Antibiotic Demand in the Presence of Antimicrobial Resistance

Pierre Dubois* and Gökçe Gökkoca†

January 2025‡

Abstract

Antimicrobial resistance (AMR) increases hospital stays, medical costs and mortality. Antibiotic consumption and the resulting selective pressure on bacteria can create AMR. We study the role of AMR in changes in prescriptions of antibiotics in France for treating bladder inflammation (cystitis) using a representative sample of general practitioners between 2002 and 2019. We propose a decision model for prescriptions when point-of-care rapid bacterial or susceptibility testing is performed or not, which affects patient-specific infection susceptibility information. The effects of resistance on demand and substitution behavior are identified by controlling for the endogeneity of resistance via the use of antibiotic sales in veterinary medicine. As resistance increases, physicians substitute other drugs, and we test whether physicians consider predictable resistance evolution in their decisions. We perform counterfactual analysis to assess the impact of decreasing the use of antibiotics in animals and limiting the use of fluoroquinolone to treat cystitis. Both policies reduce resistance to fluoroquinolones but have opposite effects on drug substitution and consumer surplus. Finally, we propose a method to evaluate the value of rapid bacterial detection and antibiotic susceptibility testing.

Keywords: health, physician prescription, antimicrobial resistance, diagnostic test, value of tests, demand.

JEL Codes: I10, D12, L11, C25

*Toulouse School of Economics, Toulouse, France, email: pierre.dubois@tse-fr.eu

†Analysis Group, Paris, France, email: gokce.gokkoca@analysisgroup.com

‡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 the Editor and three anonymous referees for very helpful comments and suggestions, as well as Jérôme Adda, Federico Ciliberto, Isabelle Tongio, Francois Lacoste, Thierry Magnac, seminar participants in Toulouse and conference participants at the IIOC 2022 conference in Boston, the EU Health Economics Association (EuHEA) Conference 2022 in Oslo, the 2022 European Association for Research in Industrial Economics (EARIE) Annual Conference in Vienna, the CEPR Conference in Health Economics in Toulouse, and the Journees Internationales du Risque in Niort in 2024 for useful comments.

1 Introduction

Motivation 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 increasing mortality rates. 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 greater the degree of 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 to cases where they are truly needed. 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 assess the effectiveness of policies intended to provide richer information on resistance or policies 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.

Contribution In this study, we identify physicians' response to AMR via their prescriptions for cystitis using prescription data in France from 2002 to 2019, a period long enough to observe meaningful variation in the susceptibility of bacteria to antibiotics. 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.

[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` (08/14/2022)) and the U.S. (`https://www.cdc.gov/onehealth/in-action/combating-ar-in-people-and-animals.html` (08/14/2022)), 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).

coli), and *iii*) the increase in extended-spectrum beta-lactamase-producing E. coli is a concern since it leads to multidrug-resistant bacteria (Martin et al., 2016). Modeling physicians' choices for this pathology allows us to abstract from the physician's expectation of what bacteria caused the disease because it is usually E. coli if it is bacterial, and consequently, we can directly use the resistance of E. coli to identify its impact on decisions.

We develop a decision model in which a physician can use rapid bacterial or susceptibility testing and then derive the model when tests are not available and information is imperfect. This method allows the integration of information on the susceptibility of the infection to an antibiotic versus the expected susceptibility when the physician has no patient-specific information in the decision process. Without a test, physicians make "empirical" prescribing decisions depending on the expected resistance of E. coli to each antibiotic. We thus estimate the model, which amounts to a discrete choice model for differentiated products, as in Berry (1994) and Berry et al. (1995); Nevo (2001), where the expected bacterial susceptibility (which is exactly the opposite of 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 accounts for bacterial susceptibility. We test the model where physicians only account for the publicly known previous-year susceptibility level against the model where they use an expected value of susceptibility for the current year, considering the antibiotic consumption of humans and animals in addition to the previous-year susceptibility level. We do not find evidence that physicians consider the expected susceptibility instead of the information on past susceptibility only. By estimating demand, we control for the endogeneity of prices and advertising by instrumenting with competition measures and BLP-type instruments. As there is also a potential simultaneity problem between demand and susceptibility to bacteria, we leverage the link between antibiotic use in animals and bacterial resistance in humans. France introduced two consecutive campaigns and regulations[4] that generated substantial exogenous (to human consumption) variations in the sales of antibiotics for animal production over time.

The decision model estimates show 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

[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.

heterogeneity, positive returns to advertisements and a preference for non-generics. We also control for the financial incentives introduced by performance-based bonuses in addition to fixed visit fees. The performance-based incentives depend on public health objectives that include *i*) increasing the share of generics prescribed (introduced in 2012) and *ii*) decreasing the share of certain groups of antibiotics (from 2017).

We also estimate a model of antibiotic resistance evolution where resistance depends on past resistance and antibiotic use by humans and animals and identify the positive effect of antibiotic usage on resistance. Then, using our demand estimates and resistance evolution model, we study the impact of two policies that have been considered to curb the increase in resistance to some class of antibiotics. Fluoroquinolones have shown increasing resistance since the early 2000s, and as broad-spectrum antibiotics with lower resistance to E. coli than other broad-spectrum antibiotics, such as amoxicillin, they are considered highly valuable for more complicated infection cases. Policies of interest are thus *i*) banning fluoroquinolones for the treatment of cystitis and *ii*) minimizing the use of fluoroquinolones for animals. The first policy changes prescriptions and then impacts bacterial resistance and subsequently even more prescriptions. The second policy first reduces resistance rates by diminishing antibiotic use for animals and then affects prescriptions for humans due to the lower resistance.

When fluoroquinolones are banned, physicians can substitute not only the most valued narrow-spectrum alternative but also other broad-spectrum antibiotics. The 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. When the veterinary use of antibiotics is reduced, physicians' prescriptions of fluoroquinolones increase as resistance decreases; this increases consumer surplus as well as expenses. However, there are also long-term benefits of this policy since it reduces antibiotic resistance in the future.

Finally, we show how to compute the prescription value of a diagnostic test at the point of care in terms of savings per prescription as well as the change in treatment success probabilities. Rapid antibiotic susceptibility testing with high accuracy is one of the key tools in combating AMR[5]. Given these values, we

[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 U.S. 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).

can determine when testing should be performed, depending on the value of being cured by the pathology and the price of the bacterial susceptibility test.

Literature Our work contributes to the literature on how physicians' prescription behavior is affected by the presence of AMR in the outpatient setting[6]. Earlier studies provided evidence on the substitution of older drugs, which are potentially less effective, with newer and more expensive drugs in outpatient and intensive care units Filippini et al. (2009); Heister et al. (2017); Howard (2004). Howard (2004) introduced a choice model for antibiotics where resistance to penicillin was the main independent variable to capture such substitution behavior. The study showed that information on an increasing level of resistance encourages substitution with newer alternatives. At a more aggregate level, Filippini et al. (2009) studied small-area variations via quarterly data on antibiotic sales in the outpatient setting in Switzerland in 2002. They proxied for resistance using the incidence rate of infections at the county level. In line with the conclusion of Howard (2004), the results indicated that the higher the proxies for bacterial resistance are, the more physicians substitute with newer and more expensive antibiotics. Bokhari et al. (2024) also investigated antibiotic demand from 2003 to 2013 in the UK via a discrete choice model of demand and supply. They studied the role of the spectrum in demand and considered different tax policies to address the gap in the prescription of narrow-spectrum antibiotics against broad-spectrum antibiotics. Therefore, they analyzed the effects of taxes in the substitution across narrow- and broad-spectrum antibiotics, but they did not allow bacterial resistance to enter the utility of the patient–physician pair. Our demand model incorporates a wide range of factors that affect decisions, such as changes in health authorities' guidelines, detailing, price and antibiotic susceptibility, and therefore provides a more complete analysis. Moreover, our data allow us to utilize not only cross-sectional variation but also time series variation in identifying the effects, especially those of resistance on demand. To the best of our knowledge, this is the first study that incorporates the susceptibility of the bacteria responsible for the pathology to all possible antibiotics. By doing so, we can identify the trade-off choice of physicians that depends on the relative susceptibility of the bacteria to

[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 due to the regulations on physician payments in France and the focus 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), allows us to assume 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).

each different antibiotic drug. We control for 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. Another novelty of this study is the consideration of the endogeneity of resistance caused by the use of veterinary antibiotics, which is related to the following literature on AMR evolution.

We also contribute to the literature concerning AMR evolution and its links to the consumption of antibiotics in humans and animals. There have been small-scale studies that have provided evidence of animal-originated resistant bacteria in humans (Hammerum and Heuer, 2009; Landers et al., 2012). A recent report by the European Centre for Disease Prevention and Control (ECDC), the European Food Safety Authority (EFSA) and the European Medicines Agency (EMA) used 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 were mixed for different groups of antibiotics. The authors noted a 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) studied the relationship between bacterial resistance and antibiotics used in both humans and animals in the U.S. across counties, time periods and multiple bacteria. He identified a positive correlation with human consumption but no significant relationship with antibiotic use in animals, which also depends on animal farming regulations and the 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 work also relates to the literature on practice style heterogeneity and point-of-care diagnostic information showing the role of bacterial susceptibility information in the selection of the correct antibiotic treatments. We integrate the use of rapid bacterial or susceptibility testing in the decision model. We consider two information models of how physicians account for bacterial resistance. We test whether physicians use information on resistance published the year before or try to have more sophisticated behavior to predict current susceptibility via past consumption of antibiotics. McAdams et al. (2019) reported that rapid point-of-care resistance diagnostics are key in the fight against antibiotic resistance, improving treatment

efficacy while limiting the costs of inappropriate antibiotic prescription. We also provide a decision model that allows us to evaluate the economic value of testing the susceptibility of bacteria before antibiotic choices. Huang et al. (2022) and Ullrich and Ribers (2023) reported that variation in antibiotic treatment may be related to variation in diagnostic information. As noted by Huang and Ullrich (2024), practice style heterogeneity can explain large differences in overall antibiotic use. Ullrich and Ribers (2023) analyzed how machine learning predictions may improve antibiotic prescribing. By estimating a binary antibiotic treatment choice model, they find differences in the ability to diagnose bacterial urinary tract infections and in how general practitioners weigh the expected cost of resistance against the curative benefits of antibiotics. In the absence of a rapid point-of-care bacterial test, another way to improve decisions consists of providing physicians with an artificial intelligence algorithm, but Ribers and Ullrich (2024) showed that the algorithm does not always provide improved outcomes over physicians who face the patient.

The remainder of this paper is organized as follows. Section 2 describes the different datasets we use and provides details on the institutional background. Section 3 provides the decision model, its estimation method, and the empirical results on physician prescription behavior. Section 4 presents the results of counterfactual policies. Section 5 presents the empirical results of the rapid bacterial detection and susceptibility tests. Section 6 concludes the paper.

2 Data and institutional setting

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) reported a decrease in antibiotic use, especially in pediatric patients, following the campaign. Carlet et al. (2020) questioned 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 they represent a serious threat to the effectiveness of the measures taken regarding human consumption (Laxminarayan et al., 2015). In 2010, France and the Netherlands were leading countries in the agricultural consumption of antibiotics. In the past decade, two consecutive campaigns, named EcoAntibio, targeted this problem in France from 2012-2016 and from 2017-2021. The first met the goal of reducing antimicrobial use by 25%. The second plan also aimed to reduce the use

of specific classes of antibiotics, such as fluoroquinolones and third- and fourth-generation cephalosporins, which are crucial resources for human medicine (ANSES, 2021). France has also taken action to incentivize physicians to prescribe antibiotics appropriately by attaching financial rewards to issuing fewer antibiotic prescriptions overall and to broad-spectrum antibiotics (Gökkoca (2024)). To understand how these policies interact and to provide a view of stewardship program outcomes, it is important to understand the role of AMR in curbing treatment decisions and the demand for available antibiotic drugs.

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); these data consist of prescription records from a panel of physicians covering the period from 2002 to 2019. We then 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 3, 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). The data on the 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 Antibiotic Prescriptions

The proprietary patient-level general practitioner visit and 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[7]. From 2009 to 2019, the representative sample size increased to approximately 2000 general practitioners. Each prescription record is identified by a patient and a physician identifier, date, diagnostic, and product

[7]These data were used in Dubois and Tunçel (2021) to study the prescription of antidepressants following a drug warning.

code of the drug prescribed[8]. Moreover, the age and sex of both the physician and patient are observed together with the region of operation for the physicians and chronic diseases for patients. We use the data from 2002-2008, where we observe the visits with and without any prescription to construct the outside good market shares. We consider the cases where there is a visit with a cystitis diagnosis but no prescription within seven days following the visit. As the data extraction changed after 2008 and did not allow us to have information on all physician visits that did not involve a drug prescription, we use the regional average rate estimated from 2002-2008 to impute the missing information on the outside good market share after 2009.

Table 1: Top 5 diagnoses with antibiotic prescriptions

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

Notes: For the 2009-2013 period, we only have access to the subset of prescriptions related to a cystitis diagnosis, so we cannot check the top diagnoses with antibiotic prescriptions 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 can be viral or bacterial in origin. Cystitis is considered bacterial, and guidelines suggest the use of antibiotic therapy[9]. Second, the bacteria responsible for cystitis is E. coli in 80% of cases (Kahlmeter, 2000; Rossignol et al., 2017). Since different antibiotic groups are prescribed for various bacteria (with overlaps), knowing which bacteria is most likely to be responsible helps us to identify the role of resistance in 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;

[8]The medical classification codes used are the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes defined by the 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 dosages 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.

[9]See recent guidelines from the 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.

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 aimed at improving the treatment of infections caused by E. coli and the development of E. coli resistance are very important.

When there is no information on the bacteria and/or its susceptibility profile, the treatment of uncomplicated cystitis remains an empirical therapy based on the physician's guess. Until 2016, the only *recommended* test to confirm bacterial infection was the urine strip test (Caron et al., 2018). This test does not report the type of bacteria or the resistance profile of the bacteria causing the infection. For cases of cystitis at risk of complications 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 aged 16 to 75 years (male patients represent 5% of cystitis diagnoses) without a cancer diagnosis (because their complication risk affects prescribing practices) and exclude all off-label prescriptions (0.6% of all prescriptions concern products with no authorized indication for cystitis). We also remove observations where multiple antibiotics are prescribed to the same patient on a given date because some patients may demand antibiotics to stock up for future use (approximately 5% of all prescriptions).

To address recurrent cystitis cases, we identify a visit as an "initial visit" if there was 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 failed treatment due to bacterial resistance or simply due to the misuse of antibiotics. To avoid any interference from this channel, we remove observations from secondary infections, which represent approximately 6.7% of all prescriptions.

Table 2 presents a summary of the prescription shares by chemical substance in 2002, 2010 and 2018 (beginning, middle and end of the data period). We observe that fosfomycin and norfloxacin are initially prescribed at a high rate, but later, especially in terms of generics, fosfomycin became the main treatment for cystitis, with more than 50% of the market share. While this is in line with the recommendations

for uncomplicated cystitis cases owing to its high effectiveness and short treatment period, the remaining antibiotic market shares do not necessarily follow the order from the guidelines. For example, nitrofurmentation was used 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 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[10].

[10]In our sample period, the guidelines were updated three times. The documents were accessed on September 2, 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, and https://www.has-sante.fr/upload/docs/application/pdf/2021-08/fiche_memo_cystite_durees_antibiotherapies_.pdf

Table 2: Prescription shares by chemical substance

	2002		2010		2018	
Class / Molecule	Branded	Generic	Branded	Generic	Branded	Generic
Amoxicillin	2.53	2.53	1.80	1.80	1.74	1.74
Amoxicillin and beta-lactamase inhibitors						
Amoxicillin and enzyme inhibitors	1.62	1.62	1.08	1.08	0.70	0.70
Pivmecillinam	0.26		0.01		6.87	
Fluoroquinolones						
Ciprofloxacin	8.04		5.47	5.47	3.29	3.29
Enoxacin	2.91		0.94			
Levofloxacin	0.02		0.17		0.16	0.16
Lomefloxacin	8.27		17.70		6.05	
Norfloxacin	25.71		20.79	20.79	4.94	4.94
Ofloxacin	5.39		4.61	4.61	5.24	5.24
Pefloxacin	0.60		0.40			
Other quinolones						
Flumequine	1.13		0.17		0.03	
Pipemidic acid	3.98		0.99		0.01	
Other antibacterials						
Fosfomycin	25.72		29.86	29.86	55.76	55.76
Nitrofurantoin		7.28		6.40		4.26
Sulfamethoxazole and trimethoprim	3.19	3.19	2.26	2.26	2.14	2.14
Third generation cephalosporins						
Cefixime	1.55	1.55	6.37	6.37	7.82	7.82
Cefpodoxime	0.13		0.24	0.24	0.16	0.16

Notes: Data are from 2002 to 2019. The data from the initial, middle and end of the period years are displayed to show the variations over time. The percentage points are reported.

2.2 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[11] by the mandatory national health insurance (Assurance Maladie, Medic'AM). We use 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 codes that can then be matched to individual prescriptions.

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

Table 3: Average price by chemical substance (in € per box)

	2002		2010		2018	
Class / Molecule	Branded	Generic	Branded	Generic	Branded	Generic
Amoxicillin	3.31	3.44	2.72	3.07	2.58	2.62
Amoxicillin and beta-lactamase inhibitors						
Amoxicillin and enzyme inhibitors	10.99	9.87	7.10	6.80	7.10	6.38
Pivmecillinam	5.40		0.00		5.35	
Fluoroquinolones						
Ciprofloxacin	25.92		21.96	11.20	11.58	9.26
Enoxacin	8.65		8.18			
Levofloxacin	25.14		23.53		12.86	10.75
Lomefloxacin	21.48		19.87		19.98	
Norfloxacin	8.22		5.95	4.39	0.00	3.61
Ofloxacin	16.41		10.64	11.12	9.35	8.96
Pefloxacin	31.03		48.38			
Other quinolones						
Flumequine	11.56		10.94		10.77	
Pipemidic acid	9.17		8.68		8.37	
Other antibacterials						
Fosfomycin	12.12		8.26	5.94	6.27	5.20
Nitrofurantoin		2.41		2.26		2.61
Sulfamethoxazole and trimethoprim	3.13	2.86	2.61	2.13	2.21	1.75
Third generation cephalosporins						
Cefixime	13.88	10.57	8.48	8.03	9.15	7.44
Cefpodoxime	13.70		8.18	6.97	7.96	6.22

Table 3 shows the average price per box (across products and brands) of the main chemical substances prescribed for cystitis. The regulation of prices for patent drugs and generics leads to a gap between the generic and branded prices of the same molecule. For molecules that experience generic entry during the period of study, we observe significant price decreases.

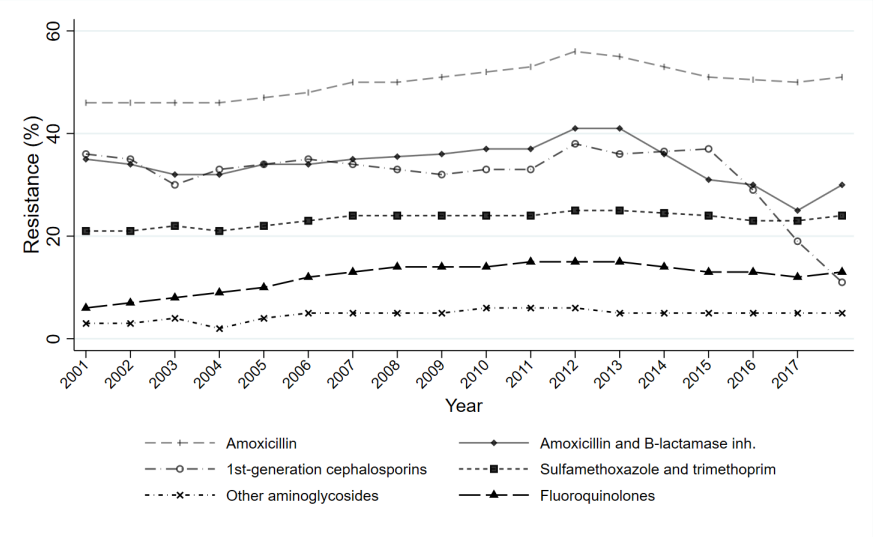
2.3 Antibiotic Resistance

We use data on resistance from a French network called REUSSIR (Réseau Epidémiologique des Utilisateurs du Système SIR), which 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 susceptibility to antibiotics reported by REUSSIR via the ONERBA reports from 2002 to 2018[12].

Figure 1 shows the evolution over time of the resistance of E. coli to each antibiotic with the average percentages of resistant strains tested for E. coli[13]. The most concerning element in this graph is the increase in resistance to aminoglycosides (gentamicin) and fluoroquinolones, which are crucial last-resort antibiotics. Notably, resistance to some antibiotics used against E. coli was not detected, which we will account for in our model using dummy variables for this missing information. The absence of resistance data for some antibiotic-bacteria pairs is usually due to low and/or relatively stable resistance.

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



2.4 Antibiotic Consumption by Animals

Data on antibiotic sales for animal use are obtained 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 to the development of resistance.

[12]See activity reports at `http://onerba.org/publications/rapports-onerba/`.

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

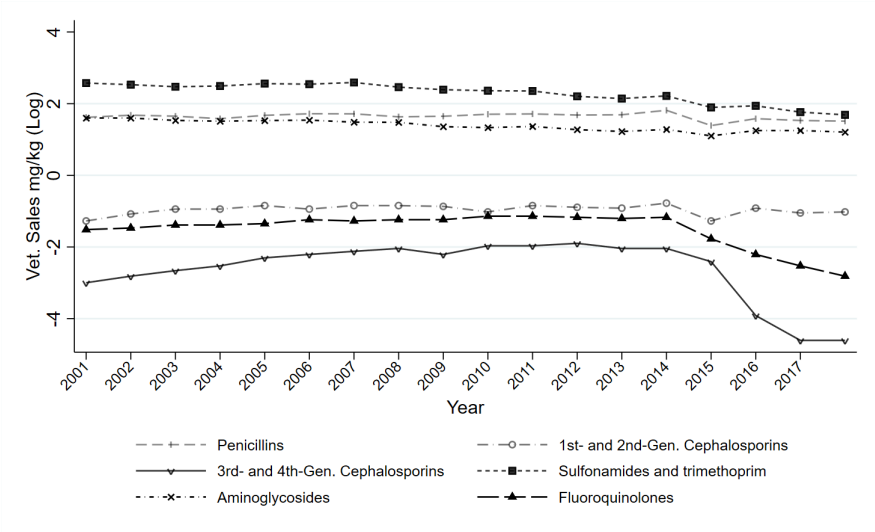
Table 4: List of antibiotics used in animals and their use in cystitis cases

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 the sales of antibiotics (on a log scale) for animals, 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 variations in the usage of antibiotics by animals that we can use to identify the link between animal use and resistance in humans.

Figure 2: (Log) Sales of antibiotics for veterinary medicine (density – mg/kg)



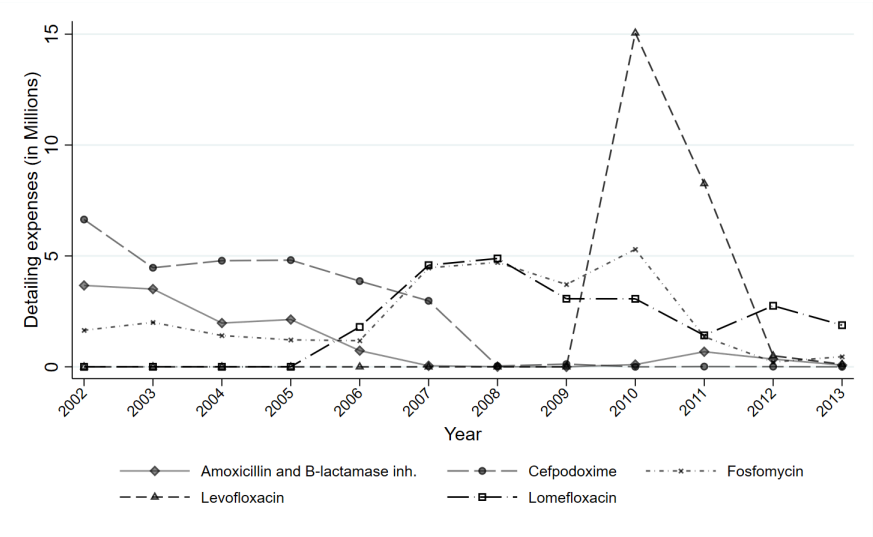
2.5 Detailing Expenses

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 the 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 in 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 detailed expenses associated with all drugs with the same active ingredient may promote the use of antibiotics for any of the possibly allowed indications, including cystitis, and thus may generate variation in the prescription of each antibiotic. Figure 3 shows an exceptional increase in advertising for levofloxacin in 2010, which comes from a particular case of entry of a branded drug copy of Tavanic (whose molecule is levofloxacin) by another company[14].

Then, advertising stopped in 2012 once generics entered the market. It is common that firms stop advertising once they face generic competition, which is explained by the fact that generic substitution is important, as pharmacists have an incentive to propose a generic substitution even if the patient brings in a branded drug prescription.

[14]Tavanic was owned by Aventis (later Sanofi-Aventis), and its generic version entered the market in France in 2012, but another company (Mediwin Limited, UK) produced the same branded drug, which entered the market in 2010 (see history of drug entry of Sanofi-Aventis product: `http://www.codage.ext.cnamts.fr/codif/bdm_it//fiche/index_fic_medisoc.php?p_code_cip=3400956189861&p_site=AMELI` and Mediwin Limited product: `http://www.codage.ext.cnamts.fr/codif/bdm_it//fiche/index_fic_medisoc.php?p_code_cip=3400949005680&p_site=AMELI`). The branded product competition might explain the peak in detailing in 2010 for Tavanic by Aventis or by Mediwin. Mediwin did not obtain a large market share, as its sales were only 10% of those of Tavanic in 2011; therefore, the peak is likely due to Aventis.

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



3 Demand Model

To study the role of antibiotic resistance in the prescription choices of antibiotics by physicians, we develop a demand model that we can estimate via our prescription data. In the case of cystitis, there is no mandatory rapid bacterial or susceptibility testing during our sample period before antibiotic prescription[15]. Those tests are thus rarely used, and drug prescriptions conditional on a test result were not allowed until very recently. Thus, decisions are made without testing, and physicians cannot observe patient-specific bacterial resistance information before deciding which antibiotics to ultimately prescribe. However, to evaluate the role of information and tests in prescription behavior, we develop a decision model allowing the existence of some testing and show how it simplifies when no test is available. This will allow us to simulate the counterfactual behavior of physicians if some tests become available and mandatory for antibiotic prescriptions.

3.1 Demand Model

We now define a decision model for the prescription of antibiotic treatments in the case of cystitis. All physician–patient pairs with a cystitis diagnosis choose among products defined as a "chemical substance" or molecule[16] from a pharmaceutical company (brand)[17].

[15] Rapid bacterial testing with urine strip tests are very infrequently used (Kinouani et al., 2017).

[16] 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.

[17] As many laboratories produce generic products with very small market shares, we define a pseudo brand "Fringe". A brand is considered 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.

We consider a general framework where a physician may have the possibility to use rapid bacterial or susceptibility testing and then derive the model when tests are not available and information is imperfect. This will allow us to simulate the counterfactual effects of the availability of rapid bacterial tests that could be used by physicians at the time of prescription. Decisions will then potentially depend on the regulatory rules concerning the use of tests and whether physicians would be able to prescribe an antibiotic conditional on a test result[18]. Without a test, physicians make "empirical" prescribing decisions depending on the expected resistance of E. coli to each antibiotic.

3.1.1 Decision model

Two types of tests can be used and sometimes coexist. The first type of tests are rapid bacterial detection tests that simply confirm whether a cystitis is due to a bacterial infection. We denote by π the probability that it is a bacterial infection[19].

The second type of tests are rapid susceptibility tests, which indicate whether the bacteria is resistant to a given antibiotic molecule l (susceptibility being the opposite of resistance). This type of test allows the physician to use patient-specific information that does not consider the expected susceptibility in the population, denoted μ_{jt} for drug j at year t, but the patient-level susceptibility is denoted μ_{ijt} for patient i.

As the French national health insurance fully reimburses the tests when they are available and then recommends (or even mandates) the use of a test together with conditional prescriptions, we consider that the patient is always tested when a rapid test is available; this simplifies the decision model, although it could be extended to the more general case where tests are not mandatory when they exist.

We start writing the decision model when the best information is available to the physician and then derive the model when the information is less precise or absent.

In the best case, the physician obtains information from a bacterial detection test and a susceptibility test for some (or several) antibiotics. We simplify the problem by considering only one susceptibility test against one antibiotic.

First, if the rapid bacterial test indicates that there is no bacterial infection, no antibiotic is prescribed.

[18] In the case of sore throat, such rapid tests exist and have been reimbursed and mandatory in France since 2021.

[19] Here, we assume that all bacterial infections are caused by the bacteria E. coli. According to Bent et al. (2002); Medina-Bombardo et al. (2003), the rate at which suspected urinary tract infections are indeed caused by a bacterial infection is approximately 50% in France.

This happens with probability $1-\pi$. With probability π, the test indicates that there is an E. coli infection. The susceptibility test is subsequently performed to determine whether the bacteria is susceptible to drug j, and the test allows the physician to use patient-specific information on susceptibility $\mu_{ijt} \in \{0,1\}$ for patient i. While developing the model with various susceptibility tests is straightforward, Thus, the available test informs the physician whether the bacteria are susceptible to the chemical substance l.

We specify the decision utility u_{ijdt} for patient i's prescription of product $j \in \{1,\ldots,J_t\}$ in region d and year t as additively separable between a mean utility δ_{jdt}, a price effect, and the decision maker's expected susceptibility of the bacteria to drug j denoted $E_\mu(\mu_{ijt})$:

$$u_{ijdt} = \delta_{jdt} - \beta_i p_{jt} + \gamma \ln E_\mu(\mu_{ijt}) + \varepsilon_{ijdt} \tag{1}$$

where p_{jt} is the price of product j and ε_{ijdt} is an idiosyncratic i.i.d. error term that follows an extreme value distribution. In this specification, γ represents the opposite of the resistance disutility or the preference for drugs to which the bacteria are more susceptible[20]. We allow the price disutility to be heterogeneous across consumers with a random coefficient $\beta_i = \beta + \sigma_p \nu_i$, where β is the mean preference, σ_p captures the degree of variation in taste and $\nu_i \sim \mathcal{N}(0,1)$. We also specify an outside good utility with the mean utility normalized to zero such that $u_{i0dt} = \varepsilon_{i0dt}$. This outside good corresponds to the choice to not prescribe any antibiotics. In practice, we consider that no antibiotic is prescribed when there is no prescription within seven days following a visit with a cystitis diagnosis.

In the case of fully resistant bacteria, where $E_\mu(\mu_{ijt}) = 0$, the model is equivalent to the case where the drug j is out of the choice set as $u_{ijdt} = -\infty$; this could occur either because there is no uncertainty in the expectation or because a test provides perfect information on μ_{ijt}. In the case where $E_\mu(\mu_{ijt}) = 1$, either because the bacteria are expected to never be resistant to j or because an informative test detects that the bacteria are not resistant to j, the indirect utility simplifies to $u_{ijdt} = \delta_{jdt} - \beta_i p_{jt} + \varepsilon_{ijdt}$.

We also specify a mean utility δ_{jdt} additively separable in several terms as follows:

$$\delta_{jdt} = x_{jdt}\beta + \xi_{m(j)} + \xi_t + \xi_d + \zeta_{jdt} \tag{2}$$

where x_{jdt} is a vector of observable characteristics of product j (except price and susceptibility), $\xi_{m(j)}$ is a

[20] We specify it with a logarithmic functional form because it appears empirically better.

molecule fixed effect for the molecule $m(j)$ of product j, ξ_t is a time fixed effect, ξ_d is a region fixed effect[21] and ζ_{jdt} is an unobserved characteristic of product j at period t and region d that affects demand.

Among the time-varying observable characteristics x_{jdt}, we include detailing expenses a_{jt} and dummy variables for changing health authorities' guidelines for prescription drugs and for changing national health insurance financial incentives to physicians. Indeed, some molecules were excluded from the guidelines or changed from first-line options to second-line options or to the list of antibiotics to be prescribed when there is a complication risk, as presented in the Appendix A.2. Moreover, some antibiotics were affected by financial incentives, as, 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 was to address increasing healthcare costs and to improve the standardization of care. Two measures of performance are relevant to our analysis. First, since 2012, physicians have been provided incentives to prescribe more generics. 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 of the interaction variable should be positive. Second, 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 "at-risk" antibiotics, and it includes amoxicillin and clavulanic acid, 3^{rd} and 4^{th} generation cephalosporins, and fluoroquinolones. As we already include molecule fixed effects, we interact the chemical subgroup 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. Thus, given a susceptibility test with respect to drug l, the decision maker behaves as described in Figure 4, where $E_\mu(\mu_{ijt})$ is the expected susceptibility of the bacteria to drug j when there is no test available for j.

As shown in Figure 4, the susceptibility information affects the consideration set of the physician by simply excluding the drugs to which the bacteria are fully resistant. It also increases the probability of choosing other drugs to which the bacteria are not resistant by an amount that depends on the expected susceptibility.

As $P(\mu_{ilt} = 1) = E(\mu_{ilt})$, the decision model above implies that the ex ante choice probability of a drug

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

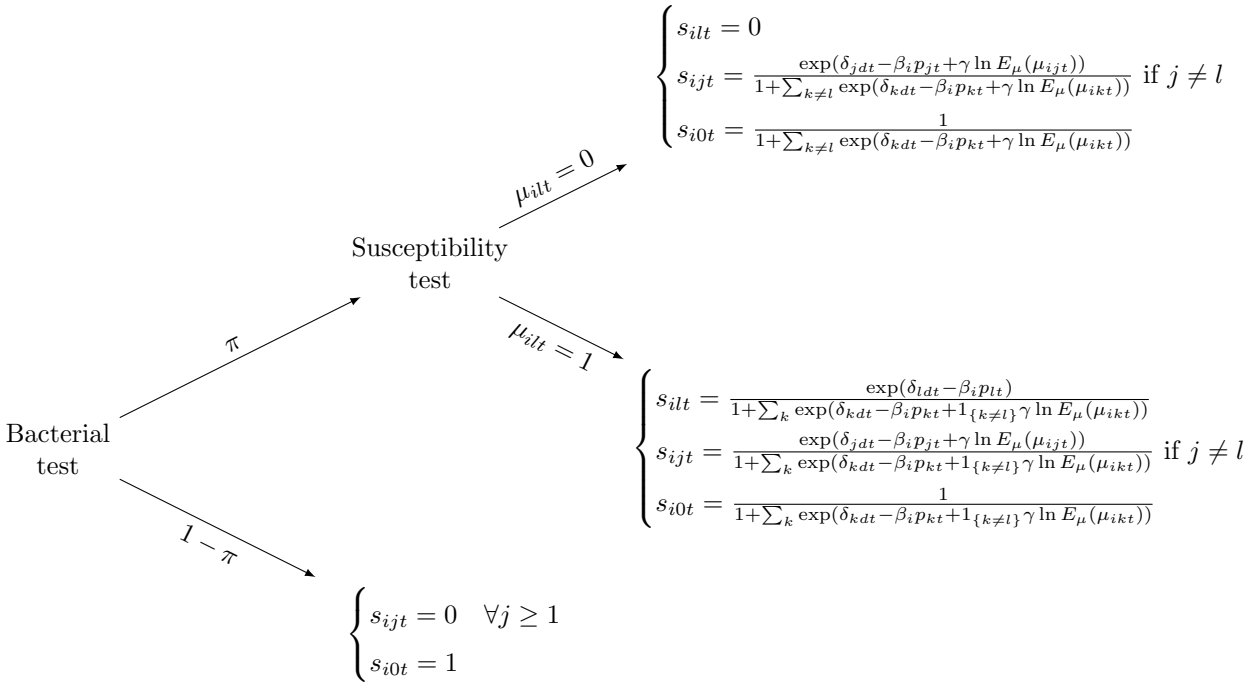


Figure 4: Prescription probabilities with bacterial and susceptibility testing

$j \in \{1,..,J\}$ can be written as (with the complementary choice probability s_{0t} for the outside good):

$$\begin{aligned} s_{jt} =& \pi\Bigg((1-E(\mu_{ilt})) \int \frac{\exp(\delta_{jdt}-\beta_i p_{jt}+\gamma \ln E_\mu(\mu_{ijt}))}{1+\sum_{k\neq l}\exp(\delta_{kdt}-\beta_i p_{kt}+\gamma \ln E_\mu(\mu_{ikt}))} d\phi(\nu_i) \\ &+ \; E(\mu_{ilt}) \int \frac{\exp(\delta_{jdt}-\beta_i p_{jt}+\gamma \ln E_\mu(\mu_{ijt}))}{1+\sum_{k}\exp(\delta_{kdt}-\beta_i p_{kt}+1_{\{k\neq l\}}\gamma \ln E_\mu(\mu_{ikt}))} d\phi(\nu_i) \Bigg) \qquad \text{if } j\neq l \end{aligned} \tag{3}$$

and

$$s_{lt} = \pi \; E(\mu_{ilt}) \int \frac{\exp(\delta_{ldt}-\beta_i p_{lt})}{1+\sum_{k}\exp(\delta_{kdt}-\beta_i p_{kt}+1_{\{k\neq l\}}\gamma \ln E_\mu(\mu_{ikt}))} d\phi(\nu_i) \tag{4}$$

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

Without a susceptibility test but only a bacterial test, the choice model becomes:

This implies that, with a bacterial test only, the ex ante choice probability of a drug $j \in \{1,..,J\}$ can be written as (with the complementary choice probability s_{0t} for the outside good):

$$s_{jt} = \pi \int \frac{\exp(\delta_{jdt}-\beta_i p_{jt}+\gamma \ln E_\mu(\mu_{ijt}))}{1+\sum_{k}\exp(\delta_{kdt}-\beta_i p_{kt}+\gamma \ln E_\mu(\mu_{ikt}))} d\phi(\nu_i) \tag{5}$$

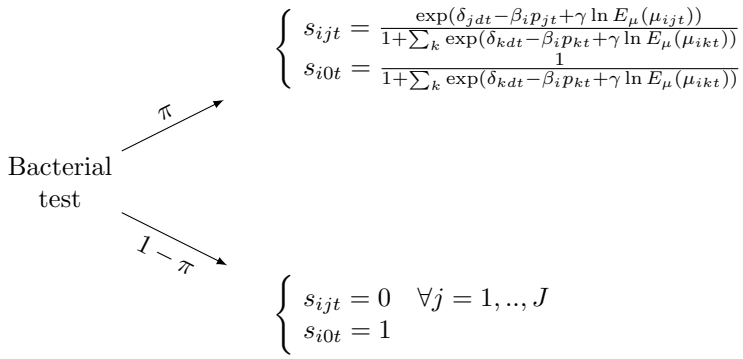


Figure 5: Prescription probabilities with bacterial testing only

and without a bacterial test, it becomes:

$$s_{jt} = \int \frac{\exp(\delta_{jdt} - \beta_i p_{jt} + \gamma \ln E_\mu(\mu_{ijt}))}{1 + \sum_k \exp(\delta_{kdt} - \beta_i p_{kt} + \gamma \ln E_\mu(\mu_{ikt}))} d\phi(\nu_i) \tag{6}$$

Thus, in the absence of a rapid detection test for cystitis, the choice probability of each antibiotic in our sample should follow equation (6). An important determinant of this choice will thus be the perceived expected susceptibility of E. coli to each antibiotic, which varies over time but can also vary across regions. The specification of the way the information on susceptibility (or resistance) affects decisions is then introduced in section 3.1.2.

3.1.2 Information models

Without testing, physicians use the expected susceptibility of each antibiotic and choose prescriptions according to the choice probabilities of antibiotics, as in equation (6).

The information we observe on resistance is identical to that the physicians can observe from the health authorities' annual publications. These data represent the average country resistance levels and vary across years[22].

While in principle, each rational decision maker should use all the information available to predict the expected susceptibility of E. coli to each possible drug, including past susceptibility and past antibiotic

[22]Note that some antibiotic drugs are not 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 greater at the beginning of the sample period and decreases with 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.

usage, we consider two possible information models, including an "unsophisticated" model where physicians simply use the previous year susceptibility level μ_{jt-1} for $E_\mu(\mu_{ijt})$ and a "sophisticated" model where they act upon the predicted susceptibility $E_\mu(\mu_{ijt})$ via the relevant available information.

Unsophisticated Information Model In this case, we specify the expected susceptibility as the lag susceptibility and allow the national average susceptibility level to interact with regional dummies to capture the possible regional variation that may be known to physicians. This approach assumes that

$$E_\mu(\mu_{ijt}) = \lambda_{d(i)}\mu_{jt-1}$$

, where λ_d is a region-specific scalar and $d(i)$ is the region of i.

Sophisticated Information Model In this case, we assume that the prescribers use the expected susceptibility of the E. coli bacteria. As we do not observe this expectation, we group the unobserved demand shock ζ_{jdt} and the unobserved effect of expected susceptibility to the product j that could be regional (d) and year (t) specific and define an "expected susceptibility" inclusive demand shock ξ_{jdt} defined as:

$$\xi_{jdt} \equiv \zeta_{jdt} + \gamma \ln E_\mu(\mu_{ijt})$$

and estimate the demand model with instrumental variables that need to be orthogonal to ξ_{jdt}. For this, a sufficient assumption is that instrumental variables be orthogonal to the demand shock ζ_{jdt} and to the expected susceptibility $E_\mu(\mu_{ijt})$ so that instruments are orthogonal to ξ_{jdt}. This identifying assumption allows us to estimate ξ_{jdt}. We then test whether decision makers account for the expected susceptibility with the following method.

Denoting ν_{jdt} as the expectation error such that $\ln \mu_{jt} = \ln E_\mu(\mu_{ijt}) + \nu_{jdt}$, we obtain:

$$\xi_{jdt} = \zeta_{jdt} + \gamma \ln \mu_{jt} - \gamma\nu_{jdt}$$

As ν_{jdt} and ζ_{jdt} can be correlated with ξ_{jdt-1}, we rewrite this equation as follows:

$$\xi_{jdt} = \rho\xi_{jdt-1} + \gamma \ln \mu_{jt} + \omega_{jdt} \tag{7}$$

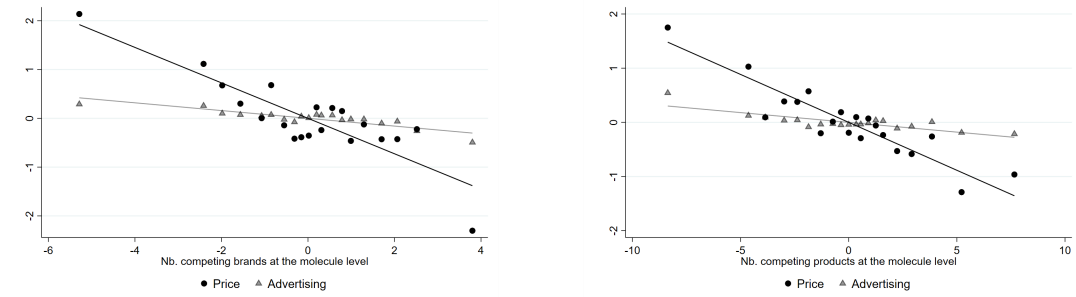
where $\omega_{jdt} \equiv \zeta_{jdt} - \gamma\nu_{jdt} - \rho\xi_{jdt-1}$. As ω_{jdt} is correlated with the susceptibility $\ln \mu_{jt}$ through the expectation error ν_{jdt}, we estimate equation (7) instrumenting susceptibility with the lag susceptibility $\ln \mu_{jt-1}$; the lagged total human usage of antibiotic j, q^h_{jt-1}; and the lagged total animal usage of antibiotic j, q^a_{jt-1} (given the known possible relationship between susceptibility and antibiotic consumption (Adda, 2020; Austin et al., 1999; Rahman and Hollis, 2023)). Then, if γ is zero, prescribers do not account for the possibility of predicting susceptibility to antibiotic consumption in animals and humans.

3.2 Identification and Estimation

We estimate the demand model via a standard General Method of Moments (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 the same molecule, the number of different products of the same molecule, 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 importantly, competition between products that have the same chemical substance.

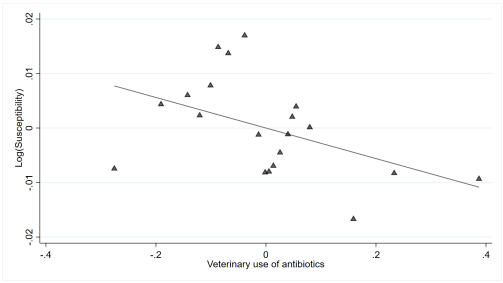
Moreover, an endogeneity problem may also arise through the evolution of resistance to antibiotics. Indeed, antibiotic resistance is affected by the use of antibiotics due to the selection of resistant strains over susceptible strains. Therefore, it is likely that the shocks to resistance and demand are correlated. To correct for endogeneity, we use antibiotic consumption in animals. Although there are debates on the roles of different channels (such as the environment, processing, farm environment, and human consumption of dairy products and meat) 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; for example, Adda (2020) did not find that the animal use of antibiotics affects bacterial resistance from human samples in the U.S. A recent joint report (European Centre for Disease Prevention and Control et al., 2021) provided an exhaustive survey of the empirical relationship in Europe between AMR in bacteria from humans and food-producing animals. As each bacterial and antimicrobial pair behaves differently in terms of the rate of

Figure 6: Relationship between price or advertising expenses (detailing) and instrumental variables



Notes: The vertical axis corresponds to the residuals of the log price or log advertising regression on the molecule, time, and region fixed effects. The linear regression lines are displayed.

Figure 7: Relationship between E. coli susceptibility and veterinary use of antibiotics



Notes: The vertical axis corresponds to the residuals of the E. coli log susceptibility regression on the molecule, time, and region fixed effects. The linear regression line is displayed.

resistance development and transmission, our focus is on the results from E. coli-related cases. Ramchandani et al. (2005) supported the link between the use of antibiotics in animals and bacterial resistance in humans. Their results indicated that urinary tract infections (i.e., nest bladder infections (i.e., cystitis)) could be a food-borne illness, as they reported that the bacteria responsible for the infection in their sample were of animal origin. Hammerum and Heuer (2009) also noted that animals are the origin of the threat of resistant E. coli and its relationship to resistant E. coli infections in humans.

Thus, we instrument resistance via antibiotic sales for animal use. The identification of the demand parameters is achieved via instruments and unobserved product characteristics to form conditional moment conditions $E\left(\zeta_{jdt} \mid x_{jdt}^{exo}, w_{jdt}\right)$, where x_{jdt}^{exo} are the exogenous characteristics in the vector x_{jdt} of (2), and w_{jdt} consists 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.

As advertising is also included and potentially endogenous in demand, we also instrument it. To evaluate the power of our instrumental variables in this demand estimation framework with multiple endogenous variables, Figure 6 shows the relationship between the residual of price or advertising (from a linear regression controlling for molecule, time, and region fixed effects) and the number of competing brands or number of competing products of the same molecule, which are used as instruments. The negative relationship is consistent with the idea that more competition leads to a lower price and that competition is correlated with lower detailing expenses. Figure 7 shows the decreasing relationship between E. coli susceptibility to each antibiotic and the veterinary use of that antibiotic, which is also used as an instrument. These figures show the power of our instrumental variables. The first-stage multivariate regression of these endogenous variables on all instrumental variables reported in Table 12 in appendix A.4 shows the significant power of the instrumental variables in explaining prices, advertising and antibiotic susceptibility.

3.3 Demand Estimates

We estimate the demand model using the data described above, which allows us to observe the antibiotic prescription choice, including the no antibiotic outside option. On average, conditional on the physician's diagnosis of cystitis, the no-antibiotic treatment option is chosen approximately 5% of the time. Antibiotic treatments of the same chemical substance and brand but with different box sizes are aggregated into a single alternative, and we use the average price for the molecule. We obtain a discrete choice model with, on average, 77 antibiotic options (molecule-brand) with important variation over time because of the entry of a few molecules and many generics (33 products from 15 molecules in 2002 to 104 products from 18 molecules in 2013). The outside option consists of prescriptions other than antibiotics (pain killers can, for example, be prescribed). We present the main results of the random coefficient logit model in Table 5. Column (1) assumes that prescribers potentially use sophisticated information and thus does not include the expected susceptibility to each antibiotic. In this case, the demand estimation step does not separately identify the unobserved demand shock from the effect of antibiotic susceptibility. Column (2) restricts the prescribing behavior to be unsophisticated where physicians use the one-year lag of antibiotic susceptibility, in which case we can directly identify its effect in the demand model.

The results show that the 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, the prevalence of complementary insurance (Grandfils et al., 2008) and the incentives to prescribe cheaper generics provided by the national health insurance system. Advertising (detailing) has the expected positive effect. We also observe that, on average, the decision maker (physician–patient pair) values generics less than branded drugs because the generic dummy is negative. With respect to 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 of the policy discouraging the prescriptions of "at-risk" antibiotic groups[23]. Moreover, the impact of the pay-for-performance program appears to increase over time.

Then, in the non-sophisticated information case, which allows for the direct identification of the effect of susceptibility to antibiotics (Column (2)), the effect of lag susceptibility on utility is positive, meaning that the more resistant E. coli is to a given antibiotic, the less valuable it becomes in the prescribing behavior of physicians.

Concerning the magnitude of the price coefficient and the detail coefficient, the empirical results show that a 100,000 euro increase in detailing (the average detailing per year is 90,000 per drug with, on average, 397,820 per branded drug and 3,750 per generic) is equivalent in terms of mean utility to a price decrease of 3.06€ in the model of Column (1) and of 3.46€ in the model of Column (2), which seems very plausible given that the average drug price is 8.15€ (6.91 for generics and 12.33 for branded drugs).

With respect to the susceptibility coefficient, the functional form implies that the effect on the mean utility is not constant over the [0,1] interval. However, as the susceptibility of E. coli to antibiotics is on average 0.75, ranging from 0.44 to 0.93, a change in susceptibility from the drug to which E. coli is the most susceptible to the drug where E. coli is the least susceptible is equivalent to a change in the mean utility of a price increase of 2.16€ for the model of Column (1) and 3.31€ for the model of Column (2).

[23] J01DD: third-generation cephalosporins, J01MA: fluoroquinolones, J01CR: amoxicillin and beta-lactamase inhibitors.

Table 5: Random coefficients logit demand estimates

		(1)		(2)	
Price	β	-0.346***	(0.077)	-0.226***	(0.045)
	σ_p	0.141***	(0.030)	0.106***	(0.022)
$\log(\mu_{j,t-1})$				5.791**	(1.864)
Detailing (in Mil.)		1.061***	(0.298)	0.782***	(0.157)
Generic		-2.836***	(0.082)	-2.780***	(0.075)
Dummies for Pay-for-Performance changes					
Generic $\times$ $\mathbb{1}_{\{t\geq 2012\}}$		0.155	(0.169)	0.329**	(0.102)
J01MA $\times$ $\mathbb{1}_{\{t\geq 2017\}}$		-0.579***	(0.150)	-0.512***	(0.133)
J01DD $\times$ $\mathbb{1}_{\{t\geq 2017\}}$		0.008	(0.179)	0.054	(0.168)
J01CR $\times$ $\mathbb{1}_{\{t\geq 2017\}}$		-0.528*	(0.213)	-1.214***	(0.296)
J01MA $\times$ Trend $\times$ $\mathbb{1}_{\{t\geq 2017\}}$		-0.416***	(0.108)	-0.334***	(0.090)
J01DD $\times$ Trend $\times$ $\mathbb{1}_{\{t\geq 2017\}}$		-0.335**	(0.125)	-0.318**	(0.117)
J01CR $\times$ Trend $\times$ $\mathbb{1}_{\{t\geq 2017\}}$		-0.272	(0.155)	-0.256	(0.146)
No Obs.		8372		8372	

Notes: Standard errors in parentheses. Significance levels: $^{*}: p < 0.05$, $^{*}*: p < 0.01$, $^{*}**: p < 0.001$. The models include fixed effects for year, region, molecule, guidelines and incentive program controls, and missing indicator variables. The coefficient σ_p is the standard deviation of the normally distributed random coefficient on price with mean β.

Robustness checks: We report in appendix A.5 several robustness checks estimates. First, Table 13 shows the random coefficient logit model when allowing lag susceptibility to affect the mean utility differently across regions. Although the differences across regional coefficients are not statistically significant, the results are in line with those of Sabuncu et al. (2009), who reported that physicians are less sensitive to antimicrobial resistance in the North. These variations could be due to variations in antibiotic use across regions[24]. Table 15 shows that the parameters of the same random coefficient logit model are similar when we use a quantity-weighted average price across different box sizes per molecule, and Table 14 shows that it is also robust when we have regional specific effects of lag susceptibility. Then, we also test which information lag on susceptibility matters. Table 16 reports the estimates with up to three years lag and shows that the one-year lag is the most relevant and that once the one-year lag susceptibility is accounted for, older information on susceptibility is statistically insignificant. Table 17 also shows the same model estimates with a proxy for susceptibility using the no revisit regional average rate within 7 days for the patient, as defined in appendix A.1. This result shows the same positive effect of the proxied susceptibility to each antibiotic in the decision.

[24]The statistics for 2015, reported in `https://www.hauts-de-france.ars.sante.fr/antibioresistance-agir-tous-ensemble`, show that antibiotic consumption varies across regions.

Finally, in Table 18, we show the estimates of the same model but use the resistance of another bacteria to each antibiotic, a bacterium that is responsible for less than 10% of the cases of cystitis in France. The results show that the effect is insignificant.

3.4 Test of Information Models

We now test which information model described in section 3.1.2 is preferred. This depends on the role of bacterial susceptibility in physician prescription decisions. We thus estimate Equation (7) and report the results with varying instruments in Table 6.

Table 6: Information model test using ξ_{jlt}

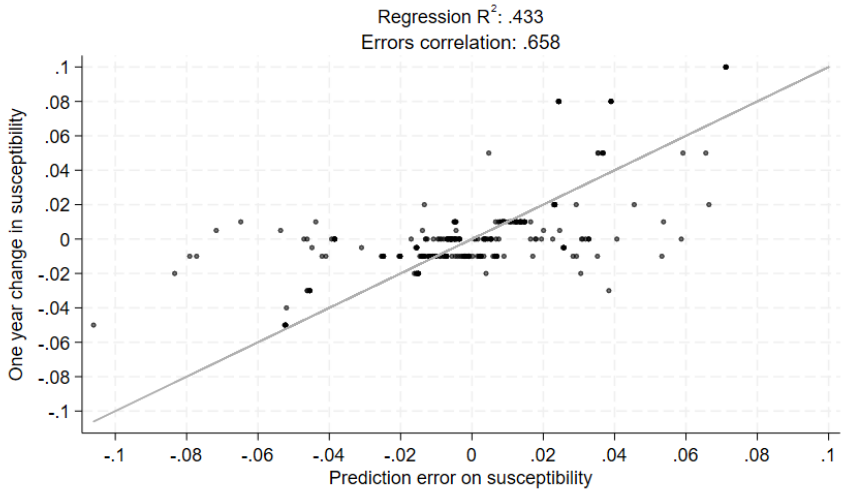
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
$\log(\mu_{j,t})$	-0.044	-0.011	0.042	0.010	0.005	0.056	0.072	0.057
	(0.055)	(0.080)	(0.063)	(0.064)	(0.069)	(0.102)	(0.072)	(0.080)
$\xi_{j,t-1}$					0.733***	0.733***	0.733***	0.733***
					(0.010)	(0.010)	(0.010)	(0.010)
Instruments		✓	✓	✓		✓	✓	✓
No Obs.	8372	8372	8372	8372	7011	7011	7011	7011

Notes: The standard errors are clustered at the market level. Significance levels: $^{*}: p < 0.05$, $^{**}: p < 0.01$, $^{***}: p < 0.001$. Instrumental variables: lag of animal usage of antibiotics for (2) and (6), lag of human use of antibiotics for (3) and (7), and lag of animal usage and human use of antibiotics for (4) and (8). The models include a constant that is not presented in the table. Table 19 in appendix A.6 shows the first stages of the 2SLS regressions.

The table shows the OLS results with or without controlling for the lag shock $\xi_{j,t-1}$ in Columns (1) and (5) and then several 2SLS results with varying instruments. All the results show that current antibiotic susceptibility is never significant, meaning that we cannot reject the hypothesis that physicians do not account for factors that potentially affect current susceptibility or allow us to predict susceptibility.

This result shows that providing physicians with better information on the antibiotic susceptibility of bacteria could aid them in their decision-making processes. They might make better decisions, as they may overestimate or underestimate current susceptibility via lagged susceptibility information, as shown in Table 5. However, the mistakes will be more or less important depending on the change in susceptibility over time and thus on the use of antibiotics by humans or animals during the previous year. For the counterfactuals that follow, we thus use the preferred demand results from Column (2) of Table 5.

Figure 8: Comparison of prediction errors and one-year changes in antibiotic susceptibility



Notes: Prediction errors $E_\mu(\mu_{ijt}) - \mu_{jt}$ when $E_\mu(\mu_{ijt}) = \hat{\mu}_{jt}$ or when $E_\mu(\mu_{ijt}) = \mu_{jt-1}$, where $\hat{\mu}_{jt}$ is the prediction of the resistance model via antibiotic usage information.

To evaluate how lag susceptibility differs from realized or predicted susceptibility[25], Figure 8 displays a scatter plot of the susceptibility prediction error ($\hat{\mu}_{jt} - \mu_{jt}$) over the yearly susceptibility change ($\mu_{jt-1} - \mu_{jt}$). This finding shows that they are not identical; thus, using the lag susceptibility information instead of a prediction using past antibiotic usage makes a difference. The results also reveal that susceptibility to antibiotics varies from year to year. The correlation of the prediction error using the prediction with antibiotic usage with that using lag susceptibility is only 0.65, whereas the R^2 of the regression is 0.43. This shows that there are meaningful differences between these errors in prediction, although not surprisingly, they are positively correlated.

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.

[25]The prediction model used is the one presented below in section 4.1.

When simulating these counterfactuals, we always keep the prices of drugs fixed. We thus assume that the price regulation would not change significantly in these counterfactual scenarios. Indeed, the reimbursement prices of prescription drugs that are still on patent are regulated and defined in a negotiation with drug companies where the regulator (the CEPS - comité économique des produits de santé) accounts for the clinical merit of the drug and the price of comparable products. Prices are set for several years and revised downward over time (almost never upward) when the product is aging. The generic prices are also set by regulations and fixed by regulations at 40% of the price of the corresponding branded drug.

For the period of our data, we thus take prices as given in our counterfactuals. Actually, in the counterfactual case where fluoroquinolones are banned for prescriptions in the case of cystitis, this does not mean that fluoroquinolones have to exit the market. The regulated price of a drug is unique for all indications. While banning fluoroquinolones in the case of cystitis reduces the market size for these products (the cystitis indication represents, on average, 40% of all sales of fluoroquinolones), they do not exit and thus do not change the degree of competition for other antibiotics that are also used in other indications for which competition is not affected by our counterfactual. We thus consider that our counterfactuals should not affect the price setting with the regulator too much.

Banning fluoroquinolones as a treatment option for the case of simple cystitis is equivalent to removing them from the choice set of the decision maker; this will inevitably reduce fluoroquinolone antibiotic use, leading to decreased resistance of E. coli to fluoroquinolones, but substitutions toward other antibiotics will occur, as predicted by our demand estimates. Regulating the veterinary use of fluoroquinolones decreases resistance, ceteris paribus. However, the demand model predicts that decreased resistance increases the prevalence of fluoroquinolones in humans in response to increased susceptibility[26].

Banning the Use of Fluoroquinolones Financial incentives to limit the prescription of fluoroquinolones have been provided to physicians in France since 2017. However, we still observe they were prescribed for cystitis even after 2017 and constituted a substantial share before that. Therefore, we simulate the effects of a stricter rule regarding the prescription of fluoroquinolones from 2002 by banning their use for the treatment of cystitis. This policy is interesting for two reasons. First, despite the increase in bacterial resistance to

[26] 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.

fluoroquinolones, they remain effective in treating bacteria that are resistant to many other drugs. Therefore, fluoroquinolones need to be saved for cases where first-line antibiotics fail[27]. Second, a large proportion of fluoroquinolone antibiotics are prescribed for cystitis.

Figure 9: Shares of cystitis diagnosis among fluoroquinolone prescriptions (2014-2019)

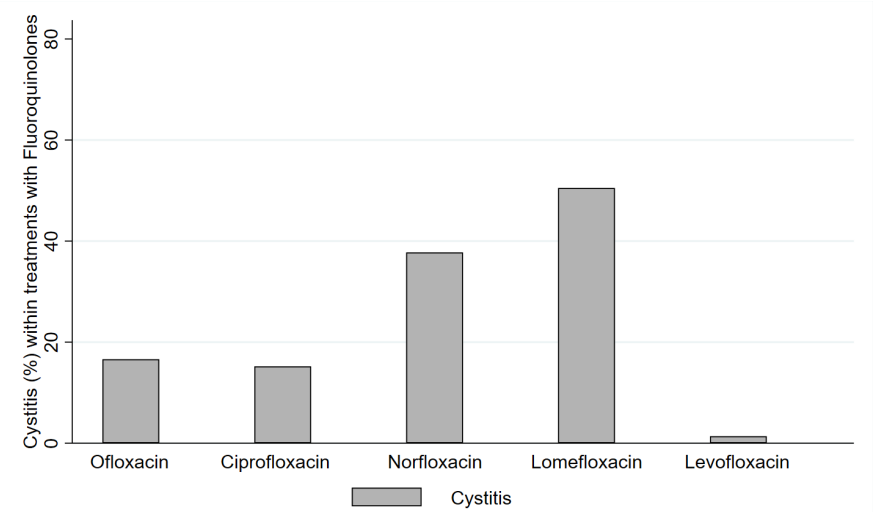


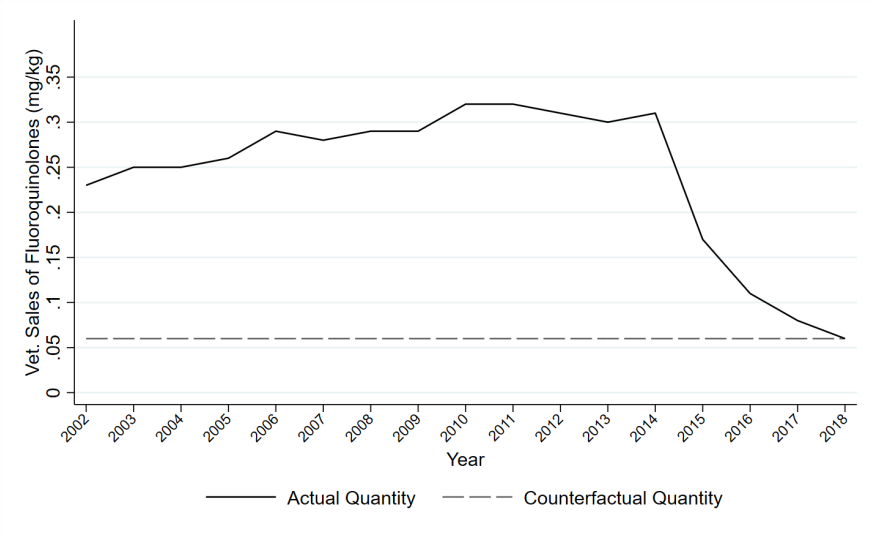
Figure 9 shows the percentage of cases of cystitis (or cystitis and urinary tract infection (UTI)) among the prescriptions of fluoroquinolone molecules for women from 2014-2019. The largest share is for lomefloxacin (J01MA07). Among all prescriptions of lomefloxacin, more than 50% were prescribed for cystitis. It is followed by norfloxacin (J01MA06), with a value of approximately 40%. Hence, this policy targeting fluoroquinolone prescriptions for cystitis would have a significant effect on the overall prescription of fluoroquinolones in outpatient care.

Limiting the Use of Fluoroquinolones for Animals This counterfactual policy is motivated by the fact that limiting antibiotic use for animals rather than humans may be less costly for the population. In fact, France implemented restrictions on the use of fluoroquinolones in animals starting in 2012 with a program aimed at increasing awareness and monitoring (a program called EcoAntibio starting in 2012), followed in 2017 until 2021 by another campaign (called EcoAntibio2) with stricter measures[28] and the ban since March 2016 of preventive use of several fluoroquinolones for animal farming (exemptions were granted for treatment purposes and after a susceptibility test). As a result, Figure 10 shows the decrease in the number

[27]These are also the reasons why fluoroquinolones are in the "at-risk" group defined by the financial incentive scheme.
[28]See `https://agriculture.gouv.fr/le-plan-ecoantibio-2-2017-2022`.

of antibiotics sold for veterinary use in terms of mg per kilogram of animal body weight after 2014. In our counterfactual simulation, we thus set sales to the minimum observed in 2018. We then examine the change in resistance and how demand has responded to this change since this policy was implemented in 2002.

Figure 10: Sales (mg/kg) of fluoroquinolones, Source: ANSES



To simulate those counterfactuals, we must first 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 Column 2 of Table 5 and the resistance evolution model, we then study the changes 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, which highlights 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. As some veterinary antibiotic uses are provided at the ATC3 aggregate level (penicillins, aminoglycosides), others are reported at the ATC4 aggregate level (without overlap), whereas the E. coli resistance of each molecule (ATC5) is observed, we use the ATC4 or ATC3 level of antibiotic use for animals in our resistance model (see Table 4). Moreover, the

resistance data do not provide resistance information for all the molecules. However, the molecules for which no resistance information is collected are unlikely to bias the model estimates because the data collection on resistance started before the increasing resistance trend occurred. Missing resistance data dummies are used as control variables in the demand model and remain identical across all counterfactuals. After some specification searches for functional forms, we obtain a model where a nonlinear transformation of the expected resistance is linearly additive in the explanatory variables. This leads to the following fractional logit model of Papke and Wooldridge (1996):

$$E\left(\ln \frac{r_{jt}}{1-r_{jt}}\right) = \beta_{0t} + \underbrace{\rho\, r_{jt-1}}_{\text{Lag resistance}} + \underbrace{\beta_1\, q^h_{jt-1} + \beta_2\, q^{h^2}_{jt-1} + \beta_3\, q^h_{ATC4(-j)t-1}}_{\text{Human prescriptions}} + \underbrace{\phi_1\, q^a_{ATC4(j)t-1} + \phi_2\, q^a_{ATC3(j)t-1}}_{\text{Veterinary sales}} \tag{8}$$

where $r_{jt} = 1 - \mu_{jt}$ and j represent the chemical substance, t denotes years, $q^a_{ATC4(j)t}$ and $q^a_{ATC3(j)t}$ represent the veterinary sales in mg of active ingredient per kilogram of animal body weight (mg/kg) of products of the ATC 4 and ATC 3 classes of j in period t, q^h_{jt} represents the total community-level quantity of molecules j and $q^h_{ATC4(-j)t-1}$ represents the quantity of other drugs in the same class because of possible resistance spillovers across antibiotics of the same family. Notably, we are not using data on hospital prescriptions of antibiotics, but in France, they represent a small fraction (approximately 10%) of the total antibiotics used. The antibiotic sales for veterinary use data come from ANSES (2021). The functional form implies that the resistance (r_{jt}) is an increasing function of the right-hand side of equation (8), but it can be convex or concave depending on the parameters.

Table 7: Resistance model estimates

	(1)	(2)	(3)
Lag resistance (r_{jt-1})		0.061***	0.065***
		(0.002)	(0.002)
Human antibiotic consumption			
q^h_{jt-1}	0.158***	0.036***	0.025**
	(0.009)	(0.008)	(0.009)
$q^{h^2}_{jt-1}$	-0.002***	-0.001***	-0.001**
	(0.000)	(0.000)	(0.000)
$q^h_{ATC4(-j)t-1}$	-0.128***	0.030***	0.041***
	(0.012)	(0.008)	(0.007)
Animal antibiotic consumption			
$q^a_{ATC4(j)t-1}$	3.176***	0.834***	0.452
	(0.424)	(0.199)	(0.351)
$q^a_{ATC3(j)t-1}$	0.170***	0.092***	0.087***
	(0.015)	(0.010)	(0.010)
Year Fixed Effects			✓
No Obs.	337	337	337

Notes: Standard errors are in parenthesis. Significance levels: $^*: p < 0.05$, $^{**}: p < 0.01$, $^{***}: p < 0.001$. One observation per molecule and year.

Table 7 shows the estimates of equation (8), including the lag resistance or not and with or without year fixed effects. Once we control for lag resistance, we find that the effect of antibiotic consumption by humans is positively correlated with resistance, but the marginal effect decreases in quantity. Given the parameters estimated, the functional form is such that resistance is an increasing concave function of antibiotic consumption (we draw that function in Figure 16 in appendix A.7). There is also a positive relationship between the use of other molecules within the same chemical subgroup, indicating cross-resistance effects. Veterinary sales of antibiotics also positively affect 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.

4.2 Counterfactual Policies' Impacts on Resistance

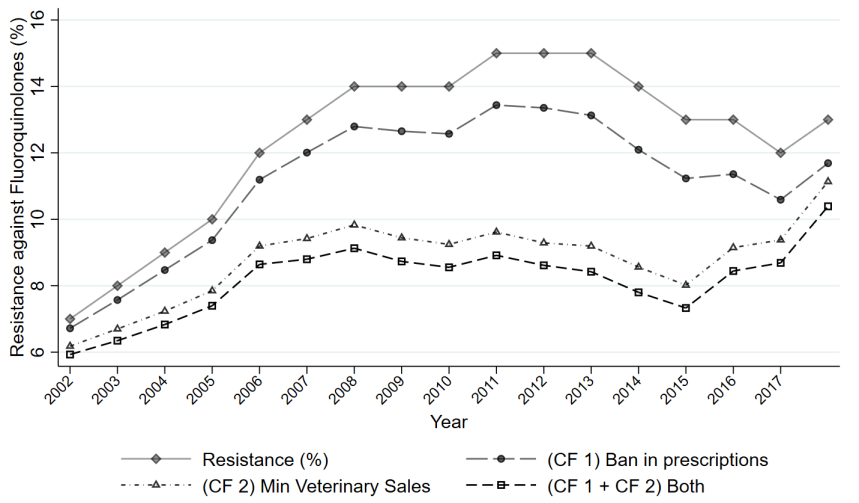
Simulating our two counterfactuals consists of using equation (8) and the demand model with either a ban of fluoroquinolones for humans or a reduction in fluoroquinolones for animals. In each case, we start from the initial period (2002) and simulate year by year the counterfactuals given that any year $t+1$ depends on the susceptibility (resistance) to each antibiotic and the consumption of antibiotics in year t so that the effects of

the counterfactual policies accumulate in parallel with the observed and unchanged time variations in other determinants, such as animal consumption of non-fluoroquinolones, the human consumption of antibiotics for other indications (using the rates shown in 9) and the entry or exit of drugs.

We first present the obtained counterfactual resistance against fluoroquinolones for each policy separately for CF1 and CF2) and in combination in Figure 11. As a result of each policy, resistance to fluoroquinolones is always lower. However, the increase in resistance from 2002 to 2011 remains, even if it is at a slightly lower rate when fluoroquinolones are banned for human prescriptions in the case of cystitis. In contrast, the other policy manages to curb the increase starting in 2007 because it prevents fluoroquinolone consumption in animals from continuing to increase until 2001, which is why resistance has increased.

By 2011, the effect of the 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.

Figure 11: E. coli resistance under counterfactual policies

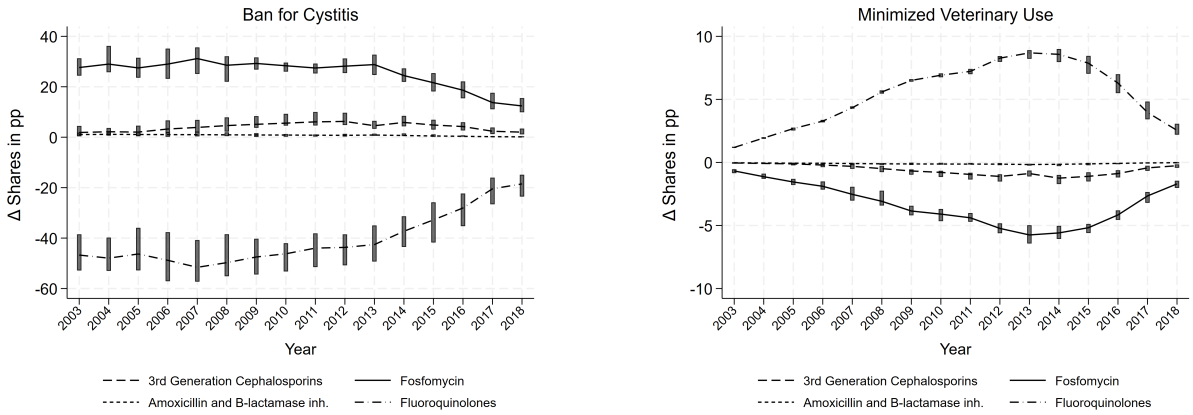


4.3 Counterfactual Market Shares

We now turn to examining the changes in the market shares of antibiotics in each counterfactual. Figure 12 shows the changes in the market shares of four antibiotic groups that represent significant market shares and are important in terms of assessing the consequences of policies for AMR. These groups or molecules are the fluoroquinolones, the fosfomycin, which has the highest market share and is the first-line therapy throughout the sample, the 3^{rd} generation cephalosporins and the family of amoxicillin and β-lactamase inhibitors, both

of which are included in the "at-risk" antibiotic groups that are crucial to preserve.

Figure 12: Change in the market shares in percentage points



Notes: The lines represent the average across France of the change in prescription probability, and the vertical bars indicate the range of variation across regions. The left graph shows the counterfactual where fluoroquinolones are banned from prescriptions in the case of cystitis, and the right graph shows the counterfactual where fluoroquinolone use for animals is reduced to its minimal quantity.

Figure 12 shows that when fluoroquinolones are banned from prescription, physicians largely replace fosfomycin with 3^{rd} 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) is a 3^{rd} generation cephalosporin that belongs to the "at-risk" list with increasing resistance of bacteria. This finding shows that policies targeting fluoroquinolones can have unintended spillover effects on other antibiotics for which antimicrobial resistance is also problematic.

In the counterfactual where animal use of fluoroquinolones is reduced to a minimum, we observe an increase in the prescription share of fluoroquinolones because resistance to fluoroquinolones decreases owing to the reduction in fluoroquinolone consumption in animals. This increase corresponds to a substitution of mostly fosfomycin and partly 3^{rd} generation cephalosporins with fluoroquinolones.

Neither counterfactual policy substantially affects the share of amoxicillin and β-lactamase inhibitors. Overall, although both policies lead to a reduction in antibiotic resistance, they have opposite impacts on the market shares of fluoroquinolones and their substitutes.

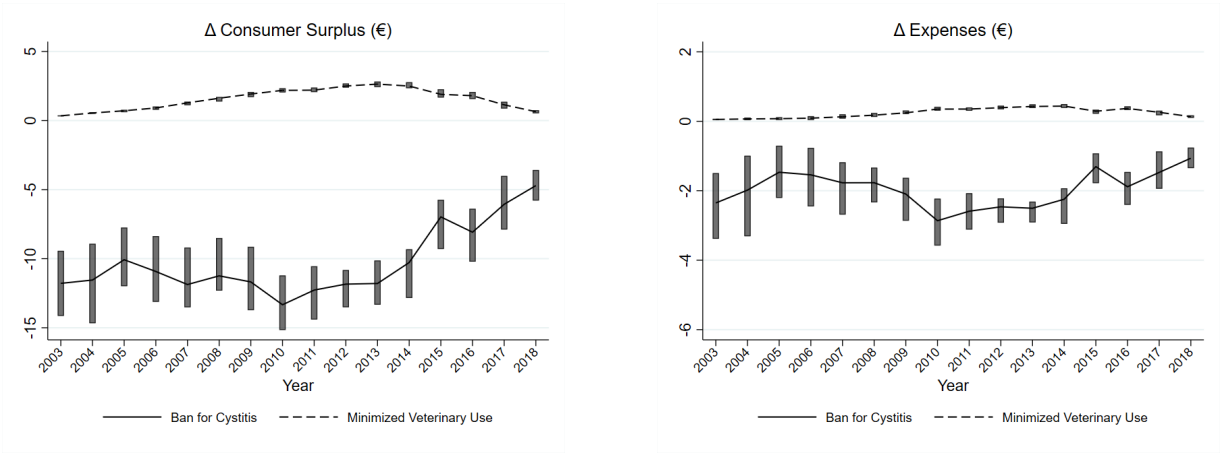
4.4 Counterfactual Changes in Consumer Surplus and Expenses

We then compute the consumer surplus change per patient following the usual method Small and Rosen (1981) due to the ban of fluoroquinolone prescriptions (MacFadden et al., 2018). Note that we abstract from

the impacts of the policy on potential follow-up visits that could change with different treatment choices. This impact is likely limited in our case because we focus on "first visits" to capture nonrecurring/initial diagnoses. More importantly, we do not account for the benefits from a potential decrease in bacterial resistance beyond the treatment of cystitis or beyond the time period of our prescription data.

Figure 13 shows the change in average consumer surplus and expenses per prescription, with vertical bars showing the minimum and maximum averages by region in a given year. The fluoroquinolone ban leads to greater effects in magnitude. On average, the loss of consumer surplus is 10 €, and the decrease in expenses is approximately 2 € until 2010 to 5 € for consumer surplus and 1 € for expenses. The decreases in magnitude after 2010 are partly a result of the generic entry of fosfomycin products with incentives for generic prescriptions. For the counterfactual that reduces the animal use of antibiotics, the changes are opposite but smaller in magnitude than when fluoroquinolones are banned. On the one hand, a decrease in resistance increases consumer surplus. On the other hand, this decrease leads to higher market shares for fluoroquinolones, whose price is greater than that of antibiotics, such as fosfomycin, from which prescriptions are substituted.

Figure 13: Changes in consumer surplus per patient and expenses per prescription in €



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

5 Value of Diagnostic Tests

We now use our framework to derive the value of diagnostic tests such as bacterial tests or susceptibility tests. As discussed by Firth et al. (2023), policymakers are also considering the use of bacterial tests to combat

increasing AMR. We therefore use our decision model to simulate the counterfactual prescriptions in the case of a rapid bacterial test as well as in the case of a rapid susceptibility test that could be used by physicians at the time of prescription. As shown in section 3, without a test, physicians make "empirical" prescribing decisions affected by the expected susceptibility of E. coli to each antibiotic. With a test, physicians become able to prescribe an antibiotic conditional on a test result.

Rapid Bacterial Detection Test As a rapid bacterial test allows physicians to confirm whether the cystitis is due to an infection, the prescription choice will essentially be scaled down by the average infection rate π by E. coli of this cystitis diagnosis, as shown in equation (5).

As the test leads to a reduction in antibiotic prescriptions, it reduces pharmaceutical spending. We define the prescription value of a rapid bacterial test $v_t^{RapidTest}$ as the savings per prescription if a test is available[29]:

$$\underbrace{v_t^{RapidTest}(\pi)}_{\substack{\text{Prescription value} \\ \text{of rapid bacterial test}}} = \sum_{j\in\{1,\dots,J_t\}} \underbrace{p_{jt}(s_{jt}^{NoTest}(\mu_{t-1}) - s_{jt}^{bact}(\pi,\mu_{t-1})}_{\substack{\text{Additional expenses on drug } j \\ \text{if no test vs bacterial test}}} \tag{9}$$

where $s_{jt}^{NoTest}(\mu_{t-1})$ is the choice probability of prescribing j in the absence of testing, as in equation (6), and $s_{jt}^{bact}(\pi,\mu_{t-1})$ is the choice probability when a bacterial test is available given the average infection rate π, as in equation (5), with, in both cases, the use of the result that the expected susceptibility rates physicians use is the one-year lag vector μ_{t-1}.

Rapid Antibiotic Susceptibility Testing When a susceptibility test for molecule l is available, the physician can use patient-specific susceptibility information.

We define the prescription value of the susceptibility test as the savings per prescription, that is, the difference in expenses per prescription with susceptibility testing for drug l and without susceptibility testing

[29]Note that the value of the test here represents only the healthcare savings per prescription without considering the impact on resistance. Using this test will save antibiotic use overall and hence help to limit resistance externalities. As bacterial resistance is associated with increased hospitalizations, deaths, and productivity loss, slowing resistance growth is likely to generate greater returns on such tests in the future.

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

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

. 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 them to diagnostic test spending.

(but with testing for bacterial infection). The value is thus:

$$\underbrace{v_t^{Susc.Test_l}(\pi)}_{\substack{\text{Prescription value} \\ \text{of rapid susceptibility test}}} = \sum_{j\in\{1,\ldots,J_t\}} \underbrace{p_{jt}s_{jt}^{Susc.Test_l}(\pi,\mu_{t-1},\mu_{lt})}_{\substack{\text{Expenses on drug } j \text{ when using} \\ \text{susceptibility test to drug } l}} - \sum_{j\in\{1,\ldots,J_t\}} \underbrace{p_{jt}s_{jt}^{bact}(\pi,\mu_{t-1})}_{\substack{\text{Expenses on drug } j \\ \text{without test}}} \tag{10}$$

where $s_{jt}^{Susc.Test_l}(\pi,\mu_{t-1},\mu_{lt})$ is the choice probability from equations (3) and (4), and $s_{jt}^{bact}(\pi,\mu_{t-1})$ is again the one from equation (5).

Example of Bacterial Detection and Rapid Susceptibility Testing to Amoxicillin We then calculate the prescription value of a rapid antibiotic susceptibility test, which would indicate whether the bacteria were 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[30], 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: in the absence of any test (current situation), when a bacterial test is available, and when an amoxicillin susceptibility test is available. The empirical treatment without a test costs € 6.78 per prescription. If rapid susceptibility testing for amoxicillin is available, one would save from € 3.21 for $\pi = 0.75$ to € 5.59 for $\pi = 0.25$. The results show that the higher the probability of bacterial infection is, the lower the savings from using a bacterial test or amoxicillin susceptibility test. With a bacterial detection test, the savings are always smaller, although when the infection rate is small, a larger part of the savings is achieved with a bacterial test without susceptibility testing.

[30] 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 (€)

Bacterial Infection Rate	No	Bacterial		Amoxicillin	
π	Test	Detection Test		Susceptibility Test	
		(€)	Δ%	(€)	Δ%
0.25	6.78	1.70	-75.0%	1.19	-82.4%
0.50	6.78	3.39	-50.0%	2.38	-64.8%
0.75	6.78	5.09	-25.0%	3.57	-47.3%

Notes: Each cell reports the drug prescription cost per patient diagnosed with cystitis according to the true bacterial infection rate in the population and the availability (with mandatory use) of different tests. We also report the change in cost in % compared to the absence of a test. In the case of a bacteria test only, savings are inversely proportional to the bacterial infection rate as prescriptions decisions do not change but are scaled down by the rate of a positive result.

Value of Tests From a welfare perspective, even without considering the 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 by assuming that in the case of bacterial infection (π), the success rate of treatment is equal either to the susceptibility rate of the bacteria to the antibiotic j prescribed, μ_{jt}, or to the probability that the patient does not revisit the physician within 7 days, $\mu_{jt}^{\text{no revisit}}$ (which is the rate we used to check the robustness of our demand model to the susceptibility measure and varies across regions and years). In the case of nonbacterial infection ($1-\pi$), the success rate of treatment does not change regardless of the antibiotic prescribed or not.

The mean probability of being cured is thus the sum over all antibiotics j of the drug choice probability $s_{jt}(\mu_{t-1})$, which, according to our demand model, depends on the lag susceptibility rate vector μ_{t-1} multiplied by the success probability of the treatment. Thus, this probability of being cured is $\sum_{j=1\in\{1,\dots,J_t\}} s_{jt}(\mu_{t-1})\mu_{jt}$ or $\sum_{j\in\{1,\dots,J_t\}} s_{jt}(\mu_{t-1})\mu_{jt}^{\text{no revisit}}$.

Upon susceptibility testing to antibiotic l, the drug choice probability becomes $s_{jt}^{Susc.Test_l}(\pi,\mu_{t-1},\mu_{lt})$. Thus, the change in the probability of being cured if we assume the probability of each treatment success if the susceptibility to the antibiotic is prescribed is as follows:

$$\Delta_{treat}^{l}(\pi) \equiv \pi \sum_{j\in\{1,\dots,J_t\}} \left[\left(s_{jt}^{Susc.Test_l}(\pi,\mu_{t-1},\mu_{lt}) - s_{jt}(\mu_{t-1})\right)\mu_{jt}\right] \tag{11}$$

while if we assume it is the no revisit rate, it becomes:

$$\Delta_{treat}^{l}(\pi) \equiv \pi \sum_{j\in\{1,\dots,J_t\}} \left[\left(s_{jt}^{Susc.Test_l}(\pi,\mu_{t-1},\mu_{lt}) - s_{jt}(\mu_{t-1})\right)\mu_{jt}^{\text{no revisit}}\right] \tag{12}$$

Table 9 shows the probability estimates of being cured for both assumptions of successful treatment, with or without susceptibility testing[31]. Notably, both measures of being cured yield similar results; one is based on observed data from physicians visiting patients with antibiotic treatment within a week after the first treatment, and the other is based on antibiotic susceptibility rates. When the antibiotic susceptibility rates are used, the probabilities of being cured are slightly greater than when the rate of no revisit is used, but the change in this probability due to susceptibility testing is slightly greater when the physician revisit rate is not used. We find, in both cases, that this probability is very large even without testing and that testing increases this probability by 4.3 or 5.8 percentage points, depending on the success rate used. Table 9 also shows that there is variation across regions, although it is relatively small in the end.

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

	Using success rate μ_{jt}			Using success rate $\mu_{jt}^{\text{no revisit}}$		
Amoxicillin Susceptibility Test	No	Yes	$\Delta_{treat}^{Amoxicillin}$	No	Yes	$\Delta_{treat}^{Amoxicillin}$
All	0.923	0.967	0.043	0.887	0.945	0.058
Region						
Center-East	0.925	0.967	0.042	0.894	0.948	0.054
Center-West	0.929	0.969	0.040	0.890	0.946	0.056
East	0.918	0.965	0.047	0.884	0.943	0.059
North	0.921	0.966	0.045	0.881	0.942	0.060
West	0.921	0.965	0.044	0.889	0.946	0.057
Paris	0.916	0.963	0.047	0.893	0.948	0.055
South-East	0.929	0.969	0.040	0.880	0.941	0.061
South-West	0.926	0.968	0.042	0.886	0.944	0.058

Notes: Columns 1 and 2 present respectively the average probability of being cured without or with susceptibility testing and success probability μ_{jt}. Columns 4 and 5 present respectively the average probability of being cured without or with susceptibility testing and success probability $\mu_{jt}^{\text{no revisit}}$. Column 3 corresponds to equation (11) and Column 6 to equation (12).

Then, the conditions under which susceptibility testing should be used will depend on the value of curing a patient. This value may depend on the opportunity costs of sick leave, the healthcare savings of not revisiting one's physician 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 the price of test p_T^l such that it is optimal to mandate a bacterial susceptibility 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,

[31] 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 the Bourgogne Franche-Comte region.

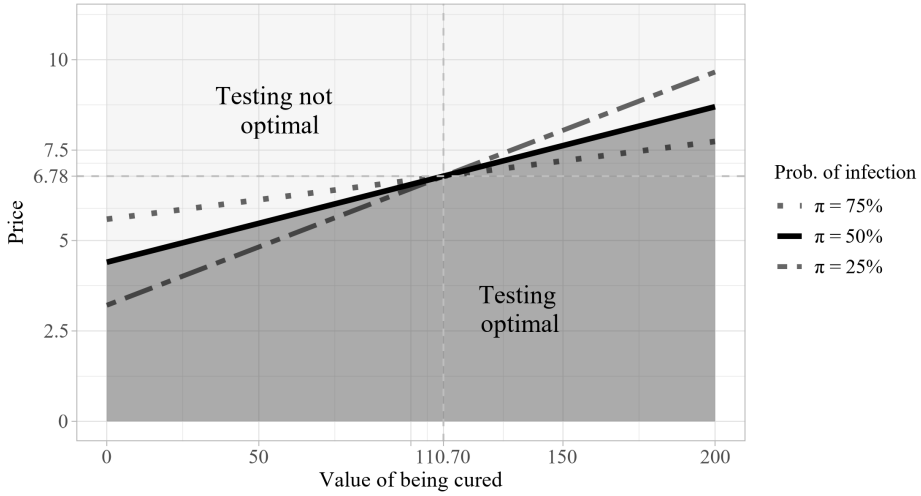
$\Delta^l_{treat}(\pi) \times V$, is greater than the healthcare cost of treatment with a rapid susceptibility test, which is $p^l_T - v_t^{Susc.Test_l}(\pi)$, where the prescription value of the susceptibility test comes from Equation (10). In other words, imposing testing will be valuable if and only if

$$\Delta^l_{treat}(\pi) \geq \frac{p^l_T - v_t^{Susc.Test_l}(\pi)}{V} \tag{13}$$

With respect to the values of (p^l_T, V) satisfying Condition (13), the higher the value of V is, the higher the maximum price that should be accepted.

Using the prescription savings from Table 8 and the change in the probability of successful treatment of equation (11) from Table 9, Figure 14 displays the regions in the (p^l_T, V) space where mandatory testing is optimal for the case of rapid susceptibility testing for amoxicillin in 2018[32].

Figure 14: Optimality of susceptibility testing



Notes: The shaded region corresponds to the optimality of testing for $\pi = 0.5$

While $\Delta^l_{treat}(\pi)$ fixes the slope of the relationship between the maximum price of the susceptibility test for antibiotic l that should be used and the value of being cured, the prescription value ($v_t^{Susc.Test_l}(\pi)$) determines the intercept. Notably, the probability of bacterial infection π affects both the level and slope, as it increases the level of the maximum price with optimal testing at the origin but decreases the slope of the indifference line. Moreover, all the indifference lines for each value of π cross at ($V = 110.70$ €, $p^l_T = 6.78$ €) because both $\Delta^l_{treat}(\pi)$ and $v_t^{Susc.Test_l}(\pi)$ are linear in π.

Thus, for values of being cured $V \leq 110.70$€, the lower the probability of bacterial infection π is, the

[32]We assume that susceptibility testing also indicates the bacterial status of the suspected infection.

higher the upper bound on the price of the test that is beneficial for society. This is because as the rate of infection decreases, the savings from avoided useless treatments increase. 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, for the value of being cured $V > 110.70$€, the maximum price of the test one should use is greater when the probability of infection is greater; this exemplifies where the use of susceptibility testing makes a difference in addition to using a detection test.

6 Conclusion

In this work, we develop a decision model for drug prescriptions in the case of infections whose responsible bacteria can be resistant to different antibiotics. We show how to account for the expected susceptibility to each antibiotic in a decision model such that we can evaluate the value of bacterial and antibiotic susceptibility testing. We first study the empirical effects of bacterial resistance to antibiotics on drug prescription choice via an exhaustive panel of general practitioner visits over a long period in France. We identify the effects of antimicrobial resistance on treatment choices and control for the endogeneity of prices and resistance using data on the veterinary use of antibiotics that affect resistance. The results indicate that bacterial resistance affects prescription behavior, as physicians replace antibiotics for which the resistance is higher. We explore two ways in which the physicians responses account for resistance. We test whether physicians act upon the expectation of current resistance instead of using resistance in the last period, a "sophisticated" information model, and find that the "unsophisticated" information model is preferred and shows that physicians consider one year lagged resistance in their prescription decisions. 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 antibiotic groups that have been targeted by the same pay-for-performance program since 2017.

We then performed counterfactual analysis via a resistance evolution model for E. coli bacteria. We study the effects of a policy in which the use of fluoroquinolones is banned for the treatment of cystitis or is reduced to a minimum quantity for veterinary use. While both policies reduce resistance to fluoroquinolone, they have

opposite effects on consumer surplus, expenses, and drug substitutions. In the case of the fluoroquinolone ban, the results highlight the substitution toward other antibiotics that are valuable but need to be saved for more complicated cases. In the case of a reduction in veterinary use of fluoroquinolone, the market share for fluoroquinolone prescriptions for humans increases due to increased susceptibility, which attenuates 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)[33]. In all the counterfactual studies we conduct, note that we do not account for the value of the long-term gains from lower antimicrobial resistance, indicating that our results can be regarded as the lower bound in terms of 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 introduced and mandatory. We show how to determine the maximum price of a susceptibility test that one should use, depending on the value of being cured. The results allow for the determination of the optimal testing policy, which also depends on the prevalence rate of bacterial infections. This maximum price that is optimal for 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 in the future and for other types of infections. As the data on resistance increased with improved surveillance of bacteria and data collection, future work could address this question while including the long-term effects on public health.

[33]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 06/21/2023.

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A Appendix

A.1 Repeated visit rates

Table 10 reports the national average rates of repeated visits (in percentages) by chemical subgroup across years. A repeat visit is defined as a revisit to a physician that results in an antibiotic prescription after an initial antibiotic treatment for a urinary tract infection. The no revisit within 7 days rate is computed regionally and used as a proxy for susceptibility to each antibiotic in our robustness checks.

Table 10: Average time (days) between two prescriptions in the 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

Notes: The visits that are not followed by another prescription within 30 days are excluded. We also exclude repeat visits, that is, those resulting in a second prescription within a month.

A.2 Guidelines

Currently, the guidelines in the U.S. for treating cystitis include a more diverse set of drugs in 2024 than their French counterparts did. In the case of uncomplicated cystitis, the recommendations include nitrofurantoin, trimethoprim-sulfamethoxazole, fosfomycin, ciprofloxacin and B-lactams such as amoxicillin-clavulanate (Colgan and Williams, 2011; Lala and Leslie, 2023) and no predefined treatment for complicated cases. As our study covers a long period, the guidelines around 2011 suggest fosfomycin, nitrofurantoin and trimethoprim-sulfamethoxazole as first-line treatment; several fluoroquinolones for second-line treatment; and amoxicillin-clavulanate, cefdinir and cefpodoxime as third-line treatment.

Table 11: Evolution of treatment recommendations in France

	Before 2008
First-line	J01XE01, J01XX01
Second-line	J01MA01, J01MA02, J01MA04, J01MA06
Complication risk	J01CA04, J01CR02, J01DD08
	2008-2013
First-line	J01XX01
Second-line	J01MA01, J01MA02, J01MA06, J01MA07, J01XE01
Complication risk	J01DD08, J01MA01, J01MA02, J01MA04, J01MA06, J01XE01
	2014-2017
First-line	J01XX01
Second-line	J01CA08
Complication risk	J01DD08, J01MA01, J01MA02
	After 2017
First-line	J01XX01
Second-line	J01CA08
Complication risk	J01CA04, J01CA08, J01XE01

Notes: ATC classes corresponds to the following molecules: J01CA04: amoxicillin, J01CA08: pivmecillinam, J01DD08: cefixime, J01MA01: ofloxacin, J01MA02: ciprofloxacin, J01MA04: enoxacin, J01MA06: norfloxacin, J01MA07: lomefloxacin, J01XE01: nitrofurantoin, and J01XX01: fosfomycin

A.3 Market shares, guidelines and generics

Figure 15 displays the changes in market shares of the main antibiotics. The dashed vertical lines show when the health authorities' prescription guidelines changed, and the solid vertical lines show when generics entered the market. Except in the case of fosfomycin (J01XX01), there are no important increases (or changes in trends) in the use of a molecule when generics enter the market, whereas there are more changes when health authorities' guidelines changed.

Figure 15: Evolution of the market shares of the molecules with generic entry during the sample period

Notes: The solid lines indicate the year of generic entry. The dashed lines indicate the changes in the guidelines. The ATC5 codes are as follows: J01CA08: pivmecillinam, J01DD13: cefpodoxime, J01MA01: ofloxacin, J01MA06: norfloxacin, J01MA12: levofloxacin, and J01XX01: fosfomycin

A.4 First-stage regressions

Table 12: First-stage regressions

	Price	Advertising	Susceptibility
Nb. of competing brands	-0.949***	-0.183***	0.008***
	(0.136)	(0.033)	(0.001)
Nb. of competing generic brands	-0.085**	0.053***	-0.000*
	(0.029)	(0.005)	(0.000)
Nb. of competing brands after 2012	-0.045	0.032***	-0.003***
	(0.052)	(0.004)	(0.000)
Nb. of competing generic brands after 2012	0.006	-0.033***	0.001**
	(0.042)	(0.005)	(0.000)
Nb. of competing products	-0.034	-0.041***	-0.005***
	(0.046)	(0.011)	(0.000)
Nb. of competing brands sq.	0.038***	0.006***	-0.000
	(0.006)	(0.001)	(0.000)
Nb. of competing products sq.	-0.001	0.000	0.000***
	(0.001)	(0.000)	(0.000)
Veterinary antibiotics density (ATC4 level)	10.146	1.226	-0.136***
	(6.703)	(0.772)	(0.023)
Veterinary antibiotics density (ATC3 level)	0.160*	-0.034***	-0.001
	(0.064)	(0.009)	(0.000)
No Obs.	8372	8372	8372
F-stat	128	32	171

Notes: (1) Competing products are defined as products with the same active substance, i.e., molecule (ATC 5 level), in the Anatomical Therapeutic Chemical (ATC) Classification System. (2) The year, region, and molecule FE as well as the included exogenous variables are not reported

A.5 Robustness Checks on the Demand Estimation

Table 13: Random coefficients logit demand estimates with regional specific susceptibility effect

		(1)		(2)	
Price	β	-0.346***	(0.077)	-0.236***	(0.045)
	σ_p	0.141***	(0.030)	0.110***	(0.021)
$\log(\mu_{j,t-1})$ × Center-East				6.090**	(1.880)
$\log(\mu_{j,t-1})$ × Center-West				6.495***	(1.893)
$\log(\mu_{j,t-1})$ × East				5.996**	(1.882)
$\log(\mu_{j,t-1})$ × North				4.724*	(1.888)
$\log(\mu_{j,t-1})$ × West				5.681**	(1.888)
$\log(\mu_{j,t-1})$ × Paris				6.334***	(1.891)
$\log(\mu_{j,t-1})$ × South-East				5.293**	(1.885)
$\log(\mu_{j,t-1})$ × South-West				5.750**	(1.885)
Detailing (in Mil.)		1.061***	(0.298)	0.814***	(0.157)
No Obs.		8372		8372	

Notes: Standard errors in parentheses. Significance levels: $^{*}: p < 0.05$, $^{*}* : p < 0.01$, $^{*}** : p < 0.001$. Models include fixed effects for year, region, molecule, guideline and incentive program controls, and missing indicator variables. The coefficient σ_p is the standard deviation of the normally distributed random coefficient on price with mean β.

Table 14: Random coefficient logit demand estimates with susceptibility regional effects and quantity weighted price

		(1)		(2)	
Price	β	-0.347***	(0.049)	-0.337***	(0.051)
	σ_p	0.081*	(0.032)	0.081*	(0.033)
$\log(\mu_{j,t-1})$ × Center-East				4.795*	(2.060)
$\log(\mu_{j,t-1})$ × Center-West				5.099*	(2.064)
$\log(\mu_{j,t-1})$ × East				4.677*	(2.062)
$\log(\mu_{j,t-1})$ × North				3.432	(2.069)
$\log(\mu_{j,t-1})$ × West				4.481*	(2.072)
$\log(\mu_{j,t-1})$ × Paris				5.131*	(2.068)
$\log(\mu_{j,t-1})$ × South-East				4.021	(2.063)
$\log(\mu_{j,t-1})$ × South-West				4.515*	(2.067)
Detailing (in Mil.)		1.010***	(0.150)	1.056***	(0.151)
No Obs.		8372	8372	8372	

Notes: Price is calculated for each molecule and brand using the sales weighted price of different doses. Standard errors in parentheses. Significance levels: $^{*}: p < 0.05$, $^{*}* : p < 0.01$, $^{*}** : p < 0.001$. The models include year, region, and molecule FEs, guideline controls, and missing indicator variables.

Table 15: Random coefficients logit demand estimates with quantity weighted prices

		(1)		(2)	
Price	β	-0.353***	(0.049)	-0.322***	(0.053)
	σ_p	0.085**	(0.033)	0.065	(0.037)
$\log(\mu_{j,t-1})$				4.627*	(2.078)
Detailing (in Mil.)		1.021***	(0.150)	1.023***	(0.157)
No Obs.		8372		8372	

Notes: Standard errors in parentheses. Significance levels: $^{*}: p < 0.05$, $^{*}* : p < 0.01$, $^{*}** : p < 0.001$. The models include fixed effects for year, region, and molecule, guideline and incentive program controls, and missing indicator variables. The coefficient σ_p is the standard deviation of the normally distributed random coefficient on price with mean β.

Table 16: Random coefficients logit demand estimates with varying information lags

		(1)	(2)	(3)	(4)
Price	β	-0.226***	-0.226***	-0.148***	-0.153***
		(0.045)	(0.046)	(0.032)	(0.041)
	σ_p	0.106***	0.086***	0.000	0.067*
		(0.022)	(0.024)	(.)	(0.029)
$\log(\mu_{j,t-1})$		5.791**			5.396**
		(1.864)			(1.850)
$\log(\mu_{j,t-2})$			3.843**		1.968
			(1.393)		(1.658)
$\log(\mu_{j,t-3})$				2.314***	-0.100
				(0.618)	(1.773)
Detailing (in Mil.)		0.782***	0.846***	0.613***	0.587***
		(0.157)	(0.167)	(0.134)	(0.128)
Generic		-2.780***	-2.785***	-2.716***	-2.767***
		(0.075)	(0.076)	(0.071)	(0.077)
Generic $\times$ $\mathbb{1}_{\{t\geq 2012\}}$		0.329**	0.304**	0.306**	0.423***
		(0.102)	(0.102)	(0.096)	(0.095)
J01MA $\times$ $\mathbb{1}_{\{t\geq 2017\}}$		-0.512***	-0.525***	-0.467***	-0.469***
		(0.133)	(0.135)	(0.131)	(0.129)
J01DD $\times$ $\mathbb{1}_{\{t\geq 2017\}}$		0.054	-0.021	-0.029	0.046
		(0.168)	(0.171)	(0.170)	(0.170)
J01CR $\times$ $\mathbb{1}_{\{t\geq 2017\}}$		-1.214***	-0.871***	-0.651**	-1.345***
		(0.296)	(0.237)	(0.204)	(0.298)
J01MA $\times$ Trend $\times$ $\mathbb{1}_{\{t\geq 2017\}}$		-0.334***	-0.334***	-0.263**	-0.282**
		(0.090)	(0.092)	(0.088)	(0.088)
J01DD $\times$ Trend $\times$ $\mathbb{1}_{\{t\geq 2017\}}$		-0.318**	-0.287*	-0.255*	-0.287*
		(0.117)	(0.118)	(0.116)	(0.114)
J01CR $\times$ Trend $\times$ $\mathbb{1}_{\{t\geq 2017\}}$		-0.256	-0.395*	-0.310*	-0.311*
		(0.146)	(0.156)	(0.148)	(0.144)
No Obs.		8372	8372	8372	8372

Notes: Standard errors in parentheses. Significance levels: $^{*}: p < 0.05$, $^{*}{*}: p < 0.01$, $^{*}{*}{*}: p < 0.001$. Models include fixed effects for year, region, molecule, guidelines and incentive program controls, and missing indicator variables. The coefficient σ_p is the standard deviation of the normally distributed random coefficient on price with mean β. Instruments when we use different lags of susceptibility rates: for susc. rate at t, the instruments come from the veterinary use at $t-1$.

Table 17: Random coefficients logit demand estimates with susceptibility proxied by the nonrepeat rates

		(1)		(2)		(3)	
Price	β	-0.244***	(0.045)	-0.226***	(0.045)	-0.210***	(0.044)
	σ_p	0.113***	(0.021)	0.106***	(0.022)	0.110***	(0.021)
$\log(\mu_{j,t-1})$				5.791**	(1.864)		
$\log(\mu_{j,t-1}^{\text{no revisit}})$						3.458*	(1.638)
Detailing (in Mil.)		0.737***	(0.156)	0.782***	(0.157)	0.550***	(0.156)
No Obs.		8372		8372		8372	

Notes: Standard errors in parentheses. Significance levels: $^{*}: p < 0.05$, $^{*}{*}: p < 0.01$, $^{*}{*}{*}: p < 0.001$. The models include fixed effects for year, region, and molecule, guideline and incentive program controls, and missing indicator variables. The coefficient σ_p is the standard deviation of the normally distributed random coefficient on price with mean β. Column 3 uses the no revisit rates as a proxy for susceptibility.

Table 18: Random coefficients logit demand estimates with Klebsiella pneumoniae susceptibility rates

		(1)		(2)	
Price	β	-0.226***	(0.045)	-0.196***	(0.045)
	σ_p	0.106***	(0.022)	0.066*	(0.026)
$\log(\mu_{j,t-1})$		5.791**	(1.864)		
$\log(\mu_{j,t-1}^{K.Pneumonie})$				-0.798	(0.668)
Detailing Expenses (in mill.)		0.782***	(0.157)	0.680***	(0.156)
Generic		-2.780***	(0.075)	-2.718***	(0.076)
Generic $\times$ $\mathbb{1}_{\{t\geq 2012\}}$		0.329**	(0.102)	0.240*	(0.100)
J01MA $\times$ $\mathbb{1}_{\{t\geq 2017\}}$		-0.512***	(0.133)	-0.628***	(0.138)
J01DD $\times$ $\mathbb{1}_{\{t\geq 2017\}}$		0.054	(0.168)	-0.234	(0.197)
J01CR $\times$ $\mathbb{1}_{\{t\geq 2017\}}$		-1.214***	(0.296)	-0.573**	(0.199)
J01MA $\times$ Trend $\mathbb{1}_{\{t\geq 2017\}}$		-0.334***	(0.090)	-0.054	(0.115)
J01DD $\times$ Trend $\mathbb{1}_{\{t\geq 2017\}}$		-0.318**	(0.117)	-0.030	(0.136)
J01CR $\times$ Trend $\mathbb{1}_{\{t\geq 2017\}}$		-0.256	(0.146)	-0.242	(0.144)
No Obs.		8372		8372	

Notes: Standard errors are in parenthesis. Significance levels: $^{*}: p < 0.05$, $^{*}{*}: p < 0.01$, $^{*}{*}{*}: p < 0.001$.

A.6 First-stage regressions of the information test

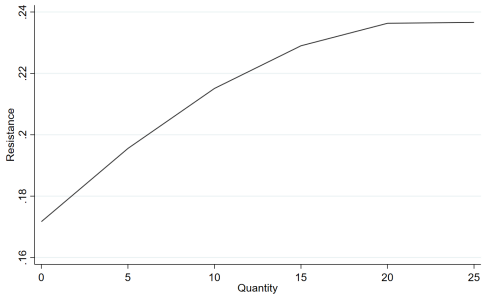
Table 19: First stage regression of the 2SLS regressions of Table 6

	(1)	(2)	(3)	(4)	(5)	(6)
$\xi_{j,t-1}$				-0.001	-0.002**	-0.002***
				(0.001)	(0.001)	(0.000)
Animal antibiotic consumption						
$q^a_{ATC4(j)t-1}$	0.432***		0.103*	0.444***		0.115*
	(0.066)		(0.042)	(0.067)		(0.045)
$q^a_{ATC3(j)t-1}$	0.004*		-0.003*	0.005**		-0.003
	(0.002)		(0.002)	(0.002)		(0.002)
Human antibiotic consumption						
q^h_{jt-1}		-0.014***	-0.010***		-0.014***	-0.010***
		(0.001)	(0.001)		(0.001)	(0.001)
$q^h_{ATC4(-j)t-1}$		0.003***	-0.000		0.003***	-0.001
		(0.000)	(0.000)		(0.000)	(0.000)
No Obs.	8372	8372	8372	7011	7011	7011

Notes: Standard errors are in parenthesis. Significance levels: $^*: p < 0.05$, $^*{*}: p < 0.01$, $^*{**}: p < 0.001$. The models include dummy variables for missing data on some animal antibiotic consumption data that are not shown in the table.

A.7 Figures

Figure 16: Resistance as a function of quantity (other variables set at means): $r_{jt} = \frac{\exp f(q_{jt})}{1+\exp f(q_{jt})}$



Notes: The 95% quantile of the distribution of quantity is 19.29245, meaning that the function is increasing concave over most of the data range.