Antibacterial resistance and the cost of affecting demand: the case of UK antibiotics [†]

Farasat A.S. Bokhari[a,b], Franco Mariuzzo[a,b] and Weijie Yan[c,d,*]

[a] *School of Economics, University of East Anglia, Norwich, UK*

[b] *Centre for Competition Policy, University of East Anglia, Norwich, UK*

[c] *Economic and Social Research Institute, Dublin, Ireland*

[d] *Department of Economics, Trinity College Dublin, Dublin, Ireland*

January 28, 2022

Abstract

Consumption of broad-spectrum antibiotics is associated with rising levels of antimicrobial resistance (AMR). We use aggregate sales data on antibiotics from the UK to estimate a structural demand model and evaluate market performance spectral activity. We find that broad-spectrum antibiotics are more profitable than narrow-spectrum drugs. We simulate alternative tax schemes to evaluate the effectiveness of shifting demand away from the subset of antibiotics identified in public health as contributing the most to the AMR problem. Our estimates suggest that these policies can be highly effective and at a relatively low cost as per changes in consumer and producer surplus.

Key words: antimicrobial resistance, demand estimation, pharmaceuticals, policy simulation, welfare change

JEL Classification: I11, I18, L11, L65

[†]This paper is based on a chapter of Weijie Yan's PhD thesis. It has benefited from comments from Steve Davies, Mark Dusheiko, Nancy Gallini, Lukas Kauer, Kai-Uwe Kühn, Margaret Kyle, Frank Verboven, as well as participants at the CCP seminar series, the annual 2017 EARIE conferences, the 4th EHEA PhD workshop and 2019 IIOC conference. The usual caveats apply.

[*]Corresponding Author: Weijie Yan (Weijie.Yan@esri.ie ; owenyanwj@gmail.com)

1. Introduction

Since the accidental discovery of penicillin by Alexander Fleming in 1928 and the first widespread use of antibiotics in the 1940s, they remain today among the most essential class of drugs worldwide. However resistance to antibiotics was also identified as early as the 1940s, and indeed the negative externality was recognized in Fleming's 1945 Nobel prize speech.[1] For 150 million annual prescriptions written in the early 1980s in the US, one estimate places the unaccounted costs due to resistance to be between $.35-$35 billion, while significantly high costs and welfare losses have also been estimated for EU/UK and 23K-25K annual deaths due to resistance in the US and EU each (Phelps, 1989, Elbasha, 2003, Smith et al., 2005, European Parliament, 2006, ECDC/EMEA, 2009, CDC, 2013). Today antimicrobial resistance (AMR) has become a global threat with an estimated 700K deaths worldwide annually and has prompted calls for a global response (WHO, 2001, CMO, 2013, O'Neill, 2016). Based on these concerns, the British government commissioned a review of AMR, which was tasked with identifying causes of rising drug resistance and proposing policy actions that can be taken internationally. The final report of the commission warns that if the problem goes unchecked, as many as 10 million lives a year, and as much as $100 trillion output worldwide would be at risk by 2050 (O'Neill, 2016). A key issue identified in this report, and relevant to this paper, is stewardship of demand management towards appropriate/optimal use.

Antibiotics can be classified as narrow- or broad-spectrum, where narrow-spectrum drugs work against a select group of bacteria and will not kill other microorganisms in the body and thus help in slowing AMR. However, they can only be prescribed when the causative organism is known. On the other hand, broad-spectrum antibiotics are prescribed more generally and when the causative organism is unknown, but they also exacerbate the AMR problem (Steinman, Landefeld and Gonzales, 2003, Steinman et al., 2003, Wood, Simpson and Butler, 2007, Kaier and Moog, 2012, CMO, 2013). If there is a cost to

[1] "*... Mr. X. has a sore throat. He buys some penicillin and gives himself, not enough to kill the streptococci but enough to educate them to resist penicillin. He then infects his wife. Mrs. X gets pneumonia and is treated with penicillin. As the streptococci are now resistant to penicillin the treatment fails. Mrs. X dies.*" Fleming, Nobel Lecture, December 11, 1945.

finding which narrow-spectrum antibiotic is appropriate, broad-spectrum antibiotics will be overprescribed relative to the narrow-spectrum antibiotics and contribute to AMR. The report recommends demand management via testing before prescribing, and where appropriate, using narrow-spectrum drugs. The O'Neill (2016) report also recommends taxes on pharmaceutical firms (labeled as 'pay or play' basis), but where firms who invest in R&D that is useful for AMR can deduct their investment from the imposed tax. To the extent that narrow-spectrum antibiotics are better in terms of AMR prevention, this subsidy would be a cost-side intervention that could potentially help with demand management if it lowers the relative price of these drugs and shifts demand toward more narrow-spectrum antibiotics.

Our primary objective is to test the feasibility of such cost-side interventions to affect demand. To that end, we use sales data from 2003 to 2013 from the UK and estimate demand via discrete choice models (Berry, Levinsohn and Pakes, 1995, Nevo, 2000, Reynaert and Verboven, 2014). We employ techniques from the empirical IO literature where we combine demand estimation with Nash-Bertrand pricing behavior and jointly estimate the supply-side equations where multi-product firms maximize their profits in an oligopolistic setting. We then simulate and test the feasibility of various tax-based interventions. Particularly, would a tax on broad-spectrum shift demand from broad to narrow-spectrum antibiotics, as suggested in some of the policy documents mentioned earlier (e.g. CMO, 2013), and if so, how effective would it be and how much would it cost society?

To our best knowledge, ours is the first paper to use empirical methods from IO to gauge the likely effects of alternative cost-side interventions, albeit in the context of just one country, to address the high and rising use of antibiotics and the associated AMR problem. We provide estimates of how much the demand will be shifted from broad- to narrow-spectrum, and what is the cost to society in terms of short-term losses in consumer and producer surplus. Our paper thus complements the large theoretical literature on the role of taxes to deal with the high use of antibiotics as well as the empirical studies focusing on the rise in prescriptions due to competitive pressures and/or financial incentives linked to physicians, both of which are summarized in the next section.

We find that at the individual brand level, demand is somewhat elastic. The share-weighted mean own-elasticity is -2.24 (un-weighted it is -3.49 with

standard deviation 1.47 and ranges from -0.25 to -9.17) and cross-elasticity is 0.099 (un-weighted 0.019, standard deviation 0.096, and range from 0 to 4.303).[2] There is generally less substitutability across the spectrum classes (narrow- to broad- or vice versa) compared to drugs within the same spectrum class: for a percent increase in the price of a broad-spectrum drug, the mean percentage increase in the demand for another broad-spectrum drug is 0.193, while that of the narrow-spectrum drug is 0.064. Our estimates also suggest that there is significant heterogeneity in individual taste parameters for the associated spectrum of a drug and switching patients from narrow- to broad-spectrum would have implications on short-run consumer welfare over and above any price effects.

We estimate the effect of ad valorem and unit taxes for all and by sub-group of drugs. In the former case, we impose a 5, 10 or 20% tax either on (i) all antibiotics, (ii) on just the broad-spectrum antibiotics, or (iii) a subset of broad-spectrum drugs that are identified in public health literature as contributing most to the AMR problem. These alternative taxes quantify various trade-offs. For instance, a 20% tax on all antibiotics reduces the overall consumption by 17.42% and that of the sub-group of broad-spectrum drugs with high AMR by 33.32%. On the other hand, imposing a similar tax on just the sub-group of broad-spectrum with the highest AMR reduces the consumption

[2]Two other papers also estimate demand for antibiotics and report elasticities, though those are for groups of drugs rather than for individual brands (as reported here). In the context of how new drugs impact the calculations for a price index, Ellison et al. (1997) use sales data from the US for the cephalosporins (a class of antibiotics) and estimate an AIDS demand model. They report group-wide elasticities by brand and generic groups, where each group itself consists of individual drugs aggregated across different manufacturers and alternative forms of the drug, but all within the same molecule. The own-elasticities range from -4.34 to +1.06. Alternatively, in the context of the impact of TRIPS on welfare, Chaudhuri, Goldberg and Gia (2006) use data on quinolones (a class of antibiotics) from India and also estimate AIDS demand by product groups. Their focus is on foreign versus domestic manufacturers and so they also provide group-wide elasticities by molecule and domestic and foreign status of manufacturers, where individual brands and forms are grouped to that level. Most of the own elasticities are lower than -2 but range from -5.94 to -0.08. While these estimates are at the group level, there are examples of estimates at the brand level as well, albeit not for antibiotics, which are more in line with our estimates. For instance, Duso, Herr and Suppliet (2014) estimate nested logit models at the brand level for anti-diabetic drugs from Germany, and reports a range from -37.349 to -0.991 with a mean value of -6.65, while Björnerstedt and Verboven (2016) estimates nested-logit and random coefficients models using brand-level data from the Swedish analgesics market and report own-elasticities in the range of -15.45 to -5.16 for the nested logits and -6.5 to -1.99 from the random coefficients models.

for this group by 50.46% with an overall reduction of only 2.18% as most patients are switched to narrow-spectrum and other broad-spectrum antibiotics.

For the 20% tax with the highest potential for distortion, the consumer welfare loss is £392 or £138.4 per 1,000 inhabitants for tax on all vs the sub-group of the broad-spectrum drugs. Multiplied by the population of the UK for the same period these translate to £25.0m and £8.8m for the year 2012 (the last year of our data). In the latter case, however, this is an additional testing cost of £78.0 per 1,000 as narrow-spectrum requires testing for the type of pathogen, but some of it is offset by the tax revenue. We also compare the effectiveness of the ad valorem tax to flat unit tax on sub-group of drugs where the unit tax is bench-marked to the estimated marginal cost differential between broad- and narrow-spectrum drugs. Here we find that the total welfare cost if such a tax is imposed on all broad-spectrum drugs is £697.1 per 1,000 (i.e., £44.4m) while the reduction in broad-spectrum quantity is 38.65%. Our total welfare calculations account for the change in consumer surplus, firm profit, tax revenue, and additional testing costs. However, we do not account for any long-term benefits that accrue to consumers due to a reduction in AMR, which would further reduce long-term loss in consumer surplus. Thus our estimates should be interpreted as an upper bound on the total cost of such a supply-side intervention. Compared to the societal cost of AMR in terms of death and direct costs cited earlier, this may not be a large price to pay for a reduction in AMR, and the supply side intervention as suggested in the O'Neill (2016) seems well worth it.

Our results also show some additional interesting patterns over time. We find that even though sales by value have decreased over time, as has the average price, profitability of several individual drugs has actually increased due to a more extensive decline in costs. For instance, the average price-cost margin for the market is around 44.8%, up from 34.4% in 2004 to 59.8% in 2012 (this margin is cumulative over manufacturers, wholesalers, and retailers). Although price-cost margins for the antibiotics market in the UK are still high overall, there is noticeable variation across different molecule groups. Broad-spectrum antibiotics tend to have lower costs and higher margins than narrow-spectrum agents, although the gap shrinks in later years. This secondary finding is important as lack of profitability for antibiotics is sometimes cited

as a reason for the lack of investments in R&D for these drugs (O'Neill, 2016, Boucher et al., 2013, Mossialos et al., 2010, IDSA, 2004, Projan, 2003).

The rest of the paper is structured as follows. The next section describes how our paper is related to prior literature. The section following that describes the antibiotics UK market and the data. Section four outlines the model as well as discusses estimation issues. Section five has all the main results including the regression coefficients, substitution patterns, and simulations. The last section concludes.

2. Related Literature on AMR

There is a small but growing empirical literature in economics related to the use of the antibiotics. In the context of Taiwan health care, Bennett, Hung and Lauderdale (2015) find that antibiotic prescriptions increase with the level of competition among health providers, largely due to pressure from patients, but that antibiotic prescriptions decreased when physician's cost of prescribing drugs increased due to a policy reform targeting antibiotic consumption. On the other hand, in a field experiment in China, Currie, Lin and Zhang (2011), Currie, Lin and Meng (2014) find that misuse of antibiotics is not driven by pressure from patients, but rather financial incentives linked to prescribing drugs. Similarly, others have investigated the link between appropriate antibiotic prescription and physician incentives. For instance, Ellegård, Dietrichson and Anell (2018) report that relative to broad-spectrum, the share of narrow-spectrum prescriptions increased significantly among children diagnosed with respiratory tract infection after physicians were exposed to pay-for-performance schemes tied to the use of narrow-spectrum antibiotics. Others have also reported positive results relating to pay-for-performance and more appropriate antibiotic prescriptions (Mullen, Frank and Rosenthal, 2010, Yip et al., 2014, Gong et al., 2016).

By comparison to the above empirical literature, there is a much more substantial but mostly theoretical literature that discusses the role of taxes, subsidies, tradable permits, and that of markets and optimal patent designs to address problems associated with AMR. Several studies highlight differences between optimal levels of antibiotic use chosen by a social planner versus

those that may emerge in different settings, including (but not limited to) single versus multiple periods, farm versus human use, choice of drugs within a hospital or community settings, global versus single country, competitiveness of the health care system, and when antibiotics may be renewable or a non-renewable resource (Tisdell, 1982, Brown and Layton, 1996, Laxminarayan and Brown, 2001, Rudholm, 2002, Laxminarayan and Weitzman, 2002, Herrmann and Gaudet, 2009, Herrmann and Nkuiya, 2017, Albert, 2021). For instance, since antibiotic use lowers the burden of treatable infections but also increases the resistance to antibiotics, Albert (2021) highlights the tradeoffs in incentives among fee-for-service healthcare providers among different market structures. Relative to a social planner, the providers over-prescribe in a competitive system and under-prescribe in a monopoly as they earn a profit on two margins due to an increased efficacy over the long run, but also by maintaining a higher infection rate in the population. He finds a Goldilock zone in the oligopolistic markets and suggests subsidies at the low level of competition and a tax when the market is more competitive.

In parallel, others have considered the role of various instruments to account for the negative externality such as direct regulation, user charges, physician charges and tradable permits when physicians are subject to defined drug budgets (as in the case of UK) (Coast, Smith and Millar, 1998, Smith and Coast, 1998, Smith et al., 2006, Herrmann and Nkuiya, 2017). For instance, Rudholm (2002) consider's a Pigouvian tax to eliminate the departure of market equilibrium from the global optimal resource allocation problem, while in a simulation-based study to control resistance to anti-malaria treatments, Laxminarayan, Over and Smith (2006) study the impact of global subsidies for artemisinin-based combination therapy (ACT) over artemisinin monotherapy (AMT), and find that even a partial subsidy can have a significant impact on delaying the emergence of artemisinin resistance. There is a third strand of literature that highlights the role of markets and optimal patent designs to address problems associated with AMR. We do not review that here but refer the interested reader to Gallini (2017) for a review of that literature.

3. Background and Data

Antibiotics are prescription-only medicines and in the UK, about 74% are prescribed via general practitioners (GPs), followed by 18% use in hospitals

(PHE, 2015*a*). Once a physician writes a prescription, patients can get it filled at a pharmacy and pay a fixed co-pay regardless of the cost of the drug (certain groups are exempt). The National Health System (NHS) will reimburse pharmacies based on a set tariff as long as the drug has been approved for reimbursement. Rules for setting the tariffs are different for branded versus generic/unbranded drugs. For the latter, NHS reimbursement is based on the weighted average of wholesale prices supplied by main generic manufacturers or wholesalers. For branded drugs, the UK does not directly control prices, but instead regulates profit on sales of drugs dispensed to NHS covered patients under its Pharmaceutical Price Regulation Scheme (PPRS). Generally, manufacturers can set the price of new drugs without pre-approval by the Department of Health (DH), but any increases over years need to be justified and approved by the DH (see ÖBIG, 2006).

Prior literature shows that GPs are aware of prices and that they may be sensitive to prices (NAO, 2007, Scoggins et al., 2006, Carthy et al., 2000). This is enforced by NHS's budgeting strategy since April 1999 to achieve *cost saving* and *efficiency* (Jacobzone, 2000). To ensure the efficiency of prescribing and control for pharmaceutical expenditure, the NHS sets an annual prescribing budget for each Primary Care Trust (PCT) at the beginning of a financial year (they have now been replaced by Clinical Commissioning Groups). PCTs in turn set individual prescribing budgets for each contracted GP in their group who are then responsible for keeping their prescription payment within the budget. PCTs track GPs' spending and report it to the NHS Prescription Services. Some PCTs also reward GPs who underspend their budget to achieve cost-saving goals (Ashworth et al., 2004). Thus drug prices may affect GP's decision.

Our data comes from British Pharmaceutical Index (BPI) data series by IMS, which provides monthly sales information for pharmacies in the UK between 2003 and 2013. It covers all antibiotic prescriptions from general practices and outpatient hospital use. Residual consumption in hospital inpatient use, dental practices, and other community settings are not included. A drug is defined as a unique combination of manufacturer, molecule, product name and formulation, and we aggregate over different pack sizes and strengths so drugs in different strengths/sizes are not counted as different products. A limitation in our data is that generic manufacturers are not separately identified in the

IMS database. Thus, if multiple manufacturers are producing a drug by non-proprietary name within the same molecule and formulation, and within the same anatomical therapeutic chemical (ATC) class, then they are lumped into one product. We also standardize quantity as daily defined dosage (DDD), which is an assumed maintenance dose per day for a specific molecule-route-of-administration combination used for its main indication among adults. Prices are computed as sales divided by quantity in DDD units (revenues and prices are deflated using UK CPI and are reported in 2003 real terms).[3]

The total market for all antibiotics in our data is £160m per year and in real terms has decreased from £208.6m in 2004 to £126.7m in 2012. This drop is driven primarily by a decrease in average real prices, which declined from £0.65 to £0.29 per DDD over the same period. By contrast, sales by volume (quantity) have increased over time, both in absolute units as well as per capita (see Figure 1). For instance, about 60m packs of antibiotics were dispensed in 2012 compared to 44.5m packs in 2004 (equivalently 0.44b and 0.32b DDD units of active ingredients respectively). This increase is only partially explained by the rise in the UK population from 60m to 64m over this period as the average DDD unit of antibiotic consumption per resident per year also increased from 5.36 to 6.94 between 2004 and 2012.

Sales are separated by broad- and narrow-spectrum groups, based on classifications in PHE (2015*b*), EARS (2015) or Madaras-Kelly et al. (2014, 2015) (penicillin V has the same spectrum score as amoxicillin but is typically classified as a narrow-spectrum antibiotic, see Table 1 for the molecule spectrum scores). Antibiotic consumption fluctuates seasonally, with peaks in winter and dips in summer. The seasonality is mainly driven by the consumption of broad-spectrum antibiotics (penicillins and macrolides), and is likely caused by the surge of respiratory tract infections and virus-induced secondary bacterial infections in cold seasons (Suda et al., 2014, Hendaus, Jomha and Alhammadi, 2015).

Enteral (or oral) drugs cover over 90% of the market in value, consisting of 44 different molecules. Parenteral (or inhaling) antibiotics are used in more limited and serious situations. Of the oral drugs, Public Health England (PHE, 2015*b*) recommends 18 different molecules as first and second-line drugs to

[3]Defined daily doses (DDD) adjustment is a measurement that allows for comparability of quantity across drugs and is maintained by the World Health Organization (WHO).

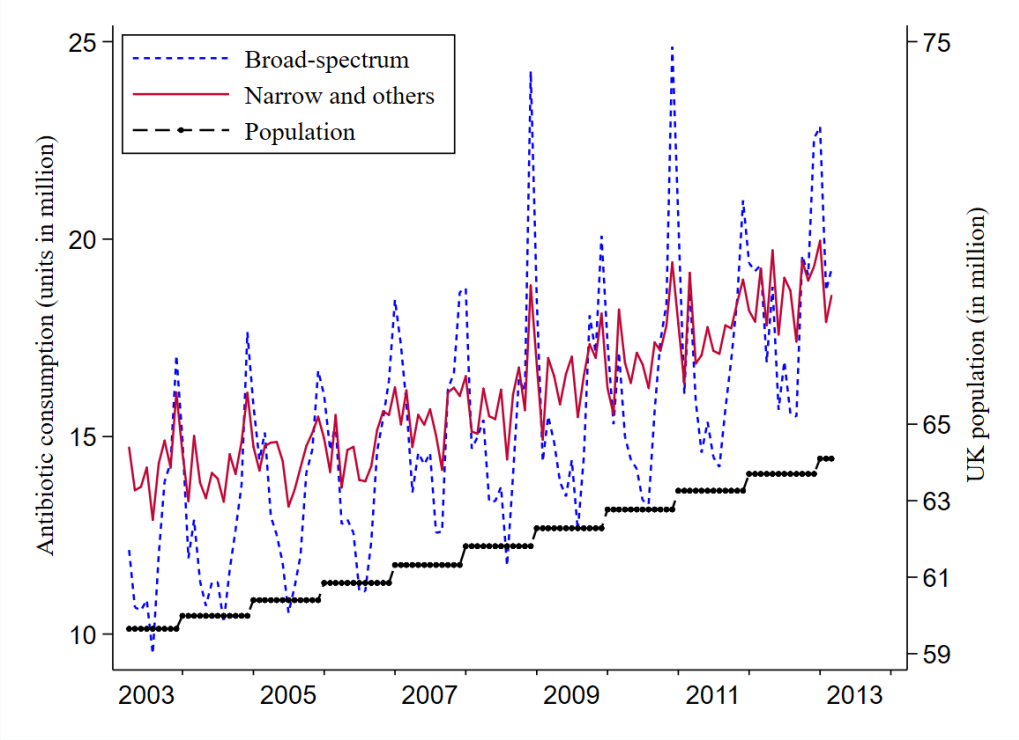

FIGURE 1. Antibiotic consumption and UK population

treat common primary community-acquired diseases, while others are to be used more sparingly. The remaining 26 are approximately about 10% of the potential market (explained later) and are included in the outside option. We focus on this sub-group of drugs classified as first or second-line treatment in our analysis. The final data set we used in our demand estimation contains 11,417 observations consisting of sales of 131 distinct products over 120 months and spanning across 18 molecules and 14 different formulations (tablets, capsules etc.). Overall, the number of products reduced slightly over the years.

Relative shares and average prices of antibiotic molecules are summarized in Table 1 (the shares are relative to the 18 molecules listed in the table). The top-selling broad-spectrum antibiotic is amoxicillin, whose shares stayed stable around 36% over the years while that of co-amoxiclav and Doxycycline increased slightly over the years. Other broad-spectrum drugs listed in the table lost market shares. There was also a movement of relative shares within the narrow-spectrum drugs. For instance, erythromycin based products lost shares at the expense of clarithromycin. Remarkably, however, the broad- to narrow-spectrum molecule share stayed relatively constant at 60/40 while the

TABLE 1. Relative shares and average prices by molecule

	Spectrum	DDD (g/day)	2004 Share (%)	2004 Price (£/DDD)	2008 Share (%)	2008 Price (£/DDD)	2012 Share (%)	2012 Price (£/DDD)
Broad-spectrum			58.57	0.56	60.12	0.25	59.07	0.15
Amoxicillin	13.50	1.0	35.55	0.26	36.3	0.15	35.55	0.10
Co-amoxiclav	29.50	1.0	5.59	1.66	6.25	0.69	6.41	0.38
Cefalexin	19.25	2.0	4.03	0.69	3.73	0.46	1.80	0.29
Ciprofloxacin	39.75	1.0	3.20	2.39	3.34	0.30	2.36	0.24
Doxycycline	38.75	0.1	8.75	0.30	9.45	0.11	12.26	0.07
Levofloxacin	39.75	0.5	0.20	2.78	0.16	2.11	0.07	1.46
Ofloxacin	39.75	0.4	0.38	1.98	0.26	0.90	0.22	1.20
Tetracycline	38.75	1.0	0.78	0.14	0.58	1.12	0.33	0.99
Cefixime	19.50	0.4	0.06	3.64	0.04	3.07	0.02	2.34
Neomycin	19.50	1.0	0.02	0.22				
Pivmecillinam	19.50	0.6	0.02	1.31	0.02	1.07	0.05	0.83
Narrow-spectrum			41.43	0.70	39.88	0.53	40.93	0.42
Azithromycin	12.25	0.3	0.49	2.62	1.00	1.98	1.84	1.18
Clarithromycin	12.25	0.5	4.23	1.61	5.65	0.63	9.50	0.34
Clindamycin	10.75	1.2	0.16	4.4	0.2	8.22	0.21	2.01
Erythromycin	12.25	1.0	14.85	0.58	12.36	0.42	8.64	0.27
Flucloxacillin	4.25	2.0	7.45	0.96	7.52	0.72	8.38	0.62
Penicillin V	13.50	2.0	5.47	0.56	5.08	0.53	4.84	0.58
Trimethoprim	4.25	0.4	8.78	0.12	8.08	0.08	7.52	0.10
Combined Inside (18)			39.66	0.62	46.56	0.36	53.76	0.26

Shares are relative to total quantity (in DDD) of all the 1st/2nd line molecules (inside option). Prices are weighted averages. 'Combined Inside' refers to share of these drugs relative to the potential size of the market. Penicillin V has the same spectrum score as amoxicillin, but is typically classified as a narrow-spectrum antibiotic.

relative prices changed significantly. Specifically, the ratio of the average price of narrow- to broad-spectrum increased from .70/.56 = 1.25 in 2004 to .42/.15 = 2.80 in 2012. Overall, average prices declined from 0.62/DDD in 2004 to 0.26/DDD as shown in the last row of the table, while the total quantity consumed increased: the last row also shows the share of all drugs for these 18 molecules relative to the potential size of the market (described later), which increased from 39.7% to 53.8%.

4. Empirical Specification

Given that the paper aims to evaluate the effectiveness of shifting the demand of broad-spectrum antibiotics towards narrow-spectrum antibiotics, in this section we first briefly describe our demand and supply-side equations, and then focus on issues related to identification and estimation.

4.1. **Demand.** We consider $t = 1, \ldots, T$ markets, each having a mass M_t of patients that have contracted a bacterial infection in the period. We model the decision-maker as a physician and patient hybrid who is sensitive to prices (see NAO, 2007) and cares about the well-being of the patient. The decision-maker i faces the choice of $j = 1, \ldots, J_t + 1$ drugs belonging to G_t groups of antibiotics, where the groups are defined at the third level of ATC, and the $+1$ denotes the outside option of no antibiotic treatment.[4] Thus the decision-maker i in market t gets indirect utility u_{ijt} from choosing drug j given by

$$u_{ijt} = x_{jt}\beta_i + \xi_{jt} + \zeta_{igt} + (1 - \rho)\epsilon_{ijt}. \tag{1}$$

In the equation above, x_{jt} is a $(1 \times k)$ vector of observed drug characteristics, including price, count of pack varieties, and drug dummies. Some drug characteristics are invariant over markets (e.g. formulation, branded/generic type, age of the molecule, or spectrum value) and hence only enter selectively in the non-linear part of the specification via the random coefficients (described below). This vector also includes mean temperature during the month (for seasonality) and a linear time trend. The scalar error term ξ_{jt} captures the unobserved (to the econometrician) drug characteristics such as the availability of the drug in the local dispensary, the knowledge of the physician about the effectiveness of the drug to treat the infection, localized detailing to the physician about the specific brand, etc. The term ζ_{igt} is common to all the drugs that are part of the same nest (molecule group) in the market and is a random variable with a probability distribution function that depends on the within-group molecule correlation parameter ρ, with $0 \leq \rho < 1$. The idiosyncratic error term ϵ_{ijt} is assumed to be identically and independently distributed extreme value, and so is the composite term $\zeta_{igt} + (1 - \rho)\epsilon_{ijt}$ (see Cardell, 1997).

[4]The third level of ATC classification corresponds to pharmacological similarities and groups the 18 molecules in our data into eight nests.

The β_i are vectors of $(k \times 1)$ random coefficients and can be expressed as the sum of means, β, and dispersion around these means. These dispersions are represented by $k \times 1$ unobservable random variables of individual heterogeneity v_i, drawn from a multivariate standard normal, and so $\beta_i = \beta + \Sigma v_i$. The matrix Σ has a vector of standard deviations σ along its diagonal, and takes value zero outside the diagonal. In our empirical analysis the vector of standard deviations sigma will be allowed to differ from zero only for the constant, the price, the number of packages, and the spectrum, i.e., we will account for three random coefficients which enter the non-linear part of the model.

Equations (1) and $\beta_i = \beta + \Sigma v_i$ characterize the random coefficients nested logit (RCNL) model described by Verboven and Grigolon (2013).[5] The decision-maker of the patient i in market t chooses the product j that gives the highest utility to the patient. In the case of the RCNL model, the conditional probability of that choice is,

$$\phi_{ijt}(x_t, \xi_t, v_i, \theta) = \frac{\exp\left(\left(x_{jt}\beta_i + \xi_{jt}\right) / \left(1-\rho\right)\right)}{\exp\left(I_{igt} / \left(1-\rho\right)\right)} \frac{\exp\left(I_{igt}\right)}{\exp\left(I_{it}\right)}, \tag{2}$$

where $\theta = \{\beta, \sigma, \rho\}$. McFadden's (1980) inclusive values I_{igt} and I_{it} used in equation (2) are the natural log sums:

$$\begin{aligned} I_{igt} &= (1-\rho) \ln \sum_{l=1}^{J_{gt}} \exp\left(\left(x_{lt}\beta_i + \xi_{lt}\right) / \left(1-\rho\right)\right), \\ I_{it} &= \ln\left(1 + \sum_{g=1}^{G_t} \exp\left(I_{igt}\right)\right). \end{aligned} \tag{3}$$

The market share of the drug j in market t, s_{jt}, can be obtained by integrating equation (2) with respect to the distribution of the vector of random variables v_i, whose solution can be approximated by Monte Carlo simulations (see Nevo, 2001, Berry, Levinsohn and Pakes, 1995) with the adjustment for the nested structure explained in Verboven and Grigolon (2013).

4.2. **Supply Side.** Drugs are assumed to have asymmetric constant marginal cost c_{jt}. Each firm $f = 1, \cdots, F$ controls the set of prices (p_{ft}) that maximizes

[5] By restricting $\rho = 0$ we get the random coefficients logit model (RCL). The additional constraint $\Sigma = 0$ produces the multinomial logit (L) version. In our empirical section, we will estimate L, RCL, and RCNL models.

its profit, given the prices of all drugs produced by the other firms p_{-ft}:

$$\max_{p_{ft}} \Pi_{ft}\left(p_{ft}, p_{-ft}\right) = \max_{p_{ft}} \sum_{l \in \mathcal{J}_{ft}} \left(p_{lt} - c_{lt}\right) q_{lt}\left(p_t\right) \tag{4}$$

where $\mathcal{J}_{ft}$ is the set of products produced by firm f in market t. Since the total unit sales can be expressed as $q_{jt} = s_{jt} M_t$, we can derive the first-order (pricing) conditions in each market t, leading to a system of J_t equations per market, which can be expressed in compact notation as:

$$p_t = c_t + \underbrace{\Delta_t^{-1} s_t}_{m_t} \tag{5}$$

where m_t is the vector of mark-ups and Δ_t is essentially the Jacobian matrix, whose element j, k equals to $-\partial s_{kt}/\partial p_{jt}$ if j and k belong to the same firm and zero if j and k belong to different firms.

We rewrite the pricing equation Eq. (5) in econometric form and it is estimated jointly with the system of demand functions obtained by numerically deriving the market shares (s_{jt}) from Eq. (2):

$$\ln(p_{jt} - \underbrace{\Delta_{jt}^{-1} s_{jt}}_{m_{jt}}) \equiv \ln(c_{jt}) = w_{jt}\gamma + \omega_{jt}, \tag{6}$$

where ω_{jt} is the error term, γ are the coefficients and w_{jt} represents a vector of observable product characteristics. These include the number of packages, a dummy for generic drug production, and formulation dummies (liquid and capsule against the baseline of tablets). For instance, drugs with a higher pack variety may have different unit marketing costs. We also include in w_{jt} other cost shifters such as the price of diesel (transportation cost), the exchange rate (to account for the cost of imported material), as well as a time trend.

4.3. **Potential market and outside good.** We rely on the WHO report on antibiotic consumption in the Europe region to define the potential antibiotic market for the UK (WHO, 2018). The report suggests that the median consumption of antibiotics was 17.9 DDD per 1000 inhabitants per day in 2015, ranging from 7.7 DDD to 38.2 DDD. Most European countries had antibiotic consumption of less than 30 DDD per 1000 inhabitants per day, and the UK antibiotic consumption was around 20 DDD per 1000 inhabitants per day. Based on this, we define the potential UK market as 30 DDD per 1000 inhabitants per day, which is roughly twice of the EU median and 1.5 times the UK antibiotic consumption in 2015. Therefore, the total potential UK

market in our model is 30 DDD $\times$ 30 days (in a month) $\times$ UK population in thousands in a given year. Accordingly, the share of each product is relative to this potential market, so $s_{jt} = q_{jt}/M_t$ and the share of the outside good is then $s_{0t} = 1 - \sum_j s_{jt}$ where q_{jt} is the quantity of drug j measured in DDD units.

4.4. **Descriptive Statistics.** Summary statistics of relevant product characteristics are given in Table 2. The mean share of a drug is 0.01 but varies from 0 to .26 with a mean price of £1.16 per DDD with also significant variation. The outside option varies from .32 to .67 with a mean value of 0.54. The mean spectrum score is 1.83 and pack variety ranges from 1 to 10 with a mean of 2.68. Note that the spectrum does not vary by individual drugs but rather by molecules. The majority of observations are on generics and the mean age of a molecule (computed as the difference between 2003 and the earliest launch year of the molecule anywhere in the world) in the sample is 39.58 years and about one third of the sample consists of drugs in liquid form.

4.5. **Identification.** The mean price coefficient can be identified via the exogenous cost shifters on the supply side. However, these are not sufficient to identify other coefficients. The random coefficients (with no observable individual demographics) can be identified with repeated cross-sections if there is sufficient variation in product characteristics or in the number of products over markets (Ackerberg and Rysman, 2005).

Table 2 shows variation in drug characteristics between (i.e., across) drugs as well as within (i.e, over time). For example, the number of packs has an overall standard deviation of 1.72, which is the result of a both between and within dispersion, 1.50 and 0.65, respectively. Most of the drug characteristics vary more across drugs than over time. However, exchange rate, the price of diesel, and the mean monthly UK temperature vary over time.[6] The dummy variable generic, the variable spectrum and the dummies of the formulation are drug-invariant, and therefore, the between variation is merely driven by the entry and exit of drugs.

[6]The exchange rate is computed based on a basket of the top five countries that the UK has antibiotics imported from China, India, Singapore, the US and the EU. The exchange rate used in the model is the sum of the bilateral exchange rates, weighted by import shares.

TABLE 2. Summary statistics and between and within variation of variables.

Variable	Description	Mean	s^2_O	s^2_B	s^2_W	Min	Max
s_{jt}	Share of drug j	0.01	0.02	0.01	0.00	0.00	0.26
s_{0t}	Share of outside option	0.54	0.07	0.03	0.07	0.32	0.67
$\ln(s_{jt}/s_{0t})$	Dependent variable	-7.13	2.47	2.35	1.10	-17.2	-0.21
$\ln(s_{(j\in g)t})$	Within nest ln(share)	-4.92	2.55	2.50	1.09	-16.2	0.00
p_{jt}	Price (in £) per DDD	1.16	1.23	0.99	0.62	0.04	11.5
x_{1jt}	Spectrum-score / 10	1.83	1.07	1.04	0	0.43	3.98
x_{2jt}	Pack varieties	2.68	1.72	1.50	0.65	1	10
x_{3jt}	Dummy: generics	0.57	0.50	0.50	0	0	1
x_{4jt}	Dummy: tablet	0.43	0.50	0.50	0	0	1
x_{5jt}	Dummy: capsule	0.23	0.42	0.42	0	0	1
x_{6jt}	Dummy: oral liquid	0.34	0.47	0.47	0	0	1
x_{7jt}	Age of molecule / 10	3.96	1.22	1.22	0	1.5	5.8
x_{8jt}	Temperature	10.2	4.59	0.63	4.58	-0.27	19.3
z_{1t}	Price of diesel (log)	0.56	0.15	0.09	0.14	0.34	0.81
z_{2t}	Exchange rate (log)	1.58	0.39	1.17	1.96	2.69	10.3
z_{3jt}	#other drugs by the same firm	4.06	5.55	5.31	0.96	0	19
z_{4jt}	#other drugs by the same firm & within the same nest	1.35	1.29	1.25	0.40	0	5
z_{5jt}	#packs over other products by the same firm and in same nest	3.54	3.67	3.54	1.22	0	17
z_{6jt}	#packs by competitors in the same nest as reference drug	45.3	23.2	23.0	4.68	0	92

Total 11,417 obs of 131 distinct products over 120 months spanning 18 molecules and 14 formulations.

Table 3 shows variation in the number of drugs due to entry and exit over time. Among the 131 drugs identified in the data, a typical market only has 95 of them. A typical drug is observed in 87 markets (of the total 120 markets). There are instances of drugs that are available in a much lower number of markets. For example, one drug is observed in only five markets. These changes in the number of products produce variation in the prices and the number of pack varieties which are essential to identify their coefficients in our analysis.

TABLE 3. Entry and exit of drugs

Variable	Obs	Mean	Std. Dev.	Min	Max
Number of drugs in a market	120	95.14	4.17	88	104
Number of markets a drug is on sale	131	87.15	37.82	5	120

Finally, the ρ coefficient in the nested logit version also needs to be identified. If patients switch drugs within the same molecule across markets, their behaviour can produce changes in within molecule (i.e. nest) market shares. Thus variation in the within nest share ($\ln s_{(j\in g)t}$) can allow for identification of this parameter. However, this too may be correlated with the error term as patients may choose to switch drugs within a molecule in response to shocks on unobserved drug characteristics. When an unobserved drug characteristic such as quality is high, the market share of that drug is high, but so is the within-nest market share. The switchers can either be patients from the same molecule or from other molecules. Thus, the within nest share needs to be instrumented as well, for which we use variation in the number of drugs and packs by the reference firm or competitors within the nest as described below.

The random coefficients models use the nonlinear method of moments as an estimator, which require the orthogonal conditions between the observed drug characteristics and the demand error term. Berry, Levinsohn and Pakes (1995) suggest using the sum of product characteristics of other products of the same firm, and the sum of product characteristics of products of other firms to generate additional instruments. Björnerstedt and Verboven (2016) suggest adding the count of other products of the same firm, and the count of products of other firms as instruments as they capture the intensity of competition. Further, they also suggest generating additional instruments by nests. We construct our additional instruments following the same procedure. For a given drug j by firm f in nest g we count the number of other drugs by the same firm (z_{3jt}) and the number of other drugs by the same firm within the same nest (z_{4jt}). Similarly, we also count the number of packs by the reference firm over other drugs within the nest (z_{5jt}) as well as the number of packs by all competitors within the same nest (z_{6jt}). In some models, we also included the squared terms or interactions of these additional variables (see Appendix B for further details). Finally, we generate and use optimal instruments for estimation as described in Reynaert and Verboven (2014).[7]

[7] Reynaert and Verboven (2014) show through Montecarlo simulations that the optimal instruments are more efficient than other instruments and find these instruments also helpful to attenuate bias when there is a limited product characteristic variation across markets. To the point, Chamberlain's 1987 optimal instruments are the expected value of the gradient of the structural error term (the product-specific unobservable) for the parameter vector. In the case of linear parameters and exogenous regressors, the gradient would be (minus) the covariates. In the case of nonlinear parameters, the optimal instruments are nonlinear predicted variables. In the presence of multiproduct

5. Results

5.1. **Regression Coefficients.** Table 4 provides selected regression coefficients from alternative demand models, i.e., simple logit as OLS, 2SLS/IV, and then jointly with supply-side moment conditions in equation (6). This is followed by our preferred specification as the random coefficients nested logit (RCNL) model, which too is estimated with supply-side and with optimal instruments as described earlier. The 2SLS/IV and the joint estimation with (6) for the simple logit case is to gauge incremental improvement in the model due to the use of price instruments alone, and gain in efficiency from supply-side moments before we turn to the more flexible model. Appendix A provides additional estimates from random coefficients logit model (i.e., without nesting) as well as the coefficients of the associated supply-side equation when we use joint estimation (see Table A-1 and Table A-2 respectively).

Starting first with the OLS estimation of the simple logit in column (1), the price coefficient is positive and not statistically significant. When we re-estimate the model using instrumental variables via simple two-stage least squares, the price coefficient becomes negative -0.802 and is significant at the 1% level (see column (2)). The first-stage regression is in column (3) and shows that the four excluded instruments are individually significant and the joint F-test for the excluded instruments is 14.81 indicating that the instruments are not collectively weak. Nonetheless, the demand is in the inelastic region for most of the sample and the implied marginal costs are negative for about 70% of the observations.[8] Next, column (4) provides estimates from the joint estimation with the supply side. The price coefficient is negative -6.328 and significant. The average price-cost margin for the joint estimation is 0.25 with only 5% of the sample obtaining negative marginal costs, showing further improvement in the estimates. Other coefficients of interest indicate that demand increases with pack variety and is greater for generics (both are

firms and differentiated products, the joint estimation of demand and supply of the nonlinear (predicted) prices can be approximated by regressing the prices on a polynomial of demand and cost shifters and possibly BLP-type instruments. A similar logic applies to the supply side error, with the markup variable replacing the price variable.

[8]Note that the regressions included product dummies and hence time-invariant product characteristics like age of molecule or formulation etc. drop out of the regressions in the first and second stage. Nonetheless, we show coefficients for these in the second stage as these were retrieved using Chamberlin's GLS regressions of brand dummies on fixed product characteristics (see Nevo, 2000).

TABLE 4. Estimation results (Logit and Random Coefficients Nested Logit)

	Logit				**RCNL**	
	OLS	IV/2SLS		IV-Joint	IV-Joint	
	(1)	(2)	(3)	(4)	(5)	(6)
	β	β	1st-stage	β	β	σ
‡Constant	-4.603***	-4.201***	1.282***	-4.152***	-0.891	0.163
	(0.895)	(0.887)	(0.070)	(0.987)	(0.642)	(0.377)
Price	0.016	-0.802***		-6.328***	-6.070***	3.122***
	(0.016)	(0.251)		(0.268)	(0.016)	(0.034)
$\ln(s_{(j\in g)})$					0.489***	
					(0.009)	
‡Spectrum	0.124	0.026		-0.083	0.162	0.553***
	(0.118)	(0.127)		(0.168)	(0.117)	(0.047)
Pack	0.538***	0.527***	-0.011	0.452***	0.283***	0.015*
	(0.025)	(0.025)	(0.008)	(0.013)	(0.018)	(0.009)
‡Age	0.016	0.012		0.024*	-0.046	
	(0.013)	(0.013)		(0.013)	(0.075)	
‡Generic	1.131***	0.986***		1.013***	-0.145	
	(0.298)	(0.312)		(0.313)	(0.188)	
‡Capsule	0.259	0.214		-0.138	-0.057	
	(0.398)	(0.398)		(0.366)	(0.224)	
‡Liquid	-0.666**	-0.743**		-0.675**	-0.084	
	(0.305)	(0.32)		(0.327)	(0.205)	
Temperature	-0.028***	-0.028***	-0.000	-0.024***	-0.033***	
	(0.002)	(0.002)	(0.001)	(0.002)	(0.002)	
Time	-0.000	-0.047***	-0.009***	-0.364***	-0.223***	
	(0.000)	(0.015)	(0.001)	(0.016)	(0.004)	
z_1:Price of diesel (log)			0.678***			
			(0.142)			
z_2: Exchange rate (log)			0.073*			
			(0.043)			
z_3 #drugs by firm j			0.055***			
			(0.009)			
z_4 #drugs by firm j in nest g			-0.113***			
			(0.028)			
Statistics						
Obs	11417	11417	11,417	11417	11417	
pseudo-Rsq	0.825	0.787	0.77	0.22	0.98	
avg $(p-c)/p$		0.61		0.25	0.36	
% mc<0		69.7		4.99	3.06	
F-stat			14.81			

Total 11,417 obs of 131 distinct products over 120 months spanning 18 molecules and 14 formulations. All regressions include product dummies. Robust standard errors are in parentheses. Superscripts (***), (**), and (*) imply significance at at 1, 5 or 10% respectively.

‡The mean β coefficient retrieved from minimum distance method as product dummies are included.

positive and significant coefficients), but that the coefficient on the spectrum is not statistically significant in either this or the earlier models.

Columns (5) and (6) provide estimates from RCNL which overcomes the restrictive substitution patterns imposed due to the independence of irrelevant alternatives (IIA) property for the simple logit models. The nesting coefficient ρ on $\ln(s_{jg})$ is 0.489 and is significantly different from zero and one, suggesting that drugs in the same nests (molecules) are more similar than drugs in other groups. Further, only 3.06% of the observations have a negative implied marginal cost and the average price-cost margin for the remaining sample is 0.36. The mean coefficient on price is -6.070 and significantly different from zero, while the distribution parameter σ_p is 3.122 and is also significant, which indicates that there is variation in marginal (dis)utility of price around the mean value. Thus price sensitivity varies in the underlying population and may stem from the fact that practitioners have uneven professional experience, and react differently to national media and guidelines on cost saving (Scoggins et al., 2006).

Similarly, the coefficient on the number of pack varieties is positive and significant, indicating higher marginal utility if a drug is available in multiple dosages and pack sizes, and the variance coefficient is also marginally significant indicating that there is some heterogeneity in the marginal valuation of pack variety (in an alternative model without nesting given in the appendix in Table A-1, the variance term is highly significant). The time trend is negative across all estimations, which implies that utility of consuming common antibiotics is reducing over time compared to the outside option which may be induced by increasing resistance level. The coefficient on average temperature which varies seasonally is negative and significant indicating that the utility of consuming antibiotics in winter is higher than in summer due to the high preference for using antibiotics to treat respiratory tract infections, and virus-induced secondary bacterial infection in cold seasons (Suda et al., 2014, Hendaus, Jomha and Alhammadi, 2015).

Among the coefficients recovered using the minimum distance method, the mean marginal utility associated with the spectrum is not significant. However the variance parameter is of similar magnitude (and significant) so there is

considerable heterogeneity in the taste parameter for spectrum.[9] This suggests that although on average patients and doctors do not exhibit strong preferences for broad- or narrow-spectrum antibiotics, some individuals do derive higher marginal utility from narrow- or broad-spectrum antibiotics, and hence, all else equal, their utility level would change if they were given drugs with a different spectrum value.

5.2. **Elasticities, Costs, and Margins.** Prior to turning to the tax simulations and their effect on demand and lower bound measures of welfare, we provide here estimates of substitution patterns, marginal costs, and profit margins as they help contextualize the results from the simulations. Based on the estimates for RCNL, we computed own- and cross-price elasticities for all the antibiotics in our sample. The averages and standard deviations are summarized in Table 5, where averages are weighted by product market share.

TABLE 5. Price elasticities

	Mean	Std
Own-price elasticity	-2.237	1.527
Cross-price elasticity	0.099	0.167
$\%\Delta s_B/\%\Delta p_B$	0.193	0.221
$\%\Delta s_N/\%\Delta p_B$	0.064	0.061
$\%\Delta s_B/\%\Delta p_N$	0.032	0.027
$\%\Delta s_N/\%\Delta p_N$	0.121	0.253

Elasticities are weighted by market shares

The mean own-price elasticity for a given antibiotic is -2.24 with a standard deviation of 1.57, while the mean cross-price elasticity is 0.01 with a standard deviation of 0.17. To understand the substitution possibilities across drugs with different antibacterial resistance, we partitioned cross-price elasticities by broad- and narrow-spectrum groups. Thus, a 1% increase in the price of a broad-spectrum antibiotic is associated with 0.19% increase in the share of another broad-spectrum drug, and only a 0.06% increase in the share of a narrow-spectrum drug. Similarly, an increase in price in the narrow spectrum drug has a larger substitution into another narrow-spectrum drug than to a broad-spectrum drug. These substitutions patterns are not just a consequence of our nesting design which was by molecules, as they are also present in the

[9]From the brand dummies we recovered the mean utility but the variable also enters the model non-linearly and hence allows us to estimate the associated σ value.

model RCL model (i.e., without any nesting). These patterns suggest that broad-spectrum drugs are closer substitutes to each other than to drugs in the narrow-spectrum. The underline reason might be that broad-spectrum molecules may have larger overlapping in indications, as one family of bacteria may be susceptible to many of them. By contrast, drugs with narrow-spectrum molecules have smaller cross-price elasticities, and shares of broad-spectrum drugs are less affected by price changes of narrow-spectrum ones.

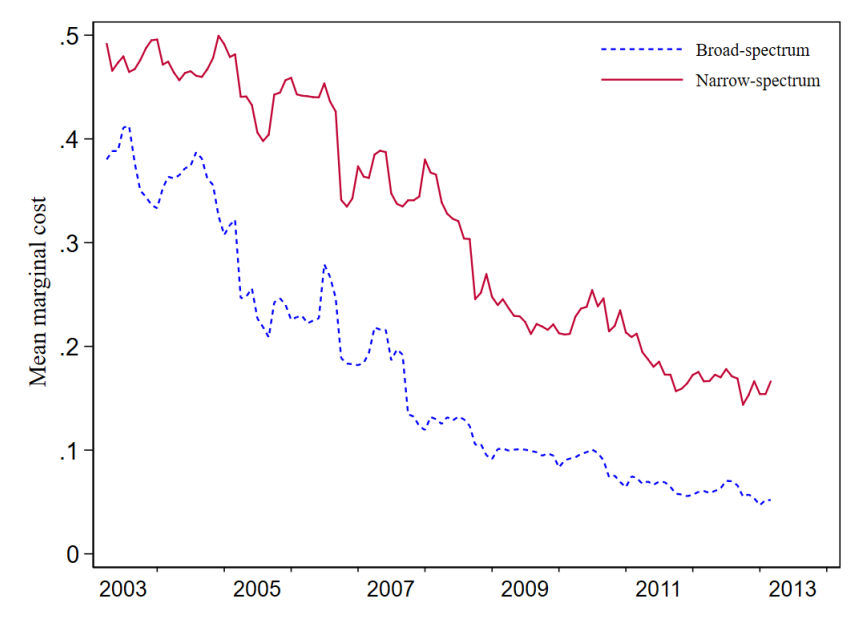

FIGURE 2. Marginal cost

The supply-side estimation shows the factors that affect the marginal cost of production (given in Table A-2 in the appendix). All estimations show fairly similar results but with different significance levels. While the marginal cost does not depend seem to depend on the spectrum per se (the coefficient on the spectrum in the supply equation is negative but not significant). Nonetheless, the marginal cost of drugs classified as broad-spectrum is lower than their counterparts (see Figure 2).

The marginal cost of producing antibiotics is decreasing over time, perhaps because of improvements in production technologies (Arcidiacono et al., 2013). Further, If a product has more pack varieties, its marginal costs are not necessarily any higher. This may be consistent with findings reported elsewhere (see Kekre and Srinivasan, 1990). The marginal costs are also lower for generics

as well as for capsules relative to tablets (they are also higher for liquid form, but significant only in logit and RCL specifications).

TABLE 6. Margins by molecule

Margins $(100 \times (p-c)/p)$	2004	2008	2012	All Years
Broad-spectrum	36.5	52.1	59.8	46.0
Narrow-spectrum	32.1	40.3	59.8	43.8
Overall	34.4	45.2	59.8	44.8

Means weighted by market shares

We also backed out the price-cost margins for all drugs in all years. Table 6 provides weighted averages by molecules for select years and overall. Note that the implied margin is between the retail price and the marginal cost of production and hence it contains margins earned by manufacturers, wholesalers and retailers. Our data and estimation strategy does not allow these to be separated into individual components in the supply chain. There is considerable variation in profitability across individual molecules, ranging from as low as 13.3% to 99.5%. For some generics in the UK, margins can be considerably high as noted elsewhere as well: by one estimate, the margin at the retail level alone can be as high as 76.6% (Kanavos, 2007). Overall broad-spectrum drugs are slightly more profitable (46% vs 43.8%), with the difference being larger in the earlier years than later.

5.3. **Policy Simulations.** We next ask what would be the effect on demand, and what is the implied welfare cost of implementing supply-side interventions that change the relative prices of broad- and narrow-spectrum drugs? The source of price sensitivity is due to NHS setting annual prescribing budgets for each PCT, which in turn set budgets for individual physicians so that GPs are responsible for keeping their prescription payments within those budgets.

To that end, we undertake two related tax exercises. First, using the last year of the data, we impose an ad valorem tax (5% or 20%) on either (i) all antibiotics, (ii) all broad-spectrum drugs, or (iii) a subset of the broad spectrum which is associated with contributing most to the rise in AMR (labeled as 'Broad-s' in the results for this subset, or 'Broad-o' for other broad-spectrum drugs). The Broad-s group consists of co-amoxiclav, quinolones (ciprofloxacin, levofloxacin and ofloxacin) and cephalosporins (cefalexin, cefixime). We use

these tax simulations to check how much would be the reduction in overall demand for antibiotics as well as for broad-spectrum antibiotics, and how much is the associated welfare loss from such a tax. In these calculations, we account for the short-run change in consumer and producer surplus, as well as any additional costs due to testing if more patients are switched to narrow-spectrum costs.[10] The tax simulation algorithm and accompanying welfare calculations are explained further in Appendix B.

It should be noted that the change in welfare in this exercise is only a partial analysis: it captures the change in demand and welfare loss associated with cost side interventions, but does not measure aggregate societal benefits accrued in the long run from the increase in demand for drugs that do not exacerbate the AMR problem as much. Thus, these exercises provide an upper bound on the costs and change in demand from implementing such tax policies but does not fully quantify the long term welfare benefits of slowing AMR. Nonetheless, given the dire predictions in the O'Neill (2016) if AMR goes unchecked, it is well worth exploring these options. Second, we repeat the exercise where we impose a unit tax on all broad-spectrum drugs. The unit tax is pegged to the average difference in estimated marginal costs between broad- and narrow-spectrum drugs, again in the last year of the data. Since we do not provide an optimal tax calculation, these sets of exercises can be used to gauge the like effects of alternative options. The detailed results from the second exercise are relegated to the appendix, and only the main conclusions are discussed here.

Starting with the ad valorem tax of 5% on all antibiotics (column (1), Table 7), it leads to a 6.17% increase in the price of broad-spectrum drugs and 7.64% increase in the price of narrow-spectrum drugs, for a combined price increase of 6.9%. However, reduction in quantity for narrow is 6.08% while that for broad-spectrum is only 2.27% for an overall reduction of 3.87% in quantity (baseline relative shares of broad- and narrow-spectrum are 59% and 41% in 2012, see Table 1). The leads to a loss in consumer and producer surplus of £104.5 and £13.8 for a total of 118.3 per 1,000 inhabitants (henceforth all numbers are per 1,000 inhabitants). In turn, this is offset by tax revenue of £74.4 and additional £164.4 in avoided testing costs, for net positive change.

[10] This exercise is in line with the suggestions by the Chair of the UK government's Review on AMR (Wasley and Parsons, 2016). See https://tinyurl.com/ydg7qe4b.

TABLE 7. Ad valorem tax (5 or 20%)

		On all antibiotics		On all broad-spectrum		On select‡ broad-spectrum	
		5% (1)	20% (2)	5% (3)	20% (4)	5% (5)	20% (6)
%Δ price	‡Broad-s	6.04	25.21	5.97	25.79	5.93	26.46
	†Broad-o	7.00	27.02	7.52	28.13	0.02	0.12
	Broad	6.17	25.77	6.32	26.42	5.46	23.31
	Narrow	7.64	32.46	-0.08	-0.36	0.01	0.06
	Combined	6.90	28.09	0.21	0.91	0.09	0.29
% Δ quantity	Broad-s	-10.86	-33.32	-11.55	-40.98	-13.39	-50.46
	Broad-o	-0.29	-6.13	-2.95	-15.93	0.70	4.50
	Broad	-2.27	-11.27	-4.55	-20.60	-1.96	-5.73
	Narrow	-6.08	-26.00	2.11	9.78	0.88	2.87
	Combined	-3.87	-17.42	-1.81	-8.11	-0.80	-2.18
Δ CS		-104.5	-392.0	-43.7	-174.2	-35.7	-138.4
Δ profits		-13.8	-71.5	2.9	5.6	5.1	13.9
Δ tax revenue		74.4	290.6	25.4	96.2	10.3	26.1
Δ testing cost		-164.4	-698.7	57.5	266.6	23.9	78.0
Total Δ		120.5	525.9	-72.9	-339.0	-44.3	-176.4

The monetary change of welfare is measured as pounds per 1000 inhabitants. The UK population in 2012 is 63,705,000. The NHS unit test cost is 8 pounds. We assume that an antibiotic script is prescribed for 7 days. Total = CS + π + Tax revenue − Testing cost. ‡Tax imposed on drugs selected broad-spectrum drugs, which include co-amoxiclav, quinolones (ciprofloxacin, levofloxacin and ofloxacin) and cephalosporins (cefalexin, cefixime). †All other broad-spectrum drugs.

The testing costs decline because fewer patients are given narrow-spectrum antibiotics.

Column (2) provides estimates when tax is set to 20%. Again there is an overall decrease in the use of antibiotics, but once again the percentage decline in narrow-spectrum drugs is more than twice that of broad-spectrum antibiotics. There is a large drop in consumer and producer surplus, and this net of the changes in tax revenue and testing costs become positive, but once again the total positive change due to avoided testing costs associated with prescribing narrow-spectrum prescriptions.

By contrast, an ad valorem tax on just the broad-spectrum antibiotics changes the calculus quite a bit (columns (3) and (4)). The drop in consumer surplus with either 5% or 20% is less than half of that when it was on all drugs.

Moreover, the usage of broad-spectrum drugs decline, while that of the narrow-spectrum increases (for the 20% tax rate, by -20.6% and 9.78% respectively). Overall firm profits increase, but this total increase in profits is due to the increase for narrow-spectrum drugs whose quantity increases rather than for broad-spectrum drugs. The total change in consumer and producer surplus net of tax revenue and testing costs is a decrease in £339.

Note that in the foregoing cases, the decline in broad-spectrum prescriptions is not even. For instance, in column (4), the decline in a subset of broad-spectrum antibiotics that are associated with contributing the most to the rise in AMR is 41% ('Broad-s') while that of the other broad-spectrum drugs are 16% ('Broad-o'). As the last two columns show (columns (5) and (6)), this balance changes even further if the tax is imposed on only this subset of broad-spectrum antibiotics. This tax allows for more substitution within broad-spectrum antibiotics from 'Broad-s' to 'Broad-o'. With a 20% tax levied on the broad-s group of antibiotics, their consumption declines by 50% with some increase in broad-o group as well as a smaller increase in narrow-spectrum drugs relative to that in column (4) scenario. The total decline in all antibiotics is only 2.18% and consequently, the change in consumer surplus and change in total welfare net of tax revenue and testing costs are also much smaller than before.

As these exercises show, it is possible to shift demand from broad-spectrum to narrow-spectrum, or at least away from broad-s group by up to 50% with a relatively modest drop in short-run welfare or total consumption. An alternative tax exercise where a unit tax is imposed on either all broad-spectrum drugs, or again on the same subset of 'Broad-s' leads to similar conclusion (exact numbers are given in Table A-3 in the appendix).[11]

6. Conclusion

In this paper we studied the market structure of first and second-line antibiotics in the UK between 2003 to 2013. Using aggregate levels sales data, we estimated discrete choice demand models. We find that while prices have declined over the last decade, marginal costs have declined even more, and

[11] We impose a unit tax which is equal to the difference in marginal costs between broad- and narrow-spectrum drugs and is of the order of £0.106 for 2012 but varies slightly for each month.

overall this sector's profitability has increased over time. Marginal costs of broad-spectrum antibiotics are lower while their profit margins are higher relative to the narrow-spectrum antibiotics.

Demand estimates reveal that there is a dispersion in tastes for antibiotics that varies by the antibiotic spectrum of the drug (the marginal utility of spectrum). Price increases in one drug do lead to significant substitution towards other cheaper drugs, but most of the substitution is within groups by spectrum of the antibiotics. This implies that while switching from broad- to narrow-spectrum is possible via changes in relative prices, it will have significant implications for consumer surplus. For an ad valorem tax of 20% on a select set of broad-spectrum drugs that contribute most to the AMR in the UK, the cost in terms of consumer welfare is £138.4 per 1000 residents and a reduced demand of 50.5% for co-amoxiclav, quinolones and cephalosporins but a small increase in demand of other broad-spectrum drugs. While our simulations show how much demand is shifted from broad- to narrow-spectrum, and at what cost, it does not calculate the long term benefits of switching to drugs with a lower AMR footprint. In addition, it is clear that the estimated loss in welfare is much smaller than the estimates of worldwide costs in O'Neill (2016) and it may be well worth our effort to consider such remedies to shift demand to narrow-spectrum drugs.

Finally, note that the consumers in our model (patient-physician combination) exhibit strong tastes by the spectrum of a drug. In principle, this could also be exploited to modify tastes in such a way as to reduce consumption of broad-spectrum drugs. Currently, demand-side interventions are mainly educational campaigns, including raising awareness of antibiotics resistance to the public, professional education to prescribers as well as stewardship of preferred prescription in primary care and in hospitals (Davies and Gibbens, 2013, Scoggins et al., 2006). However, those campaigns may not be sufficient. Since part of the preference over broad-spectrum antibiotics may stem from fear of treatment failure, especially in primary care when there is no clear clue of the specific type of bacterial pathogen, a quick and cheap diagnosis test may completely solve the puzzle. Although these tests are expensive, time-consuming and rarely used in primary care now, scientists have made huge progress to reduce the cost and time in diagnostic methods. For example, Schmidt et al. (2017)

have successfully reduced the time of testing to four hours by direct DNA sequencing. If the uncertainty of bacteria type or level of susceptibility could be reduced by widely used accurate diagnosis, the inappropriate consumption of antibiotics would be calibrated. That combined with cost-side interventions that we highlight above would imply shifting to narrow-spectrum antibiotics with much lower distortions and lower loss in consumer welfare.

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Appendix A. Additional results

A.1. **Random Coefficients Logit.** This appendix provides the results from the Random Coefficients Logit (RCL) where ρ in equation (1) is set to zero.

Table A-1. Estimation results (Logit and Random Coefficients Logit)

	Logit				**RCL**	
	OLS	IV/2SLS		IV-Joint	IV-Joint	
	(1)	(2)	(3)	(4)	(5)	(6)
	β	β	1st-stage	β	β	σ
‡Constant	-4.603***	-4.201***	1.282***	-4.152***	-3.269***	7.723***
	(0.895)	(0.887)	(0.070)	(0.987)	(0.927)	(2.225)
Price	0.016	-0.802***		-6.328***	-4.943***	2.201***
	(0.016)	(0.251)		(0.268)	(0.336)	(0.149)
‡Spectrum	0.124	0.026		-0.083	0.069	0.328***
	(0.118)	(0.127)		(0.168)	(0.193)	(0.108)
Pack	0.538***	0.527***	-0.011	0.452***	0.379***	0.137***
	(0.025)	(0.025)	(0.008)	(0.013)	(0.025)	(0.044)
‡Age	0.016	0.012		0.024*	0.072	
	(0.013)	(0.013)		(0.013)	(0.134)	
‡Generic	1.131***	0.986***		1.013***	0.412	
	(0.298)	(0.312)		(0.313)	(0.34)	
‡Capsule	0.259	0.214		-0.138	-0.124	
	(0.398)	(0.398)		(0.366)	(0.379)	
‡Liquid	-0.666**	-0.743**		-0.675**	-1.195***	
	(0.305)	(0.32)		(0.327)	(0.35)	
Temperature	-0.028***	-0.028***	-0.000	-0.024***	-0.125***	
	(0.002)	(0.002)	(0.001)	(0.002)	(0.034)	
Time	-0.000	-0.047***	-0.009***	-0.364***	-0.149**	
	(0.000)	(0.015)	(0.001)	(0.016)	(0.058)	
z_1:Price of diesel (log)			0.678***			
			(0.142)			
z_2: Exchange rate (log)			0.073*			
			(0.043)			
z_3 #drugs by firm j			0.055***			
			(0.009)			
z_4 #drugs by firm j in nest g			-0.113***			
			(0.028)			
Statistics						
Obs	11417	11417	11,417	11417	11417	
pseudo-Rsq	0.825	0.787	0.77	0.22	0.77	
avg $(p-c)/p$				0.25	0.28	
% mc<0				4.99	4.99	
F-stat			14.81			

Total 11,417 obs of 131 distinct products over 120 months spanning 18 molecules and 14 formulations (with three main characteristics, tablet, capsule, and oral liquid). All regressions include product dummies. Robust standard errors are in parentheses. Superscripts (***), (**), and (*) imply significance at at 1, 5 or 10% respectively.
‡The mean β coefficient retrieved from minimum distance method as product dummies are included.

A.2. **Supply Side Coefficients.** The table provides supply side coefficients for equation (6) when jointly estimated with the demand models.

TABLE A-2. Supply Side equation (log(mc+1))

Supply side	Logit (1) γ	RCL (2) γ	RCNL (3) γ
Constant	0.781***	0.610	0.447**
	(0.106)	(0.379)	(0.191)
‡Broad Spectrum	-0.037**	-0.006	-0.017
	(0.018)	(0.124)	(0.103)
Pack	-0.031***	-0.013	0.002
	(0.006)	(0.023)	(0.013)
Generic	-0.196***	-0.243***	-0.12***
	(0.019)	(0.065)	(0.027)
Capsule	0.048*	-0.08	-0.062*
	(0.027)	(0.053)	(0.034)
Liquid	0.241***	0.180***	0.067
	(0.021)	(0.068)	(0.054)
Time	-0.028**	-0.042*	-0.05***
	(0.013)	(0.025)	(0.017)
z_1:Price of diesel (log)	0.053	0.277	0.398
	(0.227)	(0.317)	(0.448)
z_2: Exchange rate (log)	0.034	0.072	0.073
	(0.064)	(0.219)	(0.079)
Statistics			
Obs	11417	11417	11417
pseudo-Rsq	0.15	0.13	0.19

Total 11,417 obs of 131 distinct products over 120 months spanning 18 molecules and 14 formulations (with three main characteristics, tablet, capsule, and oral liquid). Robust standard errors are in parentheses. Superscripts ***, ** and * imply significance at at 1, 5 or 10% respectively.

‡Broad Spectrum is a dummy variable that indicates if the drug has a broad-spectrum molecule. It is different than the Spectrum variable used in the demand equation.

TABLE A-3. Per unit tax

		On all broad-spectrum (1)	On select‡ broad-spectrum (2)
%Δprice	‡Broad-s	25.19	30.99
	†Broad-o	31.69	-0.27
	Broad	26.64	16.06
	Narrow	-1.22	-0.25
	Combined	0.30	-0.11
%Δquantity	‡Broad-s	-39.07	-60.98
	†Broad-o	-38.57	3.80
	Broad	-38.65	-8.20
	Narrow	19.83	4.21
	Combined	-14.66	-3.09
ΔCS		-251.9	-206.3
ΔΠ		-128.5	16.0
Δtax revenue		223.5	26.0
Δtesting cost		540.2	114.5
Total Δ		-697.1	-278.7

The monetary change of welfare is measured as pounds per 1000 inhabitants. The UK population in 2012 is 63,705,000. The NHS unit test cost is 8 pounds. We assume that an antibiotic script is prescribed for 7 days. Total = CS + Π + Tax revenue − Testing cost. ‡Tax imposed on drugs selected broad-spectrum drugs, which include co-amoxiclav, quinolones (ciprofloxacin, levofloxacin and ofloxacin) and cephalosporins (cefalexin, cefixime). †All other broad-spectrum drugs.

TABLE A-4. Unit tax per month (2012)

Month	1	2	3	4	5	6	
Tax	.116	.116	.106	.108	.112	.107	
Month	7	8	9	10	11	12	Mean
Tax	.108	.101	.103	.089	.096	.113	.106

Unit tax is the mean difference between marginal costs in broad- and narrow-spectrum drugs

Appendix B. Technical details

This appendix provides details on the instruments, the definition of the potential market, and the formula we used the for tax simulation.

B.1. **Instruments.** We first describe all the excluded instruments, and then how they were used in different models along with other exogenous variables and counts of moment restrictions. The variables z_{1t} and z_{2t} are the log of price of diesel and of exchange rate and not specific to any drug and vary only by markets (average monthly values). The next set are BLP style instruments: z_{3jt} is the total number of other drugs produced by the manufacturer of the reference drug j and z_{4jt} is the total number of other drugs by the reference firm of j restricted to the nest of the drug j. Similarly, z_{5jt}, is the total number of packs across other products by firm producing drug j within the nest of drug j, and z_{6jt} is the total number of packs by competitors within the reference nest of drug j. Interactions and higher powers include $z_7 = z_4^2$, $z_8 = z_5^2$ and $z_9 = z_4 z_5$.

For the logit model, the exogenous variables are constant, pack varieties, a time trend, the weather temperature, and drug dummies (131 minus one reference). Note that the invariant product characteristics such as spectrum value, formulation type, etc. do not enter this equation. Therefore, when the logit specification is estimated via OLS, it has 4+130 = 134 demand-side instruments. (We back out those coefficients on spectrum, age, generic, capsule, liquid and constant using Chamberlin's method). Further, when we estimate it via 2SLS, we use four additional instruments: z_1, z_2, z_3 and z_4 for a total of 138 moment restrictions.

Next, we estimate the logit jointly with the supply side equation. The supply equation includes a constant, pack variety, the log of the price of diesel (z_1), the log of the exchange rate (z_2), a time trend, a dummy variable for broad-spectrum molecules, a dummy variable for generic, a dummy variable for capsule, a dummy variable for liquid, for a total of nine instruments (the supply side does not include drug dummies). Summing up, in the logit model when estimated jointly with the supply side, there are 136 demand-side instruments (134 plus z_3 and z_4) and nine cost-side instruments (including z_1 and z_2) for a total of 145 moment restrictions.

Finally, for the RCNL estimation, we additionally use z_5 and z_6 (which provide nest specific counts) as well as z_7 and z_8 for a total of 149 moment conditions (140 for demand side and nine for the supply side). In the RCL model, we drop z_6 and z_8 and instead use z_9 for a total of 139+9=148 restrictions.

In the versions with optimal instruments, following Reynaert and Verboven (2014) we further compute six instruments: four optimal instruments for the random coefficients for the constant, price, pack variety, and spectrum, one for the price in the linear part, and one for the within-group market share. The

optimal instruments for other variables are the exogenous variables themselves. The optimal instruments replace the original instruments.

B.2. **Tax simulation algorithm.** We use the demand and pricing equations to conduct a tax simulation exercise. We impose the tax rate τ on groups of drugs of interest. Given the estimated demand parameters and the estimated marginal cost vector in market t, c_t, we calculate the new equilibrium price vector p_t^* and market shares $s_t(p_t^*)$ as,

$$p_t^* \oslash (1 + \tau_t) = c_t + \Delta_t^{-1}(s_t(p_t^*)) \cdot s_t(p_t^*).$$

In our three simulation exercises we let τ be 5%, 10% and 20% for some drugs. The surplus gained by individual i in market t is

$$cw_{it} = \frac{1}{\beta_{pi}} \max_{j \in \mathcal{J}_t} u_{ijt},$$

where β_{pi} is the random coefficient on prices (in absolute value). This money metric utility varies across consumers and by markets, and we can take its expectation to compute the average consumer welfare (Small and Rosen, 1981). For the random coefficients nested logit model, the expression of interest for the market t can be simulated in the following way,

$$E(cw_{it}) \approx \frac{1}{ns} \sum_{i=1}^{ns} \frac{1}{\beta_{pi}} \ln \left[1 + \sum_{g=1}^{G_t} \left[\sum_{l=1}^{J_{gt}} \exp\left(\frac{x_{jt}\beta_i + \xi_{jt}}{1-\rho} \right) \right]^{1-\rho} \right] + K_t \qquad (7)$$

where K_t is a period-specific constant. We do not know the value of this constant. However, it drops out of calculations when we study the change in expected consumer welfare associated with a variation in the price vector in the counterfactual situation relative to the observed factual condition. The total monetary consumer welfare is $E(cw_{it})$ times the potential market size.

We also account for the cost of testing incurred to diagnose the pathogen before prescribing narrow-spectrum drugs. This step is not necessary when prescribing broad-spectrum drugs. As a conservative estimate of the additional cost of testing, we divide the narrow-spectrum drug quantity by seven, and convert it to bouts of illnesses under the assumption that an antibiotic script is prescribed for seven days. We then multiply it by NHS tariff for microbiology testing that is in place that year.[12]

The total welfare is the sum of (CS + Π + Tax revenue − Testing cost). As mentioned above, we focus on changes of total welfare. We convert the monetary change of welfare to pounds per 1000 inhabitants, knowing that the UK population in 2012 was 63.7M.

[12] We used NHS unit cost for "currency code" DAPS07 (microbiology), which is a case-mix adjusted unit cost by service areas. See https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016.