Original Article

The Decline in Outpatient Antibiotic Use

An Analysis of Nationwide Prescription Data From 2010 to 2018

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Summary

Background: A central component of the German antibiotic resistance strategy is to monitor the outpatient prescribing of systemic antibiotics nationwide, across all of the statutory health-insurance providers, in order to provide a basis for targeted quality-assurance measures.

Methods: All outpatient drug prescription data from patients covered by the statutory health-insurance carriers in Germany in the age groups 0−14, 15−64, and ≥ 65 years were assessed. The chosen primary outcome measure under study was the prescription rate (number of antibiotic prescriptions per 1000 insurees per year) for the years 2010 to 2018.

Results: Over the period of the study, a 21% decline was seen in the use of systemic antibiotics in outpatients, from 562 to 446 prescriptions per 1000 insurees per year in 2010 and 2018, respectively. The most marked reduction in the prescription rate—by 41%—was seen among child and adolescent insurees (in other age groups: –17% among those aged 15−64, –12% among those aged 65 and older). A downward trend was seen in all regions of Germany, and for most of the active substance groups for which data were obtained. In 2018, the prescription rate varied by a factor of 1.8 among regions, with the highest rate in the Saarland (572 per 1000 insurees per year) and the lowest in Brandenburg (318 per 1000 insurees per year).

Conclusion: The observed nationwide decline in the prescription of antibiotics to outpatients in all age groups may be a result of the numerous initiatives that have been put into action to reinforce the appropriate use of antibiotics in Germany. A change in pediatric prescribing practices is demonstrated by the marked reduction in this age group. The remaining major differences across German regions underscore the importance of regionally tailored programs for the promotion of rational antibiotic use.

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Widespread use of antibiotics in situations where they are not actually indicated is thought to be a major driver of increased antibiotic resistance at both individual and population level (1–3).

The establishment of effective monitoring systems to register antibiotic use is an important precondition for targeted measures to combat the spread of resistance.

In Germany, around 85% of antibiotics in human medicine are prescribed to outpatients (4). Complementing the monitoring of inpatient antibiotic consumption, the nationwide outpatient prescription data from statutory health insurance providers that are collected in accordance with § 300 of the German Social Code book V (SGB V) provide detailed insights into the trends in outpatient antibiotic use.

In the context of Europe as a whole, outpatient antibiotic use in Germany is relatively low (5). Furthermore, decreased consumption in children and adolescents in the period 2010−2014 indicates increasingly cautious prescription of antibiotics in this segment of the population (6). However, growth in the prescription of cephalosporins and high consumption of fluoroquinolones point to excessive use of braod-spectrum antibiotics (6). Both of these substance classes are linked with the development of resistance on the part of gram-negative bacteria (7, 8) and the increased occurrence of antibiotic-associated *Clostridium difficile* infections (9, 10). Moreover, the recent trends in fluoroquinolone use merit particular attention due to new findings concerning severe adverse effects (11).

Apart from the matter of which classes of antibiotics are selected, analyses of outpatient antibiotic use up to and including 2014 show strong regional variations (6), pointing to regional differences in indication quality (12).

The aim of this study was to investigate the outpatient use of systemic antibiotics among residents of Germany with health insurance from companies belonging to the National Association of Statutory Health Insurance Funds (GKV) in the period 2010−2018, with particular emphasis on recent prescription trends by age, region, and class of antibiotic.

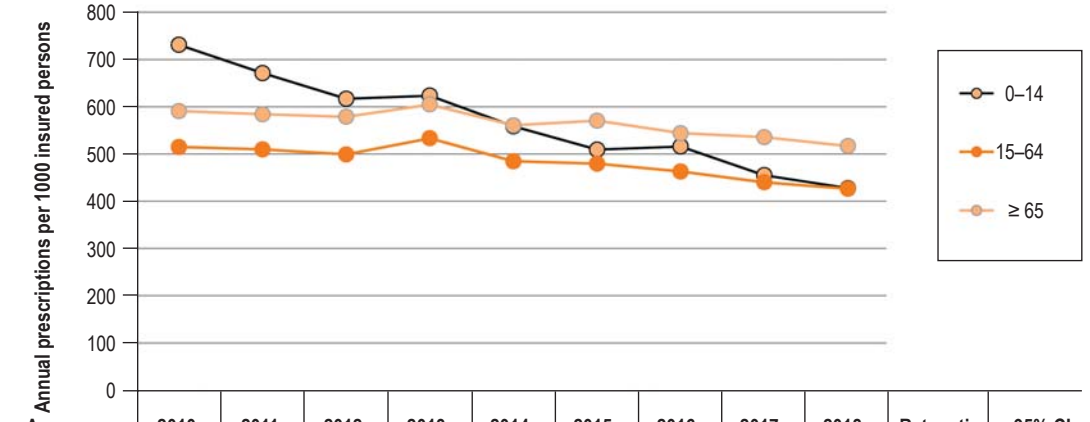
TABLE 1

Number of insured persons, number of prescriptions, defined daily doses, age-standardized prescription density, and age-standardized prescription rate: nationwide figures for each year of the observation period

	2010	2011	2012	2013	2014	2015	2016	2017	2018
Insured persons, total*	69 473 648	69 311 311	69 398 848	69 521 916	69 954 575	70 347 435	71 031 210	71 809 490	72 318 533
Prescriptions, total	38 895 086	37 905 395	36 890 353	38 951 557	35 720 548	35 396 031	34 622 284	33 241 776	32 283 527
DDD, total	361 363 831	352 727 027	346 135 843	372 296 786	342 376 706	340 866 739	337 482 661	325 185 143	315 691 180
Prescription density, stand.	5206	5091	4988	5353	4892	4842	4749	4528	4365
Prescription rate, stand.	562	548	533	561	512	504	488	463	446

DDD, Defined daily doses; stand., age-standardized
* According to KM 6 statistics (13)

FIGURE 1



Age group	2010	2011	2012	2013	2014	2015	2016	2017	2018	Rate ratio	95% CI
0–14	731	671	617	623	559	509	516	455	428	0.94	[0.93; 0.95]
15–64	515	510	499	533	485	479	463	440	426	0.97	[0.97; 0.98]
≥ 65	591	584	579	605	561	570	544	536	517	0.98	[0.98; 0.99]

Age-group specific prescription rates for systemic antibiotics (prescriptions per 1000 insured persons per year) in the period 2010 to 2018, with rate ratios for the influence of the passage of time and the corresponding 95% confidence intervals (95% CI) from age group-specific Poisson regression models based on monthly prescription rates and adjusted for seasonality

Methods

The investigation of outpatient antibiotic use was based on a complete record of nationwide prescription data from all GKV health insurance providers according to § 300 SGB V for the period 2010–2018, with the annual population of all GKV-insured German residents according to the KM 6 statistics (statutory health insurance: insured persons) compiled by the Information System of the Federal Health Monitoring as denominator (13).

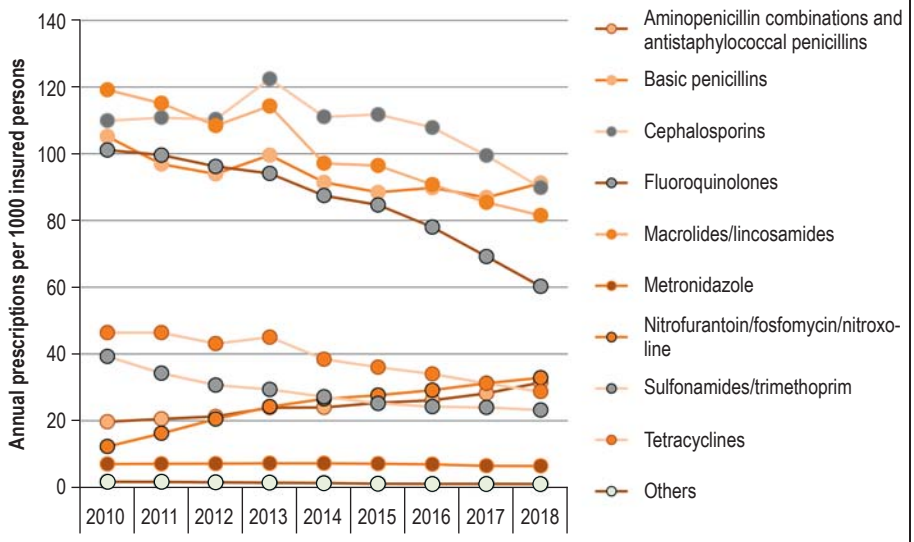
The prescription rate, i.e., the number of antibiotic prescriptions issued per 1000 insured persons per year, was chosen as the primary measure of use for systemic antibiotics in the outpatient setting. The prescription rate approximates the rate of antibiotic treatments at population level, enables the documentation of antibiotic exposure in various age groups independent of age-related dosing differences, and is robust against changes in the amount of active substance per prescription over time. The temporal trends were modeled by means of Poisson regression. A more detailed account of the methods employed can be found in the supplementary *eMethods*.

Results

Nationwide trends

Over the course of the observation period from 2010 to 2018, yearly antibiotic use decreased from 562 to 446 prescriptions per 1000 insured persons (−21 %, *Table 1*), corresponding to an annual decrease of 3% (rate

FIGURE 2



Annual nationwide prescription rates for different classes of systemic antibiotics (prescriptions per 1000 insured persons per year) in the period 2010 to 2018

ratio [RR] 0.97). Simultaneously, the age-standardized prescription density (defined daily doses [DDD] per 1000 insured persons) went down by 16% (2010: 5206; 2018: 4365). The steady reduction in these two measures of use was interrupted only by a rise of 5% in prescription rate and 7% in prescription density from 2012 to 2013 *(Table 1)*.

In the age group 0 to 14 years the annual prescription rate decreased by 41% from 731 (2010) to 428 prescriptions (2018) per 1000 insured persons (RR 0.94) *(Figure 1)*. The prescription rate also went down in older adolescents and adults, although the decreases were less pronounced, at 12% (15 to 64 years, RR 0.97) and 17% (≥ 65 years, RR 0.98) *(Figure 1)*.

Prescription rates by substance class

The prescription rates for eight of the ten classes of antibiotics investigated were found to have decreased during the observation period. The highest reduction was seen for tetracyclines (−44%), the least pronounced decline for basic penicillins (−13%) *(Figure 2, Table 2)*. The use of cephalosporins decreased by 17%. Aminopenicillin combinations and staphylococcal penicillins (+55%) and nitrofurantoin/fosfomycin/nitroxoline (+ 175 %) were the only groups for which the prescription rates increased sharply *(Figure 2, Table 2)*.

In 2018, basic penicillins and cephalosporins were the most commonly prescribed antibiotics, each accounting for 20% of all prescriptions *(Figure 3)*. They were followed by macrolides/lincosamides (18% [macrolides 15%, clindamycin 3%]) and fluoroquinolones (14%). The proportion of prescriptions accounted for by basic penicillins fell with increasing patient age (0–14 years 44%, 15–64 years 19%, ≥ 65 years 11%). In contrast, the relative contributions of the classes sulfonamides/trimethoprim and nitrofurantoin/fosfomycin/nitroxoline increased with age. Fluoroquinolones were prescribed almost exclusively to adults—corresponding to their terms of use—and made up 22% of the prescriptions among ≥ 65-year-olds. Tetracyclines were also used primarily in the two highest age groups (15–64 years 8%, ≥ 65 years 6%) *(Figure 3)*.

Seasonality

Prescription rates for eight of the ten classes of antibiotics were between 10% and 104% higher in the first quarter of the year than in the summer (third) quarter *(Table 2)*. Over the observation period as a whole, the overall prescription rate was 54% higher in the first than in the third quarter (RR 1.54). The greatest difference between the first and third quarters was seen for the macrolides/lincosamides (RR 2.04). While metronidazole and the sulfonamides/trimethoprim showed no distinct seasonal fluctuation, the use of nitrofurantoin/fosfomycin/nitroxoline was around 10% lower in the first than in the third quarter *(Table 2)*.

Regional differences

Over the period 2010 to 2018, the federal states of Thuringia and Saxony were the regions that showed the largest relative decrease in prescription rates (both −26%; *eTable 2*). The smallest reduction was in Bremen (−6%) *(eTable 2)*. In 2018 the prescription rate varied by a factor of 1.8 between the region with the most prescriptions per 1000 insured persons (Saarland: 572) and the region with the least prescriptions (Brandenburg: 318) *(eFigure)*. In the course of the study period the variation coefficient (ratio of standard

TABLE 2

Rate ratios for the trend in prescription rate over the observation period as mean quotient of the rates in a given year and the previous year and for the mean relative seasonal fluctuation*

Antibiotic class	Raw prescription rate		Mean annual change		Mean quarter-specific difference from third quarter (reference)					
	2010	2018	Rate ratio	95% CI	First quarter		Second quarter		Fourth quarter	
					Rate ratio	95% CI	Rate ratio	95% CI	Rate ratio	95% CI
Aminopenicillin combinations and antistaphylococcal penicillins	19.7	31.5	1.06	[1.05; 1.06]	1.35	[1.29; 1.40]	1.03	[0.99; 1.07]	1.19	[1.14; 1.24]
Basic penicillins	105.2	91.2	0.98	[0.97;0.99]	1.79	[1.68; 1.90]	1.17	[1.09; 1.25]	1.41	[1.32; 1.50]
Cephalosporins	109.9	89.8	0.98	[0.97; 0.99]	1.69	[1.58; 1.80]	1.10	[1.03; 1.18]	1.34	[1.26; 1.44]
Fluoroquinolones	101.0	60.2	0.94	[0.94; 0.95]	1.25	[1.20; 1.31]	0.98	[0.93; 1.02]	1.10	[1.05; 1.15]
Macrolides/ lincosamides	119.0	81.5	0.95	[0.94; 0.96]	2.04	[1.88; 2.21]	1.14	[1.05; 1.25]	1.56	[1.43; 1.70]
Metronidazole	7.0	6.2	0.99	[0.98; 0.99]	0.99	[0.96; 1.02]	0.96	[0.93; 0.99]	0.97	[0.94; 1.00]
Nitrofurantoin/ fosfomycin/ nitroxoline	12.2	32.9	1.11	[1.10; 1.12]	0.89	[0.84; 0.95]	0.89	[0.84; 0.95]	1.01	[0.95; 1.07]
Sulfonamides/ trimethoprim	39.2	23.2	0.94	[0.93; 0.94]	1.10	[1.06; 1.14]	0.96	[0.92; 0.99]	1.05	[1.01; 1.09]
Tetracyclines	46.7	28.7	0.93	[0.94; 0.95]	1.39	[1.32; 1.46]	1.05	[0.99; 1.12]	1.15	[1.09; 1.21]
Others	1.7	1.0	0.93	[0.92; 0.93]	1.39	[1.33; 1.44]	1.05	[0.99; 1.08]	1.15	[1.08; 1.20]
Total	559.1	445.6	0.97	[0.97; 0.98]	1.54	[1.47; 1.61]	1.06	[1.01; 1.12]	1.27	[1.21; 1.34]

*For the first, second, and fourth quarters compared with the third quarter, by means of class-specific Poisson regression models (see *eMethods*)
95% CI, 95% confidence interval

deviation and mean) of the regional overall prescription rates increased by 17% (2010: 0.13; 2018: 0.16). There was a cluster of high-use regions comprising Lower Saxony (480), North Rhine (503), Westphalia–Lippe (506), Hesse (473), Rhineland–Palatinate (524), and Saarland, whereas low prescription rates were observed in the eastern German regions *(eFigure)*. The prescription rates for each of the antibiotic classes in the different regions can be found in *eTable 3*. In the states of eastern Germany, with the exception of Berlin, macrolides/lincosamides were the most commonly prescribed class of antibiotics. In contrast, the highest prescription rates in Berlin and the majority of regions in western Germany were for the basic penicillins. The exceptions were Bavaria, Hesse, Rhineland–Palatinate, and Schleswig–Holstein, where the cephalosporins were prescribed most frequently.

Discussion

Overall, outpatient prescription of antibiotics decreased by 21% over the 9-year observation period. A trend towards lower use was seen for all age groups, in all regions, and for most classes of antibiotics prescribed. A substantial reduction was observed in the pediatric age group (0−14 years). Differences among the regions widened, and the proportion of all prescriptions made up by the cephalosporins remained stable.

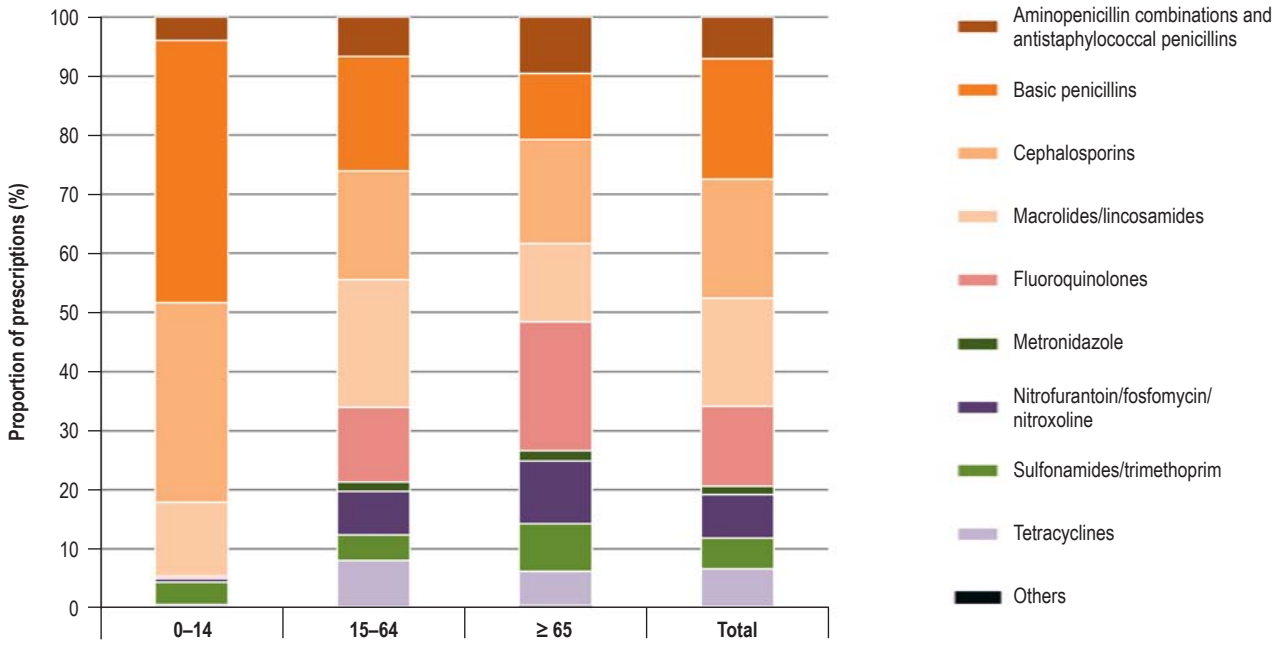
Prescription trends by age group

A European comparative study documented relatively high use of antibiotics among German children and adolescents in 2008 (14), and the results of the study reported here show the same high level of consumption in the pediatric setting for 2010. Research by Bätzing-Feigenbaum et al. showed a decreasing trend for prescriptions among children and adolescents in the subsequent period up to 2014 (6). The current data reveal a continued decline over the years up to 2018, resulting in a substantial reduction of 41% over the observation period as a whole.

In contrast to the situation in pediatric care, the outpatient use of systemic antibiotics in Germany has traditionally been low compared with other European countries (5). In 2017, only Estonia, Sweden, and the Netherlands, with 4234, 4198, and 3687 DDDs per 1 000 inhabitants, had lower levels of use (5). European consumption data from the period 2013 to 2017 show distinct reductions in seven other countries as well as Germany (5).

Despite the historically low overall use in Germany, a significant decline in prescription rates was also observed for older adolescents and adults. Altogether, the findings suggest the existence—especially in the pediatric care segment—of a trend in antibiotic use towards a more conservative approach. This transformation may have been reinforced by

FIGURE 3



Nationwide age group-specific distribution of different classes of systemic antibiotics in 2018

numerous national initiatives to promote antibiotic stewardship programs and public information measures, particularly since 2016 (15–20). Europe-wide surveys show that the increase in the awareness of the risks of antibiotic resistance between 2009 and 2018 was higher than average in the German population (e7, e8).

In the pediatric age group, the introduction of vaccination against pneumococcal infections in 2006 may have contributed to the reduction in antibiotic use. Both randomized clinical trials and observational studies showed that pneumococcal vaccination was associated with a decline in antibiotic use in children (e9, e10).

The proportion of children inoculated against pneumoccal infections at the time of medical examination before starting school increased sharply from 14% (2010) to 84% (2017) during the observation period (e11).

Class-specific prescription trends

The prescription rates of all classes of antibiotics went down during the observation period, with two exceptions: aminopenicillin combinations and staphylococcal penicillins, and nitrofurantoin/fosfomycin/nitroxoline. Because the reduction in prescription of the basic penicillins was comparatively small, their proportion of all prescriptions increased slightly, to about 20%, between 2010 and 2018. However, the outpatient use of basic penicillins in Germany is low compared with countries such as Denmark, Sweden, Norway, or the UK. In view of the low penicillin resistance displayed by pneumococci in Germany and the continuing sensitivity of all group A streptococci to penicillin (20), basic penicillins still possess unexplored potential for limiting the use of broad-spectrum agents.

In contrast, the proportion of prescriptions accounted for by cephalosporins remained high. Although cephalosporins are not the first choice in any current guidelines for the treatment of infections encountered frequently in the outpatient setting (21–28), high seasonal fluctuations in prescription rate suggest they are commonly used for acute respiratory infections. Compared with penicillin derivatives, cephalosporins increase the risk of antibiotic-associated *C. difficile* infections (9, 10) and are probably drivers of the development of resistance on the part of gram-negative bacteria, including the selection of extended-spectrum betalactamase (ESBL) producers (7, 8). A particular cause of concern is the increase in multiresistant gram-negative pathogens, owing to the restricted therapeutic antibiotic spectrum (29, 30). Future initiatives to promote the rational use of antibiotics should prioritize reduction of the frequency with which cephalosporins are prescribed.

The use of fluoroquinolones is also associated both with the emergence of ESBL-producing enterobacteria and with an increased risk of *C. difficile* infection, especially in older persons (7–10). By far the most

Key messages

- The outpatient prescription rate of systemic antibiotics to persons with statutory health insurance went down by 21% from 562 to 446 prescriptions per 1000 insurees between 2010 and 2018.
- A reduction in prescription frequency was observed for all age groups, in all regions, and for the majority of classes of antibiotics used.
- The high, albeit declining, use of cephalosporins and fluoroquinolones underlines the potential for further improvement of outpatient prescribing patterns. The use of these two classes of antibiotics increases the risk of development of resistance on the part of gram-negative bacteria and the danger of the occurrence of antibiotic-associated *Clostridium difficile* infection.
- There remains pronounced variation in antibiotic prescription rates, by a factor of 1.8, among regions.
- Regional promotion of appropriate antibiotic use in Germany should, in future, be based on comprehensive surveillance of outpatient antibiotic prescription at district level, using data from all statutory health insurance providers.

commonly prescribed substance in 2018 was ciprofloxacin (65% of all fluoroquinolone prescriptions), which has a wide range of uses (6), followed by levofloxacin (20%; principally indicated for treatment of respiratory infections) (6). Fluoroquinolones are now contraindicated for minor and moderate infections due to the high likelihood of severe adverse effects (11). In April 2019, the Federal Institute for Drugs and Medical Devices issued an information bulletin warning healthcare providers of "lasting and possibly irreversible adverse effects that impair the quality of life" (11). Despite the steeply declining trend in fluoroquinolone prescription rates, in 2018 fluoroquinolones accounted for 14% of antibiotic prescriptions as a whole and 22% for the ≥ 65 years age group. Furthermore, the fact that the rate of fluoroquinolone prescriptions was higher in the first than the third quarter of the year suggests the use of fluoroquinolones to treat respiratory infections, which does not correspond to the latest guidelines (27). Seasonal fluctuations of more than 5% in the prescription of fluoroquinolones are thought to be an indicator of potential for reduction of use in respiratory infections, including pneumonia (31). Since 2009 and 2010 respectively, fosfomycin and nitrofurantoin have been recommended for the treatment of uncomplicated urinary tract infections instead of fluoroquinolones in the practice guidelines for general medical and urology (21, 26). Together with the conspicuous reduction in fluoroquinolone prescriptions, the growing use of the nitrofurantoin/fosfomycin/nitroxoline group of antibiotics points to increasing adherence to the guidelines for the treatment of urinary tract infections. Given the recent warnings regarding drug risks, it is to be hoped that prescriptions of fluoroquinolones will decrease further.

Regional differences

An almost uniform picture of gradual reduction indicates a supraregional change in prescription patterns. All regions showed a short-term increase in prescription rates in 2013, probably related to the relatively high number of cases of influenza in that year (32). In the subsequent years 2015, 2017, and 2018, however, there was no association between influenza frequency and prescription rate despite high case numbers (32). This observation could be explained on the one hand by increasingly conservative prescription of antibiotics for viral infections, or on the other hand by a higher incidence of bacterial coinfections in 2013.

Because the eastern German regions both had a low baseline and displayed the greatest relative reduction in prescription rates over the course of the observation period, inter-regional differences increased with time. Regional variations in antibiotic use have also been reported from other European countries (e12–e14). Whether the substantial differences among the regions are explained at least in part by regional differences in disease burden cannot be determined on the basis of the data used in this study, and the widespread lack of data on regional morbidity due to infectious disease precludes any estimate. The existence within Germany of meaningful differences of this nature that remain stable over time seems improbable in view of the comparable climatic and socioeconomic conditions across the regions. It appears more likely that regional variations are explained by differing frequencies of prescription to patients with viral and self-limiting infections. An analysis by Butler et al. showed that distinct differences among European countries with regard to prescription frequency for respiratory infections also cannot be explained by variations in clinical presentation (e15). In a situation where diagnosis is challenging and time is limited, the important determinants of antibiotic prescription include not only the clinical presentation and the medical experience of the person giving the treatment (33, 34), but also, above all, the perceived expectations of the patients or their parents (35, 36). Improving awareness of antibiotic resistance among both physicians and patients and enhancing physicians' competence in doctor–patient communication are important departure points for promotion of appropriate patterns of prescription (37), as embodied in the model project RESIST, supported by national funding from the statutory health insurance (Innovationsfonds) and conducted in eight of the regions discussed here (15).

The detailed key data on regional variation in antibiotic usage presented here can be used as a basis for customized quality assurance measures. Due to specific data protection regulations, however, the regional analyses do not exhaust the full potential of this body of data from all statutory health insurance providers. For instance, analysis of data from one statutory health insurance company (Barmer) showed high variation in use at the level of German districts

(38). It would therefore be possible, in principle, to present key data at district level without violating the prevailing data protection regulations. In addition to targeted regional measures, key data from smaller areas would help physicians to reflect on their own prescription of antibiotics in the context of regional care provision.

Strengths and limitations

In contrast to data from individual health insurance companies, use of cross-provider outpatient drug billing data effectively excludes the possibility of limited representativity owing to regional clustering of insured persons or the socioeconomic characteristics of those insured by a particular provider.

No information was available about prescription of antibiotics by dentists. Since the outpatient prescription density including dental prescriptions showed a less pronounced decrease, at least up to 2017 (5), than in the population of our study, one has to assume a different developmental dynamic in dental care. Owing to the design of the study and the data used, we were not able to identify the causes of the trends we observed over time or of the inter-regional differences. The discussion is thus restricted to hypotheses on the basis of the results, insofar as they are considered plausible.

Conclusion

The finding of reductions in outpatient antibiotic use across all age groups points to increasingly conservative prescription of systemic antibiotics in Germany. The presence of marked regional variations and the fact that certain broad-spectrum antibiotics account for high proportions of all antibiotic prescriptions underline the potential for further improvement of outpatient prescribing patterns.

Conflict of interest statement
The authors declare that no conflict of interest exists.

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► **Supplementary material**

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Supplementary material to:

The Decline in Outpatient Antibiotic Use

An Analysis of Nationwide Prescription Data From 2010 to 2018

by Jakob Holstiege, Maike Schulz, Manas K. Akmatov, Winfried V. Kern, Annika Steffen, and Jörg Bätzing

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eMETHODS

Data

Our analyses were based on nationwide prescription data from all statutory health insurance providers collected as stipulated in § 300 of the German Social Code book V (SGB V). These data include all drug prescriptions, except those written by dentists, that were issued to persons with health insurance from companies belonging to the National Association of Statutory Health Insurance Funds (GKV) and filled in pharmacies. The information captured for each prescription includes the product identification number (*Pharmazentralnummer*, PZN), the cost, the prescription date, the filling date, the regional Association of Statutory Health Physicians (ASHIP) responsible for the patient's place of residence, and the patient's age. By linking the PZN with the Anatomical Therapeutic Chemical (ATC) classification, each prescription can be categorized with regard to the active substance and the defined daily dose (DDD), whereby an average daily dose is the daily average amount of substance calculated for a standard indication in an adult man in the 70-kg weight class (e1).

Classification of antibiotics

All prescriptions of systemic antibiotics (ATC codes J01 and P01AB01, metronidazole as systemic antiprotozoal agent) in the period 2010 to 2018 were documented and divided into the following classes:

- Aminopenicillin combinations and staphylococcal penicillins
- Basic penicillins
- Cephalosporins
- Fluoroquinolones
- Macrolides/lincosamides
- Metronidazole
- Nitrofurantoin/fosfomycin/nitroxoline
- Sulfonamides/trimethoprim
- Tetracyclines
- Others

The individual substances are listed with their ATC codes in *eTable 1*.

Measures of antibiotic use

The prescription rate, i.e., the annual number of antibiotic prescriptions per 1000 insured persons, was used as primary measure of outpatient usage of systemic antibiotics (ATC codes J01 and P01AB01, metronidazole as systemic antiprotozoal agent). The antibiotic prescriptions were analyzed at nationwide level for the age groups 0–14 years, 15–64 years, and ≥ 65 years, and for each ASHIP region. To investigate whether there were any changes in duration of intake over time, we compared, at nationwide level, the annual prescription rate and the prescription density, i.e., the annual number of DDD in prescriptions per 1000 persons and year. For both of these measures, direct standardization to the age structure of all GKV insurees in Germany in 2018 was carried out (13).

In contrast to the prescription density, the prescription rate enables comparative investigation of the extent of antibiotic exposure in different age groups, including children and adolescents, independently of age-related variation in dosing (e2). Because repeat prescriptions play only a minor role in outpatient care (e3), the prescription rate represents a good approximation to the incidence of antibiotic treatments across age groups at population level.

Moreover, the prescription rate is robust against changes in the amount of active substance provided (measured in DDD) that may occur, regardless of the frequency of antibiotic use, for the following reasons:

- Variations in the choice of antibiotic
- Changes in the dosage of the same antibiotic over time

In several European countries, for example, contrasting trends have been observed for prescription rate and prescription density (e4, e5). Finally, one should note the existence of the assumption that the selection pressure on bacterial pathogens exerted by outpatient antibiotic use, and thus the development of resistance at population level, is explained better by the incidence of antibiotic treatments than by the amount of active substance measured in DDD (e5, e6).

Trend analysis

For the purposes of exploring trends over time, the influence of increasing calendar year on the monthly prescription rate, adjusted for seasonal effects, was modeled by means of Poisson regression. We assumed a log-linear association between calendar year and prescription rate. For exploration of the effect of passing time, the rate ratio (RR) was determined, i.e., the ratio of the rate for a given year to that for the previous year, calculated throughout the observation period. Here, (RR−1)*100 represents the average annual percentage change in prescription rate. For the modeling of seasonal effects, the quarters of the year were included in the model as independent variables (with the third quarter as reference). Because overdispersion was anticipated, a dispersion parameter was included in the model. The analysis of trends over time was conducted using SAS 9.3, with separate regression models for the overall prescription rate and for each antibiotic class and age group at nationwide level and at ASHIP region level.

eTABLE 1

Classification of antibiotics by active substance

Class	ATC code	ATC designation
Aminopenicillin combinations and antistaphylococcal penicillins	J01CE30	Combinations
	J01CF01	Dicloxacillin
	J01CF04	Oxacillin
	J01CF05	Flucloxacillin
	J01CR01	Ampicillin and enzyme inhibitors
	J01CR02	Amoxicillin and enzyme inhibitors
	J01CR04	Sultamicillin
	J01CR05	Piperacillin and enzyme inhibitors
	J01CR21	Ampicillin and sulbactam
	J01CR22	Amoxicillin and clavulanic acid
	J01CR25	Piperacillin and tazobactam
	J01CR50	Combinations of penicillins
Basic penicillins	J01CA01	Ampicillin
	J01CA04	Amoxicillin
	J01CA08	Pivmecillinam
	J01CA10	Mezlocillin
	J01CA12	Piperacillin
	J01CE01	Benzylpenicillin
	J01CE02	Phenoxymethylpenicillin
	J01CE03	Propicillin
	J01CE04	Azidocillin
	J01CE08	Benzathine benzylpenicillin
	J01CE10	Benzathine phenoxymethylpenicillin
	J01CG01	Sulbactam
Cephalosporins	J01DB01	Cefalexin
	J01DB04	Cefazolin
	J01DC04	Cefaclor
	J01DC07	Cefotiam
	J01DC08	Loracarbef
	J01DD01	Cefotaxime
	J01DD02	Ceftazidime
	J01DD04	Ceftriaxone
	J01DD08	Cefixime
	J01DD13	Cefpodoxime
	J01DD14	Ceftibuten
	J01DD52	Ceftazidime, combinations
	J01DE01	Cefepime
	J01DI02	Ceftaroline fosamil
Fluoroquinolones	J01MA01	Ofloxacin
	J01MA02	Ciprofloxacin
	J01MA04	Enoxacin
	J01MA06	Norfloxacin
	J01MA12	Levofloxacin
	J01MA14	Moxifloxacin

Macrolides/lincosamides	J01FA01	Erythromycin
	J01FA02	Spiramycin
	J01FA06	Roxithromycin
	J01FA09	Clarithromycin
	J01FA10	Azithromycin
	J01FA15	Telithromycin
	J01FF01	Clindamycin
Metronidazole	J01XD01	Metronidazole
	P01AB01	Metronidazole
Nitrofurantoin/ fosfomycin/ nitroxoline	J01XE01	Nitrofurantoin
	J01XE51	Nitrofurantoin, combinations
	J01XX01	Fosfomycin
	J01XX07	Nitroxoline
Sulfonamides/ trimethoprim	J01EA01	Trimethoprim
	J01EC02	Sulfadiazine
	J01EE01	Sulfamethoxazole and trimethoprim
Tetracyclines	J01AA02	Doxycycline
	J01AA07	Tetracycline
	J01AA08	Minocycline
	J01AA12	Tigecycline
Others	J01DF01	Aztreonam
	J01DH02	Meropenem
	J01DH03	Ertapenem
	J01DH04	Doripenem
	J01DH21	Imipenem and cilastatin
	J01DH51	Imipenem and enzyme inhibitors
	J01GA01	Streptomycin
	J01GB01	Tobramycin
	J01GB03	Gentamicin
	J01GB05	Neomycin
	J01GB06	Amikacin
	J01GB53	Gentamicin, combinations
	J01GB55	Neomycin, combinations
	J01MB04	Pipemidic acid
	J01XA01	Vancomycin
	J01XA02	Teicoplanin
	J01XA04	Dalbavancin
	J01XB01	Colistin
	J01XX08	Linezolid
	J01XX09	Daptomycin

eTABLE 2

Age-standardized prescription rates for systemic antibiotics (annual prescriptions per 1000 insured persons) by region in the period 2010 to 2018

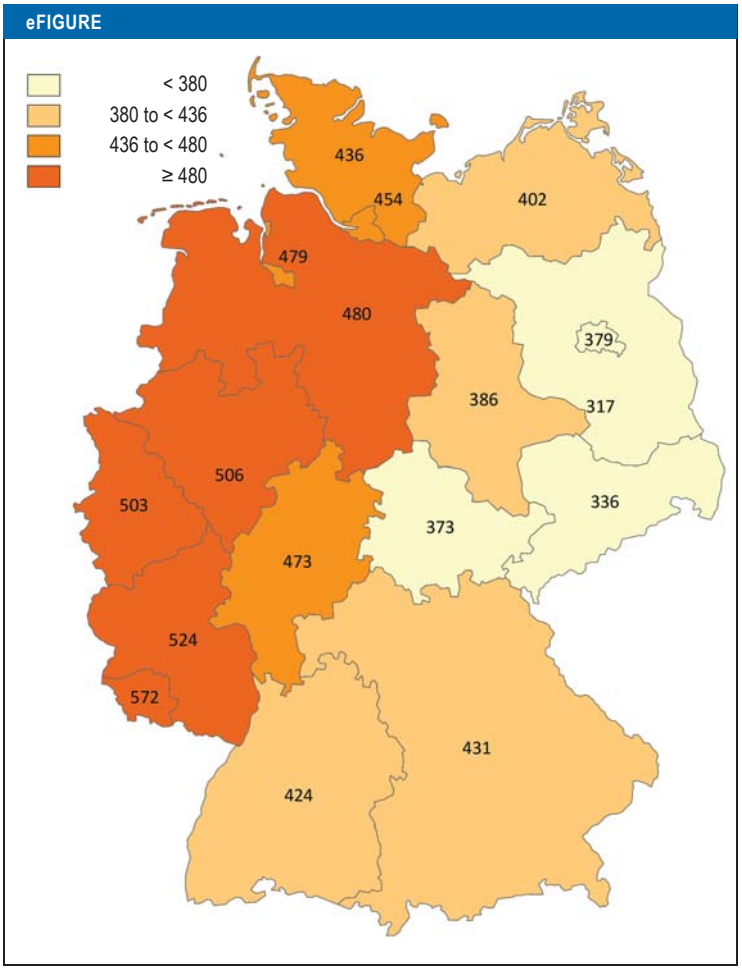
Year	2010	2011	2012	2013	2014	2015	2016	2017	2018
Brandenburg	419.3	414.2	390.3	415.4	372.1	368.8	360.6	327.8	317.4
Berlin	476.3	467.0	446.7	460.8	422.7	417.3	412.3	393.6	379.2
Baden–Württemberg	532.6	516.4	500.9	539.4	495.7	484.0	458.6	439.6	424.4
Bavaria	541.3	517.0	501.1	531.6	492.0	481.3	466.7	445.9	431.1
Bremen	509.3	503.0	505.3	523.1	482.4	479.5	467.1	493.9	479.1
Hesse	605.5	588.9	572.3	603.0	550.3	531.3	520.4	486.2	473.1
Hamburg	528.1	527.2	553.1	543.8	506.1	495.3	484.2	465.9	454.0
Mecklenburg–West Pomerania	514.7	519.1	468.1	500.6	447.1	453.3	442.9	427.4	402.1
Lower Saxony	586.8	575.7	574.5	600.6	544.6	542.8	528.9	510.7	480.5
North Rhine	632.5	619.5	606.5	628.8	576.8	573.6	553.0	511.6	502.5
Rhineland–Palatinate	644.2	642.9	628.5	673.3	602.0	586.5	572.3	534.9	524.5
Schleswig–Holstein	513.4	522.9	516.3	534.5	497.1	485.6	474.1	453.8	436.2
Saarland	677.3	666.7	645.5	695.9	633.2	622.4	605.5	581.1	572.4
Saxony	452.7	434.6	405.7	442.4	388.9	381.3	375.2	356.5	336.3
Saxony–Anhalt	516.1	502.9	473.5	506.1	459.4	457.3	436.1	417.8	386.3
Thuringia	504.7	481.3	457.5	490.8	430.9	427.9	413.4	392.7	372.5
Westphalia–Lippe	646.8	634.8	615.8	638.6	578.2	572.6	551.4	523.9	505.8

eTABLE 3

Age-standardized prescription rates for the different classes of systemic antibiotics (annual prescriptions per 1000 insured persons) by region in 2018

Region	Amino-penicillin combi-nations and anti-staphy-lococcal penicillins	Basic penicillins	Cephalo-sporins	Fluoroqui-nolones	Macro-lides/lin-cosamides	Metro-nidazole	Nitrofuran-toin/fos-fomycin/ nitroxoline	Sulfona-mides/ trimetho-prim	Tetra-cyclines	Others
Brandenburg	24.63	52.90	61.67	45.07	67.15	4.62	23.80	13.63	23.37	0.52
Berlin	29.27	85.38	60.85	45.77	67.41	6.37	35.85	16.76	30.61	0.98
Baden–Württemberg	38.37	83.81	80.64	60.40	70.44	6.33	33.44	25.52	24.52	0.89
Bavaria	39.53	75.17	95.13	60.99	74.58	6.26	29.68	22.44	26.13	1.17
Bremen	23.56	135.28	81.02	54.22	78.65	8.50	37.28	29.92	29.55	1.11
Hesse	23.94	85.74	118.20	66.58	88.25	7.41	30.96	24.77	26.05	1.2
Hamburg	44.20	103.92	80.96	50.26	71.25	8.02	39.09	24.68	30.14	1.46
Mecklenburg–West Pomerania	26.18	58.67	86.05	60.44	88.73	5.64	33.53	17.49	24.50	0.88
Lower Saxony	32.28	103.99	101.20	61.44	83.41	6.51	35.94	27.17	27.53	1
North Rhine	28.53	122.49	90.60	62.80	92.98	7.30	38.68	24.17	33.86	1.12
Rhineland–Palatinate	28.15	100.84	122.37	76.33	96.00	6.81	32.95	27.38	32.87	0.76
Schleswig–Holstein	35.79	88.45	88.53	53.16	77.76	7.75	37.01	25.97	20.61	1.11
Saarland	29.88	133.40	108.26	90.14	105.95	7.13	35.58	26.91	33.86	1.25
Saxony	23.36	50.70	68.02	50.48	71.47	4.49	24.99	15.41	26.74	0.67
Saxony–Anhalt	25.07	56.21	76.49	59.25	87.30	5.53	27.71	16.98	30.89	0.91
Thuringia	23.83	63.33	74.13	51.21	79.96	4.82	27.07	15.00	32.27	0.9
Westphalia–Lippe	30.05	124.64	89.21	63.96	94.05	6.19	34.13	26.89	35.75	0.96

eFIGURE



Age-standardized prescription rates for systemic antibiotics (prescriptions per 1000 insured persons per year) by ASHIP region in 2018 with evenly distributed four-step color scaling.