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The impact of pricing and patent expiration on the demand for pharmaceuticals: an examination of the use of broad-spectrum antimicrobials

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The impact of pricing and patent expiration on the demand for pharmaceuticals: an examination of the use of broad-spectrum antimicrobials

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Abstract

The aim of the analysis was to determine whether demand in Germany for antibiotics is driven by prices that drop considerably when generic substitutes become available. A time-series approach was therefore carried out to explore price elasticities of demand for two different classes of broad-spectrum antimicrobials (fluoroquinolones and cephalosporins) using data on ambulatory antibiotics prescribed on the German statutory health insurance scheme and data on in-hospital antibiotic use in a German teaching hospital. In short, we attempted to explain demand for different antibiotics based on changes in price, patent expiration and hospital-wide morbidity. The analysis demonstrates that patent expiration is followed by substantial decreases in the price of antibiotics. In the outpatient sector, all antibiotics included in the analysis showed significant negative own-price elasticities of demand. However, in the hospital settings, significant own-price elasticities were only determined for some antibiotics although price decreases were stronger than in the outpatient sector. We conclude that price dependence of demand for antimicrobials is present both in the ambulatory and the hospital setting However, it is especially problematic in the hospital setting because price differences among the antibiotics observed are particularly small compared to the overall cost of hospitalisation.

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Background

Antibiotics are among the most frequently used pharmaceuticals today. Since the development of penicillin, antibiotic use in all parts of the health care system has contributed significantly to reducing the likelihood of dying from an infectious disease (WHO, 2000). However, consumption tends to deplete the efficacy of the antibiotic in combating bacterial infections because the bacteria develop resistance to the antibiotic (Levy, 1992; Levy and Marshall, 2004). Accordingly, recent studies have found that use of broad-spectrum antimicrobials such as cephalosporins and fluoroquinolones influences the emergence and spread of resistant pathogens in hospital settings (Aldeyab *et al.,* 2009; Aldeyab *et al.,* 2008; Kaier *et al.,* 2009a; Kaier *et al.,* 2009b; Vernaz *et al.,* 2008). Interestingly, patents on many cephalosporins and fluoroquinolones have expired in the last two decades, and entry into the market of generics has resulted in massive price decreases in both the branded and generic version of the antibiotic. The question is whether lower prices also changes demand for antibiotics.

Like most pharmaceuticals, antimicrobials are unusual in that the consumer of the product is typically not the person deciding which product to consume (Eisenberg, 2002). Physicians have wide choice in the in the drugs they prescribe. Over the past decades, more and more prescribing guidelines have emerged to assist physicians in their decision, including information about the prices of the different agents (Frank and Tacconelli, 2009).

The aim of the present analysis was to determine whether demand for antibiotics is driven by prices that decrease significantly when generic substitutes become available. Therefore, demand for antibiotic agents was analyzed both in the ambulatory setting in Germany and in the setting of a single German teaching hospital.

Health insurance is mandatory in Germany. Patients are generally covered by statutory health insurance (SHI), and, as such, enjoy full coverage on in-hospital medication. Hospitals, on the other hand, have fixed reimbursement rates based on diagnosis-related groups (DRGs), a system implemented in January 2003, and the sole system by which recurrent expenditure is now financed in hospitals. Both in the ambulatory and the in-patient sector, benefits are provided as benefits-in-kind to patients covered by statutory health insurance, i.e. nearly 90% of the German population. In the ambulatory sector, however, patients have to make a small co-payment (between €5 and €10) for every prescription. In Germany, ambulatory care physicians are generally self-employed, and the SHI reimburses fixed budgets for pharmaceuticals the size of which depend on the number and age of the patients. Pharmaceutical price regulation differs between the inpatient and the ambulatory sector. In both sectors, prices are determined by the manufacturer without any negotiations involving government agencies, direct price or profit controls. Hospitals, can however, negotiate prices with wholesalers or manufacturers (Busse and Riesberg, 2004).

For the analysis presented here, data on annual SHI-related antibiotic consumption from 1991 through 2007 were consulted, while data on in-hospital antibiotic use at University Medical Center Freiburg, a large teaching hospital in South-West Germany, were available on a monthly base over an eight year period (2000 – 2007). The focus of the analysis relies on the antimicrobial classes of cephalosporins and fluoroquinolones because (i) they were found to be responsible for the spread of resistance (Aldeyab *et al.,* 2009; Aldeyab *et al.,* 2008; Kaier *et al.,* 2009a; Kaier *et al.,* 2009b; Vernaz *et al.,* 2008), and (ii) several generic cephalosporins and fluoroquinolones have entered the German pharmaceutical market in recent years.

Methods

At University Medical Center Freiburg (UMCF), a 1600 bed tertiary care teaching hospital with approximately 54,000 inpatient admissions annually, antibiotic agents are purchased centrally through the hospital pharmacy. Generic agents are regarded to be perfect substitutes for the existing branded version. Accordingly, the hospital pharmacy dispenses only one label of an agent for in-hospital use, either the generic or brand-name because it is able to purchase branded agents with discounts whenever a generic equivalent becomes available. In contrast, in the outpatient sector, substantial price differences exist between the brand-name and generic versions of the same antibiotic (Griliches and Cockburn, 1994),

The hospital regularly pharmacy informs physicians on the daily cost of medication in a frequently updated booklet of drugs. These estimated prices are also available in in-hospital guides to antibiotic therapy (Frank, 2008; Frank and Tacconelli, 2009).

A number of structural reforms were introduced from 1993 aimed at curbing spending on pharmaceuticals in ambulatory care by setting global budgets on expenditure for physician or the Physicians' Associations. The Act on the Limitation of Pharmaceutical Expenditure passed in 2002 also obliges pharmacists to substitute with lower-priced preparations unless the physician explicitly opposes it (*aut idem* regulation) (Busse and Riesberg, 2004).

Based on German payment and reimbursement schemes, we assume that demand for antibiotics both in the ambulatory and in the hospital settings, is only dependent on the physicians' choice of antibiotic. As stated above, antibiotic treatment is not fully reimbursed in Germany; rather, it is covered by budgets determined by other factors (DRGs or ambulatory per-capita budgets for pharmaceuticals). Accordingly, we presume that a physician' decision to prescribe an antibiotic will be guided by financial incentives. We follow the hypothesis that antibiotic use may be treated as consumption of ordinary goods, suggesting a negative own-price elasticity of demand.

In the analysis presented here, we focussed on whether demand for antibiotics is driven by decreasing prices when generic substitutes are available, and not on whether these substitutes are actually used because (1) the price of branded agents decreases after patent expiration as hospital pharmacies are able to purchase branded agents with discounts when generics are available, and (2) limited budgets put physicians under pressure to prescribe the cheapest drugs available (1993 – 2001) or pharmacists are obliged to substitute expensive preparations with low-price generics, (2002 until now).

Data collection

Annual data on antibiotics prescribed on the German statutory health scheme are routinely collected for the ambulatory sector by the Scientific Institute of General Health Insurance (WIdO), Bonn, Germany, and were available from 1991 until 2007. At UMCF, monthly quantities and the prices of all antimicrobial drugs delivered to each hospitalization unit were exported from the pharmacy accounting system. In both analyses (price elasticities in ambulatory care and in the hospital), antibiotic use was expressed in defined daily doses (DDD) following the definition of the WHO ATC index, in order to allow for a comparison of the different antimicrobial agents used. Prices were expressed in Euro (€) per DDD for each antimicrobial agent. Weighted averages of the prices were calculated for cases where different packaging sizes coexisted. All prices were CPI-deflated (2005=1). The dates of entry of the generics into the German pharmaceuticals market were derived from data on drug approval.

In Germany, the rate at which antibiotics are used in ambulatory care settings falls within the lower third of EU countries (de With *et al.,* 2004; Goossens *et al.,* 2005). Upper boundaries in regional variation in antibiotic use are still much lower than values for high-use countries like France, Spain and Portugal. Hospital antibiotic use, appears to be in the range of that reported for other countries (de With *et al.,* 2004).

Study design

A simple time-series approach was carried out to explore price elasticities of demand for the different antimicrobial agents. Multivariate ordinary least squares regressions were computed with quantities of one agent as the dependent variable and the prices of the agent as independent variable. Furthermore, the effect of patent expiration was integrated into the analysis. In the present work, the focus was to determine whether the entry of competing generic agents into the German pharmaceutical market has changed demand for the antimicrobial agent as a whole. To evaluate the effect of market entry of generics, we created dummy variables, with 0 and 1 respectively representing pre-generic periods and periods with generics available on the market.

For in-hospital antibiotic use at UMCF, we generated data on overall morbidity during the study period. In Germany, the expected care workload per patient is classified according to 'general nursing care' categories (Zerbe and Heisterkamp, 1995). According to this statistic, a series of the hospital-wide expected care workload, expressed in minutes of care per month, is available for the whole study period and was integrated in the analysis as an additional independent variable representing overall patient-morbidity at UMCF.

In the hospital setting, the physician's choice of a specific antimicrobial agent $q_{D,d}$ is described as follows:

(1) $$\Delta \log(q_{D,d}) = \eta_{D,d} + \vartheta_{D,d} g_{D,d} + \xi_D \Delta \log(R_D) + \delta_{D,d} \Delta \log p_{D,d} + \delta_m \Delta \log(m)$$

D stands for the class of antibiotics with a varying number (*d* = 1,2,3,…,*n*) of antimicrobial agents, expressed in DDDs per 1000 patient days. The variable *g* represents the dummy variable market entry of the generics. Overall demand was not assumed to be constant, but to vary according to *R*, which reflects the total revenue of the respective class of antibiotics. The variable $p_{D,d}$ reflects the price of the explained variable and *m* represents the hospital-wide expected care workload.

In the ambulatory sector, the physician's choice was formulated analogously to the hospital setting, with the small difference that no specific morbidity-variable was used, and the absolute level of antibiotic consumption (not relative to the number of patients) was used as the dependent variable.

To obtain stationarity, first-order differencing was used for all input series except the dummy variables. The estimations were tested for multicolinearity (especially between R_D and $p_{D,d}$). The Akaike Information criterion and determination coefficient, the adjusted R^2, were estimated to inform about the goodness of fit of the different analyses. Robust standard errors were calculated using the heteroskedasticity and autocorrelation consistent Newey-West estimator. All the analyses were conducted using the Eviews statistical package (Eviews 5.0, QMS, Irvine, CA, USA).

Results

In-hospital antibiotic use at University Medical Center Freiburg (2000 – 2007)

At UMCF, both overall use of antibiotics and hospital-wide morbidity increased ($p<0.001$) over the study period (January 2000 through October 2007). In 2003, the hospital reimbursement system in Germany was reformed and the DRG case-based lump sum system implemented. However, the change in the reimbursement-system was not associated with a change in demand for antimicrobial agents.

At UMCF, two second-generation cephalosporins were administered for oral application during the study period: cefuroxim-axetil and cefaclor (See Table 1). Generic preparations of the two antibiotics have been widely available on the German pharmaceutical market since 1999 (cefuroxim-axetil) and 1994 (cefaclor). In March 2003, the hospital pharmacy switched from purchasing the branded drug cefuroxim-axetil to purchasing a generic version, which resulted in a substantial decrease in the price per DDD. As shown in Table 2, demand for cefuroxim-axetil (oral application) showed a negative own-price elasticity. In contrast, no generic second-generation cephalosporins for parenteral application were available on the German pharmaceutical market. However, the prices of the two agents varied during the study period and our analysis shows that these varying prices also inversely affect demand for the antibiotic agents.

Three third-generation cephalosporins were in use at UMCF during the study period: cefotaxime, ceftazidime and ceftriaxone, all available for parenteral application only. The two main agents ceftazidime and ceftriaxone faced entry of generics into the German market in January 2004 (ceftazidime) and July 2002 (ceftriaxone). This did not change the fact that the hospital pharmacy at UMCF continued to purchase the branded versions of the two agents but led to a delayed drop in the price of the branded agents. Entry of generics into the German pharmaceutical market showed no influence. As shown in Table 2, only use of ceftazidime corresponded to changes in the price that dropped from around €35 per DDD in 2003 to around €12 per DDD in 2007.

Three fluoroquinolones for oral application were in use at UMCF during the study period: ciprofloxacin, levofloxacin, which was introduced at UMCF in March 2001 and norfloxacin. Generics were available for the main agent ciprofloxacin from the beginning of July 2001, which resulted in an immediate and substantial decrease in the price of ciprofloxacin, while the price of levofloxacin and norfloxacin remained mostly stable (see Figure 1). As for third-generation cephalosporins, the hospital pharmacy at UMCF continued to purchase the branded version of ciprofloxacin over the whole study period. Demand for the three agents was correlated with the overall revenue generated from prescription of the class of antibiotic and our analysis showed a negative own-price elasticity for ciprofloxacin, meaning that demand for ciprofloxacin increased due the price of the antimicrobial agent decreasing (see Table 2). This is also true of demand for parenteral ciprofloxacin, which was confronted with entry into the German pharmaceutical market in September 2006 of generic ciprofloxacin. The price of parenteral ciprofloxacin decreased substantially from around €33 in September 2006 to around €6 in December 2006, while the price for levofloxacin was relatively stable. Again, only the branded version of ciprofloxacin was in use over the whole study period.

Outpatient antibiotic use in Germany (1991 – 2007)

During the study period (1991 – 2007) outpatient antibiotic use was on average 279522 DDDs and neither showed an increasing nor a decreasing trend. An average of only 17 008 DDDs of second-generation cephalosporins and 22 516 DDDs of fluoroquinolones were used annually, both of which showed an increasing trend over time ($p<0.001$). Second-generation cephalosporin use was dominated by the agents cefaclor and cefuroxim (see Table 3). Demand for these agents was influenced by entry of generics into the German market in March 1994 (ceftaclor) and November 1999 (cefuroxim). Fluoroquinolone use in Germany was dominated by the agents ciprofloxacin, norfloxacin and ofloxacin. Later during the study period, the branded agents levofloxacin and moxifloxacin entered the German market in 1998 and 1999, respectively. However, in spite of the fact that new competing substances had become available, ciprofloxacin use nevertheless increased substantially because entry in August 2001 (See Figure 2) of generic competitors forced a drop in price. The same is true of norfloxacin, where generics were available in Germany from February 1999, resulting in a price decrease (from €3.85 in 1998 to €2.47 in 2000) and subsequent demand increase (from 2879 DDDs in 1998 to 4214 DDDs in 2000). Generic ofloxacin was available from December 2000 resulting in the price of the antimicrobial agent falling in subsequent years (from €5.86 in 1999 to €4,02 in 2003).

As expected, in Germany, price has a negative and significant impact on outpatient antibiotic use. As shown in Table 4, all cephalosporins and fluoroquinolones showed significant own-price elasticities of demand.

Conclusions

In the present study, we were able to demonstrate that when generic entry follows patent expiration it drives the price of the brand name antimicrobial down substantially. In the case of ciprofloxacin, for instance, in-hospital prices reduced to one third within a few months of generic entry to the German pharmaceutical market.

According to our estimations, in-hospital demand for antibiotics was in some cases driven by prices that decreased for various reasons: The price of second-generation cephalosporins decreased over the study period although generics were either already available beforehand (oral cefuroxim) or not at all (parenteral cefuroxim, parenteral cefotiam. However, generic third-generation cephalosporin preparations became available from July 2002 (ceftriaxone) and January 2004 (ceftazidime) whereupon prices dropped substantially, but only demand for ceftazidime showed to be price elastic. Prices for fluoroquinolones showed the strongest and most immediate price decrease upon availability of generics, and ciprofloxacin, the main agent, showed strong own-price effects.

As anticipated, during the period investigated, price showed to have a stronger impact on outpatient antibiotic use in Germany. According to our estimates, all the cephalosporins and fluoroquinolones included in the analysis showed significant own-price elasticities of demand. This result is not surprising because as already stated above ambulatory care physicians are generally self-employed in Germany and the SHI reimburses fixed budgets for pharmaceuticals.

Own-price elasticities for outpatient antibiotic use have been calculated before in different countries: In Switzerland, for instance, own-price elasticities ranging from -0.561 to -0.66 were determined using data on outpatient antibiotic sales from 240 small areas over the course of one year (Filippini *et al.,* 2008; Filippini *et al.,* 2006). In the United States, own-price elasticities of antibiotics were determined at -0.785 and -0.916 for compensated and uncompensated own-price effects, respectively. Another study modelled the demand for cephalosporins as a multistage budgeting problem (Ellison *et al.,* 1997). The unconditional own-price elasticities of demand for the drugs with best statistical fit are as follows. The branded version of cephalexin has an own-price elasticity of -0.38, while the own-price elasticity for the generic cephalexin is -1.04. The own-price elasticities of cephradine are -1.93 and -2.87 for the branded and generic versions, respectively. Note that these estimates are based on wholesale data which do not distinguish between in-hospital and outpatient demand To our knowledge, detailed estimates of in-hospital own-price elasticities for antibiotics do not exist.

The present analysis shows that patent expiration leads to lower prices and to an increase in demand; however, the economic implications differ for the in-hospital- and the ambulatory care sectors (Ellison *et al.,* 1997; Griliches and Cockburn, 1994). Generally, price decreases following patent expiration implies savings from spending less money on antibiotics. However, in contrast to outpatient antibiotic use, where pharmaceutical spending makes up a substantial part of the cost of care, in-hospital price differences for the observed antibiotics are extremely low compared to the overall cost of hospitalisation. The price sensitivity of the demand for cephalosporins and fluoroquinolones appears all the more problematic because recent studies have shown hospital-wide correlations between the use of these antibiotic classes and various serious hospital-specific pathogens (Aldeyab *et al.,* 2008; Kaier *et al.,* 2009a; Kaier *et al.,* 2009b; Monnet *et al.,* 2004; Vernaz *et al.,* 2008). In detail, these studies have shown that consumption of the antimicrobial agents of cephalosporins and fluoroquinolones in hospital settings has a considerable impact on the hospital-wide incidences of methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum β-lactamase (ESBL) producing strains and *Clostridium difficile*-associated diarrhoea. Hospital-acquired infections caused by these pathogens impose a substantial financial burden on hospitals through exacerbation or prolongation of illness and subsequent in-hospital treatment (Cosgrove and Carmeli, 2003; Kaier *et al.,* 2008; Smith *et al.,* 2005; Smith *et al.,* 2006; Shorr, 2007; Paladino *et al.,* 2002).

Understanding antibiotic treatment practice is necessary to reduce misuse of antibiotics and the cost of antimicrobial resistance. Because we believe there are major differences in the hospital-wide distribution of information about prices, it would be interesting to verify our results regarding price-dependencies in in-hospital use of broad-spectrum antimicrobials by repeating the analysis in other hospitals.

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Table 1. Characteristics of the different variables (University Medical Center Freiburg, monthly data from January 2001 to October 2007)

Variable[a]	Mean	SD	Minimum	Maximum
Cefuroxime	77.52	12.64	44.57	105.69
Price of one DDD Cefuroxime	1.25	0.19	0.80	1.63
Cefuroxime (IV)	64.62	18.96	31.89	94.70
Price of one DDD Cefuroxime (IV)	4.24	0.80	2.59	7.01
Cefotiam (IV)	29.24	21.41	3.98	63.40
Price of one DDD Cefotiam (IV)	9.99	1.03	5.68	12.93
Ceftacidime (IV)	16.61	5.00	5.59	30.15
Price of one DDD Ceftacidime (IV)	30.85	11.20	9.90	45.68
Ceftriaxone (IV)	21.34	12.23	7.66	53.02
Price of one DDD Ceftriaxone (IV)	9.66	8.84	1.96	28.52
Ciprofloxacin	22.89	4.41	13.11	33.18
Price of one DDD Ciprofloxacin	2.05	1.04	0.38	5.37
Levofloxacin	10.15	10.47	0.00	33.90
Price of one DDD Levofloxacin	3.10	0.61	1.81	3.67
Norfloxacin	9.73	2.33	5.35	16.05
Price of one DDD Norfloxacin	1.32	0.32	0.64	2.11
Ciprofloxacin (IV)	11.30	2.71	5.79	20.34
Price of one DDD Ciprofloxacin (IV)	34.12	10.86	4.54	44.66
Levofloxacin (IV)	1.57	1.14	0.00	5.15
Price of one DDD Levofloxacin (IV)	40.33	2.85	20.65	43.64

[a]Antibiotic use expressed in DDDs per 1000 patient days; Prices expressed in CPI-deflated Euros (2005=1)

Table 2. In-hospital own-price elasticities at University Medical Center Freiburg, Germany (January 2000 – October 2007)[a]

Drug ($q_{D,d}$)[a]	Constant	Generic ($g_{D,d}$)	Revenue (R_D)	Price ($p_{D,d}$)	Morbidity (m)	R^2
Cefuroxime	0.00	-	0.97***	-0.88***	-0.05	0.98
Cefuroxime (IV)	0.01	-	0.57***	-0.37***	0.22	0.36
Cefotiam (IV)	-0.02	-	1.05***	-0.54**	0.02	0.59
Ceftacidime (IV)	0.00	-0.01	1.16***	-1.10***	0.04	0.92
Ceftriaxone (IV)	-0.01	0.02	0.39***	-0.28	0.15	0.12
Ciprofloxacin	-0.02	-0.02	0.72***	-0.71***	0.32	0.42
Levofloxacin	0.03	-	1.05***	-0.32	-0.55	0.19
Norfloxacin	0.00	-0.01	0.47**	-0.70	0.35	0.08
Ciprofloxacin (IV)	0.00	-0.02	0.78***	-0.47***	-0.15	0.64
Levofloxacin (IV)	0.07	-	1.87***	-8.03	4.61**	0.30

$$\Delta\log(q_{D,d}) = \eta_{D,d} + \vartheta_{D,d} g_{D,d} + \xi_D \Delta\log(R_D) + \delta_{D,d}\Delta\log p_{D,d} + \delta_m \Delta\log(m)$$

**Significant at the 5% level.
***Significant at the 1% level.
[a]Antibiotic use expressed in DDDs per 1000 patient days

Table 3. Characteristics of the different variables (Prescription according to the German statutory health insurance, annual data from 1991 to 2007)

Variable[a]	Mean	SD	Minimum	Maximum
Cefaclor	7841	2578	3583	12083
Price of one DDD Cefaclor	5.36	2.47	2.92	10.34
Cefuroxime	8251	2677	4998	15270
Price of one DDD Cefuroxime	6.83	1.76	2.27	9.15
Ciprofloxacin	7472	3594	2816	15480
Price of one DDD Ciprofloxacin	11.17	3.67	4.13	15.37
Norfloxacin	3722	478	2880	4531
Price of one DDD Norfloxacin	3.73	1.11	2.39	5.46
Ofloxacin	5429	2343	2663	9076
Price of one DDD Ofloxacin	6.18	1.23	4.13	8.07

[a]Antibiotic use expressed in DDDs; Prices expressed in CPI-deflated Euros (2005=1)

Table 4. Own price elasticities for outpatient antibiotic use in Germany (1991 – 2007)

Drug ($q_{D,d}$)[a]	Constant	Generic ($g_{D,d}$)	Revenue (R_D)	Price ($p_{D,d}$)	R^2
Cefaclor	-0.1587	0.1953***	0.8304***	-0.7058***	0.74
Cefuroxime	-0.0489	0.1026**	0.9762***	-0.4840***	0.89
Ciprofloxacin	-0.0169	0.0302	0.9384***	-0.6959***	0.67
Norfloxacin	-0.1404***	0.1006**	0.7745***	-0.5927***	0.65
Ofloxacin	-0.1367**	-0.0737	0.6576***	-1.3819**	0.59

$\Delta \log(q_{D,d}) = \eta_{D,d} + \vartheta_{D,d} g_{D,d} + \xi_D \Delta \log(R_D) + \delta_{D,d} \Delta \log p_{D,d}$

**Significant at the 5% level.
***Significant at the 1% level.
[a]Antibiotic use expressed in DDDs

Figure 1: Use of fluoroquinolones for oral application at University Medical Center Freiburg (2000 – 2007)

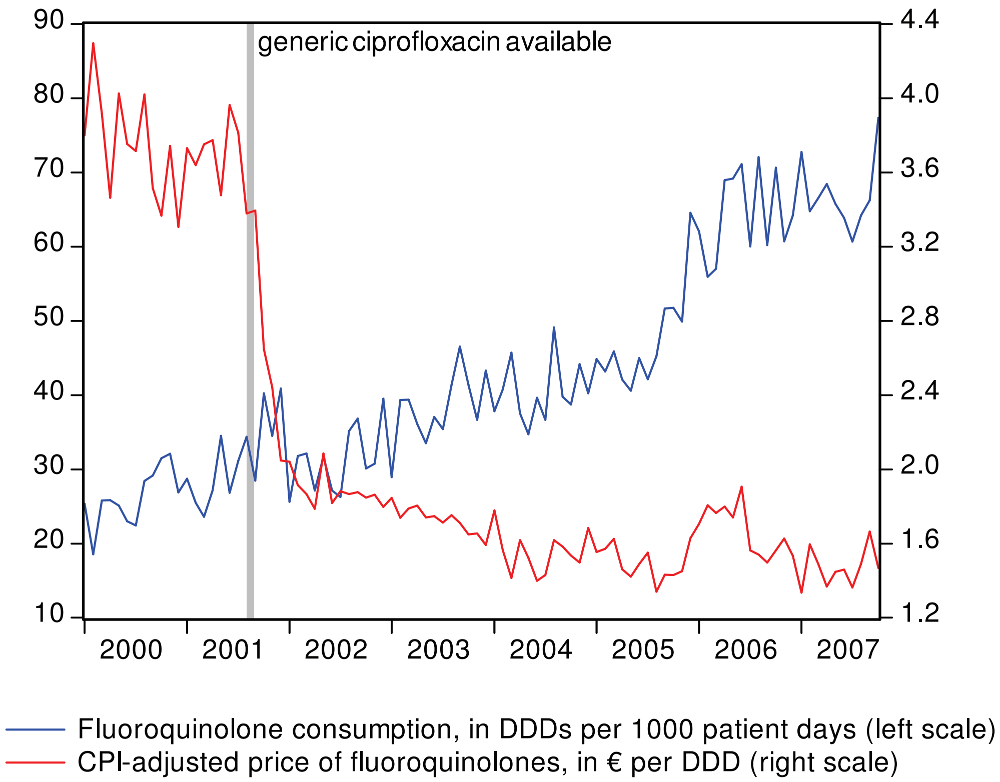
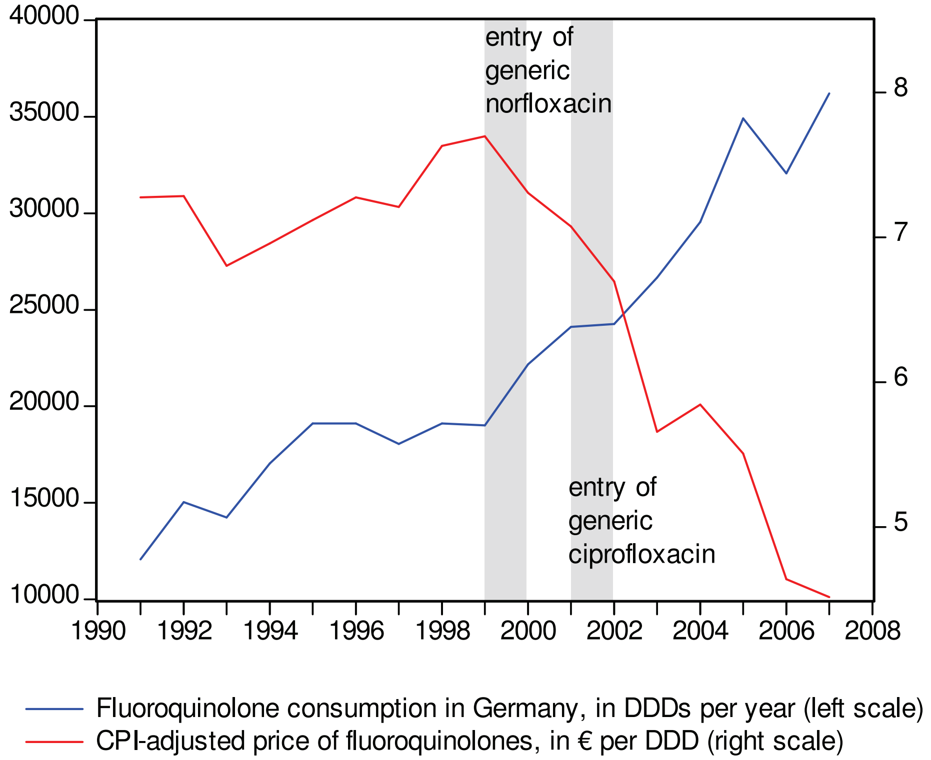


Figure 2: Fluoroquinolone consumption in Germany (SHI related prescriptions, 1991 – 2007)



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