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# Effect of generics on price and consumption of ciprofloxacin in primary healthcare: the relationship to increasing resistance

**Ulrich S. Jensen*, Arno Muller†, Christian T. Brandt‡, Niels Frimodt-Møller, Anette M. Hammerum and Dominique L. Monnet§ on behalf of the DANRES study group¶**

*National Center for Antimicrobials and Infection Control, Statens Serum Institut, Copenhagen, Denmark*

*Corresponding author. Tel: +45-3268-8183; Fax: +45-3268-3132; E-mail: uje@ssi.dk
†Present address: Laboratory of Microbiology, University of Antwerp, Wilrijk-Antwerpen, Belgium.
‡Present address: Department of Infectious Diseases, Copenhagen University Hospital, Hvidovre, Copenhagen, Denmark.
§Present address: Scientific Advice Unit, European Centre for Disease Prevention and Control, Stockholm, Sweden.
¶Participants are listed in the Acknowledgements section.

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**Background:** The introduction of generic versions of drugs has often resulted in an increase in the consumption of the agents involved. In December 2001, generic ciprofloxacin was marketed in Denmark. Our objective was to evaluate, in a community setting, the effect of price on consumption of ciprofloxacin and on ciprofloxacin resistance in *Escherichia coli* urine isolates.

**Methods:** We conducted a retrospective ecological study collecting monthly national data on the number of marketed versions and primary healthcare (PHC) sales of ciprofloxacin during January 1995–December 2005. Data were compared with a median price per defined daily dose (DDD) of ciprofloxacin during September 1999–December 2005. Yearly PHC consumption data from seven Danish counties were compared with the antimicrobial resistance profiles of PHC *E. coli* urine isolates.

**Results:** During 2002, the number of marketed versions increased from 3 to 10, and the median price per DDD decreased by 53%. From 2002 to 2005, the total consumption of oral ciprofloxacin in PHC increased significantly from 0.13 DDD/1000 inhabitant-days to 0.33 DDD/1000 inhabitant-days. During the same period, the frequency of ciprofloxacin resistance increased by 200%. A statistically significant correlation was found between the consumption of ciprofloxacin and the ciprofloxacin resistance rate in *E. coli* urine isolates, independent of the introduction of generic ciprofloxacin.

**Conclusions:** After the introduction of generic ciprofloxacin, a significant increase in the total consumption of oral ciprofloxacin in PHC was observed in Denmark. The increase in consumption was significantly correlated with ciprofloxacin resistance in *E. coli* obtained from urine isolates.

**Keywords:** fluoroquinolones, drug monitoring, antibiotic prescriptions

## Introduction

The association between the consumption of an antimicrobial agent and the occurrence of antimicrobial resistance is well established.[1,2] The worldwide increasing use of fluoroquinolones has led to an increasing prevalence of resistance to these agents.[1–6] Despite this obvious connection, the association between antimicrobial level and pattern of consumption and resistance is complex, and little is known about why the consumption increases or the prescription patterns change. Among reasons for antimicrobial overuse are defensive prescribing, pressure from patients to prescribe drugs, inadequate knowledge of the proper indications for some drugs, lack of awareness of prescription guidelines, lack of time to explain to the patient that antimicrobial agents are not needed, lack of education about resistance patterns in the community and fee-for-service remuneration of physicians. Moreover, the healthcare service structure, the pharmaceutical market and regulatory practices have been shown to influence antimicrobial use.[7–9]

Enhanced antimicrobial surveillance is one of the strategies that can be used to gain control of antimicrobial overuse or misuse. Since 1995, surveillance of bacterial resistance and consumption of antimicrobial agents in Denmark has been followed in the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme, DANMAP. In Denmark, bacterial resistance to antimicrobial agents in primary healthcare (PHC) is low compared with most other European countries.[10] Nevertheless,

both consumption of antimicrobial agents and resistance have been increasing since the late 1990s.[11]

To the consumer (patient and doctor) price may matter. According to basic economic models, when prices go down, products become affordable for a larger proportion of the population, which leads to increased consumption.[12] In Denmark patients pay for their own medicine. Since 2000, a need-dependent remuneration system has reimbursed the cost of most medicines by 50%–85% after the patient has spent >500 Danish kroner (DKK) (67 EUR) within a year. Before 2000, medicines were reimbursed by a fixed percentage (ciprofloxacin 50%, withdrawn in May 1999).

Retrospectively, in this study we examined the correlation between the introduction of generic versions and the market price of ciprofloxacin. We also investigated the effect of these variables on PHC ciprofloxacin consumption and resistance in *Escherichia coli* in Denmark, 1995–2005. We studied ciprofloxacin as opposed to other fluoroquinolones, since ciprofloxacin accounts for >90% of the total Danish fluoroquinolone consumption in PHC.

## Materials and methods

### Data collection

DANMAP was used as the data source for antimicrobial susceptibility of *E. coli* urine isolates from PHC. Seven of the 15 Danish departments of clinical microbiology were included. Departments were excluded if susceptibility testing for ciprofloxacin resistance in *E. coli* was performed only on selected isolates. The variation from year to year in the number of isolates studied was caused by variations in the number of laboratories taking part in the study and possibly not by epidemiological variation in the number of urinary tract infections (UTIs) caused by *E. coli*. During 1995–99, data from three departments of clinical microbiology were included, representing a third of the Danish population. Data from five to seven departments were included during 2000–05, representing 42%–55% of the Danish population.

The clinical microbiology laboratories provided aggregated data on the number of *E. coli* urine isolates tested and the numbers found to be resistant to ciprofloxacin, nalidixic acid, ampicillin and sulfamethoxazole from patients diagnosed and treated in PHC. Three of the laboratories removed duplicate isolates from the same patient within a window of 30 days. The other four included only one isolate per patient, in a given year, in the study.

Data on the consumption of antimicrobial agents for systemic use were obtained from the Danish Medicines Agency (DMA). The DMA has a legal obligation to monitor the consumption of medicines in Denmark. All antimicrobial agents used in Denmark are prescription medications only, and prescriptions are registered electronically and transferred to the national database. Sales data are reported on a monthly basis from all pharmacies in Denmark to the DMA. Consumption of antimicrobial agents was expressed for each individual antimicrobial (substance level) as the number of defined daily doses (DDDs) per 1000 inhabitants per day (DID) in accordance with the 2005 WHO ATC classification. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults.

Monthly data on pricing of all medications and formulations available in Danish pharmacies are reported to the DMA. A median price per DDD, of all marketed formulations in a given month, was used to monitor the price evaluation.

In the present study, the generic and imported generic formulations of an agent that were marketed by different companies were each considered to represent a trade name. However, different formulations and packages marketed by the same company were not.

### Antimicrobial susceptibility

Ciprofloxacin susceptibility was tested in the study laboratories by their individual routine methods, either tablet or disc diffusion methods or by Vitek (bioMérieux) automated susceptibility testing instrument, as reported in the DANMAP reports.[11] In some laboratories fluoroquinolone resistance was tested by a nalidixic acid disc/tablet and reported as resistance to nalidixic acid. In this study, for the sake of simplicity, we use the term ciprofloxacin resistance only.

All submitting laboratories participate in the United Kingdom National External Quality Assessment Schemes (NEQAS).

### Statistical analysis

A non-parametric Wilcoxon test was used to analyse the shift of use between the month when generic ciprofloxacin was marketed and the most recent available month. A $P$ value of $<0.05$ was interpreted as statistically significant.

We analysed the relationship between antimicrobial consumption and resistance to ciprofloxacin in the *E. coli* urine isolates, using a multilevel regression model. This approach allowed us to consider a two-level hierarchical structure of the data. Successive annual measurements (level 1) were clustered within counties (level 2). The annual rate of resistance to ciprofloxacin in the *E. coli* urine isolates was the outcome, whereas the annual consumption of the different antimicrobial agents (antimicrobial variables) was the explanatory variable.

To control for the linearity, the logarithm of the resistance rate was used in the statistical analysis. The auto-correlation of the data between the successive years was taken into account separately for each county. A delay of 1 year between consumption and resistance was retained as well as a binary variable describing before and after the introduction of generic ciprofloxacin. A basic model was constructed including only this binary variable as the explicative variable.

Then, a bivariate model was constructed by adding one antimicrobial variable to the basic model. This bivariate model was repeated for each antimicrobial variable.

Finally, a multivariate model was constructed with all antimicrobial variables that were significant with a $P$ value of $<0.05$ in the bivariate models. Modelling was performed using the nlme package of R.

## Results

From 1 January 1995 to 31 December 2005, we analysed data from 120414 *E. coli* urine isolates. The mean number of urine isolates per year was 10947 (range 6730–16152).

### Price and consumption of ciprofloxacin

In March 1988, Ciproxin®, the first version of ciprofloxacin, was marketed in Denmark. Until generics were introduced, the number of marketed versions of oral ciprofloxacin was three (Figure 1a). In December 2001, the first generic version was marketed in Denmark. Within 1 year, from December 2001 to December 2002, the number of trade names went from 3 to 10 and remained high throughout the rest of the study period (Figure 1a).

In the pre-generic period, September 1999–December 2001, the median price per DDD of oral ciprofloxacin was 49–55 DKK

(1 DKK≈0.133 EUR). During 2002 the median price per DDD dropped by 27 DKK (53%) until it reached a new level between 16 and 22 DKK, and remained at this level for the rest of the study period (Figure 1a).

The difference in pricing of the individual formulations varied from 41.70 to 62.86 DKK/DDD in the pre-generic period. From January 2002 to December 2005, the difference in price for the individual formulations varied from 1.96 to 62.86 DKK/DDD. Both top and bottom prices reflected a 10×250 mg package (August–September 2003 and January–April 2002, respectively). In December 2005 the difference between the cheapest and most expensive formulation was 54 DKK/DDD (5.45 to 59.56).

From 1995 to 1999 the 5 month average of total use of oral ciprofloxacin in PHC decreased by 23% to 0.15 DID. In May 1999, the Danish Health Care Reimbursement Scheme withdrew a reimbursement of 50% on ciprofloxacin; this was followed by an additional decrease in the 5 month average of total use of oral ciprofloxacin in PHC reaching the absolute low point of 0.10 DID in May 2000 (Figure 1b).

The 5 month average of oral ciprofloxacin use in PHC remained almost at steady state between the time of removal of reimbursement and the introduction of generic versions. From June 2002 onwards consumption increased continuously, which was concomitant with a continuous decrease in the median price per DDD (Figure 1b). Total use of oral ciprofloxacin in PHC increased significantly from 0.13 DID in January 2002 to 0.33 DID in December 2005 ($P<0.001$). Opposing these trends, the median price per DDD of oral sulfamethizole (drug of first choice) increased by 47% (13.58–20.01 DKK) from June 2002 to December 2005, whereas the total use remained at a steady level during the period.

### *Ciprofloxacin resistance in urine isolates*

During the entire study period, the frequency of ciprofloxacin resistance in *E. coli* urine isolates was generally low, <4%. The lowest reported resistance was in 1995 [57 out of 6730 isolates (0.8%)]. The highest reported resistance was in 2005 [517 out of 13496 isolates (3.8%)]. However, from 2002 to 2005 the increase in the frequency of resistance was statistically significant when comparing one year with the subsequent year. During this period the frequency of resistance increased by 200% (Figure 2).

### *Correlation between consumption and resistance*

The basic model in our study showed that the introduction to the market of generic ciprofloxacin, alone, significantly increased the ciprofloxacin resistance rate in *E. coli* urine isolates. The bivariate models showed different results according to the antimicrobial variable used. For instance, the total use of antibacterial agents for systemic use (ATC group J01) was significantly positively correlated with the resistance rate. When going down the ATC classification, at the fourth level (chemical subgroup) only the use of fluoroquinolones (ATC group J01MA) was significantly positively correlated with the resistance rate. At the fifth level, only six chemical substances had a significant effect on the resistance rate. Consumption of amoxicillin (J01CA04), sulfamethizole (J01EB02) and ofloxacin (J01MA01) had a positive effect on the resistance rate. Conversely, the consumption of clindamycin (J01FF01), ciprofloxacin (J01MA02) and moxifloxacin (J01MA14) increased the resistance rate significantly. We then constructed a multivariate model including these six

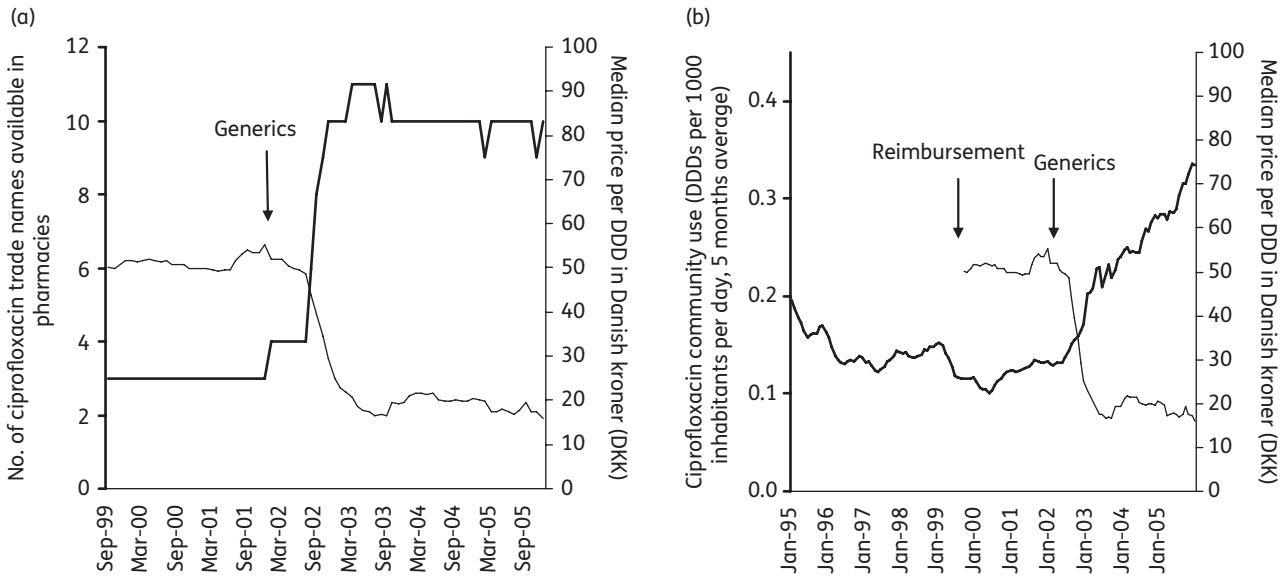


**Figure 1.** (a) Comparison of the number of ciprofloxacin trade names for oral use (thick line) and the median price per DDD registered monthly in PHC in Denmark (thin line), and the influence of the introduction of generics. The arrow marks the time of introduction of generic versions of ciprofloxacin. (b) The influence of removal of 50% reimbursement and of the introduction of generics on the total use of ciprofloxacin and median price per DDD registered monthly in PHC in Denmark (thin line). Consumption (thick line) is expressed in terms of DDDs per 1000 inhabitants per day. The arrows mark the times of removal of reimbursement of ciprofloxacin and the introduction of generic versions, respectively. 100 DDK≈13 EUR.

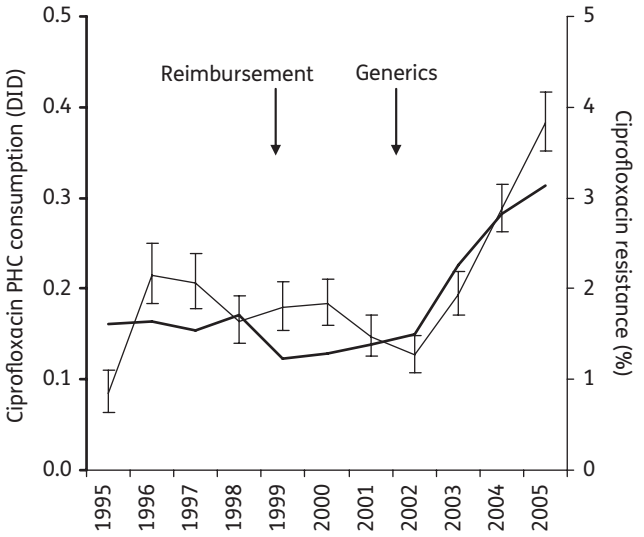


**Figure 2.** Trends in the frequency of ciprofloxacin resistance among *E. coli* urine isolates from PHC with 95% confidence intervals (thin line) and the consumption of ciprofloxacin by PHC patients from 1995 to 2005 in three to seven Danish counties (thick line) seen in the light of the removal of 50% reimbursement and the introduction of generics. Consumption is expressed in terms of DDDs per 1000 inhabitants per day. The arrows mark the times of removal of reimbursement of ciprofloxacin and the introduction of generic versions, respectively.

antimicrobial variables and the ciprofloxacin generics introduction variable. According to this analysis, only the consumption of ciprofloxacin had a significant effect on the ciprofloxacin resistance rate in *E. coli* from urine samples, independent of the introduction of ciprofloxacin generics (Table 1). Interestingly, this binary variable still had a significant positive effect on the resistance rate.

**Table 1.** Results of the multivariate model[a]

| Variables | Coefficient | *P* value |
|---|---|---|
| Intercept | 1.45 | 0.045 |
| After introduction of generics of ciprofloxacin | 0.44 | 0.004 |
| Antimicrobial variables[b] | | |
| amoxicillin | −0.39 | 0.072 |
| sulfamethizole | −2.61 | 0.200 |
| clindamycin | −8.30 | 0.470 |
| ofloxacin | −0.01 | 0.997 |
| ciprofloxacin | 3.78 | 0.003 |
| moxifloxacin | −14.82 | 0.546 |

[a]The outcome of the model was the annual rate of ciprofloxacin resistance in *E. coli* in urine samples. The retained explanatory variables were the before/after introduction of generics of ciprofloxacin and annual consumption of six antimicrobial agents ([b]which were significantly correlated with the resistance rate in bivariate analyses). The multilevel structure was a repeated measurement model with annual measurement as level 1 and county as level 2. The yearly autocorrelation was taken into account for each count.

## Discussion

This is the first study on the relationship between the introduction of generic versions and price and consumption levels, and their correlation to antimicrobial resistance.

When the patent of an antimicrobial agent expires, other companies may enter the market with generic versions of the original agent. Brand drugs are often able to keep a high price, whereas the generic versions will compete with a low-price strategy.[13,14] Part of the market will still prescribe the brand product even though it is relatively more expensive, while others will prescribe the cheaper generic version.[15,16]

We found that the number of marketed versions increased from 3 to 10 after the introduction of generic ciprofloxacin to the Danish market. We also found that within 1 year of the introduction of generic ciprofloxacin, the median price per DDD decreased by 53%. These findings accord with those of Aalto-Setälä,[17] who found that the main determinant of the price development of a drug group is the number of competitors (marketed versions).

For the patient, the cost of antimicrobial agents could influence the total level of consumption. In Turkey, an increase in fluoroquinolone consumption was seen after a reimbursement reform was introduced, making fluoroquinolones less expensive.[18]

In our study, the removal of a 50% reimbursement on ciprofloxacin was followed by a decrease in consumption. Previously, the effect of a reduction in reimbursement for antibiotics on consumption has been demonstrated with similar results.[19–21]

We also found that consumption increased by 154% after the introduction of generic ciprofloxacin. These findings are unique, but they are in accordance with those of others who have investigated market mechanisms. Monnet *et al.*[22] found that the more antibacterial trade names that are on the market, the higher the consumption of antibacterial agents. In a European study on antibiotic use in outpatients and the association with resistance, the introduction of levofloxacin to the Belgian market resulted in an increase in the overall use of fluoroquinolones.[2]

During all 11 years of our study, the consumption of ciprofloxacin by PHC patients in the represented counties (Figure 2) roughly mimicked the total use of ciprofloxacin in PHC (Figure 1b). Thus, an increase in consumption after the introduction of generics was observed.

According to Austin *et al.*,[23] the driving force for the increase in antimicrobial resistance is the extent of drug use. In a Swedish study, a positive correlation was observed between consumption of quinolones and resistance among *E. coli* from UTIs.[24] Several other studies have investigated the correlation between prescription levels and resistance at an ecological level in individual countries.[3,4,25–28] However, a few studies that sampled individual patients before and after treatment have provided the strongest scientific evidence of this correlation.[29–32]

In our study, we found that between the removal of the reimbursement and the introduction of generic versions of ciprofloxacin, consumption remained steady and the level of resistance decreased. In contrast, after the introduction of generics and the resulting increasing consumption, resistance increased—with a 1 year delay. These findings are in line with the findings of others. Indeed, Gottesman *et al.*[33] recently found a significant decline in quinolone consumption, which resulted in a significant decrease in *E. coli* resistance to quinolones. They argued that the

immediate relationship between consumption and resistance emphasizes the high fitness cost of quinolone resistance in *E. coli*.[33] Seppälä *et al.*[34] also demonstrated restoration of susceptibility in *Streptococcus pyogenes* towards macrolides after reducing its use. However, it took 3–4 years to achieve a 50% reduction in resistance.

Nevertheless, our study is subject to potential limitations. First, our study is an ecological study—where data are collected on a population rather than on an individual level—from which causality cannot be directly inferred. Therefore, the relationship between the observed levels of consumption and resistance should be interpreted with some caution. Secondly, our study has the potential for sample bias. We tried to limit this by excluding departments of clinical microbiology that did not perform susceptibility testing on all isolates, but urine samples from many patients with signs and symptoms of UTIs were not obtained. Furthermore, the urine samples sent to the laboratories probably represented more complicated cases of UTI, thereby somewhat skewing the real resistance rate. Thus, we do not know the true level of resistance in the community.

To conclude, we report that the introduction of generic ciprofloxacin resulted in a reduced price and increased ciprofloxacin consumption, which was significantly correlated with ciprofloxacin resistance in *E. coli* urine isolates. Increased ciprofloxacin consumption in PHC is of great concern, since ciprofloxacin is not the drug of first choice regarding any type of infection according to the national guideline on prudent use of antibacterial agents in Danish PHC.[35] Ciprofloxacin use should be limited in PHC to keep the drug effective for hospital infections.

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## Transparency declarations

None to declare.

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