Patient and prescriber determinants for the choice between amoxicillin and broader-spectrum antibiotics: a nationwide prescription-level analysis

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Objectives: Bacterial resistance to antibiotics, driven by antibiotic consumption, imposes a major threat to the effective treatment of bacterial infections. In addition to reducing the amount of antibiotics prescribed, avoiding broad-spectrum antibiotics could extend the lifetime of the current arsenal of antibiotic substances. Therefore, we documented prescriber and patient characteristics associated with the choice between amoxicillin and broader-spectrum alternatives (co-amoxiclav or moxifloxacin) in recent years in Belgium.

Methods: Complete reimbursement claims data (2002–09) for antibiotic prescriptions in outpatient care, including patient and prescriber characteristics, were collected for both young children (1–5 years) and the adult population (30–60 years). A backwards selection procedure within generalized estimating equations retained the most relevant determinants.

Results: The age, gender and social category of the patient were found to be predictive of the extent to which amoxicillin was prescribed instead of the broader-spectrum alternatives, with female patients generally taking a higher proportion of amoxicillin than male patients. The age category of 40–44-year-old prescribers exhibited a preference for broad-spectrum antibiotics compared with both younger and older age groups. Significant interactions between the region and the prescriber’s qualification (general practitioner or paediatrician) on the choice of antibiotic for children were found.

Conclusions: Patient (age, gender and social category) and prescriber characteristics (age, gender, region and qualification) had an influence on whether amoxicillin or the alternative broad-spectrum antibiotics were prescribed. These findings should help policy makers to better target future campaigns to promote prudent prescribing of antibiotics.

Keywords: ambulatory care, antibiotics, pharmaceuticals, Belgium, GEEs

Introduction

Rising antibiotic resistance presents a major public health threat, jeopardizing the future effective treatment of bacterial infections. The within-patient causal link between antibiotic consumption and the development of bacterial resistance to antibiotics has been shown conclusively by a double-blind placebo-controlled trial. In addition to this experimental evidence, observational studies consistently confirmed the increased risk of infection with a resistant strain after antibiotic consumption in the individual patient. This development of resistance in the individual patient, along with population-level selection mechanisms, gives rise to a population-wide antibiotic resistance problem, as shown by using mathematical models and observational studies. Goossens et al., for instance, found significant associations between the volume of use in a geographical area and the population-level resistance in that area.

Besides prescription or package volumes, other quality indicators of antibiotic prescribing practices are of importance, such as defined daily dose (DDD), efficiency in treating the illness, duration
of treatment and spectrum. Since narrow-spectrum antibiotics exert a less extensive ecological pressure than broad-spectrum antibiotics, they leave bacterial populations more susceptible to future antibiotic treatments. Mathematical models suggest that the decline of resistance after cessation of the use of a specific antibiotic in the community is typically slower than the increase due to current consumption. Thus, a rapid reduction in resistance due to lowering consumption seems doubtful. Therefore, prudently prescribing the antibiotic of choice is highly important in sustaining the effectiveness of our current range of antibiotics.

In view of the expected impact of antibiotic consumption on the public health threat of resistance, the European Surveillance of Antimicrobial Consumption (ESAC) network strives to correctly document total systemic antibiotic use, its evolution and composition. In addition to this increased surveillance of antibiotic use, several countries have implemented awareness and control campaigns in order to educate the public and influence physicians’ prescribing habits. By targeting healthcare professionals and the general public, such interventions aim to reduce the quantity and improve the quality of antibiotic prescribing in the short run, and reduce the burden of antibiotic resistance in the longer run. Some empirical evidence indicates the effectiveness of such campaigns, but to date such evidence remains relatively rare because the specific contribution of campaigns to changes in antibiotic use over time is difficult to distinguish from other influences.

A comparison of the quality of antibiotic use between European countries in 2004 and 2009 listed Belgium with Luxembourg, Italy, France and Spain at the lower end of the quality ranking based on dispensed volume of both broad-spectrum and all antibiotics. This comparison especially revealed large differences with the Nordic countries as well as with the Netherlands, a neighbouring country of Belgium, where consumption in DDDs per 1000 inhabitants is less than half that of Belgium, and adherence to guideline-recommended antibiotics is higher. This fact illustrates there is still ample room for improvement through interventions.

Therefore, in this study we set out to identify groups of patients and prescribers who deviate from the average in terms of their preference for either amoxicillin, recommended as first-choice antibiotic for most respiratory infections in Belgium, or broader-spectrum antibiotics such as co-amoxiclav and moxifloxacin. This information can serve to better target future intervention campaigns.

Methods

Reimbursement claims data

We base our analysis on all reimbursement claims data (2002–09) from Belgium. For the purpose of the analyses we divided its 10.6 million inhabitants between three main regions: the Flemish region (58%), the Walloon region (32%), and the Brussels Capital region (10%). Belgium has an accessible healthcare system with a generous basic basket of healthcare available to the entire population through compulsory social health insurance. The impact of supplementary private insurance on healthcare consumption is mainly limited to billing practices in hospitals and dental care. Although some socio-economic differences exist between the regions, we assume no major differences in infectious disease burden, which is a plausible assumption, given the size of the country, and the near-equivalence of the preventive public health programmes. Socio-economic differences have been controlled for at the patient level rather than at the regional level.

Prescription-level data on antibiotic use was sourced from the national database of the Internatuinal Activity (IMA), for the period 2002–09. The IMA database covers the entire insured population of Belgium and contains reimbursement claims data of seven sickness funds that manage compulsory health insurance in Belgium. The extraction included, for each prescription, information on the prescriber (encoded), the insured individual (encoded) and the package. Self-employed individuals (10% of the currently insured population) were excluded from the analysis since their reimbursement status changed during the study period. We extracted information related to 59876848 prescriptions.

Permission to study these detailed data was granted by the Sector Committee of Social Security and Health of the Commission for the Protection of Privacy (CPP), better known as the Belgian Privacy Commission (SCSZ/10/098 and SCSZ/10/103).

Data selection: time period, age groups and antibiotic classes

Since we were mainly interested in elucidating determinants of the choice of the antibiotic substance and not particularly in the time evolution of antibiotic consumption, we focused on the period from July 2008 to June 2009 (7301321 prescriptions). In this manner we avoided confounding with time effects and still covered a complete influenza season. The period July 2002 to June 2003 was additionally extracted for comparison.

The choice of the antibiotic as well as the amount used (in number of packages and DDDs) were stable in the age group between 30 and 60 years, but outside this age range we found the choice of the antibiotic to vary strongly with the patient’s age (Figure 1). Therefore, we focused the analysis in the current paper on two age groups: adults between 30 and 60 years and children between 1 and 5 years. For the adults, all prescriptions by general practitioners (GPs: licensed GPs with National Institute for Health and Disability Insurance number 003–004, GPs in training and other GPs), who were responsible for the vast majority of antibiotic prescriptions (76% between July 2008 and June 2009), were selected. Including specialist physicians would distort the focus of determinants in the choice of antibiotic prescribed since they encounter specific and distinct underlying pathologies, requiring specific antibiotic classes.

The age group of young children is important because of their substantial share (11% of all prescriptions) in total antibiotic use and because they form a key group for the transmission of infectious diseases. For this group we selected prescriptions of both GPs and paediatricians, who jointly accounted for 92% of all antibiotic prescriptions to children in the study period.

The definition of the antibiotic group was based on the Anatomical Therapeutic Chemical (ATC) classification system. From the ATC subgroup J01, antibacterials for systemic use, we selected three commonly used antibiotic substances, which are used to treat respiratory tract infections, especially in Belgium: (i) amoxicillin (ATC J01CA04), (ii) co-amoxiclav (ATC J01CR02), and (iii) moxifloxacin (ATC J01MA14). These antibiotics differ in their antibacterial spectrum. Indeed, co-amoxiclav is a combination of amoxicillin and clavulanic acid, a β-lactamase inhibitor, making this type of antibiotic still effective in combating β-lactamase-producing bacteria. Moxifloxacin has a broader spectrum as well, and is not recommended as the first-choice antibiotic in most, if not all, European countries, and should not be prescribed to children.

Analysis

In order to identify specific prescriber and patient groups associated with more or less amoxicillin use, we regressed the odds of amoxicillin use as opposed to co-amoxiclav use against potential determinants. In the adult group under study, we also studied the odds of amoxicillin versus co-amoxiclav and moxifloxacin. In order to identify relevant factors for the choice for or against amoxicillin, the odds of amoxicillin versus relevant
alternatives seemed a more direct and sensitive outcome measure than the proportion of amoxicillin to all antibiotics for systemic use. Table 1 gives an overview of the variables (potential determinants) and categories included in the analyses. These variables represent a categorization of large patient and prescriber groups according to basic characteristics such as gender, age, region and social status. This list is limited but fully uses the information in the insurance claims database, which has the extra advantage of being unambiguous. Medically or socially relevant two-way interactions were considered. For the analysis of prescriptions to adults, interactions between the prescriber’s gender, age category, qualification and the patient’s gender, age, social category and diabetes indicator were included. Additionally, interactions between diabetes and age and gender of the patient were included, as well as interactions between the patient’s low-income indicator and the patient’s age and gender.

For the analysis of antibiotic prescriptions to young children, only the following interactions were considered: the interaction between gender of the prescriber and gender of the patient and the interaction between qualification and region of the prescriber. No interactions with the diabetes indicator of the patient were included because of the low number of diabetes patients in these age categories.

**Statistical methodology**

Associations between antibiotic choice and both patient and prescriber characteristics were modelled using generalized estimating equations (GEEs), based on the binomial distribution with a logistic link function. This method yields consistent estimates of the population-averaged effects, treating the correlation between observations as a nuisance.

Since the prescriptions were nested within both the prescriber and the patient, whereby a patient is not limited to a unique prescriber, the GEE method must account for this. Therefore, we employed the adaptation to GEEs for non-nested clustering implemented in SAS by Miglioretti and Heagerty, based on the working independence assumption. This approach achieves valid estimates and standard errors by combining two separate GEE fits: one with the prescriber and the other with the patient as cluster indicator.

All main effects presented in Table 1 were included in the final models. The decision of which interactions to include was based on a backward search based on the quasi-likelihood under the independence model criterion (QIC) information criterion for GEEs. We present the results as ORs with 95% CIs. Note that an interaction effect represents a ratio of ORs, and should be interpreted as a main effects modifier. If, for instance, we find an interaction effect between the gender and region of the prescriber, the interaction effect is to be interpreted as the OR of gender, given a region divided by the OR of gender for the reference region.

**Results**

Figure 1 shows the numbers and proportions of prescriptions for the selected antibiotics by patient age. There is a generally decreasing trend with increasing age for amoxicillin and an increasing trend for moxifloxacin, both of which level off for the elderly. Furthermore, one can see a relatively stable proportion of prescriptions for co-amoxiclav over the lifespan. In the next sections, we discuss the results of subgroup analyses on two broad age groups of interest with a high volume of prescriptions, as shown by the bars and shaded areas in Figure 1.
Prescriptions to adults between 30 and 60 years old by GPs

Table 2 summarizes the results of the final selected models explaining variations in the odds of prescribing amoxicillin compared with co-amoxiclav and moxifloxacin combined. Prescriber–patient or within-prescriber interactions were selected but did not reach significance in explaining the choice for amoxicillin instead of these broader-spectrum alternatives. We found, however, a significant influence of the main effects of gender, region and qualification of the physician on the odds of prescribing amoxicillin. Physicians from the Walloon region had a lower preference for prescribing amoxicillin instead of either co-amoxiclav or moxifloxacin than physicians from the Flemish region. No significant differences between the Flemish region and Brussels region prescribers were observed.

Female prescribers had a higher preference for amoxicillin than males compared with co-amoxiclav alone. Active prescribers had a lower preference for amoxicillin compared with co-amoxiclav and moxifloxacin as well as compared with co-amoxiclav alone. In the latter case, however, the effect did not reach significance.

The age of the prescriber was found to have a remarkable effect. The reference age category of 40–44 years old was less likely to prescribe amoxicillin than broader-spectrum antibiotics (co-amoxiclav or moxifloxacin) compared with younger as well as with most older prescriber categories (≥55 years). The youngest age category (20–30 years old) had a substantially higher preference for amoxicillin than all older prescribers. Compared with these observed age differences, the qualification of the prescriber was less influential. GPs in training showed a lower preference for amoxicillin than for broader-spectrum antibiotics compared with GPs of the same age category and gender who were not in training.

Table 1. Determinants used in the analyses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Levels of analysis for adults</th>
<th>Reference category for adults</th>
<th>Levels of analysis for children</th>
<th>Reference category for children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescriber characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>qualification</td>
<td>licensed GPs with NIHDI number 003–004, GPs in training, other GPs</td>
<td>GP</td>
<td>GP; paediatrician</td>
<td>GP</td>
</tr>
<tr>
<td>gender</td>
<td>male; female</td>
<td>male</td>
<td>male; female</td>
<td>male</td>
</tr>
<tr>
<td>region</td>
<td>Flemish region; Walloon region; Brussels Capital region</td>
<td>Flemish region</td>
<td>Flemish region; Wallon region; Brussels Capital region</td>
<td>Walloon region</td>
</tr>
<tr>
<td>active</td>
<td>active; non-active</td>
<td>non-active</td>
<td>active; non-active</td>
<td>non-active</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age</td>
<td>age of patient in years divided by 30</td>
<td>not included</td>
<td></td>
<td></td>
</tr>
<tr>
<td>gender</td>
<td>male; female</td>
<td>male</td>
<td>male; female</td>
<td>male</td>
</tr>
<tr>
<td>reimbursement</td>
<td>higher reimbursement; no higher reimbursement</td>
<td>no higher reimbursement</td>
<td>higher reimbursement; no higher reimbursement</td>
<td>no higher reimbursement</td>
</tr>
<tr>
<td>diabetes</td>
<td>diabetes; no diabetes</td>
<td>diabetes</td>
<td>diabetes; no diabetes</td>
<td>diabetes</td>
</tr>
<tr>
<td>social category</td>
<td>active; unemployed; PWDO; other</td>
<td>active</td>
<td>active</td>
<td>not included</td>
</tr>
<tr>
<td>low income</td>
<td>not included</td>
<td>not included</td>
<td>not included</td>
<td></td>
</tr>
</tbody>
</table>

Categorical variables were coded as indicators as opposed to a reference category. Differences in variables included and reference categories used between analyses for adults and children are indicated.

A different reference category was purposely taken for children versus adults to enable illustration of the largest regional differences. The model fit was not dependent on the choice of this reference category and parameter estimates for the other variables were not influenced by this choice.

An active prescriber was defined as a GP with at least 200 assigned patients, or a specialist physician with at least 200 patient contacts a year.

A low-income patient was identified by being entitled to income guarantee for the elderly, subsistence level or a higher reimbursement of medical costs (Omno status due to his or her difficult financial family situation [www.riziv.fgov.be/citizen/nl/medical-cost/general/omno/faq.htm]).
female and male patients was bigger when the patients came from a less favourable social category [i.e. unemployed or ‘pensioners, widows, persons with disabilities and orphans’ (PWDO)]. The PWDO category and the unemployed had, regardless of gender, lower odds of having amoxicillin prescribed instead of the two broader-spectrum antibiotics.
When studying the choice between amoxicillin and co-amoxiclav only, we found a significant effect of the patient's income and a significant interaction with the patient's gender, which was absent in the comparison with co-amoxiclav and moxifloxacin combined. Having a lower income increased the odds of having amoxicillin prescribed instead of co-amoxiclav primarily for male patients. Patients with diabetes had lower odds of receiving amoxicillin instead of broader-spectrum antibiotics (co-amoxiclav). The patient's age influenced the type of antibiotic prescribed. Older patients in the group 30–60 years were less likely to receive amoxicillin. Table S1 (available as Supplementary data at JAC Online) provides the amount of prescriptions and relative importance of prescriber and patient categories in antibiotic prescribing to adults between 30 and 60 years old in Belgium.

In order to assess whether our results would also apply to older age groups (i.e. >60 years), we refitted the identified models to older age groups per 10 year age class. Prescriber determinants (age, region, active or not, and qualification) were found to exert a similar influence as in the younger age group. The prescriber's gender was, however, no longer significant in predicting the choice of amoxicillin versus broad-spectrum alternatives. Differences in the age of the prescriber had the same sign but were less pronounced. The data also suggest a regional difference, not found for younger patients, with slightly higher rates of moxifloxacin prescribing to elderly patients (>60 years) in Brussels compared with Flanders. Patient characteristics were less relevant in predicting the choice for or against amoxicillin in elderly patients. Social category, income and diabetes were not found to be significant. The gender of the patient was found to be a significant predictor of higher amoxicillin use compared with co-amoxiclav, but not when compared with co-amoxiclav and moxifloxacin.

**Prescriptions to children between 1 and 5 years old by licensed GPs and paediatricians**

Table 3 summarizes the selected models by age of the child to which the antibiotic was prescribed. Here we only modelled the odds of prescribing amoxicillin versus co-amoxiclav. Different prescriber and patient characteristics had a significant effect on this choice. A clear interaction between the region and the qualification of the prescriber was present over all patient ages. This indicates the difference in prescribing habits was strongly region dependent. Taking the size of the interaction into account, this implies that paediatricians of the Brussels Capital region prescribed a higher proportion of amoxicillin in comparison with GPs of that region. This contrasted with the reference region (Walloon region), where GPs prescribed a larger proportion of amoxicillin than paediatricians of that region. The Flemish region did not differ significantly from the reference Wallonia in this respect.

As in the analysis of prescriptions to adult patients, we found a significant effect of the age of the prescriber on the odds of prescribing amoxicillin. The age group 40–49 years prescribed a smaller proportion of amoxicillin in favour of co-amoxiclav than both younger and older age categories. Overall, the largest difference was observed between the reference category of 40–44 years and older physicians of 60–64 years. We observed again active physicians prescribing a lower proportion of amoxicillin instead of co-amoxiclav. The effect of gender of the prescriber reached significance for children >3 years of age, for whom female prescribers were more likely to prescribe amoxicillin.

Patient characteristics were also predictive of the choice between amoxicillin and amoxicillin. For patients aged 1 or 2 years, who were under a higher reimbursement regimen, we observed higher odds of having amoxicillin prescribed versus co-amoxiclav. Remarkable as well was the effect of the patient’s gender. Girls aged 1–5 years received a greater proportion of amoxicillin versus the broader-spectrum alternative co-amoxiclav than boys of the same age. For the prescriptions to patients aged 2 years, we found a significant interaction effect between patient gender and prescriber gender. Female physicians’ preference for narrow-spectrum antibiotics (amoxicillin) over broad-spectrum antibiotics (co-amoxiclav) was primarily due to their more frequent amoxicillin prescribing to male patients compared with male physicians.

**Age, time and cohort effects**

The age of the prescriber had a distinct influence on the choice between amoxicillin and broader-spectrum antibiotics, for both adult and child patients. In order to investigate whether this observation was an age effect or rather a cohort effect, we compared prescribing practices over time. A pure cohort effect would imply that differential prescribing remained constant as the cohort aged. A pure age effect, in contrast would imply that the same age groups, and not the cohorts, would stand out at different timepoints.

In order to distinguish these two effects, we compared the proportion of amoxicillin relative to a larger group (amoxicillin and co-amoxiclav or amoxicillin, co-amoxiclav and moxifloxacin) between the two most distant July–June periods available in our dataset: namely the periods 2002–03 and 2008–09. In this part of the analysis, the age cohort of the prescriber was defined based on the age at first prescription in the period from July 2002 to June 2003 only. No additional prescribers were included for the comparison with the second period.

There was a cohort effect of the preference for amoxicillin; differential prescribing remained more or less constant over time, though small age effects were possible (Figure 2). In addition, there was a strong time effect observed. The proportion of amoxicillin prescribed shifted almost in parallel upwards across the different age cohorts. This indicates that physicians partly maintained their prescribing habits of the past as they aged.

**Discussion**

In this study, we used complete antibiotic prescription-level data for the Belgian population from the period 2002–09. We selected the data for the period from July 2008 to June 2009 to identify the main patient and prescriber characteristics associated with the choice between narrow-spectrum antibiotics (amoxicillin) and broader-spectrum (co-amoxiclav, moxifloxacin) antibiotics.

**Main results**

We found significant effects of prescriber characteristics on the choice of antibiotic in multivariate analyses, while controlling for relevant patient features. Female and non-active prescribers, for instance, prescribed more amoxicillin for both children and adults. Region and qualification of the prescriber interacted significantly, but in different ways depending on patient age. For both
Table 3. Determinants of the odds of an amoxicillin prescription instead of a co-amoxiclav prescription for patients aged between 1 and 5 years by licensed GPs or paediatricians; separate model for each age group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category 1 (when interaction)</th>
<th>1 year old (based on prescriptions)</th>
<th>2 years old (based on prescriptions)</th>
<th>3 years old (based on prescriptions)</th>
<th>4 years old (based on prescriptions)</th>
<th>5 years old (based on prescriptions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescriber characteristics</td>
<td>qualification</td>
<td>paediatricians 0.835 (0.683–1.020)</td>
<td>0.852 (0.688–1.056)</td>
<td>0.758 (0.619–0.927)**</td>
<td>0.721 (0.578–0.901)**</td>
<td>0.690 (0.543–0.876)**</td>
</tr>
<tr>
<td></td>
<td>gender</td>
<td>female 1.078 (0.970–1.198)</td>
<td>1.100 (0.997–1.214)</td>
<td>1.102 (1.013–1.199)*</td>
<td>1.126 (1.036–1.224)**</td>
<td>1.146 (1.053–1.247)**</td>
</tr>
<tr>
<td></td>
<td>region</td>
<td>Brussels 0.987 (0.801–1.217)</td>
<td>1.047 (0.854–1.283)</td>
<td>1.163 (0.964–1.404)</td>
<td>1.156 (0.973–1.373)</td>
<td>1.143 (0.969–1.348)</td>
</tr>
<tr>
<td></td>
<td>active</td>
<td>Brussels 0.973 (0.905–1.045)</td>
<td>1.014 (0.947–1.086)</td>
<td>1.028 (0.962–1.098)</td>
<td>1.055 (0.985–1.129)</td>
<td>1.024 (0.953–1.100)</td>
</tr>
<tr>
<td></td>
<td>age</td>
<td>45–49 0.966 (0.830–1.124)</td>
<td>0.989 (0.867–1.128)</td>
<td>0.985 (0.869–1.117)</td>
<td>1.021 (0.905–1.152)</td>
<td>1.032 (0.912–1.168)</td>
</tr>
<tr>
<td></td>
<td>active</td>
<td>45–49 0.966 (0.830–1.124)</td>
<td>0.989 (0.867–1.128)</td>
<td>0.985 (0.869–1.117)</td>
<td>1.021 (0.905–1.152)</td>
<td>1.032 (0.912–1.168)</td>
</tr>
<tr>
<td></td>
<td>region×qualification</td>
<td>50–54 1.167 (1.022–1.333)*</td>
<td>1.164 (1.031–1.314)*</td>
<td>1.079 (0.962–1.211)</td>
<td>1.109 (0.987–1.245)</td>
<td>1.068 (0.951–1.200)</td>
</tr>
<tr>
<td></td>
<td>age</td>
<td>60–64 1.776 (1.318–2.393)**</td>
<td>1.697 (1.312–2.195)**</td>
<td>1.616 (1.295–2.018)**</td>
<td>1.649 (1.343–2.026)**</td>
<td>1.537 (1.246–1.896)**</td>
</tr>
<tr>
<td></td>
<td>active</td>
<td>60–64 1.776 (1.318–2.393)**</td>
<td>1.697 (1.312–2.195)**</td>
<td>1.616 (1.295–2.018)**</td>
<td>1.649 (1.343–2.026)**</td>
<td>1.537 (1.246–1.896)**</td>
</tr>
<tr>
<td></td>
<td>gender</td>
<td>female 1.121 (1.091–1.152)*</td>
<td>1.118 (1.082–1.155)**</td>
<td>1.085 (1.057–1.114)***</td>
<td>1.082 (1.049–1.115)***</td>
<td>1.073 (1.036–1.112)***</td>
</tr>
<tr>
<td></td>
<td>reimbursement</td>
<td>higher 1.079 (1.010–1.154)*</td>
<td>1.064 (1.003–1.129)*</td>
<td>1.028 (0.975–1.084)</td>
<td>1.026 (0.965–1.091)</td>
<td>1.040 (0.975–1.110)</td>
</tr>
<tr>
<td></td>
<td>diabetes</td>
<td>0.674 (0.302–1.506)</td>
<td>0.665 (0.378–1.169)</td>
<td>1.271 (0.804–2.008)</td>
<td>1.499 (0.927–2.422)</td>
<td>0.936 (0.507–1.727)</td>
</tr>
<tr>
<td>Interaction of patient and prescriber characteristics</td>
<td>gender of prescriber×gender of patient</td>
<td>female female — 0.943 (0.893–0.996)* — — —</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Multivariate population-based ORs with 95% CIs. ORs of the current level (level 1 and level 2) versus the reference categories in Table 1. The significance level is indicated as follows: *5%; **1%; ***0.1%.
young children and adults, physicians of the age category 40–44 years prescribed a smaller proportion of amoxicillin than both older (> 54 years) and younger (20–40 years) physicians. A comparison with the period from July 2002 to June 2003 revealed that the differences associated with prescribers’ ages were mainly due to a cohort effect, meaning prescribers tended to stick with their prescribing habits. The 40–44-year-old prescribers belonged to the high number of well-educated children of children from the baby boom generation. A possible explanation for the particular prescribing behaviour of these physicians could be the higher competition perceived, which might have driven the use of newer antibiotics. Another explanation might have been the intense marketing of amoxiclav, patented in 1984, i.e. close to the time when this generation graduated. The youngest generations of physicians, on the other hand, had been educated in the context of growing antimicrobial resistance and prudent antibiotic use, supported by the development, dissemination and implementation of guidelines for the appropriate use of antibiotics in ambulatory care. Across different age cohorts, however, the preference for amoxicillin increased in the period 2002–09. A possible explanation for this effect is the impact of public awareness campaigns and individual prescriber’s feedback during the study period.10

Patient characteristics such as gender, social category and reimbursement rights affected the choice of the antibiotic prescribed. Adults from a less favourable social category were prescribed less amoxicillin. This effect differed by their gender. A remarkable finding was that female patients, even as children, were more likely than male patients to be prescribed amoxicillin. A possible explanation might be that, as for other medical treatments, physicians treat females less intensively, which in the case of amoxicillin versus amoxiclav is producing better-quality prescribing, whereas in, e.g. the treatment of cardiovascular disease it might be harmful. Nevertheless, we believe this finding deserves further investigation to better understand this relationship and possibly identify opportunities to improve antibiotic prescribing in male patients.

**Strengths and limitations**

In this analysis, both patient and prescriber characteristics were included at the level of the prescription and appropriate statistical methodology was used to take into account both within-patient and within-prescriber clustering. The data are complete; each reimbursed antibiotic prescription in the period from July 2008 to June 2009 is included for the whole country. Therefore, this analysis had substantially more power to elucidate small differences in prescribing behaviour than more selective surveys. Notice that these moderate differences in prescribing preferences are
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important because they represent a vast number of antibiotic prescriptions. To our knowledge, this is the first time that such an analysis has been performed. Although the prescribing differences we observed might not apply to other countries with a different prescribing and reimbursement model, the methodology can in principle be applied to similar datasets from other countries.

A drawback of the use of reimbursement claims data is the absence of information on the underlying pathology for which a prescription is issued or of information on additional comorbidities, such as HIV or cancer. Possibly some of the effects related to patient characteristics could be attributed to differences in underlying pathologies or comorbidities between patient groups. However, we controlled for important covariates, such as patient age, gender, social category, diabetes and low income class, whenever relevant. In this manner, differences in prescriber categories were partially controlled for the patient mix. An additional limitation of working with prescription data is the impossibility of verifying whether an issued prescription has led to usage of the antibiotic by the patient, and if so, how well the patient has adhered to the prescribed regimen. These aspects, related to the development of resistance at the population level, remain to be investigated through quantitative analyses, and merit further attention in future survey-based work.

In addition to the quality of prescribing, the methodology could also be applied to the search for prescriber groups with a deviating quantity of antibiotic prescriptions. For this task, a physician-specific denominator is needed, which is lacking in our current dataset.

In the analysis presented, we treated the correlation between prescriptions as a nuisance parameter, although dependencies between consecutive prescriptions might also be relevant to the evaluation of prescribing practices as such. We therefore compared the first and second prescriptions within 1 month of the first for the substances amoxicillin, co-amoxiclav and moxifloxacin in 2008–09. A clear difference between amoxicillin and co-amoxiclav as first prescription was observed. When the first prescription was for amoxicillin, 55% of second prescriptions were again for amoxicillin, 37% for co-amoxiclav and 8% for moxifloxacin. On the other hand, if the first was a co-amoxiclav prescription, 10% of the second prescriptions were for amoxicillin, 77% for co-amoxiclav and 13% for moxifloxacin. Factors influencing the transition from one prescription regimen to another falls outside the scope of this work, but merit future research.

Comparison with existing literature

Few studies have evaluated the impact of prescriber and patient characteristics on the antibiotic of choice. Steinman et al.,23 for instance, studied the choice between broad-spectrum and narrow-spectrum antibiotic prescribing for acute respiratory tract infections in adult primary care based on survey data. Although different factors were identified, the conclusion that non-clinical factors, e.g. physician specialty and region, influence prescribing behaviour is also found in data from the USA. It is to be expected that contributing factors differ between countries. The method of identifying deviating groups can, however, be generally applied.

Patient and prescriber predispositions, such as the patient’s belief with regard to the appropriateness of the use of antibiotics,24 parental expectations in the case of prescribing to infants,25 desire to satisfy patient demand26,27 and the physician’s fear of complications in the patient,28 have been singled out in the literature as the main underlying factors explaining self-medication with antibiotics, paediatricians’ antibiotic prescribing, GPs’ antibiotic prescribing and misprescribing of antibiotics, respectively. These factors cannot be investigated by reimbursement claims data, but might be an underlying explanation of some of the found associations between patient characteristics and the choice of the antibiotic substance, to be investigated in future studies.

In conclusion, we identified large prescriber groups with deviating prescribing habits, while controlling for relevant patient characteristics. Interventions can be designed and targeted taking the main characteristics of these deviating groups into account, along with information on the quantity of their prescriptions. Future analysis may aim to identify physician groups with deviating quantity as well as quality of prescribing. This may facilitate actions targeted at the group level, additional to a personalized approach, through which individual physicians are confronted with their deviating prescribing versus that of their colleagues.

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Transparency declarations

None to declare.

Supplementary data

Table S1 is available as Supplementary data at JACOnline (http://jac.oxfordjournals.org/).

References


