Antibiotic Prescribing for Acute, Non-Complicated Infections in Primary Care in Germany: Baseline Assessment of in the Cluster Randomized Trial ARena

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Abstract

Background

Antimicrobial resistance is fueled by inappropriate use of antibiotics. Global and national strategies support rational use of antibiotics to retain treatment options and reduce resistance. In Germany, the ARena project (Sustainable reduction of antibiotic-induced antimicrobial resistance) intended to promote rational use of antibiotics for acute non-complicated infections by addressing network-affiliated physicians, primary care teams and patients through multiple interacting interventions. The present study documented patterns of antibiotic prescribing for patients with acute non-complicated infections who consulted a physician in these networks at the start of the ARena project. It explored variation across subgroups of patients and draws comparisons to prescribing patterns of non-targeted physicians.

Methods

This retrospective cross-sectional analysis used mixed logistic regression models to explore factors associated with the primary outcome, which was the proportion of patients with acute non-complicated infections consulting primary care practices who received an antibiotic prescription. Secondary outcomes concerned the prescription of different types of antibiotics. Descriptive methods were used to summarize the data referring to targeted physicians in primary care networks, non-targeted physicians (reference groups), and patient subgroups.

Results

Overall, antibiotic prescription rates were 31.7% in reference groups and 32.0% in primary care networks. General practitioners prescribed antibiotics more frequently than other medical specialist groups (otolaryngologists vs. General practitioners OR=0.465 CI=[0.302; 0.719], p<0.001, pediatricians vs. General practitioners: OR=0.369 CI=[0.135; 1.011], p=0.053). Quinolone prescription rates were 8.1% in reference groups and 9.9% in primary care networks. Patients with comorbidities had a higher likelihood of receiving an antibiotic and quinolone prescription and were less likely to receive a guideline-recommended substance. Younger patients were less likely to receive antibiotics (OR=0.771 CI=[0.636; 0.933], p=0.008). Female gender was associated with higher rates of antibiotic prescriptions (OR=1.293 CI=[1.201, 1.392], p<0.001).

Conclusion

At the start of the ARena project, observed antibiotic prescription rates for acute non-complicated infections showed room for improvement. This clearly supports the need for the ARENA-Project.

Background

The use of antibiotics in German primary care is lower than average in other countries [1, 2], in other countries, but there is still potential for lowering prescribing rates for specific conditions. In light of growing antimicrobial resistances, the national strategy DART 2020 follows the One Health approach in Germany to counteract microbial resistance and preserve treatment options [3]. Monitoring the use of antibiotics is an important strategy to reduce the spread of antimicrobial resistance, particularly in primary care where about 85% of the used antibiotics in Germany are prescribed [4, 5]. Antibiotics are prescribed in 41% of GP consultations for acute respiratory tract infections (ARTI) [4]. Only 52% of these prescriptions are in accordance with prevailing clinical recommendations [6].

In recent years, several research projects tested strategies that aim to enhance the rational and appropriate use of antibiotics in healthcare. In this context, the three-armed, cluster randomized trial ARena (Sustainable reduction of antibiotic-induced antimicrobial resistance) project (conducted from 2017 to 2020) aimed to foster the rational use of antibiotics for acute non-complicated infections in primary care in Germany [7]. By applying a multifaceted strategy with multiple interacting intervention components, ARena addressed primary care physicians, care teams as well as patients [7]. An innovative aspect of ARena was its embedding in 14 primary care networks (PCNs) across two German federal states. PCNs can be described as formalized collaborations of physicians and other healthcare providers who interact regularly, share patients, standardize treatment and care according to evidence-based practice guidance, regularly attend continuing education, and discuss concerns if these arise. They give support regarding practice management and quality improvement [8]and therefore were expected to amplify the impact of the ARena implementation program. More detailed description of the study design and interventions can be found elsewhere [7].

Previous research investigated the development of the antibiotic prescribing rates in primary care and found a relatively stable utilization in Germany from 2008 to 2014 [9]. However, strong variations of overall and age-group-specific distributions of antibiotic subgroups could be identified [10]. A strong awareness of antimicrobial resistance has been observed among German General Practitioners (GPs), while measures to improve rational prescribing were found to be not widely implemented [11]. In more recent research, a 5-year cohort study of antibiotic prescribing rates by family physicians in Ontario, Canada aimed to describe predictors of antibiotic prescribing and inter-physician variability in antibiotic prescribing. It was concluded that observed substantial inter-physician variability in antibiotic prescribing could not be explained by sociodemographic and clinical patient characteristics [12]. Further recent research also found that the use of antibiotics in German primary care showed large variations between and within medical specialties and seasons, and that a considerable proportion of antibiotic prescriptions lacked conformity with national guideline recommendations [13]. Though these study findings might not reflect the most current situation or guideline-conformity of prescriptions, there is an indication that antibiotics are still not prescribed appropriately regarding indication and spectrum and thus are frequently used inappropriately. For targeted quality improvement, it is relevant to know which subgroups of patients and physicians are at highest risk of inappropriate utilization of antibiotics.

For the ARena study, the outcome evaluation is based on claims-data and references established indicators of the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) [14] which were tailored to the specifics of this study. Primary and secondary outcomes are related to general prescribing of systemic and local antibiotics as well as indication-specific prescribing of currently guideline-recommended antimicrobials [15, 16]. To explore the actual antibiotics prescribing rates and their determinants, this present study aimed to present patterns of antibiotics prescribing for patients with acute non-complicated infections prior to the start of the ARena project and explore the variation across medical specialties and subgroups of patients. Also, this baseline situation was to be compared to composed reference groups (RGs) representing non-PCN usual primary care, using claims data to mirror characteristics such as patient age, gender and insurance status.

Methods

Study design

This retrospective cross-sectoral analysis was based on claims data regarding antibiotic prescribing patterns in primary care at the start of a prospective interventional trial. The outcomes evaluation (Trial registration: ISRCTN, ISRCTN58150046) is designed as a cluster randomized trial with fourteen PCNs and RGs that reflect standard care in two German federal states (Bavaria and North Rhine-Westphalia). The ARena-study was approved by the ethics committee of the Medical Faculty of the University of Heidelberg (reference number: S-353/2017). The study was planned with an intervention period of 24 months, and with two parts of evaluation: (a) an outcome evaluation based on claims-data and (b) a process evaluation based on surveys [7].

Study population

Fourteen PCNs situated in two German federal states (Bavaria and North Rhine-Westphalia) were recruited to participate in the ARena study. For administrative reasons, the focus was on their patients insured by AOK health insurance and registered within a specific healthcare delivery program (defined by German law § 140a SGB V a.F. and § 140a Abs. 1. S. 2 Alt. 1 SGB V n.F). At baseline, approximately 40 000 patients with AOK health insurance were registered in 196 participating primary care practices in these 14 networks. Medical specialties included were general practice, otolaryngologist, pediatricians, urology and gynecology. The patient population for the three intervention arms comprised patients who sought primary care for one of the following reasons: acute non-complicated infections (upper respiratory tract infections (URTI), bronchitis, sinusitis, tonsillitis and otitis media). Thus, study populations differed per indexed consultation reason regarding number of cases, age of patients and insurance status. The diagnoses were based on physician-recorded ICD codes and the prescription information in administrative data provided by the statutory health insurer AOK for quarterly reimbursement periods which were linked by the pseudonymized patient individual insurance number. Each physician-recorded ICD code for the defined index diagnoses represents a case, where each patient can produce multiple cases. A patients' case is recorded for each ICD code within each quarter. Written informed patient consent was prerequisite for participation in the study in North Rhine-Westphalia.

Measures

The primary outcome was the proportion of patients who were treated with systemic or local antibiotics of all patients with acute non-complicated infections consulting primary care practices. More precise, patients suffering from acute bronchitis (18–75 years), sinusitis (> 18 years), otitis media (> 2 years), acute URTI (acute rhino-pharyngitis, pharyngitis) (> 1 year), or tonsillitis (> 1 year) were considered in the primary outcome. Due to the structure of the provided claims data and data protection regulations, ICD codes and antibiotic prescriptions were matched for each quarter of year. Excluded were diagnoses that warrant an antibiotic therapy. Specifically excluded were diagnoses for streptococcal tonsilitis and other pathogen-caused acute forms of tonsillitis. (Additional file 1, Supplementary Table 1 details included diagnoses and related ICD codes, Supplementary Table 2 provides a list of the excluded diagnoses.)

The following secondary outcomes were examined:

1. Proportion of patients with acute non-complicated infections receiving a quinolone prescription when consulting primary care practices (patients suffering from acute bronchitis (18–75 years), sinusitis (> 18 years), otitis media (> 2 years), URTI (> 1 year), or tonsillitis (> 1 year)).
2. Proportion of patients with acute URTI (> 1 year) receiving a prescription for recommended antibiotics (amoxicillin).
3. Proportion of patients with acute bronchitis (18–75 years) receiving a prescription for recommended antibiotics (amoxicillin, tetracycline, macrolides).
4. Proportion of patients with sinusitis (> 18 years) receiving a prescription for recommended antibiotics (amoxicillin, cefuroxime).
5. Proportion of patients with tonsillitis (> 1 year) receiving a prescription for recommended antibiotics (penicillin, erythromycin).
6. Proportion of patients with otitis media (> 2 years) receiving a prescription for recommended antibiotics (amoxicillin, erythromycin, cefuroxime).
7. Consumption of broad-spectrum antibiotics in DDD% (on practice level)
8. (beta-lactam-beta-lactamase inhibitor combinations, cephalosporines of 2nd, 3rd and 4th generation, macrolides (excluding Erythromycin) and gyrase inhibitors (fluoroquinolones).

Recommended antibiotics should only be used in cases where bacterial genesis is present, patient risk factors and the complexity of an infection have to be considered, or where the patient condition significantly deteriorates. Categorization of recommended antibiotics was based on existing evidence-based clinical guidelines developed by the German College of General Practitioners and Family Physicians (DEGAM) [16]] and the Association of the Scientific Medical Societies in Germany (AWMF) [15]. (See Additional file 1, Supplementary Table 3 for currently recommended and alternative antibiotics.)

Regarding patients, the following sociodemographic, disease, and treatment characteristics in the claims data provided by AOK were included: age, sex, Charlson comorbidity index (CCI) (predicts 1-year survival in patients based on sum of relevant comorbidities [17, 18]), employment status, nationality (missing values aggregated to 'other'), insurance status (main member, family, retiree), participation in a disease management program (DMP) which is a structured treatment plan to support management of chronic disease and maintain and improve quality of life [19] (type 1 diabetes, type 2 diabetes, coronary

heart disease, breast cancer, bronchial asthma, COPD, cardiac insufficiency), classified degree of necessary nursing care [20], and season. Regarding primary care practices, type of location (urban, urbanized, countryside), type of practice (single or group) and medical specialty group are documented.

Data analysis

The baseline data of practices participating in ARena were analyzed regarding the four quarters prior to the ARena intervention (Q3 2016 – Q2 2017) with a focus on prescription rates of antibiotics for acute non-complicated self-limiting infections and the comparison between characteristics of PCNs including their member physicians and RGs that reflect usual care. In addition, patients' sociodemographic and disease-specific characteristics in either of these groups are summarized. Also focused are the use of guideline-recommended indication-appropriate antibiotics and the group of quinolones.

The primary and all secondary outcomes, as well as all documented data (patient characteristics, disease characteristics, treatment data, and practice characteristics), were first analyzed descriptively. For continuous variables, mean and standard deviation, median, 25%/75%-quantiles [Q1-Q3], min and max are provided, for categorical variables absolute and relative frequencies are given. Note that the description of patients and disease characteristics, as well as treatment data and practice characteristics differ between endpoints, because the considered patients are defined for each endpoint by the respective disease and prescription of antibiotics. Therefore, the descriptive analysis is done for each outcome individually. For the subgroups gender, DMP and the CCI, the primary and all secondary outcomes are contrasted using descriptive methods based on patients in PCNs and RGs.

A logistic mixed effects regression model was used to investigate factors which may influence the primary outcome. The model considers the nested structure of the data with patients nested in practices, which means practice is included as random effect in the logistic mixed effects model. As fixed effects, medical specialty group (Fachgruppe – FGR), urbanization, age group, sex, and the CCI as indication of health status are considered, the selection is based on clinical expertise. Secondary outcomes are analyzed using mixed logistic (1.-6.) or beta regression models (7.). Adjustment is done as described for the primary outcome model. Since this is an explorative study, all p-values do not have confirmatory value.

Results

Sociodemographic characteristics

The primary analysis considered a total of 3 129 289 cases in PCNs (n = 18 207) and RGs (n = 3 111 082) diagnosed with one of the acute non-complicated infections (tonsillitis, sinusitis, otitis media, bronchitis, and URTI). In PCNs, 92.7% of the participating practices were General Practitioners, 4.9% Otolaryngologists, and 2.1% were Pediatricians. In RGs, 73.3% were General Practitioners, 10.6% Otolaryngologists and 14.5% were Pediatricians. The total number of observed cases mentioned above (n = 3 129 289) reflects 2 102 783 patients with a mean of 1.5 cases per patient. In PCNs, 62.8% of the included cases were seen in rural area practices compared to 32.6% of cases in the RGs. Mean age of patients was higher in PCNs. In both groups, sex was equally distributed. Patient nationality was not reported for less than 1% of the cases and all cases without this information are considered in the category "other". A main group difference in terms of insurance status was apparent in the subgroup of retired insurance members (RGs: 10.3%; PCNs 20.8%). Sociodemographic characteristics of patients in PCNs and RGs are presented in Table 1.

Table 1

Sociodemographic characteristics of patients in RGs and PCNs across all cases

(n = 3 129 289)

Characteristics	RGs	PCNs
Age: Mean (SD)	34.3 (21.07)	47.5 (18.94)
Sex: female n (%)	1 633 772 (52.5)	10 594 (58.2)
Nationality: n (%)		
German	2 353 362 (75.6)	15 980 (87.8)
Eastern European	548 307 (17.6)	1 630 (9.0)
Southern European	109 871 (3.5)	355 (1.9)
Northern European	29 508 (0.9)	79 (0.4%)
Other	70 034 (2.3)	163 (0.9)
Insurance status: n (%)		
Main member	1 857 770 (59.7)	12 278 (67.4)
Family member	876 894 (28.2)	2 024 (11.1)
Retired member	: 319 600 (10.3)	3 787 (20.8)
Employment		
“yes”: n (%)	1 881 657 (60.5)	12 143 (66.7)

Antibiotic prescriptions

The observed antibiotics prescription rate for acute non-complicated respiratory infections was 31.7% in RGs and 32.0% in PCNs. Across all observed infections and cases, GPs were the largest group of treating physicians to prescribe antibiotics. In PCNs, the percentage ranged from 87.3–99.7%, in the RGs the range was lower and between 46.9% and 96.7% (See Additional file 1, Supplementary Table 5 for details on the overall distribution of medical specialty of antibiotics prescribing physicians.). In mixed logistic regression models for the primary outcome in PCNs, the specialist group otolaryngologists (OR = 0.465 CI=[0.302; 0.719], p-value < 0.001) and pediatricians (OR = 0.369 CI=[0.135; 1.011], p-value = 0.007) appeared to prescribe less frequently antibiotics compared to general practitioners (see Table 2). Looking at patients, women had a higher probability for the prescription of antibiotics compared to men (OR = 1.293 CI: [1.201; 1.392], p-value < 0.001) as well as patients over 18 years (OR = 0.771 CI:[0.636; 0.933], p-value = 0.008). An increased CCI implied higher prescription rates. Table 2 shows results of the mixed logistic regression model for the prescription rates of antibiotics in the PCNs for acute non-complicated infections of the upper respiratory tract using practice and patient-related characteristics as covariates.

Table 2
Results of the logistic mixed effects regression model for prescription rates of antibiotics in PCNs for acute non-complicated infections

	Odds Ratio	Lower CI limit	Upper CI limit	St. error	p-value
Otolaryngologist vs*. General Practitioner	0.465	0.302	0.719	0.222	< 0.001
Pediatrician vs*. General Practitioner	0.369	0.135	1.011	0.514	0.053
Other spec. groups vs*. General Practitioner	0.251	0.075	0.844	0.618	0.026
Urbanized vs*. rural location	0.832	0.512	1.351	0.248	0.457
Urban vs*. rural location	0.901	0.693	1.192	0.138	0.489
PCN** size medium vs. small	0.960	0.634	1.453	0.212	0.846
PCN** size large vs*. small	1.009	0.671	1.517	0.208	0.967
Patient age < 18 vs*. 18–65	0.771	0.636	0.933	0.098	0.008
Patient age > 65 vs*. 18–65	1.077	0.967	1.200	0.055	0.179
Female patients vs*. male patients	1.293	1.201	1.392	0.038	< 0.001
Charlson Index 1 and 2 vs*. 0	1.562	1.436	1.700	0.043	< 0.001
Charlson Index 3 and 4 vs*. 0	1.662	1.435	1.925	0.075	< 0.001
Charlson Index > = 5 vs. 0	1.760	1.505	2.059	0.080	< 0.001
*vs -= versus					
**PCN - Primary care network					

Detailed results regarding prescription rates of recommended 1st choice antibiotics and alternatives across all observed cases in PCNs and respective reference groups are given in Table 3. Listed values represent prescription of one total year.

Table 3
Prescription rates of recommended antibiotics across all cases

	RG cases 1st choice/alternative choice	PCN cases 1st choice/alternative choice
Tonsillitis %*	24.0/ 3.8	18.8/ 1.2
Sinusitis %	18.7/ 40.6	22.1/ 42.2
Otitis media %	41.0/ 32.4	28.6/ 37.5
Bronchitis %	18.5/ 43.8	23.1/ 38.6
Upper respiratory tract infections %	22.1/**	18.5/**
*diagnoses for streptococcal tonsilitis and other pathogen-caused acute forms of tonsillitis that warrant antibiotic therapy are not included		
**no alternative choices defined		

Regression analysis for the prescription rate of recommended antibiotics did not identify common influencing factors over all considered infections (see Additional file 2). Pediatricians seemed to prescribe more recommended antibiotics compared to general practitioners for patients suffering from URTI. For bronchitis, older patients (> 65 years) had a lower probability to receive a recommended antibiotic prescription than younger patients (< = 65 years).

The distribution of cases included in Disease Management Programs (DMP) is shown in Table 4. For the DMPs for Type 2 Diabetes mellitus, asthma, COPD and coronary heart disease, the inclusion rate of cases across all PCNs was > 90%. In the RGs, the highest rate was for the DMP Asthma (76.8% of the observed cases). In PCNs, 46% of observed cases were registered in a Type 1 Diabetes mellitus DMP, in RGs only 17.7% of the cases were in a DMP. In PCNs, 10.9% of cases were in a breast cancer DMP, in RGs this percentage was 5.1%.

The different levels of needed nursing care (level 1 to 5) were equally distributed across groups. Additionally, the CCI of patients in PCNs showed higher relative frequencies in high index values and lower relative frequencies in low index values compared to RGs. This indicates a higher burden of morbidity in the patient sample in PCNs. The percentage of included cases who needed extended care in a nursing home was 0.6% in PCNs (n = 116) and 0.4% in RGs (n = 13 513). Table 4 also details health status across all cases. (See Additional file 2 for detailed information on CCI per observed infection and respective patient population.)

Table 4
Treatment characteristics and health status across all cases

Treatment characteristics	RG	PCN
Disease Management Program (DMP): n (%)	Diabetes Type 2: 2 140 035 (68.8)	Diabetes Type 2: 16 754 (92.0)
	Asthma: 2 388 555 (76.8)	Asthma: 16 913 (92.9)
	COPD: 2 042 731 (65.7)	COPD: 16 805 (92.3)
	Coronary heart disease: 2 107 723 (67.7)	Coronary heart disease: 16 767 (92.1)
Care Level*: n (%)	1: 1 530 (0.0)	1: 23 (0.1)
	2: 31 036 (1.0)	2: 272 (1.5)
	3: 19 713 (0.6)	3: 164 (0.9)
	4: 10 966 (0.4)	4: 65 (0.4)
	5: 4 011 (0.1)	5: 19 (0.1)
Charlson Index: n (%)	0: 2 178 429 (70.0)	0: 10 059 (55.2)
	1, 2: 757 952 (24.4)	1, 2: 5 482 (30.1)
	3, 4: 105 140 (3.4)	3, 4: 1 334 (7.3)
	> 5: 69 561 (2.2)	> 5: 1 332 (7.3)
*The care level reflects the extent to which patients are able to manage their own needs independently. Based on an expected care dependency of at least 6 months, evaluation takes six main aspects into account: mobility, cognitive and communicative abilities, behavioral and psychological issues, self-care, management of disease-related demands and burden, and arrangements of daily life and social contacts [21].		

Cases in PCNs were older and with a higher morbidity. In line with this, antibiotic prescription rates in PCNs were slightly higher than in the RGs (32% vs. 31.7%). An exception was the prescriptions for Otitis media, where cases were included from the age of two and above. Prescription rates for quinolones were 8.1% in RGs and 9.9% in PCNs and thus, generally moderate to low.

On practice level, the prescription rate of broad-spectrum antibiotics in DDD% showed higher rates in PCNs (Median [Q1-Q3]: 100% [82.4–100]) compared to RGs (Median [Q1-Q3]: 95.9% [66.1–100]). Beta regression models on practice level indicated that specialist groups had a lower prescription rate of broad-spectrum antibiotics than GPs. (See Additional file 2, Supplementary Table 17).

Indication-specific quinolone prescriptions

In PCNs, 11.3% of the observed cases with bronchitis and antibiotics and 9.5% of the cases with URTI and antibiotics received a prescription for quinolones (in RGs 11.4% and 7.7%). Viewed separately, 4.9 % of Otitis Media cases, 3.6% of Tonsillitis cases, and 11.2% of Sinusitis cases received a prescription for quinolones in PCNs. With 5.3%, 2.7%, and 9.5%, the respective proportions of quinolone prescriptions were somewhat different in the RGs. Overall, prescriptions for quinolones amounted to 9.9 % in PCNs and 8.1% in RGs. In mixed logistic regression models for the prescription rate of quinolones for patients treated with antibiotics in PCNs, urbanization appeared to decrease the prescription of quinolones. An increased CCI implied higher quinolone prescription rates compared to a CCI of 0 (no comorbidity). Detailed results of the logistics mixed effects model are given in Table 5. (See Additional file 1, Supplementary Table 4 for diagnoses that warrant quinolone prescriptions.)

Table 5
Results of the logistic mixed effects regression model for prescription rates of quinolones for patients treated with antibiotics in PCNs

Covariate	OR	Lower CI limit	Upper CI limit	St. error	p-value
Other spec. groups vs.* General Practitioner	0.617	0.277	1.374	0.408	0.237
Urbanization vs.* rural location	0.466	0.210	1.035	0.407	0.061
Urban vs.* rural	0.558	0.371	0.840	0.209	0.005
PCN size medium vs*. small	1.975	1.028	3.793	0.333	0.041
PCN size large vs.* small	1.077	0.565	2.053	0.329	0.821
Patient age > 65 vs.* age < = 65	1.294	0.997	1.679	0.133	0.053
Female patients vs.* Male patients	0.928	0.757	1.136	0.104	0.467
Patients with Charlson Index 1 and 2 vs.*0	1.864	1.469	2.366	0.122	< 0.001
Patients with Charlson Index 3 and 4 vs.* 0	3.114	2.196	4.418	0.178	< 0.001
Patients with Charlson Index > = 5 vs.* 0	3.264	2.245	4.746	0.191	< 0.001
*vs = versus					

The descriptive subgroup analyses over all patients (PCNs and RG) support the findings of the regression models. Detailed results of the descriptive subgroups analysis corresponding to the primary and secondary outcomes are shown in Additional file 2. The rates of recommended substances were comparable between genders. Contrasting the participation in DMPs resulted in a small increase in the rate of antibiotics and quinolones for DMP participants, and smaller rates of recommended (alternative) antibiotics for observed diseases. A clear difference is observed for CCI 0 (without comorbidity) versus higher values. Antibiotics and quinolone prescription rates were more than 10% higher for patients with comorbidities and less recommended substances were used for those patients.

Discussion

This study explored antibiotic prescribing rates and aimed to assess and present patterns of antibiotic prescribing for patients with acute non-complicated infections at the start of the ARena project. In about a third of all observed cases with acute non-complicated infections, patients received an antibiotic prescription. Younger patients were less likely to receive antibiotics. More antibiotics were prescribed to females than to male patients. GPs prescribed antibiotics more frequently than other medical specialists. Prescription rates for quinolone were moderate, and patients with comorbidities had a higher likelihood of receiving an antibiotic and quinolone prescription and less likely to receive a guideline-recommended substance.

Rates of antibiotic prescriptions in German primary care overall have been decreasing constantly between 2010 and 2018, particularly with regards to children and adolescents [22] who were underrepresented in this study sample. Room for improvement can be expected to be more visible in ‘high prescribers’, but since the potential for improvement noticeably decreased in recent years already, nevertheless, there remains substantial room for further reduction of antibiotic prescribing.

A recent national cross-sectional study in USA identified that 57% of 130.5 million prescriptions for antibiotics written during ambulatory care visits in 2015 were for appropriate indications, 25% were inappropriate and 18% had no documented indication. It was noted that being an adult male, spending more time with the provider and seeing a non-primary care specialist were significantly positively associated with non-indicated antibiotic prescriptions [23]. In contrast to these findings, our data indicate that antibiotics were most frequently prescribed by general practitioners. In addition, the prescription rate of broad-spectrum antibiotics showed slightly higher rates in PCNs compared to RGs. These discrepancies in antibiotic prescription rates between PCNs and RGs might be explained by the differing specialist group distribution between PCNs and RGs and a small percentage of specialists and a higher percentage of GPs in PCNs than RGs. A contributing factor towards the slight difference in prescription rates between PCNs and RGs can also be seen in the higher patient age and

morbidity in PCNs which is in line with the findings of Shaver et al. [24]. The exception here were prescriptions for Otitis media where cases were included from the age of two and above and therefore morbidity considerations cannot deliver explanations for higher prescription rates in PCNs.

The prescription rates for quinolones were generally moderate to low in PCNs (9.9%) and RGs (8.1%) and thus match recent findings of a study that examined antibiotic prescribing in the US outpatient setting where 9.4% of investigated visits for acute respiratory infections received a broad-spectrum antibiotic [24]. Prescribing quinolones seemed to be associated with a higher number of comorbidities and higher patient age as well which complements findings of the process evaluation conducted alongside ARena where uncertainty about diagnoses, prognosis, continuity of care and perceptions about patient preferences were found to be among the reasons for non-indicated prescriptions [25]. To some extend this confirms findings from a 2010 study that investigated fluoroquinolone prescriptions for acute cough in German primary care to find predictors for unjustified prescriptions. The researchers then concluded that unjustified quinolone prescriptions were determined by patient characteristics such as severity and duration of illness and patient age. However, they also found that physicians with higher individual antibiotics prescribing rates and physicians with hospital-based specialty training - versus combined hospital and ambulatory training - were more likely to prescribe fluoroquinolones than physicians who specifically trained as GPs [26]. Interestingly, our data showed that in urbanized PCN practice locations, quinolone prescription rates were lower than in rural locations. This complements results from a previous study where German GPs working in urban areas were found to be more likely to use the strategy of delayed prescribing of antibiotics than GPs working in rural areas [11]. Such discrepancies between urban and rural prescribing habits potentially could root in more ample opportunities for self-reflection about prescribing motivated by regular peer exchange and a broader and more frequent offer of continued training and upskilling in urban locations. Efforts to educate physicians, care teams and patients continuously about current and appropriate diagnosis and therapy options as well as communication about them may remedy this to some extent.

The perceived, but not actually communicated patient request for antibiotics is often overrated by physicians [27] and may initiate unfounded assumptions of losing patients to another physician when therapy followed guideline recommendations and antibiotics are not prescribed. In this study, the rate of recommended antibiotics was remarkably low and in line with the high percentage of broad-spectrum antibiotics on practice level which is another potential indicator for physicians' uncertainty. Patients with higher comorbidity and patients participating in DMPs were more likely to get a quinolone prescription, and less likely to receive one of the recommended substances. This might be related to the higher age and poorer health status of these patients as supported by previous research [24], but also to the physicians' striving for the elimination of both their own and patients' insecurities and potential complications. One effective way to eliminate insecurities and reduce prescribing antibiotics was found to be the promotion of communication skills by means of a short communication training for primary care physicians. In a recent study in Germany, results showed a prescribing probability decrease of 6.5 percentage points for the treatment of URTI and an even stronger impact for female patients aged below 35 [28]. As the ARena project also used an intervention component to strengthen communication skills, similar effects can be expected.

The rate of prescribed broad-spectrum antibiotics in PCNs in this study seemed slightly higher compared to a previous study [24]. However, for this present study the outcome was assessed by DDD% on practice level whereas Shaver et al. evaluated on patient level. Factors associated with the prescription of recommended antibiotics for the considered infections could not be clearly identified. Information about patient nationality was not available for all cases and the percentage of nationalities other than German is low. However, our data showed that the percentage of observed cases of Eastern European patients was higher than the one of Southern Europeans in PCNs as well as in RGs. This is contrasted by findings of the process evalaution in ARena where physicians indicated their subjective perception of many Southern Europeans asking for antibiotics prescriptions [25].

Strengths and limitations

One strength of this study is the careful exclusion of patients in case there was an ICD code documented which justified the antibiotic prescription. Additionally, the type of antibiotics (recommended, quinolones, broad- versus small-spectrum) were analyzed in detail. A limitation of this retrospective cross-sectoral analysis of baseline data is the restriction on ICD Codes and claims-related health insurance data. Therefore disease, patient, and practice information are limited. Direct connection between ICD Code and prescription of antibiotics is not possible in the provided claims data, thus ICD codes and antibiotics prescription were matched by quarter which introduces a potential bias. To compensate, diagnoses that warranted antibiotic therapy were excluded. The use of DDDs for pediatric antibiotic consumption where weight-based dosing is appropriate, is an additional limitation. Participating practices and PCNs were already recruited for the ARena trial and might be more alert to the topic and supportive of appropriate prescribing already (shared attitude in the networks that might only be attractive for certain physicians). So far only one time point before the planned intervention in the ARena trial could be analyzed. Final assessment of effects will be possible through the analysis of post intervention data with a focus on the evaluation of the interventions. Findings of this present study can then serve as comparator in the final report of the outcome evaluation.

Conclusion

Antibiotics prescription rates for acute non-complicated infections were moderate prior to the intervention start of the ARena project, but still not sufficiently appropriate. Guideline-recommended substances were underrepresented and the prescription rate of broad-spectrum antibiotics was alarming. This indicates a need for creating stronger awareness of guideline-conform use of antibiotics as intended by the implementation program used in ARena. The final outcome evaluation will use this baseline evaluation as comparator and inform about potential effects of the program.

Abbreviations

ARTI - acute respiratory tract infections

AWMF - Association of the Scientific Medical Societies in Germany

CAP - community acquired pneumonia

CI – confidence interval

CCI - Charlson comorbidity Index

DDD - defined daily dose

DEGAM - German College of General Practitioners and Family Physicians

DMP - disease management program

ESAC-Net - European Surveillance of Antimicrobial Consumption Network

GP – general practitioners

ICD - International Classification of Diseases

OR – odds ratio

PCNs - primary care networks

Q - quarter

RG - reference group reflecting standard care

URTI - upper respiratory tract infections

Declarations

Ethics approval and trial registration

This study received ethical approval by the medical ethics committee of the Medical Faculty of Heidelberg University (S-353/2017). Trial registration: ISRCTN, ISRCTN58150046

Consent for publication

Not applicable.

Availability of data and material

All analyses generated for this study are included in this published article and its supplementary information files 1 and 2. The original datasets that support the findings of this study are not publicly available due to restrictions stipulated by German law and the data provider. AOK can be contacted for access to the data.

Competing interests

SZ is founder and managing director of the aQua Institut, Goettingen and Medical Director at the University Hospital Heidelberg, Germany, Department of General Practice and Health Services Research. The authors declare that they have no competing interests.

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Author's contributions

RPD and DK drafted and prepared the manuscript. DK, RPD, and MW contributed to concept and design of this study. DK, RPD, MK, MW, EA, and PKK collaborated on the construction of the statistical analysis plan. DK analyzed the baseline data. DK, RPD and MW interpreted the data. SZ was overall principal investigator of the ARena project. All authors provided substantial comments and approved the final version of the manuscript.

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