

Can branding and price of pharmaceuticals guide informed choices towards improved pollution control during manufacturing?

Johan Bengtsson-Palme[§], Lina Gunnarsson[§], D.G. Joakim Larsson^{*}

[§] Authors J.B-P. and L.G. contributed equally to this work, ^{*} Corresponding author

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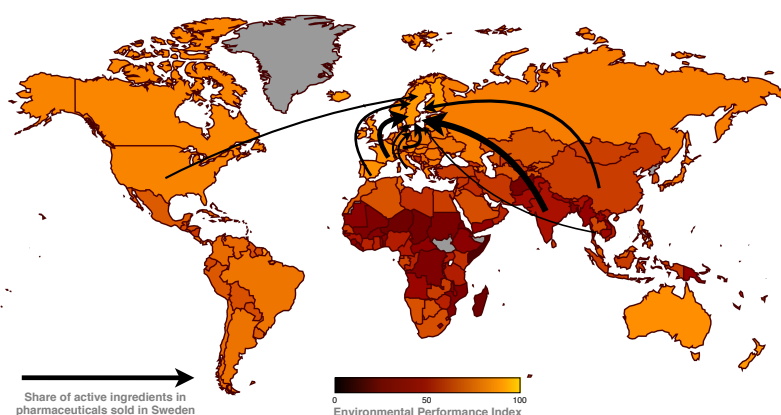
Johan Bengtsson-Palme^{a,b,§}, Lina Gunnarsson^{a,c,§}, D.G. Joakim Larsson^{a,b,*}

^a Department of Infectious Diseases, Institute of Biomedicine, the Sahlgrenska Academy, University of Gothenburg, Guldhedsgatan 10, SE-413 46, Gothenburg, Sweden

^b Center for Antibiotic Resistance research (CARE) at University of Gothenburg, Gothenburg, Sweden

^c Department of Biosciences, College of Life and Environmental Sciences, University of Exeter, Exeter, EX4 4QD, United Kingdom

* Corresponding author; § Authors J.B-P. and L.G. contributed equally to this work



Abstract

Pharmaceutical manufacturing can lead to substantial discharges of active pharmaceutical ingredients into the environment, with local consequences to the environment and, in the case of antibiotics, potentially global implications in terms of increasing risks for resistance development. In this study, we used Swedish sales data for pharmaceuticals combined with data on the origin of the active ingredients to determine if price pressure and generic substitution are related to the estimated general environmental performance and the perceived corruption levels of the production countries. In line with the general perception, India was the largest producer of generics, while Europe and the USA dominated for branded products. We found that the price and environmental performance index of the production countries were linked, but that this relationship was largely explained by whether the product was original or generic. Although this relationship would allow buyers to select products that likely originate from countries that, in general terms, have better pollution control, it lacks resolution. We conclude that to better allow consumers, hospitals and pharmacies to influence the environmental impact of their product choices, there is need for regulation as well as transparency in the production chain. To this end, emissions from manufacturing need to be measured, allowing for control and follow-up on industry commitments towards sustainable manufacturing of pharmaceuticals.

Keywords

Antibiotic resistance; Environmental performance; Generic drugs; Outsourcing; Pharmaceutical production; Transparency

1. Introduction

Pharmaceuticals are biologically potent chemicals, often designed to easily pass biological membranes and interact with target molecules that can be conserved across a range of organisms (Gunnarsson *et al.*, 2008). Hence, even low environmental concentrations (e.g. in the ng to µg/L range) of active pharmaceutical ingredients (APIs) in the environment can in some cases lead to effects on non-target organisms. Emission of APIs from urine and feces are widespread, but environmental concentrations reached via this route rarely exceed a few µg/L and are most often considerably lower (aus der Beek *et al.*, 2016). In contrast, substantial discharges of APIs into the environment may occur during the production stage, unless waste streams are appropriately managed. As a consequence, concentrations of pharmaceuticals, including antibiotics, in the order of mg/L have been found in environments polluted by waste from pharmaceutical production facilities, as reviewed by Larsson (2014).

Pollution from manufacturing clearly poses a risk to the environment and may contribute to health problems locally, but the release of antibiotics from production facilities also constitutes a substantial risk for resistance development, with potentially global consequences. High numbers of antibiotic resistance genes and resistant bacteria have indeed been associated with such pollution (Bengtsson-Palme *et al.*, 2014; Gothwal and Thatikonda, 2017; Kristiansson *et al.*, 2011; Li *et al.*, 2010; Lübbert *et al.*, 2017; Marathe *et al.*, 2013). Finally, as with most types of chemical production, pharmaceutical manufacturing often consumes extensive amounts of energy, water and other resources (Jiménez-González *et al.*, 2011; Malik *et al.*, 2015; Wernet *et al.*, 2010). The use of numerous potentially toxic chemicals and solvents used in the intermediary production steps also present environmental challenges. Furthermore, the manufacturing of pharmaceuticals has been calculated to be the second largest source of greenhouse gas emissions resulting from human health care (Chung and Meltzer, 2009). These factors complicate assessment of the overall environmental

impacts during the pharmaceutical lifecycle, but also underscore the diverse benefits that more environmentally friendly means of production would bring (Bryan *et al.*, 2013; Cespi *et al.*, 2015; Jiménez-González and Overcash, 2014).

In contrast to environmental emissions from usage and excretion of drugs, discharges from manufacturing often take place far from the final user. The origin, and therefore also the production conditions, of the APIs in pharmaceutical products are, however, most often confidential information (Ågerstrand *et al.*, 2015; Larsson and Fick, 2009). This effectively prevents hospitals, pharmacists, medical doctors and final consumers to select products that contain APIs produced in an environmentally responsible way. To date, only a few handfuls of studies have investigated API discharges from manufacturing sites (Gothwal and Shashidhar, 2014; Larsson, 2014; Lübbert *et al.*, 2017), preventing generalizations of where the risks are greatest and where management actions are most needed. Nevertheless, it seems plausible that major industrial discharges of APIs are more common at sites (and in countries) that produce large quantities of APIs and at the same time have lax environmental regulations and/or lack of adherence to existing laws, due to e.g. corruption (Lisciandra and Migliardo, 2016). The substantial price pressure within the pharmaceutical sector has been and is an important driver for the outsourcing of API manufacturing to countries with lower production costs (Chemical Pharmaceutical generic Association, 2011; Chen and Hung, 2010). The lower wages, electricity costs and the typical cost for environment and worker safety in e.g. India and China compared to Spain and Italy (the two largest generic API producers in western Europe and traditionally the leading players in the world generic API market before the booming of India and China) have hence led to a substantial increase of sales by Asian APIs manufacturing companies (Chemical Pharmaceutical generic Association, 2011). The lowered production cost has accordingly led to lower prices on pharmaceutical products on the European market (Dunne *et al.*, 2013).

Even as countries like India and China have implemented improved environmental protec-

tion regulations, such legislations are easily rendered ineffective if they are not followed up due to corruption (Damania et al., 2003; Harring, 2014). Indeed, corruption seems to have a negative effect on the discharge control systems in low-income countries (Liao et al., 2016). Accordingly, it has been argued that the price pressure associated with generic exchange of original (branded) products is linked to increased environmental risks during the production stage (Bederoff, 2010). Given a system where branded and generic products exist in parallel, there is, however, not necessarily a difference between the environmental footprint of the two; companies selling branded products may outsource their API production to countries with poor environmental standards, either while the patents are still valid, or when they expire and the price pressure kicks in due to competition. It is then possible that the same physical manufacturing sites provide both the companies producing the original products and those producing the generic copies with the APIs. Thus, if that is the case, there is no difference between the environmental risks (associated with discharges during production) for a branded, more expensive, product compared to generally cheaper generic copies. Given that the origin of the APIs in different products is confidential it is, however, difficult to know to what extent branded or generic products contain APIs produced in countries and factories with inferior environmental standards.

The aim of this study was to provide an overview of where APIs in pharmaceutical products sold in Sweden are manufactured, expressed both in terms of economic value, volume (Defined Daily Dose, DDD) and number of products. We also wanted to show how the market shares of branded and generic pharmaceuticals differ in these aspects. Finally, we aimed to understand how perceived corruption levels and the general environmental performance of API manufacturing countries are related to the final price of pharmaceutical products and whether

buyers of drugs potentially could influence their environmental impact by making conscious decisions based on branding and price. Due to the rapidly growing concerns with accelerating antibiotic resistance, we also investigate those relationships for antibiotics specifically. Knowledge of how pricing, environmental performance and corruption are related could motivate changes in the drug pricing system to promote environmentally sustainable drug production, for example as part of procurement and subsidy decisions (Läkemedels- och apoteksutredningen, 2013).

2. Materials and Methods

Sales statistics for all approved medical products sold in Sweden 2010 were provided by the Swedish eHealth Agency (www.ehalsomyndigheten.se), containing total sales data from all Swedish pharmacies but also pharmaceuticals purchased by Swedish hospitals. Unique national product identification numbers (managed by the Medical Product Agency) were used to summarize the sales statistics per product rather than on package basis. Information about the production site for 6269 of these medical products could be retrieved from the Swedish medical products agency (MPA). The production sites for parallel imported products were identified by comparing product name, active pharmaceutical ingredients, dose and administration form of the parallel imported products to the list of medical products that had information on production sites. In total, information on production site was available for 4073 of the medical products sold in 2010, and 3161 of these had a DDD. More than one possible manufacturing country per API was listed for 1965 (48%) of these products. In accordance with our agreement with the MPA, the data received is presented here in such a way that no links between individual products or APIs and specific manufacturers or sites is obvious. The classification of the Dental and Pharmaceutical Benefits Agency (TLV) was used to group interchangeable products. Generic medicines

belonging to the same exchange group contain the same active substance(s) as the reference medicine and are used at the same dose(s) to treat the same disease (European Medicines Agency, 2012; Svensk författningssamling, 2016).

To cover the large discrepancies between regulations and measures taken to reduce pollution (Sawhney and Rastogi, 2014) we have chosen to compare countries based on two output-oriented performance indices, namely the Corruption Perceptions Index 2014 (Transparency International, 2014) and the Environmental Performance Index 2016 (EPI) (Hsu et al., 2016). While such indices are far from perfect (Böhringer and Jochem, 2007; Singh et al., 2012), we think that – given the lack of publicly available data – they still have some merit (Brewer and Pojasek, 2013).

The theoretical maximal and minimal sum of retail prices, DDD and number of products were calculated for each country using custom Perl scripts. Products were assigned to either country categories of high (>80) or low EPI and high (>60) or low CPI, or to the unknown EPI/CPI categories if they could be produced in countries both below and above these cutoffs. The price per DDD was normalized within each exchange group and the data was analyzed using R (R Development Core Team, 2016). Linear regression analysis was performed for each exchange category, separately as well as for the entire dataset together, investigating to which degree the differences in best-case and worst-case EPI or CPI of the production countries could be explained by the per-dose price of the product (normalized DDD) or its product category (generic vs. original). Regression analyses were performed specifically for antibiotics in the same manner. To investigate how consumer choice could influence the EPI and CPI of the production country, we selected the original, the most expensive, the cheapest, or a random product within each exchange group, and noted if the product ended up in the high EPI/CPI, low EPI/CPI

or uncertain category. Complete methodological details are available as Supporting Information.

3. Results

3.1 *Where are active pharmaceutical ingredients manufactured?*

In total, 7066 pharmaceutical products were sold in Sweden in 2010 and production countries of the APIs contained in these products could be determined for 4073 products. In terms of total monetary value of produced APIs (total retail price), the USA and France, together with Germany and India, stood out as the largest API manufacturing countries (Figure 1a). Importantly, since many products had several possible options for the country producing the API declared, the span between the lowest possible value for each country (if it actually did not produce any API for any of those products with multiple sources indicated) and the theoretical maximum (if it produced all the APIs for every product where the country is included as a source) differ substantially. Thus, there is for most countries a large uncertainty as to how large a proportion of the APIs were actually produced there (Figure 1). That said, the correlation between the minimal and maximal possible retail price totals for each country was highly significant (Pearson correlation = 0.764; p-value < 0.0001), meaning that if the actual API producers are reasonably equally distributed across products, larger API producing countries will contribute more to the total retail price. When only generic products (1043) were investigated, India was the largest producer followed by China and the USA (Figure 1c), while France was the largest producer for original products with India and China on the eighth and twelfth place, respectively (Figure 1b).

If market share was instead measured as number of produced doses (DDD), India dominated the API market (Figure 1d), particularly with regards to generic products

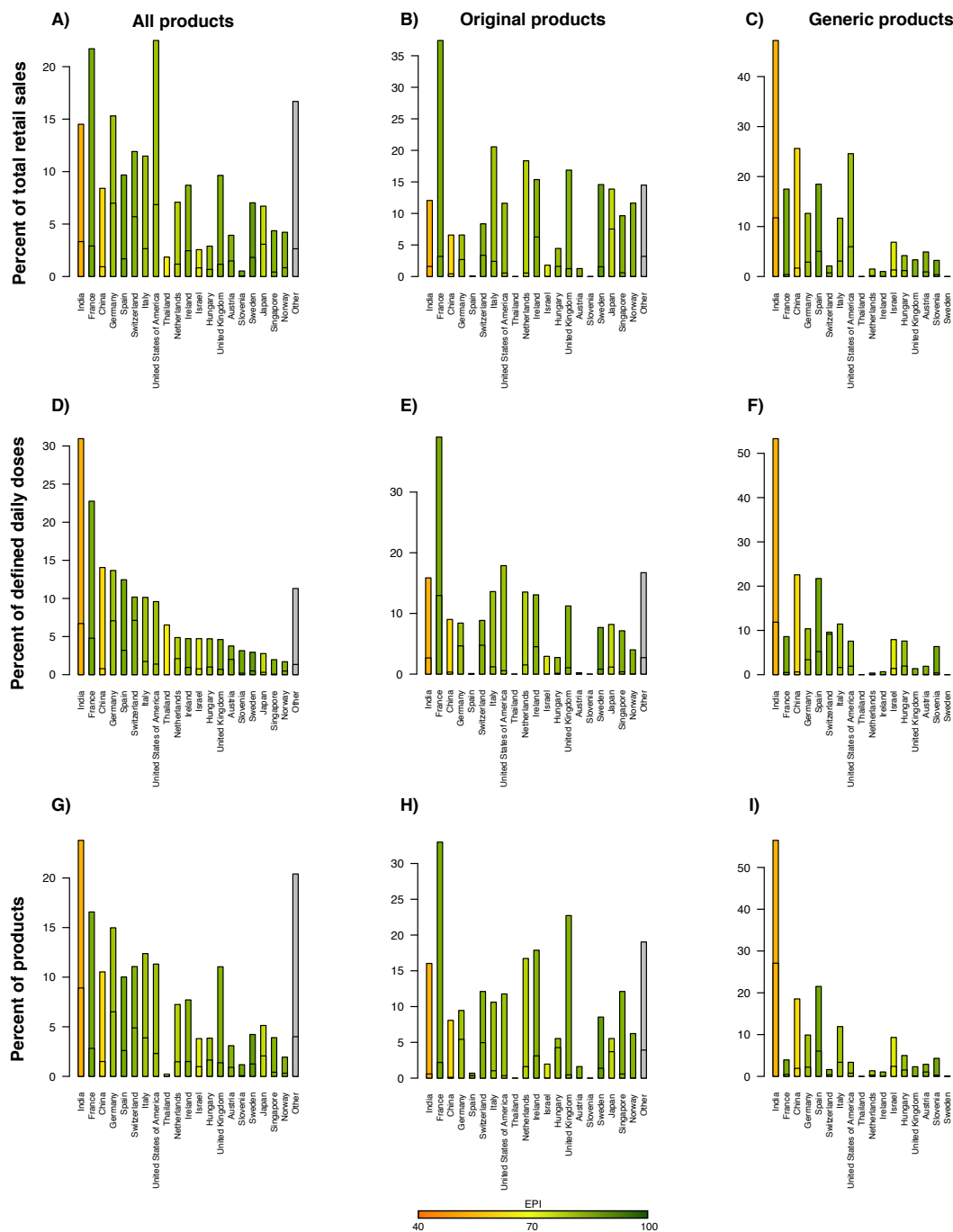


Figure 1. Production share of pharmaceutical products sold in Sweden in 2010, counted as monetary value (total retail price as percentage of total sales; a-c), defined daily doses (percentage of DDD; d-f), and percentage of different products (g-i). Coloring is according to EPI; greener colors mean higher EPI, and yellow colors correspond to lower EPI. The total height of each bar corresponds to the theoretical maximum for each country, while the lines within each bar indicate the minimum share for each country. All values are given as percentages.

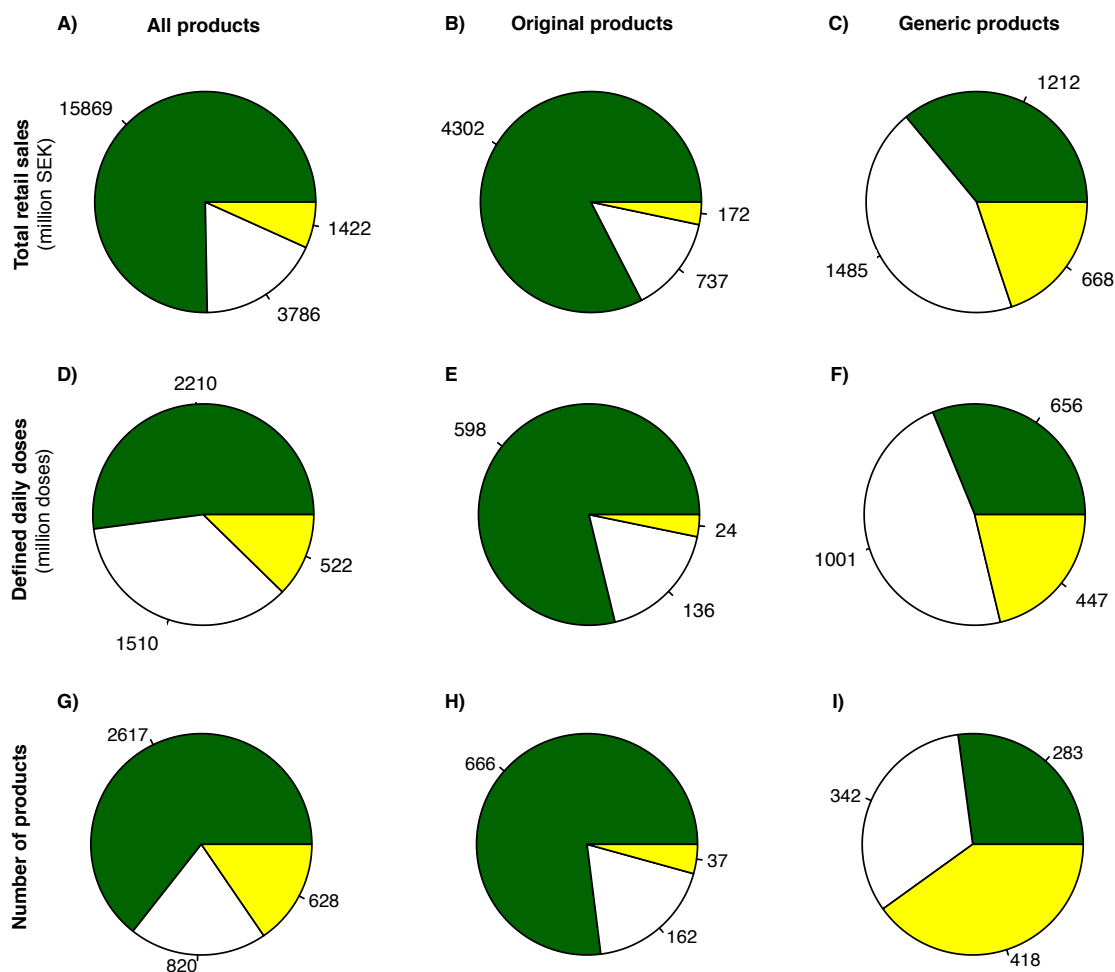


Figure 2. Pharmaceutical production divided by high-EPI (at least 80; green) and low-EPI (yellow). Products that could either be produced in low or high EPI countries are indicated as unknown (white). Values are given in millions of SEK (a-c), million defined daily doses (d-f) or number of products (g-i).

(Figure 1f). Other large production countries were France, China, Germany and Spain, of which China and Spain also had large shares of the API production for generic products. France was also by far the largest producer of APIs for original products (Figure 1e). Notably, the US share of the market was much larger when counted in monetary terms (Figure 1a) than in produced daily doses (Figure 1d) and number of products (Figure 1g).

3.2 Most pharmaceuticals sold in Sweden are produced in countries with high environmental performance

When API production was divided into countries with high versus low environmental performance index (EPI), there was a clear trend towards that generic drugs were more likely to be produced in countries with a poor EPI (Figure 2). This trend was apparent regardless of whether market share was counted in monetary terms, as doses, or as number of products. In addition, there was a substantially larger share of generic than original products with multiple production

sources with potential to be produced in low-EPI countries. Notably, more than half of the total doses (and monetary value of drugs) were produced in countries with relatively high EPI, although these proportions were below 40% for generic drugs. Stratifying the production countries by the corruption perceptions index (CPI) resulted in similar, even more pronounced, trends (Figures S1 and S2). Particularly, generic drugs showed a much stronger association with production in countries with higher degrees of corruption.

3.3 Branding, but not sales price per se, is associated with better environmental performance and less corruption in the manufacturing country

We then tested whether sales price and/or branding (original versus generic) of the products could predict the EPI or CPI of the API-producing countries. We first investigated each exchange group separately and tested whether the associations across all exchange groups were overall negative or positive (Table S1). When we did not account for branding, but only investigated the association between price and EPI, we found a strong positive link between higher price and higher EPI (Wilcoxon signed rank test; $p = 0.002$ using best case EPIs; $p < 0.0001$ for worst case EPIs). This link was, however, entirely explained by whether the products were original or generic when this factor was taken

into account (Wilcoxon signed rank test; $p = 0.023$ in best case for branding; $p = 0.0002$ in worst case; $p > 0.4$ for price in both best and worst cases). Furthermore, when only generic products were considered, there were no association between price and EPI. We also assessed the relationships between price, branding and CPI in a similar way and found the same relationships, but with stronger p -values (Table S1). The positive association between branding, but not price, and EPI (or CPI) also remained when all exchange categories were examined together (Table S2), meaning that original products were more likely to be produced in countries with high environmental performance and lower corruption than generic products. When we restricted the analysis to only generic drugs, there was, counter-intuitively, a negative association between price and EPI/CPI. That is, more expensive generic products were more likely to be produced in countries with poor EPI and CPI than cheaper alternatives (Table S2). This association was, however, entirely caused by drugs produced in India, and when India was excluded from the analysis there were no remaining negative association between price and EPI/CPI. There was a number of generic drugs produced in India with fairly high normalized prices, and indeed India was the production country with the largest range of normalized prices for generics in Sweden.

Drug choice	High EPI	Low EPI	Uncertain EPI	p	High CPI	Low CPI	Uncertain CPI	p
Original	133	7	39	5.42×10^{-11}	136	11	33	2.20×10^{-16}
Most expensive	155	57	57	0.00077	139	74	56	0.00012
Cheapest	96	92	81	0.094	69	113	87	0.024
Random average	115.9	81.7	71.4		93.9	103.8	71.3	
Random median	116	82	72		94	104	71	

Table 1. Link between systematic product choices and EPI or CPI. The numbers indicate the number of exchange groups where choosing the original product (if possible), the most expensive product, the cheapest product or a randomly selected product (reselected 1000 times) would result in selecting a product produced in a country with high, low or uncertain EPI or CPI. Significant differences between systematic choices and random choices were assessed using Fisher's exact test.

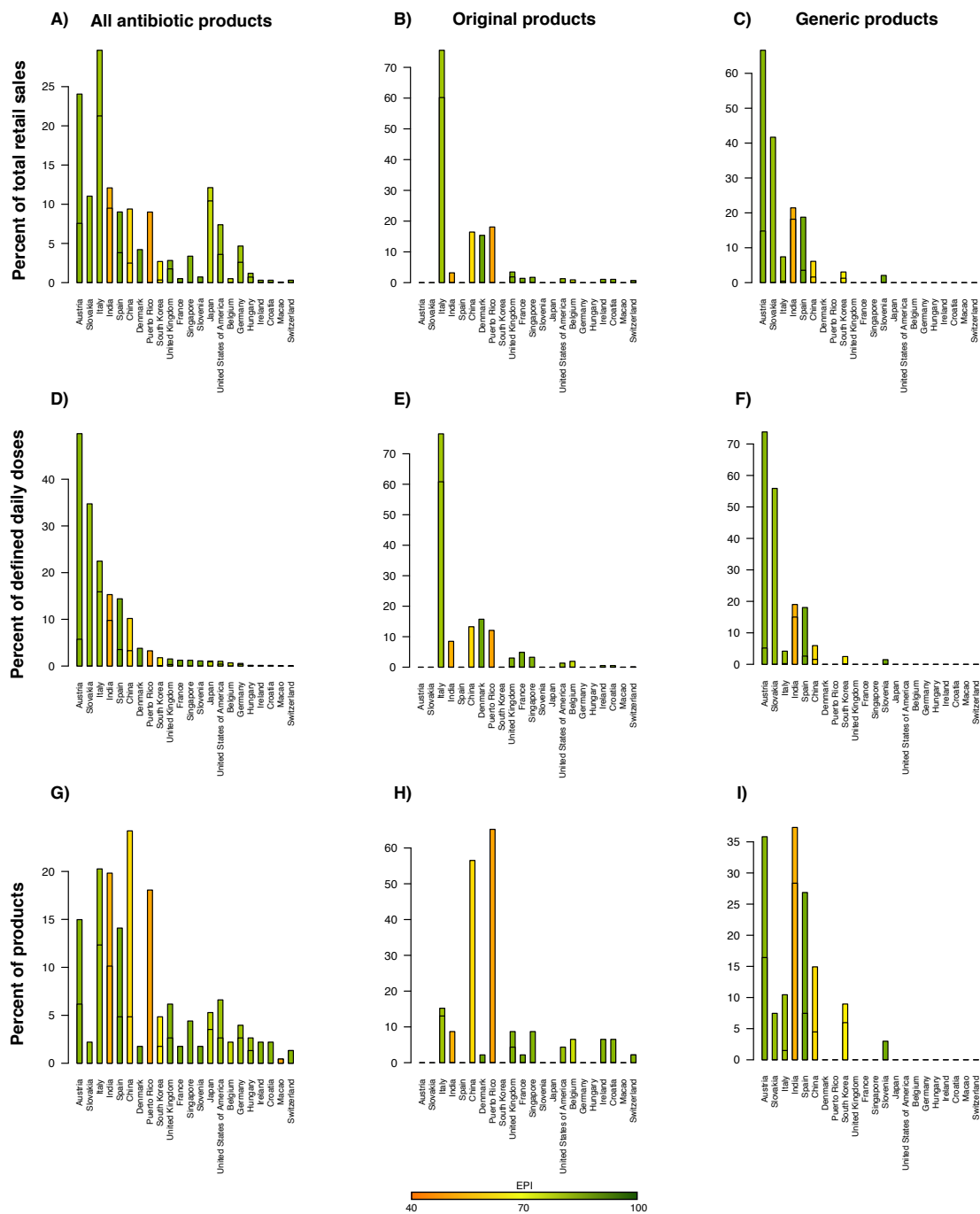


Figure 3. Production share of antibiotics sold in Sweden in 2010, counted as monetary value (total retail price as percentage of total sales; a-c), defined daily doses (percentage of DDD; d-f), and percentage of different products (g-i). The total height of each bar corresponds to the theoretical maximum for each country, while the lines within each bar indicates the minimum share for each country. All values are given as percentages.

To understand if the buyer could make any particular choice of drug to promote drugs produced in countries with higher EPI or CPI, we selected the original product (if any), the most expensive product, the cheapest product and a random product selection within each exchange group (Table 1). This analysis showed that choosing the original product when possible resulted in selecting a product produced in a country with high EPI or CPI in around three out of four cases. Selecting the most expensive product (often the same as the original) also resulted in more often choosing a product from a high EPI or CPI country than would be expected by random choice, while systematically selecting the cheapest product would result in more often selecting a product produced in a country with low CPI (not statistically significant for EPI).

3.4 Antibiotics show less clear links between price/branding and environmental/corruption indexes than do drugs in general

When we analyzed the data for antibiotics separately (Figure 3), Italy, Austria, India and Japan stood out as having the largest market shares counted in monetary value (Figure 3a). However, when market share was counted as defined daily doses, Slovakia emerged as the second largest production country (Figure 3d). It was also apparent that only a few countries produce the APIs for generic antibiotics, including Austria, Slovakia, India and Spain, while Italy grabbed the by far largest share of original antibiotic products (Figure 3e). Notably, while most of these production countries showed a high EPI (i.e. more than 80), only Austria had a CPI above 60, resulting in that a large fraction of both original and generic antibiotics were associated with low-CPI production countries (Figure S3). Finally, the proportion of antibiotics that definitively could be assigned to high-EPI or low-EPI production countries was higher than for pharmaceuticals in general (Figure 4). In terms of CPI, however, the uncertainty was overall larger among the

antibiotics than for pharmaceutical products in general (Figure S4).

We also specifically investigated the association of price and branding between antibiotics and the EPI or CPI of the production countries. As there were considerably fewer antibiotic products than overall pharmaceutical products, the correlation analyses for antibiotics are likely to be noisier and more easily influenced by individual outliers. Overall, branding or price could not predict the EPI of the production countries for antibiotics, while there was possibly a relation between those factors and CPI, particularly in the best-case scenarios (Table S2). However, when only generics were considered, there was a significant negative link between price and both EPI and CPI, such that cheap generic antibiotics were more likely to be produced in countries with higher EPI. Similarly to what was observed for all generic products taken together, this effect disappeared when India was removed from the analysis, and also in the case of generic antibiotics, products with APIs from India showed the largest price diversity of all countries. When exchange categories of antibiotics were considered separately there were no significant over- or under-representation of positive slopes (Table S1).

4. Discussion

We find that while there is a significant (weak) relationship between the drug prices to consumers and the EPI and CPI of the API production countries, this relationship is due to a stronger link, i.e. that original, branded, products are much more often produced in countries with higher EPI and CPI. As original products tend to be more expensive than generics, the end result is therefore that more expensive products still are – from this perspective – slightly less likely to be produced in countries with more lax environmental control, but this does not depend on retail price *per se*. Notably, there were no significant differences between original and generic

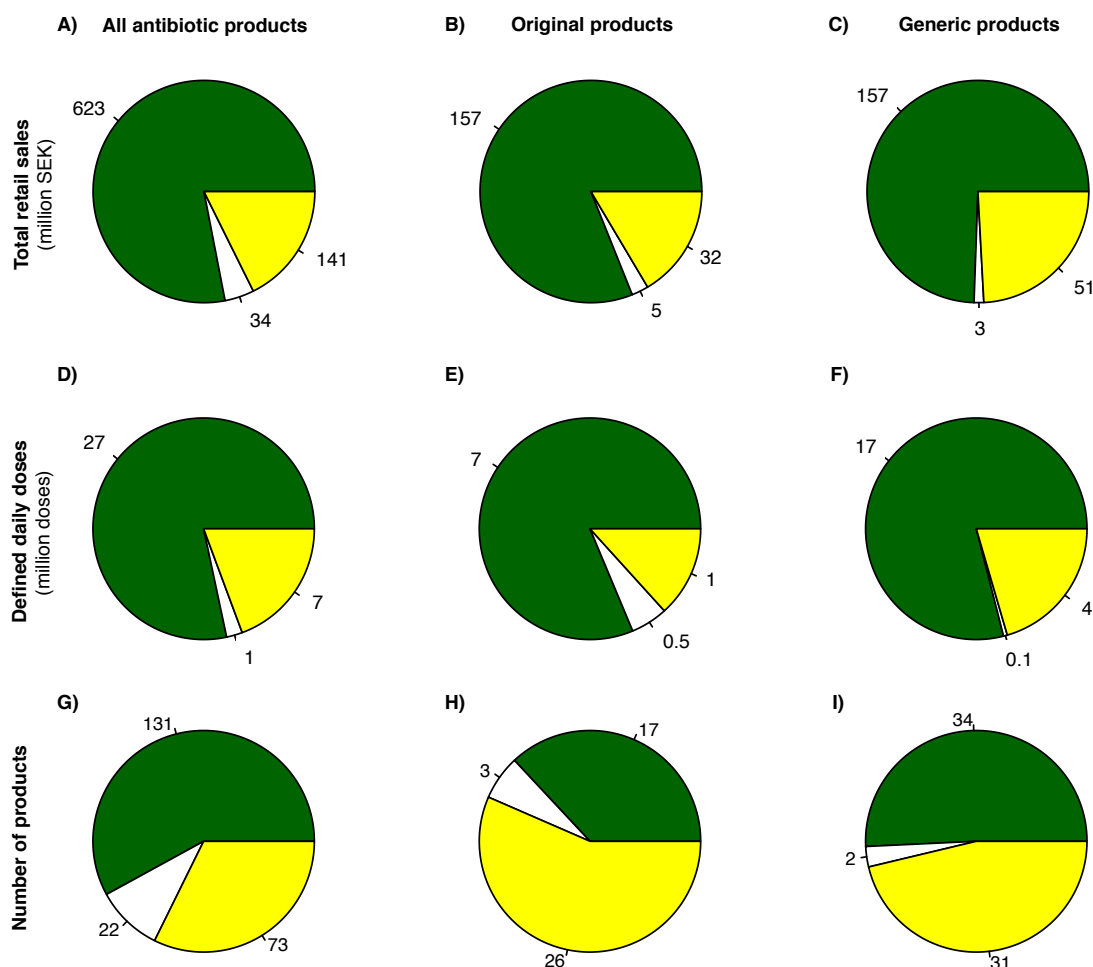


Figure 4. Antibiotic production divided by high-EPI (at least 80; green) and low-EPI (yellow). Antibiotics that could either be produced in low or high EPI countries are indicated as unknown (white). Values are given in millions of SEK (a-c), million defined daily doses (d-f) or number of products (g-i).

antibiotics products in terms of EPI or CPI of the production country. Original products were three times as likely to be produced in high-EPI countries. If these indexes reflect also the probability for large environmental emission from pharmaceutical production, buyers of pharmaceuticals would have a possibility to influence their environmental footprints by their choices of products. It is, however, important to realize that these indices are general country indices and there are unquestionably also very large variations between API manufacturers and facilities within each production country. The EPI and CPI indices only represent an overall

assessment of how many factors interact to form a country's environmental and transparency-related performance and thus say little about the conditions at individual production facilities, which may place anywhere along a wide range of the environmental pollution spectrum of each country. In addition, even if information on possible production countries was made available for all pharmaceuticals, there would still be a high degree of uncertainty as to where the API was actually produced. This introduces a great deal of ambiguity into the analysis, and is the reason for the large differences between worst-case and best-case scenarios, reiterating the need for better

transparency in the production chain to allow individual consumers as well as hospitals, pharmacies and other actors to better make conscious choices about which drugs to purchase to reduce their environmental footprint (Access to Medicine Foundation, 2017; Ågerstrand et al., 2015; Larsson and Fick, 2009).

The level of overall environmental performance or perceived corruption in a country is related to many other factors that may have direct influences on production costs of APIs, labor costs not the least, and hence also final sales price. Our analyses do therefore not allow, or infer, a direct causal relationship between environmental performance, corruption and branding or price. That said, lack of investments in pollution control could very well be such a contributing factor. Importantly, however, whether there is a direct causal link or only a correlation is not critical for how choices of drugs based on branding or price favors production in countries with lower or higher overall environmental performance.

We have in this study considered both the number of products, the number of defined daily doses, and the monetary value associated with different production countries. The number of products provides a measure of the breadth of the pharmaceutical industry in a particular country, but does not convey much information with regards to environmental consequences. The number of doses produced, on the other hand, is a good indicator of produced volumes of APIs and thus provides a measure that could be more closely related to environmental risk, while the total monetary value is to some degree informative of the relative impact legislative efforts may have on the pharmaceutical industry in different countries. The latter also roughly describes the degree to which the Swedish sales of pharmaceuticals contribute to outsourcing of production to countries with lower environmental performance. We note that three quarters of the monetary

value is spent on pharmaceuticals produced in countries with relatively high EPI. At the same time, for generic products this proportion could be as low as 36%. India dominates the Swedish pharmaceutical market in terms of doses produced, particularly for generic drugs, and is thus – together with China – of particular interest for management actions to improve environmental standards. India and China are also the largest producers of APIs for generic drugs in terms of monetary value, further emphasizing the importance of providing increased demand for environmental management actions in these countries, for example as environmental criteria within public procurement and generic exchange programs (Laurell et al., 2014; MPA (Swedish Medical Products Agency), 2011; 2009; SPHS Secreteriat, UNDP Istanbul Regional Hub, 2015). Very recently, the Indian government published their National Action Plan on Antimicrobial Resistance (Government of India, 2017) indicating an intention to monitor and regulate antibiotic discharges from manufacturing sites within three years. This reflects a similar concern about the potential consequences of continued industrial pollution.

To our knowledge there are no freely available, public reports that provide a complete overview of where APIs available on the world market are produced. India, China and the USA were the largest producers of APIs for generic drugs based on Swedish sales statistics (monetary value). This is roughly consistent with the CPA report “Competition in the world APIs Market”, which states that China produced the largest share (35.6%) of the 2010 world sales of generic APIs (measured as total sales), followed by India (22.1%), Italy (16.5%), and Spain (5.5%) (Chemical Pharmaceutical generic Association, 2011). The large overlap between our data, which is exclusively based on Swedish sales statistics, and this international report suggests that the patterns we observe in this study well represent the situation in many countries in Western Europe and North America, despite that the Swedish pharmaceutical market constitutes less than one

percent of global pharmaceutical sales (LIF - de forskande läkemedelsföretagen, 2011). However, these data describe the situation in 2010, and the pharmaceuticals market may look slightly different now. With further regards to the possibilities of extrapolating conclusions to other countries than Sweden, branded (original) products in Sweden would still be branded in other countries, and also likely to often be more expensive than the available generic copies. It seems unlikely that there would be a strong discrepancy between branded products intended for the Swedish or other markets with regards to where the APIs are produced. This suggest that the links established here, based on the Swedish market, are plausibly largely valid in many other countries as well.

The promotion of antibiotic resistant bacteria is the greatest human health risk associated with releases of APIs into the environment (Mudgal et al., 2013), and the need for integrative one-health measures have been repeatedly underscored (Laxminarayan et al., 2016; Robinson et al., 2016). The only external environments where antibiotics concentrations have been measured at therapeutic levels are those associated with waste from pharmaceutical production (Gothwal and Thatikonda, 2017; Larsson, 2014; Larsson et al., 2007). Such high concentrations have been associated with excessive numbers of resistant bacteria and resistance genes (Bengtsson-Palme et al., 2014; Kristiansson et al., 2011; Marathe et al., 2013; Pal et al., 2016). However, it is feasible that concentrations much lower than those used in therapy would select for resistant bacteria (Andersson and Hughes, 2012; Bengtsson-Palme and Larsson, 2016a; Lundström et al., 2016). In this study, we show that while the majority of the antibiotics sold on the Swedish pharmaceuticals market is produced in European countries with relatively high EPI, a third of the products are produced in regions of the world with in general poor environmental performance – including countries like India, China and

Puerto Rico – mostly in the form of generic products. In terms of perceived corruption, an even larger share of the antibiotics used in Sweden is produced in countries with low performance. If EPI and CPI reflects also the situation during pharmaceutical production, this implies that the antibiotics used in Sweden could contribute to antibiotic resistance promotion associated with production facilities, a pattern likely reflected across most of the Western world. At the same time, the large portion of antibiotics produced in Europe, both for generic and original products, suggests that improvement of European legislation to reduced emissions of APIs from pharmaceutical production could have a comparably large effect on antibiotics releases even if not effective outside of Europe. This highlights that management of pharmaceutical pollution from manufacturing on the EU level is important not only to set a global example, but also may have direct positive effects on limiting discharges.

The substantial uncertainty regarding specific production facilities and manufacturing conditions hampers our ability to make fine-grained statements on pharmaceutical production and environmental impacts from this study. However, even if there was no such uncertainty, making a choice of drug based on environmental protection or global health concerns would be punished by the state in many countries with governmental or health insurance substitution systems, including Sweden (Svensk författningssamling, 2002). When only the least expensive interchangeable product is subsidized, the individuals themselves are left to pay the full price of the medicine if they would choose another alternative. In that respect, a substitution system based solely on price-competition may be counterproductive with regards to motivating reductions of environmental emissions (Läkemedels- och apoteksutredningen, 2013). Several studies have pointed to the need of increased transparency in the pharmaceutical production chain to motivate control of discharges and improved wastewater treatment from manufacturers

(Ågerstrand et al., 2015; Larsson and Fick, 2009). Arguably, there would be several benefits for industry players to be among the first to move towards a sustainable and transparent manufacturing process (Access to Medicine Foundation, 2017; Bengtsson-Palme and Larsson, 2016b). The recent industry roadmap on combatting antimicrobial resistance (Industry Roadmap for Progress on Combating Antimicrobial Resistance, 2016) and the pharmaceutical supply chain initiative (Pharmaceutical Supply Chain Initiative, 2015) are welcome initiatives in this direction, but are in some respects not sufficiently concrete to fulfill the needs. For example, while companies are obliged to follow local environmental regulation, which vary globally, no specific emission limits for APIs in pharmaceutical waste and wastewater are yet set; and there are so far no mechanisms proposed for independent follow-up on whether criteria are fulfilled. It is therefore likely that these industry proposals are not by themselves sufficient to alleviate the problem with environmental pollution from drug manufacturing. Direct regulation of industrial emissions, on the other hand, is a very efficient means of multi-pollutant control (Testa et al., 2012). In our view, concrete emission limits for production and waste handling facilities, e.g. by amending the Good Manufacturing Framework (GMP), is more likely to be an efficient method to mitigate these issues. Amendments to the GMP would also apply fairly to all players in the industry, and not allow certain producers to avoid fulfilling standards agreed upon by the majority of pharmaceutical companies in order to undercut the costs for companies employing proper handling of their production waste.

5. Conclusions

We show that while there is a relationship between price and environmental standards of the production countries, this link is explained by whether the sold product is an original, branded, product or a generic one. However, there are many other factors influencing the pricing of drugs, and this is only an overall trend – often there were no link between branding and EPI or CPI within exchange categories. This limits the ability to contribute to environmentally sustainable drug production, and to allow individuals as well as hospitals, pharmacies and other actors to influence the industry by their product choices. Hence initiatives to increase transparency, improved procurement criteria, voluntary commitments from the industry, regulations – national as well as international – and changes in the generic substitution systems are all parts of the solution.

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Supporting Information

Can branding and price of pharmaceuticals guide informed choices towards improved pollution control during manufacturing?

Johan Bengtsson-Palme[§], Lina Gunnarsson[§], D.G. Joakim Larsson^{*}

[§] Authors J.B-P. and L.G. contributed equally to this work, ^{*} Corresponding author

Supplementary Materials and Methods

1 Sales statistics

In august 2011, the Swedish eHealth Agency (www.ehalsomyndigheten.se) kindly provided sales statistics for all approved medical products sold in Sweden 2010. This governmental agency is responsible for Sweden's national drug statistics, and compile, process and publishes statistics on pharmaceutical sales in Sweden. The sales statistics were based on the total sales from all Swedish pharmacies and to some extent on sales of over-the-counter products from food retailers, but also included pharmaceuticals purchased by Swedish hospitals. The reporting from food retailers is not complete, but the eHealth Agency estimates that they have received sales statistics for roughly 75% of the over-the-counter products. Sale statistics of certain special products, such as rare vaccines purchased directly from wholesale distributors by vaccination clinics, are also not reported to the eHealth Agency. Products that were sold on a license (not approved in 2010), magistral (*ex-tempore*) preparations and products with a sales value equal to or below zero were excluded from the analysis.

The received sales statistics were based on statistics at the packaging level, e.g. the same product can be sold in a package of 50 or 100 pills. Unique national product identification numbers (managed by the Medical Product Agency) were used to summarize the sales statistics per product (rather than on package basis). In total, 7066 different approved medical products were sold in Sweden 2010 of which 5164 had a defined daily dose (DDD). The average price/DDD for each product was also calculated.

2 Manufacturing sites of active pharmaceutical ingredients

The Swedish medical products agency (MPA) kindly extracted information about the production country for all medical products (human and veterinary usage) approved for the Swedish or European market by Swedish authorities in 2010, excluding products containing any narcotic substances, as the MPA considered this data to be too sensitive to share. In addition, information regarding the manufacturing site of APIs in centrally approved products where Sweden was not the reporter country could not be obtained. In total, information about the production site for 6269 medical products was retrieved in June 2011. Some information regarding 2058 parallel imported products were also retrieved but information on the manufacturing site were lacking. The production sites for the parallel imported products were identified by comparing product name, active pharmaceutical ingredients, dose and administration form of the parallel imported products to the list of medical products that had information on production sites. The production sites for 650 parallel imported products could thus be identified.

In total, information on production site was available for 4073 of the medical products sold in 2010, and 3161 of these had a DDD. More than one possible manufacturing country per API was listed for 1965 (48%) of these products. The Swedish MPA had no data indicating which of the reported manufacturing sites that were actually used. A small proportion of the products contain more than one API and those APIs can be produced in different countries.

In accordance with our agreement with the MPA, the data received is presented here in such a way that no links between individual products or APIs and specific manufacturers or sites can be established.

3 Groups of interchangeable products and classification (original, generic or parallel imported products)

In august 2012, the Dental and Pharmaceutical Benefits Agency (TLV) kindly extracted their classification of pharmaceutical products (2498) that belonged to any group of interchangeable products (as defined by the Swedish MPA) in 2010. TLV is the governmental agency responsible for decisions concerning subsidies and price regulation of medicine and products included in the Swedish pharmaceutical benefits scheme. Sweden has a system of generic substitution of pharmaceuticals including generic, parallel imported and original products which have been determined interchangeable by the Medical Products Agency. Generic medicines belonging to the same exchange group contain the same active substance(s) as the reference medicine and are used at the same dose(s) to treat the same disease (European Medicines Agency, 2012; Svensk författningssamling, 2016). While a clear definition of an original product is lacking, original products are usually defined as drugs marketed with a specific brand name by the company that developed and/or patented it. In addition, TLV highlighted that there was a small group of drugs for which the classification was uncertain. Finally, parallel imported products are generally defined as approved pharmaceutical products imported from another country within the European Economic Area by another party than the producer or Swedish distributor. After cross-checking this list of products against the list of sold pharmaceuticals, we classified the parallel imported products as generic or original based on the information related to the corresponding products sold through the Swedish distributor. Of the products with known API manufacturing site(s), 1043 were classified as generic products and 865 as original products. The list of pharmaceutical products that belonged to any group of interchangeable products was compared to the sales statistics from the Swedish eHealth Agency. The potential association between the price/DDD and the EPI or CPI of the manufacturing countries was analyzed based on information of all products that belonged to a group of interchangeable products that had generic competition and for which there was information from at least one other product in the same group.

4 Country indices

There are often large discrepancies between regulations and measures taken to reduce pollution (Sawhney and Rastogi, 2014). Therefore, output-oriented indicators capturing both environmental regulations and the adherence to those are probably more informative than comparisons of available regulations in different countries. Such indices are far from perfect (Böhringer and Jochem, 2007; Singh et al., 2012), but given the lack of publicly available data we think they still have some merit (Brewer and Pojasek, 2013). We have chosen to focus on two indices, namely the Corruption Perceptions Index 2014 (CPI) (Transparency International, 2014) and the Environmental Performance Index 2016 (EPI) (Hsu et al., 2016). The CPI is a composite index, a combination of surveys and assessments of corruption, collected over 24 months by a variety of independent institutions specializing in governance and business climate analysis. The 2016 Environmental Performance Index (EPI) ranks 233 countries on 20 performance indicators tracked across two broad policy areas: environmental health and ecosystem vitality.

5 Statistical analysis

The maximal (if all of the APIs for each product associated with a certain country were produced there) and minimal (if only the APIs for products associated with a single country were produced there, i.e. products with shared API production countries were not counted) sum of retail prices, DDD and number of products were calculated for each country using custom Perl scripts, and separated into categories of generic, original, and parallel imported products. Products were assigned to the high-EPI country category if they only had production countries specified with an EPI of at least 80, and to the high-CPI countries if all specified production countries had a CPI higher than 60. These cutoffs are subjectively chosen, but in practice this means that roughly 25% of countries are categorized into the high EPI and CPI groups. Products with production countries both below and above these cutoffs were assigned to the unknown EPI/CPI categories. To assess the relationship between EPI/CPI of the production countries and final price of products, data on interchangeable products were used, and the price per DDD was normalized for each exchange group, such that all prices were expressed as a multiplier of the cheapest product in the exchange category (which was given a normalized price of 1). The best-case production country (the country with highest EPI or CPI if several countries for API production were specified) and the worst-case production country (lowest EPI or CPI) were identified for each product within the exchange groups. The processed data was imported into the R statistical program (R Development Core Team, 2016). Linear regression analysis was performed for each exchange category, separately as well as for the entire dataset together, investigating to which degree the differences in best-case and worst-case EPI or CPI of the production countries could be explained by the per-dose price of the product (normalized DDD) or its product category (generic vs. original). The regression was performed using iterative weighted least squares, using price and branding, or price only, as explanatory variables. Significant linear relationships between price and/or branding and EPI or CPI across all products analyzed together were identified by the Wald test for each explanatory variable. Significant over-representation of positive or negative slopes across all exchange groups analyzed separately were identified using the Wilcoxon signed rank test with continuity correction. In addition, regression analyses were performed specifically for antibiotics in the same manner. To investigate how consumer choice could influence the EPI and CPI of the production country, we selected the original, the most expensive, the cheapest, or a random product within each exchange group, and noted if the product ended up in the high EPI/CPI, low EPI/CPI or uncertain category. Random products were chosen 1000 times for each exchange group and the median and average result was recorded. Significant differences between conscious, systematic and random choices were assessed using Fisher's exact test.

See reference list of main paper for cited literature.

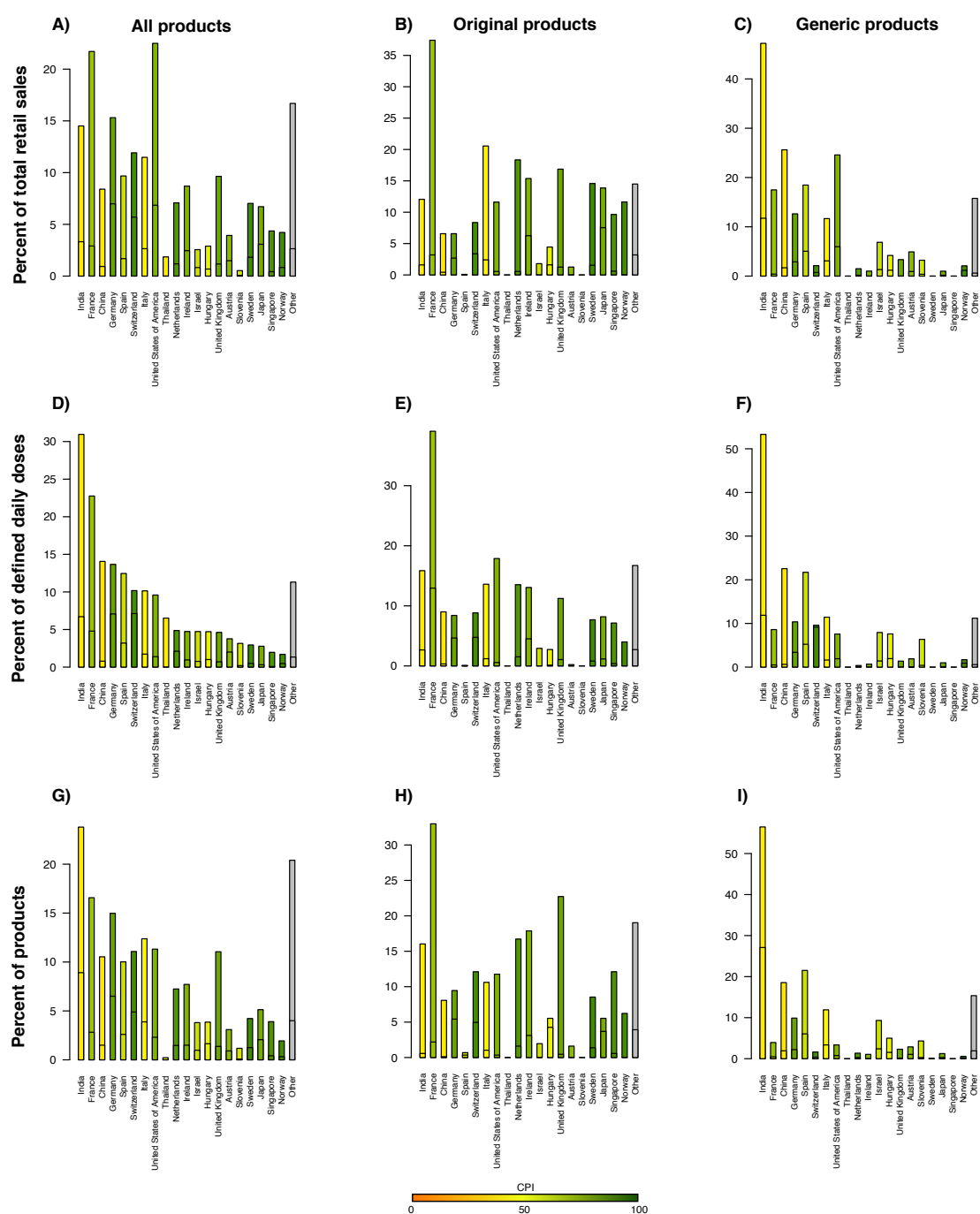


Figure S1. Production share of pharmaceutical products sold in Sweden in 2010, counted as monetary value (total retail price; a-c), defined daily doses (DDD; d-f), and number of different products (g-i). Coloring is according to CPI; greener colors mean higher CPI, and yellow colors correspond to lower CPI. The total height of each bar corresponds to the theoretical maximum for each country, while the lines within each bar indicate the minimum share for each country. All values are given as percentages.

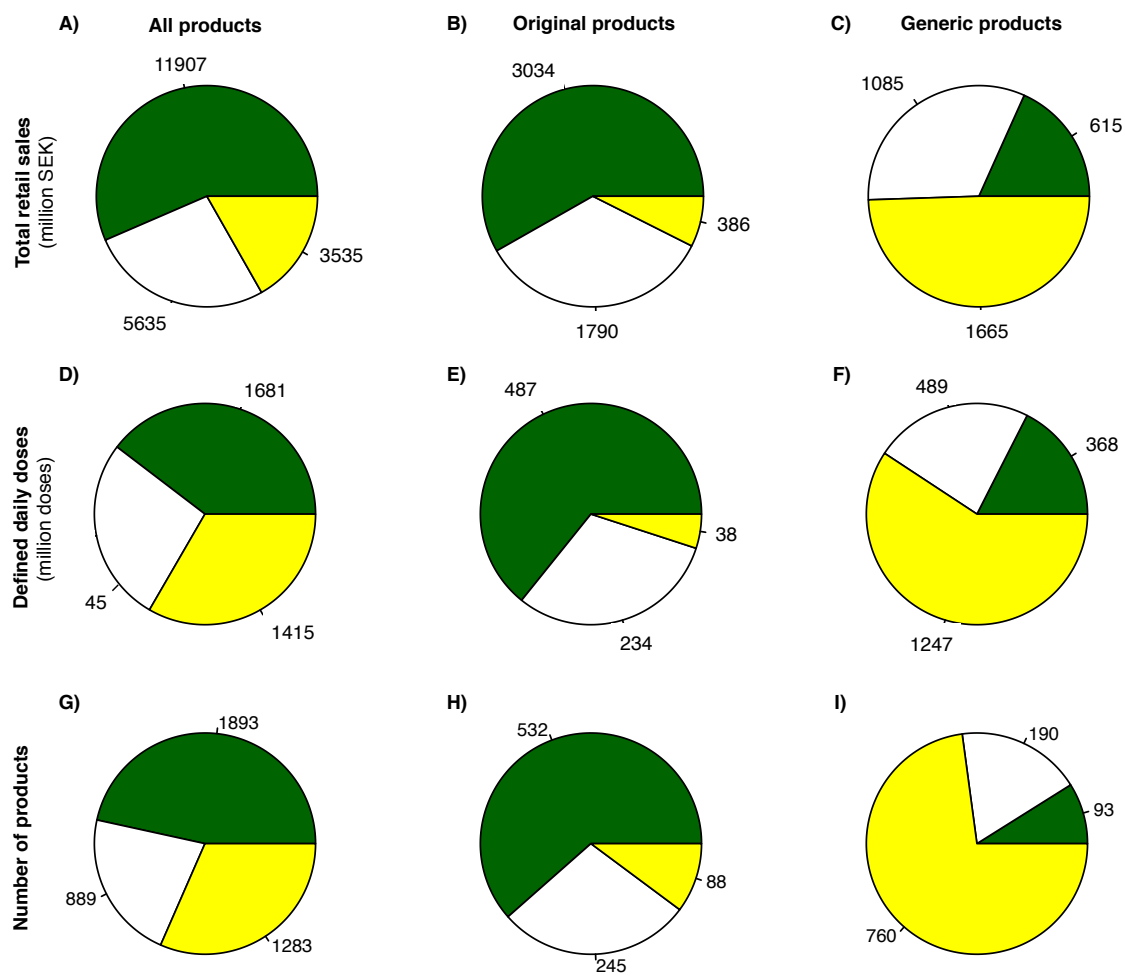


Figure S2. Pharmaceutical production divided by high-CPI (60 or more; green) and low-CPI (yellow). Products that could either be produced in low or high CPI countries are indicated as unknown (white). Values are given in millions of SEK (a-c), million defined daily doses (d-f) or number of products (g-i).

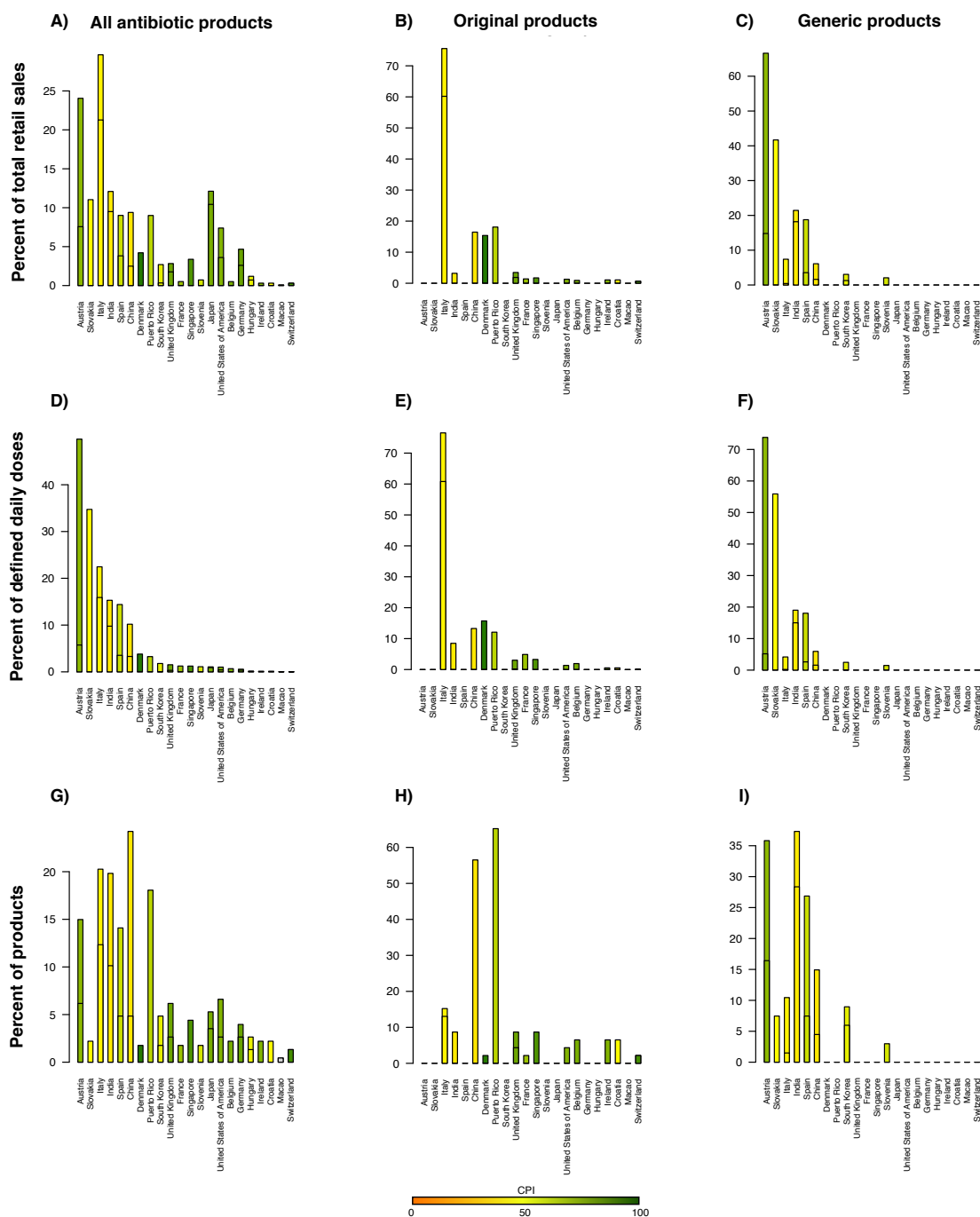


Figure S3. Production share of antibiotics sold in Sweden in 2010, counted as monetary value (retail price; a-c), defined daily doses (DDD; d-f), and number of different products (g-i). The total height of each bar corresponds to the theoretical maximum for each country, while the lines within each bar indicates the minimum share for each country. All values are given as percentages. Coloring is according to CPI.

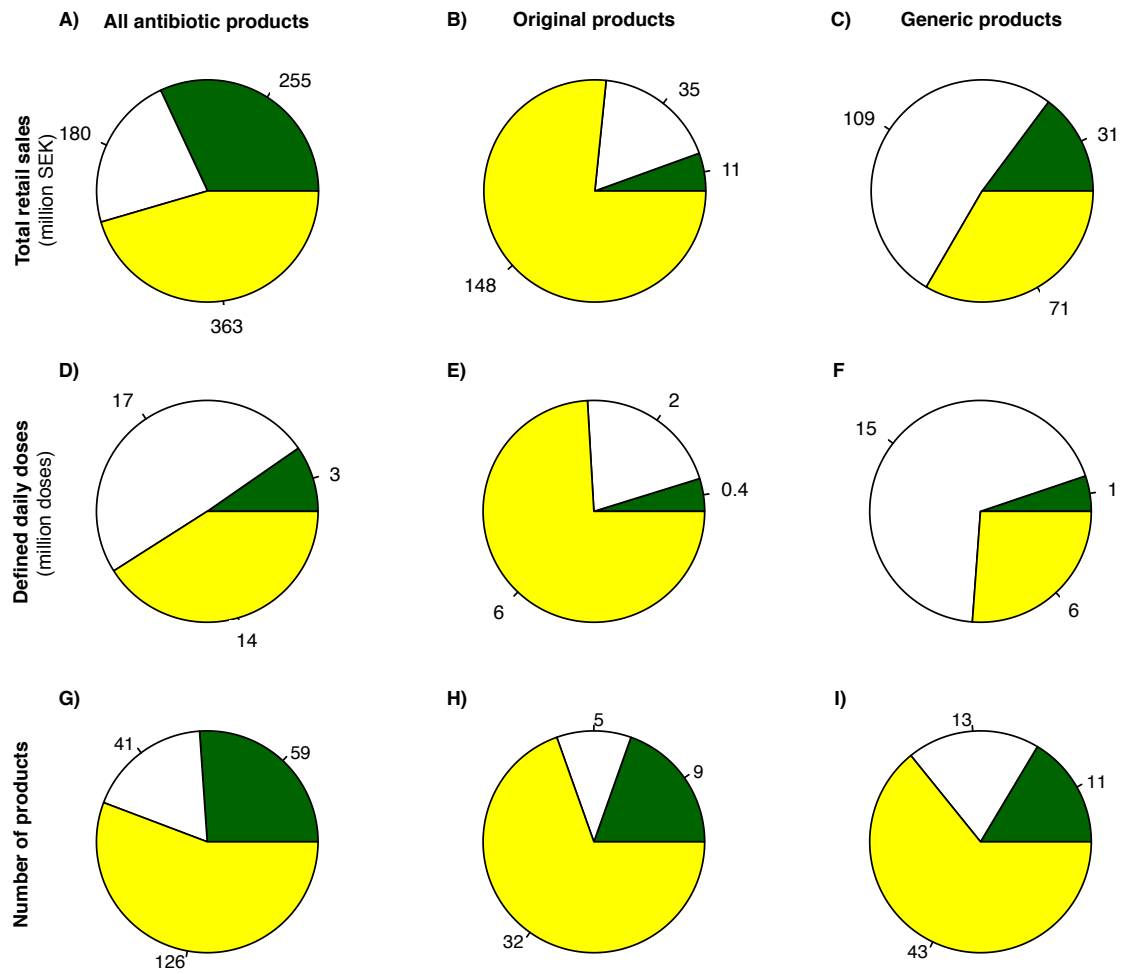


Figure S4. Antibiotic production divided by high-CPI (60 or more; green) and low-CPI (yellow). Antibiotics that could either be produced in low or high CPI countries are indicated as unknown (white). Values are given in millions of SEK (a-c), million defined daily doses (d-f) or number of products (g-i).

Prediction of EPI; all products

Original and generics

	Median	Wilcoxon signed rank test
Price Best-case	-3.22802E-16	0.632
Price Worst-case	-7.78909E-16	0.479
Branding Best-case	1.866817709	0.023
Branding Worst-case	19.16	1.70E-04

Generics only

	Median	Wilcoxon signed rank test
Price Best-case	-5.87065E-15	0.669
Price Worst-case	-1.34215E-15	0.640

Original and generics, only price regression

	Median	Wilcoxon signed rank test
Price Best-case	0.453309139	0.002
Price Worst-case	1.617772587	7.88E-06

Prediction of CPI; all products

Original and generics

	Median	Wilcoxon signed rank test
Price Best-case	-1.90491E-14	0.726
Price Worst-case	-4.70701E-17	0.503
Branding Best-case	20.6436808	2.94E-06
Branding Worst-case	27.97590857	2.12E-11

Generics only

	Median	Wilcoxon signed rank test
Price Best-case	-2.64574E-14	0.419
Price Worst-case	-1.32889E-16	0.515

Original and generics, only price regression

	Median	Wilcoxon signed rank test
Price Best-case	3.199371079	1.41E-09
Price Worst-case	3.08785025	3.58E-11

Prediction of EPI; antibiotics

Original and generics

	Median	Wilcoxon signed rank test
Price Best-case	-6.48893E-17	1.000
Price Worst-case	-6.21387E-16	1.000
Branding Best-case	-11.535	0.625
Branding Worst-case	0.37	1.000

Generics only

	Median	Wilcoxon signed rank test
Price Best-case	-0.134882203	0.094
Price Worst-case	7.63093E-16	0.787

Original and generics, only price regression

	Median	Wilcoxon signed rank test
Price Best-case	0.087784125	0.625
Price Worst-case	-0.002206935	0.625

Prediction of CPI; antibiotics

Original and generics

	Median	Wilcoxon signed rank test
Price Best-case	4.98945E-16	0.875
Price Worst-case	-9.54953E-18	1.000
Branding Best-case	4.5	0.250
Branding Worst-case	1.670545946	1.000

Generics only

	Median	Wilcoxon signed rank test
Price Best-case	-6.03992E-16	0.418
Price Worst-case	0.001233871	0.438

Original and generics, only price regression

	Median	Wilcoxon signed rank test
Price Best-case	0.471374828	0.625
Price Worst-case	-0.017894067	0.789

Table S1. Summary of the linear regression slopes for all exchange categories individually

	N	Best-case Price	Best-case Original	Worst-case Price	Worst-case Original	Interpretation
<i>All products</i>						
Prediction of EPI (original and generic products)	750	0.050	8.110	-0.101	15.205	Original products more likely to be produced in high-EPI countries
(p-values)		0.218	4.04E-13	0.012	1.48E-39	
Prediction of EPI (generic products only)	933	-3.702	-	-2.129	-	Cheaper generic products more likely to be produced in high-EPI countries
(p-values)		2.17E-10	-	7.20E-05	-	
Prediction of CPI (original and generic products)	763	0.058	21.368	-0.174	21.579	Original products more likely to be produced in high-CPI countries
(p-values)		0.194	1.98E-59	1.66E-05	1.33E-71	
Prediction of CPI (generic products only)	933	-3.367	-	-1.121	-	Cheaper generic products more likely to be produced in high-CPI countries
(p-values)		2.24E-08	-	0.011	-	
<i>Antibiotics only</i>						
Prediction of EPI (original and generic antibiotics)	43	-2.036	-3.323	-0.677	-5.070	No overall relation between price or branding and EPI
(p-values)		0.471	0.423	0.811	0.225	
Prediction of EPI (generic antibiotics only)	53	-9.058	-	-8.989	-	Cheaper generic antibiotics more likely to be produced in high-EPI countries
(p-values)		0.010	-	0.011	-	
Prediction of CPI (original and generic antibiotics)	43	-2.592	13.382	-3.653	-0.627	Original antibiotics may be more likely to be produced in high-CPI countries
(p-values)		0.331	1.27E-03	0.336	0.910	
Prediction of CPI (generic antibiotics only)	53	-8.375	-	-5.308	-	Cheaper generic antibiotics slightly more likely to be produced in high-CPI countries
(p-values)		0.014	-	0.055	-	

Table S2. Relationships between product price, EPI/CPI and branding (original or generic). Prices were normalized within each exchange group and then analyzed together through linear regression for all products or antibiotics separately. The co-efficients represent the slope of the regression line.