts are assigned to the German federal states and show the respective proportional use of the groups 1–3 in the annual total prescription density of fluoroquinolones. SHI, statutory health insurance

causative role. Due to implementation delays, it would be reasonable that the effects would be noticeable starting from 2010 onwards. Indeed, there is evidence for this from other countries (32). Vaccination rates had not risen to significantly more than 70% by 2009 (33, 34). Further analysis and modeling will allow a more detailed assessment of the vaccination effects. Intriguingly, the cephalosporin prescription rates remain lower in the new federal states, especially as compared to the southwest. In some eastern states, cephalosporin consumption density has decreased even further within the investigation period. Whether this is associated with differences in availability of pediatricians and regional socio-demographic characteristics, such as single parenthood, unemployment, and daycare availability, is unclear.

The observed leveling off of fluoroquinolone prescriptions is very important. Quinolones were no longer recommended in the relevant general medical and urological guidelines (35, 36) starting from 2009 and 2010, respectively, for uncomplicated urinary tract infections. Instead, oral administration of fosfomycin or nitrofurantoin was suggested, and our data, in contrast to previous surveys (e2, e4, e13), shows a corresponding increase in their use. Other indications for fluoroquinolones are pyelonephritis and complicated urinary tract infections, some specific respiratory infections, and, in certain circumstances, community-acquired pneu-

monia. Earlier analyses showed that respiratory infections in Germany were relatively often treated with fluoroquinolones, especially in the new federal states (e11, e12). However, the indications for this are not known in detail. It is highly possible that fluoroquinolone prescriptions can be further reduced without loss of treatment quality, such that their role as a reserve antibiotic could be strengthened. An indication for this are the discrepancies that are still present between East and West Germany. The reduced prescription rate for the ≥ 70 -years-old group should be positively valued, especially considering the complication of *C. difficile* infections that occur with severe cases and almost exclusively in older age.

A dilemma commonly faced by physicians in outpatient care is the decision for or against an antibiotic therapy, which is not straight-forward. Despite awareness about the need for a strategy against resistance development, this is often outweighed by an apprehension of overlooking a serious infection and not treating soon enough with antibiotics (37). A further role is played here by the expectations of patients or parents of sick children. For many people, a diagnosis of “acute bronchitis” is synonymous with “requires antibiotic therapy” (38). Decision-making can be supported using biomarkers for bacterial infections, such as procalcitonin (39, 40, e19), but these are not currently available for the outpatient sector and might not be in the near future either. At the regional level, quality management measures based on best practice approaches or antibiotic stewardship programs would be useful (e20, e21). The results of this study may help in identifying appropriate regionally-based approaches.

Limitations

One limitation of this study was the restriction of only using data from SHI-insured persons, which thereby excluded approximately 15% of the population. This leaves a remaining uncertainty as to the validity of the results for the whole population. Additionally, diagnostic and physician group-specific prescription data were not included in the study. Further, using age standardization only allows morbidity differences to be controlled indirectly and incompletely. Regional variations could therefore be at least partially explained by morbidity differences. In particular, prescription data for children can differ between general practitioners and pediatricians. It can not be ruled out that regional differences in medical specialists contributed to the observed variations. DDD did not correspond in all cases to the actual dose, but it is the most widely-used measurement internationally. The indicator DDD per 1000 inhabitants is based on adult doses, and its methodology is only limitedly suitable for pediatrics. In the outpatient sector, no data are currently available about the prescribed daily doses that could address this problem (e22). For instance, the European Centre for Disease Prevention and Control (ECDC) provisionally uses the number of packages rather than DDD (e3). Our own study showed that results using number of

packages and DDD are equivalent to a large extent (e4). Preferably, indicators could also be used, for example for the proportional use of different groups of active substances detected regionally (for instance, for the ratio of basic penicillin/tetracycline to cephalosporins/quinolones). Finally, a further restriction to keep in mind is that even when issued, it is certain that not all prescriptions are filled, and not all antibiotics are actually consumed. The actual volumes of outpatient antibiotic prescription are likely to be above, and those on population level, below, the values found in this study.

KEY MESSAGES

- The total antibiotic consumption density in statutory health insurance physician outpatient care in Germany has not increased in the past years, and regional differences in total consumption has likewise changed little.
- The total prescription density for children declined significantly in all regions.
- In Germany nationwide, the prescription density of cephalosporins has risen sharply.
- Prescription density of fluoroquinolones has slightly declined, especially for the elderly population.
- The age-related results and the regional variations observed here now allow more targeted planning, with quality management measures that are adapted to different regional conditions for outpatient antibiotic therapy, as well as identification of best practice areas.

Conflict of interest statement

Prof. Kern has received travel reimbursement from Bayer and payment for scientific lectures from Infectopharm and Pfizer.

The remaining authors declare that no conflict of interests exists.

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Supplementary material

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Supplementary material to:

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eBOX

In-depth details for Methods

● Data basis and data protection

The population-based antibiotic consumption was calculated based on data of nationwide Drug Prescriptions Data (AVD), which includes all statutory health insurances (SHI), and on the data of the reference population. Prescription prevalences are determined directly from age-standardized data at federal state level. Of the numerous pharmacoepidemiologic indicators, such as number of prescriptions, defined daily doses (DDD), or number of patients with antibiotic prescriptions per 1000 SHI-insured persons (e4), this study only used DDD. AVD data management at the Central Research Institute for Ambulatory Health Care in Germany (Zi) used a data security concept that is coordinated with the relevant Data Protection Supervisor.

● ATC classification system and DDD

All prescriptions for pre-packaged medications with an ATC code (Anatomical Therapeutic Chemical Classification System, ATC) assigned to group J01 (antibacterials for systemic use) were taken into account. The official version of the ATC classification, with details of the respective DDD, has been published annually since 2004 by the German Institute of Medical Documentation and Information (DIMDI) and is also available from the Scientific Institute of the AOK (WIdO) (e6, e7). ATC codes are allocated through the pharmaceutical registration number (Pharmazentralnummer, PZN) by the applicable WIdO master file. The active ingredients of the ATC group J01 (antibacterials for systemic use) were divided for the analysis, based on a pharmacologically-infectiological point-of-view, into a total of ten different antibiotic drug classes (e4). Because fluoroquinolones are contraindicated in children and adolescents, they are not included in the prescription density for the <15-year-old group.

The number of defined average daily doses according to DIMDI was used as an indicator of antibiotic use, both in general and for active ingredients (e6, e7). Regional prescription densities (DDD per 1000 SHI-insured) were calculated in total over all age groups direct as age-standardized and age-specific (under 15 years old, 15 to 69 years old, and 70 years old and older).

● Reference population

The reference population was defined as the population of all SHI-insured persons, according to KM6 statistics of the Federal Ministry of Health (BMG) (e8) and determined annually, for the study period 2008 to 2014. In these statistics, the number of SHI-insured persons is published according to age group and federal state, among other metrics. SHI-insured persons can therefore be stratified by age and region (e.g., federal state, region of KV [Kassenärztliche Vereinigung, Association of Statutory Health Insurance Physicians]), which are published in these statistics. The reference population underlying our analyses is available in *vTable 1* (*) by year, federal state, and age group (<15 years, 15–69 years, ≥70 years). From data of the reference population, following KM6 statistics, the indicator DDD per 1000 SHI-insured persons can be determined with respect to age group, federal state, and year (*vTable 2* (*) and *3* (*)).

● Trend analysis using Joinpoint regression

The regression analysis tool used for trend analysis, Joinpoint Regression, is used primarily for the trend analysis of incidence or mortality rates of cancer. In these cases, the rates are modeled as a function of time. The model fitting is based on the least-squares method. With a sufficiently long time series, trend reversal points (so-called joinpoints) can be estimated. Thus, the Joinpoint software determines the time points and intervals of joinpoints and the associated increases or the rate of annual percent change (APC). Due to the relatively short time series in the present study, determination of joinpoints was not used, but rather only APC values were given (total and by federal states) for the time interval of 2008 to 2014. The significance level of $\alpha = 0.05$ was used in all analyses. For calculations, the Joinpoint Software Version 4.2.0.2 from 23 June 2015 was used (e9, e10).

● Methodological limitations

The restriction of only using SHI-insured persons produced some limitations. Approximately 15% of the German population are insured with private health insurance (PHI), leaving a remaining uncertainty as to the validity of the results for the whole population. The proportion of privately insured persons shows an East–West discrepancy and can also vary strongly by regions (e23), so that this uncertainty may be differentially noticed at the regional level. However, it can be assumed that the same physicians are prescribing antibiotics in their regions for both SHI- and PHI-insured persons. Thus, an insurance-related difference in antibiotic prescriptions, which could be based on different socioeconomic characteristics, seems highly unlikely but cannot be excluded.

● Side note: Dentist prescribed antibiotics

Dental prescriptions, which were not included in this analysis, make up almost 10% of all antibiotics prescribed through public health insurance (SHI), according to previous results (e24). Here, the prescription spectrum is very different from that in the medical field: clindamycin at 50% clearly is most prescribed, followed by penicillin and aminopenicillins at 42%. Other antibiotics, especially fluoroquinolones and cephalosporins, play only a very minor role (e24).

(*) vTables available at Versorgungsatlas (Health Care Atlas): www.versorgungsatlas.de/themen/alle-analysen-nach-datum-sortiert/?tab=6&uid=73

eFIGURE 1

Cartographic representation of outpatient SHI medical prescription levels of fluoroquinolones by federal state in defined daily doses (DDD). Numbers are given as defined daily doses (DDD) per 1000 SHI-insured persons in the first and last years of the study period (2008 and 2014), per age group (15–69 years and ≥70 years) and directly age-standardized. Pie charts are assigned to the federal states and show the respective proportion of the groups 1–3 of the total annual prescription density of fluoroquinolones.

Note: The colour coding changes from age group to age group in this figure, meaning that the shade of blue can be used to compare areas within age groups (horizontally across the page), but not between age groups (vertically or diagonally). Since quinolones for children are contraindicated, these were not studied in the age group under 15 years. Data tables used for the map and pie charts can be downloaded from Versorgungsatlas (Health Care Atlas): www.versorgungsatlas.de/themen/alle-analysen-nach-datum-sortiert/?tab=6&uid=73

eFIGURE 2

Cartographic representation of prescription levels of cephalosporins by federal state in defined daily doses (DDD) per 1000 SHI-insured in the first and last years of the study (2008 and 2014), per age group (<15, 15–69 years, and ≥70 years) and directly age-standardized. Pie charts are assigned to the federal states and show the respective proportion of the generations 1–3 of the total annual prescription density of cephalosporins.

Note: The color coding changes from age group to age group in this figure, meaning that the shade of orange can be used to compare areas within age groups (horizontally across the page), but not between age groups (vertically or diagonally). Data tables used for the map and pie charts can be downloaded from Versorgungsatlas (Health Care Atlas) at: www.versorgungsatlas.de/themen/alle-analysen-nach-datum-sortiert/?tab=6&uid=73

eTABLE 1

Active ingredients and ATC codes for cephalosporins and fluoroquinolones (considered for this study), with subgroups

Active ingredient (single or multiple)	ATC code	Subgroup
Cephalosporine		
Cefalexin	J01DB01	1. Generation
Cefadroxil	J01DB05	1. Generation
Cefuroxime	J01DC02	2. Generation
Cefaclor	J01DC04	2. Generation
Cefixime	J01DD08	3. Generation
Cefpodoxime	J01DD13	3. Generation
Ceftibuten	J01DD14	3. Generation
Fluoroquinolones		
Ciprofloxacin	J01MA02	Group 1 ^{*1}
Levofloxacin	J01MA12	Group 2 ^{*1}
Moxifloxacin	J01MA14	Group 2 ^{*1}
Ofloxacin ^{*2}	J01MA01	Group 3 ^{*1}
Enoxacin	J01MA04	Group 3 ^{*1}
Norfloxacin	J01MA06	Group 3 ^{*1}

^{*1} The groups highlight, from a clinical pharmacology point-of-view, the main areas of indication:

Group 1: broad indication,

Group 2: respiratory infections,

Group 3: urinary tract infections.

^{*2} Ofloxacin can generally be considered as a systemically effective fluoroquinolone, belonging to group 1, but it has been assigned in this study to the active ingredients of group 3, as it is now almost exclusively indicated for urinary tract infections.

ATC, Anatomical Therapeutic Chemical Classification System

eTABLE 2a

Trend analysis of the development of outpatient prescription densities for total systemic antibiotics^{*†}

Age group	DDD per 1000 SHI-insured: Total antibiotics							
	<15 Years		15–69 Years		≥ 70 Years		Total	
Federal state	APC	p	APC	p	APC	p	APC	p
Schleswig–Holstein	–4.97	**	1.32		–0.29		0.63	
Hamburg	–6.53	**	1.39		0.39		0.42	
Bremen	–4.40	*	2.64	*	2.06		1.84	
Lower Saxony	–7.20	**	0.47		–1.41		–0.51	
North Rhine–Westphalia	–6.52	**	0.40		–0.63		–0.57	
Hesse	–6.30	**	0.04		–2.27		–0.80	
Rhineland–Palatinate	–5.93	**	1.24		–0.73		0.19	
Baden–Württemberg	–5.64	**	0.08		–1.89		–0.64	
Bavaria	–6.19	**	0.27		–1.47		–0.52	
Berlin	–6.83	**	0.48		–0.34		–0.53	
Saarland	–5.20	**	1.19		0.14		0.01	
Mecklenburg–West Pomerania	–8.27	**	1.20		–0.07		–0.25	
Brandenburg	–7.99	**	–0.86		–2.52		–1.95	
Saxony–Anhalt	–8.43	**	1.14		–3.69	**	–1.27	
Thüringen	–9.79	**	5.56	*	–13.34	**	–1.32	
Saxony	–8.84	**	0.15		–1.57		–1.35	
Federal	–6.68	**	0.60		–1.60		–0.52	

* $p < 0.05$; ** $p < 0.01$

[†] DDD per 1000 SHI-insured in the period from 2008 to 2014, broken down by federal states and age groups. APC values were calculated using Joinpoint Trend Analysis Software, and specification of significance levels by the respective p -values. DDD, defined daily doses according to ATC classification of DIMDI/WIdO (e6, e7);

APC, annual percent change calculated with Joinpoint Trend Analysis Software (e9, e10)

eTABLE 2b

Trend analysis of the development of outpatient prescription densities of cephalosporins*¹

Age group	DDD per 1000 SHI-insured: Cephalosporins							
	<15 Years		15–69 Years		≥ 70 Years		Total	
Federal state	APC	p	APC	p	APC	p	APC	p
Schleswig–Holstein	0.52		9.34	**	8.86	**	7.39	**
Hamburg	–2.73		11.98	**	9.43	**	7.93	**
Bremen	0.39		8.65	**	8.22	**	6.45	**
Lower Saxony	–1.54		9.34	**	8.00	**	6.93	**
North Rhine–Westphalia	–1.02		10.25	**	8.31	**	7.33	**
Hesse	0.57		11.73	**	8.04	**	8.89	**
Rhineland–Palatinate	–0.16		12.13	**	9.95	**	9.13	**
Baden–Württemberg	–0.50		9.22	**	7.54	**	6.63	**
Bavaria	–0.84		10.63	**	9.07	**	8.04	**
Berlin	–3.90		12.56	**	11.39	**	8.36	**
Saarland	–0.12		9.20	**	7.72	**	6.10	**
Mecklenburg–West Pomerania	–5.53	**	12.83	**	12.63	**	8.10	*
Brandenburg	–4.16		10.55	*	8.25	*	6.84	*
Saxony–Anhalt	–5.70		12.41	**	5.59	*	6.37	*
Thuringia	–4.00		18.39	**	–2.54		8.11	*
Saxony	–8.45	*	11.23	**	7.49	**	5.59	*
Federal	–1.52		10.74	**	8.05	**	7.57	**

* p < 0.05; ** p < 0.01

¹ DDD per 1000 SHI-insured in the period from 2008 to 2014, broken down by federal states and age groups. APC values were calculated using Joinpoint Trend Analysis Software, and specification of significance levels by the respective p-values.

DDD, defined daily doses according to ATC classification of DIMDI/WIdO (e6, e7);

APC, annual percent change calculated with Joinpoint Trend Analysis Software (e9, e10)

eTABLE 2c

Trend analysis of the development of outpatient prescription densities of fluoroquinolones ^{*†}

Age groups	DDD per 1000 GKV-insured: Fluoroquinolones					
	15–69 Years		≥ 70 Years		Total	
Federal state	APC	p	APC	p	APC	p
Schleswig–Holstein	–0.25		–1.49		–0.19	
Hamburg	–0.25		–1.05		–0.04	
Bremen	2.64		1.18		2.62	*
Lower Saxony	0.15		–2.17	**	–0.35	
North Rhine–Westphalia	–0.62		–2.61	**	–0.63	
Hesse	0.12		–2.11	**	–0.16	
Rhineland–Palatinate	0.52		–1.92	**	0.14	
Baden–Württemberg	–1.66	**	–3.14	**	–1.70	**
Bavaria	–1.42		–2.76	**	–1.40	*
Berlin	–0.42		–2.13	*	–0.56	
Saarland	0.54		–1.78	**	0.23	
Mecklenburg–West Pomerania	–1.38		–3.12	**	–1.51	
Brandenburg	–2.20		–3.98	**	–2.72	*
Saxony–Anhalt	–0.23		–4.61	**	–1.39	
Thuringia	4.12		–10.34	**	–2.14	
Saxony	–1.50		–3.28	**	–1.67	
Federal	–0.60		–2.89	**	–0.95	

* $p < 0.05$; ** $p < 0.01$

[†] DDD per 1000 SHI-insured in the period from 2008 to 2014, broken down by federal states and age groups.

APC values were calculated using Joinpoint Trend Analysis Software, and specification of significance levels by the respective p -values.

DDD, defined daily doses according to ATC classification of DIMDI/WIdO (e6, e7)

APC, annual percent change calculated with Joinpoint Trend Analysis Software (e9, e10)