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Consumption of general purpose broad-spectrum antibiotics is associated with rising levels of antimicrobial resistance. Additionally, industry reports suggest that lack of profitability associated with narrowly targeted pathogens is a potential reason why firms are not undertaking new antibiotic related R&D. In this paper we use aggregate sales data on antibiotics from the UK to estimate a structural demand model and evaluate market performance of firms by spectral activity. We find that broad-spectrum antibiotics are more profitable than narrow-spectrum drugs, though the profitability has increased over time for both types due to a decline in costs, the costs of narrow stay higher. We simulate counterfactual scenarios to evaluate the effectiveness of cost-side interventions to shift demand from broad- to narrow-spectrum drugs. Using the last full year of data, simulations show that if unit costs of broad-spectrum were as high as those of narrow-spectrum antibiotics (say due to a unit tax), demand for broad-spectrum would fall by 28.1%, while that of narrow-spectrum would increase by 43.8%. The total cost of such an intervention would be £962 per thousand individuals or a total of £61.26 million, and is inclusive of change in consumer welfare and additional cost of testing for pathogens. Impact of other more selective taxes on subsets of broad-spectrum drugs is also analyzed.

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

**JEL Classification: I11, I18, L11, L65**

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## 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 important and 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 (of course there is also a positive externality that it may cure an infection and thereby reduce the likelihood of transmission to uninfected persons).[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 to propose 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). Two key issues identified in this report, and relevant to this paper, are lack of incentives for firms to undertake research and development (R&D) of new antibiotics, and demand management towards appropriate/optimal use.

Indeed, there is a downward trend in the number of new antibiotics reaching the market with only twelve new drugs and two new classes introduced since 2000 (lipopeptides and oxazolidinones) where the last new antibiotic class introduced before that (trimethoprim) was in the seventies (ECDC/EMEA, 2009, Power, 2006, Spellberg et al., 2004). Moreover, since new antibiotics are reported to be not as profitable as, say cancer drugs, several R&D active pharmaceutical firms have diverted their efforts and closed down their antibiotic research laboratories, and those that remain have few projects in advanced clinical trials (Boucher et al., 2013, Mossialos et al., 2010, IDSA, 2004, Projan, 2003).[2] As stated in O'Neill's report, returns from new investments in antibiotics do not have high or guaranteed returns: if a new patented antibiotic comes to the market, its price is high while the existing generics of older strains may have lower price but also low AMR at the time, and hence sales of the newer and more expensive antibiotic would be low. By the time AMR for the older generic rises to the level that patients would be switched to the newer antibiotic,

[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.

[2] According to one recent editorial, only Merck, Roche, GlaxoSmithKline and Pfizer have active antibiotic programs (Nature Biotechnology, 2018).

patent life may be near its end, and hence the innovative newer drug may still not be profitable as generic production starts. Similarly, over and inappropriate use of antibiotics in human and farm use (mentioned in the report and elsewhere, see for instance, Hollis and Ahmed (2013), Brown and Layton (1996)) has been linked to the rise of AMR strains of pathogens.[3]

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 et al., 2003a,b, Wood et al., 2007, Kaier and Moog, 2012, CMO, 2013). If there is a cost to finding which narrow-spectrum antibiotic is appropriate, generally broad-spectrum antibiotics will be over prescribed relative to the narrow-spectrum antibiotics and contribute to AMR. The report recommends demand management via testing prior to prescribing, and where appropriate, using narrow-spectrum drugs. Interestingly, 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 for more narrow-spectrum antibiotics.

In this paper we use sales data from 2003-2013 from the UK to document the market structure for antibiotics by drug type and firms (branded, generic, R&D active firm or not, molecule class, broad/narrow spectrum). Our objective is two fold. First, we want to quantify the performance of firms by estimating price-cost margins and check if they vary by age of the molecule and drug, as well as estimate the same by the spectrum of the drugs. In order to do so, we estimate demand using discrete choice models (nested logit and random coefficients with optimal instruments, employing methods outlined in Berry et al. (1995), Nevo (2000) and Reynaert and Verboven (2014)) on aggregate sales data by individual drugs, and combine it with assumptions about forms of competition and cost functions to back out marginal costs at the product level. We jointly estimate the supply side under Nash-Bertrand equilibrium, where multi-product firms maximize their profits in an oligopolistic setting. The estimation helps us check whether newer drugs are more profitable or not, and how they compare to their generic counter parts. Second, based on estimated parameters, we simulate and test the feasibility of cost side interventions to affect demand. Particularly, would a tax on broad-spectrum (or a subsidy on narrow-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 much would it cost society?

[3]Positive correlation between antibiotics consumption and resistance is well documented, see for instance Goossens et al. (2005), Malhotra-Kumar et al. (2007), Goossens et al. (2007), Tacconelli et al. (2008).

Our results show that even though sales by value have decreased over time, as has the average price, profitability of several individual drugs has increased due to a more extensive decline in costs. For instance, the average price-cost margin for the market is around 35.2%, up from 26.3% in 2004 to 46.2% 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 and firms. Broad-spectrum antibiotics tend to have lower costs and higher margins than narrow-spectrum agents, although the gap shrinks in later years. New molecules launched after 2000 are unlikely to bring innovators large profit, as they have less than 0.01% of market share in our data. Further, firms considered research active in antibiotics earn less than 19% of revenue of all drugs in our sample which corresponds to less than 10% of industry profit. This market performance might explain why innovative pipeline in new antibiotics has dried up (Power, 2006, Cooper and Shlaes, 2011, Mossialos et al., 2010).

At the individual brand level, the drugs are fairly elastic. The share-weighted mean own-elasticity is $-3.310$ and cross-elasticity is 0.172.[4] There is generally less substitutability across 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 0.288, while that of narrow-spectrum drug is 0.148.

These estimates suggest that while it is possible to shift demand from broad- to narrow-spectrum drugs, it comes at a cost. Simulations show that if the marginal costs of broad-spectrum were as high as those of narrow-spectrum (say due to a unit tax), demand for broad-spectrum would fall by 28.1%, while that of narrow-spectrum would increase by 43.8% in 2012. The short run total cost of such a tax would be £962 per thousand individuals, or £61.26 million due to change in consumer welfare, testing costs, firm profits and tax revenue. We also provide estimates from an ad valorem tax which imposes a 5-20% tax on a subset of broad-spectrum drugs at a much lower societal cost with significant reductions in targeted drugs. Our estimates should not be taken as full calculation

[4]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 a 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 impact of TRIPS on welfare, Chaudhuri et al. (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 manufactures and so they also provide group wide elasticities by molecule and domestic and foreign status of manufactures, 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 group level, there are examples of estimates at brand level as well, albeit not for antibiotics, which are more in line with our estimates. For instance, Duso et al. (2014) estimate nested logit models at 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 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.

of welfare as we do not account for long term benefits that accrue to consumers due to reduction in AMR (which would reduce long term loss in consumer surplus). They should be interpreted as an upper bound on the total cost of such an intervention as we account for an increase in cost due to additional testing. 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.

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 et al. (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 et al. (2011, 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 et al. (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 pay-for-performance and more appropriate antibiotic prescriptions (Mullen et al., 2010, Yip et al., 2014, Gong et al., 2016).

By comparison, 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, 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). 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 et al., 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 et al. (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.

A related but distinct literature also highlights the role of markets and optimal patent designs to address problems associated with AMR. One suggestion has been to extend the patent length, which would increase monopoly period benefits of antibiotic effectiveness, and hence increase a firm's incentives to minimize resistance (Laxminarayan, 2001, Horowitz and Moehring, 2004, Towse and Kettler, 2005). Similarly, Mechoulan (2007) finds that compared to the price charged by generic industry, re-activation of monopoly via extended patents by a myopic monopolist would set the price closer to the socially optimal price if the increase in resistance is sufficiently high.[5] Herrmann (2010) adds that with a finite length of a patent, a forward looking monopolist would also set prices like a myopic monopolist, and hence it is socially desirable to extend the duration of the patent. Others have argued that because of cross-resistance, where use of one antibiotic within a class affects the resistance of another drug in the same class, antibiotic patents should be broad, which would also discourage 'marginal innovations' (Laxminarayan, 2001, 2002, Herrmann and Laxminarayan, 2010). Relatedly, Herrmann et al. (2013) show that because of AMR, innovators do not innovate at the appropriate distance from the existing molecules, so that additional regulation on patent breath or financial subsidies on R&D are needed. Only when firms launch new antibiotics at the correct position, can tax/subsidy regime correct consumption patterns.

Other policies include a *sui generis* right for expired patents within antibiotic class to a single producer (perhaps via auctioning) to permit better control over AMR, giving antitrust exemptions to allow consolidation, or issuing *wildcard* extensions to other patents if firm innovates for antibiotics (Laxminarayan et al., 2007).[6] However, Outterson et al. (2007) argue that neither extension of patent life nor wildcard can be the solution, as the reward from the former is too little and the cost (to the society) of the latter is too large. On the other hand, Eswaran et al. (2016) point out that competition from the new entrant may have two contradictory effects on resistance. Due to cross-resistance, it may increase the resistance of the originators drug, but that it can also prolong the life of the originator's drug if the resistance reduced by market stealing effect is larger. Similarly, Gallini (2017) argues that patent can facilitate innovation if protection of follow-on research and technology transfer is guaranteed.

The rest of the paper is structured as the follows. The next section describes the antibiotics UK market and the data. Section 3 outlines the model as well as discusses estimation issues. Section four has all main results including the regression coefficients, substitution patterns and simulations. The last section concludes.

[5] In fact, in 2012, President Obama signed the *Generating Antibiotics Incentives Now (GAIN)* legislation which adds five years to any original market exclusivity already conferred to certain antibiotics.

[6] More generally the idea of transferable or roaming exclusivity is in relation to all disease areas where R&D may not be as profitable, such as the orphan drugs (Kettler, 2000, Towse, 2004, Grabowski, 2005) and works as follows: if Pfizer developed a new antibiotic, it would be able to extend its patent on another blockbuster drug such as Lipitor by a set number of years, and if a firm did not have a patent on another drug, it could sell the extension to some other firm.

## 2. Background and Data

Antibiotics are prescription only medicines and about 74% are prescribed via general practitioners (GPs), followed by 18% use in hospitals (PHE, 2015a). 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 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).

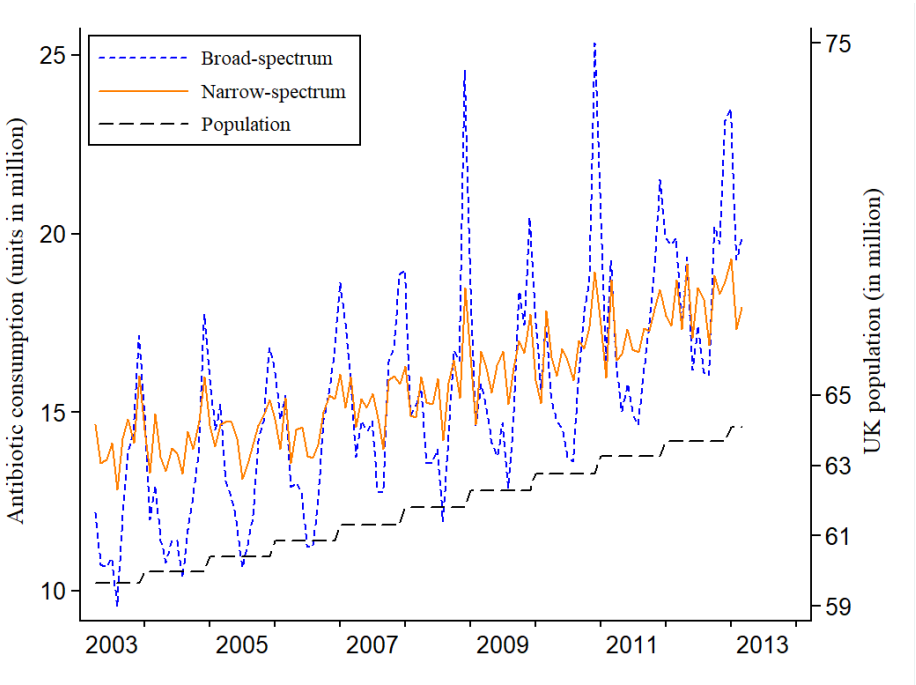
Prior literature shows that GPs are aware of prices and that they may be sensitive to prices (NAO, 2007, Scoggins et al., 2006, Carthy et al., 2000). This is enforced by NHS's budgeting strategy since April 1999 to achieve *cost saving* and *efficiency* (Jacobzone, 2000). To ensure efficiency of prescribing 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 affects 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 is 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 stengths/sizes are not counted as different products. A limitation in our data is that generic manufactures are not separately identified in the IMS data base. Thus, if multiple manufactures are producing a drug by non-proprietary name within the same molecule and formulation, and within the same 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).[7]

The total market for all antibiotics in our data is £160 million per year and in real terms has decreased from £208.6 million in 2004 to £126.7 million in 2012. This drop is driven primarily by a decrease in average real prices, which declined from £0.65 per gram to £0.31 per gram 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 60 million packs of antibiotics containing 0.4 billion grams of active ingredients (or 0.44 billion DDD units) were dispensed in 2012, while 44.5 million packs were dispensed in 2004. This is only partially explained by the rise in UK population which increased from 60 million to 64 million over this period. The average DDD unit of antibiotic consumption per resident per year also increased from 5.36 to 6.93 between 2004 and 2012.

FIGURE 1. Antibiotic consumption and UK population




Sales are separated by broad- and narrow-spectrum groups, based on classifications in PHE (2015b), 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, for further information on spectrum thresholds, see Appendix A-1). 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

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

tract infections and virus-induced secondary bacterial infections in cold seasons (Suda et al., 2014, Hendaus et al., 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, 2015b) recommends 18 different molecules as first and second line drugs to treat common primary community-acquired diseases, while others are to be used more sparingly. 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 16 molecules (we combined three molecules with very small shares into one group) and 18 different formulations (tablets, capsules etc.). Overall, the number of products reduced slightly over the years.

TABLE 1. Shares, Prices and Concentration by Molecule

| | | 2004 | | | 2008 | | | 2012 | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Spectrum | Share | Price | HHI | Share | Price | HHI | Share | Price | HHI |
| *Broad-spectrum* | | | | | | | | | | |
| Amoxicillin | 13.50 | 28.40 | 0.26 | 0.73 | 29.81 | 0.15 | 0.90 | 29.78 | 0.10 | 0.97 |
| Co-amoxiclav | 29.50 | 4.46 | 1.66 | 0.53 | 5.13 | 0.69 | 0.46 | 5.37 | 0.38 | 0.53 |
| Cefalexin | 19.25 | 3.22 | 0.69 | 0.72 | 3.06 | 0.46 | 0.53 | 1.51 | 0.29 | 0.52 |
| Ciprofloxacin | 39.75 | 2.56 | 2.39 | 0.67 | 2.74 | 0.30 | 0.49 | 1.98 | 0.24 | 0.56 |
| Doxycycline | 38.75 | 6.99 | 0.30 | 0.67 | 7.76 | 0.11 | 0.73 | 10.27 | 0.07 | 0.81 |
| Levofloxacin | 39.75 | 0.16 | 2.78 | 1.00 | 0.13 | 2.11 | 1.00 | 0.06 | 1.46 | 0.52 |
| Ofloxacin | 39.75 | 0.30 | 1.98 | 0.48 | 0.21 | 0.90 | 0.45 | 0.19 | 1.20 | 0.47 |
| Tetracycline | 38.75 | 0.62 | 0.14 | 1.00 | 0.47 | 1.12 | 1.00 | 0.28 | 0.99 | 1.00 |
| Others (3 mols) | 19.50 | 0.07 | 1.72 | 1.00 | 0.04 | 2.07 | 1.00 | 0.06 | 1.59 | 1.00 |
| *Narrow-spectrum* | | | | | | | | | | |
| Azithromycin | 12.25 | 0.39 | 2.62 | 1.00 | 0.82 | 1.98 | 0.53 | 1.54 | 1.18 | 0.52 |
| Clarithromycin | 12.25 | 3.38 | 1.61 | 0.92 | 4.64 | 0.63 | 0.55 | 7.96 | 0.34 | 0.41 |
| Clindamycin | 10.75 | 0.13 | 4.40 | 0.48 | 0.16 | 8.22 | 0.42 | 0.18 | 2.01 | 0.45 |
| Erythromycin | 12.25 | 11.86 | 0.58 | 0.52 | 10.15 | 0.42 | 0.50 | 7.24 | 0.27 | 0.56 |
| Flucloxacillin | 4.25 | 5.95 | 0.96 | 0.59 | 6.18 | 0.72 | 0.78 | 7.02 | 0.62 | 1.00 |
| Penicillin V | 13.50 | 4.37 | 0.56 | 0.96 | 4.17 | 0.53 | 0.96 | 4.06 | 0.58 | 1.00 |
| Trimethoprim | 4.25 | 7.01 | 0.12 | 0.88 | 6.64 | 0.08 | 0.89 | 6.30 | 0.10 | 0.99 |
| †1st/2nd line (18 mols) | | 79.89 | 0.62 | 0.71 | 82.13 | 0.36 | 0.75 | 83.78 | 0.26 | 0.81 |
| †Non-1st/2nd line (26 mols) | | 20.11 | 0.65 | 0.84 | 17.87 | 0.38 | 0.90 | 16.22 | 0.26 | 0.85 |

Market share is by DDD quantity. Price is per unit of DDD (weighted by share of individual drugs). HHI is calculated over different firms based on their quantity shares within each molecule.
†1st/2nd line groups refer to oral drugs recommended by PHE to be used for treating common community acquired diseases or not (and HHI is average of molecule HHI weighted by share).

The detailed market structure of selected antibiotic molecules is summarized in Table 1. The top selling broad-spectrum antibiotic is amoxicillin, whose shares stayed stable around 29% over the years while that of co-amoxiclav increased over the years. Other top broad-spectrum drugs listed in the table lost market shares. Shares of narrow-spectrum drugs generally increased except for erythromycin which declined from 11.86 to 7.24%. In addition, average price per DDD for each molecule has also dropped. For instance, price of amoxicillin has dropped from £0.26 per DDD to £0.10 between 2004 and 2012. Herfindahl-Hirschman Index (HHI) are calculated based on firm level shares within each molecule, and show that at this level the market is fairly concentrated.

This may be seen as an indicator of high profit margins in this market. Even though there are 35 different manufacturers involved in the production of these 44 different molecules, only a limited number of firms are producing the same molecule. Further, the HHI index for number of molecules has increased over time. For instance, HHIs of amoxicillin and flucloxacillin have increased from 0.73 and 0.59 to 0.97 and 1 respectively. Note that per the limitation mentioned earlier regarding identity of generic manufacturers, the HHI index is biased upward.

## 3. Econometric specification

3.1. **Utility.** We abstract away from agency problem where physician incentives may not be aligned with their patient and assume that the decision maker is a combination of a general practitioner and patient, which we will simply shorten to patient or consumer. Since the NHS sets annual budget for PCT, which in turn monitor GP spending, this would make GPs sensitive to prices. Thus our combined decision maker's utility is function of prices and drug characteristics. In this setting, the utility for patient $i$ choosing drug $j$ in period $t$ is given by

$$U_{ijt} = x_{jt}\beta_i + \alpha_i(y_{it} - p_{jt}) + \xi_{jt} + \varepsilon_{ijt}, \tag{1}$$

where $x_{jt}$ is the row vector of observable characteristics of drug $j$ in period $t$, and $\beta_i$ is the corresponding column vector of random coefficients (i.e., taste parameters) which vary by patient. The variables $p_{jt}$ and $y_{it}$ are price of drug $j$ and the budget of patient/physician $i$ in period $t$, respectively. The coefficient $\alpha_i$ is also random and captures heterogeneous preferences toward drug price and $\xi_{jt}$ is the unobserved characteristics of drug $j$ and $\varepsilon_{ijt}$ is an *iid* idiosyncratic error term.

In our regressions the vector of observable drug characteristics includes a constant, number of different packs a drug is sold by, and the spectrum of the molecule the drugs is linked to. In addition, we control for drug dummies, time trend, and seasonalities. We follow Chamberlain (1982) and Nevo (2000), and use the minimum distance method (basically a feasible GLS regression) to back out the coefficients of time invariant variables. The estimated drug dummy coefficients are regressed against a constant, the spectrum of the molecule, and dummies for generic drugs and liquids. We model taste heterogeneity of patients as functions of unobserved patient characteristics. Formally, this is expressed as

$$\begin{pmatrix}\alpha_i \\ \beta_i\end{pmatrix} = \begin{pmatrix}\alpha \\ \beta\end{pmatrix} + \Sigma v_i, \quad v_i \sim N(0, I). \tag{2}$$

The scalar $\alpha$ and the vector $\beta$ are the mean utility of price and drug characteristics and are common to all patients. The column vector $v_i$ captures unobserved patient-specific preferences towards drug price and drug characteristics. Following the literature, we model that vector to be random and follow a multivariate standard normal distribution where $\Sigma$ is a diagonal scaling matrix.

Each period $t$ patient $i$ selects the drug that maximizes his/her utility. The aggregate market share for drug $j$ in period $t$ is the average probability the drug is chosen from the set of all drugs, inclusive of an outside option. Specifically, by separating out the utility in a mean effect $\delta_{jt} = x_{jt}\beta - \alpha p_{jt} + \xi_{jt}$ and deviations for that mean $\mu_{ijt} = [p_{jt}, x_{jt}]\,\Sigma v_i$, we are able to derive the predicted market share of drug $j$ in period $t$.

3.2. **Market shares.** Letting the error term $\varepsilon_{ijt}$ follow an Extreme Value distribution, it is possible from a comparison of all utilities $U_{ijt}$ and $U_{ij't}$ with $j \neq j' = 0, 1, \cdots, J_t$, to obtain random coefficients multinomial logit probabilities. Each drug's market share is the result of the multivariate integral of these probabilities over the random vector $v_i$. This integral has no simple analytical solution, and therefore the vector of unobserved patient heterogeneity has to be simulated from the multivariate standard normal distribution, so to obtain the approximation

$$s_{jt} = \int_{v_i} \frac{exp\left(\delta_{jt} + \mu_{ijt}\right)}{\sum_l exp\left(\delta_{lt} + \mu_{ilt}\right)} dF_v \approxeq \sum_i \frac{1}{ns} \frac{exp\left(\delta_{jt} + \mu_{ijt}\right)}{\sum_l exp\left(\delta_{lt} + \mu_{ilt}\right)}, \quad j, l = 0, 1, \cdots, J_t. \tag{3}$$

Logit and nested logit models can be constructed by imposing small adjustments to the random coefficients logit model (see Berry (1994)). For instance, if the coefficients are not random, then equation (1) simplifies to the logit model, in which case the market share is simply

$$s_{jt} = \frac{exp\left(\delta_{jt}\right)}{\sum_l exp\left(\delta_{lt}\right)} \qquad j, l = 0, 1, \cdots, J_t. \tag{4}$$

The nested logit model is an extension of the logit model after decomposing the error term $\varepsilon_{ijt}$ into $\varepsilon^1_{imt} + (1-\sigma)\varepsilon^2_{ijt}$. In this case, $\varepsilon^1_{imt}$ is a random individual taste for molecule $m$ and $\varepsilon^2_{ijt}$ is a random individual taste for drug $j$. The parameter $\sigma$ measures the intensity of within molecule correlations. In this model, patients first choose the molecule and then the drug within that molecule. The market share of drug $j$ in period $t$ is obtained by interacting the within molecule market share $s_{(j\in m)t}$ and the molecule's market share $s_{mt}$. Thus, the nested logit formula is

$$s_{jt} = s_{(j\in m)t} s_{mt}, \quad \text{with} \quad s_{(j\in m)t} = \frac{\exp(\delta_{jt}/(1-\sigma))}{D_{mt}} \quad \text{and} \quad s_{mt} = \frac{D_{mt}^{(1-\sigma)}}{\exp(\delta_{0t}) + \sum_{k=1}^{M_t} D_{kt}^{(1-\sigma)}}, \tag{5}$$

where $D_{mt} \equiv \sum_l \exp(\delta_{lt}/(1-\sigma))$, $l = 1, \cdots, J_{mt}$, which captures all drugs in molecule $m$ in period $t$. We estimate logit, nested logit and random coefficients logit models.

3.3. **Outside option.** For the logit and nested logit models the econometric demand equations are derived by taking the natural log of the ratio between the market share of the product $j$ and that of the share of an 'outside' option $s_0$. Typically, the outside option is a residual category which includes the possibility of not purchasing any product, and its product characteristics (including price) are not observed and its utility is standardized to zero. The literature has taken different approaches to estimating the share of the outside option by first defining the potential market. Since the market that we study consists of antibiotics that are recommended as first or second line

use for bacterial infectious disease by PHE (2015b), we model the outside option to be all other antibiotics that are not considered first or second line use. Thus, we define the outside option as residual category of antibiotics whose sales and product characteristics we also observe in our data. This adjustment slightly changes the functional form of the 'traditional' econometric model but preserves the convenient feature of invertibility of the market share (demand) equation. For instance, when the outside good is defined as above, the simple logit specification becomes

$$\ln(s_{jt}) - \ln(s_{0t}) = (x_{jt} - x_{0t})\beta - \alpha(p_{jt} - p_{0t}) + (\xi_{jt} - \xi_{0t}). \tag{6}$$

Note that this equation requires that we observe the outside good price $p_{0t}$ and characteristics $x_{0t}$ (see also De Groote and Verboven (2018)). We set these equal to the price and characteristics of the antibiotic with the maximum share among all the drugs in the residual category and $s_0$ as the sum of their shares. Thus by defining $\hat{x}_{jt} \equiv x_{jt} - x_{0t}$, $\hat{p}_{jt} \equiv p_{jt} - p_{0t}$ and $\hat{\xi}_{jt} \equiv \xi_{jt} - \xi_{0t}$, we update our definitions of $\delta_{jt}$ and $\mu_{ijt}$ and use these to compute the share equations as given above.

3.4. **Oligopoly supply.** The supply side is the result of multi-drug profit maximizing companies that choose prices as strategic variables in a differentiated products setting. The resulting equilibrium in the market is Nash in prices. The pricing equations obtained from the profit maximization are used for two purposes. Firstly, they are utilized to back out the marginal costs. Secondly, after the parameters are estimated and marginal costs backed out, they are employed to calculate the new equilibrium prices that follow the counterfactual scenario we wish to study.

In this model, drugs are assumed to have constant marginal cost of production and distribution, $c_{jt}$. Each firm $f = 1, \cdots, F_t$ controls the vector of prices $(p_{ft})$ and maximizes its profit, given the prices of all drugs produced by other firms $p_{-ft}$:

$$\max_{p_{ft}} \Pi_{ft}\left(p_{ft}, p_{-ft}\right) = \max_{p_{ft}} \sum_{l \in \mathcal{F}_{ft}} \left(p_{lt} - c_{lt}\right) q_{lt}\left(p_t\right), \tag{7}$$

where $\mathcal{F}_{ft}$ is the set of antibiotics produced by firm $f$ in period $t$. Since the total unit sales can be expressed as $q_{jt} = s_{jt}M_t$, where $M_t$ is the population of individuals that have contracted a bacterial infection in period $t$. The first order condition of profit maximization is

$$s_{jt}\left(p_t\right) + \sum_{l \in \mathcal{F}_{ft}} \left(p_{lt} - c_{lt}\right) \frac{\partial s_{lt}\left(p_t\right)}{\partial p_{jt}} = 0 \quad \forall j \in \mathcal{F}_{ft}. \tag{8}$$

By defining $\Delta_t$ a matrix whose element $\Delta_{(jk)t} = -\partial s_{kt}/\partial p_{jt}$ if $j$ and $k$ belong to the same firm and zero otherwise, it is possible to rewrite the system of first order conditions in matrix form as

$$p_t = c_t + \underbrace{\Delta_t^{-1} s_t}_{m_t}, \tag{9}$$

where $m_t$ captures the vector of mark-ups.

Each period $t$, from the vector of pricing equations in Eq. (9) it is possible to construct a log-transformation of the marginal cost for drug $j$ as:

$$\ln(p_{jt} - \underbrace{\Delta_{j.t}^{-1} s_t}_{m_{jt}}) = \ln(c_{jt}) = w_{jt}\gamma + \omega_{jt}, \tag{10}$$

where $\gamma$ are coefficients and $w_{jt}$ represents a vector of observable drug characteristics, which includes firm, molecule and form dummies, along with pack variety and time trend. The idea behind the inclusion of pack variety as control is that if drugs have different pack varieties, they may also have a different unit marketing and production cost. In addition, with firm dummies we capture firm efficiencies as well as heterogeneity in transportation and import costs. With form dummies we express cost asymmetries in producing different forms and, finally, with molecule dummies we represent disparities in producing drugs that are more or less complex to manufacture. The term $\omega_{jt}$ is the random unobserved part of marginal cost.

Given that the marginal costs are constant, they remain unvaried under different counterfactuals, in which case under the new counterfactual scenario it is possible, each period $t$, to find the new set of equilibrium prices that solve the new system of nonlinear simultaneous equations in Equation 9.

3.5. **GMM Estimation.** We assume that the unobservables in demand and pricing equation are conditionally independent of all observed product characteristics $x_t$ and cost shifters $w_t$, yielding $E(\xi_{jt}|z_t) = E(\omega_{jt}|z_t) = 0$, with $z_t \equiv (x_t, w_t)$. We estimate demands and pricing equations simultaneously and account for correlation between these. We therefore avoid imposing the restrictive assumption of a diagonal covariance matrix $E\left((\xi_{jt}, \omega_{jt})'(\xi_{jt}, \omega_{jt})\,|z_t\right) = \Omega$. Further, we denote with $\tilde{\xi}_{jt}$ and $\tilde{\omega}_{jt}$ the standardised version (based on $\Omega^{-1}$) of unobservables in demand and pricing equations. Finally, let $H_{jt}(z_t)$ be a $L \times 2$ matrix of instruments. With these elements it is possible to express a generalised method of moments (GMM) function that the estimator of parameters $\theta$ can minimise,

$$\theta^* = \arg\min\ G = \left(\frac{1}{T}\sum_{t=1}^{T}\frac{1}{J_t}\sum_{j=1}^{J_t} H_{jt}(z_t)\begin{pmatrix}\tilde{\xi}_{jt}\\ \tilde{\omega}_{jt}\end{pmatrix}\right)' \left(\frac{1}{T}\sum_{t=1}^{T}\frac{1}{J_t}\sum_{j=1}^{J_t} H_{jt}(z_t)\begin{pmatrix}\tilde{\xi}_{jt}\\ \tilde{\omega}_{jt}\end{pmatrix}\right). \tag{11}$$

The vectors of linear parameters $\beta$ and $\gamma$ can be concentrated out of the minimisation of equation (11), so to relegate the nonlinear search over the $(\alpha,\ \sigma)$ vector of parameters. To estimate the model we employ the fixed points (NFP) algorithm in `Matlab` with tight convergence criterion ($10^{-12}$) for the inner loop.[8] We recalculate the optimum under several starting points, since the nested fixed points algorithm may sometimes only give local minima, as illustrated by Knittel and Metaxoglou

[8] We also considered Mathematical Programming with Equilibrium Constraints (MPEC) algorithm suggested by Dubé et al. (2012), where the contraction mapping in NFP is replaced by constrained minimization based on market shares. However, in our case we have too many products to handle MPEC. Nevertheless, Reynaert and Verboven (2014)) show that both algorithms give, in principle, identical results when a tight inner loop is used. So, we are confident that NFP does a satisfactory job.

(2014). Our results are robust to the initial values of the nonlinear parameters, especially when the optimal instruments (discussed below) are used.[9]

3.6. **Instruments.** Price and, in the case of nested logit econometric specification the within group market share, are endogenous variables. The price variable is endogenous because of its correlation with unobserved drug quality; the within group share variable is endogenous because is calculated using market shares and therefore is, by construction, correlated with the error term in demand.

We use the exogenous product characteristics and a proxy for wholesale price as instruments for prices. The proxy for wholesale price is a good instrument as it is correlated with the retail price by definition (see Appendix A-3 for further description of this variable). In addition, we employ BLP instruments, which are constructed as the sum of other drug characteristics produced by the same firm. They are correlated with prices as they enter the mark up function via the set of first order conditions. In our data, the constant and the pack varieties are used to construct the BLP instruments. Additionally, count of drugs by molecule is a good instrument for the within market share. Variation over time of number of drugs produced by a firm and of number of dugs clustered in a molecule allow us to control for drug dummies in demand. The instruments have to be consistent with the exogenous variables and therefore need to be demeaned by the outside option (see equation (6)).

In a version of our estimates we use optimal instruments. These can be constructed as conditional expectations of the derivative of unobservables with respect to the parameters. This procedure minimizes the asymptotic covariance matrix of parameters (Chamberlain, 1987). Unfortunately, computing the expected value of the derivatives of the unobservables directly from data is infeasible because it requires us to know the true value of parameters, as discussed in Berry et al. (1995). Fortunately, approximations of optimal instruments are normally used (see Berry et al. (1999) and Reynaert and Verboven (2014)). These are improvement relative to the original instruments but are not as efficient as the true optimal instruments. The idea is that it is possible to compute the derivatives evaluated at the expected value of the unobservables (i.e. $E[\xi_{jt}] = E[\omega_{jt}] = 0$), which means that it is practicable to compute the optimal instruments from derivatives of predicted market equilibrium prices and shares estimated in the first stage of a GMM procedure. Specifically, we first use all non-optimal instruments mentioned above to obtain the initial values of the parameters and then calculate new equilibrium prices and market shares from the pricing and demand equations - these calculated at the expected mean utilities and marginal costs, and conditional on the parameters. Optimal instruments are Jacobian matrices of the new predicted prices and market shares at the given estimated parameters.[10]

[9] Berry et al. (1995) provide details on the functioning of the algorithm for the random coefficients logit model.

[10] See appendix in Berry et al. (1999) and Reynaert and Verboven (2014) for detailed explanation of the procedure.

## 4. Results

4.1. **Regression Coefficients.** 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 .33 with a mean price of £1.16 per DDD with also significant variation. The outside option (other antibiotics) varies from .13 to .22 with a mean value of 0.18. Pack variety varies from 1 to 10 with a mean of 2.68.

Table 2. Summary statistics

| Variable | Description | Mean | Std. Dev. | Min | Max |
|---|---|---|---|---|---|
| $s_{jt}$ | Share of drug $j$ | 0.009 | 0.029 | 0 | 0.331 |
| $s_{0t}$ | Share of the outside option | 0.182 | 0.019 | 0.130 | 0.224 |
| $ln(s_{jt}/s_{0t})$ | Dependent variable | -5.459 | 2.465 | -15.63 | 0.929 |
| $ln(s_{(j\in m)t})$ | Within molecule nest market share | -3.842 | 2.677 | -15.96 | 0 |
| $p_{jt}$ | Price (in pounds) per DDD | 1.162 | 1.232 | 0.038 | 11.46 |
| $x_{1jt}$ | Spectrum-score | 18.30 | 10.66 | 4.250 | 39.75 |
| $x_{2jt}$ | Pack varieties | 2.684 | 1.721 | 1 | 10 |
| $x_{3jt}$ | Dummy: Unidentified generics | 0.337 | 0.473 | 0 | 1 |
| $x_{4jt}$ | Dummy: tablet | 0.418 | 0.493 | 0 | 1 |
| $x_{5jt}$ | Dummy: capsule | 0.227 | 0.419 | 0 | 1 |
| $x_{6jt}$ | Dummy: oral liquid | 0.341 | 0.474 | 0 | 1 |
| $x_{7jt}$ | Dummy: extented release | 0.014 | 0.116 | 0 | 1 |
| $x_{8jt}$ | Age | 39.58 | 12.24 | 15 | 58 |

Data consists of 11,417 observations of 131 distinct products over 120 months spanning 16 molecules and 18 different formulations. These 18 different formulations are collapsed into four broad categories: tablet, capsule, extended release (tablet or capsule), and oral liquid in the regression analysis.

Table 3 provides selected regression coefficients from alternative specifications. The top part of the table shows estimates for the demand model, while the lower part shows selected regression coefficients for the price equation (equation 15) when it is estimated jointly with the demand side. Column (1) is a simple OLS estimate of the logit demand, column (2) provides IV estimates where the instruments are as described earlier, and column (3) is also an IV estimate of the logit demand model, but is now estimated jointly with the supply equation (parameters for which are given in the lower part of the table). All three regressions include brand dummies and the first-stage F-statistic for the excluded instruments in column (2) is 66.75. Moving from column (1) to (3), the coefficient on price becomes negative and increases in magnitude. Consequently, demand becomes elastic more often, i.e. for more products and in more periods (markets), as indicated in the last row of the table (for the simple logit case, own elasticity for product $j$ in period $t$ is given be $\eta_{jt} = \alpha s_{jt}(1 - s_{jt})$ and hence varies by product and period).

As a first attempt to overcoming the IIA problem associated with logit demand, column (4) shows IV results from a nested logit model, also jointly estimated with the price equation. We treat both price and $\ln(s_{(j\in m)t})$ as endogenous. The nests are based on molecules and the model allows for correlations of the error term between drugs in the same nest. The estimated group parameter $\sigma$ is 0.529 and is significantly different from both zero and one, suggesting that drugs in the same nests are more similar than drugs in other groups. Also, demand is elastic in most cases as shown in the last table. However, unlike the previous logit models, the coefficient on pack varieties is

TABLE 3. Selected parameters

| | L | L IV | L DS | NL DS | RCL DS | | RCL DS opt | |
|---|---|---|---|---|---|---|---|---|
| | (1) | (2) | (3) | (4) | (5) | | (6) | |
| **Demand side parameters** | | | | | | | | |
| | | | | | $\beta$ | $\sigma$ | $\beta$ | $\sigma$ |
| Price | 0.024 | -0.810$^a$ | -6.499$^a$ | -10.283$^a$ | -9.989$^a$ | 5.256$^a$ | -9.995$^a$ | 5.263$^a$ |
| | (0.016) | (0.136) | (0.135) | (0.123) | (0.368) | (0.243) | (0.353) | (0.189) |
| $ln(s_{(j\in m)t})$ | | | | 0.529$^a$ | | | | |
| | | | | (0.043) | | | | |
| Packs | 0.419$^a$ | 0.403$^a$ | 0.306$^a$ | -0.057$^a$ | 0.219$^a$ | 0.447 | 0.252$^a$ | 0.447$^a$ |
| | (0.02) | (0.015) | (0.011) | (0.019) | (0.040) | (0.419) | (0.022) | (0.064) |
| †Spectrum | | | 0.013 | -0.003 | -0.010 | 0.818$^a$ | -0.027 | 0.817$^a$ |
| | | | (0.012) | (0.010) | (0.036) | (0.226) | (0.035) | (0.039) |
| Time | -0.006$^a$ | -0.012$^a$ | -0.051$^a$ | -0.079$^a$ | -0.049$^a$ | | -0.048$^a$ | |
| | (0.0004) | (0.001) | (0.001) | (0.001) | (0.008) | | (0.002) | |
| Spring | 0.049$^b$ | 0.057$^b$ | 0.066$^a$ | 0.048$^b$ | 0.688$^a$ | | 0.680$^a$ | |
| | (0.027) | (0.030) | (0.026) | (0.026) | (0.315) | | (0.044) | |
| Fall | 0.057$^a$ | 0.077$^a$ | 0.228$^a$ | 0.301$^a$ | 0.389$^a$ | | 0.286$^a$ | |
| | (0.027) | (0.031) | (0.026) | (0.026) | (0.093) | | (0.030) | |
| Winter | 0.146$^a$ | 0.168$^a$ | 0.298$^a$ | 0.396$^a$ | 1.459$^a$ | | 1.410$^a$ | |
| | (0.028) | (0.031) | (0.026) | (0.026) | (0.662) | | (0.076) | |
| †Generics | | | 2.184$^a$ | 0.223 | 1.290$^a$ | | 1.281$^a$ | |
| | | | (0.289) | (0.246) | (0.326) | | (0.328) | |
| †Oral Liquid | | | -0.748$^a$ | 0.099 | -1.095$^a$ | | -1.072$^a$ | |
| | | | (0.342) | (0.241) | (0.348) | | (0.353) | |
| †Cons | -8.585$^a$ | -8.139$^a$ | -2.651$^a$ | -1.430$^a$ | -3.978$^a$ | 0.743 | -3.213$^a$ | 1.160 |
| | (0.332) | (0.212) | (0.502) | (0.406) | (1.191) | (3.061) | (1.144) | (0.826) |
| **Supply side parameters**‡ | | | | | | | | |
| Packs | | | -0.063$^a$ | -0.160$^a$ | -0.053 | | -0.053$^a$ | |
| | | | (0.011) | (0.008) | (0.463) | | (0.025) | |
| Time | | | -0.003$^a$ | -0.012$^a$ | -0.003 | | -0.003 | |
| | | | (0.0004) | (0.0003) | (0.0125) | | (0.0026) | |
| Cons | | | 0.567$^a$ | -0.148$^a$ | 0.572 | | 0.576$^a$ | |
| | | | (0.051) | (0.035) | (1.660) | | (0.229) | |
| Obs | 11417 | 11417 | 11417 | 11417 | 11417 | | 11417 | |
| % inelastic | | >50 | 5.3 | 1.9 | 3.5 | | 3.5 | |

Robust standard errors are in parentheses. Superscripts $a$, $b$ imply the significance of coefficient differing from zero at 5 or 10% respectively. Instruments used in regressions (2-6). Columns (3-6) jointly estimate demand and supply side equations. Column (6) uses optimal instruments.

†Coefficients retrieved from minimum distance method as product dummies are included.

‡ Supply side also includes other product characteristics not shown.

negative and significant. To further relax the IIA restrictions (and to avoid treating $ln(s_{(j\in m)t})$ as endogenous), the next two specifications show estimated regression coefficients from random coefficients logit model (RCL) which allow free correlation of the error term across all drugs. These two models are also estimated jointly with the price equation, where the difference in that in column (6) we additionally use the 2-step optimal instruments. Further, we use brand dummies in the linear part of the model, and hence mean coefficient on spectrum, generic, and formulation (liquid) are

recovered via the distance method described earlier. However, in the non-linear part, we include number of pack varieties and spectrum value of the drug (and price).

As we move from column (1) to column (6), generally the price coefficient increases in magnitude. Further, between (5) and (6), estimates are mostly similar but the standard errors become smaller in (6), especially for the non-linear parameters. We choose the last column as the main set of results which we describe further (but where appropriate will also provide comparisons with other specifications). In column (6), $\sigma_p$ is 5.26 and is statistically different from zero indicating that there is significant variation in marginal (dis)utility of price around the mean value of $-9.99$. 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, while the coefficient on number of pack varieties is positive (excepted for the nested logit), indicating higher marginal utility if drug is available in multiple dosages and pack sizes, there is again a statistically significant variation around the mean marginal utility indicating that some patients value the increase in dosage and size variety more than others. Time trend is negative across all estimations, which implies that utility of consuming common antibiotics is reducing over time compared to the outside option (not first or second line antibiotics), which may be induced by increasing resistance level. As expected, the utility of consuming antibiotics in other seasons, especially in winter, is higher than in summer due to the high preference of using antibiotics to treat respiratory tract infections, and virus-induced secondary bacterial infection in cold seasons (Suda et al., 2014, Hendaus et al., 2015).

Among the coefficients recovered using the minimum distance method, the mean marginal utility associated with the spectrum is not statistically different from zero, but the RCL shows there is significant heterogeneity in the taste parameter for spectrum.[11] Intuitively, it 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 broad-spectrum antibiotics and vice-versa and hence, all else equal, their utility level would change if they were given drug with a different spectrum value. The supply side estimation shows the factors that affect the marginal cost of production. All estimations show similar results (the equation also included dummy variables for firm, molecule and formulation, where the firm and molecule combination also controls for generic-branded differences). Over time, the marginal cost of producing antibiotics is decreasing, perhaps because of improvements in production technologies (Arcidiacono et al., 2013). Further, If a product has more pack varieties, its marginal cost tends to be lower. This may be consistent with findings reported elsewhere (see Kekre and Srinivasan, 1990).

[11] 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 $\sigma$ value.

TABLE 4. Price elasticities

| | $\eta$ | SD |
|---|---|---|
| Own-price elasticity | -3.310 | 4.835 |
| Cross-price elasticity | 0.172 | 0.308 |
| $\%\Delta s_B/\%\Delta p_B$ | 0.288 | 0.471 |
| $\%\Delta s_N/\%\Delta p_B$ | 0.148 | 0.199 |
| $\%\Delta s_B/\%\Delta p_N$ | 0.058 | 0.113 |
| $\%\Delta s_N/\%\Delta p_N$ | 0.166 | 0.171 |

Elasticities are weighted by market shares

4.2. **Elasticities and substitution patterns.** Based on the estimates in column (6), we computed own- and cross-price elasticities for all the antibiotics in our sample. For the 131 drugs, we have 131 own-price elasticities and $131 \times 130$ cross-price elasticities for each market (120 months). The averages and standard deviations are summarized in Table 4, where averages are weighted by product market share (weighting methodology is described in Appendix A-2). Mean own-price elasticity for a given antibiotic is -3.31 with standard deviation of 4.84, while the mean cross-price elasticity is 0.17 with standard deviation of 0.31.

To understand the substitution possibilities across drugs with different antibacterial resistance spectrum, we partitioned cross-price elasticities by broad- and narrow-spectrum groups. Thus, a 1% increase in price of a broad-spectrum antibiotic is associated with 0.288% increase in share of another broad-spectrum drug, and only a 0.148% 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 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 share of broad-spectrum drugs is less affected by price changes of narrow-spectrum ones.

As discussed previously, the antibiotic market is in urgent need of new molecules as bacteria develop resistance to old ones. There are only nine new molecules that got approved by FDA since 2000, of which we observed sales for five in the UK data set. Since these new molecules are not considered as first or second line drugs for common infections, they are included in our 'outside' option. For the remaining, we tabulated un-weighted own-price elasticities by the age of the molecule (where age is computed as the difference between 2003 and the earliest launch year of a molecule anywhere in the world). If newly launched molecules are more sensitive to price changes, it may indicate that they are less profitable than older products and hence firms may hesitate to invest further. Figure 2 shows that indeed newer molecules tend be more elastic to their own price changes and are potentially less profitable relative to the older ones.

FIGURE 2. Elasticity by molecule age

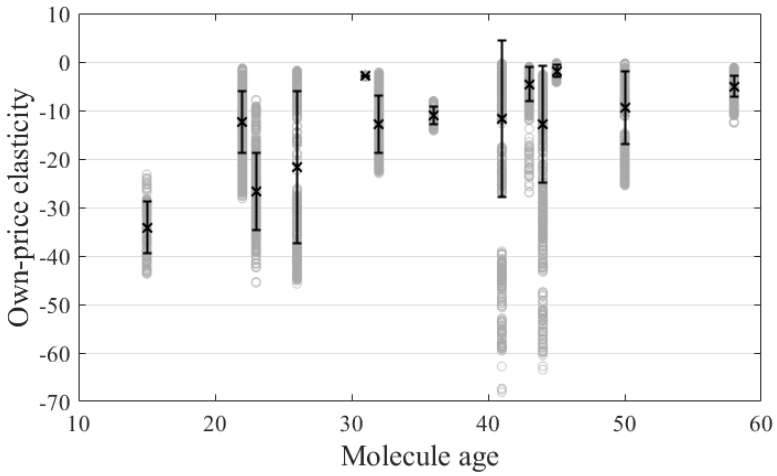
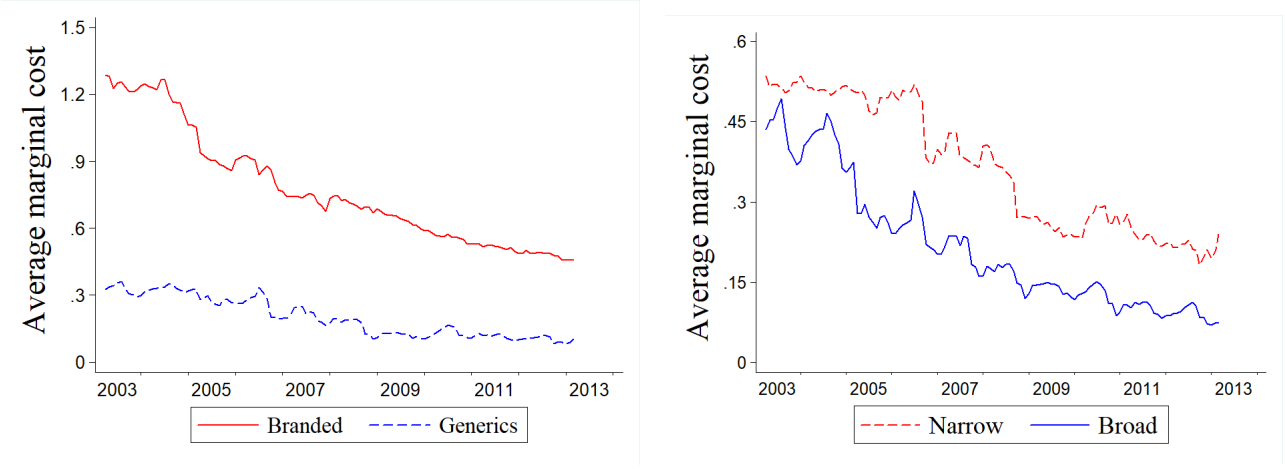



FIGURE 3. Marginal costs




4.3. **Costs and profitability.** Using the estimated demand coefficients, we use Equation 9 to back out marginal costs and profit margins for each product. Figure 3 shows average (weighted by volume) marginal costs over time for both branded and generic drugs, as well as by antibacterial spectrum classification. Overall marginal cost declined by more than 50% over this period, and branded drugs have higher estimated marginal costs than unbranded ones. Our result is consistent with Arcidiacono et al. (2013) who find that marginal cost of generics tend to decrease faster over time than those of branded ones even though their costs are similar when the generic just entered. They argue that generics may benefit more from scale effects and from efficient distribution channels. Additionally, Ball et al. (2018) find that in the US manufacturing recalls are higher for generic drugs, especially when competition is intense. They argue that generic manufacturers may be able to compensate for the quality of drugs in response to price competition and generic firms intentionally seek to save production costs to improve efficiency. For example, they can reduce labour costs,

purchase cheaper ingredients from suppliers, find cheaper ways of making their products, replace expensive manufacturing process with lower cost substitutes and reduce non-value-added activities.

Similarly, our estimates suggest that broad-spectrum antibiotics are cheaper to produce than the more specialized narrow-spectrum antibiotics. Since an increase in resistance is a negative externality, we investigate further how demand (and welfare) would be affected if production costs were the same.

Next, using Equation 9 again, we also backed out the price-cost margins associated with each drug. 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. Table 5 summarizes associated margins (weighted averages) by molecules, broad-narrow spectrums, snap-shots over-time and also provides comparison with estimates from the nested logit model.

TABLE 5. Price-cost margins

| | Margin | | Margin by year and type from RCL | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | NL | RCL | 2004 | | | 2008 | | | 2012 | | |
| | | | All | Branded | Generics | All | Branded | Generics | All | Branded | Generics |
| *Broad-spectrum* | 32.7 | 41.2 | 28.8 | 5.8 | 35.5 | 45.2 | 10.4 | 58.6 | 57.9 | 15.5 | 72.7 |
| Amoxicillin | 63.3 | 81.6 | 71.8 | 9.7 | 82.5 | 84.9 | 12.3 | 88.2 | 94.0 | 15.6 | 94.9 |
| Co-amoxiclav | 8.3 | 10.7 | 5.3 | 4.8 | 5.4 | 11.6 | 11.5 | 11.8 | 21.5 | 16.7 | 30.5 |
| Cefalexin | 13.1 | 15.9 | 11.9 | 12.8 | 11.8 | 18.0 | 19.8 | 17.2 | 28.0 | 31.5 | 26.3 |
| Ciprofloxacin | 11.6 | 11.4 | 5.4 | 2.5 | 6.1 | 26.1 | 2.8 | 49.2 | 29.6 | 3.4 | 41.7 |
| Doxycycline | 56.1 | 70.9 | 63.7 | 10.3 | 75.5 | 85.5 | 8.1 | 98.8 | 89.3 | 11.2 | 98.5 |
| Levofloxacin | 4.2 | 3.0 | 3.4 | 3.4 | - | 2.8 | 2.8 | - | 3.7 | 3.4 | 3.9 |
| Ofloxacin | 4.7 | 4.4 | 3.1 | 3.2 | 2.9 | 6.3 | 4.7 | 7.6 | 4.6 | 6.0 | 3.7 |
| Tetracycline | 14.2 | 9.2 | 45.5 | - | 45.5 | 5.9 | - | 5.9 | 6.1 | - | 6.1 |
| Others (3 mols) | 3.1 | 4.7 | 4.1 | 3.5 | 34.0 | 4.3 | 4.3 | - | 8.2 | 8.2 | - |
| *Narrow-spectrum* | 15.1 | 30.5 | 23.5 | 16.6 | 29.0 | 27.9 | 19.7 | 31.4 | 40.1 | 18.8 | 44.9 |
| Azithromycin | 4.2 | 8.1 | 5.3 | 5.3 | - | 6.8 | 6.7 | 7.1 | 11.1 | 10.0 | 11.6 |
| Clarithromycin | 9.8 | 18.3 | 9.5 | 9.5 | 9.5 | 19.0 | 15.9 | 25.4 | 35.0 | 22.3 | 45.6 |
| Clindamycin | 1.4 | 3.6 | 4.3 | 4.7 | 3.8 | 2.6 | 4.4 | 2.4 | 6.1 | 4.7 | 8.1 |
| Erythromycin | 16.7 | 28.1 | 21.0 | 16.0 | 23.3 | 30.0 | 19.2 | 35.8 | 44.2 | 25.4 | 52.1 |
| Flucloxacillin | 12.5 | 47.9 | 37.8 | 51.8 | 32.8 | 43.6 | 64.9 | 40.7 | 60.3 | 24.1 | 60.3 |
| Penicillin V | 17.2 | 20.1 | 19.7 | - | 19.7 | 22.0 | - | 22.0 | 21.0 | - | 21.0 |
| Trimethoprim | 68.2 | 82.5 | 79.7 | 30.3 | 82.2 | 80.5 | 36.6 | 83.2 | 83.5 | 43.7 | 83.5 |
| Mean | 22.9 | 35.2 | 26.3 | 12.7 | 33.0 | 35.1 | 16.0 | 43.0 | 46.2 | 17.4 | 53.9 |

The mean listed in the last row is the weighted average for all drugs not considered as the outside option.

Price-cost margin estimated by NL model is around 22.9%. In the nested logit, if some drugs in different molecule groups are in fact close substitutes, the model specification would not be able to properly account for this substitution pattern, and could give a downward bias in price-cost margins. By comparison, RCL would in principle overcome this difficulty. Based on the RCL model, the price-cost margin for antibiotics industry is 35.2% on average, rising from 26.3% in 2004 to 46.2% in 2012. This increase in profitability is associated with the decline in marginal costs noted earlier.

TABLE 6. Revenue, estimated profits and margins for selected firms

| | 2004 | | | 2008 | | | 2012 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Revenue (£.m) | Profit (£.m) | Margin (%) | Revenue (£.m) | Profit (£.m) | Margin (%) | Revenue (£.m) | Profit (£.m) | Margin (%) |
| Abbott | 22.01 | 2.59 | 11.30 | 7.54 | 1.37 | 16.23 | 5.47 | 1.43 | 22.32 |
| Bayer | 3.81 | 0.10 | 2.47 | 1.56 | 0.05 | 2.83 | 0.65 | 0.03 | 3.45 |
| GSK | 14.63 | 3.30 | 21.66 | 7.43 | 0.96 | 11.56 | 6.02 | 1.17 | 16.64 |
| Novartis | 2.51 | 0.35 | 13.47 | 3.10 | 0.34 | 9.63 | 1.87 | 0.56 | 25.82 |
| Pfizer | 5.37 | 0.35 | 6.33 | 4.85 | 0.37 | 6.74 | 3.72 | 0.39 | 9.05 |
| Sanofi | 3.45 | 0.12 | 3.47 | 1.71 | 0.06 | 3.28 | 0.72 | 0.04 | 5.17 |
| Generic | 3.98 | 1.36 | 22.11 | 3.30 | 1.58 | 27.96 | 2.97 | 1.85 | 30.68 |

Revenue and profit is the sum of all products related to the firm within the year, and is deflated by CPI in 2003. Price-cost margin is the quantity weighted average margin over all products by a given manufacturer. The generic firm is the weighted average across all such manufacturers.

Margins also vary across molecule groups and differ by brand types (branded or generics). Generally, narrow-spectrum antibiotics have relatively smaller margins than broad-spectrum ones, though the gap shrank in recent years. In 2012, the average margin for broad-spectrum molecules is 49.0%, and 44.1% for narrow-spectrum agents. To familiarize with the price-cost margin for each molecule group, we take amoxicillin as an example, but similar patterns hold for other molecule groups. Amoxicillin has a relatively high margin (81.6%), which increases over time to reach 94% in 2012. It is not surprising that the margin between retail price and manufacturer cost can be high. In fact, by one estimate, the margin at retail level alone can be as high as 76.6% (Kanavos, 2007). On the other hand, branded amoxicillins have significantly lower margins (less than 20%), while their generic counterparts have much higher ones.

Generic drugs are on average much more profitable than branded ones. Although their margins are similar for some molecule groups (e.g., cefalexin), the difference is dramatic in others (e.g. ciprofloxacin), where unbranded drugs are much more profitable than branded ones. This difference is mainly driven by the fact that unbranded drugs have lower prices, and also much lower marginal costs. Interestingly, similar findings are reported in the U.S. market. Investigation from journalisms finds that although prices of generics are generally lower than their branded counterparts, price-cost margins can be higher for generics (Tanouye, 1998, Freudenheim, 2002), especially at the pharmacy level.[12] Due to consolidation in generic markets, margins earned by large generic manufacturers can surpass that of many big brand-name companies as well. In addition, the slower rise of price-cost margin of branded products may link to the aspect that branded drugs were required to cut price in 2005 (7%) and 2009 (3.9%) by the Pharmaceutical Price Regulation Scheme (PPRS) in the UK.

Following on from that, we also computed profit margins at firm level and tabulated those that are generally considered research active firms (classification is based on Spellberg et al., 2004). These

[12]They find that pharmacies can mark up 1000% more than purchasing cost on generics, comparing to 10-30% on branded drugs. It roughly equals to 90% margins for generics or 9-23% for branded drugs if retail price is used as the base.

were then compared to a typical generic manufacturer. While a drug can be classified as branded or generic, such classification is not always straightforward at firm level as a research active firm may have subsidiaries that produce generic drugs for them.[13] Nonetheless Table 6 shows revenues and estimated profits (combined for manufacturer, wholesaler, and pharmacy) of all drugs associated with select firms including those derived from their generic products. Among these research active firms, Abbott and GSK have the highest revenues and profits in 2004 which declined substantially by 2012. GSK's decline in revenues and profits may be associated with price drop of their branded amoxicillin product (Augmentin) which halved between 2004 and 2008. On the other hand, Bayer (and later on Sanofi as well) have comparatively small profits. Overall though, other than GSK, the profit margin for these firms have increased. By contrast, the price-cost margin of a typical generic firm is 30.68% in 2012, up from 22.11% in 2004. Increasing margins in generic firms may be the consequence of market consolidation as argued in Freudenheim (2002).

4.4. **Policy Simulations.** In this section we seek to answer what would be the effect on demand and welfare cost of implementing supply side interventions that change the relative prices of broad- and narrow-spectrum drugs conditional on the fact that PCTs operate under a fixed budget, and GPs are responsible for keeping their prescription payments within those budgets. To that end, we undertake two related exercise. First, if the marginal costs of producing broad-spectrum antibiotics were on average as high as those of narrow-spectrum drugs, how much would it impact prices and demand, and what would be the associated welfare loss of such an increase in production costs? We take into account the change in consumer and producer surplus, as well as any additional costs due to testing if more patients are switched to narrow-spectrum costs. Second, we carry out a more refined exercise which imposes an ad valorem tax on a selected subset of broad-spectrum drugs and ask the same question.[14] It should be noted that the change in welfare computed in these exercises is a partial story: it captures the change in demand and welfare loss associated with cost side interventions, but does not measure aggregate societal benefits accruing from increasing demand for drugs which do not exacerbate the AMR problem as much. As such these exercises provide an upper bound on the costs and change in demand of implementing such policies, but do not quantify the full long term benefits of slowing AMR. Nonetheless, given the dire predictions in the O'Neill (2016) if AMR goes unchecked, it is well worth to explore these options.

[13]For example, GlaxoSmithKline (GSK) covers products produced by Beecham, which produces branded antibiotics. Most products sold under Novartis are manufactured under its generic manufacturer Sandoz. Products under Sanofi are produced by Zentiva (unbranded drugs) and Aventis (branded drugs).

[14]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.

**Algorithm**. In the first exercise, we set the marginal cost of broad-spectrum molecules to the same level as that of narrow-spectrum antibiotics.[15] Next, given the original demand parameters and the new marginal cost vector $\tilde{c}_t$, we calculate the new equilibrium price vector $p_t^*$ and market shares in each period such that

$$p_t^* = \tilde{c}_t + \Delta_t^{-1}(s_t(p_t^*))s_t(p_t^*)$$

holds. In the second exercise, we modify the equation to be solved prices as $p_t^{**}/(1+\tau) = c_t + \Delta_t^{-1}(s_t(p_t^{**}))s_t(p_t^{**})$, where $\tau$ is a vector capturing $5\%, 10\%$ or $20\%$ tax imposed on a subset of broad-spectrum drugs but no tax on other drugs (thus, in the case of $5\%$ tax, $\tau_j = 0.05$ for some drugs and $\tau_j = 0$ for the non-taxed drugs). Given the estimated demand parameters, prices, and product characteristics, individual indirect utility for patient $i$ in market $t$ from consuming drug $j$ is $U_{ijt}$ and the associated consumer welfare $cw_{it}$ with this choice is

$$cw_{it} = \frac{1}{\alpha_i} \max_{j \in J_t} U_{ijt}.$$

This money metric utility varies across consumers and by markets, and we can take it's expectation to computed expected consumer welfare (Small and Rosen, 1981). For the random coefficients logit model, this expression simplifies to

$$E(cw_{it}) = \frac{1}{ns} \sum_{i=1}^{ns} \frac{1}{\alpha_i} \ln \left[ \exp(\delta_{0t}) + \sum_{l=1}^{J_t} \exp(\delta_{lt} + [p_{lt}, x_{lt}] H v_i) \right] + K_t \tag{12}$$

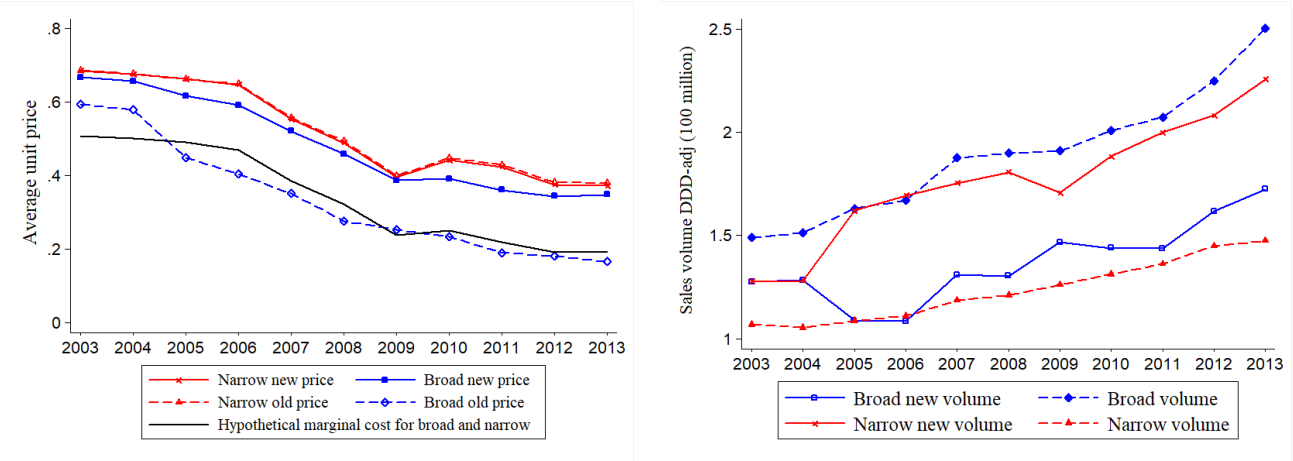
where $K_t$ is period specific constant. While we do not know the value of the constant, it drops out of calculations when we consider the change in expected consumer welfare associated with a change in the price vector. For each simulation exercise, since we compute the change in quantity of each drug (which is measured in defined daily dosages), we convert the change in quantity to bouts of illnesses under the assumption that an antibiotic script is prescribed for 7 or 14 days. Next, as a conservative estimate of additional cost of testing, we divide the change in quantity of narrow-spectrum drugs by 7, and then multiply it by NHS tariff for microbiology testing for that year, again under the conservative assumption that each of these additional bouts of infections would be first tested for pathogen before prescribing any narrow-spectrum drugs.[16] Finally, we also compute the change in firm profits to consider the combined effects.

For our first scenario where we set the marginal costs of the broad-spectrum drugs to be same as narrow-spectrum drugs, the left panel in Figure 4 plots the mean values of original and new (equilibrium) prices by year. While the mean price of narrow-spectrum does not change much, prices of broad-spectrum antibiotics jump up but stay slightly below those of the narrow-spectrum

[15] We first compute the share weighted average marginal cost for broad- and narrow-spectrum drugs, and then added this difference to the actual marginal cost of each broad-spectrum drug. This was done separately for each period but average increase the cost by about £0.20.

[16] 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.

FIGURE 4. Counterfactual prices and sales




drugs. However, there is a significant shift in demand as shown in the panel on the right, where the demand for broad-spectrum falls below that of the narrow-spectrum drugs, and the demand for narrow-spectrum antibiotics shifts up (by 28.4% and 43.4% on average respectively).

TABLE 7. Welfare Changes – Counter factual: higher marginal costs of broad-spectrum

| Year | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | Mean |
|---|---|---|---|---|---|---|---|---|---|---|
| $\%\Delta q$ (Broad) | -15.2 | -33.2 | -35.1 | -30.2 | -31.3 | -23.2 | -28.3 | -30.7 | -28.1 | -28.4 |
| $\%\Delta q$ (Narrow) | 21.6 | 49.3 | 52.7 | 48.0 | 49.3 | 35.4 | 43.5 | 46.9 | 43.8 | 43.4 |
| $\Delta$ CS | -183.3 | -442.7 | -470.9 | -452.3 | -450.1 | -341 | -401.9 | -465.2 | -503.4 | -412.3 |
| $\Delta$ profit | -61.3 | -109.8 | -130.1 | -147.4 | -176.7 | -144.5 | -185.7 | -199.8 | -220.4 | -152.9 |
| $\Delta$ testing cost | -358.7 | -814.8 | -869.7 | -945.5 | -836.3 | -699.2 | -867.6 | -928.6 | -784.3 | -789.4 |
| $\Delta$ tax revenue | 199.3 | 380.6 | 422.6 | 451.1 | 489.8 | 407.4 | 466.3 | 505.2 | 546.4 | 429.8 |
| Total | -403.9 | -986.7 | -1048.1 | -1094.2 | -973.3 | -777.3 | -988.9 | -1088.5 | -961.7 | -924.8 |

*Note:* Welfare changes are per 1000 UK population in that year.

The associated change in welfare per 1000 population by year is summarized in Table 7. On average, the estimated loss is £925 per 1000 per year, of which £412 is the loss in consumer welfare and £153 is the loss to the companies due to increased unit costs. The largest component, £789 is due to additional testing for patients who would be prescribed narrow-spectrum drugs. However, some of this can be off set by the increase in tax revenue (£430) if unit cost for broad spectrum is increase via taxes. Losses are larger in later years as greater number of consumers are shifted from broad- to narrow-spectrum drugs. In year 2012 (the last complete year of our data), the total loss in welfare is £962 per 1000 capita, which adds up to £61.26 million for the UK in total.

For the hypothetical tax exercise with selective taxing, we use data from 2012 and apply 5%, 10% or 20% tax rate to co-amoxiclav, quinolones and cephalosporins. These are broad-spectrum antibiotics that are often highlighted in public health documents as contributing to AMR problem in the UK.[17] Table 8 summarises the result of this exercise. Note that in 2012, this group of molecules take up

[17]See for instance, https://www.nice.org.uk/advice/ktt9/chapter/Evidence-context and CMO (2013).

TABLE 8. Tax on select broad-spectrum drugs

| | | Percent Tax | | |
|---|---|---|---|---|
| | | 5% | 10% | 20% |
| %Δ price | $\text{Broad}_g$ | 4.74 | 9.47 | 18.90 |
| | $\text{Broad}_o$ | 2.46 | 4.84 | 9.33 |
| | Narrow | -0.05 | -0.10 | -0.20 |
| %Δ quantity | $\text{Broad}_g$ | -9.83 | -18.56 | -33.34 |
| | $\text{Broad}_o$ | 1.39 | 2.57 | 4.44 |
| | Narrow | 0.96 | 1.88 | 3.61 |
| Δ profits | $\text{Broad}_g$ | -5.38 | -10.08 | -17.89 |
| | $\text{Broad}_o$ | 18.47 | 35.60 | 66.23 |
| | Narrow | 2.29 | 4.50 | 8.62 |
| Δ profits (all) | | 15.38 | 30.02 | 56.95 |
| Δ consumer surplus | | -34.90 | -67.33 | -126.09 |
| Δ tax tevenue | | 10.01 | 17.94 | 29.26 |
| Δ testing cost | | -17.18 | -33.77 | -64.74 |
| Total | | -26.69 | -53.14 | -104.61 |

Tax imposed on drugs in group $\text{broad}_g$, which includes co-amoxiclav, quinolones (ciprofloxacin, levofloxacin and ofloxacin) and cephalosporins (cefalexin).

9.1% of the total market share by volume, while the remaining broad-spectrum drugs consist of 40.4% of market share. A 5% tax on this group reduces their demand by 9.83%, and that of other broad- and narrow-spectrum drugs increases by 1.39% and 0.96% respectively, with negligible impact on demand for the outside option (-0.03%). Switching is more significant when we increase the tax rate to 20% when demand for these molecules reduces by 33.34% which could help substantially with the AMR problem. In terms of the cost of this intervention, the loss in consumer surplus is £34.9 and £126.1 per 1000 residents for the 5% and 20% tax rates respectively, which is far less than that in the earlier exercise.[18] Further, most of the tax burden is passed on to consumers (NHS in this case) as the pass-on rate is more than 90% in all cases. Also, because many broad-spectrum drugs are strategic complements, even the drugs with molecules on which tax is not imposed increase their prices in equilibrium. Combined with a shift in demand for other broad-spectrum drugs, the tax leads to an overall increase in firm profit for companies producing other broad-spectrum drugs (implying that further consideration should be given to recovering windfall increase in profits due to such a tax, or requiring that an increase in any firm profits be directed towards research activities for AMR).

## 5. CONCLUSION

In this paper we studied the market structure of first and second-line antibiotics in the UK between 2003-2013. Using aggregate levels sales data, we estimated discrete choice demand models. We find

[18]For a rough comparison, the earlier exercise of increasing cost of broad-spectrum roughly translates to a 100% tax on all broad-spectrum drugs.

that while prices have declined over the last decade, marginal costs have declined even more, and overall this sector's profitability has increased over time. While generics have higher profit margins, branded firms also earn positive profits. Similarly, 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. When we increase the marginal cost of broad-spectrum drugs to match that of narrow-spectrum drugs, which is roughly equivalent to a unit tax that doubles the cost, demand switches significantly from broad- to narrow-spectrum with an associated consumer welfare loss of £503.4 per 1000 residents. For an ad valorem tax of 20% on a select set of broad-spectrum drugs, the cost in terms of consumer welfare is £126.1 per 1000 residents and a reduction demand of 33% 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 lower AMR footprint. While the two tax regimes differer in how much demand will shift and what it will cost in terms of consumer welfare, it is clear that these are much smaller than the estimates of world wide 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 is 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, 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.

## References


**Arcidiacono, Peter, Paul B Ellickson, Peter Landry, and David B Ridley**, "Pharmaceutical followers," *International Journal of Industrial Organization*, 2013, *31* (5), 538–553.

**Ashworth, Mark, Robert Lea, Heather Gray, Gill Rowlands, Hugh Gravelle, and Azeem Majeed**, "How are primary care organizations using financial incentives to influence prescribing?," *Journal of Public Health*, 2004.

**Ball, George P, Rachna Shah, and Kaitlin D Wowak**, "Product competition, managerial discretion, and manufacturing recalls in the US pharmaceutical industry," *Journal of Operations Management*, 2018.

**Bennett, Daniel, Che-Lun Hung, and Tsai-Ling Lauderdale**, "Health care competition and antibiotic use in Taiwan," *The Journal of Industrial Economics*, 2015, *63* (2), 371–393.

**Berry, Stephen, J. Levinsohn, and Ariel Pakes**, "Automobile prices in market equilibrium," *Econometrica*, 1995, *63* (4), 841–890.

**Berry, Steven, James Levinsohn, and Ariel Pakes**, "Voluntary export restraints on automobiles: evaluating a trade policy," *American Economic Review*, 1999, pp. 400–430.

**Berry, Steven T.**, "Estimating discrete-choice models of product differentiation," *The RAND Journal of Economics*, 1994, *25* (2), 242–262.

**Björnerstedt, Jonas and Frank Verboven**, "Does merger simulation work? Evidence from the Swedish analgesics market," *American Economic Journal: Applied Economics*, 2016, *8* (3), 125–64.

**Boucher, Helen W., George H. Talbot, Daniel K. Benjamin Jr, John Bradley, Robert J. Guidos, Ronald N. Jones, Barbara E. Murray, Robert A. Bonomo, David Gilbert, and for the Infectious Diseases Society of America**, "10 × '20 Progress-Development of new drugs active against gram-negative bacilli: an update from the Infectious Diseases Society of America," *Clinical Infectious Diseases*, 2013, *56* (12), 1685–1694.

**Brown, Gardner and David F Layton**, "Resistance economics: social cost and the evolution of antibiotic resistance," *Environment and Development Economics*, 1996, *1* (03), 349–355.

**Carthy, Patricia, Ian Harvey, Richard Brawn, and Chris Watkins**, "A study of factors associated with cost and variation in prescribing among GPs," *Family Practice*, 2000, *17* (1), 36–41.

**CDC**, "Antibiotic resistance threats in the United States, 2013," Technical Report, Centers for Disease Control and Prevention April 2013.

**Chamberlain, Gary**, "Multivariate regression models for panel data," *Journal of Econometrics*, 1982, *18* (1), 5–46.

———, "Asymptotic efficiency in estimation with conditional moment restrictions," *Journal of Econometrics*, 1987, *34* (3), 305–334.

**Chaudhuri, Shubham, Pinelopi K Goldberg, and Panle Gia**, "Estimating the effects of global patent protection in pharmaceuticals: a case study of quinolones in India," *American Economic Review*, 2006, *96* (5), 1477–1514.

**CMO**, "Annual Report of the Chief Medical Officer, Volume Two, 2011, Infections and the rise of antimicrobial resistance," Technical Report, Department of Health, London March 2013.

**Coast, Joanna, RD Smith, and MR Millar**, "An economic perspective on policy to reduce antimicrobial resistance," *Social Science & Medicine*, 1998, *46* (1), 29–38.

**Cooper, Matthew A and David Shlaes**, "Fix the antibiotics pipeline," *Nature*, 2011, *472* (7341), 32–32.

**Currie, Janet, Wanchuan Lin, and Juanjuan Meng**, "Addressing antibiotic abuse in China: an experimental audit study," *Journal of Development Economics*, 2014, *110*, 39 – 51.

———, ———, **and Wei Zhang**, "Patient knowledge and antibiotic abuse: evidence from an

audit study in China," *Journal of Health Economics*, 2011, *30* (5), 933–949.

**Davies, SC and N Gibbens**, "UK five year antimicrobial resistance strategy 2013–2018," Technical Report, Department of Health, London 2013.

**Dubé, Jean-Pierre, Jeremy T Fox, and Che-Lin Su**, "Improving the numerical performance of static and dynamic aggregate discrete choice random coefficients demand estimation," *Econometrica*, 2012, *80* (5), 2231–2267.

**Duso, Tomaso, Annika Herr, and Moritz Suppliet**, "The welfare impact of parallel imports: a structural approach applied to the German market for oral anti-diabetics," *Health Economics*, 2014, *23* (9), 1036–1057.

**EARS**, "Antimicrobial resistance surveillance in Europe," *European Centre for Disease Prevention and Control*, 2015.

**ECDC/EMEA**, "The bacterial challenge: time to react," Technical Report, ECDC/EMEA Joint Working Group September 2009.

**Elbasha, Elamin H**, "Deadweight loss of bacterial resistance due to overtreatment," *Health Economics*, 2003, *12* (2), 125–138.

**Ellegård, Lina Maria, Jens Dietrichson, and Anders Anell**, "Can pay-for-performance to primary care providers stimulate appropriate use of antibiotics?," *Health Economics*, 2018, *27* (1), e39–e54.

**Ellison, Sara Fisher, Iain Cockburn, Zvi Griliches, and Jerry Hausman**, "Characteristics of demand for pharmaceutical products: an examination of four cephalosporins," *The Rand Journal of Economics*, 1997, pp. 426–446.

**Eswaran, Mukesh, Nancy Gallini et al.**, "Rescuing the golden age of antibiotics: can economics help avert the looming crisis?," 2016. Working paper.

**European Parliament**, "Antibiotic resistance," Technical Report, European Parliament, Policy Department, Economic and Scientific Policy, Brussels October 2006.

**Freudenheim, Milt**, "As patents on popular drugs end, costs for generics show a surge," *The New York Times*, December 2002, (27).

**Gallini, Nancy**, "Do patents work? Thickets, trolls and antibiotic resistance," *Canadian Journal of Economics/Revue canadienne d'économique*, 2017, *50* (4), 893–926.

**Gong, Sitang, Xiu Qiu, Yanyan Song, Xin Sun, Yanling He, Yilu Chen, Minqing Li, Rui Luo, Liya He, Qing Wei et al.**, "Effect of financially punished audit and feedback in a pediatric setting in China, within an antimicrobial stewardship program, and as part of an international accreditation process," *Frontiers in Public Health*, 2016, *4*, 99.

**Goossens, Herman, Matus Ferech, Robert Vander Stichele, Monique Elseviers, ESAC Project Group et al.**, "Outpatient antibiotic use in Europe and association with resistance: a cross-national database study," *The Lancet*, 2005, *365* (9459), 579–587.

———, ———, **Samuel Coenen, Peter Stephens, European Surveillance of Antimicrobial Consumption Project Group et al.**, "Comparison of outpatient systemic antibacterial use in 2004 in the United States and 27 European countries," *Clinical Infectious Diseases*, 2007, *44* (8), 1091–1095.

**Grabowski, Henry G**, "Increasing R&D incentives for neglected diseases: lessons from the Orphan Drug Act," in Keith E. Maskus and Jerome H. Reichman, eds., *International public goods and transfer of technology under a globalized intellectual property regime*, Cambridge University Press, 2005.

**Groote, Olivier De and Frank Verboven**, "Subsidies and time discounting in new technology adoption: evidence from solar photovoltaic systems," TSE Working Paper series TSE-957, Toulouse School of Economics September 2018. Forthcoming (AER).

**Hendaus, Mohamed A, Fatima A Jomha, and Ahmed H Alhammadi**, "Virus-induced secondary bacterial infection: a concise review," *Therapeutics and Clinical Risk Management*,

August 2015, *11*, 1265—1271.

**Herrmann, Markus**, "Monopoly pricing of an antibiotic subject to bacterial resistance," *Journal of Health Economics*, 2010, *29* (1), 137–150.

_____ **and Bruno Nkuiya**, "Inducing optimal substitution between antibiotics under open access to the resource of antibiotic susceptibility," *Health Economics*, 2017, *26* (6), 703–723.

_____ **and Gérard Gaudet**, "The economic dynamics of antibiotic efficacy under open access," *Journal of Environmental Economics and Management*, 2009, *57* (3), 334–350.

_____ **and Ramanan Laxminarayan**, "Antibiotic effectiveness: new challenges in natural resource management," *Annual Review of Resource Economics*, 2010, *2* (1), 125–138.

_____**, Bruno Nkuiya, and Anne-Renée Dussault**, "Innovation and antibiotic use within antibiotic classes: market incentives and economic instruments," *Resource and Energy Economics*, 2013, *35* (4), 582–598.

**Hollis, Aidan and Ziana Ahmed**, "Preserving antibiotics, rationally," *New England Journal of Medicine*, 2013, *369* (26), 2474–2476.

**Horowitz, John B and H Brian Moehring**, "How property rights and patents affect antibiotic resistance," *Health Economics*, 2004, *13* (6), 575–583.

**IDSA**, "Bad bugs, no drugs," Technical Report, Infectious Diseases Society of America July 2004.

**Jacobzone, Stéphane**, "Pharmaceutical policies in OECD countries," 2000.

**Kaier, Klaus and S Moog**, "Economic consequences of the demography of MRSA patients and the impact of broad-spectrum antimicrobials," *Applied Health Economics and Health Policy*, 2012, *10* (4), 227–234.

**Kanavos, Panos**, "Do generics offer significant savings to the UK National Health Service?," *Current Medical Research and Opinion*, 2007, *23* (1), 105–116.

**Kekre, Sunder and Kannan Srinivasan**, "Broader product line: a necessity to achieve success?," *Management Science*, 1990, *36* (10), 1216–1232.

**Kettler, Hannah E**, "Narrowing the gap between provision and need for medicines in developing countries," Research Report, Office of Health Economics, London 2000.

**Knittel, Christopher R and Konstantinos Metaxoglou**, "Estimation of random-coefficient demand models: two empiricists' perspective," *Review of Economics and Statistics*, 2014, *96* (1), 34–59.

**Laxminarayan, R**, "Fighting antibiotic resistance: can economic incentives play a role?," *Resources*, 2001, (143), 9–12.

**Laxminarayan, Ramanan**, "How broad should the scope of antibiotics patents be?," *American Journal of Agricultural Economics*, 2002, *84* (5), 1287–1292.

_____ **and Gardner M Brown**, "Economics of antibiotic resistance: a theory of optimal use," *Journal of Environmental Economics and Management*, 2001, *42* (2), 183–206.

_____ **and Martin L Weitzman**, "On the implications of endogenous resistance to medications," *Journal of Health Economics*, 2002, *21* (4), 709–718.

_____**, Anup Malani et al.**, "Extending the cure: policy responses to the growing threat of antibiotic resistance," Resources for the Future Washington DC 2007.

_____**, Mead Over, and David L Smith**, "Will a global subsidy of new antimalarials delay the emergence of resistance and save lives?," *Health Affairs*, 2006, *25* (2), 325–336.

**Madaras-Kelly, Karl, Makoto Jones, Richard Remington, Christina Caplinger, Benedikt Huttner, and Matthew Samore**, "Description and validation of a spectrum score method to measure antimicrobial de-escalation in healthcare associated pneumonia from electronic medical records data," *BMC Infectious Diseases*, 2015, *15* (1), 197.

_____**,** _____**,** _____**, Nicole Hill, Benedikt Huttner, and Matthew Samore**, "Development of an antibiotic spectrum score based on veterans affairs culture and susceptibility data for the purpose of measuring antibiotic de-escalation: a modified Delphi approach," *Infection*

*Control & Hospital Epidemiology*, 2014, *35* (09), 1103–1113.

**Malhotra-Kumar, Surbhi, Christine Lammens, Samuel Coenen, Koen Van Herck, and Herman Goossens**, "Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo-controlled study," *The Lancet*, 2007, *369* (9560), 482–490.

**Mechoulan, Stéphane**, "Market structure and communicable diseases," *Canadian Journal of Economics/Revue canadienne d'économique*, 2007, *40* (2), 468–492.

**Mossialos, Elias, Chantal M Morel, Suzanne Edwards, Julia Berenson, Marin Germmill-Toyama, and David Brogan**, "Policies and incentives for promoting innovation in antibiotic research," 2010.

**Mullen, Kathleen J, Richard G Frank, and Meredith B Rosenthal**, "Can you get what you pay for? Pay-for-performance and the quality of healthcare providers," *The Rand Journal of Economics*, 2010, *41* (1), 64–91.

**NAO**, "Prescribing costs in primary care," *National Audit Office*, 2007.

**Nature Biotechnology**, "Wanted: a reward for antibiotic development," *Nature Biotechnology*, July 2018, *36* (555). Editorial.

**Nevo, Aviv**, "A practitioner's guide to estimation of random-coefficients logit models of demand," *Journal of Economics and Management Strategy*, 2000, *9* (4), 513–548.

**ÖBIG**, *Surveying, assessing and analysing the pharmaceutical sector in the 25 EU member states*, ÖBIG, 2006. [Online; Accessed on 11/08/2015].

**O'Neill, Jim**, "Tackling drug-resistant infections globally: final report and recommendations," *Wellcome Trust & HM Government*, 2016.

**Outterson, Kevin, Julie Balch Samora, and Karen Keller-Cuda**, "Will longer antimicrobial patents improve global public health?," *The Lancet Infectious Diseases*, 2007, *7* (8), 559–566.

**PHE**, "English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) 2010 to 2014, Report 2015," Technical Report, Public Health England 2015.

———, "Management of infection guidance for primary care for consultation and local adaptation," Technical Report, Public Health England 2015.

**Phelps, Charles E**, "Bug/drug resistance: sometimes less is more," *Medical Care*, February 1989, *27* (2), 194–203.

**Power, E**, "Impact of antibiotic restrictions: the pharmaceutical perspective," *Clinical Microbiology and Infection*, 2006, *12* (s5), 25–34.

**Projan, Steven J**, "Why is big Pharma getting out of antibacterial drug discovery?," *Current Opinion in Microbiology*, 2003, *6* (5), 427–430.

**Reynaert, Mathias and Frank Verboven**, "Improving the performance of random coefficients demand models: the role of optimal instruments," *Journal of Econometrics*, 2014, *179* (1), 83–98.

**Rudholm, Niklas**, "Economic implications of antibiotic resistance in a global economy," *Journal of Health Economics*, 2002, *21* (6), 1071–1083.

**Schmidt, K, S Mwaigwisya, LC Crossman, M Doumith, D Munroe, C Pires, AM Khan, N Woodford, NJ Saunders, J Wain et al.**, "Identification of bacterial pathogens and antimicrobial resistance directly from clinical urines by nanopore-based metagenomic sequencing," *Journal of Antimicrobial Chemotherapy*, 2017, *72* (1), 104–114.

**Scoggins, A, J Tiessen, T Ling, and L Rabinovich**, "Prescribing in primary care, understanding what shapes GPs' prescribing choices and how might these be changed," Technical Report, RAND Corporation, Cambridge, UK 2006.

**Small, Kenneth A and Harvey S Rosen**, "Applied welfare economics with discrete choice models," *Econometrica*, 1981, *49* (1), 105–30.

**Smith, Richard D and Joanna Coast**, "Controlling antimicrobial resistance: a proposed transferable permit market," *Health policy*, 1998, *43* (3), 219–232.

———, **Milton Yago, Michael Millar, and Jo Coast**, "Assessing the macroeconomic impact of a healthcare problem: the application of computable general equilibrium analysis to antimicrobial resistance," *Journal of Health Economics*, 2005, *24* (6), 1055–1075.

———, ———, ———, **and Joanna Coast**, "A macroeconomic approach to evaluating policies to contain antimicrobial resistance," *Applied Health Economics and Health Policy*, 2006, *5* (1), 55–65.

**Spellberg, Brad, John H Powers, Eric P Brass, Loren G Miller, and John E Edwards**, "Trends in antimicrobial drug development: implications for the future," *Clinical Infectious Diseases*, 2004, *38* (9), 1279–1286.

**Steinman, Michael A, C Seth Landefeld, and Ralph Gonzales**, "Predictors of broad-spectrum antibiotic prescribing for acute respiratory tract infections in adult primary care," *JAMA*, 2003, *289* (6), 719–725.

———, **Ralph Gonzales, Jeffrey A Linder, and C Seth Landefeld**, "Changing use of antibiotics in community-based outpatient practice, 1991-1999," *Annals of Internal Medicine*, 2003, *138* (7), 525–533.

**Suda, Katie J, Lauri A Hicks, Rebecca M Roberts, Robert J Hunkler, and Thomas H Taylor**, "Trends and seasonal variation in outpatient antibiotic prescription rates in the United States, 2006 to 2010," *Antimicrobial Agents and Chemotherapy*, 2014, *58* (5), 2763–2766.

**Tacconelli, Evelina, Giulia De Angelis, Maria A Cataldo, Emanuela Pozzi, and Roberto Cauda**, "Does antibiotic exposure increase the risk of methicillin-resistant Staphylococcus aureus (MRSA) isolation? A systematic review and meta-analysis," *Journal of Antimicrobial Chemotherapy*, 2008, *61* (1), 26–38.

**Tanouye, Elyse**, "Price markups on generics can top brand-name drugs," *The Wall Street Journal*, December 1998, (31).

**Tisdell, Clem**, "Exploitation of techniques that decline in effectiveness with use," *Public Finance*, 1982, *37* (3), 428–437.

**Towse, A**, "Developing the idea of transferable intellectual property rights (TIPP) to incentivise R&D in drugs and vaccines for neglected diseases," Technical Report, OHE Consulting, London 2004.

**Towse, Adrian and Hannah Kettler**, "A review of IP and non-IP incentives for R&D for diseases of poverty. What type of innovation is required and how can we incentivise the private sector to deliver it?," *Innovation and Public Health*, 2005.

**Wasley, Andrew and Victoria Parsons**, "Exclusive: Minister floats tax on antibiotics to tackle drug resistance crisis," *The Bureau of Investigative Journalism*, 2016.

**WHO**, "WHO global strategy for containment of antimicrobial resistance," Technical Report, World Health Organization, Geneva 2001.

**Wood, Fiona, Sharon Simpson, and Christopher C Butler**, "Socially responsible antibiotic choices in primary care: a qualitative study of GPs' decisions to prescribe broad-spectrum and fluroquinolone antibiotics," *Family Practice*, 2007, *24* (5), 427–434.

**Yip, Winnie, Timothy Powell-Jackson, Wen Chen, Min Hu, Eduardo Fe, Mu Hu, Weiyan Jian, Ming Lu, Wei Han, and William C Hsiao**, "Capitation combined with pay-for-performance improves antibiotic prescribing practices in rural China," *Health Affairs*, 2014, *33* (3), 502–510.

## Appendix A.

A-1. **Spectrum.** In our estimations we use antibacterial spectrum of activity score of a drug as a characteristic which varies by molecule. This allows us to estimate preference over spectrum scores. Spectrum of activity score for select molecules is listed in the second column in Table 1 and the score itself is taken from Madaras-Kelly et al. (2014, 2015) and related sources (if a specific molecule is not listed in their paper, we match it the molecule's family and indications). Briefly, they calculated the spectrum score for each antibiotic as follows: For each organism-antibiotic domain pair, an ordinal scale, between 0 (susceptibility $< 20\%$) and 4 (susceptibility $> 80\%$) was given to score the antibiotic susceptibility. The spectrum score associated with an antibiotic is then the sum of scores of all organism-antibiotic domain pairs for that antibiotic. In their metric, 60 is the theoretical maximum score and zero is the minimum, where the larger the score the broader is the spectrum. In our data, the values range from 4.25 (penicillin) to 39.75 (fluoroquinolones). It is important to note that for a given molecule, its spectrum score is potentially varying across different regions and over time. Importantly, it is decreasing with antibiotic resistance, and thus can be thought of as a potential indicator of antibiotic resistance levels. Due to limited availability of the scores, we only use the static value provided in Madaras-Kelly et al. (2014). Finally, our classification for narrow- and broad-spectrum drug is as given by EARS (2015), which is roughly equivalent to score value of amoxicillin or higher as broad-spectrum and narrow-spectrum otherwise.

A-2. **Share weighted elasticities.** In this appendix, we describe how to calculate share weighted own- and cross-price elasticities. We take one market for example, and in the data we have 120 such markets. To sum up over 120 markets, we use the DDD-adjusted quantity as weight.

For the random coefficients logit model, the formula for computing elasticity of product $j$ with respect to price change of product $k$ in market $t$ is given by

$$\eta_{jkt} = \frac{\partial s_{jt}/s_{jt}}{\partial p_{kt}/p_{kt}} = \begin{cases} -\frac{p_{jt}}{s_{jt}} \frac{1}{ns} \sum_{i=1}^{ns} \alpha_i s_{ijt}(1 - s_{ijt}) & \text{if} \quad j = k \\ \frac{p_{kt}}{s_{jt}} \frac{1}{ns} \sum_{i=1}^{ns} \alpha_i s_{ijt} s_{ikt} & \text{if} \quad j \neq k \end{cases}$$

where $\alpha_i$ is individual taste on price and

$$s_{ijt} = \frac{\exp(\delta_{jt} + \mu_{ijt})}{\exp(\delta_{0t}) + \sum_{l=1}^{J_t} \exp(\delta_{lt} + \mu_{ijt})}$$

which is the purchasing probability of drug $j$ by individual $i$ in market $t$. In our case, the elasticity matrix for each market (120 such markets) is $131 \times 130$ and is first computed individually for each market. This appendix briefly explains how we applied weights to compute share weighted averages across $J = 131$ drugs and then over $t = 120$ markets.

For illustration, consider a single market and suppose there are only four drugs and the the outside option so that $1 \equiv s_0 + s_1 + s_2 + s_3 + s_4$, and where first two are classified as broad-spectrum and next two as narrow-spectrum. Then the average own elasticity in this market is just $\eta^o = \sum_{j=1}^{4} w_j \eta_{jj}$ where $w_j = s_j / \sum_{j=1}^{4} s_j$. We can take a similarly weighted average across the $T$ markets to compute the overall mean own-elasticity.

Next, to compute the mean cross-price elasticity, for each drug $j$ first compute $\eta_j$ as a weighted average across all other $k$ drugs, so $\eta_1 = \frac{s_2\eta_{12} + s_3\eta_{13} + s_4\eta_{14}}{s_2 + s_3 + s_4}$ which gives us mean price elasticity of drug $j$ with respect to price changes in all other drugs, and then compute weighted average responsiveness of all drugs as $\eta^c = \frac{s_1 w_1 + s_2 w_2 + s_3 w_3 + s_4 w_4}{s_1 + s_2 + s_3 + s_4}$.

TABLE 9. $\eta_{jk} : \%\Delta s_j / \%\Delta p_k$

| Price-Share | | B | | N | |
|---|---|---|---|---|---|
| | | $J_1$ | $J_2$ | $J_3$ | $J_4$ |
| B | $J_1$ | $\eta_{11}$ | $\eta_{12}$ | $\eta_{13}$ | $\eta_{14}$ |
| | $J_2$ | $\eta_{21}$ | $\eta_{22}$ | $\eta_{23}$ | $\eta_{24}$ |
| N | $J_3$ | $\eta_{31}$ | $\eta_{32}$ | $\eta_{33}$ | $\eta_{34}$ |
| | $J_4$ | $\eta_{41}$ | $\eta_{42}$ | $\eta_{43}$ | $\eta_{44}$ |

The shares in the formulas above can be adjusted to compute weighted averages *within* or *between* spectrum groups. For instance, within broad-spectrum, mean cross-elasticity is

$$\eta^c_{bb} = \frac{s_1\eta_{1b} + s_2\eta_{2b}}{s_1 + s_2}$$

where $\eta_{1b} = s_2\eta_{12}/s_2 = \eta_{12}$ and, $\eta_{2b} = s_1\eta_{21}/s_1 = \eta_{21}$. Similarly, if want to compute the mean share elasticity of broad-spectrum drugs with respect to a price change of narrow-spectrum drugs, we would compute it as

$$\eta^c_{bn} = \frac{s_1\eta_{1n} + s_2\eta_{2n}}{s_1 + s_2}.$$

where $\eta_{1n} = \frac{s_3\eta_{13}+s_4\eta_{14}}{s_3+s_4}$ and $\eta_{2n} = \frac{s_3\eta_{23}+s_4\eta_{24}}{s_3+s_4}$.

A-3. **Wholesale price of generics.** We obtained the additional dataset wholesale price of generics from Dispex.net.[19] This dataset is collected by surveying wholesalers' willingness to sell for unbranded generic medicines. The data reveals that the average percentage price difference between the NHS reimbursement price and the market price is about 44%, with a mode of 53%. Similar discount rates are also found in Kanavos (2007). Unfortunately, due to rebates and unobserved discounts along the supply chain, this data does not record prices with 100% precision. Moreover, as this data set is collected only in quarters (January, April, July and October), we have to expand this data to make it compatible with our original monthly data. We do that by filling out missing observations with the nearest available data points. We also match unbranded drugs to be comparable to branded ones (by molecule and form) and assume that the wholesale prices in this dataset are correlated with the prices of branded drugs.[20] We use this data to generate an additional instrument to correct for the price endogeneity in the demand-side regression.

[19] http://www.dispex.net/

[20] Since we only deal with commonly prescribed antibiotics, whose patent has expired long before our study period, we do not have patent or market exclusivity issues in this data.