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ORIGINAL PAPER

Assessing the impact of national antibiotic campaigns in Europe

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Abstract Because of evidence of causal association between antibiotic use and bacterial resistance, the implementation of national policies has emerged as a interesting tool for controlling and reversing bacterial resistance. The aim of this study was to assess the impact of public policies on antibiotic use in Europe using a differences-in-differences approach. Comparable data on systemic antibiotics administered in 21 European countries are available for a 11-year period between 1997 and 2007. Data on national campaigns are drawn from the public health literature. We estimate an econometric model of antibiotic consumption with country fixed effects and control for the main socio-economic and epidemiological factors. Lagged values and the instrumental variables approach are applied to address endogeneity aspects of the prevalence of infections and the adoption of national campaigns. We find evidence that public campaigns significantly reduce the use of antimicrobials in the community by 1.3–5.6 defined daily doses per 1,000 inhabitants yearly. This represents an impact of roughly 6.5–28.3 % on the mean level of antibiotic use in Europe between 1997 and 2007. The effect is robust across different measurement methods. Further research is needed to investigate the effectiveness of policy interventions targeting different social groups such as general practitioners or patients.

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Introduction

The overuse of antibiotics is the main force driving the increase of bacterial resistance, which represents a major threat to public health. Antimicrobials may lose effectiveness since they are prescribed frequently for viral infections [1] or can be obtained without an official medical prescription [2, 3]. Large volumes of antimicrobials are also used in agriculture and veterinary medicine, and in many consumer products where benefits are often unclear [4]. As illustrated in Fig. 1, differences across European countries in antibiotic prescribing practices measured in defined daily doses per 1,000 inhabitants (DID) partially mirror differences in the levels of bacterial resistance captured by the rate of penicillin-non-susceptible *Streptococcus pneumoniae* isolates (PNSP) [5, 6].

Efforts to reduce bacterial resistance through controlled antibiotic use include the limitation of prescriptions, surveillance, and more careful use of antibiotics in agriculture. More recently, public authorities have taken an interest in encouraging appropriate consumption of antibiotics in the community [7, 8]. Cost-effectiveness studies on antibiotic treatments are now developed to consider the influence of bacterial resistance [9]. Because the association between antibiotic use and bacterial resistance may cross regional borders within countries, the implementation of national policies towards antibiotic consumption has emerged as an important tool for controlling and reversing bacterial resistance. However, the effects of these policies are still unclear.

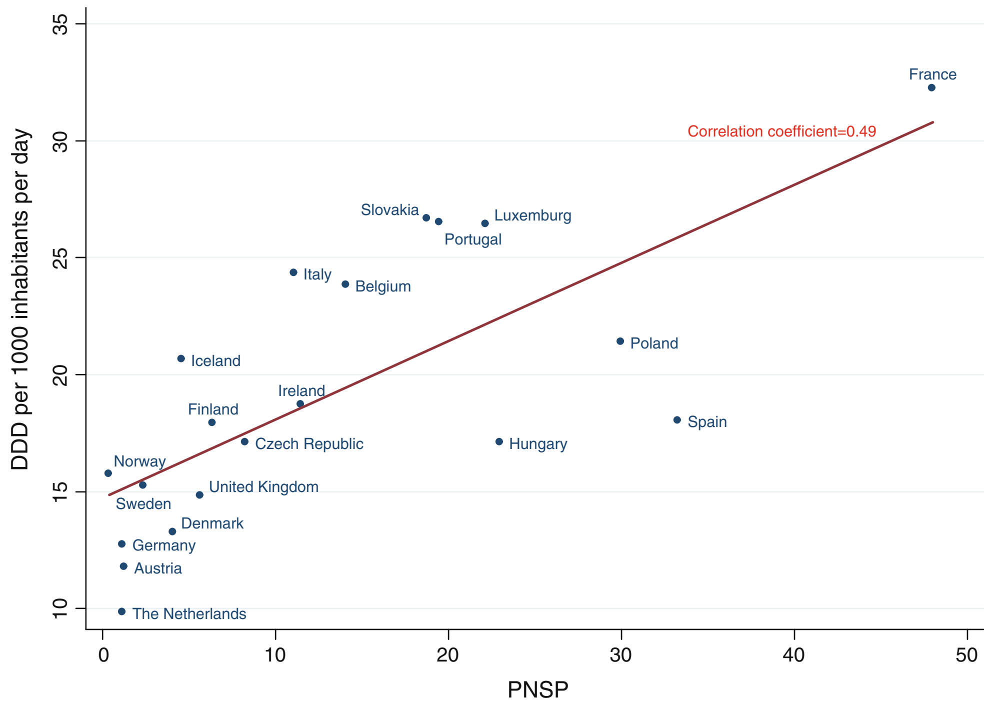


Fig. 1 Antibiotic consumption and levels of bacterial resistance in PNSP (proportion of penicillin-non-susceptible *Streptococcus pneumoniae* isolates) in 21 European countries in 2005. Data source: European Surveillance of Antimicrobial Consumption (ESAC) and European Antimicrobial Resistance Surveillance System (EARSS)

Several studies describe and review national policies towards antibiotic consumption in specific countries. Goossens et al. [10] and Chahwakilian et al. [11], for instance, consider policies towards the efficient use of antibiotics in Belgium and France. However, the literature lacks studies providing empirical evidence on the impact of national policies across Europe. Huttner et al. [12] summarize the characteristics of public campaigns in high-income countries but fail to provide sufficient statistical evidence on their impact. An econometric approach is used by Masiero et al. [13] to investigate socioeconomic determinants of antibiotic use across Europe. The authors do not account for the effects of public policies towards the consumption of antimicrobials.

The aim of this study is to assess the impact of public education campaigns on antibiotic use in Europe by means of a differences-in-differences approach, a widely used empirical methodology on the effects of various treatments [14]. We draw information on national campaigns from the public health literature and use publicly available data on antibiotic consumption and socioeconomic determinants for an 11-year period (1997–2007). We control for unobserved individual heterogeneity by means of fixed-effects estimations and address endogeneity aspects of infections and policies with lagged and instrumental variables methods.

The paper is organized as follows. The section "Public policies aiming to reduce antibiotic consumption" reviews the literature on policies towards the use of antibiotics and provides a brief overview of public interventions implemented in European countries. "The empirical approach" proposes an econometric model of antibiotic consumption where the impact of national campaigns is assessed after controlling for the main determinants of consumption. Data are described in the "Data" section. Estimation results and discussion of main findings are presented in the "Results" section. A "Conclusion" summarizes the methodology and the main findings of our exercise, and suggests possible improvements to current research.

Public policies aiming to reduce antibiotic consumption

Antimicrobial agents represent a scarce resource since their effectiveness decreases with consumption because of bacterial resistance. Different interventions may act as an effective way to tackle the problem. These can be characterized according to the type of intervention, the geographical area involved, the targeted agents, the instruments used and their message.

Regarding the type of intervention, policies to improve the use of antibiotics can be categorized into four classes according to the list proposed by Quick et al. [15]. There are educational interventions, which are persuasive and consider training of prescribers by means of seminars, workshops, face to face or supervisory visits, and assorted printed materials aimed at patients or prescribers. Managerial strategies aim at guiding decision-making; they concentrate, for instance, on carrying drug utilization reviews, giving cost information, following standard treatment guidelines to prescribe, and encourage completion of the full course of antibiotic therapy, for instance by offering a full course of treatment in a single dose. Regulatory interventions legally constrain prescribers to control their decision making via instruments such as registering drugs for marketing, licensing prescribers, and limiting prescribing or dispensing. Finally, economic interventions aim at providing financial incentives to institutions, providers and patients. The effects of these strategies crucially depend on the pricing structure, the price setting and the reimbursement mechanism adopted.

Among the educational strategies that promote the appropriate use of antibiotics and raise public awareness of bacterial resistance, public campaigns are one of the most widely used. In European countries, national or regional health authorities are in charge of adopting these campaigns, depending on the level of decentralization of health care systems. Although antibiotic policies can be implemented at national or subnational level, public campaigns are generally implemented within a national strategy to abate resistance to antimicrobials [12]. International organizations are sometimes involved. Rudholm [16] suggests that the problem of resistance is a global one. Consequently, optimal policies should consider the fact that antibiotic resistance can cross country borders and travel far distances. Coast et al. [17] argue that policies aimed at reducing antibiotic use within a country may not work in another country since local epidemiological factors affect the spreading mechanism of antibiotic resistance. González Ortiz and Masiero [18] suggest that regional policies could blunt the impact of policies in neighbouring regions through the generation of local spillovers.

As observed by Huttner et al. [12], the majority of public campaigns are addressed to the general public, focusing on parents of young children. Health-care professionals, specifically primary care physicians, are also targeted. The public is targeted by distributing informational material to patients and by displaying posters in waiting rooms and pharmacies. General practitioners receive educational material such as guidelines, information sheets and booklets. Some campaigns combine different instruments such as advertising on television and radio networks, newspapers and public transports, through the internet or using billboards. The use of the internet to spread information about the program is common to almost all campaigns.

Finally, regarding the message of the intervention, Huttner et al. [12] explain that most campaigns attempt to inform the public that antibiotics are not needed for treating viral infections. They focus on respiratory tract infections and combine negative and positive messages. The main message is that bacterial resistance is a major public health issue caused largely by the misuse of antibiotics. This encourages people to follow rigorously the antibiotic dosage regime prescribed by their physician.

Previous studies on the impact of antibiotic policies

The literature on the impact of antibiotic policies is limited to studies using a descriptive and qualitative approach. Goossens et al. [10] analyse national campaigns in two European countries—Belgium and France—with high antibiotic use between 1997 and 2003.[1] To assess the impact of antibiotic policies, the authors compare rates of antibiotic consumption between the two countries and England, where the rates of antibiotic use are lower and persistent. Findings suggest evidence of reduced antibiotic prescribing in both countries. However, these findings cannot be generalised to countries with lower or already declining levels of antibiotic use. Moreover, the study does not control for differences between the two countries related to the impact of infections, the characteristics of prescribers or demographic aspects over the time period considered.

To assess the impact of antibiotic policies in Central and Eastern European countries, Cizman et al. [19] administer a questionnaire to national representatives. The questionnaire includes information about national antimicrobial resistance surveillance, national consumption of antibiotics in the community and in hospitals, and strategies to optimize the use of antimicrobials. The authors identify countries that have restricted the use of some antibiotics for outpatients and inpatients and describe briefly other types of interventions implemented by these countries. Findings show that only few countries have restricted the use of antimicrobials in ambulatory care, as compared to the common practice of restricting the use of antibiotics in hospitals. The authors realise that antibiotic policy interventions are lacking or apply only to specific interventions or problems.

Using an exhaustive search strategy and structured interviews, Huttner et al. [12] classify and examine the characteristics and outcomes of 22 public campaigns for a more rational use of antibiotics implemented at national or regional level in high-income countries between 1990 and 2007. The majority (16) of these campaigns are located in Europe. Looking at data on the consumption of outpatient antibiotics, the authors try to evaluate the effect of the campaigns. The study concludes that there is probably a relationship between a decline in the use of antibiotics and the implementation of public campaigns. However, this

[1] For more evidence on the impact of the French campaign to reduce inappropriate use of antibiotics, see also the recent study by Chahwakilian et al. [11], who analyse trends in antibiotic prescriptions between 1980 and 2009.

conclusion is based on a qualitative analysis rather than on a statistical or econometric analysis. The approach has some shortcomings since most campaigns do not include a control population and trends in consumption before the interventions are not considered. The analysis cannot clarify whether antibiotic consumption would still have increased without the campaign or if the duration of the intervention was too short to observe measurable effects.

In conclusion, evidence presented in empirical studies on the impact of antibiotic policies is currently weak, mainly based on descriptive statistics and graphical analysis. In the following section, we will use an econometric approach to provide more convincing evidence of the association between the adoption of antibiotic policies and antibiotic consumption rates.

The empirical approach

To investigate the effects of national campaigns for a more rational use of antibiotics, we estimate a model of outpatient antibiotic consumption using a panel data set for a sample of 21 European countries over the period 1997–2007. The model serves as a reduced form that considers both demand- and supply-side factors. In our simple frame, individuals are assumed to follow doctors' prescriptions and to be compliant with the antibiotic therapy.[2] We hypothesize that the consumption of outpatient antibiotics depends upon sociodemographic characteristics of the population, individuals' health status, antibiotic price, the characteristics of health care supply and the adoption of national campaigns to improve the use of antibiotics.

Antibiotic prescribing practices vary widely across European countries. Mean figures of defined daily doses per 1,000 inhabitants for 21 countries collected by the European Surveillance of Antimicrobial Consumption (ESAC) project between 1997 and 2007 show that France, Greece, and Luxembourg, among others, exhibit significantly higher values of antibiotic use than Austria, Denmark, and the Netherlands (see Figs. 2, 3; Tables 3, 4 in the "Appendix").[3] Some of these countries implemented policy interventions to reduce antibiotic consumption during the period considered; other countries did not adopt any type of public campaign.[4] Figure 3 provides an illustration of the adoption of national campaigns to improve antibiotic use in Europe. We refer the reader to the "Data" section for details about the construction of this figure.

Since we have information on antibiotic consumption before and after a policy instrument has been introduced, we are able to estimate the effect of policy interventions using a differences-in-differences (DD) approach [14].[5] The general idea of this approach is to compare the outcome—in our case the per capita consumption of antibiotics—of two groups of countries before and after the introduction of a campaign. One group, denoted the "control", is composed of countries that did not introduce any policy instrument to reduce antibiotic consumption. The other group, the "treatment", includes all countries that have adopted some policy measures. The control group and the treatment group change in each year since countries did not implement campaigns at the same time. Looking at differences in the outcomes observed between the two groups after the introduction of a policy, we can then estimate the impact of antibiotic policy interventions. The typical DD estimation with panel data with more than two periods considers countries and years fixed effects. Therefore, our estimation method exploits both the within-country variation as well as the comparison between countries, and takes into account unobserved time-invariant heterogeneity.

Our empirical approach draws from Giavazzi and Tabellini [23], who apply a DD technique to a large sample of countries to investigate the impact of economic and political liberalizations on economic performance, macroeconomic policy and structural policies. We estimate the following model in the whole sample of treated and control countries:

$$DID_{it} = \beta \cdot POLICY_{it} + \phi \cdot \mathbf{x}_{it} + \omega_i + \nu_t + \varepsilon_{it}, \qquad (1)$$

where DID_{it} denotes defined daily doses of antibiotic consumption per 1,000 inhabitants in country i at time t;

[2] Antibiotic consumption data generally derive from reimbursement data or distribution/sales data, depending on the method for measuring antibiotic use employed by each national database. Assuming patient's non-compliance to be a negligible factor implies that the quantity of antibiotics sold matches the quantity actually consumed. The latter is associated to antimicrobial resistance and represents the target of antibiotic policies.

[3] Data are reliable and exhibit a good degree of comparability since the ESAC network screens for detection bias in sample and census data, bias by over-the counter sales and parallel trade, errors in assigning medicinal product packages to the Anatomical Therapeutic Chemical Classification (ATC), and errors in calculations of defined daily doses [20].

[4] *Public campaigns* and *policies* are used interchangeably throughout the remaining of the paper. The reader should be aware that public campaigns represent a subset of possible antibiotic policies. The Netherlands, for instance, have strong antibiotic policies in place although the country did not conduct any public campaign during the study period.

[5] In the literature, several approaches are discussed to estimate the causal impact of a "treatment variable" on an outcome variable, such as the DD estimator and the propensity score matching estimator. In this study, we use a differences-in-differences approach because of the relatively small panel data set with observations at the country level rather than at individual level. Using a propensity score matching approach requires, for instance, a large data set regarding the number of variables and the sample size. For a discussion on this issue, we refer the reader to studies by Frolich [21] and Heinrich et al. [22].

Fig. 2 Outpatient antibiotic use in DID (defined daily doses per 1000 inhabitants per day) for countries that did not implement any public campaign between 1997 and 2007. Data source: ESAC

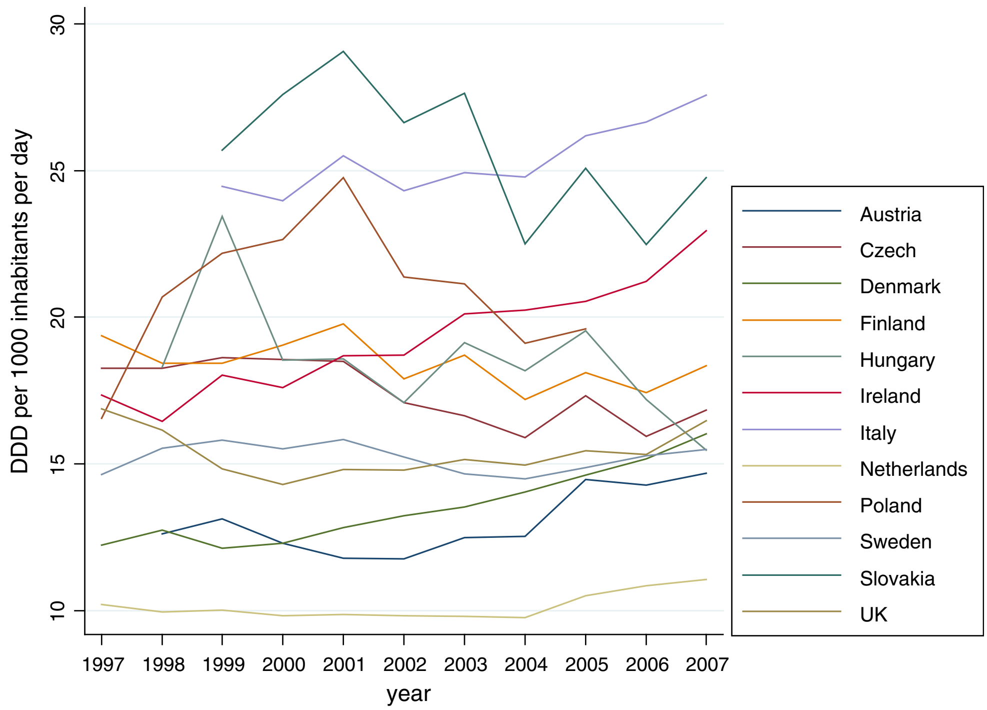
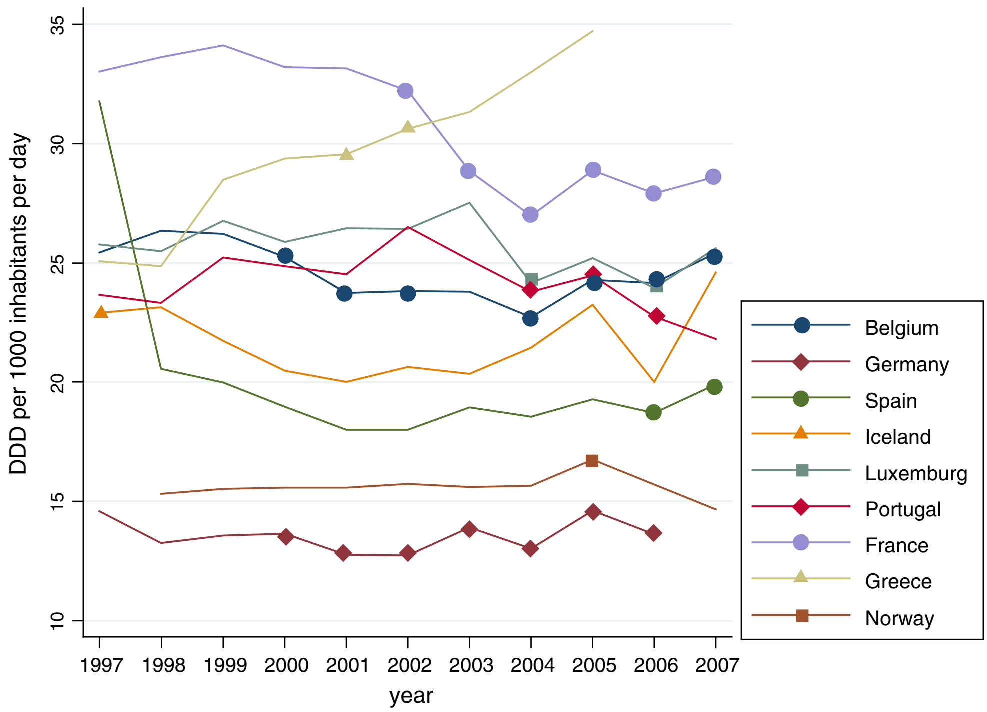


Fig. 3 Outpatient antibiotic use in DID for countries that implemented public campaigns between 1997 and 2007 (years of campaign implementation are marked). Data source: ESAC and [12]



$POLICY_{it}$ is a dummy variable that assumes a value equal to 1 only in the year of policy implementation, and 0 otherwise. $\mathbf{x}_{it}$ is a vector of other covariates that includes the per capita national income (Y_{it}), physician density (DPH_{it}), the percentage of the population below 14 years of age, between 15 and 24, 25 and 64, 65 and 79, and over 80 ($POP_{1it}\ldots POP_{5it}$), the price level of pharmaceuticals (P_{it}), and the population health status measured by the impact of infectious diseases (INF_{it}). ω_i captures the country-level fixed effects, which are assumed constant over time and take unobserved time-invariant variables, such as cultural aspects, into account. v_t is the year-specific fixed effect, which is assumed constant across countries. Finally, ε_{it} is an unobserved error term with Z distribution.

Note that model (1) is a common generalization of the most basic DD setup, which is valid under the restrictive assumption that changes in the consumption of antibiotics over time would have been the same in both treatment and control groups in the absence of the campaign.

By including both time and country fixed effects in Eq. (1), we are able to disentangle the impact of public campaigns per se from other determinants related to country characteristics or time effects.[6] The main coefficient of interest is β, which measures the effect of public campaigns on antibiotic consumption. A negative and significant coefficient would suggest that antibiotic policies were effective in reducing antibiotic consumption over the period 1997–2007.

To correctly identify the impact of antibiotic policy interventions, the econometric model has to satisfy some assumptions. First, we need to exclude the presence of unobserved variables affecting antibiotic consumption that move systematically over time in a different way between the two groups of countries. This does not exclude observation of individual patterns within each group. Although in our analysis all countries belong to Europe, the general trend in antibiotic consumption may not be the same. Indeed, European countries showed different trends even in the absence of campaigns. However, we do not observe different geographical or political clusters between the two groups of countries.

The possibility of unobserved heterogeneity bias may not be negligible even though our regressions include important socioeconomic determinants of differences in antibiotic use across countries ($\mathbf{x}_{it}$), such as income, the population age structure, and density of practitioners. Generally, unobserved heterogeneities in the use of antibiotics among countries, such as cultural factors, are notoriously difficult to measure and may also be present (see, for instance, the studies by Borg [24], Deschepper et al. [25] and Harbarth et al. [26]). Although we cannot account explicitly for cultural aspects, the fixed-effects approach should consider these effects at least partially. Moreover, if cultural differences between the two groups of countries—with and without policies—are stable over time, the estimated effect of public campaigns should not be biased.

One further assumption that will be relaxed later in the analysis is that the decision to introduce a public campaign is independent of the level of antibiotic consumption in a country, i.e. policies are exogenous. This implies that pressure to promote information campaigns does not depend directly on antibiotic consumption. More likely, it depends on the increasing levels of antibiotic resistance. Still, this is a limitation since antibiotic resistance is caused partially by the consumption of antibiotics, which may then influence indirectly the adoption of antibiotic policies. Moreover, the link between antibiotic use and antimicrobial resistance is now well documented and we cannot exclude that some countries may have conducted campaigns because of high levels of antibiotic consumption.

From an econometric point of view, if campaigns are nonrandom and occur more frequently where the chance of success is higher, then the estimate of the average treatment effect may be biased. As mentioned before, we control for this unobserved heterogeneity by means of a FE approach with clusters by country. However, the above relationship between antimicrobial resistance and antibiotic consumption generates an endogeneity problem, which may also lead to biased results in the estimation of Eq. (1). For this reason, we check the robustness of our initial results (Model 1) by endogenizing the policy variable using an instrumental variable approach (Model 2). As we will discuss later, the use of instrumental variables decreases the number of observations. The density of foreign population and the production of milk and pig meat are used as instruments for policies. These variables also measure indirectly the level of bacterial resistance within a country. Masiero et al. [13] observe that these instruments are well correlated with bacterial resistance. Levels of bacterial resistance can be related to the extensive use of antibiotics in agriculture and in animal breeding. For instance, *Campylobacter* is the most frequently reported zoonotic pathogen to cause human illness, and resistant bacteria tend to be harboured in meat produced commercially [27]. The common practice of using milk produced during antibiotic treatment for feeding calves and pigs causes a marked selection for resistant bacterial strains (i.e. enterococci), which may enter the food chain. Finally, the density of foreign population may be considered an indicator of human population movements across countries, which increases the spread of bacterial resistance [16]. In contrast to bacterial resistance, our instrumental variables are correlated poorly with antibiotic use. Consequently, we believe they can reasonably be used as appropriate instruments for policies.

Another explanatory variable is potentially endogenous in our model: population health status, which is captured by mortality for infectious diseases. Infections are potentially endogenous since a low level of antibiotic use may favour poorer health conditions in the population, e.g. increased spread of severe infections. To tackle this problem, we estimate our models using the lagged mortality rate for infectious diseases (INF_{it-1} instead of INF_{it}). This is a simple, but fairly effective, instrumental variable approach. The variation within the observations of each country for this variable is in general as large as the variation in other covariates and higher than the within-variation in the consumption of antibiotics.

[6] Initially, we also estimate Eq. (1) using ordinary least-squares (OLS) and random effects (RE) approaches.

For robustness check, we also estimate our models using a two-period lagged mortality rate for infectious diseases. The main results are confirmed. Finally, we can rule out possible endogeneity regarding the price variable (P_{it}) since this is constructed by combining the harmonized annual average price index for pharmaceuticals (HICP) and the comparative price level index (PLI), as explained later in "Data".

One last issue is that the DD estimation results can be affected by positive serial correlation. Although this correlation does not bias the estimated average treatment effect, it could lead us to underestimate the standard error and to reject the null hypothesis of no effect of public campaigns. To cope with this problem, we report standards errors clustered by country.[7] Note also that the variation over time in our data is not negligible and represents around 30 % of total variation.

Data

The consumption rate of antibiotics is available for 21 European countries between 1997 and 2007. This is collected by the European Surveillance of Antimicrobial Consumption (ESAC) project. The consumption rate is expressed most commonly as the number of defined daily doses (DDD) per 1,000 inhabitants per day (DID). The DDD is a technical unit based on the assumed average maintenance dose per day for a drug used for its main indication in adults. Antibiotic use is standardized using the ATC/DDD index for international drug consumption studies [30].[8]

Annual data available on the determinants of outpatient antibiotic use are summarised in Table 1. Details for each country are provided in Tables 3 and 4 in the "Appendix". These determinants include socioeconomic characteristics of the population (income and demographic structure), supply-side factors (density of doctors), price of pharmaceuticals, and the incidence of bacterial infections measured by the rate of mortality.[9] We use the mortality rate for infectious diseases as a proxy for the incidence of infections since morbidity indicators are less complete and reliable.

Data are obtained from a variety of sources. Information on the per capita income (measured in US dollars in purchasing power parity), the density of physicians, and the incidence of infections are extracted from publications by the OECD [32].[10] The demographic structure of the population is derived from Eurostat tables [33]. Information on instruments for policies (population density, production of milk and pig meat) are also obtained from the Eurostat statistics [33].

Since antibiotic prices are not easily available for all countries and years, we approximate price levels for antibiotics using the pharmaceutical price index. This is clearly a more general price index as compared to the antibiotic price index. Still, antibiotics represent a considerable part of all pharmaceutical sales and their prices are likely well correlated with the pharmaceutical price index in all countries. The harmonized annual average price index for pharmaceutical products (HICP) provided by Eurostat [33] includes information on price trends for pharmaceuticals for each country between 2000 and 2005, where 2005 = 100. Since this price index is equal to 100 for all countries in 2005, we rescale the pharmaceutical index of each country using the comparative price level index (PLI) which varies across countries. The PLI indicates the price level of each country compared to the average price level of the 25 EU countries in 2005. Using this index is equivalent to assuming that differences in pharmaceutical prices across countries reflect differences in the general level of prices.

As for public campaigns, data collection is cumbersome and may result in incomplete data. Moreover, little information is available in scientific journals. For our purpose, we draw the information on campaign characteristics from the recent review by Huttner et al. [12]. The authors identify public campaigns implemented at national level in high income countries between 1990 and 2007. Using information from this study, we generate a dummy variable ($POLICY_1$) which takes a value equal to 1 in the year of implementation of the campaign, and 0 in the pre-campaign and post-campaign years (see Fig. 3). As an example,

[7] As discussed by Bertrand et al. [14], conventional differences-in-differences standard errors may be biased because of serial correlation. A solution proposed by Arellano [28] is to compute cluster-robust standard errors. Kezdi [29] shows that cluster-robust estimates perform well in typical-sized panels, although they can be biased slightly downward if the number of countries is very small. In a Monte Carlo experiment, Kezdi [29] considers $N = 10$ to be a very small number of countries. In our case, N is equal to 20. Therefore, although the sample is relatively small, we believe that cluster-robust standard errors represent a viable solution to autocorrelation.

[8] Although comparing antibiotic use among countries using DDD has a large consensus among researchers, one limitation is that this measure is not appropriate for all age groups. Indeed, using other measures may give different results, as illustrated by Goossens et al. [31].

[9] Information on mortality for infectious diseases and price of pharmaceuticals are not available for all countries or years. This reduces the total number of observations in our final regressions.

[10] It is important to underline that this variable is obtained from OECD data and is likely difficult to compare between countries. Mortality for infectious diseases is generally based on diagnostic discharge codes. Consequently, differences among countries may depend on different methods of determining this variable.

Table 1 Variables notation and summary statistics for the whole period (1997–2007) for the 20 countries considered in the econometric analysis

Description	Variables	*N*	Mean	SD	Minimum	Maximum
Outpatient antibiotic consumption	DDDs per 1,000 inhabitants per day (DID)	207	19.77	5.96	9.75	34.73
Income per capita	Per capita GDP in US $ in PPP (Y)	220	26,582.70	10,538.74	8,898	71,400
Price of pharmaceuticals	Comparative price levels for pharmaceutical products (P)	187	92.82	21.22	36.65	135.81
Demographic structure of population	Proportion of population under 14 (POP_1)	220	17.53	2.12	13.90	25.70
	Proportion of population 15–24 (POP_2)	220	13.20	1.83	10.20	17.50
	Proportion of population 25–64 (POP_3)	220	54.02	1.81	47.90	58.10
	Proportion of population 65–79 (POP_4)	220	11.69	1.46	8.20	15.20
	Proportion of population over 80 (POP_5)	220	3.57	0.83	1.80	5.40
Density of doctors	Number of doctors per 1,000 inhabitants (DPH)	220	3.20	0.67	1.85	5.35
Infections	Mortality rate for infectious diseases (INF)	189	6.89	3.47	2.00	20.10
Density of foreign population	Foreign residents per km^2	215	6.24	7.93	0.09	41.64
Animal production	Cow's milk (in thousand of tons)	217	6,557.08	7,303.11	254.64	28,723.91
	Number of pigs (in thousand)	216	7,492.50	7,743.45	73.72	27,113

Years	Number of countries with data on antibiotic consumption
1997	15
1998	18
1999–2005	20
2006–2007	17

DDDs defined daily doses, *GDP* gross domestic product, *PPP* purchasing power parity

Data sources: European Surveillance of Antimicrobial Consumption (ESAC), OECD, Eurostat, and European Observatory of Health Systems and Policies

consider a single country, for instance Belgium. Huttner et al. [12] register that this country implemented a national campaign from 2000, except in winter 2003–2004. Consequently, our policy dummy assumes value 1 between 2000 and 2002 and between 2004 and 2007, and 0 in 2003. Alternatively, we consider a different policy indicator ($POLICY_2$). This is a dummy variable that takes the value 1 in the years of campaign adoption and in the years post-campaign, and 0 in years before the campaign is adopted. To complete our example, the policy dummy ($POLICY_2$) for Belgium takes the value 1 in all years from 2000 until 2007. The construction of these indicators has been facilitated by some similar characteristics of the campaigns such as their main message. However, as shown by Huttner et al. [12], other characteristics (e.g. the intensity of the campaigns) may vary significantly, which is not taken into account by our policy measures. We are also aware that our policy indicators may suffer from other limitations discussed in the review by Huttner et al. [12]. Some campaigns were not included in the review due to limitations in the search method or available information. Since we focus on national campaigns, we exclude campaigns implemented at regional level within a country (e.g. Emilia Romagna for Italy). Moreover, we cannot exclude that some countries adopted strategies other than public campaigns to reduce antibiotic consumption. Although we are aware of possible missing data to correctly identify all types of campaigns, these missing policies could be highly heterogeneous and, consequently, hardly measurable by means of appropriate variables. However, we do not see specific reasons why excluded campaigns should affect the control group of countries differently from the treatment group.

Since almost all countries implemented some policies to increase public awareness of antibiotic use from 2000, and in order to have a satisfactory control group, we excluded Iceland from the final dataset. Iceland adopted a campaign at the beginning of the period considered (1997 and 1998). The final dataset is an unbalanced panel dataset with 153 observations for Model 1 and 122 observations for Model 2. Since information on instrumental variables for policies is not available for all countries or years, the number of observations in Model 2 is lower. Estimations are performed by means of the statistical software STATA (version 11.1) developed by the StataCorp LP (College Station, TX).

Results

Our initial tests indicate that the OLS model can be rejected in favour of the fixed effects (FE) model.[11] The Breusch and Pagan Lagrangian multiplier test indicates that there are other effects than those captured by the exogenous variables in OLS regressions. The *F* test that constant terms are homogeneous across regions and time periods is also rejected. Moreover, the Hausman test suggests that the FE approach should be preferred to the random effects approach. The parameter estimates obtained using the DD estimator are reported in Table 2 (Model 1). Table 2 also reports the results of the two-stage least squares regression (Model 2) to correct for endogeneity.

As explained in "The empirical approach", all regressions include country fixed effects and year dummy variables. The results are stable and no structural differences were observed across the two models. Time dummies do not show any significant increase in the use of outpatient antibiotics per capita over time. In both models some coefficients are statistically significant and carry the expected sign. The relatively low number of statistically significant coefficients of socioeconomic variables could be explained, as suggested by Cameron and Trivedi [34], by the low within variation of these variables. The number of significant coefficients increases in the two-stage least squares model. Although this is worth noting, we remind the reader that our main goal is to estimate the coefficient of the policy dummy variable using a DD approach.

Effects of policies

The effects of antibiotic policies on outpatient antibiotic consumption are reported in Table 2. As explained in "The empirical approach" section, the control group consists of all the countries that did not undertake a public campaign to improve antibiotic use during 1997–2007. Thus, when we study the effects of public campaigns, the controls are the countries that did not adopt any campaign. We remind the reader that our control and treatment groups can change in each year since countries did not implement campaigns at the same time. Moreover, our estimation method exploits both the within-country variation as well as the comparison between groups.

The variable $POLICY_1$ is a dummy variable equal to 1 in the year of adoption of the campaign and 0 afterwards for the treated countries only. Its estimated coefficient captures the average effect of the policy. In line with our expectations, policy coefficients are significant in both models. The dummy variable shows a negative sign, which suggests that the implementation of public campaigns leads to a reduction in the use of antibiotics. One could speculate that individuals informed about the social implications of antibiotic use are more likely to use antibiotics carefully.[12]

Using the estimated coefficients of $POLICY_1$ in Model 1 and Model 2, we observe that the implementation of a public campaign may reduce antibiotic consumption by 1.3–5.6 defined daily doses per 1,000 inhabitants. This represents an impact of roughly 6.5–28.3 % on the mean level of antibiotic use in Europe between 1997 and 2007.

Our results cannot be compared easily with earlier findings in the literature. There is no comparable study we are aware of on the association between outpatient antibiotic use and public campaigns. The few papers that have investigated the correlation between antibiotic policies and antibiotic use either focus on specific countries or do not use quantitative methods, as presented in "Public policies aiming to reduce antibiotic consumption" section.

Other effects of covariates

The coefficient on physician density deserves some comment since it is positive and significant in Model 2. An increase in physician density by 0.1 % increases antibiotic consumption by 3.13 DID. This result might suggest some evidence of supply-induced demand. However, the assumption of a positive relationship between the amount of prescriptions and the number of doctors per capita does not necessarily follow. It is known that countries with a greater number of doctors per inhabitant use more

[11] Preliminary OLS regressions show an R^2 adjusted of 0.59. The goodness-of-fit increases slightly with the inclusion of temporal dummy variables. The *F* test is 24.58 (12.51 with time dummies). This suggests that overall regressors has a significant impact on the dependent variable. Moreover, the mean variance inflation factor is lower than 3. Finally, the Shapiro-Wilk test as well as the Jarque-Bera test for normality of errors cannot be rejected using the conventional 95 % level of significance.

[12] The results are confirmed if we include in the model the dummy variable $POLICY_2$ instead of $POLICY_1$. This takes a value equal to 1 in the years of campaign adoption as well as in the years post-campaign. The rationale of this indicator is that policies may take some time to show their effects or may have carryover effects. Although $POLICY_1$ seems to reflect more closely information collected in the review by Huttner et al. [12], $POLICY_2$ may provide a robustness check of our results based on $POLICY_1$. Since countries in the treatment group are assumed to implement policies for longer periods under $POLICY_2$ than under $POLICY_1$, the effect of policies could be biassed. We find that the estimated coefficients of $POLICY_2$ are slightly less significant than the coefficients of $POLICY_1$, which confirms the results and may suggest that policies have carryover effects beyond the year of policy implementation.

Table 2 Parameter estimates for differences-in-differences models of antibiotic consumption

Variables	Model 1 (fixed effects)			Model 2 (2SLS)		
	N = 153			N = 148		
	Coefficient	SE	P value	Coefficient	SE	P value
Constant	14.23987	10.84761	0.205	–	–	–
Y	−0.000006	0.000076	0.937	0.000034	0.000104	0.742
INF_{t-1}	−0.026964	0.131664	0.840	0.133130	0.159960	0.405
DPH	2.675357	1.745052	0.142	2.037980	1.287773	0.114
POP_1	−0.149416	0.315799	0.642	0.939162	0.725505	0.195
POP_2	−0.504244	0.330286	0.143	−0.518750	0.269742	0.054
POP_4	1.739930	0.347879	0.000	1.732788	0.423205	0.000
POP_5	−2.234688	1.780598	0.225	−0.977550	1.484881	0.510
P	−0.047670	0.035893	0.200	−0.049779	0.041672	0.232
$POLICY_1$	−1.278340	0.569823	0.037	−5.601114	2.320015	0.016
dt_1	−0.665328	1.892860	0.729	−3.036271	2.490521	0.223
dt_2	−1.319394	1.816378	0.476	−3.069590	2.242963	0.171
dt_3	−1.579900	1.647785	0.350	−2.352010	1.796504	0.190
dt_4	−1.062183	1.482873	0.483	−1.564164	1.528752	0.306
dt_5	−1.516438	1.239671	0.236	−1.655402	1.324945	0.212
dt_6	−1.278312	0.944794	0.192	−1.682968	1.067949	0.115
dt_7	−1.827697	0.770119	0.028	−1.606953	0.800390	0.045
dt_8	−0.848300	0.661260	0.215	−1.095777	0.693138	0.114
dt_9	−1.381653	0.505751	0.013	−0.811843	0.537460	0.131
σ_u	5.900249	–	–	–	–	–
σ_e	1.152637	–	–	–	–	–
ρ	0.963240	–	–	–	–	–

Y Income per capita, INF_{t-1} mortality for infectious diseases lagged one year, *DPH* density of doctors, POP_1 population under 14, POP_2 population 15–24, POP_4 population 65–79, POP_5 population over 80, *P* price of pharmaceuticals, $POLICY_1$ implementation of public campaigns, $dt_1 - dt_9$ time dummies, σ_κ standard deviation of common residuals, σ_ε standard deviation of unique (individual) residuals, ρ variance not explained by differences across entities

antibiotics than countries with a smaller number of doctors per inhabitant [35], and that doctors who spend more time with their patients prescribe fewer antibiotics [36].

Although physicians are more informed than patients about drug resistance and are ethically constrained to avoid unnecessary antibiotics, they may overprescribe antimicrobials either to meet patient's expectations or because they fear misdiagnosing bacterial infections [37]. Patients usually regard antibiotics as a valid alternative to anti-inflammatory drugs for colds or flu. They also suffer from poor information in relation to physicians and look for evidence of physician's quality. The physician's willingness to prescribe antibiotics may then appear as a mark of quality [38]. Patients may favour immediate treatment and the physician must decide between prescribing or persuading the patient that a delay is appropriate.

We found no significant effect of changes in average national income. Nevertheless, the coefficient of income is positive in both regressions. Positive income effects for antimicrobials are observed by Baye et al. [39] using US data, Filippini et al. [40] using aggregated Swiss data at small area level, and in a previous study on European country data with a shorter time period than ours, i.e. 2000–2005 [13]. Conversely, negative income effects are found by Filippini et al. [41] using Swiss data at Cantonal level. One possible explanation for the relatively low value of the coefficient of income is that the increasing concern on the effects of bacterial resistance from the 1990s may have reduced income elasticity of outpatient antibiotic expenditure over time. Another explanation is that high-income countries are more likely to substitute other treatments for antibiotics, ceteris paribus.

The pharmaceutical price index is not significant. Generally, antibiotics are perceived as necessary in the case of presumed bacterial infections. Furthermore, antibiotics are purchased under doctor's prescription and the price share borne directly by the patient is usually very low.

Even without insurance coverage, the cost to the patient would be low since most antibiotics are relatively cheap and have to be taken for a short time. This may imply that individuals are not very responsive to changes in antibiotic prices, although price demand elasticities may also vary according to the type of antibiotic therapy, e.g., newer and more expensive antibiotics are more price elastic than traditional ones [42].

The coefficients of mortality rate for infectious diseases are not significant. As for demographic covariates, we observe only a significant association between the proportion of individuals aged 65–79 and increasing levels of antimicrobial consumption. This result seems to support the hypothesis that increasing prevalence of chronic health problems as people grow older may determine an increase in the utilization of health care goods and services, including drugs. Di Matteo and Grootendorst [43] also observe a slightly significant increase in drug expenditure in the population between 64 and 74, although the evidence is not confirmed by the more recent study by Di Matteo [44].

Conclusion

Several studies show that a decrease in the use of antibiotics may reduce levels of bacterial resistance. During the last decade, many European countries undertook public health programs to optimise antibiotic use in the community. Nevertheless, the effectiveness of policies encouraging a rational use of antibiotics is still unclear. In particular, the influence of public campaigns on antimicrobial usage, and therefore on bacterial resistance, has not been assessed accurately [12].

In this paper, we estimated the impact of antibiotic policies in Europe by means of a differences-in-differences methodology. The approach allowed us to identify the effect of campaigns on antibiotic use by relating differential changes in antibiotic consumption across countries and over time to changes in the relevant policy variables.

The results provide some evidence that public campaigns represent an effective strategy to reduce the use of outpatient antibiotics. Countries that adopt public campaigns succeed in terms of reducing their levels of antibiotic use over time. Further research is necessary to assess the impact of policy interventions on the levels of bacterial resistance through the reduction of antibiotic consumption.

Appendix

See Tables 3 and 4.

Table 3 Mean values for the whole period for countries that did not implement any public campaign between 1997 and 2007

Variables	Austria	Czech Republic	Denmark	Finland	Hungary	Ireland	Italy	Netherlands	Poland	Slovakia	Sweden	United Kingdom
Outpatient antibiotic consumption (in DID)	13.00	17.45	13.53	18.43	18.55	19.26	25.38	10.15	20.90	25.72	15.22	15.37
Per capita income in US$ in PPP (Y)	30,059.27	17,085.73	30,387.73	27,702.82	14,239.09	32,264.73	26,661.36	29,944.73	11,606.36	12,996.64	28,189.09	28,044.00
Price index of pharmaceuticals (P)	104.66	65.58	122.94	100.83	69.71	111.42	110.99	110.08	58.50	57.13	92.84	93.39
Proportion of population												
Under 14 (POP_1)	16.69	15.97	18.5	17.95	16.39	21.49	14.25	18.46	18.55	18.75	18.07	18.65
15–24 (POP_2)	12.12	14.68	11.55	12.55	14.16	16.34	11.39	12.01	16.55	16.67	11.95	12.57
25–64 (POP_3)	55.50	55.47	55.02	54.23	54.23	50.99	55.73	55.75	52.38	53.09	52.69	52.88
65–79 (POP_4)	11.84	11.20	10.95	11.67	12.26	8.60	14.16	10.45	10.26	9.37	12.17	11.73
Over 80 (POP_5)	3.85	2.69	3.99	3.58	2.96	2.58	4.48	3.34	2.24	2.10	5.14	4.17
Density of doctors per 1,000 inhabitants (DPH)	4.06	3.39	3.08	2.52	3.02	2.52	4.06	3.39	2.28	3.10	3.26	2.14
Mortality rate for infectious diseases (INF)	3.99	2.7	7.25	4.98	4.84	4.46	6.45	7.93	5.60	3.51	6.58	6.38
Density of foreign population (per km^2)	9.18	2.32	4.92	1.93	1.37	5.46	3.28	4.24	0.10	0.50	5.42	4.60
Animal production (in thousand)												
Tons of cow's milk	2,655.07	2,547.72	4,478.94	2,393.33	1,718.13	5,215.02	10,263.16	10,670.97	7,683.32	977.76	3,221.65	14,189.76
Number of pigs	3,362.86	3,319.28	12,696.18	1,449.17	4,651.46	1,721.61	8,861.79	11,756.32	18,113.61	1,389.27	1,964.05	5,759.07

Data sources: ESAC, OECD, Eurostat, and European Observatory of Health Systems and Policies. *DID* Defined daily doses per 1,000 inhabitants per day, *PPP* purchasing power parity

Table 4 Mean values for the whole period for countries that implemented public campaigns between 1997 and 2007

Variables	Belgium	France	Germany	Greece	Iceland	Luxemburg	Norway	Portugal	Spain
Outpatient antibiotic consumption (in DID)	24.65	30.97	13.57	29.67	21.68	25.75	15.60	24.19	20.24
Per capita income in US$ in PPP (Y)	28,831.18	27,292.64	27,447.00	23,109.73	31,193.55	56,536.45	37,703.82	18,474.00	23,077.73
Price index of pharmaceuticals (P)	103.40	87.98	115.58	73.52	145.60	102.82	120.42	96.68	78.15
Proportion of population									
Under 14 (POP_1)	17.45	18.75	15.15	15.15	22.88	18.65	20.91	16.06	14.84
15–24 (POP_2)	12.15	13.07	11.39	13.55	15.04	11.49	12.3	13.83	13.76
25–64 (POP_3)	53.52	52.06	56.15	54.15	50.44	55.67	52.34	53.70	54.77
65–79 (POP_4)	12.95	11.84	13.32	13.89	8.76	10.98	10.66	12.88	12.66
Over 80 (POP_5)	3.93	4.13	4.01	3.27	2.85	3.15	4.43	3.52	3.97
Density of doctors per 1000 inhabitants (DPH)	3.91	3.35	3.32	4.63	3.53	2.43	3.22	3.23	3.27
Mortality rate for infectious diseases (INF)	9.63	10.21	7.98	4.55	4.75	9.36	7.63	18.20	12.02
Density of foreign population (per km^2)	8.52	5.57	8.77	4.69	3.34	38.25	4.24	3.16	5.95
Animal production (in thousand)									
Tons of cow's milk	3,011.70	23,382.87	27,156.27	672.42	117.47	258.29	1,607	1,861.47	5,826.78
Number of pigs	6,755.28	15,333.65	26,256.33	967.95	69,758.09	79.60	93.36	2,346.33	23,558.74

Data sources: ESAC, OECD, Eurostat, and European Observatory of Health Systems and Policies *DID* defined daily doses per 1,000 inhabitants per day, *PPP* purchasing power parity

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