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ORIGINAL REPORT

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Comparing outpatient oral antibiotic use in Germany and the Netherlands from 2012 to 2016

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Abstract

Purpose: Overuse of antibiotics is of concern, but may differ between European countries. This study compares outpatient use of oral antibiotics between Germany (DE) and the Netherlands (NL).

Methods: For DE, we used the DAPI database with information on dispensings at the expense of the Statutory Health Insurance Funds from > 80% of community pharmacies. For NL, data were obtained from the Dutch Foundation for Pharmaceutical Statistics. Use of oral antibiotics was estimated as defined daily doses per 1000 inhabitants per day (DID), except for age comparisons as packages per 1000 inhabitants annually. National time trends were assessed with linear regression, stratified for the major antibiotic classes, and individual substances.

Results: From 2012 to 2016, outpatient antibiotic use was lower in NL than in DE (9.64 vs 14.14 DID in 2016) and non-significantly decreased slightly over time in both countries. In DE, dispensings of oral antibiotics to children were higher compared with NL for the age groups 2 to 5 (2.0-fold in 2016) and 6 to 14 years (2.7-fold in 2016). Use of cephalosporins was very low in NL (0.02 DID in 2016), but the second most frequently dispensed class in DE (2.95 DID in 2016).

Conclusion: From 2012 to 2016, outpatient use of oral antibiotics was lower in NL than in DE. Differences were primarily observed in the age groups 2 to 5 and 6 to 14 years, although the recommendations of evidence-based guidelines in both countries were in agreement.

KEYWORDS

ambulatory care, anti-bacterial agents, drug utilization, Germany, Netherlands, pharmacoepidemiology

1 | INTRODUCTION

The use of systemic antibiotics is subject to continuous surveillance to understand antibiotic resistance development.[1,2] This problem is increasing and threatens the possibilities to treat common infection

"All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation."

Statement about prior postings and presentations

Parts of the results have been presented at the 46th ESCP Symposium on Clinical Pharmacy (Heidelberg, Germany 9-11 Oct 2017) as a poster.

diseases effectively.[3] Thus, restrained use of antimicrobial medicines is urgently advocated worldwide. The focus of improvement programs in human medicine should be on outpatient prescribing of antibiotics since during recent years, 85% to 95% of antibiotics have been dispensed in the community in many countries worldwide.[1,4]

Numerous studies have quantified the overall use of systemic antibiotics and elucidated specific antibiotic groups or substances in European countries[5] and use in different age groups.[6-10] Within the European Union, Germany (DE) and the Netherlands (NL) belong to countries with a low antibiotic consumption.[2] Both countries are culturally comparable, in direct geographical neighborhood, and with highly developed health care systems. However, antibiotic consumption was substantially higher in DE during recent years compared with NL.[1,11,12] National preferences for types of antibiotics prescribed in both countries, with the exception of penicillins as the antibiotic drug class mostly prescribed, differed strongly between 2004 and 2015. Most strikingly, cephalosporins were hardly used at all in NL whereas their use has increased in DE.[13,14] In DE, most patients who received an antibiotic in ambulatory care in 2008 were diagnosed with respiratory tract (RTI) or genitourinary tract infections whereas in NL other diagnoses were more frequent.[13] The application of broad spectrum agents for viral self-limiting infections is of concern in DE, especially in children and adolescents.[8] In-depth and contemporary studies, however, are lacking, which may help to understand the reasons for the differences for outpatient oral antibiotics dispensings in both countries, eg, by looking at national guideline recommendations.

The goal of our study was, therefore, to compare directly the outpatient use of oral antibiotics in DE and NL during the 5-year period 2012 to 2016 and by age groups, antibiotic classes, and individual drugs in particular. We further aimed at comparing actual guideline recommendations for the two countries for RTI and urinary tract infections (UTI). Since in DE frequent prescribing of clindamycin by dentists had been observed,[15-19] another focus of the study was dispensing of clindamycin by dentists and the guidelines for odontogenic infections in DE.

KEY POINTS

- From 2012 to 2016, outpatient use of oral antibiotics was lower in the Netherlands (NL) than in Germany (DE) (9.64 DID vs 14.14 DID in 2016)
- Outpatient use of oral antibiotics non-significantly decreased slightly over time in both countries
- In DE, use of oral antibiotics in children was higher compared with NL for the age groups 2 to 5 years (2.0-fold in 2016) and 6 to 14 years (2.7-fold in 2016)
- Use of cephalosporins was very low in NL (0.02 DID in 2016) but the second most frequently dispensed class of antibiotics in DE (2.95 DID in 2016)

2 | METHODS

2.1 | Study design

A longitudinal drug utilization study[20] for oral antibiotic use during the years 2012 and 2016 was performed.

2.2 | Data sources

In DE, information was available from the DAPI database, which contains anonymous claims data of drugs prescribed and subsequently dispensed at community pharmacies at the expense of the Statutory Health Insurance (SHI) Funds. Nearly 87% of DE's population is insured by the SHI system.[21,22] The database covers all claims data from a representative sample of more than 80% of the community pharmacies throughout all regions. Dispensing data were linked to the ABDA database containing information about the (brand) name, composition, active ingredient, strength, package size, dosage form, and route of administration of German medicinal products.[23] Prescriptions by dentists could be identified by a specific code on the prescriptions. Prescriptions for privately insured patients and payed out-of-pockets are not available in the DAPI database. Data on indication, treatment duration, or dosages as well as data on individual patients including gender are also not available, except for year of birth.

In NL, data were available from the Dutch Foundation for Pharmaceutical Statistics (SFK) that collects dispensing data for drugs prescribed from nearly 95% of all community pharmacies.[24] All prescriptions are registered for the concerning patient in the computer system of the pharmacy. This registration is mandatory in NL to achieve a complete file on all patient's medication in use, regardless of the insurance status. Besides, all inhabitants are covered by a mandatory health insurance system. These data provide detailed information on the drugs prescribed, including the codes from the Anatomical Therapeutic Chemical (ATC) classification system of the WHO,[25] and the amount dispensed. Thus, information on (brand) name, composition, active ingredient, strength, package size, dosage form, and route of administration for the dispensed antibiotics was available in the database of the SFK for each individual antibiotic product on patient level. In the SFK, patients are coded by an anonymous number from the computer system of the local pharmacy. The only information further available is on patient's gender and year of birth. Detailed information about the specialty of the prescriber and the reason for prescribing is not available.

In both countries, oral antibiotics are prescription-only and reimbursed by health insurance funds. In DE, data were extrapolated by regional factors based on 80% to 100% of all community pharmacies, and thus 100% of the SHI insured population. In NL, data were extrapolated from 95% available to 100% of the community pharmacies, and thus 100% of the total population. To enhance comparability, in NL, the extrapolated data were related to the total population in the NL, whereas in DE the extrapolated data were related to the SHI insured population.

2.3 | Measurement of antibiotic use

Systemic antibiotics, ATC Code J01,[26] were analyzed on substance level for orally administered antibiotics (ATC 5th level codes). For achieving comparability between DE and NL, antibiotic use was estimated by defined daily doses[26] per 1000 inhabitants per day (DID). For DE, all

persons insured by the SHI system were used as a reference. These numbers were obtained from the Federal Ministry of Health[21] except for children under 15 years of age. For the analysis of age groups (0-1, 2-5, 6-14, and ≥15 years of age), detailed numbers of SHI insured children were needed. To estimate those, overall numbers of children in DE for the years under investigation were obtained from the Federal Statistical Office.[22] An estimate for the number of subjects insured by SHI was calculated subsequently as follows: The proportion of SHI insured children in the age group 0 to 14 within the corresponding year was multiplied by the total number of children in DE in the age groups 0 to 1, 2 to 5, and 6 to 14. For NL, overall population numbers retrieved from the Central Agency of Statistics[27] were used as a reference.

For the analysis by age group, the year of birth was available on prescription level. Thus, during a year, a person contributed data to a corresponding age group based on his or her age on 31 December. In the sub-analysis that focused on dispensings to children, antibiotic use was defined as annual package numbers per 1000 inhabitants, assuming one package as therapy unit. Defined daily doses could not be used here as these are based on the average dosage for adults and do not take into account age-based and weight-based dosing in children of different age groups.[28]

2.4 | Statistical analysis

Comparison of oral antibiotic drug use between DE and NL was achieved by the assessment of DIDs. DIDs dispensed in DE and NL were calculated in total, for the different major antibiotic classes (penicillins, cephalosporins, tetracyclines, quinolones, macrolides, lincosamides, and others comprising sulfonamides/trimethoprim, aminoglycosides, glycopeptides, fosfomycin, and nitrofuran derivatives) and for different individual substances. Annual differences (increase or decrease) between 2012 and 2016 were calculated for DE and NL for the total oral antibiotic drugs and on the level of antibiotic classes and substances, respectively.

The total annual package numbers of oral antibiotics dispensed per 1000 inhabitants in DE and in NL were compared within different age groups. Increase/decrease from 2012 to 2016 was calculated for each age group in DE and NL.

Furthermore, linear regression analyses were performed to investigate associations between time (as increasing calendar year) and the amount of antibiotic dispensings within both countries. For these analyses, a linear relationship was assumed between time and antibiotic dispensings. The average annual change estimates as well as the corresponding *t*-test *P*-values were calculated. Statistical analyses were conducted using IBM SPSS 22. Results with *P*-values ≤0.05 were considered statistically significant.

2.5 | Review of national guidelines

We scanned DE and NL guidelines for treatment of RTI, UTI, and odontogenic infections for their recommendations of oral antibiotic use. The Clinical Practice Guidelines compiled by the Association of the Scientific Medical Societies[29] (AWMF) were extracted. Information for treatment of odontogenic infections was additionally retrieved from the website of the Federal Chamber of Dentists, the professional body of all dentists in DE.[30] Only current guidelines were included, those with expired date were not taken into account. In NL, guidelines for general practitioners are consolidated by the Dutch College of General Practitioners, Nederlands Huisartsen Genootschap (NHG), and they were extracted from their website.[31]

3 | RESULTS

3.1 | Overall use of antibiotics

Since 2012, the overall consumption of oral antibiotics showed a non-significant decrease of −2.2% in DE and −6.9% in NL (Table 1 and

TABLE 1 Trends in dispensing of oral antibiotics in Germany and the Netherlands from 2012 to 2016

		DID						Results from Linear Regression	
Group		2012	2013	2014	2015	2016	Δ	Avg	*P*-value
All systemic antibiotics	DE	14.45	15.48	14.16	14.36	14.14	−2.2%	−0.176	0.389
	NL	10.36	10.02	9.69	9.93	9.64	−6.9%	−0.153	0.075
Penicillins	DE	4.45	4.85	4.59	4.75	4.89	9.9%	0.079	0.213
	NL	4.14	4.08	3.88	4.04	3.97	−4.0%	−0.037	0.286
Cephalosporins	DE	2.68	3.10	2.85	3.01	2.95	10.2%	0.046	0.448
	NL	**0.03**	**0.03**	**0.03**	**0.03**	**0.02**	**−21.3%**	**−0.002**	**0.003**
Tetracyclines	DE	**2.29**	**2.38**	**2.03**	**1.93**	**1.88**	**−17.6%**	**−0.125**	**0.036**
	NL	**2.28**	**2.16**	**2.06**	**2.09**	**1.94**	**−14.9%**	**−0.075**	**0.018**
Quinolones	DE	**1.43**	**1.41**	**1.31**	**1.32**	**1.24**	**−13.6%**	**−0.048**	**0.011**
	NL	0.75	0.71	0.73	0.72	0.69	−7.6%	−0.011	0.091
Macrolides	DE	1.85	1.98	1.68	1.71	1.59	−14.4%	−0.081	0.088
	NL	1.23	1.13	1.08	1.11	1.08	−12.1%	−0.031	0.096
Lincosamides	DE	**0.75**	**0.75**	**0.72**	**0.69**	**0.67**	**−10.7%**	**−0.023**	**0.014**
	DE[a]	**0.50**	**0.50**	**0.47**	**0.44**	**0.41**	**−17.8%**	**−0.024**	**0.006**
	NL	**0.15**	**0.16**	**0.16**	**0.18**	**0.19**	**27.5%**	**0.010**	**0.001**
Others	DE	**1.01**	**1.01**	**0.98**	**0.95**	**0.93**	**−8.8%**	**−0.024**	**0.005**
	NL	1.79	1.75	1.75	1.76	1.75	−2.4%	−0.008	0.132

[a]Dentists' prescriptions only.

Abbreviations: Avg, average annual change in DID, significant changes in bold; DE, Germany; DID, defined daily doses per 1000 inhabitants per day; Δ, percentage difference between 2016 and 2012 values; NL, the Netherlands.

Figure 1). In 2016, almost all systemic antibiotics in outpatient care were dispensed in oral dosage forms (14.14 of 14.18 DID in DE, 9.64 of. 9.69 DID in NL). Overall use of oral antibiotics in DE was 47% higher than in NL (Figure 3).

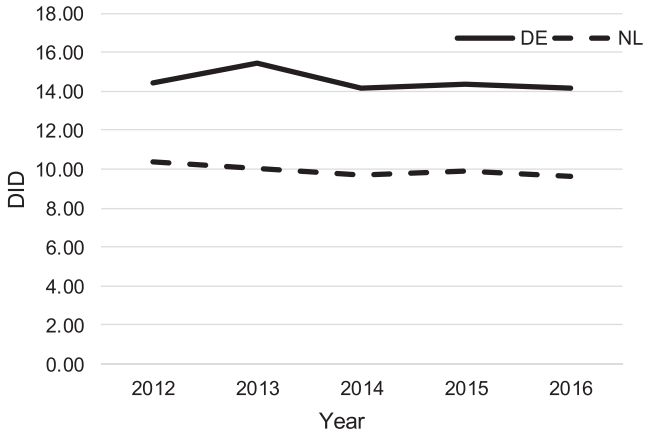

FIGURE 1 Dispensing of all oral antibiotics in Germany and the Netherlands from 2012 to 2016. DE, Germany; DID, defined daily doses per 1000 inhabitants per day; NL, the Netherlands

3.2 | Use of antibiotics in different age groups

During 2012 to 2016, consumption of oral antibiotics by children was higher in DE compared with NL particularly for the age groups 2 to 5 years (831 vs 408 packages per 1000 inhabitants in 2016) and 6 to 14 years (434 vs 160 packages per 1000 inhabitants in 2016) (Figure 2). The use decreased significantly in the age groups 0 to 1 and 2 to 5 years in DE (Table 2).

3.3 | Use of major classes of antibiotics in 2016

Penicillins were the most frequently used oral antibiotic class in both countries (4.89 DID in DE, 3.97 in NL) (Table 1). Cephalosporins were the second most frequently consumed class in DE (2.95 DID), but hardly used in NL (0.02 DID). A further difference could be observed in the use of lincosamides with clindamycin as the only representative of this class (0.67 DID in DE vs 0.19 DID in NL). In addition, in DE, more oral quinolones (+79%, Figure 3) and macrolides (+47%) were consumed than in NL. Dispensing of oral tetracyclines was comparable in both countries (1.88 DID in DE vs 1.94 DID in NL), whereas in NL, the group of "other antibiotics" was used more frequently than in DE (1.75 DID in NL vs 0.93 in DE).

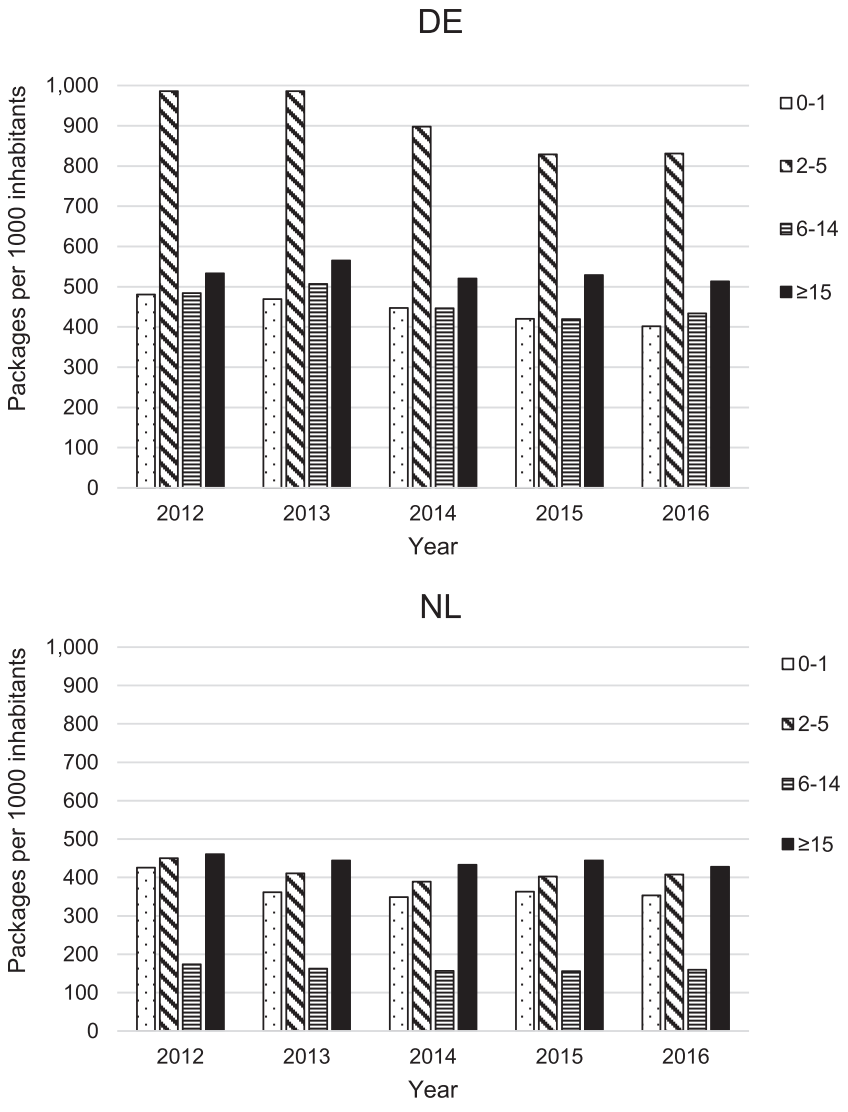

FIGURE 2 Dispensing of oral antibiotics by age group in Germany and the Netherlands from 2012 to 2016. DE, Germany; NL, the Netherlands

TABLE 2 Trends in dispensing of oral antibiotics in Germany and the Netherlands from 2012 to 2016, by age group

Age Group [years]		Packages per 1000 Inhabitants						Results from Linear Regression	
		2012	2013	2014	2015	2016	Δ	Avg	*P*-value
0-1	DE	**480**	**469**	**447**	**420**	**402**	**−16.4%**	**−20.638**	**0.001**
	NL	425	361	349	363	353	−17.0%	−14.299	0.169
2-5	DE	**986**	**986**	**898**	**829**	**831**	**−15.8%**	**−46.739**	**0.015**
	NL	450	410	389	403	408	−9.4%	−9.242	0.243
6-14	DE	484	507	446	419	434	−10.4%	−18.795	0.089
	NL	173	163	156	156	160	−8.0%	−3.432	0.133
≥15	DE	533	565	520	529	513	−3.7%	−7.541	0.290
	NL	461	445	433	444	428	−7.1%	−6.637	0.082

Abbreviations: Δ, percentage difference between 2016 and 2012 values; Avg, average annual change in packages per 1000 inhabitants, significant changes in bold; DE, Germany; NL, the Netherlands.

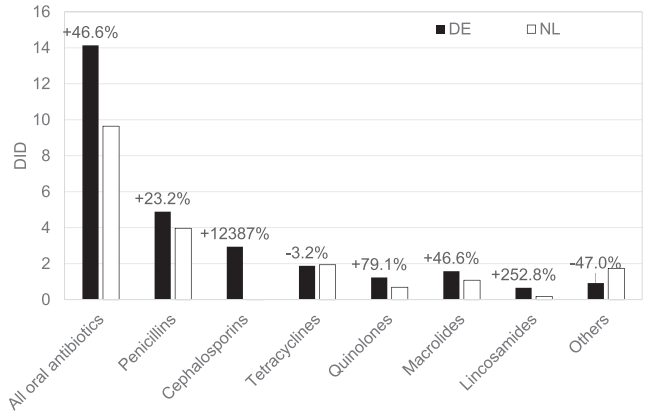

FIGURE 3 Dispensing of oral antibiotics according to different classes in Germany and the Netherlands in 2016. Percentage differences as DE − NL. DE, Germany; DID, defined daily doses per 1000 inhabitants per day; NL, the Netherlands

3.4 | Trends in use of major classes of antibiotics

Between 2012 and 2016, within the major antibiotic classes, only the use of penicillins and cephalosporins increased (+9.9% /+10.2%) in DE and lincosamides (clindamycin, +27.5%) in NL, respectively; only the increase in lincosamide consumption in NL was statistically significant ($P = 0.001$). The use of other antibiotic classes decreased significantly for quinolone antibacterials, lincosamides, tetracyclines, and other antibiotics in DE compared with cephalosporins and tetracyclines in NL, respectively. Dentists prescribed 62% of oral clindamycin dispensed in DE in 2016, but clindamycin dispensings based on dentists' prescriptions decreased significantly ($P = 0.006$) from 0.50 DID in 2012 to 0.41 in 2016.

3.5 | Use of individual antibiotics

Seven of the 10 most frequently used oral antibiotics in 2016 were in agreement in both countries. Amoxicillin was the most frequently used oral antibiotic in both countries, followed by cefuroxime and doxycycline in DE and by doxycycline and amoxicillin with enzyme inhibitor in NL (Table 3). Three of the 10 most frequently used oral antibiotics in both countries (ciprofloxacin, azithromycin, and clarithromycin) belong to the "Watch group antibiotics" according to the WHO. Oral fosfomycin showed the highest increase from 2012 to 2016 in both countries (87% in DE, 257% in NL, Table 4).

3.6 | Overview of guidelines for antibiotic use

Table 5 provides an overview over current DE and NL guidelines for the treatment of RTI, UTI, and odontogenic infections and lists the corresponding recommendations for antibiotic use provided.

For acute RTI, the guidelines of both countries advise to be very reserved in the use of oral antibiotics as they are mainly caused by viruses. If antibiotics are indicated, penicillins are recommended as the first choice in most cases. Cephalosporins are not mentioned by the NL RTI guidelines but listed in DE guidelines for the treatment of acute exacerbation of chronic obstructive pulmonary disease (COPD), for rhinosinusitis and as second choice for otitis media acuta and for pneumonia in patients with risk factors or moderate forms. Furthermore, cephalosporins are mentioned for certain indications in case of allergy or intolerance towards penicillins. Fosfomycin and nitrofurantoin are examples that are recommended in both countries for the treatment of uncomplicated UTI in women. Guidelines for odontogenic infections in DE recommend the use of penicillins as a first choice and erythromycin, clindamycin, or tetracyline as second choice or in case of penicillin allergy. Experts discourage the systemic use of antibiotics in NL as well as DE guidelines for peri-implantation infections.[47,48]

4 | DISCUSSION

4.1 | Overall difference in outpatient use of oral antibiotics between DE and NL—contextual factors

Oral antibiotic dispensing to outpatients from 2012 to 2016 was higher in DE compared with NL. Changes during this period were small. These data are in agreement with consumption of systemic antibiotics in these countries.[1]

In NL, a lot of attention is given for cautious use of antibiotics. General practitioners (GPs) act as gatekeepers in outpatient care and are educated to a reserved antibiotic prescribing according to their guidelines.[49] This may explain the lower outpatient antibiotic dispensing rates, compared with DE. For example, a study for antibiotic

TABLE 3 Ten most frequently dispensed oral antibiotic substances in Germany and the Netherlands in 2016 (ranking by DID)

Rank (DE)	Antibiotic	Group	DE (DID)	NL (DID)
1	Amoxicillin	Penicillins	3.45	1.92
2	Cefuroxime	Cephalosporins	2.26	0.01
3	Doxycycline	Tetracyclines	1.72	1.68
4	Amoxicillin and enzyme inhibitor	Penicillins	0.76	1.41
5	Ciprofloxacin[a]	Quinolones	0.73	0.56
6	Clindamycin	Lincosamides	0.67	0.19
7	Phenoxymethylpenicillin	Penicillins	0.55	0.01
8	Azithromycin[a]	Macrolides	0.54	0.75
9	Clarithromycin[a]	Macrolides	0.54	0.30
10	Nitrofurantoin	Others	0.39	1.29
Rank (NL)	**Antibiotic**	**Group**	**NL (DID)**	**DE (DID)**
1	Amoxicillin	Penicillins	1.92	3.45
2	Doxycycline	Tetracyclines	1.68	1.72
3	Amoxicillin and enzyme inhibitor	Penicillins	1.41	0.76
4	Nitrofurantoin	Others	1.29	0.39
5	Azithromycin[a]	Macrolides	0.75	0.54
6	Ciprofloxacin[a]	Quinolones	0.56	0.73
7	Flucloxacillin	Penicillins	0.42	0.01
8	Clarithromycin[a]	Macrolides	0.30	0.54
9	Sulfamethoxazole and trimethoprim	Others	0.26	0.39
10	Minocycline	Tetracyclines	0.26	0.14

[a]Watch group antibiotics (antibiotics according to WHO that have higher resistance potential and so are recommended only for a specific, limited number of indications as first or second treatment choices[32]).

Abbreviations: DE, Germany; DID, defined daily doses per 1000 inhabitants per day; NL, the Netherlands.

TABLE 4 Five oral antibiotics with highest growth rates from 2012 to 2016 in Germany and the Netherlands (ranking by DID, only antibiotics with >0.0003 DID dispensed in 2016)

		DID						Results from Linear Regression	
Rank	Antibiotic	2012	2013	2014	2015	2016	Δ	Avg	*P*-value
DE									
1	Fosfomycin	**0.030**	**0.040**	**0.046**	**0.051**	**0.057**	**87.5%**	**0.006**	**0.001**
2	Amoxicillin and enzyme inhibitor	**0.537**	**0.611**	**0.626**	**0.697**	**0.756**	**40.8%**	**0.052**	**0.002**
3	Linezolid	0.003	0.003	0.003	0.003	0.004	39.9%	0.000	0.103
4	Flucloxacillin	**0.009**	**0.010**	**0.011**	**0.011**	**0.012**	**32.8%**	**0.001**	**0.009**
5	Cefuroxime	1.806	2.194	2.113	2.279	2.257	25.0%	0.099	0.095
NL									
1	Fosfomycin	**0.012**	**0.018**	**0.027**	**0.035**	**0.043**	**256.7%**	**0.008**	**0.000**
2	Phenoxymethylpenicillin	0.002	0.001	0.001	0.006	0.006	200.1%	0.001	0.097
3	Linezolid	0.001	0.001	0.001	0.001	0.002	30.3%	0.000	0.227
4	Clindamycin	**0.148**	**0.157**	**0.163**	**0.177**	**0.189**	**27.5%**	**0.010**	**0.001**
5	Azithromycin	**0.633**	**0.648**	**0.669**	**0.740**	**0.748**	**18.2%**	**0.032**	**0.010**

Abbreviations: Avg, average annual change in DID, significant changes in bold; DE, Germany; DID, defined daily doses per 1000 inhabitants per day; Δ, percentage difference between 2016 and 2012 values; NL, the Netherlands.

prescribing in outpatient care for RTI in 2006/2007 reported a 2.4-fold higher noncongruent prescribing with European Respiratory Society guidelines in DE compared with NL.[50]

In DE, many patients expect an antibiotic when visiting their GP for a common cold.[51] This expectation was associated with a misperception about how antibiotics should be used, although there was basic knowledge regarding their action and awareness about antibiotic resistance. Frequent prescribing of antibiotics for the treatment of mostly viral conditions, particularly to children, has been described in DE before.[8,52,53] This may explain the higher consumption of antibiotics in children in DE. Due to the lack of additional information on patient level, we could not analyze the role of contextual factors in the differences in antibiotic prescribing between DE and NL.

TABLE 5 Recommendations for oral antibiotics use in national guidelines

Guideline	Indication	Antibiotic Substance	Comment
DE			
Upper respiratory tract infections			
S2k† guideline "Rhinosinusitis", 2017, AWMF-Reg.-no. 017-049, 053-012, DGHNO-KHC[a], DEGAM[b] [33]	Acute rhinosinusitis	First choice: Amoxicillin or cephalosporins (cefuroxime) Second choice: Macrolides, amoxicillin and enzyme inhibitor, doxycycline or co-trimoxazole	Generally no antibiotic Consider only for patients with specific risk factors (eg, chronic inflammatory lung diseases, immunodeficiency, immunosuppression) or suspected complications
S2k guideline "Rhinosinusitis", 2017, AWMF-Reg.-no. 017-049, 053-012, DGHNO-KHC[a], DEGAM[b]	Chronic rhinosinusitis	Clarithromycin, doxycycline	Consider for cases when standard therapy fails
S2k guideline "Earache", 2014, AWMF-Reg.-no. 053-009, DEGAM[b] [34]	Otitis media acuta	First choice: Amoxicillin (if necessary with enzyme inhibitor) Second choice: second generation cephalosporin If allergic to penicillins or cephalosporins: Macrolides	Immediate antibiotic therapy only in patients with high risk (eg, children <6 months of age, children 6-23 months of age with bilateral otitis, patients with ventilation tubes, otorrhea, immunosuppression; persistent vomiting) For all others: Generally no immediate antibiotic therapy
S2k guideline "Earache", 2014, AWMF-Reg.-no. 053-009, DEGAM[b]	Otitis media chronica	Depends on antibiogram	For cases when standard therapy (local antiseptic/antibiotic) fails
S2k guideline "Treatment of inflammatory diseases of the tonsils - Tonsillitis", 2015, AWMF-Reg.-no. 017-024, DGHNO-KHC[a] [35]	Tonsillitis/ tonsillopharyngitis	(Benzathine) Phenoxymethylpenicillin In case of intolerance towards penicillins: Erythromycin estolate, first generation cephalosporins	Consider only for patients with confirmed or strongly suspected streptococcal tonsillitis
Lower respiratory tract infections			
S3‡ guideline "Cough", 2014, AWMF-Reg.-no. 053-013, DEGAM[b] [36]	Uncomplicated acute bronchitis		Antibiotics are not recommended Consider only for patients with severe cardiac or respiratory diseases, immunodeficiencies, or elderly patients, eg, in case of pneumonia (see below)
S3 guideline "Cough", 2014, AWMF-Reg.-no. 053-013, DEGAM[b]	Acute exacerbation of chronic obstructive pulmonary disease (COPD)	Aminopenicillins (and enzyme inhibitor), cephalosporins, macrolides, tetracyclines	
S3 guideline "Cough", 2014, AWMF-Reg.-no. 053-013, DEGAM[b]	Pneumonia	For patients without risk factors: Aminopenicillins, tetracyclines, or macrolides For patients with risk factors: First choice: Aminopenicillins and enzyme inhibitor, second choice: second generation cephalosporins	Risk factors include, eg, antibiotic therapy within the past 3 months, residents of nursery homes, COPD, diabetes mellitus due to extended spectrum of pathogens
S3 guideline "Cough", 2014, AWMF-Reg.-no. 053-013, DEGAM[b]	Pertussis	Azithromycin, clarithromycin	
S3 guideline "Management of adult community-acquired pneumonia and prevention", 2016, AWMF-Reg.-no. 020-020, DGP[c], DGI[d], PEG[e] [37]	Pneumonia	Mild form without comorbidities: Aminopenicillins In case of intolerance towards penicillins First choice: Fluorochinolones (moxifloxacin, levofloxacin) Second choice: Macrolides, tetracyclines Mild form with comorbidities: Aminopenicillins and enzyme inhibitor In case of intolerance towards penicillins: Fluorochinolones (moxifloxacin, levofloxacin) Moderate form: Aminopenicillins and enzyme inhibitor, possibly with macrolides	

(Continues)

TABLE 5 (Continued)

Guideline	Indication	Antibiotic Substance	Comment
S2k guideline "Management of community-acquired pneumonia in children and adolescents", 2017, AWMF-Reg.-no. 048-013, DGPI[f], GPP[g] [38]	Pneumonia	Amoxicillin, in case of intolerance towards penicillins: Cephalosporins, macrolides or tetracyclines (≥ 9 years of age) In case of complications or treatment failure: Aminopenicillins and enzyme inhibitor or second generation cephalosporins	Not every patient has to be treated with an antibiotic
Odontogenic infections			
Information on dental medication, 2017, BZÄK[h], KZBV[i] [39]	Bacterial infections	For gram (+) pathogens First choice: Oral penicillins Second choice: Erythromycin, clindamycin For mixed infections with gram(−) pathogens First choice amoxicillin (and enzyme inhibitor) In case of penicillin allergy Tetracyclines	No routine application, restricted indication only!
Information on dental medication, 2017, BZÄK[h], KZBV[i]	Prophylaxis of infective endocarditis	Amoxicillin In case of penicillin allergy: Clindamycin, cephalosporins, macrolides	In specific patient groups with high risk
Information on dental medication, 2017, BZÄK[h], KZBV[i]	Parodontitis	Metronidazole, doxycyline, ciproflocaxin	Only in severe cases or when standard therapy fails in specific patient groups
S3 guideline "Odontogenic infections", 2016, AWMF-Reg.-no. 007-006, DGMKG[j], DGZMK[k] [40]	Odontogenic infection	Phenoxymethylpenicillin, amoxicillin (and enzyme inhibitor) In case of penicillin allergy: Clindamycin	Only in case of infiltrates or local infections in patients with risk factors or if the infection tends to spread
Urinary tract infections			
S3 guideline "Epidemiology, diagnostics, therapy, prevention, and management of uncomplicated bacterial community acquired urinary tract infections", 2017, AWMF-Reg.-no. 043-044, DGU[l] [41]	Uncomplicated cystitis	For pre- and postmenopausal women fosfomycin, nitrofurantoin, nitroxolin, or pivmecillinam For men (if prostate is not involved) pivmecillinam or nitrofurantoin	Choice of antibiotic depends on individual risk, pathogen spectrum, adverse drug reactions, collateral damage Fluorochinolones and cephalosporins should **NOT** be used as first choice
S3 guideline "Epidemiology, diagnostics, therapy, prevention and management of uncomplicated bacterial community acquired urinary tract infections", 2017, AWMF-Reg.-no. 043-044, DGU[l]	Pyelonephritis	For pre- and postmenopausal women and moderate cases ciprofloxacin, levofloxacin, cefpodoxim, ceftibuten For men fluorochinolones	
S3 guideline "Epidemiology, diagnostics, therapy, prevention and management of uncomplicated bacterial community acquired urinary tract infections", 2017, AWMF-Reg.-no. 043-044, DGU[l]	Prevention	For premenopausal women co-trimoxazol, trimethoprim, nitrofurantoin, fosfomycin	Cefaclor, ciprofloxacin, norfloxacin, cefalexin, ofloxacin only if other substances can **NOT** be used.
NL			
Upper respiratory tract infections			
Guideline "Acute rhinosinusitis" (NHG[m]), 2014, M33[42]	Acute rhinosinusitis	Amoxicillin For penicillin allergy doxycycline or, when doxycycline is contraindicated (pregnancy, children <8 years) co-trimoxazol	For severe cases
Guideline "Acute keelpijn" (NHG[m]), 2015, M11[43]	Pharyngotonsillitis	Pheneticillin or phenoxymethylpenicillin Alternatively amoxicillin + enzyme inhibitor For penicillin allergy azithromycin For penicillin allergy during pregnancy or breastfeeding erythromycin	For severe cases
Guideline "Otitis media acuta bij kinderen" (NHG[m]), 2015, M09[44]	Otitis media acuta	Amoxicillin	

(Continues)

TABLE 5 (Continued)

Guideline	Indication	Antibiotic Substance	Comment
		In case of contra-indications for amoxicillin: Co-trimoxazol If amoxicillin shows no effect: Amoxicillin and enzyme inhibitor	
Lower respiratory tract infections			
Guideline "Acuut hoesten" (NHG[m)]), 2013, M78[45]	Uncomplicated acute infections of the upper airways	No antibiotics	
Guideline "Acuut hoesten" (NHG[m)]), 2013, M78	Complicated acute infections of the upper airways, pneumonia	Amoxicillin, doxycycline For children trimethoprim/sulfamethoxazol	
Guideline "Acuut hoesten" (NHG[m)]), 2013, M78	Pertussis	Azithromycin	
Urinary tract infections			
Guideline "Urineweginfecties" (NHG[m)]), 2013, M05[46]	Cystitis	For healthy, non-pregnant women First choice: Nitrofurantoin Second choice: Fosfomycin Third choice: Trimethoprim For children nitrofurantoin, amoxicillin, and enzyme inhibitor	Complicated cases: Amoxicillin and enzyme inhibitor, co-trimoxazol

[†]S2k guidelines are a formal consent of an expert group.[29]

[‡]S3 guidelines include all elements of a systematic development (logic, decision, and outcome analysis).[29]

[a)]German Society of Oto-Rhino-Laryngology, Head and Neck Surgery.

[b)]German College of General Practitioners and Family Physicians.

[c)]The German Respiratory Society.

[d)]German Society of Infectious Diseases.

[e)]Paul-Ehrlich Society of Chemotherapy.

[f)]German Society for Pediatric Infectious Diseases.

[g)]The Society for Pediatric Pneumology.

[h)]Bundeszahnärztekammer—Arbeitsgemeinschaft der Deutschen Zahnärztekammern (BZÄK), the professional body of all dentists in Germany.

[i)]National Association of Statutory Health Insurance Dentists.

[j)]The German Society for Oral and Maxillofacial Surgery.

[k)]German Society of Dentistry and Oral Medicine.

[l)]German Society of Urology.

[m)]Nederlands Huisartsen Genootschap (NHG).

Abbreviations: DE, Germany; NL, the Netherlands.

4.2 | Comparing guidelines and looking at use of individual substances based on medical evidence

Guidelines are based on medical evidence and, assuming a similar prevalence of indications, can reveal reasons for differences in prescribing behaviour between countries.[33-48] The most frequent indications for antibiotic prescriptions to children in DE are otitis media, tonsillitis, other upper RTI and bronchitis.[8,52] These indications are responsible for between 70% and 80% of all antibiotic prescriptions to children younger than 15 years. DE and NL RTI guidelines do not differ substantially with respect to their first choices of oral antibiotics. There are also no large differences with respect to restrictive use of clindamycin, chinolones, and cephalosporins.

We have no evidence for differences in infection prevalence in both countries (eg, respiratory diseases[54]) which would justify the huge discrepancies in, for example, use of cefuroxime or clindamycin between NL and DE. The use of oral cefuroxime is only justified for pathogens (except for UTI) with a minimum inhibitory concentration well below 1 μg/mL, which is the case for, eg, *Streptococcus pneumoniae*. Many other pathogens require much higher concentrations of cefuroxime which cannot be reached with approved oral products.[55] The high consumption for oral cephalosporins in outpatients in DE corresponds with earlier findings for all cephalosporins and suggests overuse.[56]

Due to actual resistance patterns and more side effects compared with penicillins, in German guidelines for dental diseases, clindamycin is only recommended in case of penicillin allergy or as second choice treatment.[39] This recommendation does not match with the high dispensing rates for prescriptions by dentists. Overprescription of clindamycin by German dentists has been described before.[57,58] Our data suggest, however, that guideline adherence by dentists may have improved over the past years.

According to the summary of product characteristics, fosfomycin is primarily prescribed for UTI in women. Although we could not analyze fosfomycin use by gender, the fact that the use of oral fosfomycin remarkedly increased in both countries let us assume it is

increasingly used for this indication. For UTI in women, it can replace fluoroquinolones, cephalosporins, and co-trimoxazol, in line with guidelines for treatment of uncomplicated UTI (guideline in NL since 2013).[59,60] The latter are associated with a higher risk of side effects and a selection of multiresistant pathogens.[59,61]

4.3 | Strengths and limitations

The strength of employing pharmacy claims-based databases for drug utilization studies is the access to a very large study population. Both databases dispose of information on dispensings to the majority of the population in DE and NL. It should be noted that the study was limited to the population insured by the SHI system in DE and that dispensings of antibiotics to privately insured patients were not included. This might have introduced a bias in the comparison with NL. However, this is not expected to be substantial. Another particular strength of the DAPI and the SFK databases is actuality of their data enabling us to cover the most recent period.

A major shortcoming of our study is that individual patient data such as prescribed doses for DE and information on diagnosis for both countries were lacking and comparison of antibiotic use was limited to overall dispensing data. Differences in consumption between both countries may thus originate in differences in absolute patient numbers treated per 1000 in the total population as well as in differences in dose or therapy duration of the antibiotics. We have noted that recommendations for antibiotic use in Dutch guidelines for treatment of RTI were more conservative with respect to dose in some cases, eg, for otitis media and amoxicillin,[34,44] but without individual patient data the extent of such effects is merely speculative. A further limitation is that analyses of age groups were hampered by a potential underestimation of the group 0 to 1 years of age since exact date of birth was not available. However, since in both countries the algorithm for assigning the year of age to a prescription was similar, the extent of underestimation is comparable in both countries. Dispensing data, finally, are only a surrogate for drug use because how many units of the packages dispensed are actually taken is unknown.

5 | CONCLUSION

A comparison of outpatient antibiotic use between DE and NL shows that from 2012 to 2016 in NL this use was much lower than in DE (9.64 DID vs 14.14 DID in 2016). Differences were primarily observed in the age groups 2 to 5 (2.0-fold in 2016) and 6 to 14 years (2.7-fold in 2016). A further remarkable difference could be identified in the amount of cephalosporins dispensed. There was almost no use in NL (0.02 DID in 2016), but cephalosporins were the second most utilized class in DE (2.95 DID in 2016). In both countries, fosfomycin had the highest growth rate by DID from 2012 to 2016.

National guidelines for most common infections in DE and NL were comparable for their recommendations in antibiotic use. Consequently, this could not account for the higher antibiotic use in DE compared with NL. Obviously, in NL the guidelines have to be better implemented than in DE for appropriate antibiotic prescribing. Further research is needed on how to improve antibiotic use in DE and learn from NL. In addition, this might address details on infection incidences and diagnoses as well as GP education and patient information for a more restrictive antibiotic use. Pharmacists might play a role in this as well by monitoring GP prescribing and counseling patients. In NL, pharmacists confront GPs in regular pharmacotherapy audit circles with their prescription data for different diseases and drug classes.

ETHICS STATEMENT

The authors state that no ethics approval was required.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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