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Determinants of between-country differences in ambulatory antibiotic use and antibiotic resistance in Europe: a longitudinal observational study

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Objectives: To identify key determinants explaining country–year variations in antibiotic use and resistance.

Methods: Ambulatory antibiotic use data [in defined daily doses per 1000 inhabitants per day (DIDs)] for 19 European countries from 1999 to 2007 were collected, along with 181 variables describing countries in terms of their agriculture, culture, demography, disease burden, education, healthcare organization and socioeconomics. After assessing data availability, overlap and relevance, multiple imputation generalized estimating equations were applied with a stepwise selection procedure to select significant determinants of global antibiotic use (expressed in DIDs), relative use of subgroups (amoxicillin and co-amoxiclav) and resistance of *Escherichia coli* and *Streptococcus pneumoniae*.

Results: Relative humidity, healthcare expenditure proportional to gross domestic product, feelings of distrust, proportion of population aged >65 years and availability of treatment guidelines were associated with higher total antibiotic use expressed in DIDs. Restrictions on marketing activities towards prescribers, population density, number of antibiotics, educational attainment and degree of atheism were associated with a lower number of total DIDs used. Relative prescribing of amoxicillin and co-amoxiclav was mainly determined by healthcare system choices [e.g. general practitioner (GP) registration and restricted marketing]. Specific antibiotic use was found to be a significant determinant of resistance for some but not all drug/organism combinations. Incentives to stimulate GP gatekeeping were associated with lower levels of resistance, and life expectancy at age 65+ and atheism were associated with more resistance.

Conclusions: Myriad factors influence antibiotic use and resistance at the country level and an important part of these can be modified by policy choices.

Keywords: infectious diseases, pneumococcus, *Staphylococcus*, socioeconomics, healthcare systems

Introduction

It is well established that the use of antibiotics (usually expressed as the number of packages or number of defined daily doses sold or expended) and the prevalence of resistance to various groups of antibiotics vary substantially between countries and over time.[1–3]

Although many factors are presumed to influence these observed differences, formal data analysis to establish contributing factors has been scarce. In the rare analyses that have been published to date,[4–12] the focus has been on a small number of potential determinants based on medical and economic theory. We, in contrast, attempted to identify determinants of total outpatient antibiotic use, relative use of antibiotic subgroups and antibiotic resistance from as naive a starting point and for as many European countries as feasible. Determinants were selected based on statistical significance rather than a preconceived judgement of the relative importance of variables in explaining the observed variations in antibiotic use and resistance.

In the next section, we introduce the data sources, describe the data and outline the methodologies used for addressing the different research questions. The subsequent sections present

the results of our analyses and discuss our approach and results in the wider context of antibiotic use and of previous studies.

Methods

Data sources

A list of more than 100 potential determinants of antibiotic use in primary care, produced at an international workshop during the European Conference on Antibiotic Use in Europe (Brussels, 15–17 November 2001), was used as a basis for discussing and developing an updated list of variables of potential influence on antibiotic use and resistance during two consecutive international meetings of the European Surveillance of Antimicrobial Consumption (ESAC) network (see the Acknowledgements section for participant lists).

On the basis of the list of potential variables, we constructed a dataset by searching the following international databases: Eurostat,[13] the WHO Health for All database,[14] the WHO European mortality database,[15] the 2009 Organisation for Economic Co-operation and Development (OECD) database,[16] the Hofstede indices,[17] the Food and Agriculture Organization statistical database (FAOSTAT[18]), the World Values Survey,[19] the World Bank,[20] the EARS-Net database on microbial resistance,[21] Transparency International's Corruption Perceptions Index[22] and Mathematica's WeatherData.[23] Eurostat was used as the primary source when other sources were identified for the same variable. The database was complemented by a survey of the lead national representatives in the ESAC project to obtain information on the general characteristics of the healthcare system in each country. The questions put forward about the respective countries were broad in nature and asked about the organization of prescribing antibiotics to patients by different types of prescribers. Yearly data were retrieved from 1999 until 2007 for 32 European countries (see Table S1, available as Supplementary data at *JAC* Online). A complete list, describing the 181 potential determinants and the sources from which they were obtained can be found in Table S2 (available as Supplementary data at *JAC* Online). Based on medical plausibility, overlap and availability, the list of potential determinants was reduced to a short list of 57. We numbered this short list of variables (Table S2, available as Supplementary data at *JAC* Online) and repeated the complete variable description in the results tables (Tables 2 and 3) for clarity. In the Results section we refer to the determinant number.

Table S1 (available as Supplementary data at *JAC* Online) describes the countries for which data were gathered, as well as data availability after imputation of missing values. The imputation methodology is described in the Statistical methodology subsection and in more detail in the Supplementary data available at *JAC* Online.

Antibiotic consumption data were sourced from the ESAC database.[24] The WHO Anatomical Therapeutic Chemical (ATC) classification system[25] was used to define antibiotic substances. In this manner, total antibiotic use was defined as the total number of defined daily doses per 1000 inhabitants per day (DIDs) for every year/country combination in the ATC class J01 (antibiotics for systemic use).

Besides total antibiotic use, we also identified determinants of the use of subgroups of antibiotics relative to a larger class of antibiotic substances. Amoxicillin (ATC J01CA04) and co-amoxiclav (ATC J01CR02) consumption was expressed relative to all antibiotics (ATC J01) and to penicillins (ATC J01C). These consumption values can be seen as rough quality indicators, using the interpretation that proportionately more amoxicillin and less co-amoxiclav is to be preferred.

A similar dataset was obtained from IMS Health, with the aim of checking the consistency of the findings in relation to the outcome measure of consumption.

Resistance data were extracted in the form of count data. The number of isolates with intermediate or full resistance and the total number of isolates taken were sourced from the EARS-Net database on microbial resistance[21] for five resistance types from two bacterial groups. For *Escherichia coli* we obtained data on resistance to aminopenicillins (AMINOPEN), third-generation cephalosporins (CEPH) and fluoroquinolones (FLUORO). For *Streptococcus pneumoniae* we extracted data on resistance to penicillins (PNSP) and joint resistance to penicillins and macrolides (PNSP).

Statistical methodology

We encountered several statistical challenges: missing covariate data, within-country correlations, time-dependent covariates and a large number of potential covariates. Although methods have been described and used to deal with each of these challenges, when they arise jointly a generally agreed methodology is not readily available. Therefore, we used a practical but valid selection and modelling approach summarized below; details can be found in the Supplementary data available at *JAC* Online. The limitations of this method and potential alternative methods are raised in the Discussion section.

We augmented the data availability using multiple imputation[26] wherever possible to avoid losing incomplete records. We created five imputed datasets to account for the uncertainty related to the imputation process. Remaining missingness in the covariate data was eliminated by selecting a complete subset suggested by biclustering[27] performed on the data availability matrix. Table S1 (available as Supplementary data at *JAC* Online) illustrates the impact of multiple imputation on data availability and of biclustering on the number of observations selected for each country.

We conducted a stepwise search using generalized estimating equations (GEEs[28,29]) to identify relevant predictors for each imputed dataset separately. We subsequently combined all identified variables in a final multiple imputation GEE (MI-GEE[26]) model and employed a backward selection step to obtain the final estimates with valid *P* values. A working independence matrix was used for the GEE and MI-GEE models to preserve the unbiasedness and consistency properties of GEE estimation in the presence of time-dependent variables.[30,31]

MI-GEE based on the log-normal distribution was used to find determinants of total antibiotic use. Subgroups of antibiotic consumption were modelled using MI-GEE based on the Poisson distribution with a logarithmic link function and using the larger group as the offset. To model resistance rates, the Poisson distribution was used with the number of resistance counts as the response and the total count of bacterial samples per country–year were taken as an offset. In this part of the analyses, we were mainly interested in assessing cross-sectional associations between the rate of resistance and antibiotic use in specific subclasses, expressed in DIDs as summarized in Table 1.

Results

In this section, we summarize and explain the identified determinants of variations in total antibiotic use, use of subgroups and antibiotic resistance. Indicated associations should be interpreted as cross-sectional, since we did not consider associations at different timepoints. For clarity, we indicate the variable number in brackets to indicate which determinants of the list of 57 determinants (see Table S2, available as Supplementary data at *JAC* Online) were selected by the stepwise search. The terms 'positive' and 'negative' are used throughout the text to indicate the sign of the association, not to describe the potential desirability of the effect. A positive association means that an increase in a determinant will cause an increase in the dependent variable (i.e. antibiotic use), whereas a negative association means that an increase in the determinant will cause a decrease in the dependent variable. Categorical variables [e.g. restrictions on pharmaceutical companies: yes/no (D10)] are represented as an indicator of whether the

Table 1. Specific consumption data used for analyses of antibiotic resistance

		Pathogen				
		E. coli			*S. pneumoniae*	
		resistance to aminopenicillins	resistance to third-generation cephalosporins	resistance to fluoroquinolones	resistance to penicillins	combined resistance to penicillins and macrolides
ATC	description	AMINOPEN	CEPH	FLUORO	PNSP	PNSP & ENSP
J01CA	penicillins with extended spectrum	X	X		X	X
J01CE	β-lactamase-sensitive penicillins	X	X		X	X
J01CR	combinations of penicillins, including β-lactamase inhibitors	X	X		X	X
J01DB	first-generation cephalosporins	X	X		X	
J01DC	second-generation cephalosporins	X	X		X	
J01DD	third-generation cephalosporins		X	X		
J01F	macrolides lincosamides, streptogramins					X

statement is true (yes). Thus, a positive association means that the presence of the indicator is associated with more antibiotic use. When more than two levels were present multiple indicator variables were used. We refer to all levels in brackets when one or several indicators were selected, since the interpretation of selected determinants depends on which indicator variables are included or excluded.

Determinants of total antibiotic use

The final MI-GEE model retained 14 factors explaining variations in antibiotic use between countries as measured in DIDs (see Table 2).

The extent to which feelings of religiousness (D45) and trust (D46) are present tends to vary between countries, but was stable over the time horizon of our analyses. Both of these worldview aspects were found to be significantly associated with total antibiotic consumption. The larger the proportion of the population describing themselves as religious instead of atheistic, the more antibiotics were used. Additionally, antibiotic consumption was larger in countries where a larger percentage of inhabitants indicated that they distrust other people.

The organization of the healthcare system was also found to be predictive of the amount of antibiotics used in outpatient care. The presence of restrictions on the conduct of pharmaceutical companies towards physicians (D10), for instance, was associated with less antibiotic use. Perhaps surprisingly, countries in which guidelines have been implemented to treat respiratory tract infections (D12) used relatively more antibiotics measured in DIDs. Guidelines may suggest the prescription of higher dosages, which might explain this effect. The general practitioner (GP) – patient relationship was also identified as a significant factor. If patients are obliged to register with the GP they consult and it is not easy for them to consult another GP (D6-9), the country's observed antibiotic consumption was lower than in countries where this was not the case. Furthermore, the existence of a financial incentive to register with and consult a single GP, in the absence of an obligation to do so (D6-9), did not have a significant impact on ambulatory antibiotic use. Additionally, the number of antibiotic products available in a country (D4) was found to be negatively associated with antibiotic use. However, the significance of this negative association was conditional on the other variables included in the model. By contrast, the percentage of gross domestic product (GDP) spent on healthcare (D23) was positively associated with antibiotic use.

Several other factors related to climate, burden of disease, demography and socio-economics were found to contribute significantly to differences in antibiotic use. Relative humidity, expressed as the year-average dew point (D41), was positively associated with total antibiotic use. There was also a positive association between the rate of resistance of *E. coli* to third-generation cephalosporins (D51) and total antibiotic use. Furthermore, the proportion of elderly persons in the population (D36) was positively associated with antibiotic use. Higher educational attainment (D25) and higher unemployment rates (D2) were negatively associated with antibiotic use.

Determinants of relative amoxicillin and co-amoxiclav use

When focusing on subgroups of antibiotics (amoxicillin, co-amoxiclav) relative to either total antibiotic consumption (ATC

Table 2. Determinants of total antibiotic consumption and relative consumption of subgroups

Number	Determinant, relative to ATC class (offset in the Poisson-based MI-GEE model)	Total	Amoxicillin		Co-amoxiclav	
			J01[a]	J01C[a]	J01[a]	J01C[a]
8	patients have to be registered with a GP and it is not easy to change between GPs (1 = true, 0 = false)	0.77506 (0.72512; 0.82845)***	0.45751 (0.39601; 0.52855)***	0.75417 (0.66335; 0.85742)***	0.05571 (0.02384; 0.13019)***	0.08623 (0.04148; 0.17926)***
10	are there any restrictions on pharmaceutical companies regarding providing dinners, conferences, breakaways or presents to physicians? (1 = yes; 0 = no)	0.93564 (0.87815; 0.99689)*	0.47573 (0.40238; 0.56245)***	0.36274 (0.33016; 0.39853)***	1.61544 (1.35970; 1.91929)***	—
12	do pulmonologists, GPs or paediatricians have guidelines for treating respiratory tract infections? (1 = yes; 0 = no)	1.55419 (1.46024; 1.65418)***	—	1.28301 (1.14111; 1.44254)***	0.43350 (0.37925; 0.49550)***	0.62380 (0.51162; 0.76059)***
35	average population density per km^2	0.99869 (0.99849; 0.99889)***	—	1.00067 (1.00055; 1.00079)***	1.00351 (1.00235; 1.00467)***	1.00373 (1.00293; 1.00454)***
6	patients do not have to be registered at a GP, but there is a financial benefit for being registered at a GP (1 = true, 0 = false)	1.44540 (1.33553; 1.56431)***	1.59878 (1.36419; 1.87372)***	1.44046 (1.28565; 1.61393)***	—	—
41	year average dew point in °C as measure of relative humidity of the air	1.02570 (1.01603; 1.03546)***	1.04991 (1.03443; 1.06562)***	—	—	0.96677 (0.93527; 0.99933)*
45	extent to which persons describe themselves as atheistic versus religious[b]	0.58275 (0.51005; 0.66583)***	—	—	0.33437 (0.21598; 0.51765)***	0.49015 (0.33852; 0.70969)***
46	percentage of people who feel one should be careful in trusting others	1.25635 (1.00296; 1.57376)*	—	—	8.63797 (4.35628; 17.12805)***	7.63833 (3.97661; 14.67183)***
25	percentage of adult population (25–64 years old) that has completed upper secondary education	0.98997 (0.98834; 0.99160)***	—	0.99507 (0.99216; 0.99799)**	—	0.98800 (0.98103; 0.99502)***
4	number of different antibiotic products for sale in the pharmacy	0.99247 (0.99082; 0.99412)***	—	1.00687 (1.00359; 1.01015)***	—	—
23	total health expenditure as percentage of GDP	1.07235 (1.05021; 1.09496)***	—	0.90676 (0.86947; 0.94566)***	—	—
51	*E. coli* percentage intermediate and fully resistant to third-generation cephalosporins	2.26948 (1.19773; 4.30024)*	—	—	—	—
36	percentage of population aged ≥65 years	1.03833 (1.02906; 1.04769)***	—	—	—	—
2	unemployment rate of active population (15–64 years)	0.99079 (0.98377; 0.99787)*	—	—	—	—

15	private households' out-of-pocket expenditure on health as a percentage of total health expenditure	—	0.97921 (0.97354; 0.98491)***	0.96517 (0.95925; 0.97113)***	—	0.98271 (0.96930; 0.99632)*
21	percentage of infants vaccinated against mumps	—	—	0.98451 (0.98091; 0.98812)***	1.01992 (1.01206; 1.02783)***	1.02133 (1.01078; 1.03200)***
28	average household size	—	0.77523 (0.62737; 0.95795)*	—	2.57056 (1.84774; 3.57614)***	4.27265 (2.69035; 6.78557)***
52	percentage of *E. coli* intermediate and fully resistant to fluoroquinolones	—	—	—	2.91147 (1.54210; 5.49682)***	2.19601 (1.14969; 4.19459)*
14	is there any incentive for seeing a GP before seeing a pulmonologist, paediatrician or gynaecologist? (1 = yes; 0 = no)	—	—	—	0.22677 (0.16104; 0.31934)***	0.17332 (0.11338; 0.26496)***
7	patients have to be registered with a GP and it is easy to change between GPs (1 = true, 0 = false)	—	—	—	0.30283 (0.16669; 0.55017)***	0.31159 (0.18321; 0.52995)***
13	do patients have to consult a GP first before seeing a gynaecologist, pulmonologist or paediatrician? (1 = yes; 0 = no)	—	—	1.29602 (1.21364; 1.38399)***	—	—
57	age-standardized death rate per 100 000 due to pneumonia	—	—	—	0.98506 (0.97309; 0.99717)*	—
39	percentage of people living in an urban environment	—	—	—	0.98918 (0.98118; 0.99724)**	—
44	extent to which people consider greater respect for authority undesirable	—	0.51082 (0.40281; 0.64780)***	0.71836 (0.59898; 0.86152)**	0.47984 (0.39649; 0.58071)***	—
5	number of hospital beds per 100 000 inhabitants	—	0.99836 (0.99791; 0.99880)***	—	0.99734 (0.99581; 0.99886)***	—
34	male life expectancy at birth in years	—	0.92217 (0.90642; 0.93819)***	—	0.76378 (0.67984; 0.85809)***	—
38	percentage of population aged between 0 and 14 years	—	—	0.96679 (0.94362; 0.99052)*	—	0.92592 (0.87095; 0.98436)*
27	number of women per 100 men	—	—	1.08127 (1.06617; 1.09659)***	—	1.14822 (1.09639; 1.20251)***
26	percentage of people who know antibiotics do not kill viruses	—	0.99402 (0.99102; 0.99703)***	—	—	—
1	poverty rate: percentage of people earning <60% of the median income (made equivalent after social transfers)	—	1.02693 (1.01132; 1.04278)***	—	—	—

Continued

Table 2. *Continued*

Number	Determinant, relative to ATC class (offset in the Poisson-based MI-GEE model)	Total	Amoxicillin		Co-amoxiclav	
			J01[a]	J01C[a]	J01[a]	J01C[a]
11	do gynaecologists, pulmonologists, GPs or paediatricians receive any feedback on their antibiotic prescriptions? (1 = yes; 0 = no)	—	1.23020 (1.10800; 1.36589)***	—	—	—
42	standard deviation over a year of the daily dew point in °C as a measure of variability of relative humidity of the air	—	—	0.94325 (0.91077; 0.97689)**	—	—
16	total health expenditure in purchasing power parity per capita, WHO estimates	—	—	0.99992 (0.99987; 0.99998)*	—	—
29	female life expectancy at birth in years	—	—	—	1.26238	—

Selected determinants of total antibiotic use and relative rate of amoxicillin and co-amoxiclav consumption are displayed as exponentiated regression coefficients (with 95% Wald CI) of an MI-GEE model based on the normal distribution with log link for total antibiotic consumption and based on the Poisson distribution with log link for subgroup consumption.
[a]For subgroup consumption, amoxicillin or co-amoxiclav consumption was used as the response, with the larger group, indicated by the ATC class (J01 or J01C), as the offset.
The effects have a multiplicative interpretation. One unit increase in the determinant leads to a multiplication of the specific effect. For instance, if the year average dew point increases by 1°C, the expected total antibiotic consumption is 1.02570 times higher.
The significance level is indicated as *5% level, **1% level and ***0.1% level. Selection was based on a 5% significance threshold.
[b]In this case the average of a religiousness score is used, where people who declared themselves to be atheist were assigned the value 1 and those who declared themselves religious were assigned the value −1. Thus, this variable indicates the balance between self-declared atheists and self-declared religious people.

Table 3. Determinants of antibiotic resistance

Number	Determinant	*E. coli*[a]			*S. pneumoniae*[a]	
		AMINOPEN[a]	CEPH[a]	FLUORO[a]	PNSP[a]	PNSP [a]
	specific antibiotic consumption in DIDs (see Table 1)	—	1.07072 (1.02583; 1.11758)**	1.47305 (1.24508; 1.74277)***	1.05373 (1.03159; 1.07635)***	—
14	is there any incentive for consulting a GP before seeing a pulmonologist, paediatrician or gynaecologist? (1=yes; 0=no)	1.45912 (1.25990; 1.68985)***	0.07116 (0.03586; 0.14122)***	0.57484 (0.43048; 0.76760)***	0.15250 (0.11657; 0.19950)***	0.08294 (0.04580; 0.15019)***
28	average household size	—	3.89885 (2.21390; 6.86617)***	2.29673 (1.67231; 3.15430)***	4.11615 (2.74895; 6.16334)***	4.94626 (2.38363; 10.26395)***
25	percentage of adult population (25–64 years old) that has completed upper secondary education	—	1.06721 (1.05352; 1.08107)***	1.01914 (1.01108; 1.02727)***	0.98799 (0.98211; 0.99390)***	0.98350 (0.97313; 0.99397)**
35	average population density per km^2	—	1.00184 (1.00129; 1.00239)***	—	0.99766 (0.99709; 0.99824)***	0.99619 (0.99542; 0.99696)***
45	extent to which persons describe themselves as atheistic versus religious[b]	—	6.10699 (3.05528; 12.20686)***	—	3.31854 (2.06193; 5.34098)***	3.37354 (1.00576; 11.31561)*
23	total health expenditure as percentage of GDP	—	0.57758 (0.47577; 0.70117)***	0.88853 (0.81774; 0.96545)**	—	0.74035 (0.66933; 0.81891)***
8	patients have to be registered with a GP and it is not easy to change between GPs (1=true, 0=false)	0.87416 (0.82796; 0.92293)***	3.93602 (2.85456; 5.42718)***	—	0.55970 (0.41187; 0.76059)***	—
12	do pulmonologists, GPs or paediatricians have guidelines for treating respiratory tract infections? (1=yes; 0=no)	1.20760 (1.15617; 1.26132)***	0.27224 (0.18846; 0.39327)***	0.66118 (0.54228; 0.80615)***	—	—
31	male life expectancy at 65 years of age in years	1.09635 (1.05151; 1.14309)***	1.38112 (1.22127; 1.56189)***	1.69226 (1.26273; 2.26790)***	—	—
11	do gynaecologists, pulmonologists, GPs or paediatricians receive any feedback on their antibiotic prescriptions? (1=yes; 0=no)	0.82829 (0.77094; 0.88991)***	0.26917 (0.20095; 0.36057)***	—	1.94714 (1.61149; 2.35271)***	—
7	patients have to be registered with a GP and it is easy to change between GPs (1=true, 0=false)	—	0.62580 (0.48436; 0.80856)***	—	0.66452 (0.57708; 0.76522)***	—
36	percentage of population aged ≥65 years	—	1.51076 (1.36833; 1.66802)***	—	—	1.25671 (1.20325; 1.31255)***
49	age-standardized death rate per 100 000 due to other acute respiratory infections	—	1.18996 (1.03638; 1.36629)*	—	—	1.21739 (1.00676; 1.47210)*
30	female life expectancy at 65 years of age in years	—		—	1.28346 (1.11564; 1.47651)***	1.22345 (1.06272; 1.40849)**
41	year average dew point in °C as measure of relative humidity of the air	—		—	1.11300 (1.07824; 1.14887)***	1.13243 (1.07221; 1.19604)***
21	percentage of infants vaccinated against mumps	—		—	1.01357 (1.00049; 1.02682)*	1.02890 (1.00860; 1.04960)**
1	poverty rate: percentage of people earning <60% of the median income (made equivalent after social transfers)	0.98408 (0.97654; 0.99168)***	1.09020 (1.04048; 1.14230)***	—	—	—
4	number of different antibiotic products for sale in the pharmacy	—	1.02919 (1.01378; 1.04484)***	—	—	—

Continued

Table 3. *Continued*

Number	Determinant	*E. coli*[a]			*S. pneumoniae*[a]	
		AMINOPEN[a]	CEPH[a]	FLUORO[a]	PNSP[a]	PNSP [a]
29	female life expectancy at birth in years	—	—	0.75706 (0.62134; 0.92242)**	—	—
38	percentage of population aged between 0 and 14 years	—	—	0.88545 (0.85278; 0.91937)***	—	—
44	extent to which people consider greater respect for authority undesirable	—	—	0.60454 (0.45439; 0.80430)***	—	—
34	male life expectancy at birth in years	—	—	—	0.80166 (0.74347; 0.86441)***	—
6	patients do not have to be registered with a GP, but there is a financial benefit for being registered with a GP (1 = true, 0 = false)	—	—	—	—	2.08997 (1.53685; 2.84215)***
5	number of hospital beds per 100 000 inhabitants	—	—	—	—	1.00364 (1.00261; 1.00468)***
22	number of GPs per 100 000 inhabitants	0.99912 (0.99845; 0.99979)*	—	—	—	—
3	United Nations Development Programme (UNDP) Human Development Index (HDI)	0.20759 (0.05868; 0.73435)*	—	—	—	—
15	private households' out-of-pocket expenditure on health as a percentage of total health expenditure	1.01833 (1.01453; 1.02214)***	—	—	—	—
18	public sector expenditure on health as a percentage of total government expenditure, WHO estimates	1.04707 (1.03371; 1.06061)***	—	—	—	—
43	percentage of regular daily smokers in the population aged >15 years	0.98939 (0.97999; 0.99889)*	—	—	—	—
10	are there any restrictions on pharmaceutical companies regarding providing dinners or conferences or breakaways or presents to physicians? (1 = yes; 0 = no)	1.41848 (1.30029; 1.54742)***	—	—	—	—

Determinants of resistance rates, displayed as exponentiated regression coefficients (with 95% Wald CI), in an MI-GEE model based on the Poisson distribution with log link. Numbers of intermediate and fully resistance counts were used as the response and the total number of tests was used as the offset. The effects have a multiplicative interpretation. One unit increase in the determinants leads to a multiplication of the specific effect. For instance, if specific consumption increases by 1 DID, the expected proportion of resistance counts is 1.47305 times higher.

[a]For *E. coli* we studied resistance to aminopenicillins (AMINOPEN), third-generation cephalosporins (CEPH) and fluoroquinolones (FLUORO). For *S. pneumoniae* we studied resistance to penicillins (PNSP) and joint resistance to penicillins and macrolides (PNSP).

Significance level: *5%, **1%, ***0.1% level. Selection was based on a 5% significance threshold.

[b]In this case the average is based on a religiousness score where people who declared themselves atheist were assigned the value 1 and those who declared themselves religious were assigned the value −1. Thus, this variable indicates the balance in a country between self-declared atheists and self-declared religious people.

J01) or the consumption of β-lactam antibacterials and penicillins (ATC J01C), somewhat different sets of significant determinants were identified. Table 2 lists these results, ordered by the number of times they were selected as a significant determinant.

A number of variables were significantly associated with the relative prescribing rate of both amoxicillin and co-amoxiclav. Regulations concerning the position of the GP within the healthcare system were important in explaining which of these antibiotics were prescribed and to what extent. For instance, mandatory patient registration with a single GP (D6-9) independently reduces the relative rate of co-amoxiclav and amoxicillin prescribing (relative to all antibiotics and to penicillins only), especially if it is difficult to change between GPs (D6-9). The existence of a financial incentive, when registration with a GP is not mandatory (D6-9), was associated with higher relative amoxicillin use. The existence of restrictions on the conduct of pharmaceutical companies (D10) towards physicians was associated with a decreased rate of amoxicillin consumption and an increased rate of co-amoxiclav use (relative to penicillins only). The use of guidelines for treating respiratory tract infections (D12), in contrast, was associated with lower co-amoxiclav prescribing and with a higher rate of amoxicillin prescribing.

In addition to the influence of GP-related issues, other factors explained the remaining variation in relative prescribing rates of both amoxicillin and co-amoxiclav. Indeed, a higher percentage of private households' share in total health expenditure (D15) was associated with a lower rate of amoxicillin prescribing (relative to both total antibiotic use and penicillin use only) and with a lower rate of co-amoxiclav prescribing (relative to penicillin use only). A larger population density (D35) was associated with a higher relative use of both co-amoxiclav (relative to both total antibiotic use and penicillin use) and amoxicillin (relative to penicillins). A higher population density was also negatively associated with total antibiotic consumption. Furthermore, the percentage of infants vaccinated against mumps (D21) was associated with relatively more co-amoxiclav (relative to both total use and penicillins) and less amoxicillin prescribing (relative to penicillins).

Some remaining factors were significantly associated with co-amoxiclav, but not with amoxicillin. A larger average household size (D22) was strongly associated with a higher rate of co-amoxiclav consumption relative to other penicillins. The size of this effect was smaller when we modelled the rate of co-amoxiclav use relative to all antibiotics. The percentage of *E. coli* intermediately and fully resistant to fluoroquinolones (D52) was positively associated with a higher relative rate of co-amoxiclav use (relative to all antibiotics and to a lesser extent to penicillins).

Some other remaining factors were mainly associated with the extent to which amoxicillin was prescribed. A mandatory visit to a GP before seeing a gynaecologist, pulmonologist or paediatrician (D13) was associated with a higher relative rate of amoxicillin prescribing versus other penicillins. Providing feedback to GPs, gynaecologists, paediatricians or pulmonologists on how they prescribed antibiotics relative to their peers (D11) was found to be associated with a higher rate of amoxicillin prescribing relative to total antibiotic use.

We also found that the percentage of people who knew that antibiotics do not kill viruses (D26) was associated with a lower rate of amoxicillin prescribing relative to all antibiotics. Finally, a higher poverty rate (D1) was associated with a higher rate of amoxicillin prescribing relative to total antibiotic use.

Determinants of resistance

Table 3 summarizes the determinants significantly associated with antibiotic resistance. Antibiotic class-specific consumption was included in the selection procedure as a potential covariate (see Table 1). Since the resistance data were not imputed as an outcome measure, the analysis of determinants of resistance was conducted on a subset of the observations used in the consumption analysis. With specific antibiotic consumption expressed in DIDs, a significant association was identified for *E. coli* resistance to CEPH and FLUORO, but not for resistance to aminopenicillins AMINOPEN. For *S. pneumoniae* we found a significant association for resistance to PNSP, but not for combined resistance to PNSP .

Cross-country variations in resistance cannot fully be accounted for by the specific consumption expressed in DIDs. Alternative factors explain this better, and in the case of AMINOPEN and PNSP , specific consumption in DIDs was not even selected as an explanatory variable. We discuss the determinants in addition to consumption below. By comparing these determinants, we observed a clear difference between the factors found for AMINOPEN and other drug/organism combinations. A subgroup of variables exerted similar effects on the various combinations, with the possible exception of AMINOPEN. We discuss factors found to be significant over different drug/organism combinations, in order not to over-interpret the results. All identified factors can, however, be found in Table 3.

As for antibiotic consumption, the gatekeeper role of GPs was found to be important in explaining the observed differences in resistance levels. Most notably, the presence of any incentive for consulting a GP first before seeing a pulmonologist, paediatrician or gynaecologist (D14) was negatively associated with the resistance rate for all resistance classes, except for AMINOPEN. For this latter class, a positive association was observed. A larger average household size was positively associated with increased resistance over all classes investigated except for AMINOPEN, where it was not selected. The extent to which people described themselves as atheistic rather than religious (D45) correlated with higher resistance to CEPH, PNSP and PNSP , but was not retained in the final model for AMINOPEN or FLUORO. A higher life expectancy at 65 years (D31 and D49) of age was related to higher resistance levels for both males (PNSP and PNSP) and females (AMINOPEN, CEPH and FLUORO), albeit for different groups and pathogens. Total health expenditure as a percentage of GDP (D23), in contrast, correlated negatively with all resistance rates studied except for AMINOPEN, where this variable was not retained.

Other factors contributed to the explanation only of resistance rates of specific pathogens or even specific drug/organism combinations.

Discussion

Main determinants of consumption and resistance

We identified factors exerting a significant influence on either antibiotic use or resistance from a large determinant database by means of statistical significance testing within a multivariate MI-GEE model.

Several factors describing the organization of the healthcare system were found to be associated with either higher (guidelines

for treating respiratory tract infections) or lower (restrictions on the commercial conduct of pharmaceutical companies; number of antibiotics available) antibiotic use (measured in number of DIDs). In addition to the healthcare system, factors describing climate, burden of disease, demography and socio-economics each partially explained differences in antibiotic prescribing. Relative humidity and health expenditure as a percentage of GDP, feelings of distrust and the proportion of the population aged over 65 were positively associated with antibiotic use. Population density, the proportion of adults who completed upper secondary education and the extent to which people described themselves as atheistic rather than religious were negatively associated with antibiotic use.

The existence of guidelines for treating respiratory infections counter-intuitively increased antibiotic use. This might be due to guidelines being developed under the auspices of pharmaceutical companies, or to 'better prescribing' leading to 'more prescribing' when it is measured in DIDs. We did not consider guidelines for non-respiratory infections as a potential determinant in our analysis. Therefore, if the existence of such guidelines was associated with those for respiratory infections, we might have captured part of the effect of the existence of guidelines for non-respiratory infections. The impact and effectiveness of different guidelines on the quantity and quality of antibiotic use remain to be studied in detail.

The (average) extent to which people in a country described themselves as being an atheist rather than religious was found to have a highly significant association with both total use and antibiotic resistance of specific groups (CEPH, PNSP and PNSP). That is, a higher proportion of people in a country who classified themselves as atheistic rather than religious predicted lower antibiotic consumption and, counter-intuitively, higher antibiotic resistance. This variable might contain information on culture and perceptions of illness. Baquero *et al.*[30] suggested that religion plays a role in antibiotic consumption, in that antibiotic use is consistently lower in predominantly Protestant populations than in predominantly Catholic populations. In the dataset we used there were no separate indicators for Protestantism and Catholicism, but secularization (as indicated by feelings of no religiousness) has been documented to be more pronounced in historically protestant countries.[31] In this regard this finding is in line with that of Baquero *et al.*[30]

In our efforts to capture the defining characteristics of culture and community values for countries that could be relevant for antibiotic use, we used data from the World Values Survey (WVS). The WVS is a recurring survey of values (currently the sixth wave), and a commonly used resource in the social sciences. It adheres to a strict methodology for data collection to elicit community values and beliefs in many countries. Although one could argue that subjective valuations on feelings of religiousness and trust can be challenging to summarize at the population level, we believe that our multidisciplinary approach to determinant collection has enriched the analysis and the insights it provides.

The relative prescribing rate of amoxicillin and co-amoxiclav was found to be associated with the organization of the healthcare system (GP registration, restrictions on pharmaceutical companies, treatment guidelines for respiratory tract infections) and two factors linked to the transmissibility of infections (humidity and population density). Remaining explicative factors for relative prescribing rates differed between the different analyses.

The same methodology was applied to search for determinants of antibiotic resistance, whereby specific consumption in DIDs was added as a potential determinant. Specific consumption in DIDs was, however, only retained as a significant variable for CEPH, FLUORO and PNSP, and not for AMINOPEN and PNSP .

Previous studies[32–34] linking antibiotic use and resistance at the country level have found a significant association between specific ambulatory use and resistance for the same drug/organism combinations as we considered. These studies, however, did not include any other determinants in the analysis. Overall we discovered several factors to be highly associated with higher (average household size, life expectancy at 65 years old either for males or females, and non-religious feelings) or lower (incentives to visit a GP before consulting a specialist physician) resistance levels in a country for all drug/bug combinations except for AMINOPEN. For AMINOPEN the selected group of determinants differs from those for all other resistance types studied. In addition to these overall factors, a wide range of other determinants were only selected for specific resistance outcomes. The fact that so many different factors are selected in addition to, and in some cases instead of, antibiotic consumption, illustrates that antibiotic resistance is a complex phenomenon, whereby specific antibiotic consumption expressed in DIDs is not a sensitive enough measure to fully predict antibiotic resistance. It has to be considered that antibiotic consumption is the main driver of antibiotic resistance. For resistance to occur, however, several aspects interplay: (i) the amount of dispensed antibiotic, for which we modelled the total amount of DIDs; (ii) the quality of dispensing, which we assessed with relative prescribing rates of amoxicillin and co-amoxiclav; and (iii) appropriate use, for which we used a large set of determinants that might be related to resistance in addition to DID dispensing. The large set of determinants also determines the quantity and quality of antibiotic dispensing.

Significant determinants identified through our analyses might express differences in disease epidemiology, prescribing practices or compliance with treatment. Selective pressure exerted by antibiotic use as such might not coincide with DID measurements either. Relatively lower dosage consumption may eventually lead to more resistance than higher dose consumption.[35] An analysis based on packages per 1000 inhabitants per day was not considered because this information was unavailable for too many countries.

Furthermore, in our analyses we did not consider hospital antibiotic use as a potential determinant of resistance, as the resistance data do not allow a distinction between community-associated and healthcare-associated strains. Because of this mismatch between response and determinant, we are probably underestimating the significance of the association between antibiotic consumption and resistance. The distinct influence of hospital and ambulatory antibiotic use on resistance development is a topic for future research. This requires country-representative antibiotic use and resistance data from hospitals, as well as being able to distinguish community from healthcare-associated bacterial isolates. Both of these are currently lacking.

Methodological strengths, weaknesses and alternatives

To our knowledge, this is the first study using multi-country longitudinal data to investigate the potential impact of a large number of potential covariates on both antibiotic use and resistance by a combination of expert screening and analysis of statistical significance. This naive starting point results in the discovery of

distinct determinants for antibiotic consumption and resistance that would otherwise remain undiscovered. Previous attempts to find determinants of antibiotic use of aminopenicillins[4,5,7–12,36] correlated a limited set of *a priori*-defined determinants with consumption data. Masiero *et al.*,[4] for instance, explained causes of variation in antibiotic consumption in Europe using some of the same data that we used. The approach taken in the current work is, however, very different. Masiero *et al.*[4] started by proposing an *a priori* econometric model containing only a limited number of covariates, such as GDP per capita, and subsequently fitted this model to data to test the theory-based hypothesis. Conversely, we took an empirical approach and identified potential determinants based on the significance of their association with the response, with as few *a priori* assumptions as methodologically feasible. The discovery of factors associated with antibiotic consumption and resistance, in turn, enables scientific hypotheses to be proposed for a causal structure in an area where scientific evidence and relevant theory are sparse. In future research, these identified factors can be used to enrich theoretical models such as the mixed model approach used by Masiero *et al.*,[4] provided correct lag times are investigated.

We did not use any causal discovery algorithms, as did Rettenmaier and Wang[37] when they searched for determinants of health. Note that the approach taken by Rettenmaier and Wang[37] makes use of an underlying multivariate normal distribution, which is not satisfied here due to the use of various categorical variables. Furthermore, the causal discovery algorithms they used are cross-sectional, and extension to longitudinal data with fixed country effects removed is not backed by relevant statistical theory or simulation studies. This might be an interesting route for future studies on determinants of country-level differences in health outcomes provided appropriate statistical methodology is available.

An additional strength of our analysis is that it uses proper statistical methodology to incorporate relevant information, both between countries and over time. By using multiple imputation, we avoid losing too many sparsely available country–variable combinations. It should be noted that the statistical methodology used here is different from that used by Masiero *et al.*[4] Firstly, we took a marginal (GEE) approach versus a country-specific approach (mixed model). Secondly, we did not include geographical indicators because we did not want to obfuscate the underlying determinants of geographical differences. Lastly, we dealt with time-dependent variables such as antibiotic resistance differently. Masiero *et al.*[4] explored two options for this problem: using instrumental variables and including lagged covariates. The instrumental variable approach assumes a cause–effect relationship between instrument and covariate, which we tried to avoid. Taking lagged covariates in turn relies on the strict condition required for unbiasedness. That is, that all information (past and future) of all time-dependent variables with respect to the response should be included,[38,39] even when using the mixed model approach. We believe this is not satisfied by taking one fixed time lag. Therefore, we used GEE based on the working independence correlation matrix, which always provides unbiased cross-sectional associations when time dependent variables are present.

In order to test the stability of the results, we repeated the analysis using IMS Health antibiotic consumption data for a selection of 117 country–year combinations instead of the 153 country–year combinations available in the ESAC-based consumption analysis. The overall determinants of antibiotic consumption, such as education, regulation concerning GPs, the proportion of people aged 65+ in the population and the influence of religion, still clearly emerge as determinants of total IMS Health-based antibiotic use. We found that the selection of significant determinants became smaller and slightly different. The differences were mainly due to lower data availability using IMS Health, which implies that some variables no longer reach significance and are therefore not retained in the final model. This is especially the case for the resistance analysis based on IMS Health data. Another reason for the differences is the instability of the stepwise variable selection procedure under multicollinearity. Multicollinearity implies that overlapping information is present in the variables, and different subsets of determinants can explain the same variation in the response. For example, female and male life expectancies are highly correlated and could be equally predictive of antibiotic resistance. Therefore, the causal interpretation of the identified determinants has to be treated with caution. Recently new statistical methodology has been proposed to perform determinant selection for multicollinearity and time dependence; however, its performance with multiple imputation has not been investigated, but might provide more stable selection.[40]

Furthermore, in this study only cross-sectional associations were investigated, whereas antibiotic resistance evolves dynamically, with current resistance levels being determined by selection pressure over time. Identifying the dynamics of resistance development would require longer and more precise data on both antibiotic consumption and resistance measurements.

Conclusions

Our study showed that, apart from societal aspects over which policy has no control in the short run (such as population density, religiousness and trust), there are a number of aspects that can be modified by policy makers and that are likely to have a significant impact on antibiotic use and resistance in the short run. Such policies include strengthening the gatekeeping function of GPs and the authority of physicians over their patients. This can be done, for instance, by restricting the freedom of patients to consult many different GPs or to consult specialists directly. However, it should be accompanied by placing restrictions on direct marketing activities by pharmaceutical companies aimed at prescribing physicians, as this would also have a significant impact on consumption of antibiotics. Furthermore, it would seem prudent to provide feedback to physicians on their prescribing habits versus those of their peers. Clearly, such measures would have consequences far beyond the prescription of antibiotics. Therefore, they should be considered in their country-specific context, balancing aspects of access, quality, affordability, equity and cost-effectiveness of care.

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Transparency declarations

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Supplementary data

Tables S1 and S2 and details of the statistical methodology are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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