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Antibiotic susceptibility of unselected uropathogenic *Escherichia coli* from female Dutch general practice patients: a comparison of two surveys with a 5 year interval

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Abstract

Objectives To optimize empirical treatment of urinary tract infections (UTIs), regular evaluation of the antibiotic susceptibility of the most common uropathogen, *Escherichia coli*, is necessary. We compared the antibiotic prescription rate for UTIs in women and the *E. coli* antibiotic susceptibility results, including the prevalence of extended-spectrum β-lactamase (ESBL)-producing strains, in 2009 with data collected 5 years earlier.

Patients and methods Urinary samples from female patients with symptoms of uncomplicated UTI in 42 general practices were collected over a 6 month period. Uropathogens were identified and the antibiotic susceptibility of *E. coli* was determined.

Results We analysed 970 urine cultures, of which 785 (81%) were considered positive ($\geq 10^3$ cfu/mL). *E. coli* accounted for 72% of the isolates. ESBLs showed an increase between the two surveys (0.1% versus 1%; $P < 0.001$), while no difference in antibiotic susceptibility to the commonly used antimicrobial agents for UTIs was observed. A significantly lower susceptibility rate to co-amoxiclav was observed in the eastern region of the Netherlands, as compared with the northern region (80% versus 92%; $P < 0.05$). Consistent with national guidelines, the prescription rate of trimethoprim decreased over time (19% versus 5%; $P < 0.05$) whereas nitrofurantoin and fosfomycin rates showed an increase (58% versus 66% and 0% versus 6% respectively, both $P < 0.05$).

Conclusions Over a 5 year period, the antibiotic susceptibility of uropathogenic *E. coli* did not change in female patients with uncomplicated UTI in the Netherlands, but ESBL prevalence increased. With respect to the prescription of antimicrobial agents, compliance with national UTI guidelines was good.

Introduction

Acute, uncomplicated urinary tract infections (UTIs) form one of the most common bacterial infections seen in general practice. Especially in adult female patients, acute cystitis is frequently diagnosed, with an incidence of 70 per 1000 women each year in the Netherlands.[1]

In addition to instructions for the patient, including among other things sufficient fluid intake and regular emptying of the bladder, the essential element in the treatment of UTIs is antimicrobial drug prescription, which is usually performed on an empirical basis. In the Netherlands the antimicrobial agents of first and second choice for UTIs, according to the guidelines of the Dutch College of General Practitioners (NHG) nitrofurantoin and trimethoprim, accounted for 12% of the total antibiotic use outside hospitals in 2008.[2]

With the high prevalence of UTIs and empirical antibiotic treatment as common practice, there is a substantial risk of the emergence of antimicrobial resistance in uropathogens. Recently, Coque *et al*.[3] described increased prevalence of extended-spectrum β-lactamases (ESBLs) in community-acquired infections in Europe, especially among isolates of *Escherichia coli*, which is the most commonly isolated uropathogen.

To control the increasing prevalence of antibiotic resistance, an optimal empirical choice based on current data is essential. These data will be used to update the NHG guideline 'Urinary Tract Infections'. General practitioners (GPs) are requested to comply with these guidelines.

In the last revision of this guideline (2005) nitrofurantoin became the only antimicrobial agent of first choice and trimethoprim changed from first to second place because antibiotic susceptibility to trimethoprim was decreasing.[4] Fosfomycin was named as the antimicrobial agent in third place.

For the revision in 2005, data from a surveillance study performed by our research group of unselected uropathogenic *E. coli* isolated from GP patients were used.[5–7] General practices (n = 21) in the Sentinel Stations project of the Netherlands Institute for Health Services Research (NIVEL) participated in that surveillance study.[8]

In 2009 we used the same network of general practices in order to evaluate changes in the antibiotic susceptibility of unselected uropathogenic *E. coli*, and changes in antibiotic use for UTIs, over time. Also the prevalence of ESBL-producing strains was assessed as several studies described an increase in the prevalence of ESBLs among *E. coli* isolates.[3,9]

Furthermore, we wanted to determine possible regional differences in antibiotic susceptibility of the isolated *E. coli*, since these have been reported in community[10] and hospital[11,12] isolates in several other countries.

MATERIALS AND METHODS

Participating GP practices

For the recruitment of patients, general practices (n = 42) from the NIVEL Sentinel Stations network participated in this study. This network is nationally representative for age, gender, regional distribution and population density.[8]

In order to assess regional differences, the Netherlands was divided into four regions, as described by NIVEL: North (provinces Groningen, Friesland and Drenthe), East (Overijssel, Gelderland and Flevoland), West (Utrecht, Noord- and Zuid-Holland) and South (Zeeland, Noord-Brabant and Limburg).[8]

Patient selection and urine collection

Eligible for inclusion in this study were non-pregnant women aged ≥11 years who consulted their GP practice with symptoms indicating an acute uncomplicated UTI, i.e. strangury, dysuria, urinary frequency and urgency without the presence of fever >38°C. Exclusion factors were urological or nephrological problems, diabetes mellitus or other immunocompromising diseases. Catheterized patients were also excluded. The period for inclusion was from January 2009 to July 2009.

A short questionnaire was filled in by the GP with questions about the patient's antibiotic use in the past 3 months and whether or not a previous UTI had been diagnosed in the past year. Empirical antimicrobial treatment was recorded when started during the patient's visit.

Finally, a dipslide (Uriline, 56508; BioMérieux, Plainview, NY, USA) was prepared from the urine sample obtained following the instructions of the manufacturer. For incubation and further microbiological analysis the dipslides were sent by mail to the Laboratory of Medical Microbiology of the Maastricht University Medical Centre in the Netherlands.

Identification and antimicrobial susceptibility testing of the uropathogens

After the arrival of the dipslides at Maastricht University, bacterial growth was determined and considered positive at $\geq 10^3$ cfu/mL.[1] If no growth was observed on the day of arrival, the assessment of bacterial growth was repeated after an incubation period of 24 h at 37°C.

Dipslides showing growth of two or more bacterial species were excluded from the final analysis. Standard microbiological methods were used for the identification of the uropathogens.[13]

After isolation and identification, all bacterial strains were kept at −20°C in peptone/glycerol (30% w/v) for further testing.

The antimicrobial susceptibility of the *E. coli* isolates was determined according to the CLSI criteria[14] using the microdilution method. This involved Mueller–Hinton II cation-adjusted broth (Becton, Dickinson and Company, Sparks, MD, USA), an inoculum of 5×10^5 cfu/mL and overnight incubation at 35°C. The MIC plates with freeze-dried antimicrobial agents were provided by MCS Diagnostics (Swalmen, The Netherlands).

The following antimicrobial agents (range in mg/L) were tested: amoxicillin (0.06–128), co-amoxiclav (0.06–128), trimethoprim (0.03–64), co-trimoxazole (0.03–64), norfloxacin (0.03–64), ciprofloxacin (0.003–16) and nitrofurantoin (0.5–512). *E. coli* ATCC 35218 and ATCC 25922 were used as control strains. The breakpoints for susceptibility were in accordance with the EUCAST guidelines.[15]

Susceptibility to fosfomycin was determined by the Kirby–Bauer method (Neo Sensitabs, Rosco Diagnostica, Denmark) and read according to the CLSI guidelines as no EUCAST breakpoints were available for this antimicrobial agent.[14,15]

The *E. coli* isolates resistant to co-amoxiclav were assessed for the presence of ESBL production by means of a combination disc diffusion test (Neo Sensitabs, Rosco Diagnostica, Denmark) with ceftazidime and cefotaxime with and without clavulanic acid, conforming to the guidelines of the Dutch Society of Medical Microbiology (NVMM).[16] This procedure was also performed on the isolates from the 2004 study.

Comparability of the 2004 and 2009 data

In order to make a reliable comparison, the chosen categories (age, region and uropathogens) and the conditions, including the network of the participating GPs, in the two studies were the same, except for the guidelines used for the *E. coli* susceptibility breakpoints. However, this difference was dealt with by adjusting the original 2004 susceptibility data to the EUCAST breakpoints in the comparison analysis. Because the same research group carried out both studies, the files containing the exact MIC values from the previous study were available and the susceptibility rates of the 2004 data could be calculated according to the EUCAST guidelines.

Statistical methods

For the statistical analysis SPSS 16.0 was used. For comparison of antibiotic susceptibility patterns and antibiotic prescription rates between the two periods the χ^2 test was performed. To assess regional differences, the odds ratio (OR) and 95% confidence interval (CI) between the region with the highest susceptibility and the other regions was calculated using a logistic regression model adjusted for age, UTI in the past year and antibiotic use in the past 3 months. $P < 0.05$ was considered statistically significant.

Sample size

Our aim at the start of the study was to determine whether trimethoprim resistance had increased since 2004, and was based on two factors. First, the prescription rate of trimethoprim in the outpatient setting in the Netherlands has decreased in past years,[2] which could indicate that GPs regularly encounter trimethoprim therapy failure. For this reason GPs might have decided to prescribe this antimicrobial agent to a lesser extent, irrespective of the revision of the treatment regimen in the NHG guidelines. Secondly, several surveillance studies in past years have described a decrease in *E. coli* susceptibility to trimethoprim.[5,17] Also NETHMAP, the annual report on the use of antimicrobial agents and antimicrobial resistance in the Netherlands based on data from ongoing surveillance systems, reported a decrease to 69% in *E. coli* susceptibility to trimethoprim among selected urinary strains from outpatient clinics and general practices in 2008.[2]

As the 2004 study described a trimethoprim susceptibility of 77% we estimated a decrease in susceptibility from ~ 80% to 70%. With $\alpha = 0.05$ and $\beta = 0.2$, ~300 *E. coli* strains were needed to detect this difference. Based on the 2004 study we assumed that 10% of the samples were negative, that 15% showed a mixed culture and that 65% of the positive samples were *E. coli*.[5] With these figures a total of ~600 samples would be needed for this study. Because we did not want to be dependent on unexpected changes in these figures, we decided to include ~1000 samples.

RESULTS

Overall characteristics

A total of 970 urine samples were collected, of which 785 (81%) were considered positive. Of these samples 109 (14%) contained two or more bacteria, with a relatively large proportion in the age group >70 years: 48 out of 230 samples (21%). The median age of the female patients included was 53 years (range 11–101 years).

No significant difference was observed in antibiotic use in the past 3 months between patients >70 years of age, of whom 41% (n = 69) used an antimicrobial agent during this time period, and those in the 11–70 year age groups [35% (n = 164)] (P = 0.15). Regarding the number of patients with a history of UTI in the past year, the difference between these two age categories was more obvious: 57% (n = 93) in the group >70 years compared with 42% (n = 189) among the patients 11–70 years of age ($P < 0.05$).

E. coli was the uropathogen most commonly isolated in all age categories (72%), followed by *Enterococcus faecalis* (6%). *Staphylococcus saprophyticus* was mainly detected in the younger age category (11–20 years), whereas the prevalence of *Klebsiella pneumoniae* increased with increasing age.

Antibiotic use and susceptibility patterns

Empirical antimicrobial treatment was prescribed in 74% (n = 719) of the cases. Nitrofurantoin was the antimicrobial agent most frequently prescribed regardless of age (66%). Quinolones and co-amoxiclav were the next most frequently prescribed antimicrobial agents (10% and 8%, respectively) and for the former the prescription rate increased with increasing age.

The overall susceptibility of *E. coli* to nitrofurantoin, fosfomycin and fluoroquinolones (ciprofloxacin and norfloxacin) was high (100%, 100% and 97%, respectively). *E. coli* showed the lowest susceptibility to amoxicillin (66%). No significant differences were observed between the various age groups (Table 1).

[TABLE 1]

Five *E. coli* strains from the 2009 survey were found to be ESBL positive by the combination disc diffusion test (1% of all *E. coli* isolates).

Regional differences

When the antimicrobial susceptibilities alone were considered in the statistical analysis, isolates from the eastern region showed statistically more resistance to amoxicillin and co-amoxiclav when compared with isolates from the northern part of the country (OR 2.1, CI 1.1–4.1 and OR 4.0, CI 1.4–11.3, respectively). When the variables age, UTI in the past year and antimicrobial agents received in the past 3 months were taken into account, only the co-amoxiclav resistance in the eastern region was significantly higher (OR 3.9, CI 1.3–11.8) in comparison with the northern region. For the other antimicrobial agents no significant regional differences were found (Table 2).

[TABLE 2]

Comparison of 2004 and 2009 data

Regarding the distribution of the isolated uropathogens between the two surveys, the percentage of *E. coli* increased from 64% to 72% ($P < 0.05$), mainly due to the different *E. coli* rates in the category >70 years (61% versus 73%; $P < 0.05$). An increase was also observed in *Enterococcus faecalis* from 3% to 6% ($P < 0.05$).

On the other hand, the rate of the 'non-fermenters' group decreased from 6% to 3% ($P < 0.05$). This also applied to the group 'Other Gram-negatives', which decreased from 9% to 4% ($P < 0.05$).

The prescription rates of commonly used antimicrobial agents for UTIs in the 2004 and 2009 surveys are given in Table 3.

[TABLE 3]

The susceptibility of uropathogenic *E. coli* to the most commonly used antimicrobial agents for a UTI did not change over time. In 2004 comparably high *E. coli* susceptibilities were found to nitrofurantoin, fosfomycin and the fluoroquinolones (99%, 99% and 96%, respectively). This also applied to amoxicillin (67%), trimethoprim (77%), co-trimoxazole (80%) and co-amoxiclav (88%).

On the other hand, the prevalence of ESBL-producing *E. coli* significantly increased from 0.1% (1/1378) in 2004 to 1% (5/489) in 2009 (P = 0.001).

DISCUSSION

No differences were detected in the antibiotic susceptibility of unselected uropathogenic *E. coli* isolates to frequently used antimicrobial agents over a 5 year period in the Netherlands. A similar result has been described in a Belgian study with a 10 year study interval.[18] These results are remarkable, since several European surveillance studies reported a significant increase in resistance among community isolates in the past decade.[9,17]

The ARESC study, an international survey on antimicrobial resistance in uncomplicated UTIs, showed a substantial increase in resistance to β-lactams, trimethoprim/sulfamethoxazole, nitrofurantoin and quinolones.[9] However, only 29 *E. coli* isolates were collected in the Netherlands, contributing little to the study outcome. This fact could account for the difference in results from our study, in which 489 *E. coli* strains were examined.

The number of ESBLs, on the other hand, showed a significant increase among our community isolates, with a prevalence of 1% in the present study as compared with 0.1% in 2004. The European Antimicrobial Resistance Surveillance System (EARSS), collecting resistance data from nosocomial isolates throughout Europe, also showed that third-generation cephalosporin resistance in *E. coli* has increased from <1% in 2001 to 5% in 2008 in the Netherlands.[19] In addition, Sturm *et al*.[20] reported recently an ESBL increase from <1% in 1995 to 2.1% in 2009 among unselected clinical *E. coli* isolates in a Dutch university hospital.

According to these results, the prevalence of ESBL-positive strains seems to be increasing among invasive *E. coli* isolates in this country. In the present study this trend was also observed in isolates collected in the outpatient setting.

This increase in ESBLs highlights the emerging problem of the ESBLs and emphasizes the importance of future surveillance studies to determine whether this trend continues among unselected uropathogenic *E. coli* isolates.

The reason we chose assessment of co-amoxiclav-resistant isolates for the detection of ESBL-positive strains was a practical one, since this antimicrobial agent was already included in the MIC plates used in this survey. However, we did check whether this was an adequate method for the detection of all ESBL-positive strains. This was done by checking a database from another project[2] that included selected *E. coli* isolates (n = 603) for which the MIC values of co-amoxiclav were available. In this database the MIC values of cefotaxime and ceftazidime, which are the two antimicrobial agents named in most guidelines for the assessment of ESBLs, were also available. We concluded that 99% (n = 597) of these isolates were assessed correctly according to our approach. We performed the combination disc diffusion test on the 31 *E. coli* isolates that were resistant to ceftazidime or cefotaxime according to the EUCAST guidelines (MIC values of ≥2 mg/L) and observed 15 ESBL-positive strains, of which two were co-amoxiclav susceptible.

For this reason, we acknowledge that the given ESBL rates could be a small underestimation of the actual rates, but this effect would apply to both years. Therefore, our conclusion on the ESBLs, which is an increase over the period between 2004 and 2009, is still valid as the difference between the two rates found was highly significant.

Looking at the comparability of the 2004 and 2009 surveys, the only difference was the duration of the inclusion period and the sample size. With regard to the inclusion period, participation of GPs was encouraged more in the 2009 study than in 2004, resulting in more practices being involved in the present study (42 versus 21) and less time being needed to collect our data (6 versus 24 months).

Considering that in both surveys the participating general practices were part of the NIVEL Sentinel Stations network and chosen in a way that made them representative of the Dutch population, the difference in the number of general practices involved is unlikely to have influenced the comparability of the two surveys.

The shorter duration of the 2009 survey should also be considered, since there are studies which describe seasonal peaks in *E. coli* infections with a higher incidence in the summer.[21] As the 2009 study was performed between January and July, both winter and summer were represented in this period, thus diminishing the possible effect of this difference.

The high percentage of positive samples (81%) in comparison with other studies[9,17,22] was possibly due to the low cut-off value (10^3 cfu/mL). Nowadays, the Kass criteria (10^5 cfu/mL) are frequently used for the diagnosis of lower UTIs in female patients, but these were originally developed for the diagnosis of acute pyelonephritis and asymptomatic bacteriuria. Several studies have indicated, however, that the lower cut-off value (10^3 cfu/mL) has diagnostic relevance, especially when the patient has clinical symptoms.[23,24] Based on these results, the European urinalysis guidelines recommended reporting results according to this lower cut-off value.[25] Also other recent studies on the susceptibility of *E. coli* in general practice patients, such as the ECO.SENS study,[17] described their data based on this cut-off value. Finally, the 2004 survey also used the 10^3 cfu/mL cut-off value when describing their results.

The large number of mixed cultures in this study (14%), not observed to this extent in most other studies,[18,26] was mainly influenced by the inclusion of older female patients. The percentage of contaminated cultures was much higher among the included patients aged ≥70 in comparison with patients between 11 and 70 years of age. Owing to a higher co-morbidity, such as urinary incontinence, technical difficulties in obtaining a representative urine sample occur more often in the elderly, resulting in a higher frequency of contamination.[27]

Compared with the 2004 study the higher percentage of *E. coli* among the isolated uropathogens was mainly due to the difference in the group >70 years of age.

One would expect that the elderly would use more antimicrobial agents and that UTIs would occur more frequently, thereby influencing the distribution of species: fewer susceptible *E. coli* isolates and a wider spectrum of resistant microorganisms.[28] However, in our study population the percentage of patients who had used antimicrobial agents in the past 3 months was comparable between the elderly (aged >70 years) and the younger age group. This applied to a lesser extent to the patients with a history of UTI in the past year. Altogether, it appears that the included patients aged >70 were relatively healthy, resulting in susceptibility rates similar to those in the other age groups and a higher percentage of *E. coli* isolates in this age category in comparison with the 2004 data.

The relatively healthy population >70 years of age in this study could account for these observations, but this could also be a representative sample of the elderly with uncomplicated UTIs, as similar results were described by Grover *et al*.[29] They compared the distribution of uropathogens and *E. coli* susceptibility results to co-trimoxazole, the first-choice drug for UTIs in the United States, between three UTI groups: younger uncomplicated patients, uncomplicated elderly (>65 years) and complicated elderly. They concluded that not age, but medical complications, changed the distribution of species, and that *E. coli* susceptibility did not significantly differ between the three groups. Although their study lacked statistical power, together with our data it can support the antibiotic policy that the treatment of uncomplicated UTIs in the elderly can be similar to the treatment of younger patients, provided adequate renal function has been confirmed.

In this way the use of quinolones, an antimicrobial group prescribed more frequently for UTIs in the elderly, can be restricted. This will have a beneficial effect, as prudent use of quinolones has been emphasized regularly in the last decade due to emerging resistance of uropathogenic *E. coli*.[5,6,30] This problem has already been highlighted by the Dutch guidelines, which recommended the use of fluoroquinolones only after antibiotic susceptibility testing has been performed and not on an empirical basis. Our prescription data confirmed that fluoroquinolones were prescribed less frequently in 2009 than in 2004, whereas co-amoxiclav, the other antimicrobial agent prescribed more often for UTIs in the elderly, showed a rise in prescription rate. On the basis of our data even co-amoxiclav should only be prescribed when the preferred antimicrobial agents, nitrofurantoin, trimethoprim and fosfomycin, are rejected due to factors such as allergies, co-morbidity or side effects.

A decrease in the trimethoprim prescription rate, which was also reported by NETHMAP,[2] was observed during this 5 year period. In earlier studies a rise in the resistance of uropathogens to trimethoprim had been described and the Dutch guidelines concerning treatment of UTI in general practice had changed trimethoprim from the first to the second place in the choice of drugs, while nitrofurantoin remained the first-choice agent for uncomplicated UTI. Fosfomycin was named as third-choice antimicrobial agent.[4–6,17] The lower prescription rate of trimethoprim and the higher rates of nitrofurantoin and fosfomycin in this study are consistent with the NHG guidelines, as was the decrease in the prescription rate of fluoroquinolones, thus confirming successful implementation of these guidelines.

The current resistance data from 2009 still show high trimethoprim resistance. This could lead to further adaptation of the guidelines, placing fosfomycin instead of trimethoprim as second-choice drug for uncomplicated UTIs, with nitrofurantoin remaining the antimicrobial agent of first choice. However, in addition to the susceptibility results, financial consequences and the side effects of the drugs need to be considered before this decision is taken.

The low susceptibility rate to co-amoxiclav (87%) found, considerably lower than in earlier studies performed in the Netherlands, was remarkable.[5,6,17] In earlier studies the susceptibility data were based on the CLSI criteria,[15] which have higher breakpoints than the EUCAST guidelines used in the present study. After adjusting our data to the criteria defined by CLSI, the susceptibility rate for co-amoxiclav rose to 98%, which is more consistent with the earlier reported percentages. For the other antimicrobial agents no differences in susceptibility percentages were observed when the EUCAST breakpoints were applied to the 2004 data.

To our knowledge this is the first time a regional difference in *E. coli* susceptibility among community UTI isolates has been observed in the Netherlands. Even after correcting for the factors age, antibiotic use in the past 3 months and a history of UTIs in the past year, the isolates from the eastern part of the country showed a significantly lower susceptibility rate to co-amoxiclav than those from the northern region. The relevance and cause of this regional difference and other associated factors, such as recent hospitalization, could be assessed in future studies.

In conclusion, over a time period of 5 years no significant changes in the antibiotic susceptibility of unselected uropathogenic *E. coli* were observed in the Netherlands, although the prevalence of ESBL-producing strains showed an increase to 1% in 2009. Changes in prescription rates of antimicrobial agents over the past 5 years were consistent with changes in the Dutch guidelines for UTI, confirming successful implementation of these guidelines. The choice of antimicrobial agent for the treatment of uncomplicated UTIs should not depend solely on the age of the patient, although co-morbidity has to be taken into consideration.

Regular surveillance studies need to be performed in the Netherlands in order to optimize empirical treatment and control antimicrobial resistance, especially monitoring for ESBLs.

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None to declare.

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TABLES

Table 1. *E. coli* susceptibility rates (%) per age category in 2009

	Age category (years)				
	11–20 $n=57$	21–50 $n=154$	51–70 $n=147$	>70 $n=131$	Total $n=489$
Amoxicillin	61	68	64	70	66
Co-amoxiclav	89	89	85	86	87
Trimethoprim	81	82	77	83	81
Co-trimoxazole	81	86	82	84	84
Norfloxacin	97	98	95	97	97
Ciprofloxacin	98	99	95	97	97
Nitrofurantoin	100	100	99	100	100
Fosfomycin	100	100	99	100	100

No differences were found between the age categories [χ^2 test; $P>0.05$: range 0.08 (norfloxacin)–0.41 (co-amoxiclav)].

Table 2. Susceptibility rates (%) of *E. coli* per region in 2009

	Region				
	North $n=91$	East $n=94$	West $n=205$	South $n=97$	Total $n=487$[a]
Amoxicillin	73	57	64	72	66
Co-amoxiclav[b]	92	80	87	90	88
Trimethoprim	84	73	81	86	81
Co-trimoxazole	88	78	83	86	84
Norfloxacin	97	98	96	97	97
Ciprofloxacin	97	99	96	97	97
Nitrofurantoin	100	100	100	99	100
Fosfomycin	100	100	100	100	100

[a]In the case of two *E. coli* isolates the region was unknown.
[b]Difference between eastern and northern regions calculated with a multivariable analysis including the covariables age, UTI in the past year and antibiotic use in the past 3 months; OR 3.9, CI 1.3–11.8.

Table 3. Comparison of the UTI prescription rates between the participants of the 2004 and 2009 surveys

	Number of prescriptions (%)	
	2004 (n=2024)[a]	2009 (n=719)[a]
Nitrofurantoin[b]	1179 (58)	472 (66)
Co-amoxiclav[b]	64 (3)	54 (8)
Amoxicillin	42 (2)	13 (2)
Trimethoprim[c]	387 (19)	38 (5)
Co-trimoxazole	62 (3)	27 (4)
Fluoroquinolones[c]	290 (14)	75 (10)
Fosfomycin[b]	0 (0)	40 (6)

[a]Represents all participants that were prescribed an antimicrobial agent per survey.
[b]Increased prescription rate in 2009 (χ^2 test; $P<0.05$).
[c]Decreased prescription rate in 2009 (χ^2 test; $P<0.05$).