WORKING PAPERS

N° 1457

July 2023

"Antibiotic Demand in the Presence of Antimicrobial Resistance"

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June 2023‡

Abstract

Antimicrobial resistance (AMR) increases hospital stays, medical costs and mortality. Antibiotic consumption and resulting selective pressure on bacteria can create AMR. We study the role of AMR on changes in prescriptions of antibiotics in France for treating bladder inflammation (cystitis) using a representative sample of general practitioners between 2002 and 2019. Effects of resistance on demand and substitution behavior are identified via a random coefficient logit model, controlling for the endogeneity of resistance using antibiotics sales in veterinary medicine. As resistance increases, physicians substitute to other drugs, and we test whether physicians consider predictable resistance evolution in their decisions. We perform counterfactual analysis assessing the impact of decreasing veterinary use of antibiotics and limiting fluoroquinolone use to treat cystitis. Both policies reduce resistance against fluoroquinolones but have opposite effects on substitution behavior and consumer surplus. Finally, we propose a method for the optimal pricing of rapid bacterial detection and antibiotic susceptibility testing.

Keywords: health, physician prescription, antimicrobial resistance, diagnostic test, demand.
JEL Codes: I10, D12, L11, C25

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‡The authors gratefully acknowledge funding from the Agence Nationale de la Recherche under grant Antibionomics - 16-CE36-0004-02 and ANR-17-EURE-0010 (Investissements d'Avenir program), funding under the "PSPC" call for projects operated on behalf of the French government by Bpifrance as part of the "investments for the future" program (PIA) ARPEGE and funding from the TSE-P Health Center whose lists of sponsors can be found at https://www.tse-fr.eu/health. We thank GERS CEGEDIM for access to the THIN data. We thank Jérôme Adda, Federico Ciliberto, Isabelle Tongio, François Lacoste, seminar participants in Toulouse and conference participants at the IIOC 2022 conference in Boston, EU Health Economics Association (EuHEA) Conference 2022 in Oslo, the 2022 European Association for Research in Industrial Economics (EARIE) Annual Conference in Vienna, and the CEPR Conference in Health Economics in Toulouse for useful comments.

1 Introduction

Antibiotic resistance poses an immense threat to modern medicine. The consequences of infections becoming untreatable with antibiotics range from longer hospital stays and riskier surgeries to death in the most severe case. Recent estimates by Murray et al. (2022) attribute 1.27 million deaths to bacterial antimicrobial resistance (AMR) in 2019 worldwide (with 4.95 million associated with bacterial AMR)[1]. There are two reasons for the gravity of the situation. First, there are negative consumption externalities (Ventola, 2015). The higher antibiotic use is, the faster resistance develops. This effect is also present in antimicrobial usage in livestock production and agriculture, exacerbating the problem[2]. Second, a steady decrease in the number of new antibiotics developed and approved emphasizes that the consequences of antibiotic resistance will continue to be a concern[3] (CDC, 2013). Therefore, it is important to preserve the antibiotics that are currently effective by limiting their consumption. Action plans from health authorities worldwide recognize this issue and are intended to slow the development of resistance by limiting externalities through antibiotic stewardship programs. To design such programs, we first need to understand to what extent physicians consider bacterial resistance when treating an infection. This would help to assess the effectiveness of policies intended to provide richer information on resistance or that limit the use of certain antibiotics. We address this question by studying antibiotic prescriptions for cystitis (bladder inflammation), one of the most common reasons for antibiotic prescription in the outpatient setting in France.

France has been struggling with high resistance rates and consumption levels, leading to campaigns to encourage antibiotic use only in necessary cases such as a nationwide campaign called "Antibiotics are not Automatic" in 2002. Sabuncu et al. (2009) shows a decrease in antibiotics use, especially in pediatric cases, following the campaign. Carlet et al. (2020) questions the continuation and preservation of this decrease after the campaign. Efforts to decrease the veterinary use of antibiotics have also been on the agenda for the last decade because it represents a serious threat to the effectiveness of the measures taken regarding human

[1]For the European Union/European Economic Area, estimates by WHO Regional Office for Europe/European Centre for Disease Prevention and Control (2022) predict that each year 670,000 resistant infections lead to 33,000 deaths

[2]National- or multinational/regional-level plans against AMR address the problem with one health approach, acknowledging the links between actions regarding animals (such as farming practices), agriculture and the environment, and people. Examples include France (`https://solidarites-sante.gouv.fr/IMG/pdf/brochure_mesures_innovantes_lutte_atbr-en_vf.pdf` (14/08/2022)) and the US (`https://www.cdc.gov/onehealth/in-action/combating-ar-in-people-and-animals.html` (14/08/2022)) among many others.

[3]There is consensus that additional incentives for innovation against AMR are needed, and various incentive policies for different stages of the research and development of antibiotics have been proposed (Dubois et al., 2022; Majewska, 2022; Simpkin et al., 2017).

consumption (Laxminarayan et al., 2015). In 2010, France and the Netherlands were leading countries in agricultural consumption of antibiotics. In the past decade, there have been two consecutive campaigns named EcoAntibio during 2012-2016 and 2017-2021 that target this problem in France. The first met the goal of reducing antimicrobial use by 25%. The second plan also set a goal of reducing use in specific classes such as fluoroquinolones and third- and fourth-generation cephalosporins, which are crucial resources for human medicine (ANSES, 2021). France has also taken action on incentivizing physicians to prescribe antibiotics appropriately by attaching financial rewards to issuing fewer antibiotic prescriptions overall and to broad-spectrum antibiotics. To understand how these policies interact and to provide a view of stewardship programs' outcomes, it is important to understand the role of AMR in curbing treatment decisions and the demand for the available antibiotic drugs.

In this paper, we identify physicians' response to AMR in their prescriptions for cystitis using prescription data in France from 2002 to 2019, a period long enough to observe meaningful variation in resistance. We focus on this specific infection because i) it is one of the most common reasons for antibiotic prescription, ii) in most cases it is caused by the bacteria Escherichia coli (E. coli), and iii) the increase in extended-spectrum beta-lactamase (ESBL) producing E. coli is a concern since it leads to multi-drug resistant bacteria (Martin et al., 2016). Therefore, modeling physicians' choices in this diagnostic allows us to abstract from the physician's expectation of what bacteria caused the disease, and consequently, to directly use the resistance of E. coli to identify the impact.

We first estimate a discrete choice model for differentiated products à la Berry (1994) and Berry et al. (1995) where bacterial resistance to antibiotics serves as an observable product characteristic and enters the utility function. We consider two information models in terms of how the decision-maker takes bacterial resistance into account. We test the model where physicians only account for the publicly known previous-year resistance level against the model where they use an expected value of resistance for the current year taking into account the antibiotic consumption of humans and animals in addition to the previous-year resistance level. We fail to reject the null that physicians consider the expected resistance instead of the information on past resistance only. Estimating demand, we control for the endogeneity of prices and advertising by instrumenting with competition measures and BLP-type instruments. As we also have a

potential simultaneity problem between demand and resistance, we leverage the link between antibiotic use in animals and bacterial resistance in humans. As mentioned above, France introduced two consecutive campaigns and regulations[4] that generated substantial exogenous (to human consumption) variations in sales of antibiotics for animal production over time.

Our results indicate that physicians substitute away in response to an increase in resistance. Moreover, the degree of substitution varies by region. We also identify a negative price impact with heterogeneity, positive returns to advertisement and a preference for nongenerics. This is because during our sample period, payments to general practitioners started to include performance-based bonuses in addition to fixed visit fees. We also control for the financial incentives introduced under this remuneration based on public health objectives and find the expected effects: *i*) increasing the share of generics prescribed and *ii*) decreasing the share of certain groups of antibiotics.

We also estimate a model of resistance evolution where resistance depends on past usage, past resistance and antibiotic use by humans and animals and identify a positive correlation between past antibiotics usage and resistance. Then, using our demand estimates and resistance evolution model, we study the impact of two policies: *i*) banning fluoroquinolones for the treatment of uncomplicated cystitis and *ii*) minimizing the use of fluoroquinolones in animals. The first policy changing prescriptions then impacts bacterial resistance and subsequently even more prescriptions. The second policy first reduces resistance rates by diminishing antibiotic use in animals and then affects prescriptions due to the lower resistance. When banning fluoroquinolones, we find that physicians substitute not only toward the most valued narrow-spectrum alternative but also to other broad-spectrum antibiotics. Consumer surplus per prescription decreases because, on average, the decision makers (patients and physicians) value broad-spectrum antibiotics more and fluoroquinolones are an example of this case despite the increasing resistance. However, there are also long-term benefits of this policy since our model predicts that resistance decreases by 1 percentage point for the fluoroquinolones ban for cystitis and by 4 percentage points for the veterinary usage reduction, which will extend the life of the antimicrobial agent. However, when reducing veterinary use of antibiotics, physicians' prescriptions of fluoroquinolones increase as resistance is lowered. This increases consumer surplus but also

[4]In 2016, some groups of antibiotics belonging to third- and fourth-generation cephalosporins and fluoroquinolones were assigned a status of critical importance by a decree banning preventive use of these drugs and requiring susceptibility testing before curative use.

expenses. Finally, we provide a framework to analyze the added value of a diagnostic test at the point of care in terms of savings per prescription and the change in treatment success probabilities. Rapid antibiotic susceptibility testing with high accuracy is identified as one of the key tools in combating AMR [5]. Using our demand model, we provide a lower bound on the maximum price that would be optimal for an insurer to reimburse the test in a mandatory testing scheme. This maximum price depends on the probability of infection in society and the value of treatment and is a lower bound because of the additional long-term benefits of lower resistance.

Our work contributes to the literature on how physicians' prescription behavior is affected by the presence of AMR in the outpatient setting[6]. Earlier work provides evidence on substitution away from older drugs, which are potentially less effective, to newer and more expensive drugs in outpatient and intensive care units Filippini et al. (2009); Heister et al. (2017); Howard (2004). Howard (2004) introduces a choice model for antibiotics where resistance to penicillin appears as the main independent variable to capture such substitution behavior. The paper shows that information on an increasing level of resistance encourages substitution to newer alternatives. At a more aggregate level, Filippini et al. (2009) studies small-area variations using quarterly data on antibiotic sales in the outpatient setting in Switzerland in 2002. They proxy for resistance using the incidence rate of infections at the county level. In line with the conclusion of Howard (2004), the results indicate that the higher physicians' expectations of bacterial resistance are, the more they substitute toward newer and more expensive antibiotics. Bokhari et al. (2019) also study antibiotic demand from 2003 to 2013 in the UK using a discrete choice model of demand and supply. They study the role of spectrum in demand and consider different tax policies to address the gap in the prescription of narrow-spectrum antibiotics against broad-spectrum antibiotics. Therefore, they analyze the effects of taxes in the substitution across narrow- and broad-spectrum antibiotics, but they do not allow bacterial resistance to enter the utility of the patient–physician pair.

[5]For the French health context, see `https://sante.gouv.fr/IMG/pdf/brochure_mesures_innovantes_lutte_atbr-en_vf.pdf` retrieved on 21/06/2023. For the US context, see `https://www.cdc.gov/drugresistance/us-activities/national-action-plan.html`. Some recent reviews on testing include Gajic et al. (2022); van Belkum et al. (2020).

[6]In our setting, we can focus on the effects of resistance in isolation of other factors that might affect antibiotic prescription behavior. This is thanks to the regulations on physician payments in France and focusing on a disease that is almost always of bacterial cause. First, the physician payment system prevents any supply-side-driven effects on prescription drugs due to financial benefits to physicians such as those observed in Japan Iizuka (2007) or China Currie et al. (2014). Moreover, the gatekeeper system where each patient has a registered first-contact physician (usually a general practitioner) lets us assume away the effects of potential competition across physicians Bennett et al. (2015). Second, focusing on cystitis, which is a type of bladder infection, minimizes the risk of physician- or patient-driven abuse of antibiotics Currie et al. (2011).

Our contribution to the literature on antibiotic prescription decisions is threefold. First, our demand model incorporates a wide range of factors that affect the decision and therefore provides a more complete analysis. Moreover, our data allow us to utilize not only cross-section variation but also time-series variation in identifying the effects, especially that of resistance on demand. Second, we consider two information models of how physicians account for bacterial resistance. It would be important for informational campaigns to differentiate between the two models because the response of a physician's to the information would differ. Third, we consider the endogeneity of resistance. As resistance develops due to the consumption of antibiotics and the consumption of antibiotics is also affected by resistance, we face a simultaneity problem. We control for endogeneity by using veterinary use of antibiotics, which relates to the second stream of literature we add to.

We also contribute to the literature on AMR evolution and its links to the consumption of antibiotics in humans and animals. There have been small-scale studies providing evidence on animal-originated resistant bacteria in humans (Hammerum and Heuer, 2009; Landers et al., 2012). A recent report by European Centre for Disease Prevention and Control (ECDC), European Food Safety Authority (EFSA) and European Medicines Agency (EMA) uses EU-wide surveillance networks for 2016–2018 to document the relationships between antibiotic use in farm animals and resistance in Europe. The findings for E. coli are mixed for different groups of antibiotics. They present some correlation between the use of third- and fourth- generation cephalosporins, fluoroquinolones and other quinolones and aminopenicillins in animals and resistance in humans. At a larger scale, Adda (2020) studies the relationship between bacterial resistance and antibiotics used in both humans and animals in the US across counties, time periods and multiple bacteria. He identifies a positive correlation with human consumption but no significant relation with antibiotic use in animals, which also depends on animal farming regulations and population density. In our analysis, we model E. coli resistance as a function of past resistance and antibiotic use in humans and animals. In line with the dynamics of the epidemiological model (Laxminarayan and Brown, 2001), we find strong time dependence of resistance. Moreover, we identify a positive correlation between resistance and past antibiotic use in humans and animals.

Our last contribution to the literature is to develop within our structural model a method for evaluating

the optimal pricing of rapid bacterial detection and antibiotic susceptibility testing using the role of information on resistance in decision making.

The remainder of this paper is organized as follows. Section 2 describes the different data sets we use and provides details of variable construction. Section 3 provides the framework for demand estimation, our methodology for testing the role of antibiotic resistance in physician prescription and the empirical results. Section 4 presents the results of counterfactual policies. Section 5 describes the evaluation of rapid diagnostic tests, and Section 6 concludes the paper.

2 Data

In our analysis, we employ multiple data sources to i) observe choice decisions regarding antibiotics for the treatment of cystitis, ii) measure prices and aggregate sales of antibiotics, iii) account for bacterial resistance in demand and iv) account for advertising. Regarding demand, we use patient-level proprietary data from the company Cegedim (Cegedim Health Data) that consist of prescription records from a panel of physicians covering the period from 2002 to 2019. Then, we use publicly available reimbursement data from the national French Health Insurance to measure total drug-level antibiotic use in France and the prices of drugs that are uniform across pharmacies by regulation. To account for bacterial resistance, we employ data made public by the French observatory (ONERBA). As explained in Section **model**, resistance evolves endogenously with antibiotic usage among humans and animals. Thus, we also use data on antibiotic use in livestock production provided by the French Agency for Food, Environmental and Occupational Health & Safety ANSES (2021). Data on veterinary sales of antibiotics serve two purposes. First, they are used in the demand estimation to control for the endogeneity of resistance. Second, they serve as explanatory variables in predicting resistance in counterfactual scenarios. Finally, we use proprietary data on advertising from IMS Health (IQVIA) Global Promotional Track for France.

2.1 Data on Antibiotic Prescriptions

The proprietary patient-level prescription data cover the period from 2002 to 2019. From 2002 to 2009, the data consist of an exhaustive record of prescriptions and visits to a representative panel of approximately 400 general practitioners who have over 1.5 million patients registered (these data were used in Dubois and

Tunçel (2021) to study the prescription of antidepressants following a drug warning). From 2009 to 2019, the representative sample size increased to approximately 2002 general practitioners. Each prescription record is identified by a patient and a physician identifier, date, diagnostic, and product code of the drug prescribed [7]. Moreover, the age and gender of both physicians are patients are observed together with region of operation for physicians and chronic diseases for patients.

Table 1: Top 5 diagnoses with antibiotic prescription

2002 - 2008		2014 - 2019	
Diagnostic	Perc. (%)	Diagnostic	Perc. (%)
Acute nasopharyngitis	13.79	Bronchitis	12.5
Bronchitis	11.12	Acute pharyngitis	12
Acute Sinusitis	5.70	Otitis	7.55
Sore throat	4.53	Acute nasopharyngitis	6.13
Cystitis	4.52	Cystitis	6.06

Note: For the 2009-2013 period, we only have access to the subset of prescriptions with a cystitis diagnostic, so we cannot check the top diagnoses with antibiotic prescription during that period. However, we have 252,508 prescriptions for that period for cystitis.

We focus on cystitis (bladder infection) for three main reasons. First, it is one of the most prevalent infections in the outpatient setting. Table 1 presents the most prevalent diagnoses for antibiotic prescriptions, which are acute nasopharyngitis and bronchitis. However, they are usually caused by viral infections against which antibiotics have little to no effect. They are followed by sinusitis and otitis, which could be viral or bacterial in origin. Cystitis is considered to be bacterial, and guidelines suggest the use of antibiotic therapy[8]. Second, the bacteria responsible for cystitis is E. coli in 80% of the cases (Kahlmeter, 2000; Rossignol et al., 2017). Since different antibiotic groups are prescribed for various bacteria (with overlaps), knowing which bacteria is the most likely responsible helps us to identify the role of resistance on the prescription behavior of physicians by abstracting from uncertainty over the type of bacteria. Finally, the increasing prevalence of extended-spectrum β-lactamase-producing E. Coli is a growing concern in France (Martin et al., 2016; Nicolas-Chanoine et al., 2013) because these bacteria are difficult to treat and complicate the treatment of infections such as urinary tract infections and cystitis. Therefore, policies targeting better treatment of E.

[7]The medical classification used is the International Statistical Classification of Diseases and Related Health Problems code (ICD-10) defined by World Health Organization. CIP7/CIP13 are the standard French drug identification codes that differentiate products at the box level. Two products with the same brand and active ingredient but different dosage and units are assigned different CIP codes. The data also include information on active substances and the corresponding Anatomical Therapeutic Chemical Classification System (ATC) Code.

[8]See recent guidelines from French Health Authority (HAS), accessed at `https://www.has-sante.fr/upload/docs/application/pdf/2021-08/fiche_memo_cystite_durees_antibiotherapies_.pdf` on 02 November 2022.

coli-caused infections and containing the resistance are very important.

When there is no information on the bacteria and/or on its susceptibility profile, the treatment of uncomplicated cystitis remains an empirical therapy based on the physician's guess. Until 2016, the only *recommended* test was still the urine strip test to confirm the bacterial infection (Caron et al., 2018). This test does not report the type of bacteria or the resistance profile of the bacteria causing the infection. For the cases of cystitis at risk of complication or recurrent cystitis, the recent guidelines suggest performing susceptibility testing if delayed treatment is possible and empirical treatment guidelines if delay is not possible. In this paper, we focus on uncomplicated cystitis and the role of bacterial resistance in the first-line (empirical) treatment to minimize the effect of the unobserved heterogeneity in complication risk and differing guidelines based on this risk.

In our sample, we retain only female patients from 16 to 75 years old (male patients represent 5% of cystitis diagnoses) without a cancer diagnostic (because their complication risk affects prescriptions) and exclude all off-label prescriptions (0.6% of the total prescriptions concern products with no authorized indication for cystitis). We also drop observations where multiple antibiotics are prescribed to the same patient on a given date because there may be patient demand to accumulate stocks for future use (approximately 5% of total prescriptions).

To address recurrent cystitis cases, we identify a visit as an "initial visit" if there is no other prescription for cystitis or urinary tract infection in the preceding 30-day period. Visits following another prescription within the 30 days after the initial visit are defined as a "secondary" prescription. A secondary prescription could be a result of the failure of treatment due to bacterial resistance or simply due to misuse of antibiotics. To avoid any interference from this channel, we drop observations from secondary infections, which represent approximately 6.7% of all prescriptions.

Table 2 presents a summary of prescription shares by chemical substance between 2004 and 2019 (every three years). We observe that Fosfomycin and Norfloxacin are initially prescribed at a high rate, but later, especially after generic entry, Fosfomycin became the main treatment for cystitis with a more than 50% market share. While this is in line with the recommendations for uncomplicated cystitis cases due to high effectiveness and short treatment periods, the remaining antibiotics market shares do not necessarily follow

the order from the guidelines. For instance, Nitrofurantion is presented as a substitute in the guidelines before 2008 and was removed after 2008. Similarly, some critical groups of antibiotics, namely, Cefixime, Ciprofloxacin, and Ofloxacin (fluoroquinolones), which are last-resort treatments, have considerable market shares, especially in the early 2000s. Whether the physicians follow the guidelines in France for the treatment of urinary tract infections remains an open question with contradictory results (Denes et al., 2012; Piraux et al., 2021). In our demand estimate, we control for the changing guidelines with antibiotic-specific time effects[9].

Table 2: Prescription shares by chemical substance

Year	2004		2007		2010		2013		2016		2019	
Molecule (ATC5)	Branded	Generic	Branded	Generic	Branded	Generic	Branded	Generic	Branded	Generic	Branded	Generic
Cefixime	2.09		3.19		5.62	0.75	4.48	1.16	6.72	3.16	4.92	2.83
Ciprofloxacin	8.72	0.02	4.68	1.12	3.97	1.50	3.71	1.80	3.16	1.84	1.96	0.92
Fosfomycin	29.71		27.34		29.42	0.43	20.79	16.08	23.78	24.72	28.09	31.86
Lomefloxacin	7.78		17.56		17.70		14.56		9.41		3.64	
Nitrofurantoin		6.16		5.86		6.40		4.63		4.92		4.25
Norfloxacin	23.66	2.33	17.20	8.11	12.85	7.95	10.98	7.62		9.04		3.24
Ofloxacin	4.17	0.26	3.20	0.89	3.30	1.31	4.05	2.15	3.30	2.51	2.15	1.62
Sulfamethoxazole and trimethoprim	2.90	0.11	2.35	0.28	2.09	0.17	2.15	0.22	1.97	0.28	1.75	0.36

Notes: The molecules listed are the top 8 molecules by total market share and represent 92% of antibiotic prescriptions on the sample period. Generics entered after patent expiration dates that are September 2007 for Cefixime, September 2003 for Ofloxacin, April 2003 for Norfloxacin and August 2010 for Fosfomycin.

2.2 National Health Insurance Data on Antibiotic Expenses

We use national health insurance data to measure prices and total antibiotic usage. Antibiotics are prescription drugs in France and are partly reimbursed[10] by the mandatory national health insurance (Assurance Maladie, Medic'AM). We use the publicly available aggregate national data on expenses by the health insurance and quantities to recover the average prices of drugs. The data provide information for all years between 2002 and 2019 on the total value of reimbursements and the number of boxes (of drugs) reimbursed by CIP pharmaceutical code that can then be matched to individual prescriptions.

Table 3 shows the average prices per box (across products and brands) of the main chemical substances prescribed for cystitis. The regulation of prices on patent drugs and generics leads to a gap between the

[9]In our sample period, the guidelines were updated three times. The documents were accessed on September 02 2022 from `https://urgences-serveur.fr/IMG/pdf/LIVRET_ANTIBIOGUIDE_2002.pdf`, `https://www.infectiologie.com/UserFiles/File/spilf/recos/infections-urinaires-spilf.pdf`, `https://www.infectiologie.com/UserFiles/File/spilf/recos/infections-urinaires-spilf-argumentaire.pdf`, `https://www.has-sante.fr/upload/docs/application/pdf/2021-08/fiche_memo_cystite_durees_antibiotherapies_.pdf`

[10]Antibiotics are in the "major or important medical service" category and therefore are reimbursed at 65% at the baseline.

generic and branded price of the same molecule. For molecules that experience generic entry during the period of study, we observe significant price decreases.

Table 3: Average price by chemical substance

Year	2004		2007		2010		2013		2016		2019	
Molecule (ATC5)	Branded	Generic	Branded	Generic	Branded	Generic	Branded	Generic	Branded	Generic	Branded	Generic
Cefixime	12.20		12.18		8.96	8.47	8.85	8.28	8.56	7.21	8.27	6.68
Ciprofloxacin	25.23	15.03	22.21	12.34	23.21	11.63	23.03	10.35	20.16	9.60	10.38	8.37
Fosfomycin	12.16		12.14		8.73	6.48	8.38	6.55	6.48	5.01	5.68	4.36
Lomefloxacin	21.16		21.06		21.00		20.65		19.29		17.80	
Nitrofurantoin		2.42		2.42		2.42		2.58		2.28		2.68
Norfloxacin	7.05	5.87	5.57	4.82	6.29	4.64	6.23	4.69		3.63		3.35
Ofloxacin	16.44	15.96	11.02	11.97	11.25	11.75	11.27	11.56	10.21	10.47	8.04	7.43
Sulfamethoxazole and trimethoprim	3.13	2.78	2.78	2.28	2.75	2.26	2.93	2.45	1.98	1.52	2.09	1.66

Note: Price in € per box.

2.3 Data on antibiotic resistance

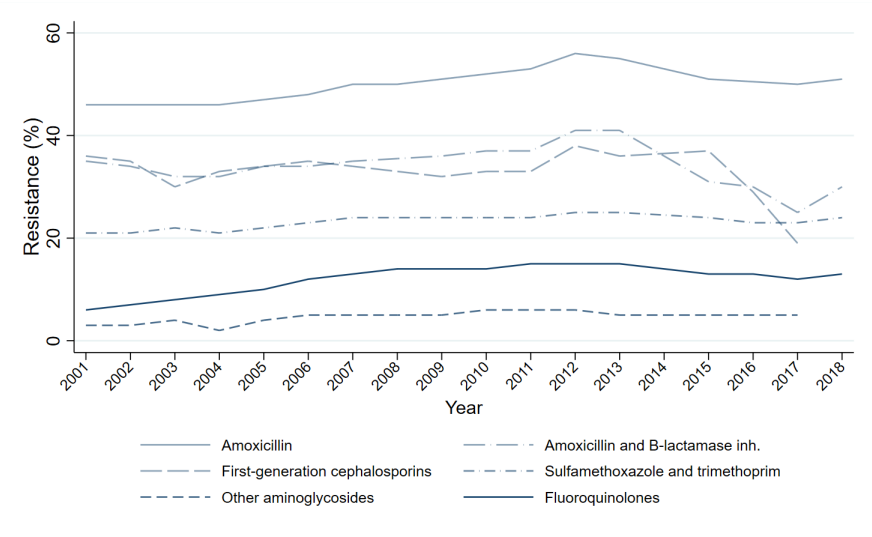
We use data on resistance from a French network called REUSSIR (Réseau Epidémiologique des Utilisateurs du Système SIR) that was founded in 1995. It provides data from France to the European Antimicrobial Resistance Surveillance Network (EARS-Net). It is a network of hospital laboratories. We extract data on E. coli's susceptibility to antibiotics reported by REUSSIR using reports of ONERBA from 2002 to 2018[11].

Figure 1 shows the evolution over time of the resistance of E. coli to each antibiotic with the average percentages of resistant strains tested of E. coli [12]. The most concerning element in this graph is the increase in resistance against aminoglycosides (Gentamicin) and fluoroquinolones, which are crucial last-resort antibiotics.

[11]There are ONERBA Activity reports, accessed at `http://onerba.org/publications/rapports-onerba/` on 27 October 2022.

[12]As the REUSSIR data do not include resistance for the year 2014, we impute the resistance value in 2014 by taking the average of the 2013 and 2015 values.

Figure 1: Resistance of E. coli against each antibiotic group



2.4 Data on Antibiotic Consumption for Animals

Data on antibiotic sales for animal use come from The French Agency for Veterinary Medicinal Products, Sales survey (ANSES, 2021). We used the sales by antimicrobial class since 1999 in mg of active ingredient per kilogram of animal body weight (mg/kg). The antimicrobial groups and corresponding ATC codes used for animal farming are listed in Table 4, which shows that there is a significant overlap between the chemical substances used for animals and humans that could pose a threat regarding the development of resistance.

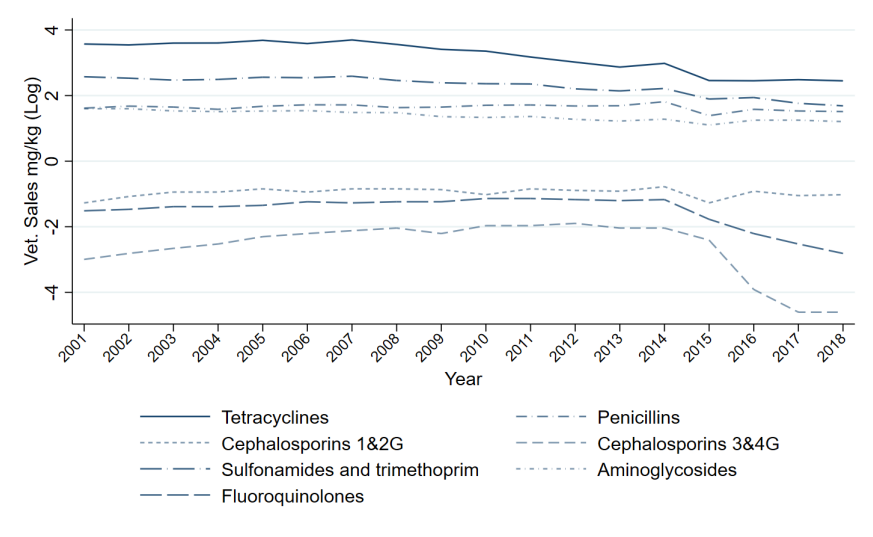
Table 4: List of antibiotics used in animals and their use in cystitis cases

Antibiotic Class	ATC Code	Prescribed for cystitis
Tetracyclines	J01AA	✓
Phenicols	J01BA	
Penicillins	J01C	✓
Cephalosporins 1&2G	J01DB	✓
Cephalosporins 3&4G	J01DD	✓
Sulfonamides+Trimethoprim	J01E	✓
Macrolides	J01FA	✓
Lincosamides	J01FF	✓
Aminoglycosides	J01G	✓
fluoroquinolones	J01MA	✓
Quinolones	J01MB	✓
Polymyxins	J01XB	✓
Pleuromutilins	J01XQ	

Note: List of antibiotics used in animals from ANSES (2021).

Figure 2 shows the data on sales of antibiotics (in log scale) for veterinary use, which are obtained from ANSES (2021). Regulations on antibiotic use were introduced with the EcoAntibio 2012-2016 and EcoAntibio 2017-2021 government plans and generated variation in animal usage of antibiotics that we can use to identify the link between animal use and resistance in humans.

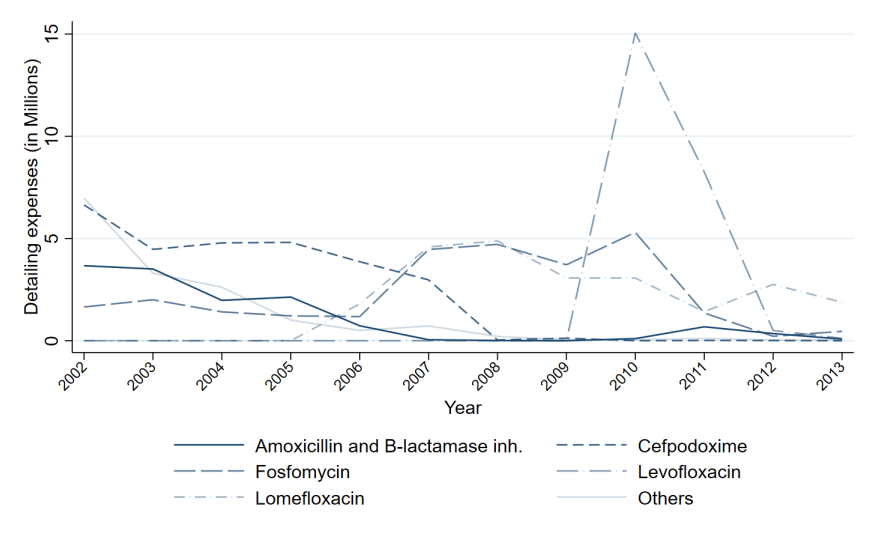
Figure 2: (Logs) Sales of antibiotics for veterinary medicine (Density – mg/kg)



2.5 Data on Detailing Expenses

Direct-to-consumer advertising of prescription drugs is strictly prohibited in France, but marketing activities to healthcare professionals (detailing) are allowed. We use monthly data between 2002 and 2013 from IMS Health Global Promotional Track on advertising expenses for each product. Figure 3 shows the total expenses aggregated at the molecule level (ATC5) by year for the top 5 advertised molecules and the total for others. We can see that firms engage more advertising at the time of generic entry than earlier in their patent protection period. Then, as generics enter, detailing expenses decline. It is also typical that detailing increases when a new indication is approved for an authorized drug. The detailing expenses on all drugs with the same active ingredient may promote the use of the antibiotic for any of the possibly allowed indications, including cystitis, and thus may generate variation in the prescription of each antibiotic.

Figure 3: Detailing expenses by molecule (millions € per year)



3 Demand Model and Estimation

3.1 Demand Model

We now define the demand model for antibiotic treatments in the case of cystitis. In the model, the decision maker chooses to prescribe the utility-maximizing medication among a set of alternatives without disentangling the physician and patient incentives. We model the random utility discrete choice of differentiated products following Berry (1994) and Berry et al. (1995); Nevo (2001). In our setting, within a region and given year, all physician–patient pairs with a cystitis diagnostic choose among products defined as a chemical substance[13] from a pharmaceutical company (brand)[14].

We specify the decision utility u_{ijlt} for patient i's prescription of product $j \in \{1, \ldots, J_t\}$ in period $t \in \{2002, ..., 2019\}$ and region l[15] as additively separable between various terms:

$$u_{ijlt} = \delta_{jlt} - \beta_i^p p_{jt} + \varepsilon_{ijlt} \tag{1}$$

where δ_{jlt} is the mean utility, p_{jt} is the price of product j and ε_{ijlt} is an idiosyncratic i.i.d. error term that follows an extreme value distribution. We allow the price disutility to be heterogeneous across consumers

[13] We create a specific group including antibiotics that are prescribed fewer than 1,000 times during the 18 year period because they have very small individual market shares. On average they represent 0.8% of the market in our sample.

[14] As there are many laboratories that produce generic products with very small market shares, we define a pseudo brand "Fringe". A brand is Fringe if the maximum market share observed in the 18-year period is less than 3%. The total average market share of Fringe ranges from 4% to 7% across years.

[15] In our specifications, there are eight regions: Center-East, West, Center-West, East, North, South-West, South-West, Paris (Ile-de-France)

with a random coefficient $\beta_i^p = \beta^p + \sigma_p \nu_i^p$ where β^p is the mean preference, σ_p captures the degree of variation in taste and $\nu_i^p \sim \mathcal{N}(0,1)$. We also specify an outside good utility with mean utility normalized to zero such that $u_{i0lt} = \varepsilon_{i0lt}$.

The mean utility is decomposed into an additively separable function with

$$\delta_{jlt} = x_{jlt}\beta + \xi_{ATC5(j)} + \xi_{Brand(j)} + \xi_t + \xi_l + \xi_{jlt}$$

where x_{jlt} is a vector of observable characteristics of product j except price, $\xi_{Brand(j)}$ is a brand fixed effect, ξ_t is a time fixed effect, ξ_l is a region fixed effect and ξ_{jlt} is an unobserved characteristic of product j at period t and region l that affects demand. Observable characteristics can be grouped into four categories. First, we observe resistance that varies annually at the chemical subgroup level[16]. We detail in Section 3.1.1 how we allow resistance to play a role in decision making. Second, we include detailing expenses among time-varying observable characteristics, a_{jt}. Third, during our sample period, the guidelines for prescriptions changed, with some molecules either being excluded from the guidelines or changing from first-line options to second-line or to the list of antibiotics to be prescribed when there is a complication risk. Finally, some antibiotics were affected by financial incentives that were introduced starting in 2012. In 2012, a pay-for-performance system was introduced in addition to the existing fixed-fee scheme for physician payments. The goal of the program is to address increasing healthcare costs and increase the standardization in provided care. There are two measures of performance that are relevant to our analysis. Physicians have been provided incentives to prescribe generics since 2012 and to prescribe less of certain antibiotics. The impact on generic prescriptions is captured by the generic dummy interacted with the post-2012 dummy. If we expect the program to work, the coefficient on the interaction variable should be positive. In addition to the generics bonus, following an update in 2017, physicians have also been given financial rewards for decreasing the prescription of certain groups of antibiotics to a preset level. We call this group the "at-risk" antibiotics, and it includes amoxicillin and clavulanic acid, 3rd and 4th generation cephalosporins, and

[16]Note that not every drug in our sample is included in the surveillance resistance data. Therefore, for some drugs, neither we nor the physicians observe resistance. The chemical subgroups presented in Section 2.3 cover approximately 66% of products in 2018, and 22% percent in shares. The coverage is higher at the beginning of the sample period and decreases with the increasing market share of fosfomycin, which is more than 50% at the end. The data collected from the different ONERBA networks indicate that resistance is low (approximately 1% –2%) (retrieved from `https://bigdata.onerba.org/` on 27 October 2022) and does not present time variation. Note that the demand model includes chemical substance (ATC 5) fixed effects, so that what matters is to capture the physician's information on the time variation of resistance.

fluoroquinolones. As we already include chemical substance fixed effects, we interact the chemical subgroups dummy with the post-2017 dummy and allow the effect to follow a trend. Similarly, we expect that if the incentives have been successful, prescriptions of these drugs should decrease.

Assuming ε_{ijlt} follows an extreme value distribution, the market share of product j, s_{jlt}, is:

$$s_{jlt} = \int \frac{\exp\left(\delta_{jlt} - \beta_i^p p_{jt}\right)}{1 + \sum_k \exp\left(\delta_{klt} - \beta_i^p p_{kt}\right)} d\phi\left(\nu_i\right) \tag{2}$$

where ϕ is the $\mathcal{N}(0,1)$ cumulative distribution function.

3.1.1 Information models

The mean utility of drug j may depend on the E. coli resistance to that drug j's chemical subgroup. To specify how, we explore two possible information models:

i) physicians consider the previous year's resistance level, which is public information, or

ii) physicians consider the expected value of resistance for the current year.

We denote the first case as the unsophisticated information model where physicians solely consider the available information on the previous year's resistance and the second as the sophisticated information model where physicians act upon the predicted resistance using the relevant available information. In both cases, we allow the national average resistance level to interact with regional dummies to capture the possible regional variation that may be known to physicians.

Unsophisticated Information Model Denoting by $r_{jt} \in [0, 100]$ the bacterial resistance of E. coli to drug j in year t, we use the lagged value of resistance as an observable characteristic and let the utility depend on log susceptibility $\log\left(100 - r_{jt-1}\right)$. This specification follows from the intuition that if a drug is certainly not working against a bacteria, it should not be considered a possible treatment option. Therefore, in our model, as resistance against drug j goes to 100%, meaning all the bacteria are resistant to treatment by drug j, susceptibility goes to 0. Hence, drug j effectively drops out of the choice set as the utility attached to it goes to $-\infty$. We then specify the unobserved demand shock ζ_{jlt} such that:

$$\xi_{jlt} = \beta_r^l \log \underbrace{\left(100 - r_{jt-1}\right)}_{\text{Susceptibility}} + \zeta_{jlt} \tag{3}$$

In the following, we denote by $susc_{jt} \equiv 100 - r_{jt}$ the susceptibility rate of the bacteria to drug j at time t.

Then, the estimation method of the demand model relies on the moment condition obtained from the mean independence between the demand shock ζ_{jlt} and instruments w_{jlt}.

Sophisticated Information Model In the sophisticated information model, we assume that the prescribers use the expected susceptibility of the E. coli bacteria. In this case, the demand shock will follow:

$$\xi_{jlt} = \rho\xi_{jlt-1} + \beta_r^l E_t[\log(susc_{jt})] + \zeta_{jlt} \tag{4}$$

where $E_t[\log(susc_{jt})]$ is unobserved to the econometrician but equal to the beginning-of-period-t expected susceptibility of E. coli to drug j conditional on the information available at t. Defining the prediction error as $\nu_{jt} \equiv \log(susc_{jt}) - E_t[\log(susc_{jt})]$, we can then identify β_r^l instrumenting $\log(susc_{jt})$ by the lag susceptibility $\log(susc_{jt-1})$, lagged total human usage of antibiotic j, q_{jt-1}^h, and lagged total animal usage of antibiotic j, q_{jt-1}^a (given the known possible relationship between resistance and antibiotic consumption (Adda, 2020; Austin et al., 1999)), in the following equation:

$$\xi_{jlt} = \rho\xi_{jt-1} + \beta_r^l \log(susc_{jt}) - \beta_r \nu_{jt} + \zeta_{jlt}$$

In this case, the estimation method of the demand model relies on the moment condition obtained from the mean independence between the demand shock ξ_{jlt} and instruments w_{jlt}.

Note that if one were willing to identify the demand parameters by directly introducing the expected susceptibility or resistance $E(\log r_{jt}|r_{jt-1}, q_{jt-1}^h, q_{jt-1}^a)$ obtained after the estimation of Equation (5), introducing the estimation error ν_{jt} in the ξ equation, one would need instrumental variables orthogonal not only to the demand shock ζ_{jlt} but also the resistance prediction error ν_{jt}.

3.2 Identification and Estimation

We estimate the demand model using standard GMM (Berry et al., 1995) based on orthogonality conditions between instrumental variables and unobservable demand shocks ζ_{jlt}. As prices may be correlated with unobserved demand shocks and create endogeneity problems, we use the following instruments to construct corresponding moment conditions: the number of different brands producing same ATC5 group products,

the number of different products in ATC5 group products, and their interactions with a generic indicator and years after generic entry. As we observe generic entry during the sample period in several chemical subgroups, the instruments serve as indicators of competition in the market and, more important, competition between products that have the same chemical substance.

Moreover, an endogeneity problem may also arise through the evolution of resistance to antibiotics. Indeed, antibiotic resistance is affected by the use of antibiotics due to resistant strains' selection over susceptible strains. Therefore, it is likely that the shocks to resistance and demand are correlated. To correct for endogeneity, we use antibiotic use in animals. Although there are debates on the roles of different channels (such as environmental, processing, farm environment, and human use) through which antibiotic use in farming affects antibiotic resistance in humans, many results indicate the presence of a link (Phillips et al., 2004; Tang et al., 2017). However, this may depend on the environmental context, the rules concerning farming and the population density, as for example, Adda (2020) does not find that the animal use of antibiotics affects bacterial resistance from human samples in the US. In Europe, a recent joint report (European Centre for Disease Prevention and Control et al., 2021) provides an exhaustive survey of the empirical relationship in Europe between AMR in bacteria from humans and food-producing animals. As each bacteria and antimicrobial pair behaves differently in terms of rate of resistance development and transmission, our focus is on the results from E. coli related cases. Ramchandani et al. (2005) supports the link between animal use of antibiotics and resistance in humans. Their results indicate that urinary tract infections (which nest bladder infections (i.e., cystitis)) could be a food-borne illness, as they find that the bacteria responsible for the infection in their sample are of animal origin. Hammerum and Heuer (2009) also explains the threat of resistant E. coli with animal origin and its relation to resistant E. coli infections in humans.

Thus, we instrument resistance using antibiotic sales for animal use. The identification of the demand parameters is achieved using instruments and unobserved product characteristics to form conditional moment conditions $E\left(\zeta_{jlt} \mid x_{jlt}^{exo}, w_{jlt}\right)$ where x_{jlt}^{exo} are the exogenous characteristics, and w_{jlt} consist of price and resistance instruments. To more precisely identify variances in the random coefficients, we use optimal instruments Chamberlain (1987); Reynaert and Verboven (2014) constructed as conditional expectations of

the derivative of the conditional moment restriction with respect to nonlinear parameters.

3.3 Demand Estimates

Table 5 presents the estimates of the demand model using a simple logit model in Columns 1 (without accounting for price endogeneity) and 2 (accounting for price endogeneity) and a random coefficient logit with sophisticated information in Column 3 and with unsophisticated information in Column 4. The first-stage regression of the endogenous variables on the instrumental variables is reported in Appendix A.2.1. The differences in the estimates indicate that the comovement of resistance and price over time and across products might also affect the results if the endogeneity of resistance is not accounted for.

The results show that price has a negative effect on mean utility and that there is significant heterogeneity in price sensitivity, which may come from the partial reimbursement of antibiotics by the national mandatory health insurance and the prevalence of complementary insurance (Grandfils et al., 2008) and from the incentives to prescribe cheaper generics provided by the national health insurance system. Advertising (detailing) has the expected positive effect. The effect of resistance on utility differs by region, although the differences are not significant, which is consistent with variation in antibiotic use across regions[17]. Our results are in line with Sabuncu et al. (2009), who documents that physicians are less sensitive to AMR in the North. We also observe that the decision-maker (physician–patient pair) values generics less than branded drugs on average. Then, regarding the coefficients capturing the impact of the pay-for-performance program, we find a positive impact of the policy incentivizing generic prescriptions and a negative impact for the policy discouraging the prescriptions of "at-risk" antibiotic groups[18]. Moreover, the impact of the pay-for-performance program appears to increase over time. A robustness check in Appendix A.2.2 shows that demand parameters are similar when using a quantity-weighted average price across different box sizes per product.

[17] `https://www.hauts-de-france.ars.sante.fr/antibioresistance-agir-tous-ensemble` (accessed on 14/01/2022) provides information on antibiotic consumption in defined daily dose/1,000 inhabitants in 2015 across regions. The highest consumption is observed in the North of France, followed by the Paris region and South-West.

[18] J01DD: Third-generation Cephalosporins, J01MA: Fluoroquinolones, J01CR: Amoxicillin and beta-lactamase inhibitor.

Table 5: Estimation results of the demand models

	Logit OLS	Logit 2SLS	RC Logit Sophisticated	RC Logit Unsophisticated
Price (β^p)	-0.012**	-0.155***	-0.482***	-0.455***
	(0.0041)	(0.0177)	(0.0586)	(0.0584)
Price SD (σ_p)			0.211***	0.199***
			(0.0224)	(0.0223)
log($susc_{j,t-1}$) Center-East	0.308	7.787***		8.438***
	(0.5880)	(1.5189)		(1.6723)
log($susc_{j,t-1}$) Center-West	0.119	7.344***		8.151***
	(0.5983)	(1.5295)		(1.6815)
log($susc_{j,t-1}$) East	-0.104	7.431***		8.189***
	(0.5881)	(1.5209)		(1.6738)
log($susc_{j,t-1}$) North	-0.566	6.700***		7.297***
	(0.5881)	(1.5247)		(1.6788)
log($susc_{j,t-1}$) West	-0.037	7.448***		8.002***
	(0.5891)	(1.5254)		(1.6808)
log($susc_{j,t-1}$) Paris	0.478	8.065***		8.835***
	(0.5876)	(1.5291)		(1.6831)
log($susc_{j,t-1}$) South-East	-0.495	6.759***		7.414***
	(0.5884)	(1.5239)		(1.6778)
log($susc_{j,t-1}$) South-West	0.095	7.631***		8.279***
	(0.5881)	(1.5240)		(1.6779)
Detailing (in Mil.)	-0.065**	0.388***	1.087***	1.143***
	(0.0228)	(0.0743)	(0.1540)	(0.1551)
Generic	-3.722***	-3.602***	-4.132***	-4.150***
	(0.0894)	(0.1049)	(0.1238)	(0.1247)
Guidelines				
Guidelines - First	0.081	0.245	-0.830***	-0.396
	(0.1670)	(0.1952)	(0.2290)	(0.2446)
Guidelines - Second	0.147**	0.122*	0.145*	0.171**
	(0.0521)	(0.0574)	(0.0626)	(0.0633)
Guidelines - Complicated	0.144***	0.016	-0.004	-0.084
	(0.0353)	(0.0419)	(0.0453)	(0.0493)
Pay-for-Performance				
Generic (post 2012)	0.829***	0.708***	0.637***	0.703***
	(0.0573)	(0.0747)	(0.0809)	(0.0826)
J01MA*Post 2017	-0.323**	-0.499***	-0.718***	-0.786***
	(0.1010)	(0.1118)	(0.1317)	(0.1335)
J01DD*Post 2017	0.110	0.133	-0.104	-0.066
	(0.1339)	(0.1459)	(0.1629)	(0.1641)
J01CR*Post 2017	-0.549**	-1.391***	-0.502**	-1.452***
	(0.1742)	(0.2497)	(0.1921)	(0.2756)
J01MA*Post 2017 Trend	-0.144*	-0.231**	-0.506***	-0.442***
	(0.0668)	(0.0747)	(0.0910)	(0.0921)
J01DD*Post 2017 Trend	-0.180	-0.237*	-0.319**	-0.334**
	(0.0927)	(0.1010)	(0.1122)	(0.1132)
J01CR*Post 2017 Trend	-0.166	-0.196	-0.268	-0.275
	(0.1163)	(0.1266)	(0.1397)	(0.1408)
N	8372	8372	8372	8372

Note: Standard errors in parentheses. Significance levels: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. All regressions include ATC 5 (chemical substance) and brand (pharmaceutical company), region and year fixed effects. We control for missing price and resistance information using missing indicator variables.

3.4 Test of Information Models

We now use the demand model estimates shown previously to test the two information models of physician behavior with respect to the role of bacterial resistance in their prescriptions decisions. To do so, we estimate Equation (4) in Table 6, which amounts to testing the null hypothesis that physicians do not account for factors that potentially affect current resistance once past resistance is controlled for, against the alternative that physicians consider factors other than past resistance that potentially affect current resistance, indicating expectation formation for current resistance. Using the unsophisticated model, if we incorrectly omitted the expectation of current resistance, it must be correlated with the error term of Equation (4) ζ_{jlt}.

Table 6: Unsophisticated information model test using ξ_{jlt}

	(1) (OLS) b/se	(2) (2SLS) b/se	(3) (OLS) b/se	(4) (2SLS) b/se
ξ_{jt-1}			0.668***	0.667***
			(0.014)	(0.014)
$\log(susc_{j,t})$ Center-East	-0.185	-0.037	-0.191	-0.168
	(0.160)	(0.188)	(0.131)	(0.194)
$\log(susc_{j,t})$ Center-West	0.102	-0.042	0.369	0.330
	(0.189)	(0.182)	(0.190)	(0.193)
$\log(susc_{j,t})$ East	-0.203	-0.076	-0.433*	-0.435
	(0.218)	(0.280)	(0.182)	(0.225)
$\log(susc_{j,t})$ North	0.085	-0.045	0.177	-0.030
	(0.169)	(0.180)	(0.114)	(0.171)
$\log(susc_{j,t})$ West	0.049	0.019	-0.094	0.018
	(0.195)	(0.179)	(0.114)	(0.130)
$\log(susc_{j,t})$ Paris	-0.129	-0.049	-0.356**	-0.294
	(0.200)	(0.183)	(0.133)	(0.162)
$\log(susc_{j,t})$ South-East	0.057	-0.071	0.254	0.051
	(0.225)	(0.210)	(0.134)	(0.178)
$\log(susc_{j,t})$ South-West	-0.090	0.015	-0.206*	-0.011
	(0.170)	(0.127)	(0.100)	(0.128)
Constant	0.006	0.006	0.041*	0.041*
	(0.021)	(0.021)	(0.020)	(0.020)
No Obs.	8372	8372	7011	7011

Note: The standard errors are clustered at the market level.

The results presented in Table 6 fail to reject that current resistance does not affect prescription choice once we control for past resistance. Columns (1) and (2) do not control for the lag shock ξ_{jlt-1}, while

Columns (3) and (4) do. Columns (2) and (4) instrument for susceptibility to account for the measurement error in expectations. Columns (2) and (4) confirm that current susceptibility does not matter. This result is interesting because it shows that providing physicians with better information on the antibiotic resistance environment could aid them in their decision-making processes. They might make better decisions, as they may overestimate or underestimate current resistance using lagged resistance information since the unsophisticated demand model estimates in Table 5 show that they account for lagged susceptibility. Of course, the mistakes will be more or less important depending on the change in resistance over time and thus on the use of antibiotics by humans or animals during the previous year. For the counterfactuals that follow, we will thus use the preferred demand results from Column 5 of Table 5.

4 Regulating the Use of Antibiotics in Humans and Animals

We use our demand model to study counterfactual scenarios that target antibiotic resistance externalities by regulating antibiotic use in humans and animals. The first policy consists of a ban on fluoroquinolone prescriptions. The second consists of limiting the use of fluoroquinolones in veterinary practices. While the policy goals are the same, how these policies affect the market, consumer surplus and expenses differ and are affected by the response to bacterial resistance.

Banning fluoroquinolones as a treatment option for the case of simple cystitis is equivalent to removing it from the choice set of the decision maker. This will inevitably reduce fluoroquinolone antibiotics use, leading to decreasing resistance of E. coli to fluoroquinolones but substitutions toward antibiotics will occur as predicted by our demand estimates. Regulating the veterinary use of fluoroquinolones will decrease resistance, ceteris paribus. However, the demand model predicts that decreased resistance will increase prescriptions of fluoroquinolones in response to increased susceptibility[19].

Banning the Use of Fluoroquinolones Limiting the prescription of fluoroquinolones has been part of the financial incentives provided to physicians in France since 2017. However, we still observe that it is prescribed for cystitis in our data even after 2017 and constituted a substantial share at the beginning of the sample. Therefore, we simulate the effects of a stricter rule regarding the prescription of fluoroquinolones

[19]We take as given the use of antibiotics for other infections. Modeling the changes in treatments of other bacterial diseases due to the change in resistance is beyond the scope of this paper. Hence, one can read our results as an upper bound in terms of the change in resistance and the counterfactual quantities.

from 2002 by banning their use for the treatment of cystitis. This policy is interesting for two reasons. First, it has been documented that bacterial resistance to fluoroquinolones has been increasing rapidly, but the antibiotic remains effective in treating bacteria that are multidrug resistant. Therefore, fluoroquinolones need to be saved for cases where first-line antibiotics fail[20]. Second, a large proportion of fluoroquinolone antibiotics are prescribed for cystitis.

Figure 4: Shares of diagnoses for fluoroquinolone prescriptions (2014-2019)

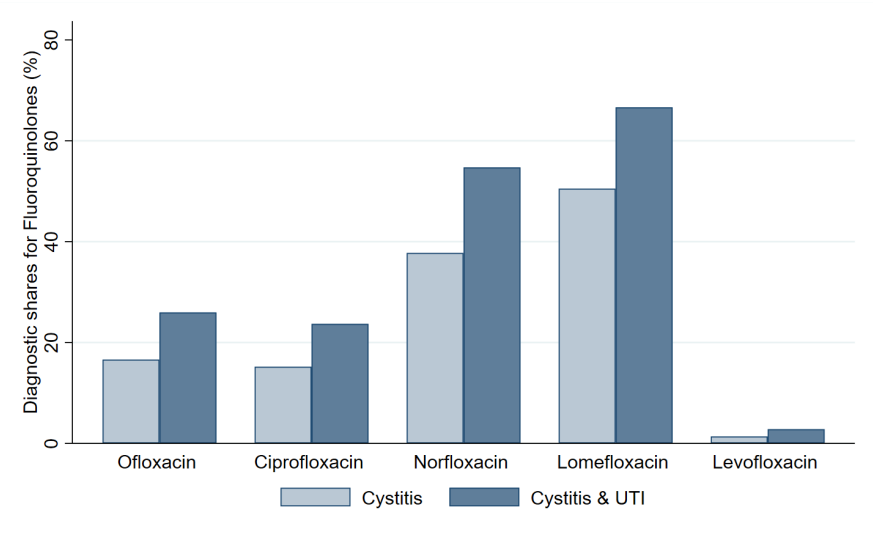


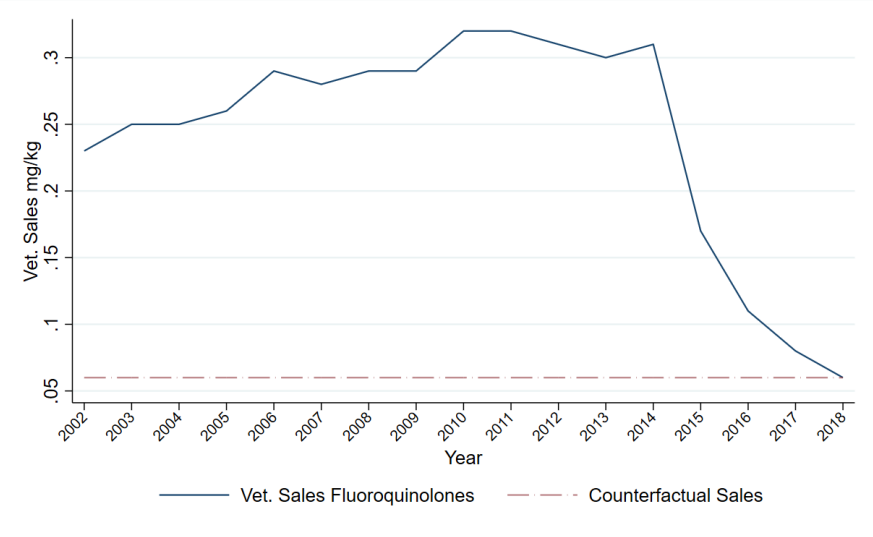
Figure 4 shows the percentage of a diagnosis (cystitis or cystitis and urinary tract infection (UTI)) in the prescriptions of fluoroquinolone molecules for women during the period 2014-2019. The most striking share belongs to J01MA07 (Lomefloxacin). Over all prescriptions of Lomefloxacin, more than 50% were prescribed for cystitis. It is followed by J01MA06 (Norfloxacin) at approximately 40%. Hence, this policy would generate a significant impact on the overall prescription of fluoroquinolones in outpatient care.

Limiting the Use of Fluoroquinolones in Veterinary Practices This counterfactual policy is a stricter version of a policy restricting the use of fluoroquinolones in animals. Indeed, as part of the battle against AMR, the EcoAntibio campaigns have been in action since 2012 with the objective of decreasing antibiotic use, increasing awareness and monitoring. The second wave of the campaign (EcoAntibio2 2017-2021), presented stricter measures,[21] and a decree published in March 2016 banned preventive use of several fluoroquinolones for animal farming. Exemptions required a susceptibility test if the use is strictly

[20] These were also the reasons why fluoroquinolones were in the "at-risk" group defined by the financial incentive scheme.
[21] Accessed from `https://agriculture.gouv.fr/le-plan-ecoantibio-2-2017-2022` on 31 October 2022.

necessary for treatment purposes. Figure 5 presents the change in the antibiotics sold for veterinary use in terms of mg per kilogram of animal body weight and the stark decrease by the end of the sample period. In counterfactual simulation, we set sales to the minimum observed in the data (a level that has been shown to be attainable), also presented in Figure 5. Then, we examine the change in resistance in response to this policy being implemented in the early 2000s and how demand responds to this change in resistance.

Figure 5: Sales (mg/kg) of fluoroquinolones, Source: ANSES



To simulate those counterfactuals, we first need to identify the link between the consumption of antibiotics and the evolution of resistance. We do so by estimating a simple model of resistance evolution in the following section. Using the demand estimates from the unsophisticated information model (Column 5 of Table 5) and the resistance evolution model, we then study the change in market shares, consumer surplus and expenses in the two counterfactual cases. Note that the estimates of consumer surplus and expenses are those at the time of prescription, not accounting for the long-term value of lower resistance.

4.1 Escherichia Coli Resistance Evolution

In line with the literature on the evolution of resistance that shows the role of antibiotic consumption in both humans and animals, as well as epidemiological models of infections (Adda, 2020; Austin et al., 1999; Čižman et al., 2001; Hammerum and Heuer, 2009; López-Lozano et al., 2000), we model E. coli resistance as a function of antibiotic use in humans and animals and past resistance levels. We assume that a nonlinear transformation of the expected resistance is linear additive in the explanatory variables, which leads to the

following fractional logit model of Papke and Wooldridge (1996):

$$E\left(\frac{\log r_{jt}}{1-\log r_{jt}}\right) = \beta_0 + \underbrace{\rho r_{jt-1}}_{\text{Past resistance}} + \underbrace{\beta_1 q^h_{jt-1} + \beta_2 q^{h^2}_{jt-1} + \beta_3 q^h_{ATC4(-j)t-1}}_{\substack{\text{Quantities reimbursed from} \\ \text{National Health Insurance}}} + \underbrace{\sigma_1 q^a_{jt-1}}_{\text{Veterinary sales (mg/kg)}} \tag{5}$$

where j indexes the chemical substance (ATC5), t denotes years, q^a_{jt} represents veterinary sales in mg of active ingredient per kilogram of animal body weight (mg/kg) of product j in period t, and q^h_{jt} is the quantities reimbursed by the French national insurance at the ATC5 level. The effect of antibiotic use by humans is captured using quantities reimbursed at the ATC5 level provided by the French Health Insurance. The antibiotic sales for veterinary use data come from ANSES (2021).

Two points are important to note in the interpretation of the results presented. First, as seen in Table 4, some veterinary antibiotic uses are provided at the ATC3 level (Penicillins, Aminoglycosides), whereas others are reported at the ATC4 level (note that there is no overlap), while the level of observation of E. coli resistance is at the ATC5 level, which prevents us from estimating the effect of the use of certain antibiotic molecules in animals on resistance. Second, as we explain in Section 2.3, the data on bacterial resistance have some missing information. Therefore, the analysis is conducted using the chemical molecules for which we have resistance data, which could introduce selection bias. However, given that the time period is long, data collection on resistance started before the growing resistance trend occurred, and the selection of tested antibiotic resistance of E. coli is based on the value of antibiotics, selection bias should be limited.

The results are presented in Table 7. First, the effect of consumption by humans positively correlates with resistance, but the marginal effect is decreasing in quantity. We also find a positive relation between the use of other chemical substances within the same chemical subgroup, indicating possible cross-resistance effects. Past resistance also plays an important role, which is in line with infectious disease models. Finally, we observe a positive link between the veterinary sales of antibiotics and resistance. Next, we use the results in Column 2 (as preferred by the BIC and AIC) to simulate the counterfactual resistance in each policy scenario.

Table 7: Estimation results for Equation (5)

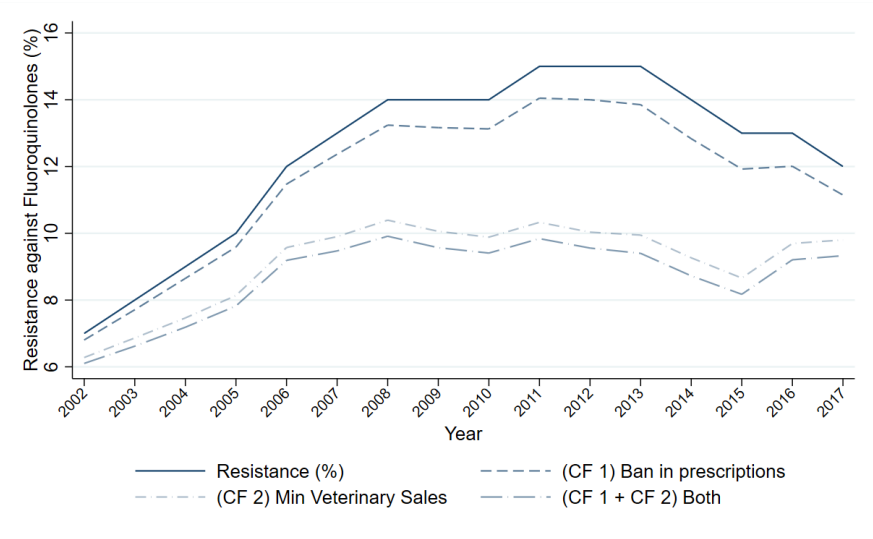
	(1)	(2)	(3)
Lag Resistance		0.058***	0.061***
		(0.002)	(0.002)
Lag Quantity (ATC5)	0.154***	0.041***	0.038***
	(0.009)	(0.008)	(0.008)
Lag Quantity sq	-0.002***	-0.001***	-0.001***
	(0.000)	(0.000)	(0.000)
Lag Quantity - Others ATC4	-0.152***	0.014	0.032***
	(0.010)	(0.008)	(0.006)
Lag sales ATC4 (Vet.)	2.594***	0.728***	0.997**
	(0.354)	(0.215)	(0.304)
Lag sales ATC3 (Vet.)	0.164***	0.095***	0.097***
	(0.015)	(0.011)	(0.010)
Year FE	No	No	Yes
No Obs.	330	330	330
BIC	256.755	257.8954	350.2318
AIC	230.1613	227.5027	259.0536

Note: The regressions include corresponding dummy variables to control for sales information being provided at different ATC levels.

4.2 Counterfactual Policies' Impacts on Resistance

To obtain the counterfactual quantities of antibiotics after the ban on fluoroquinolones for treatment of cystitis, we decrease the quantity of each chemical subgroup of fluoroquinolones by the rates shown in 4. For the second counterfactual, we implement the change in sales presented in Figure 5. The counterfactual resistance for each policy separately and in combination is provided in Figure 6.

Figure 6: E. coli resistance under counterfactual policies

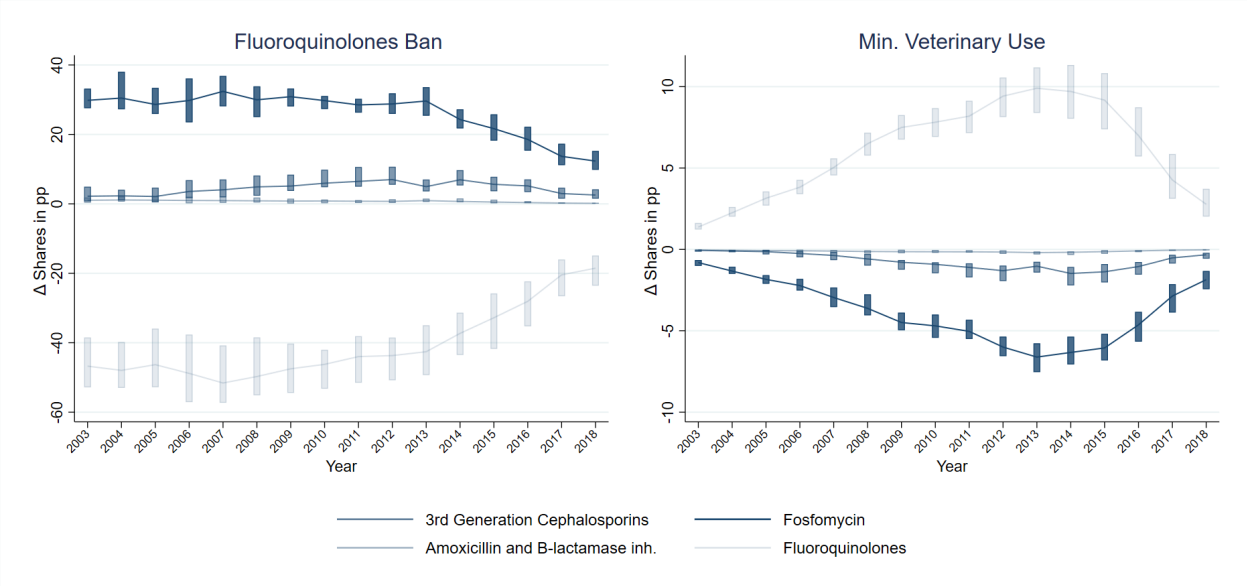


We see that at the beginning of the sample period, resistance increases as a result of increasing use of fluoroquinolones. By 2010, the effect of policies reaches a stable difference of approximately 1 percentage point for the ban on fluoroquinolones for cystitis and 4 percentage points in the minimum veterinary sales case.

4.3 Counterfactual Market Shares

Figure 7 plots the changes in market shares for both counterfactuals. We focus on four groups that represent significant market shares and are important in terms of assessing the consequences of policies for AMR. Additional to fluoroquinolones, we present the change in market shares for i) fosfomycin, which has the highest market share and is the first-line therapy throughout the sample, ii) 3rd generation cephalosporins and iii) Amoxicillin and β- lactamase inhibitors, both of which are included in the "at-risk" antibiotic groups because they are crucial to preserve for the future.

Figure 7: Change in market shares in percentage points



Note: The time variation in mean differences is plotted. The vertical bars around mean estimates indicate the range of variation across regions.

The takeaway from the results of the fluoroquinolone ban is that while physicians largely substitute toward fosfomycin, there is also significant substitution toward 3rd generation cephalosporins. Fosfomycin (J01XX01) is a narrow-spectrum antibiotic to which E. coli responds at a high rate and is recommended as a first-line therapy in uncomplicated cystitis cases. However, cefixime (J01DD08) belongs to the "at-risk" list as a result of bacteria becoming highly resistant to treatment. Therefore, a policy that targets one antibiotic group might create unintended consequences for AMR.

Minimizing veterinary use, on the other hand, affects the market through a change (here, a decrease) in resistance. As expected from the demand estimates, we observe that the share of fluoroquinolones increases in response to decreasing resistance. This substitution is mostly from fosfomycin, partly from 3rd generation cephalosporins and then other antibiotics. Neither policy substantially affects the share of amoxicillin and β- lactamase inhibitors. Overall, we see that although they serve the same purpose of decreasing resistance, the two policies have quite opposite impacts on the market.

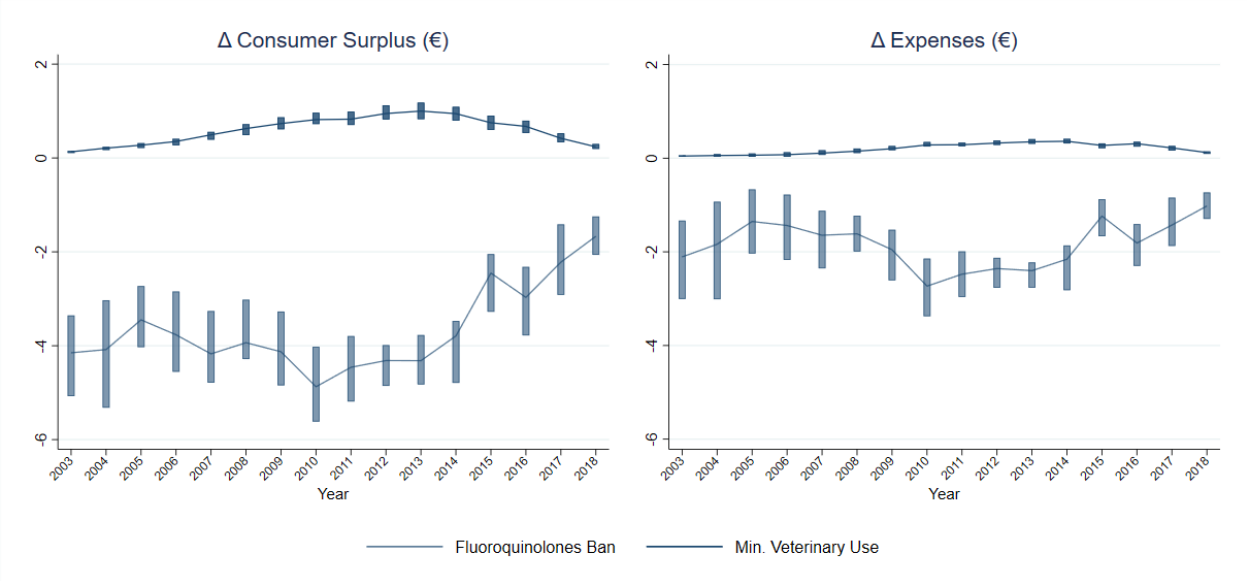
4.4 Counterfactual Changes in Consumer Surplus and Expenses

We then compute the compensating variation per patient following the usual Small and Rosen (1981) formula with differentiated product demand and using the changes in utility as a result of banning fluoroquinolone

prescriptions (MacFadden et al., 2018). Note that we abstract from the impacts of the policy on potential follow-up visits. This impact is likely limited in our case because we focus on "first visits" to capture nonrecurring/initial diagnoses. More important, we do not account for future benefits from a potential decrease in bacterial resistance. Therefore, these results should be considered with caution and only reflect the immediate consequences at the time of prescription.

Figure 8 provides the change in average consumer surplus and expenses per prescription, where the vertical bars show the variation across regions around the mean effect in a given year. The fluoroquinolone ban leads to greater effects in magnitude. On average, the loss of consumer surplus is 4 € and the decrease in expenses is approximately 2 € until 2010. Then, both of these effects decrease in magnitude after 2010. This is partly a result of generic entry of fosfomycin products and incentives for generic prescriptions. From minimizing veterinary use, the changes are smaller than when banning fluoroquinolones but of a different sign. On the one hand, the decrease in resistance increases consumer surplus. On the other hand, this decrease leads to higher market shares for fluoroquinolones, whose price remains well above average and above that of their largest competitor, fosfomycin.

Figure 8: Changes in consumer surplus per patient and expenses per prescription in €



Note: The time variation in the mean differences is plotted. The vertical bars indicate the range of variation across regions.

5 The Value of Diagnostic Tests

We now use our framework to simulate the counterfactual effects of the availability of rapid diagnostic tests that could be used by physicians at the time of prescription. We assume that a new test becomes available and that physicians would be able to prescribe an antibiotic conditional on a test result. Without a test, physicians make "empirical" prescribing decisions affected by the mean resistance of E. coli to each antibiotic. We have shown that the previous year's resistance indeed affects their decision such that the mean utility term of each drug in our discrete choice model depends negatively on the mean resistance.

The effect of mandatory testing for antibiotic prescriptions will depend on the information provided by the test. Assuming that a test would provide information about whether the patient is infected by E. coli and/or whether the bacteria is resistant to an antibiotic, we can infer how the decision model would be affected. As discussed by Firth et al. (2023), policy makers are also considering the use of diagnostic tests to combat growing AMR.

5.1 Rapid Bacterial Detection Test

First, if the test simply confirms whether cystitis is due to an E. coli infection[22], the prescription choice will essentially be scaled down by the average infection rate π by E. coli of this cystitis diagnosis[23]. With probability $1-\pi$, the test indicates no bacterial infection, and hence no antibiotic is prescribed, and with probability π, the test indicates E. coli infection, in which case the physician will prescribe according to the same model while considering average resistance information. Thus, the prescription probability of drug j depending on π will be:

$$s_{jt}^{bact}(\pi) = \pi \int \frac{\exp(\delta_{jt} - \beta_i^p p_{jt})}{\sum_k \exp(\delta_{kt} - \beta_i^p p_{kt})} d\phi(\nu_i) \tag{6}$$

[22]Here, we assume that when the bacterial infection is detected, the probability of the bacteria being E. coli is 1.

[23]The population value of π depends on two quantities, the rate of physician visits for suspected urinary tract infections conditional on having symptoms and the rate at which the suspected cases are indeed caused by bacterial infection. The former is rather difficult to specify. However, for the latter, conditional on having suggestive symptoms, the infection rate is approximately 50% but increases with certain symptoms (Bent et al., 2002; Medina-Bombardo et al., 2003).

The savings per prescription in the presence of a test in year t, or the value of a rapid bacterial test $v_t^{RapidTest}$, can be calculated as follows[24]:

$$\underbrace{v_t^{RapidTest}(\pi)}_{\text{Value of rapid bacterial test}} = \sum_{j\in\{1,...,J_t\}} \underbrace{p_{jt}(s_{jt}^{NoTest} - s_{jt}^{bact}(\pi))}_{\substack{\text{Additional expenses on drug } j \\ \text{if no test vs bacterial test}}} \tag{7}$$

where s_{jt}^{NoTest} denotes the choice probability of prescribing j in the absence of testing.

5.2 Rapid Antibiotic Susceptibility Testing

If, in addition, the test indicates whether the bacteria is resistant to drug j, the test allows the physician to use patient-specific information that does not consider the average resistance in the population but the patient-level resistance r_{ijt}. The resistance information will affect the consideration set of the physician by simply excluding the drugs to which the bacteria is resistant. It will also increase the mean value of each drug to which the bacteria is not resistant by an amount that is proportional to the expected resistance that was considered before testing. Our framework allows one to predict choice probability under any susceptibility testing as shown in Appendix A.3. We consider here the simpler case of susceptibility testing for a single molecule.

Suppose that the test informs the physician whether the bacteria is resistant to chemical substance l (for example, Amoxicillin (J01CA04)). For any drug $l \in \{1,..,J\}$, the choice probability for individual i is written as:

$$s_{ilt}(\pi, r_{ilt}) = \pi\ 1_{\{r_{ilt}\neq 1\}} \frac{\exp\left(\tilde{\delta}_{lt} - \beta_i^p p_{lt}\right)}{\sum_{k=1}^{J} 1_{\{r_{ikt}\neq 1\}} \exp\left(\tilde{\delta}_{kt} - \beta_i^p p_{kt}\right)}$$

where $\tilde{\delta}_{jt} \equiv \delta_{jt} - \beta_r r_{jt-1}$ if $r_{ijt} = 0$ since δ_{jt} is the mean utility (excepting the price effect) of drug j when

[24]Note that the value of the test here represents a lower bound and reflects the health care savings per prescription without considering the impact on resistance. Using the test will save antibiotic use overall and hence help to limit resistance externalities. As bacterial resistance is attached to increased hospitalizations, deaths, and productivity loss, slowing resistance growth is likely to generate higher returns on such a test in the future.

To account for the changes in resistance that would result from the reduced usage of antibiotics, one needs to approximate the effect of the test for other diseases, which is beyond the scope of this paper. However, knowing μ_j for drug j, the scale factor of drug j consumption, one can calculate the counterfactual usage $\tilde{q}_{jt}^h$ of antibiotic j as

$$\tilde{q}_{jt}^h = (1-\mu_j)q_{jt}^h + \mu_j q_{jt}^h \frac{s_{jt}^{test_l}(\pi)}{s_{jt}}.$$

Then, using the counterfactual quantities, it is possible to compute the path of counterfactual resistance and the paths of prescriptions, expenses and consumer surplus and compare it them to diagnostic test spending.

physicians expect a resistance level of r_{jt-1}[25]. At the population level, we have $E[1_{\{r_{ilt}=1\}}] = r_{lt}$. Therefore, the choice probability of drug j when physicians perform susceptibility testing for chemical substance l before any prescription becomes:

$$s_{jt}^{Susc.Test_l}(\pi) = \pi\, r_{lt} \int \frac{\exp(\delta_{jt} - \beta_i^p p_{jt})}{\sum_{k \notin L} \exp(\delta_{kt} - \beta_i^p p_{kt})} d\phi(\nu_i) + \pi\, (1 - r_{lt}) \int \frac{\exp(\tilde{\delta}_{jt} - \beta_i^p p_{jt})}{\sum_{k \in L} \exp(\tilde{\delta}_{kt} - \beta_i^p p_{kt})} d\phi(\nu_i)$$

We can then compute the total expenses per prescription with susceptibility testing, or the value of the susceptibility test, for drug l and without susceptibility testing (but with diagnostic testing for bacterial infection). The change in expenses will be given by the following expression.

$$\underbrace{v_t^{Susc.Test_l}(\pi)}_{\text{Value of rapid susceptibility test}} = \sum_{j \in \{1,\ldots,J_t\}} \underbrace{p_{jt} s_{jt}^{Susc.test_l}(\pi)}_{\substack{\text{Expenses on drug } j \text{ when using} \\ \text{susceptibility test of drug } l}} - \sum_{j \in \{1,\ldots,J_t\}} \underbrace{p_{jt} s_{jt}(\pi)}_{\substack{\text{Expenses on drug } j \\ \text{without test}}} \tag{8}$$

We then calculate the value of rapid antibiotic susceptibility testing, which would indicate whether the bacteria is susceptible to amoxicillin in 2018, where the resistance rate of E. coli was approximately 51%. We chose amoxicillin because of its relevance in this context. In the recent treatment guidelines by the French health authority ("Haute autorité de santé") for cystitis [26], differential treatment following antibiotic sensitivity testing suggests amoxicillin as the first choice. Table 8 shows the expenses per prescription in 2018 for the treatment of cystitis for three values of the bacterial infection rate π. The empirical treatment without a test costs € 6.76 per prescription, and savings range from € 3.22 for $\pi = 0.75$ to € 5.58 for $\pi = 0.25$ if rapid susceptibility testing for amoxicillin and a bacterial detection test were implemented. Table 8 shows that the higher the probability of bacterial infection is, the lower the savings from using a bacterial test or penicillin susceptibility test. Conversely, the lower the probability of bacterial infection is, the larger the savings in terms of treatment costs when using a test.

[25] Note that we could also assume that physicians keep in their choice set drugs to which they know the bacteria is resistant and assume that they update their valuation of the drug for patient i using $\delta_{ijt} = \delta_{jt} - \beta_r^l r_{jt-1}$ if $r_{ijt} = 0$ in addition to $\delta_{ijt} = \delta_{jt} + \beta_r^l (1 - r_{jt-1})$ if $r_{ijt} = 1$.

[26] Accessed from `https://www.has-sante.fr/upload/docs/application/pdf/2021-08/fiche_memo_cystite_durees_antibiotherapies_.pdf` on 31 October 2022

Table 8: Expenses per prescription in 2018 (€)

π	Treatment cost without test	Treatment cost with Detection test	Treatment cost with Amoxicillin Susc. Test
0.25	6.76	1.69	1.18
0.50	6.76	3.38	2.36
0.75	6.76	5.07	3.54

From a welfare perspective, even without considering long-term effects on resistance, we should also value the health outcome implied by the change in treatment that the test will lead to. We approximate this effect using the success rate of treatment. In the following, we assume that a bacterial infection is present and, therefore, focus solely on the effects of antibiotic choices with and without susceptibility testing.

The mean probability of being cured by antibiotic j is a function of all drugs' resistance multiplied by the choice probability of each drug (which of course also depends on resistance) $\sum_{j\in\{1,\dots,J_t\}} s_{jt}(1-r_{jt})$. Upon testing, the change in the probability of being cured is then:

$$\Delta^{l}_{treat}(\pi) \equiv \pi \left(\sum_{j\in\{1,\dots,J_t\}} s_{jt}^{Susc.Test_l}(1-r_{jt}) - \sum_{j\in\{1,\dots,J_t\}} s_{jt}(1-r_{jt}) \right)$$

Table 9 shows the probability estimates of being cured with or without susceptibility testing[27]. In the case of cystitis, this probability is very large even without testing, but testing still increases this probability by 3.4 percentage points.

Table 9: Treatment success with and without susceptibility testing for $\pi = 1$

	No Susceptibility Testing (Empirical Treatment)	Susceptibility Testing (Amoxicillin)
	All regions (Mean Change)	
Probability of being cured	94.2%	97.6%
$\Delta^{Amoxicillin}_{treat}$		3.4%
	Region: West (Min Change)	
Probability of being cured	94.9%	97.8%
$\Delta^{Amoxicillin}_{treat}$		2.9%
	Region: East (Max Change)	
Probability of being cured	93.4%	97.4%
$\Delta^{Amoxicillin}_{treat}$		4.0%

[27]For 2018, we calculate the probabilities based on the resistance rates from the REUSSIR network, where the missing values for fosfomycin, cefixime, pivmecillinam and sulfamethoxazole and trimethoprim are taken from the OSCAR Network of Onerba, a network of private laboratories from Bourgogne Franche-Comte region.

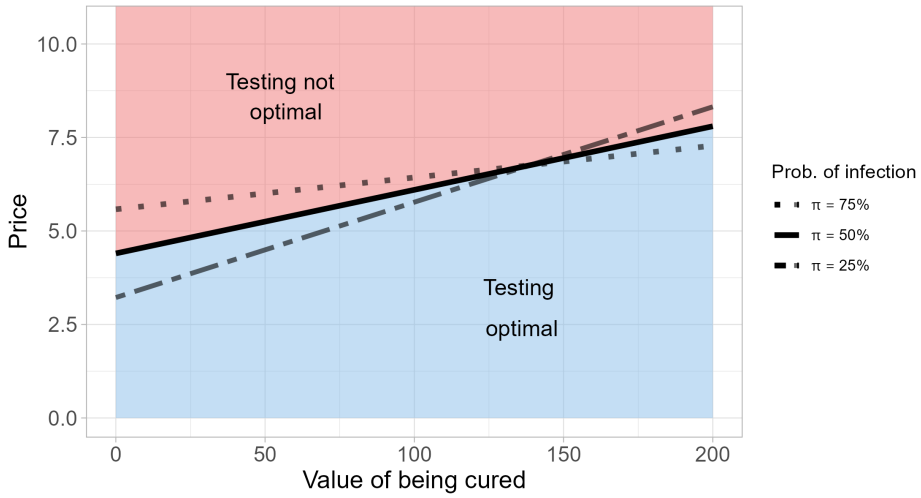
Then, the conditions under which susceptibility testing should be used will depend on the patient's value of being cured. This value may depend on the opportunity costs of sickness leave and the welfare loss in terms of quality of life in the particular case of each disease (cystitis in this particular application). We thus determine the set of values of being cured per patient V and price of tests p_T^l such that it is optimal to mandate a bacterial resistance test before the prescription of drug l. It is indeed desirable if the value of the test due to an increased probability of being cured, $\Delta_t^l \times V$, is greater than the health care cost of treatment with a rapid susceptibility test, which is $p_T^l - v_t^{Susc.Test_l}(\pi)$, where the value of the susceptibility test comes from Equation (8). In other words, imposing testing will be valuable if and only if

$$\Delta_t^l(\pi) \geq \frac{p_T^l - v_t^{Susc.Test_l}(\pi)}{V} \tag{9}$$

Regarding the values of (p_T^l, V) satisfying Condition (9), the higher the value V is, the higher the maximum price that should be accepted (provided that the net health cost of testing is positive).

Using the savings from Table 8 and the change in the probability of successful treatment from Table 9, Figure 9 displays the regions in the {Value of treatment, Price} space where mandatory testing is optimal for the case of rapid susceptibility testing for Amoxicillin in 2018[28].

Figure 9: Optimality of susceptibility testing



Note: The colored regions are provided for $\pi = 0.5$

While $\Delta_t^l(\pi)$ fixes the slope of the relationship between the value of the treatment and the price of

[28] We assume that susceptibility testing also indicates the bacterial status of the suspected infection. Therefore, the relevant comparison for expenses is between Columns 1 and 3 of Table 8.

the susceptibility test for antibiotic l, the net health care costs (i.e., change in expenses) determines the intercept. The probability of bacterial infection in the population of suspected cystitis infections π changes the level of the maximum prices that should be paid, as it changes the expected savings due to testing and the probability of treatment.

Moreover, we can see that for lower values of being cured V, the lower the probability of bacterial infection π is, the higher the upper bound on the price of the test that is beneficial for society. This is because as the rate of infection is lower, the savings from avoided useless treatments will be higher. However, the lower the probability of bacterial infection is, the smaller the slope. Thus, an incremental value of being cured is (ex ante) valued less than in the case in which the bacterial infection rate is higher. This is because the change in the probability of the treatment is weighted by the rate of infection. Therefore, if the value of being cured is high enough, the price that the insurer is willing to reimburse is higher if the probability of infection is high (e.g., 75%) as opposed to low (e.g., 25%). This exemplifies where the use of susceptibility testing makes a difference in addition to using a detection test.

6 Conclusion

In this paper, we study the effects of bacterial resistance on antibiotic prescription choice using a long and exhaustive panel of general practitioner visits in France. We employ additional data on resistance and the veterinary use of antibiotics to identify the effect of AMR on treatment choices and control for the endogeneity of prices and resistance. The results indicate that bacterial resistance affects prescription behavior, as physicians substitute away from antibiotics for which the resistance is higher. We explore two ways in which physician response takes accounts for resistance. Using the estimation of an "unsophisticated" information model, we test whether physicians might act upon the expectation of current resistance instead of using resistance in the last period. We do not find evidence that physicians act based on expectations of resistance. The results from the ("unsophisticated" information) demand specification where physicians consider past resistance shows that they respond to resistance as they substitute toward antibiotics for which the bacteria has higher susceptibility. We also find that physicians have a tendency to prescribe more branded products. We find that physicians start to prescribe more generics upon the introduction of a pay-for-performance bonus in 2012. Similarly, we observe a decline in preference for specific antibiotics

groups that are targeted by the same pay-for-performance program since 2017.

We then develop counterfactuals analysis using a resistance evolution model for E. coli bacteria. We study the effects of a policy where the use of fluoroquinolones are banned in the treatment of cystitis or regulated for veterinary use. We obtain opposing effects for these two policies on consumer surplus and expenses, as well as the substitutions realized, while both policies reduce resistance against fluoroquinolones. In the case of the fluoroquinolones ban, the results highlight the substitution toward other antibiotics that are as valuable and need to be saved for more complicated cases. In the case of a veterinary regulation on fluoroquinolone use, there is an increased market share for fluoroquinolone prescriptions in humans in the face of decreasing resistance, which is likely to attenuate the impact of the policy. These findings highlight the importance of a unifying approach that considers the entire ecosystem (such as the "One Health" approach)[29]. In all the counterfactual studies we conduct, note that we do not account for the value of the long-term gains from lower AMR, indicating that our results can be regarded as a lower bound on the benefits of the policies.

Finally, we use our demand model to assess the value of bacterial detection and susceptibility testing. We examine the savings per prescription and probability of being cured in the case where a rapid susceptibility test for amoxicillin is present and mandated using counterfactual shares generated as a result of the mandates. In our setting, we show that the effects of the prevalence of bacterial infections in the suspected cases of cystitis plays a role in identifying the price that comes from the changes in expenses due to testing only, i.e., when there is no value of treatment. However, when accounting for the health care spending implied by the treatment and the probability of being cured, we show that as the value of being cured increases, the maximum price for which testing is optimal increases but that this maximum price decreases or increases depending on whether the probability of infection is high or low. This maximum price that is optimal for mandatory testing should be interpreted as a lower bound because we focus only on a particular infection and do not incorporate the social value generated by testing through reduced antibiotic resistance. As the data on resistance grows richer with improved surveillance of bacteria and data collection, future work could address the question while including the long-term effects on public health.

[29]One Health French National Action Plan on Antimicrobial Resistance. Retrieved from `https://sante.gouv.fr/IMG/pdf/brochure_mesures_innovantes_lutte_atbr-en_vf.pdf` on 21/06/2023.

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A Appendix

A.1 Data

Repeated visit rates

In the following, we report the repeated visit rates (in percentages) by chemical subgroup across years. A repeat visit is defined as a re-visit to physician that results in an antibiotic prescription after an initial antibiotic treatment for a urinary tract infection.

Table 10: Average time (days) between two prescriptions in case of a repeat visit

	All	ATC 4					Avg. time between
Year		J01CA	J01CR	J01DD	J01MA	J01XX	two repeat visits
2009	6.42	8.97	9.96	6.46	5.76	7.27	12.00
2010	6.43	8.32	12.66	7.44	5.78	6.96	12.00
2011	6.31	8.88	7.69	7.40	5.64	6.84	11.87
2012	6.43	8.53	7.00	7.18	5.73	7.10	12.13
2013	6.39	8.28	7.53	8.10	5.47	7.14	11.83
2014	6.71	8.66	10.59	7.22	5.93	7.14	11.86
2015	6.39	8.83	9.95	6.47	5.37	6.95	11.86
2016	6.60	7.81	10.59	6.71	5.72	6.97	11.69
2017	6.68	7.76	12.91	6.75	5.76	6.81	12.00
2018	7.03	8.51	7.45	7.15	6.34	7.02	11.96
2019	6.65	8.06	10.69	6.74	5.86	6.52	11.73

Note: The visits that are not followed by another prescription within 30 days are excluded. We also drop repeat visits, that is, the second prescription within a month.

A.2 Additional Tables

A.2.1 First-stage instrumental variables regressions

In this section, we report the first stage of the IV regressions used in Column 2 of Table 5 and the corresponding F statistics for the joint significance of excluded instruments.

Table 11: First stage – IV (Part I)

	Price	Susc. Reg. 1	Susc. Reg. 2	Susc. Reg. 3	Susc. Reg. 4	Susc. Reg. 5	Susc. Reg. 6	Susc. Reg. 7	Susc. Reg. 8	Detailing
Nb. of labs in ATC5	-0.853***	0.000	0.001	0.000	0.000	0.001	0.001	0.001	0.001	-0.110***
	(0.0818)	(0.0011)	(0.0009)	(0.0011)	(0.0011)	(0.0011)	(0.0012)	(0.0011)	(0.0011)	(0.0142)
Nb. of labs in ATC5 * Generic	-0.006	0.000	0.000	0.000	0.000	-0.000	-0.001	-0.000	0.000	0.122***
	(0.0349)	(0.0005)	(0.0004)	(0.0005)	(0.0005)	(0.0005)	(0.0005)	(0.0005)	(0.0005)	(0.0061)
Nb. of labs in ATC5 ¿ 2011	0.071**	-0.000	-0.000	-0.000	-0.000	-0.000	-0.000	-0.000	-0.000	0.029***
	(0.0263)	(0.0003)	(0.0003)	(0.0003)	(0.0004)	(0.0003)	(0.0004)	(0.0003)	(0.0003)	(0.0046)
Nb. of labs in ATC5 gen ¿ 2011	-0.068*	0.000	0.000	-0.000	-0.000	-0.000	0.000	0.000	-0.000	-0.026***
	(0.0341)	(0.0004)	(0.0004)	(0.0004)	(0.0005)	(0.0004)	(0.0005)	(0.0004)	(0.0004)	(0.0059)
Nb. of CIP in ATC5	0.052	-0.000	-0.001	-0.000	-0.000	-0.001	-0.001	-0.001	-0.000	-0.044***
	(0.0404)	(0.0005)	(0.0004)	(0.0005)	(0.0005)	(0.0005)	(0.0006)	(0.0005)	(0.0005)	(0.0070)
Nb. of labs in ATC5 sq.	0.026***	0.000	-0.000	0.000	0.000	0.000	0.000	0.000	-0.000	0.002**
	(0.0035)	(0.0000)	(0.0000)	(0.0000)	(0.0000)	(0.0000)	(0.0000)	(0.0000)	(0.0000)	(0.0006)
Nb. of CIP in ATC5 sq	-0.001**	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000*
	(0.0005)	(0.0000)	(0.0000)	(0.0000)	(0.0000)	(0.0000)	(0.0000)	(0.0000)	(0.0000)	(0.0001)
Year since generic entry	-0.376***	-0.000	0.000	-0.000	-0.000	-0.000	-0.000	0.000	0.000	0.028***
	(0.0363)	(0.0005)	(0.0004)	(0.0005)	(0.0005)	(0.0005)	(0.0005)	(0.0005)	(0.0005)	(0.0063)
lag mg/kg sq. (atc4) * Region 1	38.081***	1.556***	-0.095	-0.124	-0.155	-0.151	-0.124	-0.139	-0.147	-11.003***
	(10.1986)	(0.1325)	(0.1062)	(0.1318)	(0.1357)	(0.1345)	(0.1437)	(0.1329)	(0.1336)	(1.7656)
lag mg/kg sq. (atc4) * Region 1	-39.440	-3.108***	0.107	0.225	0.203	0.271	0.167	0.198	0.199	20.904***
	(22.7725)	(0.2959)	(0.2370)	(0.2942)	(0.3030)	(0.3003)	(0.3209)	(0.2969)	(0.2984)	(3.9424)
lag mg/kg (atc3) * Region 1	0.066	-0.103***	0.013***	0.010*	0.014**	0.015***	0.014**	0.016***	0.015***	-0.190**
	(0.3387)	(0.0044)	(0.0035)	(0.0044)	(0.0045)	(0.0045)	(0.0048)	(0.0044)	(0.0044)	(0.0586)
lag mg/kg sq. (atc4) * Region 2	37.315***	-0.140	1.690***	-0.131	-0.168	-0.154	-0.145	-0.148	-0.160	-12.256***
	(11.1610)	(0.1450)	(0.1162)	(0.1442)	(0.1485)	(0.1472)	(0.1573)	(0.1455)	(0.1462)	(1.9322)
lag mg/kg sq. (atc4) * Region 2	-39.456	0.220	-3.418***	0.241	0.237	0.279	0.210	0.224	0.231	23.701***
	(25.5605)	(0.3321)	(0.2661)	(0.3303)	(0.3400)	(0.3370)	(0.3602)	(0.3332)	(0.3349)	(4.4250)
lag mg/kg (atc3) * Region 2	0.209	0.012**	-0.105***	0.011*	0.015**	0.016***	0.014**	0.017***	0.015***	-0.213***
	(0.3472)	(0.0045)	(0.0036)	(0.0045)	(0.0046)	(0.0046)	(0.0049)	(0.0045)	(0.0045)	(0.0601)
lag mg/kg sq. (atc3) * Region 2	-0.010	-0.001***	0.008***	-0.001***	-0.001***	-0.001***	-0.001***	-0.001***	-0.001***	0.010**
	(0.0203)	(0.0003)	(0.0002)	(0.0003)	(0.0003)	(0.0003)	(0.0003)	(0.0003)	(0.0003)	(0.0035)
lag mg/kg sq. (atc4) * Region 3	37.502***	-0.134	-0.095	1.639***	-0.162	-0.155	-0.135	-0.144	-0.154	-10.079***
	(9.9737)	(0.1296)	(0.1038)	(0.1289)	(0.1327)	(0.1315)	(0.1406)	(0.1300)	(0.1307)	(1.7266)
lag mg/kg sq. (atc4) * Region 3	-38.114	0.209	0.111	-3.285***	0.226	0.284	0.202	0.216	0.217	18.897***
	(22.4313)	(0.2915)	(0.2335)	(0.2898)	(0.2984)	(0.2958)	(0.3161)	(0.2924)	(0.2939)	(3.8833)
lag mg/kg (atc3) * Region 3	0.111	0.011*	0.012***	-0.099***	0.013**	0.014**	0.013**	0.015***	0.014**	-0.221***
	(0.3337)	(0.0043)	(0.0035)	(0.0043)	(0.0044)	(0.0044)	(0.0047)	(0.0044)	(0.0044)	(0.0578)
lag mg/kg sq. (atc3) * Region 3	-0.003	-0.001***	-0.001***	0.008***	-0.001***	-0.001***	-0.001***	-0.001***	-0.001***	0.010**
	(0.0196)	(0.0003)	(0.0002)	(0.0003)	(0.0003)	(0.0003)	(0.0003)	(0.0003)	(0.0003)	(0.0034)
No Obs.	8372	8372	8372	8372	8372	8372	8372	8372	8372	8372

Table 12: First stage – IV (Part II)

	Price	Susc. Reg. 1	Susc. Reg. 2	Susc. Reg. 3	Susc. Reg. 4	Susc. Reg. 5	Susc. Reg. 6	Susc. Reg. 7	Susc. Reg. 8	Detailing
lag mg/kg sq. (atc4) * Region 4	39.513***	-0.116	-0.082	-0.117	1.466***	-0.142	-0.110	-0.130	-0.137	-9.541***
	(9.7885)	(0.1272)	(0.1019)	(0.1265)	(0.1302)	(0.1291)	(0.1380)	(0.1276)	(0.1283)	(1.6946)
lag mg/kg sq. (atc4) * Region 4	-45.152*	0.150	0.072	0.196	-2.845***	0.232	0.121	0.159	0.158	17.626***
	(21.9461)	(0.2852)	(0.2284)	(0.2836)	(0.2920)	(0.2894)	(0.3093)	(0.2861)	(0.2876)	(3.7993)
lag mg/kg (atc3) * Region 4	0.070	0.011*	0.012***	0.010*	-0.096***	0.015***	0.014**	0.015***	0.014***	-0.229***
	(0.3296)	(0.0043)	(0.0034)	(0.0043)	(0.0044)	(0.0043)	(0.0046)	(0.0043)	(0.0043)	(0.0571)
lag mg/kg sq. (atc3) * Region 4	-0.001	-0.001***	-0.001***	-0.001***	0.008***	-0.001***	-0.001***	-0.001***	-0.001***	0.011***
	(0.0188)	(0.0002)	(0.0002)	(0.0002)	(0.0003)	(0.0002)	(0.0003)	(0.0002)	(0.0002)	(0.0033)
lag mg/kg sq. (atc4) * Region 5	45.424***	-0.123	-0.088	-0.120	-0.145	1.531***	-0.112	-0.132	-0.147	-11.253***
	(9.6856)	(0.1259)	(0.1008)	(0.1251)	(0.1289)	(0.1277)	(0.1365)	(0.1263)	(0.1269)	(1.6768)
lag mg/kg sq. (atc4) * Region 5	-58.605**	0.173	0.089	0.208	0.173	-2.963***	0.138	0.172	0.185	21.482***
	(21.8183)	(0.2835)	(0.2271)	(0.2819)	(0.2903)	(0.2877)	(0.3075)	(0.2844)	(0.2859)	(3.7772)
lag mg/kg (atc3) * Region 5	-0.001	0.011*	0.012***	0.010*	0.014**	-0.095***	0.014**	0.015***	0.014**	-0.203***
	(0.3329)	(0.0043)	(0.0035)	(0.0043)	(0.0044)	(0.0044)	(0.0047)	(0.0043)	(0.0044)	(0.0576)
lag mg/kg sq. (atc3) * Region 5	0.004	-0.001***	-0.001***	-0.001***	-0.001***	0.007***	-0.001***	-0.001***	-0.001***	0.009**
	(0.0188)	(0.0002)	(0.0002)	(0.0002)	(0.0002)	(0.0002)	(0.0003)	(0.0002)	(0.0002)	(0.0033)
lag mg/kg sq. (atc4) * Region 6	38.860***	-0.118	-0.092	-0.116	-0.146	-0.138	1.545***	-0.127	-0.140	-12.674***
	(9.2880)	(0.1207)	(0.0967)	(0.1200)	(0.1236)	(0.1225)	(0.1309)	(0.1211)	(0.1217)	(1.6079)
lag mg/kg sq. (atc4) * Region 6	-39.537	0.164	0.092	0.204	0.175	0.239	-3.057***	0.168	0.173	24.810***
	(20.7363)	(0.2694)	(0.2158)	(0.2679)	(0.2759)	(0.2734)	(0.2922)	(0.2703)	(0.2717)	(3.5899)
lag mg/kg (atc3) * Region 6	0.106	0.011*	0.012***	0.010*	0.013**	0.014***	-0.094***	0.015***	0.014***	-0.222***
	(0.3260)	(0.0042)	(0.0034)	(0.0042)	(0.0043)	(0.0043)	(0.0046)	(0.0042)	(0.0043)	(0.0564)
lag mg/kg sq. (atc3) * Region 6	-0.003	-0.001***	-0.001***	-0.001***	-0.001***	-0.001***	0.007***	-0.001***	-0.001***	0.010**
	(0.0184)	(0.0002)	(0.0002)	(0.0002)	(0.0002)	(0.0002)	(0.0003)	(0.0002)	(0.0002)	(0.0032)
lag mg/kg sq. (atc4) * Region 7	40.493***	-0.120	-0.087	-0.118	-0.147	-0.148	-0.116	1.529***	-0.147	-12.719***
	(10.0147)	(0.1301)	(0.1042)	(0.1294)	(0.1332)	(0.1320)	(0.1411)	(0.1305)	(0.1312)	(1.7338)
lag mg/kg sq. (atc4) * Region 7	-47.916*	0.161	0.085	0.199	0.170	0.248	0.140	-2.974***	0.178	24.734***
	(22.6455)	(0.2943)	(0.2357)	(0.2926)	(0.3013)	(0.2986)	(0.3191)	(0.2952)	(0.2967)	(3.9204)
lag mg/kg (atc3) * Region 7	-0.006	0.011*	0.012***	0.010*	0.013**	0.014**	0.013**	-0.093***	0.014**	-0.216***
	(0.3316)	(0.0043)	(0.0035)	(0.0043)	(0.0044)	(0.0044)	(0.0047)	(0.0043)	(0.0043)	(0.0574)
lag mg/kg sq. (atc3) * Region 7	0.004	-0.001***	-0.001***	-0.001***	-0.001***	-0.001***	-0.001***	0.007***	-0.001***	0.010**
	(0.0186)	(0.0002)	(0.0002)	(0.0002)	(0.0002)	(0.0002)	(0.0003)	(0.0002)	(0.0002)	(0.0032)
lag mg/kg sq. (atc4) * Region 8	44.525***	-0.125	-0.098	-0.124	-0.152	-0.151	-0.122	-0.142	1.543***	-11.211***
	(10.4429)	(0.1357)	(0.1087)	(0.1349)	(0.1389)	(0.1377)	(0.1472)	(0.1361)	(0.1368)	(1.8079)
lag mg/kg sq. (atc4) * Region 8	-56.540*	0.183	0.115	0.224	0.193	0.261	0.161	0.197	-3.083***	21.453***
	(23.3296)	(0.3031)	(0.2428)	(0.3014)	(0.3104)	(0.3076)	(0.3288)	(0.3041)	(0.3057)	(4.0388)
lag mg/kg (atc3) * Region 8	0.055	0.012**	0.013***	0.011*	0.014**	0.015***	0.014**	0.016***	-0.100***	-0.217***
	(0.3281)	(0.0043)	(0.0034)	(0.0042)	(0.0044)	(0.0043)	(0.0046)	(0.0043)	(0.0043)	(0.0568)
lag mg/kg sq. (atc3) * Region 8	0.000	-0.001***	-0.001***	-0.001***	-0.001***	-0.001***	-0.001***	-0.001***	0.008***	0.010**
	(0.0186)	(0.0002)	(0.0002)	(0.0002)	(0.0002)	(0.0002)	(0.0003)	(0.0002)	(0.0002)	(0.0032)
No Obs.	8372	8372	8372	8372	8372	8372	8372	8372	8372	8372
F Stat (56, 8228)	15.33	380.48	442.00	377.39	378.63	398.63	377.64	379.49	399.18	30.92

Note: Standard errors in parentheses. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. All regressions include ATC 5 (chemical substance) and brand (pharmaceutical company), region and year fixed effects. We control for missing price and resistance information with dummy variables.

A.2.2 Robustness check with weighted average price

Table 13: Estimation results of demand models

	Logit OLS	Logit 2SLS	RC Logit Sophisticated	RC Logit Unsophisticated
Weighted Price (β^p)	-0.025***	-0.244***	-0.368***	-0.340***
	(0.0045)	(0.0239)	(0.0391)	(0.0405)
Price SD (σ_p)			0.127***	0.101***
			(0.0145)	(0.0160)
log($susc_{j,t-1}$) Center-East	0.340	8.988***		8.301***
	(0.5870)	(1.6206)		(1.5910)
log($susc_{j,t-1}$) Center-West	0.145	8.529***		7.926***
	(0.5974)	(1.6306)		(1.5954)
log($susc_{j,t-1}$) East	-0.072	8.616***		7.935***
	(0.5872)	(1.6230)		(1.5921)
log($susc_{j,t-1}$) North	-0.536	7.886***		7.177***
	(0.5872)	(1.6269)		(1.5979)
log($susc_{j,t-1}$) West	0.003	8.705***		7.962***
	(0.5882)	(1.6286)		(1.6006)
log($susc_{j,t-1}$) Paris	0.518	9.341***		8.694***
	(0.5867)	(1.6324)		(1.5980)
log($susc_{j,t-1}$) South-East	-0.458	7.982***		7.306***
	(0.5875)	(1.6263)		(1.5950)
log($susc_{j,t-1}$) South-West	0.133	8.878***		8.164***
	(0.5872)	(1.6266)		(1.5965)
Detailing (in Mil.)	-0.059*	0.559***	0.754***	0.804***
	(0.0227)	(0.0842)	(0.1046)	(0.1081)
Guidelines				
Guidelines - First	0.066	0.217	-0.426*	0.000
	(0.1667)	(0.2083)	(0.1893)	(0.2124)
Guidelines - Second	0.147**	0.155*	0.141*	0.158**
	(0.0520)	(0.0610)	(0.0571)	(0.0582)
Guidelines - Complicated	0.140***	-0.019	0.039	-0.041
	(0.0353)	(0.0451)	(0.0392)	(0.0434)
Generic	-3.753***	-3.825***	-4.025***	-4.018***
	(0.0895)	(0.1106)	(0.1092)	(0.1124)
Pay-for-Performance				
Generic (post 2012)	0.827***	0.622***	0.599***	0.640***
	(0.0572)	(0.0811)	(0.0737)	(0.0762)
J01MA*Post2017	-0.333***	-0.541***	-0.528***	-0.601***
	(0.1008)	(0.1197)	(0.1123)	(0.1155)
J01DD*Post2017	0.103	0.091	-0.046	0.007
	(0.1337)	(0.1561)	(0.1478)	(0.1508)
J01CR*Post2017	-0.553**	-1.514***	-0.502**	-1.429***
	(0.1739)	(0.2664)	(0.1751)	(0.2582)
J01MA*ROSP_Trend	-0.151*	-0.263***	-0.370***	-0.316***
	(0.0667)	(0.0798)	(0.0763)	(0.0789)
J01DD*ROSP_Trend	-0.183*	-0.262*	-0.281**	-0.292**
	(0.0926)	(0.1081)	(0.1018)	(0.1038)
J01CR*ROSP_Trend	-0.167	-0.208	-0.229	-0.232
	(0.1162)	(0.1353)	(0.1271)	(0.1296)
N	8372	8372	8372	8372

Note: Standard errors in parentheses. Significance levels: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. All regressions include ATC 5 (chemical substance) and brand (pharmaceutical company), region and year fixed effects. We control for missing price and resistance information using missing indicator variables.

A.3 Generalization of Antibiotic Susceptibility Testing

Suppose that the test is fully informative on all drugs, meaning that it indicates whether the infection is resistant to each of the available antibiotics. The aggregate choice probability of drug j in this case will be:

$$s_{jt}^{full}(\pi) = \int \left(\int s_{ijt}^{full}(\pi, r_{i1t}, .., r_{iJt}) d\phi(\nu_i) \right) \, dF(r_{i1t}, .., r_{iJt} | r_{jt}, .., r_{Jt})$$

where s_{ijt}^{full} is given by

$$s_{ijt}^{full}(\pi, r_{i1t}, .., r_{iJt}) \quad = \quad \pi \; 1_{\{r_{ijt} \neq 1\}} \; \frac{\exp\left(\tilde{\delta}_{jt} - \beta_i^p p_{jt}\right)}{\sum_k 1_{\{r_{ikt} \neq 1\}} \exp\left(\tilde{\delta}_{kt} - \beta_i^p p_{kt}\right)}$$

Assuming for simplicity that the resistance of a bacteria is independently distributed across drugs (an assumption that can be relaxed using data on correlations), this choice probability can be computed using the average resistance rates at t and the estimated model parameters as follows:

$$s_{jt}^{full}(\pi) = \pi \sum_{n=0}^{J} \Bigg(\sum_{\substack{(k_1, .., k_n) \in \{1, .., J\} \\ | k_l \neq k_m, \forall l, m}} \underbrace{\prod_{l=1}^{n} r_{k_l t}}_{\substack{\text{probability resistant} \\ \text{to all } k_l, \forall l = 1, .., n}} \underbrace{\prod_{\forall k \neq k_l, \forall l}^{J} (1 - r_{kt})}_{\substack{\text{probability non resistant} \\ \text{to all } k \neq k_l, \forall l = 1, .., n}} \underbrace{\int s_{ijt}^{full}(\pi, r_{i1t}, .., r_{ik_1 t}, .., r_{ik_n t}, .., r_{iJt}) d\phi(\nu_i)}_{\substack{\text{choice probability of } j \\ \text{given information} \\ \text{on resistance to each drug}}} \Bigg)$$