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Diffusion of Pharmaceuticals: Cross-Country Evidence of Anti-TNF drugs

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Abstract:	This paper studies the diffusion of biopharmaceuticals across European countries, focusing on anti-TNF drugs, which are used to treat autoimmune diseases (e.g., rheumatism, psoriasis). We use detailed sales information on the three brands Remicade, Enbrel and Humira for nine European countries covering the period from the first launch in 2000 until becoming blockbusters in 2009. Descriptive statistics reveal large variations across countries in per-capita consumption and price levels both overall and at brand level. We explore potential sources for the cross-country consumption differences by estimating several multivariate regression models. Our results show that large parts of the cross-country variation are explained by time-invariant country-specific factors (e.g., disease prevalence, demographics, health care system). We also find that differences in income (GDP per capita) and health spending (share of GDP) explain the cross-country variation in consumption, while relative price differences seem to have limited impact.
Response to Reviewers:	See attachments.

1 Introduction

Diffusion of new medicines is important for pharmaceutical companies as it increases the returns on their R&D investments and thereby their innovation incentives. Diffusion of new medicines is also crucial for patients as they get access to new drug therapies that might be more effective in treating their disease. Despite the obvious importance of diffusion of pharmaceutical innovations, the existing knowledge is scarce.[1]

Our paper aims at filling this gap in the literature by exploring the cross-country variation in pharmaceutical sales. We focus on a group of biopharmaceuticals called Tumor Necrosis Factor inhibitors, hereafter called anti-TNF drugs, that treat autoimmune diseases such as arthritis and psoriasis. The first brand, Remicade, was introduced on the US market in the end of 1998. The second brand, Enbrel, entered the market shortly after, while the third brand, Humira, was launched a couple of years later. These products are now global blockbusters with total sales revenues exceeding $20 billion in 2011.[2]

To study the diffusion of anti-TNF drugs, we use a data set with detailed sales information of anti-TNF brands (Remicade, Enbrel, and Humira) across nine European countries (Denmark, Finland, France, Germany, Italy, Norway, Spain, Sweden, and Switzerland). Our data include monthly product-level information over a ten year period from 2000 to 2009, which covers the first launch of anti-TNF drugs in Europe until these drugs become top-sellers on national markets. The descriptive statistics reveal surprisingly large cross-country differences. The average per-capita consumption in the country with highest consumption (Norway) is more than 350 percent higher than the country with the lowest consumption (Italy). The consumption differences are also large between neighbouring countries. For instance, Spain has 75 percent higher per-capita consumption than Italy.

To explore the sources of the cross-country variation, we estimate several multivariate regression models. Since we have a panel data set with monthly product-level observations across several countries, we can control for time-invariant country-specific factors that are

[1] There are a few recent exceptions, e.g., Jönsson et al. (2008), Berndt et al. (2007), Desiraju et al. (2004), and Frech and Miller (2004). We return to these studies below.

[2] These figures are collected from the annual reports of Abbott, Merck, Amgen and Pfizer for 2011, which are publicly available on the companies' webpages.

likely to explain differences in consumption.[3] This includes factors such as population size, health status, health-care system, and, importantly, the prevalence of autoimmune diseases. As expected, the estimated differences in per-capita consumption across countries are much smaller than indicated by the descriptive statistics. For instance, the difference between the countries with the highest (Norway) and lowest (Italy) consumption is now reduced to about 170 percent. Thus, country-specific (time-invariant) factors account for about half of the cross-country variation in per-capita consumption of the anti-TNF drugs.

We analyse the remaining cross-country differences in consumption by successively introducing sets of explanatory variables. First, we include the number of approved indications for each of the anti-TNF drugs. This variable varies across products and over time, but not across the countries in our sample, since the approvals are EU wide. As expected, we find a positive effect of the number of approvals on the average per-capita consumption. Second, we include the price of the anti-TNF brands. Differences in relative prices across countries might explain the variation in consumption. We find that lower prices are associated with higher consumption levels, but the cross-country differences are almost the same as before. Third, we include income, measured by the gross domestic product (GDP) per-capita, as well as health expenditures as a share of GDP. We find that both higher income and health spending have a positive effect on the consumption of anti-TNF drugs, but also explain consumption differences across countries. Thus, we conclude that cross-country variation in the diffusion of anti-TNF drugs is to a large extent due to time-invariant country-specific factors (e.g, disease prevalence, demographics, health status, etc.) but also country (per-capita) income and health spending, while relative price differences across countries have no significant impact.

As mentioned above, the literature on diffusion of pharmaceuticals across countries is scarce.[4,5] However, there are some recent exceptions. Jönsson et al. (2008) offer a

[3] We also control for time-invariant product-specific factors (e.g., treatment effects, side-effects, administration form, etc.) that are likely to explain differences in consumption across the anti-TNF brands, as well as time trends in consumption.

[4] The empirical literature on cross-country differences in the prices of pharmaceuticals is much larger, see e.g., Danzon (1999), Danzon and Chao (2000), Danzon and Furukawa (2003), and Brekke et al. (2011).

[5] There are some studies on diffusion of pharmaceuticals within countries, see e.g., Berndt et al. (2003) and Chintagunta et al. (2009).

descriptive analysis of the sales of anti-TNF drugs in a wide set of countries (also outside Europe) for the period of 2000 to 2006. They find large cross-country variation in the per-capita sales revenues. High-income countries have substantially higher per-capita sales revenues of anti-TNF drugs than poorer countries, but there is also large variations across countries with fairly similar income levels.[6] Berndt et al. (2007) study the diffusion of new drugs across 15 countries and three therapeutic classes (antihypertensives, antidepressants, antiepileptics) using quarterly sales data over a 12-year period from 1992 to 2003. They find substantial heterogeneity across therapeutic classes and countries in diffusion of new medicines.[7] Desiraju et al. (2004) study the diffusion of new pharmaceuticals in developed and developing countries. Using data from fifteen countries, they find that developing countries tend to have lower diffusion speed and maximum penetration level compared to developed countries. They also find that per-capita expenditures on health care have a positive effect on diffusion speed (particularly for developed countries), while higher prices tend to decrease diffusion speed.[8]

The contribution of our study is two-fold. First, we contribute to the particular study of the consumption of anti-TNF drugs. We do so by offering a detailed, exploratory analysis of the diffusion of anti-TNF drugs. The literature on anti-TNF drugs is scarce despite the fact that these drugs are among the most significant pharmaceutical innovations in recent time, especially if measured in sales. We complement the study by Jönsson et al. (2008) by focusing on the consumption (not sales revenues) of these drugs, and extend their study by investigating more closely the sources of the large cross-country differences that are observed. In particular, we use multivariate regression that allows us to statistically test the relationship between consumption of anti-TNF drugs and several explanatory

[6]There is also a study by Dalen et al. (2012) on the anti-TNF drug market using Norwegian data. They find that changing the funding of anti-TNF drugs from the central government (social insurance agency) to the public hospital enterprises has a significant effect on pricing and market shares of the three anti-TNF brands.

[7]Berndt et al. (2007) also study the role of promotion on the overall consumption and the relative share of old and new medicines within a therapeutic class. They find that promotion has a strong market share effect within therapeutic class, while the effect on overall consumption is weaker.

[8]There is also a study by Frech and Miller (2004) that analyse the cross-national differences in utilisation of overall pharmaceuticals. However, this study is mainly concerned with the impact of cross-national consumption differences on quality of life and obesity.

variables (e.g., income, health spending, etc), but also test for the importance of country- and product-specific time-invariant factors. Second, our study contribute to the more general literature on diffusion of new medicines. We focus on more "similar" countries than in Berndt et al. (2007) and Desiraju et al. (2004), but still find substantial variation in per-capita consumption. Our contribution is to demonstrate that the cross-country variation to a large extent is explained by time-invariant country-specific factors, such as disease prevalence, demographics, health care system, and that empirical studies need to account for such factors when analysing diffusion of new drugs across countries. We also show that income and health spending are important explanatory variables, while perhaps somewhat surprisingly price differences seem to have limited impact.

The rest of the paper is organised as follows. In Section 2 we briefly present the market for anti-TNF drugs. In Section 3 we describe our data and sample, and provide some descriptive statistics on cross-country variation in consumption, prices, etc. In Section 4 we present the empirical model and report our empirical results. Finally, in Section 5 we draw some conclusions and make some concluding remarks.

2 The market for anti-TNF drugs

Tumor necrosis factor (TNF) is a cytokine (chemical messenger) that is involved in the regulation of immune cells by promoting the inflammatory responses. If the body produces excessive amounts of TNF, this can cause several medical problems related to autoimmune disorders such as rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, psoriasis, etc. These disorders can be treated by using anti-TNF drugs, which reduce the effect of TNF and, in turn, the inflammatory reactions associated with autoimmune diseases. However, since TNF is a part of the immune system, treatment with anti-TNF drugs can generate potentially severe side-effects related to infections, blood disorders, and sometimes also cancer and heart failure.

The anti-TNF drugs were introduced on the US market by the end of 1998. The first anti-TNF brand to receive marketing authorisation in Europe was Remicade (infliximab),

which was approved for treatment of patients with Crohn's disease – a fairly rare disease – in August 1999 by the European Medicines Agency (EMA). The second anti-TNF brand on the European market was Enbrel (etanercept), which got a marketing approval in February 2000 for rheumatoid arthritis, which is a much more frequent disease than Crohn's disease. Remicade was also approved for rheumatoid arthritis by the EMA just a couple of months later in June 2000. The third entrant on the anti-TNF market was Humira (adalimumab). In Europe, Humira got its first marketing approval in September 2003 for treatment of rheumatoid arthritis.[9]

In Table 1 below we provide an overview of the marketing authorizations by the EMA for the anti-TNF drugs considered in this study.

[Table 1 about here]

We see that the three anti-TNF drugs cover in total seven indications. Notably, the indication approvals are not completely overlapping for the three drugs. Remicade is not approved for juvenile rheumatoid arthritis, Enbrel is not approved for Crohn's disease and ulcerative colitis, and Humira is not approved for ulcerative colitis. We also see that the approvals were given at different dates to the anti-TNF drugs. For instance, Remicade was the only anti-TNF drug that could be used on patients with Crohn's disease until 2007 when Humira also got an approval for treatment of this disease.

The set of marketing approvals will, of course, affect the consumption of the anti-TNF drugs. The magnitude of the effect on consumption is likely to be influenced by the number of approvals and the prevalence of the disease for which the drug is approved for in the population. Some diseases are rare, such as Crohn's disease, while others are much more prevalent, such as rheumatoid arthritis. In the empirical analysis, we will make use of the information on indication approvals when studying the consumption of anti-TNF drugs

[9]There are now more anti-TNF drugs on the market. Cimzia (certolizumab pegol) got marketing authorization for rheumatoid arthritis in October 2009 by the EMA (but was refused for Crohn's disease). Simponi (golimumab) was also introduced in October 2009, and is approved for rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis.

over time. However, the marketing authorizations by the EMA apply to all countries in our sample, and will therefore not explain cross-country (but only cross-product) variation in consumption.

Since the introduction of the anti-TNF drugs on the US market in 1998, the sales of these drugs have increased tremendously. Over a decade, Remicade, Enbrel and Humira have become global blockbusters. Their total sales revenues globally exceeded $20 billion in 2011. Humira generated the largest sales revenues of the three anti-TNF drugs with more than $7.9 billion, followed by Enbrel and Remicade that produced global sales revenues of $7.3 and $5.5 billion, respectively, in 2011.[10] The sales are expected to increase even further in the future, despite the entry of new competing products.

Biologics are often discovered and developed by smaller biotech firms that (if successful) are acquired by the large pharmaceutical companies. This is also the case for the anti-TNF drugs. Remicade was discovered by researchers at New York University School of Medicine and developed by Centocor Biotech (now Janssen Biotech) – a subsidary of Johnson&Johnson. Janssen Biotech is marketing Remicade in the US, while Schering-Plough (now part of Merck) is marketing the drug elsewhere (except in some Asian countries). Enbrel was discovered by researchers in the biotech company Immunex, and is now marketed by Amgen in North America, and by Wyeth (a subsidary of Pfizer) or Pfizer itself in the rest of the world (except in some Asian countries). Humira was discovered through a collaboration between BASF Bioresearch and Cambridge Antibody Technology, and then developed by BASF Pharma. This drug is now manufactured and marketed by Abbott Laboratories after the acquisition of BASF Pharma by Abbott.

The three anti-TNF drugs are different biologics that vary in their treatment effect and side-effects. Remicade (infliximab) and Humira (adalimumab) are artifical (monoclonal) antibodies that binds and inhibits the action of TNF. Enbrel has a similar effect, but is instead a fusion protein that function as a decoy receptor that binds to TNF. The administration of these drugs differ. Remicade is given as an intravenous infusion under the supervision of health care professionals at hospital or some other treatment facility.

[10] These figures are collected from the annual reports of Abbott, Merck, Amgen, and Pfizer for 2011.

Enbrel and Humira, however, can be injected by the patient themselves at home. The treatment intensity is higher for Enbrel and Humira than for Remicade. While the latter only requires about 6 treatments per year, patients would need to take Enbrel and Humira once or twice per week. In the empirical analysis we will take into account the differences in product characteristics when analysing the consumption of the anti-TNF drugs.

The anti-TNF drugs are generally prescribed by hospital specialists or specialists outside hospitals (rheumatologists, dermatologists, etc.). Primary-care doctors are usually not allowed to prescribe these drugs. Due to the fact that Remicade needs to be injected under the supervision of health care professionals, this drug is almost exclusively prescribed by hospital specialists and dispensed through hospitals. However, Enbrel and Humira are prescribed by both hospital and non-hospital specialists, and dispensed through either hospitals or retail pharmacies. Table 2 below offers an overview of the prescribers and dispensing channels for the anti-TNF drugs in the countries in our sample, as well as the funding body and level of copayments.

[Table 2 about here]

The anti-TNF drugs are very expensive medicines. As we see from the table, the medical expenses are covered by health insurance with a (close to) 100 percent coverage. Remicade, which is provided in hospitals, have no copayments, while consumers of Enbrel and Humira are in some countries exposed to marginal copayments usually associated with prescriptions outside hospitals. When it comes to the funding body, we notice that there are some differences across the countries whether this is a public central or regional government or private health insurance funds.

The countries in our study are Western European countries with fairly similar characteristics along many dimensions such as demographics, health status, health care system, income levels, educational levels, etc. However, there are also differences across these countries, as can be seen from Table 2. The Scandinavian and Southern European countries have a National Health Service with predominantly public funding through general

taxation and public provision of health care. However, we see that the funding body can be either the central or regional government.[11] The Continental countries have typically a social insurance system with a mixture of public and private funding and provision. This applies basically to Germany and Switzerland, but not France, as shown in Table 2.

There are also differences across the European countries when it comes to regulation and price control schemes. Some countries make use of direct price control through price cap regulation (Finland, Italy, Norway and Spain), where the price cap is usually based on international price comparisons. Other countries (Denmark, France, Germany, Sweden and Switzerland) rely more on indirect price controls through negotiations with the pharmaceutical companies or the design of reimbursement scheme, such as reference pricing (interal referencing).[12]

Finally, the prevalence of diseases varies across countries (and also ethnicities). Epimediological studies tend to find that the prevalence of autoimmune diseases such as rheumatoid arthitis and psoriasis are substantially lower in Southern European countries compared to Northern European countries.[13] In the empirical analysis we will account for such country-specific factors.

3 Data and descriptive statistics

We have obtained data from IMS Health[14] containing detailed sales information of the three leading anti-TNF brands (Remicade, Enbrel and Humira) in nine European countries (Denmark, Finland, France, Germany, Italy, Norway, Spain, Sweden and Switzerland). The data cover the ten year period from the launch of anti-TNF drugs on the European market in 2000 up to 2009 when these drugs have become blockbusters in almost every

[11] The study by Dalen et al. (2012) on the reimbursement of anti-TNF drugs in Norway shows that the choice of funding body (central government or public hospitals) has a significant effect on the pricing and market shares of the anti-TNF brands.

[12] See, for instance, Danzon and Ketcham (2004), Pavcnik (2002), Brekke et al. (2009, 2011), and Dalen et al. (2011) for studies of reference pricing and its effects on pricing and pharmaceutical expenditures.

[13] According to, for instance, Chandran and Raychaudhuri (2010) the prevalence of psoriasis in Europe varies between 0.6 to 6.5 percent. Alamanos and Drosos (2005) report similar differences for rheumatoid arthritis.

[14] IMS Health is a US-based market-research company that provides pharmaceutical and health care information globally.

Western country.

The data set contains detailed product-level data for each of the anti-TNF drugs in each country, including monthly information about sales values and sales volumes for each anti-TNF product (pack) on the national markets. Sales values are measured in local currency at ex-manufacturer level, while sales volumes are measured as the number of defined daily doses (DDDs)[15] of each anti-TNF product (pack) sold in each country. The data set also contains detailed information about manufacturer, product name, pack size, dosage, and formulation. Hospital and retail sales are reported separately for all countries except for Denmark and Sweden, where we have only the combined sales.

Based on the data set, we construct the following variables. First, we aggregate the monthly sales volumes (the number of DDDs) of all packs with the same substance in each country. This gives us a measure of the aggregate consumption per month of the anti-TNF brands in the different countries. In order to compare the consumption levels across countries, we normalize the monthly sales volumes by country population (per 10,000 inhabitants), so that we obtain the monthly per-capita consumption of the anti-TNF drugs. Second, we compute the monthly (sales-weighted) average price per DDD for each of the anti-TNF brands by dividing the sales value by the sales volumes (the number of DDDs) of all packs with the same substance. For the countries with local currencies, we convert these unit prices to Euros using contemporaneous monthly average exchange rates. Finally, we compute the proportion of hospital sales and parallel imports relative for total sales for each anti-TNF drug in each country. Table 3 below summarizes the descriptive statistics.

[Table 3 about here]

3.1 Entry

As mentioned above, Remicade and Enbrel received their marketing authorization on the European market by just before and after the year 2000, while Humira's first approval

[15]Defined daily dose (DDD) is a dosage measure developed by the World Health Organization. This measure is based on the assumed average daily maintenance dose for its main indication use in adults. The DDDs are 3.75 mg for Remicade, 7 mg for Enbrel, and 2.9 mg for Humira.

was in mid of 2003. The marketing approvals are EU wide and therefore applies to all countries in our sample. However, the data reveal considerable variation in launch dates across countries, especially for Enbrel, but also to some extent for Humira. We see from Table 3 that Enbrel was launched in January 2000 in Norway, France and Switzerland, but not before mid of 2003 in Denmark and Germany. Humira was first launched in Norway in October 2002, while not before July 2004 in Italy.[16] However, the launch of Remicade is in the beginning of 2000 in all of the countries in our sample.

The launch of products on national markets is a strategic decision by the pharmaceutical firms depending on the expected profits relative to the entry cost. If the expected sales and prices are sufficiently high, entry will occure in a given market. In pharmaceutical markets the launch decision is likely to be influenced by regulatory schemes, such as the reimbursement and pricing of these drugs in the various countries.[17] Clearly, delays in launching of products will influence the diffusion of anti-TNF drugs, and might be a source of cross-country differences in consumption of these products.

3.2 Consumption

If we consider the per-capita consumption of anti-TNF drugs, the figures in Table 3 show considerable cross-country variation. We see that Germany and Italy have the lowest (overall) consumption rates of anti-TNF drugs with almost 78 DDDs per 10,000 capita per month on average over the period 2000-2009. Norway has, by far, the highest consumption rate with 375.6 DDDs per 10,000 capita per month. This is more than four times the consumption of Germany and Italy. Interestingly, there are large variations between neighbouring countries. For instance, the consumption in Norway is 85 percent higher than in Denmark, and the consumption in Spain is 77 percent higher than in Italy.

If we compare the consumption of the three anti-TNF drugs, we see that Remicade has

[16] Note that the first marketing approval of Humira by the EMA was in September 2003. The reason we observe sales of Humira before that date in Norway is due to the fact that hospitals may start using these drugs before the actual approval date.

[17] See, for instance, the studies by Danzon et al. (2005) and Kyle (2007) who find that countries with strict price control have fewer launches of new drugs, and that pharmaceutical companies tend to delay launch into price-controlled markets.

the highest consumption rate (market share) in all countries except for Germany, where Enbrel has a slightly higher level. The consumption rates of Enbrel and Humira vary across countries. In Denmark, Finland, Germany and Switzerland, Humira has a higher consumption level than Enbrel, wheras the opposite is true in the rest of the countries.

Since we have monthly data for the ten year period 2000-2009, we can study the diffusion of the anti TNF drugs in the various countries. This also allows us to take a closer look at how the late entry of Humira affects the sales of Enbrel and Remicade. The figure below plots the monthly average consumption (in DDDs) per 10,000 capita for each brand in each country.

[Figure 1 about here]

We see that the three anti-TNF brands have experienced a significant growth in consumption in all countries. The consumption growth is particularly strong in the Scandinavian countries. In almost every country, Remicade has the highest consumption per capita throughout the period. Indeed, in Norway the monthly consumption of Remicade per 10,000 inhabitant exceeds 300 DDDs by the end of 2009.

Interestingly, Humira quickly achieves a high consumption level after its late entry. However, the consumption growth of Remicade and Enbrel continues in all countries. This illustrates that the anti-TNF market is expanding over the period. Humira is not just "stealing" patients from Enbrel and Remicade, but also expands the market for anti-TNF drugs. We will analyze the diffusion of anti-TNF drugs more carefully in Section 4, but first we take a closer look at the pricing of these products in the different countries.

3.3 Pricing

The anti-TNF drugs are very expensive. In Table 3 we report the average price per DDD for each product in each country. We see that the average price of Remicade is considerably lower than Enbrel and Humira in all countries. In many countries Remicade is almost 50 percent cheaper than Enbrel and Humira. The average price of Enbrel and Humira are almost the same in most countries, except for in Germany, France and Spain where Humira

has a slightly higher average price.

The price variation across brands is likely to be due to differences in product characteristics. The three anti-TNF brands differ in their treatment efficacy and side-effects, as well as the set of indications that they are approved for. Importantly, these drugs also differ in the administration. Remicade requires injections administrated by health personnel usually at hospital facilities, while Enbrel and Humira can be administrated by the patients themselves at home. This can be one reason for the lower price on Remicade compared to Enbrel and Humira.

More interestingly, we observe that there are considerable price differences across countries for the same product. For instance, the average price per DDD of Humira varies from € 34.36 in Italy to € 52.82 in Germany. The average price of Enbrel also differ considerably, while cross-country price variation of Remicade is much smaller. Germany tends to be the high-price country. This is also consistent with the fact that we observe parallel imports for this country only, with the exception of Enbrel in Sweden. Italy, on the other hand, tends to be the low-price country.

Let us also take a look at the development in prices over time. Figure 1 below reports the monthly average price per DDD (in Euros) for each of the anti-TNF brands in each country over the period 2000-2009.

[Figure 2 about here]

We see that the prices are fairly stable in most countries. The figure confirms that Remicade is priced lower than the two competing anti-TNF brands in every country. We also see that Humira enters the market with a price equal to or sometimes even higher than Enbrel. This pricing strategy reflects that Humira is perceived to be of same quality than Enbrel, but of higher quality than Remicade.

How do the pricing of Remicade and Enbrel respond to the entry of Humira? In Denmark and Italy we cannot spot any price responses. In Finland and Norway there seem to be some price reductions (competition) taking place after the entry of Humira,

while, in France and Germany, the price of Enbrel is in fact increasing after the entry. The price of Humira is gradually reduced, and the two prices eventually converge in these two countries.

As mentioned in the previous section, the prices of the anti-TNF drugs are not set freely by the pharmaceutical firms, but are subject to price control mechanisms or negotiations with payers in the different countries. Thus, price changes can be induced by regulations or through re-negotiations. This is also likely to explain parts of the differences in price levels and developments across countries. However, pharmaceutical companies can also make (especially downwards) adjustments of the pricing of their products. In any case, the prices of the anti-TNF drugs are likely to influence the diffusion, which will be taken into account in the empirical analysis in the next section.[18]

4 Empirical method

We now proceed by analyzing the potential sources of cross-country variation in the consumption of the anti-TNF drugs. Since we have a product-level panel data set with detailed sales information of the three anti-TNF brands over ten years (120 months) in nine countries, we are able to control for all product- and country-specific factors (both observed and unobserved) that are time invariant. We estimate the following multivariate regression model:[19]

$$\begin{aligned} \ln Y_{cit} &= \beta_1 \ln P_{cit} + \beta_2 \ln GDP_{ct} + \beta_3 HE_{ct} + \beta_4 I_{it} \\ &\quad + \alpha_i + \gamma_c + \delta \ln t + \varepsilon_{cit}, \end{aligned} \tag{1}$$

where the dependent variable ($\ln Y_{cit}$) is the (natural logarithm of) consumption per (10,000) capita of product i in country c at time t. In the regression we include dummy

[18] The study by Desiraju et al. (2004) shows that the diffusion speed is lower in countries with high prices. However, we may also expect that high price levels imply quicker launch (less delay) of new products, as found by Kyle (2007).

[19] All variables are measured at a monthly basis except for gross domestic product (GDP) and health expenditures (HE) that are measured on a yearly basis.

variables to capture product- and country-specific effects. The product-specific dummies (α_i) capture characteristics of the anti-TNF drugs that are constant over time and common across countries. The different brands are separate biological substances with different properties in treatment. One brand might be more effective in treating some patients (or diseases), while less effective for others. The brands also differ in their side-effects, and for this reason could be more suitable for some patients (or diseases), while less suitable for others. The product-specific effects also include properties of the drug treatment like the fact that the use of Remicade requires assistance by health personnel, whereas Enbrel and Humira can be administrated by the patients themselves at home. In the regressions we use Remicade as the reference product.[20]

The country-specific dummies (γ_c) capture all characteristics of national markets that are constant over time and common across the products, such as market (or population) size, health status of population (mortality and morbidity), health care system (public or private), funding schemes, etc. Importantly, the country-fixed effects also capture the prevalence of diseases that are relevant for treatment with anti-TNF drugs. For instance, the share of the population with rheumatism is likely to vary across countries, but not over time within a country. Norway is used as the reference country in the regressions.

The descriptive statistics show that the consumption of anti-TNF drugs increases over time in all countries in our sample. To account for this, we include a time trend ($\ln t$) in the regression. In this way we control for time variations in the consumption of anti-TNF drugs that are common across countries and brands.

The regression model also includes a set of explanatory variables. First, we include the (natural logarithm of) average price per DDD ($\ln P_{cit}$) of product i in country c at time t. We expect the consumption to decrease in price, but the correlation might be weak due to the presence of health insurance. As shown in Table 2, the copayments for anti-TNF drugs are either zero or very marginal relative to the treatment cost. Patients are therefore not

[20]Product characteristics that vary over time and are correlated with our explanatory variables can generate an endogeneity problem and lead to biased estimates. For instance, marketing effort may affect perceived product quality, which is likely to affect sales and prices in most markets. However, prices of anti-TNF drugs are regulated in most European countries, which implies that this kind of endogenity problem is less severe in our study.

very likely to respond much to price changes. However, the payer may impose cost-sharing incentives on the providers (hospitals or specialists), such as allocation of fixed budgets, to induce price responsiveness in the utilization of anti-TNF drugs.[21] Moreover, the payer may engage in negotiations with the pharmaceutical firms or regulate the price directly. Since we estimate the effect of price and not copayment on consumption, our demand elasticity measure includes both patient and provider/payer responses.

Our estimate on the price elasticity can, however, be biased due to the standard endogeneity problem related to prices and demand being determined simultaneously. On one hand, higher prices are expected to reduce demand, all else equal. On the other hand, higher demand implies that firms can profitably increase their prices. The estimate of the price effect on consumption of anti-TNF drugs is therefore likely to be downward biased. However, endogenity is not a crucial problem in our case, since the anti-TNF drug market is expanding during the period and pharmaceutical firms face restrictions on price increases due to regulation.

Second, we use (the natural logarithm of) GDP per (10,000) capita ($\ln GDP_{ct}$) for each country per year. GDP per capita is a measure of the average income level in each country. We expect a positive correlation between income and consumption of anti-TNF drugs, but the income elasticity of demand might be weak due to the presence of health insurance. On the other hand, the financing of expensive medicines, such as anti-TNF drugs, might be more generous in "richer" countries, i.e., countries with higher GPD per capita. Table 4 reports the annual averages of the GPD per capita variable. We see that GDP per capita varies both over time and across countries.

[Table 4 about here]

Third, we control for health expenditures by including a variable (HE_{ct}) measuring the

[21] A recent study by Dalen et al. (2012) finds that a change in the financing of anti-TNF drugs from central government (social insurance agency) to public hospital enterprises induced a shift in the consumption from the higher-priced Enbrel to the lower-priced Remicade. They argue this is due to the funding being based on a fixed hospital budget rather than regular social insurance payments with no expenditure caps.

total spending on health as a percentage of GDP in each country per year. It is reasonable to expect a positive correlation between total health expenditures and the consumption of anti-TNF drugs.[22] Countries that spend much on health in general are more likely to also spend more on anti-TNF drugs, which in turn would lead to a higher consumption of these drugs. Table 4 shows that there is also variation in health expenditures over time and across countries.

Fourth, we include a variable (I_{it}) that measures the number of indications each of the anti-TNF drugs are approved for by the European Medicines Agency (EMA) per period (month). The set of approved indications is a measure of market size. We expect a positive correlation between the number of approved indications and the consumption of anti-TNF drugs. The indication variable varies across products and over time, but is common across countries, since the EMA approvals apply to all countries in our sample. In Table 4 we report the number of approved indications for each product by end of year.[23]

Finally, the regression model includes an error term (ε_{cit}) that represents unobserved, time-varying factors that affect the consumption of anti-TNF drugs in the different countries. The explanatory variables are allowed to be correlated with the product- and country-specific effects, but not with error term.

5 Results

Table 5 below reports the results from the regressions.[24] To better understand the impact of the different explanatory variables, we start out with estimating a model including only country-specific effects, product-specific effects, and a time trend (model 1). Consistent with the descriptive statistics, the regression results show large cross-country variation in consumption of anti-TNF drugs. The consumption of anti-TNF drugs tends to be higher in the Nordic countries. Norway, which is the base country, has the highest consumption

[22] The anti-TNF drug expenditures are of course a part of the overall health expenditures, but the share is negible, so including health expenditures as an explanatory variable should not involve any endogeneity problems.

[23] See Table 1 for which diseases the three anti-TNF drugs are approved for at what time.

[24] The reason we have 2744 observations over 120 months (and not 3240) is that all three anti-TNF brands are not present in every period in every country, as can be seen from Table 3 (see also Section 3.1).

level among the countries in our sample. The per-capita consumption in Norway is 173 percent higher than in Italy, which has the lowest consumption level. However, compared with the descriptive statistics, the magnitude of the cross-country variation is substantially reduced. Indeed, country-specific time-invariant factors, such as disease prevalence, health care system, health status, etc., account for about half of the cross-country variation in per-capita consumption.

The results also show systematic differences in per-capita consumption across the three anti-TNF brands. We see that Remicade has a substantially higher market share than Enbrel and Humira. In model 1 the per-capita consumption of Remicade is estimated to be 74 and 102 percent higher than Enbrel and Humira, respectively. These are the average figures across all countries. The results also show a positive time trend, which is consistent with the descriptive statistics reported in the previous section.

[Table 5 about here]

Despite the fact that country-specific effects explain a substantial share of the cross-country variation in consumption of anti-TNF drugs, there is still large unexplained variation even between neighbouring countries. Within the Nordic countries, Denmark has 63 percent and Sweden 14.4 percent lower consumption than Norway. The same observation applies to Southern Europe, where Italy has 60 percent higher consumption of anti-TNF drugs than Spain.

To study the remaining cross-country variation in the diffusion of anti-TNF drugs, we successively introduce the explanatory variables in the regression analysis. In model 2 we include prices and the number indication approvals. The results show that both variables have the expected effects. We estimate a price elasticity of -0.45, which means that consumption of anti-TNF drugs is fairly inelastic.[25] Since copayments of anti-TNF drugs are close to zero, patients are not likely to respond much to price changes. The demand

[25]This estimate is perhaps somewhat high compared to more recent studies. For instance, Contoyannis et al. (2005), who use a policy experiment in Canada, report price elasticities in the range of -0.12 to -0.16. However, these studies estimate the effect of patients' copayment (and not the full price) on consumption.

elasticity is more likely due to payers imposing cost-containment incentives on providers, such as allocation of fixed budgets, or directly regulating or negotiating prices with the pharmaceutical companies.[26] A general problem when estimating price elasticities is that the estimates might be biased due to entry (or exit) of products. In our case Enbrel and particularly Humira enter national markets later than Remicade. Thus, the price elasticity estimate must be interpreted with some caution.

The effect of indication approvals on consumption is as expected. One extra approval increases the average per-capita consumption of anti-TNF drugs with almost 27 percent on average. Thus, increasing the set of approved indications is crucial for the diffusion of anti-TNF drugs, and is important in explaining the growth in consumption of these drugs.

Although we find that prices and indication approvals have significant effects on the consumption levels of anti-TNF drugs, the cross-country differences change only marginally when we include these variables in the regression analysis. The number of indication approvals vary across products, but are common to all countries, and are therefore not likely to influence the cross-country differences in consumption of anti-TNF drugs. Moreover, we observe from the descriptive statistics in Table 3 that the cross-country variation in prices of the anti-TNF brands is fairly low, which suggests that including prices in the regressions should not contribute much to explaining the cross-country variation in consumption.

Finally, in model 3, we include income (GDP per capita) and health expenditures (health spending as a percentage of GDP) in the regression analysis. Both variables have the expected effects. The income elasticity is 0.9, which seems reasonable due to the presence of health insurance. The results also show that one percentage point increase in the health expenditures (relative to GDP) increases the consumption of anti-TNF drugs by 11.1 percent on average.

More interestingly, the results show that the inclusion of income and health expenditures in the regression analysis has a significant effect on the estimated cross-country differences in the consumption of anti-TNF drugs. With the exception of Switzerland, controlling for income and health expenditures reduces the cross-country variation in con-

[26] See, for instance, Dalen et al. (2012) who offer some empirical evidence on this issue.

sumption. The magnitude of these reductions vary across countries. For some countries, such as Spain, Italy and Finland, the estimated consumption differences relative to Norway become substantially smaller. We also see that Sweden in fact has a higher consumption than Norway when controlling for income and health expenditures. For other countries, such as France and Germany, the reduction in the estimated consumption is more marginal. These findings are consistent with the cross-country variation in income and health expenditures, as reported in Table 4.

However, there are still considerable differences in consumption of anti-TNF drugs across countries, as reflected by the country dummy variables in model 3. In particular, Germany, Switzerland and Italy have substantially lower consumption than Norway even after controlling prices, income and health expenditures. There might be many country-specific (time-invariant) factors that can explain the residual cross-country differences. One such factor could be the prevalence of diseases subject to medical treatment by anti-TNF drugs. As mentioned above, rheumatism and psoriasis tend to be less frequent in Southern European countries. This could partly explain why Italy has a low consumption level, but does not explain the large difference between Italy and Spain. The same argument applies to other neighbouring countries, such as Denmark and Norway, that have significant differences in the per-capita consumption of anti-TNF drugs.

Another possible source for the observed cross-country variation in the diffusion of anti-TNF drugs can be the differences in the funding schemes. The countries in our sample vary according to whether the pharmaceutical expenditures are financed through taxation or social insurance contributions. They also vary according to whether insurance is provided publicly (by the state) or privately. The results show that there is a tendency that countries with social insurance schemes and private provision, such as Germany and Switzerland, have a lower consumption of anti-TNF drugs than countries that base the funding on taxation, with the exception of Italy.[27]

There are also differences according to the regulatory schemes. The strictness in the

[27] Unfortunately, we do not have information on (changes in) funding schemes over time within a country. This information would have made it possible to test the importance of funding schemes for the diffusion of anti-TNF drugs.

price control should be captured by the price variable included in the regression analysis (model 2 and 3). However, there are other regulatory instruments that may affect the diffusion of new medicines, such as the criteria for inclusion on the reimbursement list, medical guidelines, or other measures that influence the utilization of anti-TNF drugs. Such information is hard to obtain for specific drug therapies. However, if the regulatory schemes are fairly constant over time, the country-specific effects should capture the impact of different schemes.

6 Concluding remarks

Diffusion of new medicines is important for pharmaceutical firms' profits, but also for patients' access to new medical treatments. In this paper we have studied the cross-country diffusion of anti-TNF drugs across a set of European countries from the first launch in 2000 until becoming blockbusters in 2009. To examine the cross-country consumption patterns, we use of a data set with detailed product-level information about the sales of the three anti-TNF brands Remicade, Enbrel and Humira.

The descriptive statistics show substantial growth in the per-capita consumption of the anti-TNF drugs in all countries over the sample period, but reveal also very large variation across countries. Interestingly, the consumption differences between neighbouring countries, such as Spain and Italy or Norway and Denmark, are large. In order to explore the sources of the cross-country variation in the consumption of anti-TNF drugs, we estimate several multivariate regression models. We find that time-invariant country-specific factors (e.g., disease prevalence, demographics, health care system, etc.) explain substantial parts of the cross-country variation in consumption, but the residual differences are still large.

We therefore successively introduce sets of explanatory variables. First, we include prices and the number of approved indications for each of the three anti-TNF drugs in the different countries. Both variables have the expected effects on the per-capita consumption, but do not influence the cross-country differences in consumption. Second,

we include income (GDP per capita) and health expenditures (as a percentage of GDP) as explanatory variables. These variables influence the cross-country differences. With the exception of Switzerland, controlling for income and health expenditures lead to a reduction in the differences in per-capita consumption across countries. The remaining cross-country variation is therefore likely to be explained by unobserved factors that might have been changing over time, such as, for instance, medical guidelines, funding schemes, or marketing strategies by the pharmaceutical firms. We leave these issues to future research.

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Tables and Figures

Table 1: Indication approvals and marketing authorizations for anti-TNF drugs by EMA.

Indications	Date of issue of marketing authorization		
	Remicade (infliximab)	Enbrel (etanercept)	Humira (adalimumab)
Crohn's disease	13 August 1999	-	4 June 2007
Rheumatoid arthritis	27 June 2000	3 February 2000	8 September 2003
Ankylosing spondylitis	15 May 2003	16 January 2004	1 June 2006
Psoriatic arthritis	24 September 2004	5 December 2002	1 August 2005
Plaque psoriasis	29 September 2005	24 September 2004	19 December 2007
Ulcerative colitis	28 February 2006	-	-
Juvenile idiopathic arthritis	-	3 February 2000	25 August 2008

Table 2. Prescriptions, dispending channels and funding of anti-TNF drugs across countries, 2010 (IMS Health).

	Anti-TNF drug	Prescribers	Dispensing channels	Funding	Copayment
Denmark	Remicade	Hospital specialists	Hospitals	Regional government funds	No
	Enbrel	Community dermatologists	Hospitals and pharmacies	Regional government funds	Marginal (<1%)
	Humira	Community dermatologists	Hospitals and pharmacies	Regional government funds	Marginal (<1%)
Finland	Remicade	Hospital specialists	Hospitals	Central government (social insurance institute)	No
	Enbrel	Rheumatologists	Pharmacies	Central government (social insurance institute)	Marginal (4%)
	Humira	Rheumatologists	Pharmacies	Central government (social insurance institute)	Marginal (4%)
France	Remicade	Hospital specialists	Hospitals	National Health Service	No
	Enbrel	Private specialists	Pharmacies	National Health Service	No
	Humira	Private specialists	Pharmacies	National Health Service	No
Germany	Remicade	Hospitals and private specialists	Hospitals and pharmacies	Health insurance organizations and private insurance funds	No
	Enbrel	Hospitals and private specialists	Pharmacies	Health insurance organizations and private insurance funds	No
	Humira	Hospitals and private specialists	Pharmacies	Health insurance organizations and private insurance funds	No
Italy	Remicade	Hospital specialists	Hospitals	Regional government with national subsidy	No
	Enbrel	Hospital specialists	Hospitals and pharmacies	Regional government with national subsidy	No
	Humira	Hospital specialists	Hospitals and pharmacies	Regional government with national subsidy	No
Norway	Remicade	Hospital specialists	Hospitals	Central government	No
	Enbrel	Hospital and private specialists	Hospitals and pharmacies	Central government	No
	Humira	Hospital and private specialists	Hospitals and pharmacies	Central government	No
Spain	Remicade	Hospital specialists	Hospitals	Central government	No
	Enbrel	Hospital specialists	Hospitals	Central government	No
	Humira	Hospital specialists	Hospitals	Central government	No
Sweden	Remicade	Hospital specialists	Hospitals and pharmacies	Regional government with national subsidy	No
	Enbrel	Hospital specialists	Hospitals and pharmacies	Regional government with national subsidy	Marginal (<1%)
	Humira	Hospital specialists	Hospitals and pharmacies	Regional government with national subsidy	Marginal (<1%)
Switzerland	Remicade	Hospital and private specialists	Hospital, pharmacy and self-dispensing doctors	Health insurance funds	Marginal
	Enbrel	Hospitals and private specialists	Hospital, pharmacy and self-dispensing doctors	Health insurance funds	Marginal
	Humira	Hospitals and private specialists	Hospital, pharmacy and self-dispensing doctors	Health insurance funds	Marginal

Table 3: Descriptive statistics.

Country	Molecule	Drug	In the data set	Average price (national currency)	Average price (EURO)	Average DDD per month	Average DDD per 1000 inhabitants (per month)	Proportion hospital sales	Proportion parallel import
Norway (hospital and retail data)	INFLIXIMAB	REMICADE	Jan 2000	156.63	19.37	76715.77	164.29	0.76	0
	ADALIMUMAB	HUMIRA	Oct 2002	297.59	36.59	34582.32	73.53	0.02	0
	ETANERCEPT	ENBREL	Jan 2000	295.77	36.63	64286.31	137.78	0.01	0
		ALL DRUGS	-	245.66	30.40	166074.30	355.38	0.29	0
Sweden (combined data only)	INFLIXIMAB	REMICADE	Jan 2000	185.72	19.96	125377.80	138.34	-	0
	ADALIMUMAB	HUMIRA	Sep 2003	382.66	40.41	61073.32	66.82	-	0
	ETANERCEPT	ENBREL	May 2000	368.67	39.58	81710.46	89.82	-	0.01
		ALL DRUGS	-	295.05	31.68	243044.30	267.48	-	0.003
Denmark (combined data only)	INFLIXIMAB	REMICADE	Jan 2000	156.68	21.04	56063.78	102.93	-	0
	ADALIMUMAB	HUMIRA	Oct 2003	319.31	42.86	39790.71	72.78	-	0
	ETANERCEPT	ENBREL	Jul 2003	308.26	41.38	36438.28	66.75	-	0
		ALL DRUGS	-	222.96	29.94	104617.80	191.80	-	0
Finland (hospital and retail data)	INFLIXIMAB	REMICADE	Jan 2000	20.62	20.62	41948.44	79.74	1.00	0
	ADALIMUMAB	HUMIRA	Mar 2004	38.71	38.71	37808.08	71.51	0.03	0
	ETANERCEPT	ENBREL	Jun 2000	39.13	39.13	26413.42	50.05	0.29	0
		ALL DRUGS	-	31.24	31.24	89316.01	169.42	0.51	0
Germany (hospital and retail data)	INFLIXIMAB	REMICADE	Jan 2000	22.48	22.48	238780.93	29.01	0.24	0.05
	ADALIMUMAB	HUMIRA	Sep 2003	52.82	52.82	269399.60	32.77	0.01	0.10
	ETANERCEPT	ENBREL	May 2003	46.78	46.78	242120.43	29.42	0.01	0.10
		ALL DRUGS	-	37.65	37.65	641432.70	77.96	0.10	0.08
France (hospital and retail data)	INFLIXIMAB	REMICADE	Jan 2000	24.26	24.26	384132.40	60.65	1.00	0
	ADALIMUMAB	HUMIRA	Jul 2003	41.74	41.74	219419.11	34.43	0.29	0
	ETANERCEPT	ENBREL	Jan 2000	32.91	32.91	227589.25	35.87	0.37	0
		ALL DRUGS	-	31.40	31.40	754344.40	118.90	0.59	0
Spain (hospital and retail data)	INFLIXIMAB	REMICADE	Jan 2000	20.82	20.82	277832.93	63.15	1.00	0
	ADALIMUMAB	HUMIRA	Mar 2004	37.53	37.53	189223.02	42.13	1.00	0
	ETANERCEPT	ENBREL	Apr 2001	33.41	33.41	258574.59	57.77	0.91	0
		ALL DRUGS	-	28.52	28.52	614465.70	138.29	0.97	0
Italy (hospital and retail data)	INFLIXIMAB	REMICADE	Apr 2000	18.26	18.26	232429.55	39.43	1.00	0
	ADALIMUMAB	HUMIRA	Jul 2004	34.36	34.36	141886.17	23.88	1.00	0
	ETANERCEPT	ENBREL	May 2001	34.51	34.51	180303.32	30.43	1.00	0
		ALL DRUGS	-	27.15	27.15	460918.90	77.95	1.00	0
Switzerland (hospital and retail data)	INFLIXIMAB	REMICADE	Mar 2000	36.54	23.70	54417.17	72.38	0.84	0
	ADALIMUMAB	HUMIRA	Jul 2003	59.88	38.26	38921.66	51.46	0.08	0
	ETANERCEPT	ENBREL	Jan 2000	57.56	37.29	22415.71	29.77	0.32	0
		ALL DRUGS	-	50.03	32.38	101225.00	134.39	0.45	0

Table 4. Descriptive statistics per year. Number of indications, GDP per capita (US dollars) and health spending as percentage of GDP

		2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Number of indications (measured at the end of each year)	Remicade	2	2	3	3	4	5	6	6	6	6
	Enbrel	2	2	3	3	5	5	5	5	5	5
	Humira	0	0	0	1	1	2	3	5	6	6
Norway.	GDP per capita	35860	37530	39200	40010	53200	62760	68830	76950	85580	86130
	Health spending as percentage of GDP	8.4	8.8	9.8	10.0	9.7	9.1	8.6	8.9	8.6	9.6
Sweden	GDP per capita	29490	27670	27190	30680	37190	42920	45680	48900	52390	48830
	Health spending as percentage of GDP	8.2	8.9	9.2	9.3	9.3	9.1	8.9	8.9	9.2	10.0
Denmark	GDP per capita	31830	30620	30060	33940	41560	48590	52250	54700	59040	58350
	Health spending as percentage of GDP	8.7	9.1	9.3	9.5	9.7	9.8	9.9	10.0	10.3	11.5
Finland	GDP per capita	25440	24810	24660	27640	33980	38550	41130	44200	47960	46540
	Health spending as percentage of GDP	7.2	7.4	7.8	8.2	8.2	8.4	8.4	8.1	8.4	9.2
Germany	GDP per capita	25300	23870	22850	25400	30750	34780	37210	39440	42470	42540
	Health spending as percentage of GDP	10.3	10.4	10.6	10.8	10.6	10.7	10.6	10.5	10.7	11.6
France	GDP per capita	24270	23080	22330	25130	30420	34850	36760	38900	41940	42390
	Health spending as percentage of GDP	10.1	10.2	10.5	10.9	11.0	11.1	11.0	11.0	11.1	11.8
Italy	GDP per capita	21010	20310	19910	22310	26980	30880	32560	34030	35760	35570
	Health spending as percentage of GDP	8.1	8.2	8.3	8.3	8.7	8.9	9.0	8.7	9.0	9.5
Spain	GDP per capita	15420	15060	15120	17570	21590	25450	27490	29400	31850	32140
	Health spending as percentage of GDP	7.2	7.2	7.3	8.2	8.2	8.3	8.4	8.5	9.0	9.5
Switzerland	GDP per capita	41160	38690	36670	43480	51290	58530	60610	59040	59340	66630
	Health spending as percentage of GDP	10.2	10.6	10.9	11.3	11.3	11.2	10.8	10.6	10.7	11.4

Data source: GNP: http://data.worldbank.org/indicator/NY.GNP.PCAP.CD. Health spending: http://www.oecd.org/health/

Table 5. Regression results, consumption of anti-TNF drugs (DDD per 10,000 capita).

	(1)	(2)	(3)
Number of indication approvals	-	0.268*** (0.013)	0.193*** (0.011)
Ln price	-	-0.445*** (0.135)	-0.328*** (0.130)
Ln GDP per capita	-	-	0.896*** (0.126)
Ln health spending as percentage of GDP	-	-	0.111*** (0.027)
Base: Remicade			
Enbrel	-0.742*** (0.027)	-0.534*** (0.080)	-0.583*** (0.078)
Humira	-1.024*** (0.028)	-0.404*** (0.088)	-0. 497*** (0.083)
Base: Norway			
France	-1.210*** (0.048)	-1.189*** (0.046)	-0.968*** (0.101)
Sweden	-0.144*** (0.050)	-0.124*** (0.049)	0.230** (0.074)
Denmark	-0.630*** (0.047)	-0.601*** (0.047)	-0.460*** (0.066)
Finland	-0.777*** (0.052)	-0.764*** (0.049)	-0.221*** (0.087)
Germany	-1.497*** (0.046)	-1.398*** (0.059)	-1.177*** (0.108)
Italy	-1.731*** (0.055)	-1.765*** (0.050)	-1.039*** (0.118)
Spain	-1.137*** (0.054)	-1.145*** (0.048)	-0.221* (0.129)
Switzerland	-1.211*** (0.052)	-1.177*** (0.054)	-1.256*** (0.079)
Time trend (ln period)	1.209*** (0.029)	0.782*** (0.036)	0.629*** (0.049)
Constant	0.273** (0.128)	2.280*** (0.411)	0.228 (0.455)
R^2	0.772	0.821	0.823
Observations	2744	2744	2744

***: significant at the 1% level, **: significant at the 5% level, *: significant at the 10% level,

Figure 1. Consumption levels in DDD per capita.

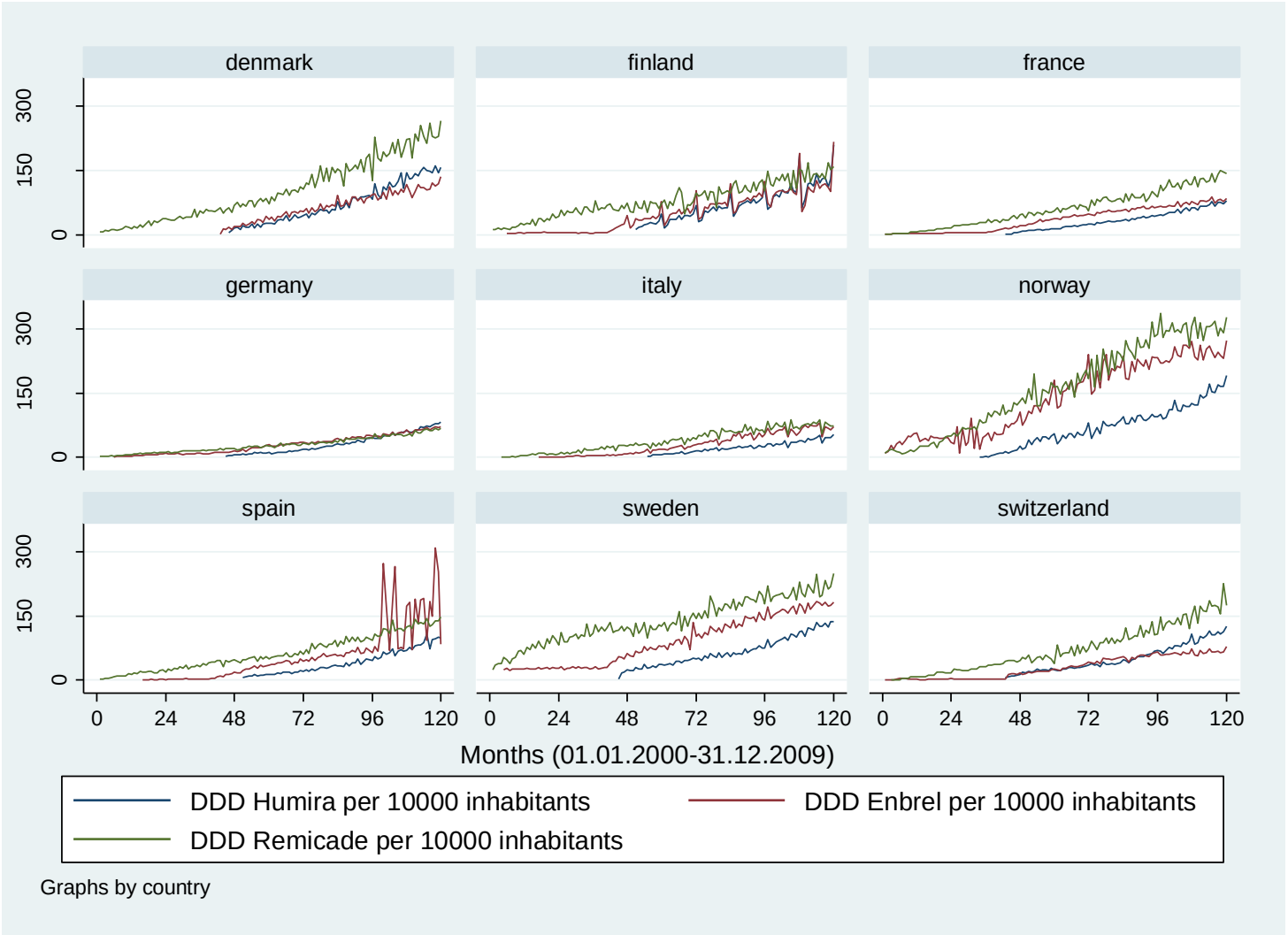
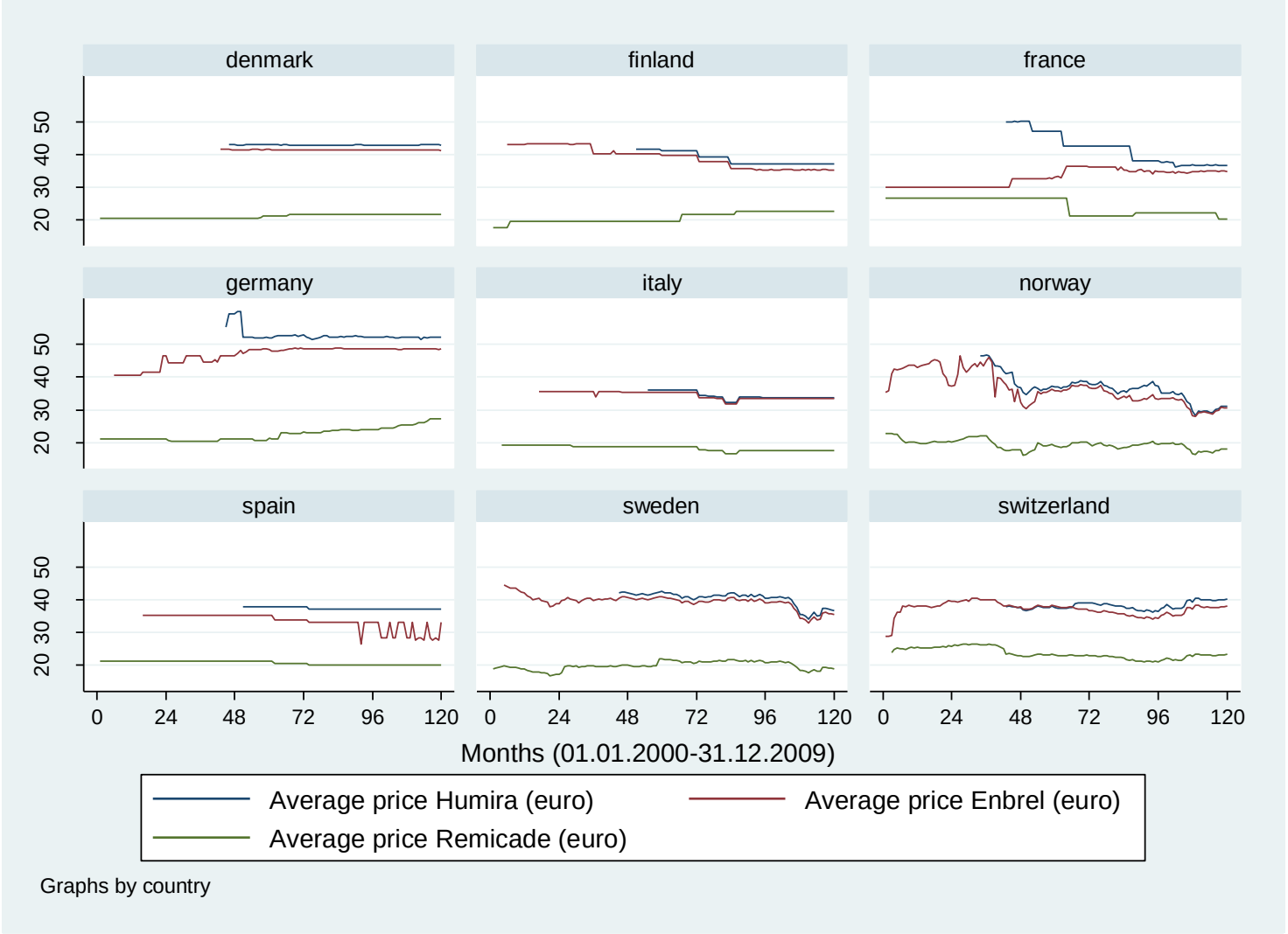


Figure 2. Prices per DDD in Euros.



Response to Reviewer 1

We are grateful for your careful review of our paper. Below we explain how we have dealt with your comments and suggestions as they appeared in your report. The reply is in bold text.

1) Entry. Remicade and Enbrel entered the market around year 2000, while Humira entered the market in 2003. Is entry affected by some of the explanatory variables in the regression? If yes, the estimates of the regression might be biased. **This is a relevant comment. The time of entry is mainly related to the time of the discovery of a new medicine. This applies to the anti-TNF drugs, where Humira was discovered later than Remicade and Enbrel. However, the launch in national markets might be delayed if entry cost is higher than the expected profits. In our data we observe launch delay for Enbrel and Humira in some countries. We cannot rule out that the launch delay is correlated with some of our explanatory variables, such as the price variable. Entry (or exit) of products (brands) is a general problem for most empirical studies measuring price effects on consumption (or demand elasticities). To deal with this issue, one needs an instrument that affects prices but not consumption. This is hard to obtain and beyond the scope of our study. The fact most countries regulate prices may reduce the concern about biased price estimates, but since we cannot rule this out, we now explicitly mention the potential problem related to correlation between entry and price on page 18.**

2) Price is one of the explanatory variables. In many markets unobserved characteristics (here say, side effects) are priced out in the market. If this is the case here, then the error term and/or the product-specific effects may be correlated with price. A statistical check on this should be included in the paper. **Time invariant unobserved characteristics, such as side-effects, are capture by the product-specific dummies. Correlation between the product-specific dummies and the price variable is allowed in our specification, and should not lead to biased estimates. However, correlation between the error term and the price variable can be problematic. We are not aware of any statistical test for checking this (endogeneity) problem besides the Durbin-Wu-Hausman test, but then we need a valid instrument, which hard to find in our case. On the other hand, the endogeneity problem might be less severe in our case, since prices are regulated in most of the countries in our sample. We now comment on this potential problem in footnote 20 on page 14.** Moreover, and discussed at some length in the paper, the funding scheme of the drugs vary across countries and time. These varying funding schemes may affect the impact of price on total consumption and market shares. One way of dealing with this is to interact price with dummies reflecting types of funding schemes. **Unfortunately, we do not have information about (changes in) funding schemes over time within a given country. Thus, it is not possible to identify the effect of funding schemes in our model with country-specific effects. We could drop the country-specific dummies and instead use dummies for funding scheme, which in turn could be interacted with price. We have run such a model, but the results do not appear reasonable. Moreover, we do not think it is a good idea to ignore the country-specific effects, as this would most likely introduce a strong endogeneity problem. Using only dummies for funding schemes implies that we assume that countries like Norway and Spain (with a central government funding) are similar and do not vary according to unobserved characteristics. An alternative approach is to interact the price variable with the country-specific dummies. The results, which are reported in the table below, indicate no tendency for countries with similar funding scheme to have similar price effects. We do not think this is very surprising since the countries with similar funding schemes are likely to differ in other important dimensions that may influence the consumption. We have**

therefore decided to not include this in the paper (unless you think otherwise). However, we offer a brief discussion of this issue on page 19 and footnote 27.

3) It is mentioned in the paper that the error terms in the regression are allowed to be correlated with the product- and country specific dummies. No specification of this possible correlation nor empirical results are shown. **Clearly, this was an incorrect statement. What we meant was that the explanatory variables are allowed to be correlated with the product- and country-specific effects, but not with the error term. This has now been corrected (see page 16).**

4) GDP per capita and total health expenditure relative to GDP are among the explanatory variables. These two variables vary across years, while the left hand side variables in the regression vary across months. This is ok, but because a country specific dummy is among the explanatory variables these dummies could be correlated with GDP and total health expenditure relative to GDP. The reason why is that the few years of observations of GDP and health expenditure across countries may function as sort of country dummies in an observation set which otherwise is on a monthly basis. **We would be worried about this if GDP and HE were fairly time invariant. However, this is not the case. We have produced a new table (Table 4) where we report GDP and HE per year. As the table shows, there is considerable variation over time in both variables within each country. In the regressions we utilize only within country variation of the explanatory variables, and find that GDP and HE have significant effects on per-capita consumption. Thus, we do not think this is a major problem in our paper. In the revised version we now include Table 4 and comment on the variation in these two variables (see page 15-16).**

5) The results make sense (there is a misprint on page 17, the income elasticity is +0.96, not -0.96), although I find the price elasticity to be on the rather high side, given the fact that the agent pays a rather small fraction of the price. So, what is the interpretation of the price coefficient: Is it related to the response among patient, or is it a result of a bargaining between the authorities and the pharmaceutical firms, or is it due to switching over time between the three drugs? **We agree that the price elasticity may be on the high side. However, most of the previous studies focus on the demand responses to changes in copayments (consumer price) rather than the full price (producer price). Since the copayments for anti-TNF drugs are really small (compared to the full price), we think the price elasticity is mainly driven by cost containment incentives imposed by the payers on the providers (hospitals or specialists). It can also be due to negotiations or regulation. We now discuss this more carefully in the paper; see pages 14-15 and 17-18, as well as footnote 25.**

Table. Regression results, consumption of anti-TNF drugs (DDD per 10,000 capita).

Number of indication approvals	0.188*** (0.011)
Ln price	-0.414*** (0.215)
Ln GDP per capita	0.860*** (0.122)
Ln health spending as percentage of GDP	0.120*** (0.027)
Base: Remicade	
Enbrel	-0.251*** (0.097)
Humira	-0. 240** (0.106)
Ln price * France	-0.545*** (0.174)
Ln price * Sweden	-0.586*** (0.153)
Ln price * Denmark	-0.543*** (0.136)
Ln price * Finland	-0.857*** (0.150)
Ln price * Germany	0.307** (0.135)
Ln price * Italy	-0.528*** (0.161)
Ln price * Spain	-1.060*** (0.152)
Ln price * Switzerland	-0.993*** (0.183)
Base: Norway	
France	0.976*** (0.554)
Sweden	2.233*** (0.501)
Denmark	1.420*** (0.417)
Finland	2.709*** (0.491)
Germany	-2.187*** (0.402)
Italy	0.678*** (0.522)
Spain	3.310*** (0.507)
Switzerland	2.163*** (0.600)
Time trend (ln period)	0.635*** (0.048)
Constant	0.275 (0.725)
R^2	0.839
Observations	2744

***: significant at the 1% level, **: significant at the 5% level, *: significant at the 10% level

Response to Reviewer 2

1. The following references cited in the paper are not reported in the reference list:
- Page 1 (note 1): Miller and Frech (2004) **This is now corrected. (It should have been Frech and Miller, not Miller and Frech).**
- Page 1 (note 2): Abbott, Merck, Amgen and Pfizer for 2011. **These are annual reports that are publicly available at each company's webpage. This is now explained in the footnote.**

2. pag 18 There is a reference to Table A in appendix, but this table is inserted in appendix as Table A.1. **We have now included a new version of the table in the paper (Table 4).**

3. Table 3 does not include a complete list of descriptive statistics. It is necessary to give descriptive statistics of all the variables included in the estimation. **This is now done in Table 4. Table 3 and 4 should cover the full list of descriptive statistics.**

To estimate the different regression specifications, the authors added to the data set the variable GDP (the natural logarithm of GDP per (10000) capita) for each country and period, the variable (Iit) number of indications, the variable (HEct) measuring total spending on health as percentage of GDP and seasonal variations by dummies for quarter (Qt)..
More details on these variables are necessary:
- In the paper at page 15, row 29, it is said that GDP per capita is for each country (c) and for each period (t), but Table A1 reports the descriptive statistics of GDP and total health expenses without specifying the reference year (or if they are the average over years). Furthermore, it is necessary to mention the source of data. **We have now added a new Table 4 reporting GPD and HE for each year. The table also includes a footnote with the data sources.**

- It is also necessary to give the source of the variable (HEct) measuring total spending on health as percentage of GDP and if it is on yearly base or period (t) or an average over 2000-2009 (page 15, row 45 and Table A1). **We now report the source in Table 4. We have also modified the text explaining that GDP and HE are measured at a yearly basis, while the others at a monthly basis; see the text associated with Table 4 and Footnote 19).**

- Page 16, row 10: it is necessary to describe with more details how the variable (Iit) (i.e. number of indications) has been generated. Also, the whole sentence is not clear enough. **This is now done. See page 16 and Table 4. We also explain the estimate more carefully (see page 18).**

- Pag. 14, rows 41- 43. I wonder if it is useful to include the dummies for quarters to control for seasonal variations since anti-TNF drugs are used in chronic diseases. **We agree and have therefore estimated the regression without controlling for seasonal effects (see Table 5 and specification of model on page 13).**

Important remark: Data of the data set are on monthly base, and the above variables are presumably on year base. In the estimation, does the author include the value reported in table A.1 taking into account the year/period or not? Specify it. **In the estimation we use yearly information on GDP and HE. We now explain this more clearly in the paper. See Footnote 19 and the text associated with Table 4.**

4. Table 2. For Switzerland the authors indicate in the column copayment 'Marginal' without indicating

any value. Specify what it means. **IMS health only reported that the copayment was marginal in Switzerland, and did not provide an estimate of the copayment share. Unfortunately, we have not been able to get this figure from IMS or from other sources.**

5. Table 4. It is better to specify the significant level associated to the symbols ***, **, * (i.e. 1%, 5%, 10%). I also wonder what selection has been done on data. It would be better to specify how the authors end up with 2744 observations over 120 months. **We now use the significant symbols as suggested. The reason that end up with 2744 over 120 months is that the three anti-TNF drugs are not present in every period in every country. We now explain this in Footnote 24.**

6. Furthermore, I think that 'copayment' is important in the diffusion of drug, but among the regressors the authors do not include any variable regarding the copayement (see table 2 column 6). **The main reason for not including this variable in the regression is that we do not have information of (changes) in the copayment over time within the countries in our sample. Thus, with country-specific effects we cannot identify the impact of copayments. Moreover, the copayments are usually related to price, which implies that our price variable should pick up the impact of copayments on consumption. However, the copayments for anti-TNF drugs are really small and in many countries actually zero, which means that the copayments are likely to play a limited role for consumption of these drugs. We now discuss this more carefully in the paper; see pages 14-15 and 17-18.**