Infect Dis Ther
https://doi.org/10.1007/s40121-024-00916-3

ORIGINAL RESEARCH

Comparative Analysis of Outpatient Antibiotic Prescribing in Early Life: A Population-Based Study Across Birth Cohorts in Denmark and Germany

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Received: October 4, 2023 / Accepted: January 2, 2024
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ABSTRACT

Introduction: Comparing antibiotic prescribing between countries can provide important insights into potential needs of improving antibiotic stewardship programs. We aimed to compare outpatient antibiotic prescribing in early life between children born in Denmark and Germany.

Methods: Using the Danish nationwide healthcare registries and a German claims database (GePaRD, ~ 20% population coverage), we included children born between 2004 and 2016, and followed them regarding outpatient antibiotic prescriptions until end of enrollment or the end of 2018. We then determined the median time to first antibiotic prescription. Based on all prescriptions in the first 2 years of life, we calculated the rate of antibiotic treatment episodes and for the children's first prescriptions in this period, we determined established quality indicators. All analyses were stratified by birth year and country.

Results: In the 2016 birth cohorts, the median time to first antibiotic prescription was ~ 21 months in Denmark and ~ 28 in Germany; the rate of antibiotic treatment episodes per 1000 person-years was 537 in Denmark and 433 in Germany; the percentage of prescribed antibiotics with higher concerns regarding side effects and/or resistance potential was 6.2% in Denmark and 44.2% in Germany. In the 2016 birth cohorts, the age at first antibiotic prescription was 50–59% higher compared to the 2004 birth cohorts; the rate of antibiotic treatment episodes was 43–44% lower.

Prior presentation: 38th International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE), 24–28 August 2022, Copenhagen, Denmark; published as an abstract in *Pharmacoepidemiology and Drug Safety* 2022;31(Suppl. 2):470. 29th Annual Meeting of the German Drug Utilisation Research Group (GAA), 24–25 November 2022, Münster, Germany; published as an abstract available from https://doi.org/10.3205/22gaa02.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40121-024-00916-3.

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Published online: 23 January 2024

Conclusions: Infants in Denmark received antibiotics markedly earlier and more frequently than in Germany, while quality indicators of antibiotic prescribing were more favorable in Denmark. Although both countries experienced positive changes towards more rational antibiotic prescribing in early life, our findings suggest potential for further improvement. This particularly applies to prescribing antibiotics with a lower potential for side effects and/or resistance in Germany.

Keywords: Antibiotics; Cross-national comparison; Drug utilization research; Healthcare data; Pediatrics; Antibiotic stewardship

Key Summary Points

Why carry out this study?

Avoiding inappropriate antibiotic prescribing during early life is important for the prevention of possible side effects (including negative effects on the gut microbiome) and antibiotic resistance.

Cross-national drug utilization studies can provide important insights into potential needs to improve antibiotic stewardship programs but there is a lack of studies focusing on antibiotic prescribing in early life.

This study compared outpatient antibiotic prescribing in early life between Denmark and Germany including changes over time among children born between 2004 and 2016.

What was learned from the study?

Danish children received outpatient antibiotic prescriptions earlier and at a higher rate in the first 2 years of life than German children; quality indicators were substantially worse in Germany than in Denmark; in both countries, positive changes over time were observed.

Our findings may stimulate reflection on the potential for and the need of further improvement of antibiotic stewardship in infants. This particularly applies to prescribing antibiotics with a lower potential for side effects and/or resistance in Germany.

INTRODUCTION

The first 2 years of life—also referred to as "early life" in the following—are critical for the development of the microbiome [1]. During this period, the infant's gut microbiome is prone to disruptions by antibiotic exposure [2]. At the same time, children in this age group often have infections, particularly in the upper respiratory tract, which may require antibiotic treatment [3, 4]. Although the benefits of antibiotics to treat severe infections in early life are undisputed, unnecessary prescribing must be avoided, as antibiotics can also have negative effects. This includes short-term side effects such as diarrhea and allergic reactions. Furthermore, studies have suggested an association between antibiotic use in early life and serious long-term health outcomes such as obesity, detrimental neurodevelopmental outcomes, asthma, allergies, and inflammatory bowel disease [5–9]. Finally, avoiding inappropriate prescribing of antibiotics in early life is fundamental in the prevention of antibiotic resistance [2, 10].

In the outpatient setting, antibiotics are among the most frequently prescribed drugs for children [11]. The most common indications for antibiotics in infants are upper respiratory tract infections [12]. However, pediatric respiratory tract infections are predominantly caused by viruses [13], against which antibiotics are ineffective. Research suggests that a substantial proportion of outpatient antibiotic prescribing is likely inappropriate [14–16]. To counteract this inappropriate use, many countries have implemented antibiotic stewardship programs. For example, Denmark has implemented a national antibiotic stewardship program in 2017, which explicitly addresses outpatient care and which has a concrete goal of 30% reduction of antibiotic use [17]. In Germany, the federal government presented the “German Antimicrobial Resistance Strategy (DART)” in 2008 [18]. A national action plan with concrete targets regarding reduction of antibiotic use is lacking in Germany, but there are efforts to rationalize the use of antibiotics, in particular broad-spectrum antibiotics [19].

Drug utilization studies based on routinely collected healthcare data are valuable tools for examining drug prescribing patterns in populations while avoiding recall and non-responder bias. Drug utilization studies comparing different geographical areas—such as local, regional, national, or supra-national comparisons—can provide important insights into potential needs to improve antibiotic stewardship programs. Currently, there is a lack of cross-national drug utilization studies that specifically focus on antibiotic prescribing in early life using longitudinal healthcare data.

The objective of this study was to compare outpatient antibiotic prescribing in early life between Denmark and Germany including changes over time among children born between 2004 and 2016.

METHODS

We conducted an observational cohort study using healthcare data from 2004 to 2018 from individuals born between 2004 and 2016 in Denmark and Germany. All analyses followed a common protocol.

Data Sources

The Danish healthcare registries provide universal coverage of the Danish population, which amounted to ~ 5.8 million inhabitants at the beginning of 2018. The Danish National Prescription Registry holds information on all prescription drugs dispensed at all community pharmacies in Denmark since 1995 [20]. Data on migrations and vital status can be obtained from the Danish Civil Registration System which holds information on all individuals living in Denmark since 1968 [21]. As there is no comparable registry in Germany, we used the German Pharmacoepidemiological Research Database (GePaRD). GePaRD is based on claims data from four statutory health insurance providers in Germany and currently includes information on more than 25 million persons who have been insured with one of the participating providers since 2004 or later [22]. Per calendar year, there is information on approximately 20% of the general population and all geographical regions of Germany are represented. For this study, we used demographic and prescription data—which include all reimbursed drugs dispensed at community pharmacies. The health care systems in Denmark and Germany share some common features such as universal coverage and free choice of provider, but there are also differences. For example, in Denmark, general practitioners are the first-line providers for all inhabitants regardless of age, whereas in Germany, pediatricians typically provide primary healthcare for children.

Study Population

The study population consisted of all live births between January 1, 2004 and December 31, 2016. Cohort entry was defined as the exact date of birth for Denmark and the start of the insurance period for Germany, while cohort exit was defined as the earliest occurrence of death, end of study period (December 31, 2018), or gap of enrollment of more than 14 days (e.g., due to emigration or change of health insurance provider). In addition, for Denmark, we excluded children who did not live in Denmark at cohort entry.

Antibiotic Prescriptions

Antibiotic prescriptions were identified based on outpatient dispensings of drugs with Anatomical Therapeutic Chemical (ATC) codes and included “antibacterials for systemic use” (ATC J01) and metronidazole (P01AB01) (version as of May 2019 for this study). In both Denmark and Germany, antibiotics are available by prescription only. All antibiotic prescriptions for the study population with a dispensing date between cohort entry and cohort exit were considered.

To assess the quality of antibiotic prescribing, we classified antibiotics based on the "2019 World Health Organization (WHO) Access, Watch, Reserve (AWaRe) classification of antibiotics for evaluation and monitoring of use" [23], which considers the antibiotics' side effects and potential for resistance (see Text S1 in the Supplementary Material for details). This resulted in four categories: the Access group (e.g., amoxicillin and phenoxymethylpenicillin), the Watch group (e.g., second-generation cephalosporins), the Reserve group (antibiotics typically used in the inpatient setting), and a group with antibiotics not classified in Access, Watch, or Reserve.

Statistical Analyses

All analyses were carried out separately for each country and stratified by birth cohort (2004–2016, if not otherwise stated). We estimated the cumulative probability over time of receiving at least one antibiotic prescription as well as the median time from birth to the first outpatient antibiotic prescription using Kaplan–Meier analyses. Furthermore, in a sub-cohort comprising all children with at least 2 years of follow-up, we determined the rate of antibiotic treatment episodes, defined as the number of different treatment episodes per 1000 person-years. One treatment episode was defined as a single dispensing or consecutive dispensings separated by less than 14 days. In supplementary analyses, we estimated the number of antibiotic prescriptions per 1000 person-years, the prescription prevalence, and the number of Defined Daily Doses (DDDs) per 1000 children per day (see Text S2 in the Supplementary Material for details). We calculated the rate of antibiotic treatment episodes for the first 2 years of life combined as well as separately for the first and the second year of life. We also assessed the number of antibiotic treatment episodes per person in the first 2 years of life.

Furthermore—among all individuals of the study population with at least one antibiotic prescription in the first 2 years of life and considering the children's first prescription—we determined the ten most frequently prescribed antibiotics. Finally, based on the same (first) prescriptions, we calculated the Access percentage defined as the percentage of DDDs of Access antibiotics out of the total DDDs of antibiotics (analogous calculations for the other categories).

Analyses were conducted using Stata (version 17.0) for the Danish data and SAS (version 9.4; SAS Institute, Cary, NC, USA) for the German data. Kaplan–Meier curves were created using Stata.

Ethics

According to Danish legislation, approval from an ethics Committee is not required for registry-based studies. The study was approved by the Danish Data Protection Agency (11.106). In Germany, the utilization of health insurance data for scientific research is regulated by the Code of Social Law. All involved health insurance providers as well as the Federal Office for Social Security and the Senator for Health, Women and Consumer Protection in Bremen as their responsible authorities approved the use of GePaRD data for this study. Informed consent for studies based on claims data is required by law unless obtaining consent appears unacceptable and would bias results, which was the case in this study. According to the Ethics Committee of the University of Bremen studies based on GePaRD are exempt from institutional review board review.

RESULTS

Overall, the study population comprised 798,883 children born in Denmark and 1,610,575 children born in Germany (Table S1 in the Supplementary Material). In both countries, 48.7% of the study population were female. The median length of follow-up was 95 months in the Danish and 66 months in the German study population. The follow-up was at least 2 years for 98.1% of the Danish and 89.8% of the German study population.

Quantification of Antibiotic Prescribing on the Population Level

In both countries, the estimated cumulative probability of at least one outpatient antibiotic prescription increased steeply immediately after birth, and the curve flattened gradually at the age of 1.5–2 years (Fig. 1). Compared to Germany, there was a steeper increase during early life in Denmark. In both countries, the curves became flatter over time. In the 2015 birth cohort, about 56% of children in Denmark and 48% of those in Germany received at least one outpatient antibiotic within the first 2 years of life. In both countries, the median time to first outpatient antibiotic prescription remained relatively stable in the cohorts with children born between 2004 and 2009 (Germany)/2010 (Denmark) and began to rise thereafter (Table S2 in the Supplementary Material). In the 2016 birth cohort, it was about 21 months in Denmark and 28 months in Germany; it had increased by 50% in Denmark and 59% in Germany compared to the 2004 birth cohort.

In the 2016 birth cohort, the rate of antibiotic treatment episodes (considering the first 2 years of life combined) was 537 per 1000 person-years in Denmark and 433 in Germany (Fig. 2). In both countries, the rate had decreased by 43–44% compared to the 2004 birth cohort and it began to decline steadily from the 2010 birth cohort onwards. The rate of antibiotic treatment episodes was almost twice as high in the second compared to the first year of life (Fig. S1 in the Supplementary Material). For all supplementary quantification measures, the patterns regarding relative differences between the countries and trends over time were similar as described for the rate of antibiotic treatment episodes above (see Fig. S2 for number of prescriptions, Fig. S3 for prescription prevalence, and Fig. S4 for number of DDDs; all in the Supplementary Material).

Among all children in the 2016 birth cohort, 26.5% in Denmark and 25.0% in Germany had one treatment episode of antibiotics in the first 2 years of life (Fig. 3); 13.5% (Denmark) and 11.3% (Germany) had two treatment episodes; 6.8% (Denmark) and 4.9% (Germany) had three; 3.4% (Denmark) and 2.3% (Germany) had four; and 3.2% (Denmark) and 2.3% (Germany) had five or more treatment episodes. Compared to the 2004 birth cohort, the proportions of children with one treatment episode remained almost unchanged over time; however, in Denmark and Germany, respectively, the proportions of children with two treatment episodes decreased by 22% and 25%, the proportions with three decreased by 41% and 45% and the proportions with more than three decreased by > 50%. In both countries, these

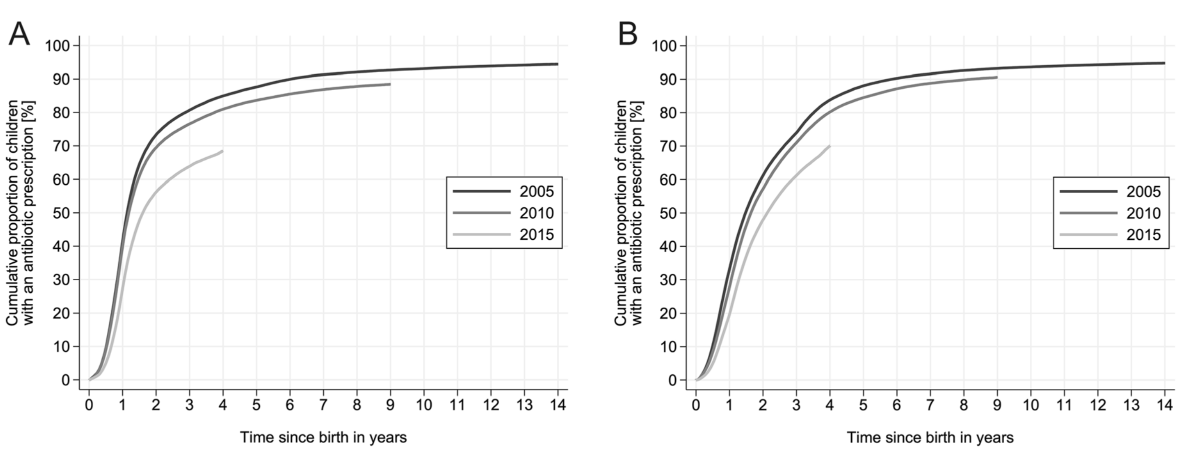

Fig. 1 Cumulative probability over time of receiving at least one outpatient antibiotic prescription for the birth cohorts 2005, 2010, and 2015 in Denmark (**a**) and Germany (**b**)

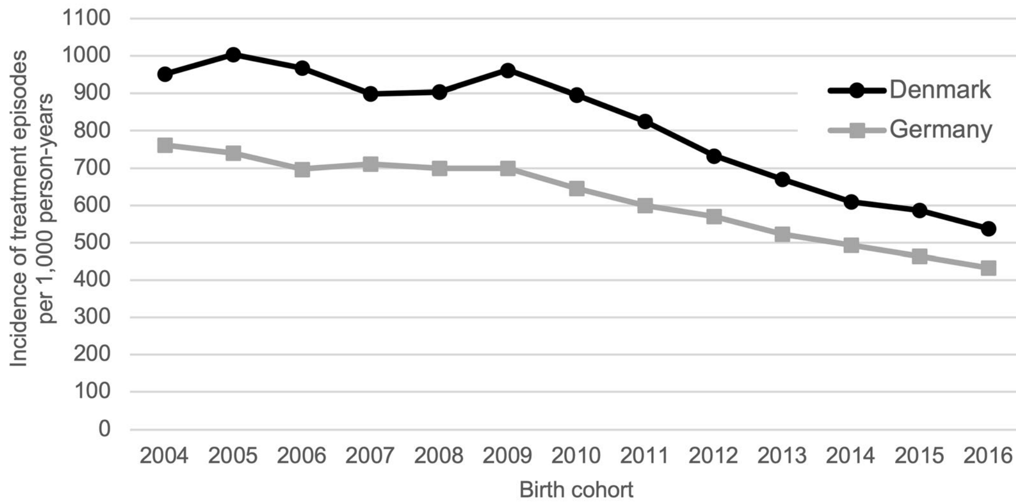

Fig. 2 Rate of outpatient antibiotic treatment episodes per 1000 person-years considering the first 2 years of life combined, stratified by birth cohort

changes occurred from the 2010 birth cohort onwards.

Quality Indicators of Antibiotic Prescribing Over Time

In the Danish 2016 birth cohort, amoxicillin (47.1%) and phenoxymethylpenicillin (44.0%) were the most frequently antibiotics prescribed first during early life (Table 1). In the German 2016 birth cohort, amoxicillin (41.5%) and the second-generation cephalosporin cefaclor (27.7%) were the most frequently antibiotics prescribed first during early life. The third-generation cephalosporin cefpodoxime (5.6%), the second-generation cephalosporin cefuroxime (4.9%), erythromycin (4.8%), and phenoxymethylpenicillin (4.0%) were also among the ten most frequently prescribed antibiotics in Germany in the 2016 birth cohort. Comparing the birth cohorts of 2004 and 2016, the proportions for amoxicillin and phenoxymethylpenicillin did not change substantially in Denmark. In Germany, the proportions particularly increased for amoxicillin (from 31.7 to 41.5%) and cefaclor (from 20.9 to 27.7%), and they decreased for erythromycin (from 14.5 to 4.8%) in the same period.

The proportion of antibiotics with a low risk of side effects and resistance (i.e., Access group)

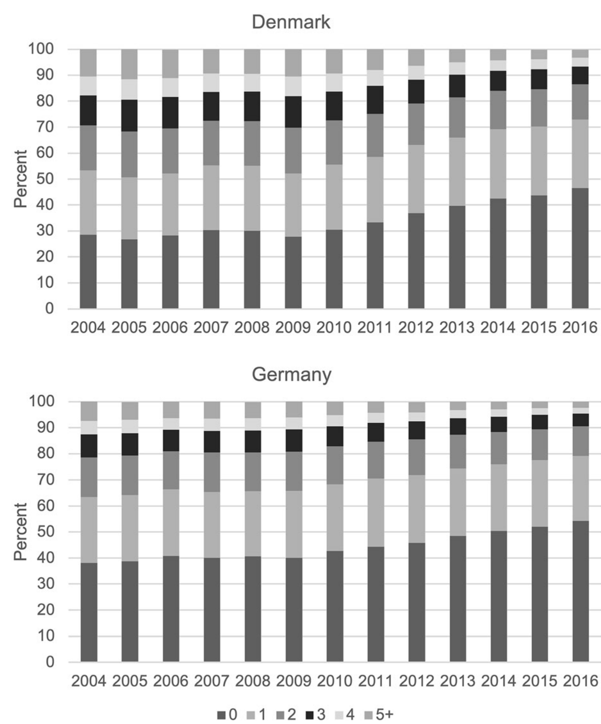

Fig. 3 Distribution of the number of outpatient antibiotic treatment episodes per person in the first 2 years of life, stratified by birth cohort

among all antibiotics prescribed first in the 2016 birth cohort was 93.8% in Denmark and 53.5% in Germany (Fig. 4a); compared to the 2004 birth cohort, it increased by 4% in

Table 1 Most frequently outpatient antibiotics prescribed first in early life for the birth cohorts 2016 and 2004

		Denmark	%	Germany	%
2016		***n*** **= 32,718**		***n*** **= 70,313**	
	1:	Amoxicillin (J01CA04)	47.1	Amoxicillin (J01CA04)	41.5
	2:	Phenoxymethylpenicillin (J01CE02)	44.0	Cefaclor (J01DC04)	27.7
	3:	Clarithromycin (J01FA09)	3.2	Cefpodoxime (J01DD13)	5.6
	4:	Amoxicillin and beta-lactamase inhibitor (J01CR02)	3.0	Cefuroxime (J01DC02)	4.9
	5:	Erythromycin (J01FA01)	0.8	Erythromycin (J01FA01)	4.8
	6:	Azithromycin (J01FA10)	0.8	Phenoxymethylpenicillin (J01CE02)	4.0
	7:	Trimethoprim (J01EA01)	0.5	Amoxicillin and beta-lactamase inhibitor (J01CR02)	2.8
	8:	Dicloxacillin (J01CF01)	0.3	Benzathine phenoxymethylpenicillin (J01CE10)	2.3
	9:	Metronidazole (P01AB01)	0.1	Azithromycin (J01FA10)	2.2
	10:	Fusidic acid (J01XC01)	0.1	Sulfamethoxazole and trimethoprim (J01EE01)	1.0
		Any of above	99.9	Any of above	96.6
2004		***n*** **= 45,886**		***n*** **= 63,104**	
	1:	Amoxicillin (J01CA04)	46.0	Amoxicillin (J01CA04)	31.7
	2:	Phenoxymethylpenicillin (J01CE02)	44.8	Cefaclor (J01DC04)	20.9
	3:	Erythromycin (J01FA01)	4.4	Erythromycin (J01FA01)	14.5
	4:	Dicloxacillin (J01CF01)	1.6	Cefixime (J01DD08)	6.2
	5:	Azithromycin (J01FA10)	0.8	Cefpodoxime (J01DD13)	5.6
	6:	Pivampicillin (J01CA02)	0.7	Phenoxymethylpenicillin (J01CE02)	4.5
	7:	Clarithromycin (J01FA09)	0.6	Clarithromycin (J01FA09)	4.3
	8:	Amoxicillin and beta-lactamase inhibitor (J01CR02)	0.4	Azithromycin (J01FA10)	3.5
	9:	Trimethoprim (J01EA01)	0.3	Cefuroxime (J01DC02)	2.1
	10:	Fusidic acid (J01XC01)	0.1	Sulfamethoxazole and trimethoprim (J01EE01)	1.7
		Any of above	99.7	Any of above	94.1

Anatomical Therapeutic Chemical codes are shown in parentheses

Denmark and by 16% in Germany. The increase in Germany started from the 2011 birth cohort onwards and it continued to rise in later birth cohorts. The proportion of antibiotics with higher concerns regarding side effects and/or resistance potential (i.e., Watch group) among all antibiotics prescribed first was 6.2% in Denmark and 44.2% in Germany in the 2016 birth cohort (Fig. 4b); compared to the 2004 birth cohort, it decreased by 37% in Denmark and by 15% in Germany. In both countries, the decrease started from the 2011 birth cohort onwards and it continued in later birth cohorts. The proportion of antibiotics in the Reserve group was low in both countries (not higher than 0.1%). The same applied for unclassified ones (maximum: 0.1% in Denmark and 2.3% in Germany).

DISCUSSION

Our study, which is the first to comprehensively compare outpatient antibiotic prescribing in early life between different countries, provided three key insights. First, Danish children received outpatient antibiotic prescriptions earlier and at a higher rate in the first 2 years of life than German children. Second, quality indicators for the first outpatient antibiotic prescription according to definitions by WHO were substantially worse in Germany than in Denmark. Third, in both countries, positive changes over time were observed—particularly starting with the 2010/2011 birth cohorts and increasingly in later birth cohorts; specifically, the age at first outpatient antibiotic prescription increased, the frequency of antibiotic prescribing decreased, and the quality of antibiotic prescribing improved even though quality indicators remained suboptimal in Germany compared to Denmark.

Earlier and More Frequent Prescribing of Antibiotics in Denmark as Compared with Germany

Results from a prior study comparing use of antibiotics in the first years of life between the Aarhus metropolitan area in Denmark and Germany (GePaRD data from 2005 to 2008) partly differed from the present study (higher prescribing rates in Germany than in Denmark in 2005/2006; in 2007/2008, it was the other way round) [24]. Prior research showed that Aarhus has one of the lowest antibiotic prescribing frequencies during infancy in Denmark [25], which most likely explains why the results differ from the present study covering the entire Danish population.

More Favorable Quality Indicators in Denmark Than in Germany

A higher quality of outpatient antibiotic prescribing in Denmark as compared with Germany has also been reported previously (based on other quality indicators) using aggregated data from the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) database [26]. Although

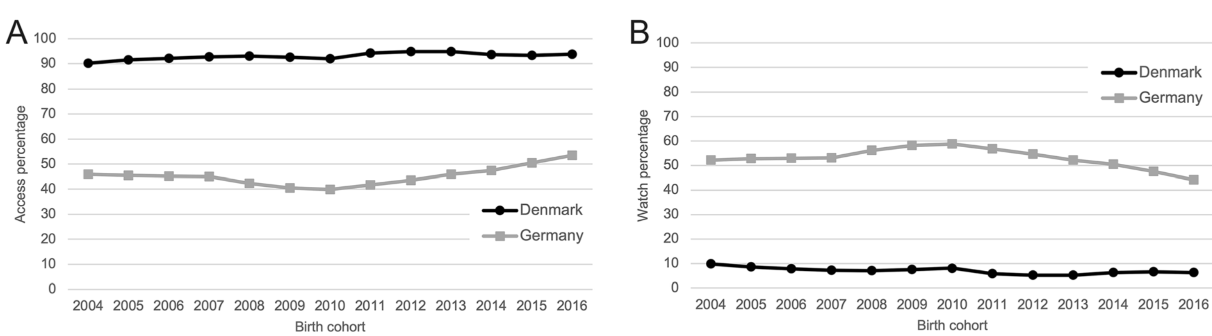

Fig. 4 Access (**a**) and Watch percentage (**b**) of the outpatient antibiotics prescribed first in the first 2 years of life, stratified by birth cohort (see "Methods" section regarding the classification into Access and Watch)

phenoxymethylpenicillin is recommended in Danish guidelines as the first choice for most infectious diseases in children, and the adherence to guidelines for antibiotics is generally high [27], amoxicillin showed to be slightly more common in the present study. This is consistent with previous studies and is likely explained by easier intake due to the better taste of amoxicillin compared to phenoxymethylpenicillin [28, 29].

The quality indicators for Germany were mainly found to be poor in our study due to frequent prescribing of second- and third-generation cephalosporins, which was also reported for this age group in another study from Germany [30]. In Denmark, no antibiotics from these groups of broad-spectrum antibiotics were among the ten most frequently antibiotics prescribed first. Also, in the Netherlands, it has been reported that practically no cephalosporins are prescribed in the first years of life [31].

Notably, our study focused on the first ever outpatient antibiotic prescription in early life, revealing that second- and third-generation cephalosporins were frequently used as first-choice antibiotic treatment in Germany, despite their unfavorable properties—e.g., low oral bioavailability and increased risk of antibiotic resistance [32, 33]. This practice contradicts recommendations from international guidelines, which either do not recommend cephalosporins at all [34–36] or only as second-line treatment [37, 38]. Further indications partly mentioned in guidelines include penicillin allergy [37, 38]—the true prevalence of which is considered low (< 1%) [39]—or life-threatening infections [40]. German guidelines for standard antibiotic treatment of common pediatric infectious diseases in the outpatient setting only recommend two second- and third-generation cephalosporins (cefixime and cefpodoxime) as first-line treatment for uncomplicated pyelonephritis [33]. Cefaclor, which was the second most common initial antibiotic prescribed in early life in Germany in our study (almost 30%), is only mentioned for some rare skin infections as an alternative to cefadroxil (a narrow-spectrum first-generation cephalosporin). The guideline otherwise clearly advises against the use of cephalosporins; so, there is a discrepancy between recommendations and practice in Germany.

Positive Trends Over Time in Both Countries

Decreasing trends in the quantity of outpatient antibiotic prescriptions in early life in Denmark and Germany from 2010/2011 onwards have been described before [28, 30]. We additionally showed positive trends regarding both age at first outpatient antibiotic prescription and quality of antibiotic prescribing. The reasons for these trends are likely multifactorial and rooted in coordinated and EU-wide initiatives promoting prudent use of antimicrobials [41].

Implications

It is unlikely that differences in antibiotic prescribing frequency between European countries can be explained by differences in the burden of infectious diseases. A study collecting primary data in five European countries (including Germany) showed no inter-country differences in the frequency of episodes of infectious diseases such as upper respiratory tract infections and otitis media among infants up to 1 year of age [42]. Also, the guidelines regarding antibiotic use are largely similar, i.e., the observed differences cannot be explained by different recommendations. The same holds true for reimbursement. In both countries, antibiotics for children are either provided free of charge or at a very low cost. Thus, there may be other explanations for the observed differences between Denmark and Germany. These might include different attitudes and beliefs of physicians and parents regarding antibiotics. It might also be relevant that general practitioners in Denmark have direct access to well-prepared information and infection-specific recommendations for antibiotics [43].

However, this is highly speculative, so further research is needed to evaluate reasons for the observed differences between the countries. Future studies may also assess whether there is an impact on antibiotic prescribing due to the fact that, as has been mentioned before, in

Denmark, general practitioners are the first-line providers for all inhabitants regardless of age, whereas in Germany, pediatricians typically provide primary healthcare for children.

Our findings suggest that both Denmark and Germany may benefit from critical reflection on how to improve rational prescribing of outpatient antibiotics in infants. For Denmark, this might relate to the potential of reducing antibiotic prescribing to infants. For Germany, there is obviously large potential for improving the quality of antibiotic prescribing in terms of the choice of antibiotic agent—specifically by prescribing narrow-spectrum antibiotics such as phenoxymethylpenicillin or amoxicillin instead of cephalosporins. While programs specifically targeting high-prescribers or prescribers not adhering to guidelines have been suggested [44], interventional research—partly already underway [45]—is required to assess the effectiveness of such strategies.

Strengths and Limitations

The strengths of this study include the use of large healthcare databases with no recall or non-responder bias. Both data sources fully capture reimbursed prescription drugs, and they use the same drug coding system. Our study population covers all of Denmark and a large proportion of Germany. As shown before, GePaRD can be considered representative regarding antibiotic prescriptions for all persons covered by statutory health insurance in Germany (~ 90% of the German population), including the investigated age group [46]. Another strength as compared to previous studies in this field is our use of the comprehensive 2019 list of the WHO AWaRe classification, which substantially reduced the percentage of unclassified antibiotics prescribed in Germany.

Our study also has limitations. First, as we assessed the antibiotic prescribing behavior based on antibiotics that were actually dispensed, it is unknown whether there were additional prescriptions of antibiotics not redeemed in pharmacies, e.g., in the context of delayed prescribing (i.e., when prescribers issue a prescription but advise the patient to fill it only if symptoms persist/worsen or once the test results are known). Second, the delay between actual birth and start of the insurance period in GePaRD is unknown. We do, however, not expect this delay to be particularly long, as it is in the interest of parents to enroll their child in statutory health insurance as early as possible. Moreover, parents are legally required to register their newborn within two months. Third, as we used a sub-cohort comprising all children with at least 2 years of follow-up for determining the frequency of antibiotic prescribing, about 10% of the German study population was not included in this analysis—mainly because of change in the health insurance provider. This could have led to selection bias. It has been shown that persons who changed the health insurance provider are more highly educated compared to persons who did not change but the difference was not very pronounced [47]. Therefore, if at all, we do not think that selection bias had a relevant impact on the rates of antibiotic treatment episodes estimated in the German sub-cohort.

CONCLUSIONS

Over the first 2 years of life, children born in Denmark received antibiotics markedly earlier and more frequently than in Germany, while quality indicators of antibiotic prescribing were more favorable in Denmark. Over time, positive changes occurred towards more rational antibiotic prescribing in early life in both countries, particularly for children born in 2010 and later. Given the large differences in antibiotic prescribing between Denmark and Germany, our findings may stimulate reflection on the potential for and the need of further improvement of antibiotic stewardship in infants in both countries. This particularly applies to prescribing antibiotics with a lower potential for side effects and/or resistance in Germany.

ACKNOWLEDGEMENTS

The authors would like to thank all statutory health insurance providers that provided data for this study, namely AOK Bremen/Bremerhaven, DAK-Gesundheit, Techniker Krankenkasse (TK), and hkk Krankenkasse. They would also like to thank Alina Ludewig, Inga Schaffer, and Jacob Harbo Andersen for the statistical programming of the data.

Medical Writing and/or Editorial Assistance. The authors acknowledge Dr. Heike Gerds from the Department of Clinical Epidemiology at the Leibniz Institute for Prevention Research and Epidemiology – BIPS for proofreading the final manuscript. No external funding was received for her assistance.

Author Contributions. Oliver Scholle contributed to the study concept and design, analyzed and interpreted the data, and prepared the original draft of the manuscript. Lotte Rasmussen and Jost Viebrock contributed to the study concept and design, analyzed and interpreted the data, and revised the manuscript. Mette Reilev and Ulrike Haug contributed to the study concept and design, interpreted the data, and revised the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding. This work received no external funding. The journal's fee was funded by the authors.

Data Availability. Due to Danish legislation, individual-level data are not available. Deidentified Danish data can be made available for authorized researchers after application to Forskerservice at the Danish Health Data Authority. As we are not the owners of the data, we are not legally entitled to grant access to the data of the German Pharmacoepidemiological Research Database. In accordance with German data protection regulations, access to the data is granted only to BIPS employees on the BIPS premises and in the context of approved research projects. Third parties may only access the data in cooperation with BIPS and after signing an agreement for guest researchers at BIPS.

Declarations

Conflict of Interest. Oliver Scholle, Jost Viebrock, and Ulrike Haug are working at an independent, non-profit research institute, the Leibniz Institute for Prevention Research and Epidemiology – BIPS. Unrelated to this study, BIPS occasionally conducts studies financed by the pharmaceutical industry. These are post-authorization safety studies (PASS) requested by health authorities. The design and conduct of these studies as well as the interpretation and publication are not influenced by the pharmaceutical industry. The study presented was not funded by the pharmaceutical industry. Lotte Rasmussen participates in a regulator-mandated phase IV-study funded by Novo Nordisk with funds paid to the institution where she is employed (no personal fees) and with no relation to this study. Mette Reilev declares no conflicts of interest.

Ethical Approval. According to Danish legislation, approval from an ethics Committee is not required for registry-based studies. The study was approved by the Danish Data Protection Agency (11.106). In Germany, the utilization of health insurance data for scientific research is regulated by the Code of Social Law. All involved health insurance providers as well as the Federal Office for Social Security and the Senator for Health, Women and Consumer Protection in Bremen as their responsible authorities approved the use of GePaRD data for this study. Informed consent for studies based on claims data is required by law unless obtaining consent appears unacceptable and would bias results, which was the case in this study. According to the Ethics Committee of the University of Bremen studies based on GePaRD are exempt from institutional review board review.

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