

**Variation in presentation, microbiology, antibiotic prescribing, and patient outcomes of uncomplicated urinary tract infection: a prospective four-country primary care observational cohort study**

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## Abstract

**Background:** Regional differences in presentation of uncomplicated urinary tract infection (UTI) and pathogen sensitivity to antibiotics have been used to justify variation in management, including broad spectrum antibiotic prescribing.

**Aim:** To describe presentation and management of urinary tract infection in primary care settings, and explore the association with patient recovery, taking microbiological findings and case mix into account.

**Design and setting:** Prospective observational study of women with symptoms of uncomplicated UTI presenting to primary care networks in England, Wales, the Netherlands, and Spain, between November 2012 and February 2014.

**Method:** Clinicians recorded history, symptom severity, management, and requested mid-stream urine culture. Participants recorded symptom severity each day for 14 days in a diary. Time to recovery was compared between patient characteristics and between countries using two-level Cox proportional hazards models, with patients nested within practices.

**Results:** 797 women attending primary care networks in England (246 (30.9%)), Wales (213 (26.7%)), the Netherlands (133 (16.7%)) and Spain (205 (25.7%)) were included: 91.1% had urine cultured, and 71.1% returned their diary. Participants were slightly younger in Wales, had less severe symptoms in Spain, and had waited longer before consulting in the Netherlands. 259 (35.7%, 95% CI 32.3 to 39.2) were urine culture positive for UTI, with similar proportions in England and Wales but much higher in Spain and the Netherlands. Pathogens and antibiotic sensitivities were similar. Empirical antibiotics were prescribed for > 90% of women in England, Wales and Spain (n = 232 (95.1%) n = 196 (92.9%) and n = 195 (95.1%) respectively), but lower in the Netherlands (79 (59.4%)). Antibiotic of choice was trimethoprim (46.1%) or nitrofurantoin (48.7%) in England, trimethoprim (76.5%) in Wales, nitrofurantoin (79.7%) in the Netherlands and fosfomycin (75.9%) in Spain, where co-amoxiclav (9.7%) or ciprofloxacin (9.2%) were also prescribed. Antibiotic prescribing was associated with faster recovery (median 9 days (IQR 5 to 14 days) vs. 13 (IQR 7 to 14 days)), and overall median time to full recovery was 9 days (IQR: 6 to ≥14 days), with no meaningful differences at a country network level before and after controlling for severity, prior UTIs, and antibiotic prescribing.

**Conclusion:** Variation in presentation and management of uncomplicated UTI at a country primary care network level is clinically unwarranted and highlights lack of consensus concerning optimal symptom control and antibiotic prescribing.

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### **Study registration**

REC reference: 12/WA/0111

### **How this fits in**

Regional differences in presentation of uncomplicated urinary tract infection (UTI) and pathogen sensitivity to antibiotics have been used to justify variation in management, including broad spectrum antibiotic prescribing. However, regional differences in primary care presentation, management have not been prospectively described, and the association with patient recovery, taking microbiological findings into account, is unknown.

Ours is the first prospective study to describe presentation and management of uncomplicated urinary tract infection in primary care settings in Europe, and explore the association with patient recovery, taking microbiological findings and case mix into account. We found little variation in patient presentation, or aetiology and sensitivity of urinary pathogens cultured in the urine of women with symptoms of uncomplicated UTI in four European primary care settings. However, the proportion of urine cultures meeting laboratory definitions of UTI, patients prescribed an antibiotic, antibiotic classes commonly prescribed, whether antibiotic choice was concordant with culture results, and subsequent consulting and prescribing did, however, differ markedly. Despite these differences, patient reported recovery measures did not vary at the country network level, before and after controlling for severity, prior urine infections, and antibiotic prescribing. The most cost effective care pathway for uncomplicated UTI should now be determined and care standardised, as the current variation in care for UTI is not warranted on clinical grounds.

## Introduction

Variation in the presentation and management of symptoms of uncomplicated urinary tract infection (UTI) has been identified (1-3), but we do not know whether such variation is warranted by differences in symptom presentation, prevalence of microbiologically-confirmed UTI, characteristics of infecting pathogens between settings, and whether such factors are associated with patient recovery. Variation in antibiotic prescribing that is not warranted on clinical grounds could waste resources, put patients at unnecessary risk of delayed recovery and adverse events, and unnecessarily drive antimicrobial resistance, particularly where broad-spectrum antibiotics are used. Antibiotic resistance is a growing international problem that does not respect national borders.

We previously investigated variation in antibiotic prescribing for acute cough/lower respiratory tract infection (LRTI) in Europe, and found a four-fold variation between primary care networks in 14 countries that was not meaningfully associated with patient recovery, and huge variation in the choice of first line antibiotics.(4) This highlighted the need for standardising clinical care and promoting self-care.(5) While that analysis controlled for presentation and case mix, it was not able to take microbiological findings into account. This is important as clinicians may justify their antibiotic prescribing on the basis of assumed differences in patient characteristics as well as aetiology and presumed bacterial antibiotic susceptibility.(6, 7)

Uncomplicated UTI is one of the most common bacterial infections managed in primary care. Nearly 40% of women report having had at least one UTI, more than 10% report at least one episode and about 3% report three or more episodes (recurrent UTI) in the past year.(8, 9) Most women in the UK consult a health professional when they have symptoms attributable to a UTI, and about three quarters of these have some form of urine test and are prescribed an antibiotic for their symptoms.(9) However, up to 70% of women with symptoms attributable to UTI are found not to have a UTI confirmed microbiologically when routine urine culture is performed, but this is dependent on the thresholds and criteria used by laboratories and study design and population.(10-14)

Antimicrobial stewardship interventions and clinical practice guidelines aimed at optimising standard routine care would therefore be enhanced by a better understanding of the variation in presentation and care (e.g. patient characteristics, dipstick results and requesting urine culture, proportion and appropriateness of antibiotic prescribing, non-antibiotic prescribing, planned follow-up

arrangement, subsequent antibiotic prescribing, and re-consultations), and the association with microbiological findings and recovery. We therefore aimed to describe variation in the presentation and the variation in management, and the association with outcomes for women presenting with symptoms of uncomplicated UTI to primary care research networks in four European settings.

## **Methods**

### ***Setting and participants***

This study was conducted in primary care general practices that were part of primary care networks in England, Wales, Spain and the Netherlands between November 2012 and February 2014. These primary care research networks were selected on the basis of having well-established primary care research capability and reflected the countries in which the investigators were based. Each primary care network aimed to recruit approximately 10 general practices based on their interest and capacity to deliver the study protocol. Each country network was set a target to recruit 200 eligible women. The primary care clinicians in the practices were asked to sequentially recruit adult women presenting with symptoms of uncomplicated UTI, record patient demographics, their usual care diagnostic procedures and treatment, and collect and send a urine sample for laboratory culture.

Eligible participants were women aged 16 years or older, able to provide written informed consent, presenting to primary care with at least one of three key urinary tract symptoms (dysuria, urgency including nocturia, and frequency) and where the clinician suspected uncomplicated UTI (no known urological abnormalities, non-pregnant women). (15) Exclusions were: terminal illness, receiving treatment for life-threatening cancer, severe systemic symptoms, on long-term antibiotic treatment or have received antibiotics for urinary tract infection within the past four weeks, bladder surgery (including cystoscopy) within the past four weeks, significant immune compromise (e.g. long-term corticosteroid or chemotherapy, insulin dependent diabetes), functional or anatomical abnormalities of the genitourinary tract, history of pyelonephritis, and, pregnancy.

### ***Clinical Examination***

On a case report form (CRF) clinicians were asked to record details of the participant's presenting clinical symptoms including fever, pain in the side, blood in urine, smelly urine, burning or pain when passing urine, urgency, daytime frequency, night time frequency, tummy pain, restricted activities, and feeling generally unwell) using a scale of 0-6 for each feature (with 0 being 'normal/not affected' and 6 being 'as bad as it could be'), temperature, their antibiotic management for the suspected UTI and any planned follow-up. This scale was similar to the one used in the patient diary, and represent

a slight modification of previously used instruments.(16) The severity of three symptoms (day-time frequency, night-time frequency, and urgency) were summed to create a GP-rated symptom severity score ranging from 0 to 18 (see online supplementary material for more detail).

### ***Antibiotic prescribing***

We assessed antibiotic prescribing at the index consultation (yes/no), and whether or not prescriptions were 'concordant' (a UTI on laboratory culture and prescribed antibiotics matching pathogen sensitivity, or, no UTI on culture with no antibiotic prescribed) or 'not concordant' (a UTI on laboratory culture and prescribed an antibiotic to which the pathogen was resistant, or, a UTI on culture and no antibiotic prescribed, or, no UTI on culture and an antibiotic prescribed).

### ***Urine dipstick and culture***

Participants were asked to provide a mid-stream urine sample at baseline, in addition to any urine samples the responsible clinician wished to obtain to guide usual care. Clinicians were asked to record whether they undertook urine dipstick testing and the results of dipstick tests performed, and whether the urine was cloudy or had an offensive smell. Urine samples were then referred by usual post to a microbiology laboratory (Public Health Wales Specialist Antimicrobial Chemotherapy Unit [PHW SACU] for England and Wales, Tarragona, Madrid and Bon Pastor respectively for Spain, and University Medical Center [UMC] Utrecht for the Netherlands) in a boric acid sample container for microbiological investigation. Isolated bacteria considered to be causing a UTI were frozen and subsequently sent to the PHW SACU laboratory in Cardiff where sensitivities to urinary tract antimicrobials were determined using agar dilution and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints. Urine samples were considered positive for UTI if pure or predominant ( $10^3$  difference between the first and the second most abundant isolate on any subsequent pathogens) culture at  $\geq 10^5$  CFU/mL of any organisms.(17) We conducted a sensitivity analysis using a European definition that required a lower quantification threshold:  $\geq 10^3$  CFU/mL of any organism cultured.(18)

### ***Participant follow up***

Participants were asked to complete a paper daily diary each day for 14 days recording their symptoms (fever, pain in the side, blood in urine, smelly urine, burning or pain when passing urine, urgency, daytime frequency, night time frequency, tummy pain, restricted activities, and feeling generally unwell) on a scale of 0 (no problem) to 6 (as bad as it could be). Any follow up consultations for their UTI and medication use (including medication purchased over-the-counter)



was also recorded in the diary. Participants were contacted by telephone by the research team if diaries were not returned within an acceptable timeframe.

All data collection forms were translated for use in Spain and the Netherlands and were back translated to check meaning and validity of translations.

### ***Patient-reported recovery***

Recovery was assessed in terms of time to full recovery (the first day that all 11 symptoms were scored zero (normal / not a problem)); time to resolution of moderately bad symptoms (the first day that all 11 symptoms were scored two (slight problem or less), and; time to resolution of daytime frequency, night-time frequency, and urgency (the first day that all three symptoms were scored zero). The latter recovery outcome was derived following a factor analysis of all 11 symptoms. See online supplementary material for more detail.

### ***Sample size estimation***

The sample size was based on achieving a 95% confidence interval of 45% to 55% around a prevalence of antibiotic prescribing estimate of 50%; 50% was chosen as this gave the most conservative estimate (higher or lower percentages will have produced narrower confidence intervals). This required 385 participants but was inflated to a total of 800 participants to account for an estimated practice-level intra-cluster correlation coefficient (ICC) of 0.057. This value is in line with previous work.<sup>(19)</sup> No additions were made to this sample size for potential dropout as data on prescribing antibiotics were collected at the initial baseline visit immediately after recruitment.

### ***Data Analysis***

Descriptive statistics by country and overall were calculated using means and standard deviations (SD) inflated for clustering, medians (interquartile ranges), and proportions as appropriate. The odds of having i.) a dipstick test performed; ii.) a microbiologically-confirmed UTI; iii.) being prescribed antibiotics; iv.) receiving an antibiotic prescription concordant with urine culture results; v.) having a urine sample that would have normally been sent for culture by a GP; vi.) having a planned follow-up arrangement; vii.) being prescribed subsequent antibiotics; and viii.) re-consulting in the two-weeks following the index consultation were compared between various patient characteristics and between countries using two-level logistic regression models, with patients nested within practices. The practice-level ICC was estimated using the standard  $\pi^2/3$  estimator.<sup>(20)</sup>

Time to recovery (full recovery, resolution of moderately bad symptoms, and resolution of daytime frequency, night-time frequency, and urgency) was compared between various participant characteristics and between countries using two-level Cox proportional hazards models, with participants nested within practices.

Results are presented as odds ratios or hazard ratios, with 95% confidence intervals and p-values. Candidate variables related to case-mix comprised: age of participant at baseline; clinician-rated symptom severity score; number of days off work (0/1 or more); previous number of days with symptoms (0 to 7/8 to 14/15 to 21/22 or more); level of leukocytes found in urine on dipstick testing (negative/+ /++ /+++); presence of nitrites, protein, blood and pH level of urine (5 to 7/7.5 to 8.5) on dipstick testing; cloudy urine; offensive smelling urine; temperature of participant at baseline; diagnosed with a urine infection in the past; number of treated urine infections in the past year (0/1/2/3 or more). Candidate variables related to patient management comprised: performed a dipstick test; would have collected urine sample under normal circumstances; prescribed an antibiotic; organised follow-up. All candidate variables that were associated with the response variable at the 10% significance level (p-value <0.1) in a univariable model were entered into a multivariable model. The findings from the univariable analyses can be viewed in the online supplementary material. We compared each country to the overall average in our regression models using a sum-to-zero contrast. However, we also compared each country to England (the country from whom we recruited the most number of participants (21) to ensure our findings were not strongly influenced by our choice of contrast.(21)

Data management was performed using IBM SPSS Statistics 20. (22) All analyses were performed using R (version 3.0.1) (23) and the lme4 package.(24)

### ***Ethical Approval***

A Research Ethics Committee recognised by the United Kingdom Ethics Committee Authority (UKECA) and relevant European Committees in the Netherlands and Spain approved the study.

### ***Role of the funding source***

The funders had no role in determining the study design, data collection, analysis, writing the report and in the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

A total of 797 women were included, with a smaller proportion recruited in the Netherlands (England n = 246, Wales n = 213, Spain n = 205, and the Netherlands n = 133). Baseline data was returned for 793 participants. Urine samples that were analysed for the primary UTI identification were provided by 726 participants (91.1%). For the missing samples, urines were either not provided (n= 39), leaked on transit (n= 24) to the laboratory or were unable to be processed by the laboratory (n= 5). The two-week follow-up diary was returned by 567 participants (71.1%) (Figure 1). Those who did not return their diaries were younger on average (median age 34 years, interquartile range (IQR) 23 to 48 years vs. median 50 years, IQR 35 to 64 years), but had similar GP rated symptom severity scores at enrolment.

### **Presentation**

Symptom severity at baseline, as rated by recruiting GPs, were lowest for participants in Spain (mean 8.1, SD 3.65), followed by the Netherlands (mean 9.8, SD 4.19), England (mean 10.1, SD 4.00) and then Wales (mean 10.5, SD 4.57). Participants in the Netherlands were symptomatic for longer before consulting (median number of days 5, IQR 3- to 10 days) vs. overall median of 3 days, IQR 2 to 7 days). Median age ranged from 39 years (IQR 27 to 54 years) in Wales to 50 years (IQR 31 to 63 years) in England. The proportion in paid employment was similar in Wales, England and the Netherlands but slightly lower in Spain. The proportion that had taken one or more days off work was highest in England and lowest in the Netherlands. Before consulting, 184 participants (32.5%, ranging from 1.3% (2/155) in Spain to 46.6% (61/131) in Wales) reported that they tried managing their urine infection with cranberry juice. Mean body temperature at baseline was normal in all networks (Table 1).

### **Dipstick testing**

A total of 669/791 (84.6%) participants had a dipstick test performed at baseline, with the highest number of tests performed in the Netherlands (127/133, 95.5%) and the lowest in Spain (141/205, 68.8%).

### **Microbiological confirmation of a UTI**

Overall, 259/726 (35.7%, 95% CI 32.3 to 39.2) participants were identified with a UTI according to our primary microbiological definition, with similar proportions in England (24.3%, 95% CI 19.1 to 30.4) and Wales (24.1%, 95% CI 18.7 to 30.5) but higher in Spain (42.3%, 95% CI 35.4 to 49.6) and in the Netherlands (63.8%, 95% CI 55.1 to 71.6). Enterobacteriaceae (most commonly *Escherichia coli*) were implicated in 88.8% (230/259) and Coagulase negative staphylococci in 5.8% (15/259) of UTIs

(Table 2). Resistance to at least one of the tested antibiotics was recorded in 52.7% (110/209) of isolated strains. Trimethoprim resistance was similar between countries (16.7% (8/48) in England to 22.7% (10/44) in Wales) but nitrofurantoin resistance was higher in England and the Netherlands. However, numbers are small (Table 3).

Slightly more participants had a microbiologically confirmed UTI according to the European definition for a UTI, which requires a lower quantification threshold of  $10^3$  CFU/mL (285 participants, 39.3%). The prevalence of UTI in the Netherlands (65.4%, 83/127) remained at the highest compared to other countries (England: 22.5%, 49/218; Wales: 26.6%, 53/199; Spain: 54.9%, 100/182) using this definition.

### ***Antibiotic prescribing***

A total of 232/244 participants in England (95.1%), 196/211 in Wales (92.9%), 195/205 in Spain (95.1%) and 79/133 in the Netherlands (59.4%) were prescribed empirical antibiotics (Table 4). After adjusting for participant characteristics, the odds of being prescribed an antibiotic were 150% higher for participants in England (OR: 2.50, 95% CI 1.11 to 5.62,  $p=0.027$ ) compared to the overall average. The odds of being prescribed an antibiotic in the Netherlands were 82% lower (OR: 0.18, 95% CI 0.08 to 0.39,  $p<0.001$ ) compared to the overall average. Changing the comparison from the overall average to comparing countries to England, we found that participants in Wales and The Netherlands had lower odds of receiving an antibiotic prescription (multivariable odds ratio for Wales: 0.28, 95% CI: 0.08 to 0.97; The Netherlands: 0.07, 95% CI: 0.02 to 0.27). The odds of being prescribed an antibiotic were also higher for those participants with a positive dipstick test for blood in urine (OR: 2.95, 95% CI 1.42 to 6.14,  $p=0.004$ ) or having a higher clinician-rated symptom severity score (for one-unit increase OR: 1.20, 95% CI 1.10 to 1.31,  $p<0.001$ ). Trimethoprim was the most commonly prescribed antibiotic in Wales (76.5%, 150/196), fosfomycin in Spain (75.9%, 148/195), nitrofurantoin in the Netherlands (79.7%, 63/79), and trimethoprim and nitrofurantoin in England (46.1%, 107/232 and 48.7%, 113/232 respectively). Spain had the highest proportion of co-amoxiclav (9.7%, 19/195) and ciprofloxacin (9.2%, 18/195) prescribing. Ten participants (1.4%) received a prescription for cephalosporins (Table 4). Overall, 13/702 (1.9%) participants were given a delayed antibiotic prescription.

A total of 225/675 (33.3%) participants were prescribed an antibiotic that was concordant with the culture result (antibiotic class matched to a microbiological definition for UTI on culture and to pathogen sensitivity as well as those who did not have a microbiological UTI and were not prescribed

an antibiotic). The Netherlands had the highest proportion of concordant prescribing and Wales had the lowest (66·7%, 82/123 compared to 23·8%, 46/193). In total 450/675 (66·7%) participants were prescribed antibiotic non-concordantly. Overall, most non-concordant antibiotic prescribing related to women with a culture negative for UTI being prescribed an antibiotic (400 women, 59·3%), and few prescriptions were non-concordant because of resistance to the prescribed antibiotic (28/675, 4·8%) (Table 3). The proportion of participants prescribed a concordant antibiotic was almost identical (32·5%, 203/625) when the European laboratory criteria for UTI were used.

### ***Non-antibiotic prescribed medication***

Spain had the highest proportion of prescribed paracetamol (20·5%, 42/205) or ibuprofen (5·9%, 12/205), whilst England had the highest proportion of clinicians who advised their patients to take paracetamol (28·5%, 70/246) or ibuprofen (10·6%, 26/246). Prescriptions for paracetamol or ibuprofen, or advice to self-medicate with these was negligible in the other research networks.

### ***Planned follow-up with a GP or nurse***

Overall, 225/779 (28·9%) participants had follow-up contact arranged with a GP or nurse. This varied widely between countries, from 12% (30/242) of participants in England to 55% (112/204) of those in Spain. After adjusting for participant characteristics, having a follow-up contact arranged was associated with the age of the participant (OR for ten-year increase: 1·16, 95% CI 1·01 to 1·32,  $p=0\cdot029$ ), presence of Leukocytes (+++ result compared to a negative result: 0·43, 95% CI 0·21 to 0·88,  $p=0\cdot021$ ), positive dipstick test for nitrites (OR: 0·55, 95% CI 0·32 to 0·96,  $p=0\cdot035$ ), having cloudy urine (OR: 1·69, 95% CI 1·00 to 2·86,  $p=0\cdot049$ ) and temperature of participant (OR for one degree Celsius increase: 1·83, 95% CI 1·10 to 3·04,  $p=0\cdot019$ ).

### ***Participant recovery***

The median time to full recovery was 10 days (IQR: 6 to 14 days). However, it was 9 days for those who had a microbiologically confirmed UTI (IQR: 6 to 14 days), and 10 days for those who did not (IQR: 6 to 14 days). Antibiotic prescription at the index consultation was associated with time to full recovery (adjusted HR = 1·69, 95% CI 1·05 to 2·72,  $p=0\cdot006$ ). Those who were prescribed an antibiotic recovered faster than those who were not (median 9 days (IQR 5 to 14 days) vs. 13 (IQR 7 to 14 days)). While the median time to recovery in those who had a microbiologically confirmed UTI and were prescribed antibiotics was the shortest, and those who had neither the longest, there was no evidence of any differential association between antibiotic prescribing and a microbiologically confirmed UTI (Section 2.1 of the online supplementary material). There was also no evidence of any

differences in recovery at a country level. Similarly, there was no evidence of any differences by country in the time to resolution of moderately bad symptoms or daytime frequency/night-time frequency/urgency (See Tables in sections 3 and 4 of the online supplementary material). Findings were similar in unadjusted and adjusted models (see Tables in section 2 of the online supplementary material).

### ***Subsequent antibiotic prescribing***

In the two weeks following inclusion, 55/531 (10·4%) participants were prescribed at least one subsequent antibiotic for their UTI symptoms, with 19/133 participants in Wales (16·8%), 24/165 in England (14·5%), 11/104 in Netherlands (10·6%), and 1/147 in Spain (0·7%).

### ***Re-consultation***

During the follow up period, 130/547 (23·8%) participants reported that they had consulted with their GP or out of hours' provider for their UTI symptoms, with 41/121 participants in Wales, 28/102 in Netherlands (27·5%), 47/172 in England (27·3%), and 14/152 in Spain (9·2%).

## **Discussion**

This observational study of the presentation, management and outcomes of uncomplicated UTI in primary care in four European countries involving nearly 800 well described participants found remarkably little differences in GP rated symptoms severity at presentation, pathogens and sensitivity, but considerable differences in UTI positivity on culture, antibiotic prescribing, subsequent antibiotic prescriptions and re-consultations at the country primary care network level. Antibiotic prescribing was favourably associated with recovery. However, there was no notable difference in participant recovery at the country -level, after controlling for case-mix and initial antibiotic prescribing. Delayed antibiotic prescribing was rare, as were non-antibiotic prescriptions. These findings indicate considerable unwarranted clinical variation in care, particularly in the use of broad spectrum antibiotics, and thus highlight opportunity for determining the most cost effective pathway of care for uncomplicated UTI to minimise unnecessary exposure to antibiotics.

### ***Comparison with existing studies***

Our systematic search in January 2014 (10, 11, 13, 14, 25-32) and update in November in 2016(2, 33, 34) found that ours is the first prospective study that compared routine management of urinary tract infection in primary care between country settings, taking case mix and microbiological findings into account.

Daytime frequency and urgency were both the most prevalent and severely graded (as 'bad') symptoms across all networks. Frequency and dysuria were the most prevalent symptoms reported in previous European studies, although urgency was reported by fewer studies and had a lower prevalence.(11, 26, 27, 32, 34) Women in the Netherlands waited longer before consulting: this may explain to some extent the higher proportion of those with a microbiological confirmed UTI.

Urinalysis dipsticks were the most commonly used tests across all four networks, and was similar to studies in Spain, Sweden and Germany and where use of dipstick urinalysis ranged from 84% to 93%.(25, 29, 32)

We identified UTI on culture in 35·7% of cases overall, with similar proportions in England and Wales (24·3% and 24·1% respectively), but much higher in Spain (42·3%) and the Netherlands (63·8%). Vellinga and colleagues found that 70% of urines from patients with suspected UTI had no evidence of UTI on culture in a study in Ireland.(14) Hummers-Pradier found 65·6% of patients in Germany had a positive result (using a definition of 10<sup>3</sup> CFU/mL and no more than two pathogens),(29) and Etienne(33) found 78% had a positive urine culture in a French study; however both of these studies used a lower threshold for positivity compared to our primary definition. Three UK studies reported positivity of samples between 25% and 38%(10, 13, 27), while Little and colleagues' observational study, also in the UK, found that 50% of women with symptoms attributed to a UTI met similar microbiological criteria for a UTI that was used in our study (16) and they also found that women treated with antibiotics recovered faster.(11)

As with our study, Etienne and colleagues found that *Escherichia coli* predominated with generally high rates of sensitivity to commonly used antibiotics; 13% of isolates resistant to trimethoprim-sulfamethoxazole compared to our overall finding for trimethoprim resistance of 18·7%.(33)

In our study overall, antibiotics were prescribed for 88·5% (59·4% in the Netherlands and over 92% in the other settings). Antibiotic prescribing ranged from 56% to 98·6% in previous European studies.(14, 26, 29) Two English studies(11, 27) found prescribing rates similar to those we report for our network in England, and a Spanish study found a similar proportion to the prescribing rate in our Spanish network.(32) A Welsh study found a much lower prescribing rate than ours, but that study relied on patient recall of antibiotic prescription rather than GPs recording this at the time of consultation.(10)

Trimethoprim (in Wales), nitrofurantoin (in Wales, England and the Netherlands) and fosfomycin (in Spain) were prescribed most commonly in our study. The highest proportion of quinolone prescription was in the Spanish network, where high levels of quinolone prescribing for

uncomplicated UTI has previously been identified.(30, 33) Studies from across Europe also demonstrate the wide variation between counties in choice of antibiotics prescribed for uncomplicated UTI.(2, 25, 26, 28, 30, 31, 33, 34)

We found that guideline concordant antibiotic prescribing ranged from 23·8% in Wales to 66·7% in the Netherlands. Philips and colleagues compared adherence to guidelines regarding the type of antibiotics prescribed for the primary care *out of hours*’ management of UTI in four European countries, and found that adherence to antibiotic prescribing guidelines ranged from 25% to 100%.(1) Other studies have similarly confirmed poor adherence to guidelines for managing uncomplicated UTI in primary care.(2, 25, 26, 30, 32, 35)

### ***Strengths and weaknesses***

We deliberately did not try to standardise investigations and management across the centres because our goal was to describe variation and explore whether any variation we identified was associated with recovery and microbiological findings and thus clinically warranted. This prospective study recruited participants using the same eligibility criteria, outcome measures and data collection tools in four contrasting European settings, and was adequately powered to determine variation at a primary care network level. Susceptibility testing was standardised in a central microbiology research laboratory. However, diary return rates were lower in Wales and women recruited in Wales tended to be younger than in the other networks. Clinicians may have altered their behaviour because of research conditions, despite clear communication that our purpose was to describe routine care. Their assessment of the patients’ symptoms at study inclusion may have been influenced by personal, interpersonal, and cultural factors. In addition, while our study largely met our pre-specified power requirements, relatively few patients from each network were included, and fewer participants were recruited in the Netherlands.

We did not include primary care research networks in an Eastern or Northern European country. Participating networks were local organising groups that recruited general practices into the study. Networks were selected partly because of their research experience and their ability to implement the study protocol to a high standard. We do not suggest that each of the four networks necessarily reflect consulting behaviour and care of the whole country. Study participants may have been selectively rather than sequentially invited to participate, and we have no reliable logs of patients who were eligible but not invited to participate. Studies in both hospitals and primary care that rely on opportunistic recruitment of acutely unwell patients during times of busy service delivery may be



prone to selection bias that is hard to fully assess. Participants for whom we have outcome data were older but with similar symptom severity scores at inclusion compared to those lost to follow up. While local laboratories followed their standard operating procedures for urinalysis and storage of microorganisms, sample transport times and arrangements may have differed. Usual primary care management of uncomplicated UTI in the Netherlands, where we identified the biggest differences in UTI positivity and antibiotic prescribing, differs in important ways from the other countries. For example, it is common for symptomatic women to first drop off a urine sample at the practice, and if positive for nitrite on dipstick, it is then tested with a dipslide culture, before any antibiotic prescribing decision is made and urine sent for laboratory culture. In addition, the higher proportion of women who were positive for a UTI on culture may be related to waiting longer before consulting.

### ***Implications***

We have demonstrated little variation in presentation, pathogens and sensitivity of pathogens causing UTI in four European settings. However, in contrast, the proportion meeting laboratory definitions of UTI, the proportion prescribed an antibiotic, the antibiotics commonly prescribed, subsequent antibiotics prescribed, and consulting behaviour did differ markedly. Despite this, a variety of participant-reported recovery measures showed no variation at the country level. Antibiotics were associated with improved outcomes overall. While more of the UTI treatment in the Netherlands was “concordant” according to our study definition, it was also at a cost of undertreating microbiologically confirmed UTI at a higher rate than other countries (16% versus <1% for other countries).

Further research needs to better define the relationship between microbiological findings (using optimal diagnostic testing), patient symptoms at presentation, prognosis, and response to antimicrobials. Given the low rates of microbiologically-confirmed UTI on culture, especially in the UK, and response of some women with uncomplicated UTI to non-antibiotic treatment such as ibuprofen(36), it is likely that symptoms of uncomplicated UTI represent a syndrome that is caused by a range of aetiology that includes infection that may or may not be routinely cultured,(37) but also inflammation at various sites in the urinary tract due to non-infectious causes. The most cost effective care pathway for managing symptoms of uncomplicated UTI should now be determined and care standardised to maximise symptom resolution, resource use, and better targeted antibiotic prescribing, as current variation in care is not warranted on clinical grounds.

**Authors' contributions**

CCB was the chief investigator and acts as guarantor of the trial in its entirety. CCB led the development of the research question, study design and implementation of the study protocol, along with NF, CL, PL, MM, ETJ, MG, KH and TV. JB was the Study Manager and ETJ the Senior Study Manager who coordinated the operational delivery of the study protocol across the four networks. NK coordinated data management for all four networks and ML and TP undertook analyses supervised by DG and KH respectively based on a Statistical Analysis Plan developed by TP & KH. DG performed quality assurance checks for all statistical analysis. PL, CL and TV were principal investigators, responsible for study oversight, at Southampton, Spain and the Netherlands respectively with KR, MM, NF, JB and CB coordinating recruitment. MW provided expert microbiology input and supervised the microbiological work in the Specialist Antimicrobial Chemotherapy Unit (SACU). All authors listed provided critical review and final approval of the manuscript.

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**Conflict of interest**

All authors have declared no conflict of interest.

**Table 1: Participant characteristics at study inclusion**

Demographic		Wales		England		Spain		Netherlands		Overall	
		n		n		n		n		N	
Age at baseline (Median, IQR)		211	39 years (27, 54)	245	50 years (31, 63)	205	45 years (30, 61)	133	45 years (34, 62)	793	45 (30, 61)
GP symptom severity score (Mean, SD)	Urgency	204	3.6 (1.9)	239	3.7 (1.6)	205	2.9 (1.6)	133	3.2 (1.8)	781	3.4 (1.7)
	Daytime frequency	203	3.8 (1.7)	239	3.6 (1.4)	205	3.1 (1.48)	133	3.4 (1.58)	780	3.5 (2.45)
	Night time frequency	202	3.0 (2.0)	239	2.9 (1.8)	205	2.1 (1.6)	132	2.5 (1.9)	778	2.7 (1.9)
	Summary score of above three-items	202	10.5 (4.6)	239	10.1 (4.0)	205	8.1 (3.8)	132	9.1 (4.2)	778	9.5 (4.2)
Paid employment	Yes (%)	132	62.6	147	60.2	88	42.9	84	63.2	451	56.9
	No (%)	79	37.4	97	39.8	117	57.1	49	36.8	342	43.1
Of those who work; has they been off work because of this illness	0 (%)	114	90.5	107	78.7	72	84.7	77	96.2	370	86.7
	1 or more days (%)	12	9.5	29	21.3	13	15.3	3	3.8	57	13.3
Number of days with symptoms before consulting (Median, IQR)		210	3 (2, 7)	240	4 (2, 6)	204	2.5 (1, 5)	131	5 (3, 10)	785	3 (2, 7)
Temperature at baseline (degree Celsius) (Mean, SD)		204	36.6 (0.5)	239	36.7 (0.5)	205	36.2 (0.4)	122	36.7 (0.5)	770	36.5 (0.5)
Managing their UTI with cranberry juice*	Yes (%)	61	46.6	81	45.8	2	1.3	40	38.1	184	32.5
	No (%)	70	53.4	96	54.2	153	98.7	65	61.9	383	67.5

\*Based on participants who had returned diaries

**Table 2: Prevalence of UTI and urinary pathogens identification**

		Wales		England		Spain		Netherlands		Overall	
		n	%	n	%	n	%	n	%	N	%
<b>No UTI confirmed</b>	Mixed growth (2 or more organisms)	103	51.8	118	54.1	9	4.9	37	29.1	267	36.8
	Single organism grow at $<10^5$	34	17.1	37	17.0	26	14.3	2	1.6	99	13.6
	No growth	14	7.0	10	4.6	34	18.7	7	5.5	65	9.0
	Unclear organism names (mixed growth)	0	0.0	0	0.0	36	19.8	0	0.0	36	5.0
	<b>TOTAL</b>	151	75.9	165	75.7	105	57.7	46	36.2	467	64.3
<b>UTI-confirmed</b>	Pure culture at $10^5$ or above	34	17.1	38	17.4	77	42.3	81	63.8	230	31.7
	Predominant culture at $10^5$ or above	14	7.0	15	6.9	0	0.0	0	0.0	29	4.0
	<b>TOTAL</b>	48	24.1	53	24.3	77	42.3	81	63.8	259	35.7
<b>Urinary pathogen identification*</b>	<b>Enterobacteriaceae</b>	44	91.7	48	90.6	66	85.7	72	88.9	230	88.8
	<b>Coagulase negative staphylococci (<i>S. saprophyticus</i>)</b>	2	4.2	1	1.9	9	11.7	3	3.7	15	5.8
	<b>Other pathogens</b>	2	4.2	4	7.6	2	2.6	6	7.3	14	5.6
	<b>Total</b>	48	100.0	53	100.0	77	100.0	81	100.0	259	100.0

\*Based on those who have a microbiologically-confirmed UTI

**Table 3:** Resistance profiles of identified urinary pathogens\*

	<b>Wales (n=44)</b>		<b>England (n=48)</b>		<b>Spain (n=44)</b>		<b>The Netherlands (n=73)</b>		<b>Total (n=209)</b>	
	n	%	n	%	n	%	n	%	n	%
<b>Amoxicillin</b>	15	34.1	25	52.1	27	61.4	18	24.7	85	40.7
<b>Trimethoprim</b>	10	22.7	8	16.7	8	18.2	13	17.8	39	18.7
<b>Co-amoxiclav</b>	0	0.0	4	8.3	12	27.3	0	0.0	16	7.7
<b>Nitrofurantoin</b>	0	0.0	4	8.3	1	2.3	6	8.2	11	5.3
<b>Fosfomycin</b>	3	6.8	2	4.2	3	6.8	3	4.1	11	5.3
<b>Ciprofloxacin</b>	2	4.5	1	2.1	2	4.5	2	2.7	7	3.3
<b>Gentamicin</b>	1	2.3	2	4.2	1	2.3	1	1.4	5	2.4
<b>Cefalexin</b>	0	0.0	2	4.2	2	4.5	1	1.4	5	2.4
<b>Meticillin</b>	0	0.0	2	4.2	3	6.8	0	0.0	5	2.4
<b>Cefotaxime</b>	0	0.0	2	4.2	0	0.0	2	2.7	4	1.9
<b>Ceftazidime</b>	0	0.0	1	2.1	1	2.3	2	2.7	4	1.9
<b>Ertapenem</b>	0	0.0	1	2.1	2	4.5	0	0.0	3	1.4
<b>Temocillin</b>	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
<b>Sensitive to all tested antibiotics</b>	24	54.5	16	33.3	13	29.5	46	63.0	99	47.4
<b>Resistant to single antibiotic</b>	12	27.3	18	37.5	13	29.5	14	19.2	57	27.3
<b>Resistant to more than one antibiotic</b>	8	18.2	14	29.2	18	40.9	13	17.8	53	25.4

\*Based on those who have a microbiologically-confirmed UTI

**Table 4: Antibiotic prescriptions at the initial consultation**

		Wales		England		Spain		Netherlands		Overall	
		n	%	n	%	n	%	n	%	N	%
<b>No Prescribed antibiotics</b>		15	7.1	12	4.9	10	4.9	54	40.6	91	11.5
<b>Prescribed antibiotics</b>		196	92.9	232	95.1	195	95.1	79	59.4	702	88.5
<b>Prescription of antibiotic</b>	<b>Fosfomycin</b>	0	0.0	0	0.0	148	75.9	5	6.3	153	21.8
	<b>Trimethoprim</b>	150	76.5	107	46.1	0	0.0	9	11.4	266	37.9
	<b>Nitrofurantoin</b>	34	17.3	113	48.7	6	3.1	63	79.7	216	30.8
	<b>Co-amoxiclav</b>	2	1.0	1	0.4	19	9.7	1	1.3	23	3.3
	<b>Cephalosporins</b>	3	1.5	5	2.2	2	1.0	0	0.0	10	1.4
	<b>Ciprofloxacin</b>	2	1.0	0	0.0	18	9.2	1	1.3	21	3.0
	<b>Other antibiotic*</b>	5	2.6	6	2.6	2	1.0	0	0.0	13	1.9
<b>OR for receiving an antibiotic prescription (95% CI), p-value†‡</b>		0.70 (0.34, 1.46), 0.346		2.50 (1.11, 5.62), 0.027		3.22 (1.32, 7.86), 0.010		0.18 (0.08, 0.39), <0.001		1.00	
<b>Concordant antibiotic prescriptions</b>	<b>UTI &amp; antibiotic &amp; sensitive</b>	33	17.1	40	19.0	38	25.7	51	41.5	162	24.0
	<b>No UTI &amp; no antibiotic</b>	13	6.7	12	5.7	7	4.7	31	25.2	63	9.3
	<b>Total</b>	<b>46</b>	<b>23.8</b>	<b>52</b>	<b>24.6</b>	<b>45</b>	<b>30.4</b>	<b>82</b>	<b>66.7</b>	<b>225</b>	<b>33.3</b>
<b>non-concordant antibiotic prescriptions</b>	<b>UTI &amp; antibiotic &amp; resistance</b>	10	5.2	8	3.8	4	2.7	6	4.9	28	4.1
	<b>UTI &amp; no antibiotic</b>	1	0.5	0	0.0	1	0.7	20	16.3	22	3.3
	<b>No UTI &amp; antibiotic</b>	136	70.5	151	71.6	98	66.2	15	12.2	400	59.3
	<b>Total</b>	<b>147</b>	<b>76.2</b>	<b>159</b>	<b>75.4</b>	<b>103</b>	<b>69.6</b>	<b>41</b>	<b>33.3</b>	<b>450</b>	<b>66.7</b>
	<b>Overall</b>	193	100.0	211	100.0	148	100.0	123	100.0	675	100.0
<b>OR for receiving an concordant antibiotic prescription (95% CI), p-value†§</b>		0.57 (0.43, 0.77), <0.001		0.60 (0.45, 0.79), <0.001		0.80 (0.59, 1.08), 0.144		3.66 (2.67, 5.02), <0.001		1.00	

\*Other antibiotic includes: Amoxicillin, Metronidazole, Pipemidic Acid and Doxycycline· †Two-level model (with Centre as the 2<sup>nd</sup> level and Participants as the 1<sup>st</sup> level)· ‡Compared to the overall average· Adjustment made for participant characteristics including; age, clinician-rated symptom severity score, previous number of days with symptoms, positive protein test, and positive blood test· Model based on 455 participants (57.1%) nested within 47 practices, Practice-level ICC=0.140· §Adjusted for country.

## References

1. Philips H, Huibers L, Holm Hansen E, Bondo Christensen M, Leutgeb R, Klemenc-Ketis Z, et al. Guidelines adherence to lower urinary tract infection treatment in out-of-hours primary care in European countries. *Qual Prim Care*. 2014;22(4):221-31.
2. Hawker JL, Smith S, Smith GE, Morbey R, Johnson AP, Fleming DM, et al. Trends in antibiotic prescribing in primary care for clinical syndromes subject to national recommendations to reduce antibiotic resistance, UK 1995-2011: analysis of a large database of primary care consultations. *J Antimicrob Chemother*. 2014;69(12):3423-30.
3. Ironmonger D, Edeghere O, Bains A, Loy R, Woodford N, Hawkey PM. Surveillance of antibiotic susceptibility of urinary tract pathogens for a population of 5.6 million over 4 years. *J Antimicrob Chemother*. 2015;70(6):1744-50.
4. Butler CC, Hood K, Verheij T, Little P, Melbye H, Nuttall J, et al. Variation in antibiotic prescribing and its impact on recovery in patients with acute cough in primary care: prospective study in 13 countries. *BMJ*. 2009;338:b2242.
5. Wennberg JE. Forty years of unwarranted variation--and still counting. *Health Policy*. 2014;114(1):1-2.
6. Wood F, Simpson S, Butler CC. Socially responsible antibiotic choices in primary care: a qualitative study of GPs' decisions to prescribe broad-spectrum and fluoroquinolone antibiotics. *Fam Pract*. 2007;24(5):427-34.
7. Wood F, Phillips C, Brookes-Howell L, Hood K, Verheij T, Coenen S, et al. Primary care clinicians' perceptions of antibiotic resistance: a multi-country qualitative interview study. *J Antimicrob Chemother*. 2013;68(1):237-43.
8. Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. *Am J Med*. 2002;113 Suppl 1A:5S-13S.
9. Butler CC, Hawking MK, Quigley A, McNulty CA. Incidence, severity, help seeking, and management of uncomplicated urinary tract infection: a population-based survey. *Br J Gen Pract*. 2015;65(639):e702-7.
10. O'Brien K, Hillier S, Simpson S, Hood K, Butler C. An observational study of empirical antibiotics for adult women with uncomplicated UTI in general practice. *J Antimicrob Chemother*. 2007;59(6):1200-3.
11. Little P, Merriman R, Turner S, Rumsby K, Warner G, Lowes JA, et al. Presentation, pattern, and natural course of severe symptoms, and role of antibiotics and antibiotic resistance among patients presenting with suspected uncomplicated urinary tract infection in primary care: observational study. *BMJ*. 2010;340:b5633.
12. McIsaac WJ, Low DE, Biringer A, Pimlott N, Evans M, Glazier R. The impact of empirical management of acute cystitis on unnecessary antibiotic use. *Arch Intern Med*. 2002;162(5):600-5.
13. Nazareth I, King M. Decision making by general practitioners in diagnosis and management of lower urinary tract symptoms in women. *BMJ*. 1993;306(6885):1103-6.
14. Vellinga A, Cormican M, Hanahoe B, Bennett K, Murphy AW. Antimicrobial management and appropriateness of treatment of urinary tract infection in general practice in Ireland. *BMC Fam Pract*. 2011;12(1):108.
15. Nicolle LE, Committee\* ACG. Complicated urinary tract infection in adults. *Can J Infect Dis Med Microbiol*. 2005;16(6):349-60.
16. Little P, Turner S, Rumsby K, Jones R, Warner G, Moore M, et al. Validating the prediction of lower urinary tract infection in primary care: sensitivity and specificity of urinary dipsticks and clinical scores in women. *Br J Gen Pract*. 2010;60(576):495-500.
17. Health Protection Agency. Diagnosis of UTI: quick reference guide for primary care 2002 [updated 2011. Available from: [https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/323398/UTI\\_guidelines\\_with\\_RCGP\\_logo.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/323398/UTI_guidelines_with_RCGP_logo.pdf).

18. Grabe M, Bjerklund-Johansen TE, Botto H, Çek M, Naber KG, Pickard RS, et al. Guidelines on Urological Infections: European Association of Urology; 2013 [Available from: [http://uroweb.org/wp-content/uploads/18\\_Urological-infections\\_LR.pdf](http://uroweb.org/wp-content/uploads/18_Urological-infections_LR.pdf).
19. Flottorp S, Oxman AD, Havelsrud K, Treweek S, Herrin J. Cluster randomised controlled trial of tailored interventions to improve the management of urinary tract infections in women and sore throat. *BMJ*. 2002;325(7360):367.
20. Snijders TAB, Bosker RJ. Multilevel Analysis: An Introduction to Basic and Advanced Multilevel Modeling. London: Sage Publishers; 2012.
21. Hardy M. Regression with Dummy Variables. Newbury Park, CA: Sage; 1993.
22. IBM C. IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp.; 2011.
23. Team. RC. A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2012.
24. Bates D, Maechler M, Bolker B. Linear mixed-effects models using S4 classes. R package version 0.999999-0 ed2012.
25. Andre M, Molstad S, Lundborg CS, Odenholt I, Swedish Study Group on Antibiotic U. Management of urinary tract infections in primary care: a repeated 1-week diagnosis-prescribing study in five counties in Sweden in 2000 and 2002. *Scand J Infect Dis*. 2004;36(2):134-8.
26. Canbaz S, Peksen Y, Tevfik Sunter A, Leblebicioglu H, Sunbul M. Antibiotic prescribing and urinary tract infection. *Int J Antimicrob Agents*. 2002;20(6):407-11.
27. Fahey T, Webb E, Montgomery AA, Heyderman RS. Clinical management of urinary tract infection in women: a prospective cohort study. *Fam Pract*. 2003;20(1):1-6.
28. Galatti L, Sessa A, Mazzaglia G, Pecchioli S, Rossi A, Cricelli C, et al. Antibiotic prescribing for acute and recurrent cystitis in primary care: a 4 year descriptive study. *J Antimicrob Chemother*. 2006;57(3):551-6.
29. Hummers-Pradier E, Ohse AM, Koch M, Heizmann WR, Kochen MM. Management of urinary tract infections in female general practice patients. *Fam Pract*. 2005;22(1):71-7.
30. Martinez MA, Inglada L, Ochoa C, Villagrasa JR, Spanish Study Group On Antibiotic T. Assessment of antibiotic prescription in acute urinary tract infections in adults. *J Infect*. 2007;54(3):235-44.
31. Skerk V, Skerk V, Jaksic J, Lakos AK, Matrapazovski M, Malekovic G, et al. Research of urinary tract infections in family medicine physicians' offices--empiric antimicrobial therapy of urinary tract infections--Croatian experience. *Coll Antropol*. 2009;33(2):625-31.
32. Llor C, Rabanaque G, Lopez A, Cots JM. The adherence of GPs to guidelines for the diagnosis and treatment of lower urinary tract infections in women is poor. *Fam Pract*. 2011;28(3):294-9.
33. Etienne M, Lefebvre E, Frebourg N, Hamel H, Pestel-Caron M, Caron F, et al. Antibiotic treatment of acute uncomplicated cystitis based on rapid urine test and local epidemiology: lessons from a primary care series. *BMC Infect Dis*. 2014;14:137.
34. Willems CS, van den Broek D'Obrenan J, Numans ME, Verheij TJ, van der Velden AW. Cystitis: antibiotic prescribing, consultation, attitudes and opinions. *Fam Pract*. 2014;31(2):149-55.
35. Vellinga A, Galvin S, Duane S, Callan A, Bennett K, Cormican M, et al. Intervention to improve the quality of antimicrobial prescribing for urinary tract infection: a cluster randomized trial. *CMAJ*. 2016;188(2):108-15.
36. Gagyor I, Haasenritter J, Bleidorn J, McIsaac W, Schmiemann G, Hummers-Pradier E, et al. Predicting antibiotic prescription after symptomatic treatment for urinary tract infection: development of a model using data from an RCT in general practice. *Br J Gen Pract*. 2016;66(645):e234-40.
37. McLellan LK, Hunstad DA. Urinary Tract Infection: Pathogenesis and Outlook. *Trends Mol Med*. 2016.



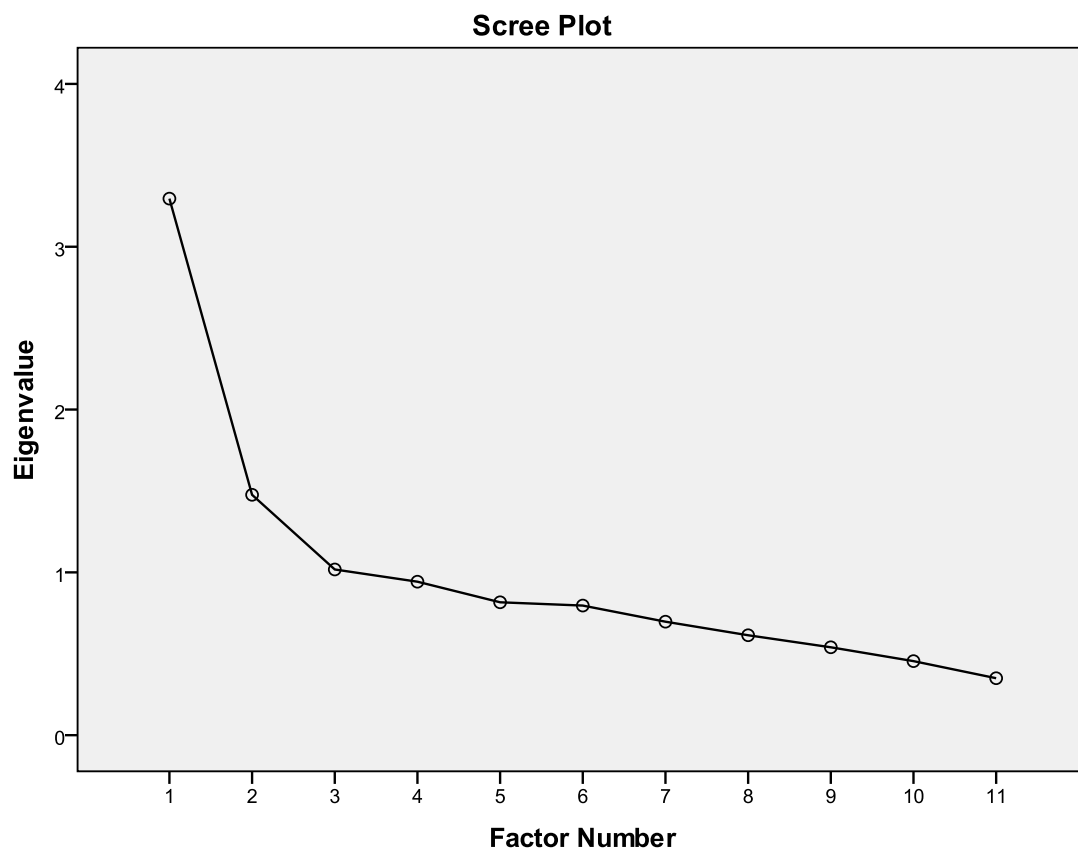
## ONLINE SUPPLEMENTARY MATERIAL:

### 1. Description of factor analysis to create GP-rated symptom severity score and ‘time to resolution of day-time frequency, night-time frequency, and urgency’ variable

#### *GP-rated symptom severity score*

All 11 GP-rated symptoms were subject to a factor analysis to determine if there were any patterns or clustering among symptoms. Factors were extracted using maximum likelihood and rotated using the oblique method (direct oblimin). Any participants who had missing values were not included. Three factors were identified, with factor 1 having an eigenvalue of 3.30 accounting for 30.0% of the total variance, factor 2 an eigenvalue of 1.48 and accounting for 13.4% of the variance, and factor 3 an eigenvalue of 1.02 and account for 9.3% (Figure i). The symptoms forming Factor 1 included urgency, daytime frequency and nighttime frequency, and therefore these items were combined into a summary GP-rated symptom severity score and used in analysis presented throughout this paper.

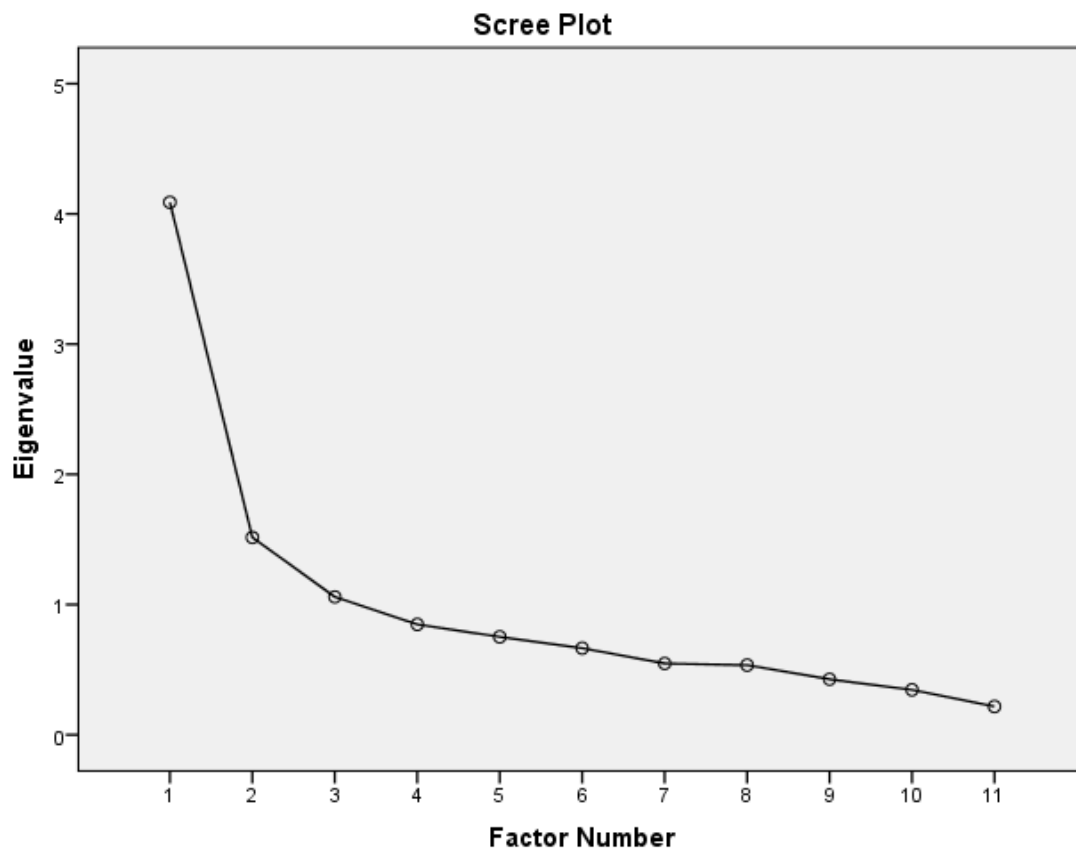
**Figure i:** Scree plot of eigenvalues from a factor analysis of the GP-rated symptoms



### *Time to resolution of daytime frequency, nighttime frequency, and urgency*

Similarly, all 11 participant-rated symptoms were subjected to a factor analysis to determine if there were any patterns among symptoms in terms of time to recovery from them. Any participants who had missing values were not included, nor were patients whose symptoms had not recovered after 14 days. From examining both the scree plot (Figure ii) and the eigenvalues after extraction, two factors were identified showing two groups of symptoms that clustered together with regards to their time to recovery. Factor 1 displayed an eigenvalue of 3.51 accounting for 31.9% of the variance, and Factor 2 displayed an eigenvalue of 1.18 and accounted for 10.76% of the variance. The symptoms forming Factor 1 included urgency, daytime frequency and nighttime frequency, and this factor was used as part of the analysis of outcomes.

**Figure ii:** Scree plot of eigenvalues from a factor analysis of the participant-rated symptoms



## 2. Time to full recovery analysis

### 2.1 Univariable analyses

Variable type	Variable	n	Hazard Ratio	95% Confidence Interval		p-value	Retain in multivariable analysis
				Lower	Upper		
Case-mix	Participants age at baseline	551	0.99	0.99	1.00	0.076	Yes
Case-mix	Clinician-rated symptom severity score	543	0.96	0.93	0.98	0.002	Yes
Case-mix	Number of days off work	0 day	258				No
		1 or more	35	0.91	0.59	1.40	
Case-mix	Previous number of days with symptoms	0 to 7 days	439			0.026	Yes
		8 to 14 days	62	0.67	0.47	0.96	
		15 to 21 days	23	0.89	0.52	1.53	
		22 days or more	22	0.48	0.26	0.91	
Case-mix	Leukocytes	Negative	80			0.068	No*
		+	87	1.31	0.87	1.98	
		++	109	1.55	1.04	2.29	
		+++	169	1.58	1.11	2.27	
Case-mix	Nitrites	Negative	291				No
		Positive	169	0.97	0.76	1.23	
Case-mix	Protein	Negative	245				No
		Positive	186	0.97	0.75	1.24	
Case-mix	Blood	Negative	125				No
		Positive	217	1.21	0.91	1.61	
Case-mix	pH	5 to 7	323				No
		7.5 to 8.5	28	1.06	0.67	1.69	
Case-mix	Cloudy urine	No	260				No*
		Yes	207	1.25	1.00	1.57	
Case-mix	Offensive smell urine	No	320				No
		Yes	148	0.87	0.68	1.11	
Case-mix	Temperature of participants at baseline	533	1.05	0.85	1.30	0.644	No
Case-mix	Diagnosed a urine infection in the past	No	86				Yes
		Yes	455	0.69	0.54	0.87	
Case-mix	Number of treated urine infections in the past year	0	221			<0.001	Yes
		1	88	0.62	0.45	0.85	
		2	85	0.79	0.59	1.07	
		3 or more	120	0.50	0.37	0.67	
Management	Performed a dipstick test	No	78				No

		Yes	471	0.85	0.63	1.17	0.317	
Management	Would have collected a urine sample under normal circumstances	No	282					No
		Yes	235	0.92	0.73	1.16	0.492	
Management	Prescribed antibiotic	No	56					Yes
		Yes	494	1.66	1.10	2.50	0.015	
Management	Organised follow-up	No	371					No
		Yes	169	0.84	0.65	1.09	0.196	
Exposure	UTI	No	307					Yes
		Yes	194	1.24	0.98	1.57	0.074	
Exposure	Wales		128	0.95	0.79	1.14	0.919	Yes
	England		169	1.00	0.85	1.19		
	Spain		150	1.06	0.89	1.26		
	Netherlands		104	0.99	0.82	1.21		

\*Due to the high number of missing responses regarding level of leukocytes and cloudy urine, these variables were not retained in the multivariable model.

## 2.2 Two-level Cox proportional hazards model of time to full recovery (participants nested within practices)

Variable		Hazard Ratio	95% Confidence Interval		p-value
			Lower	Upper	
Age of participants at baseline		0.99	0.99	1.00	0.096
Symptoms Severity Score		0.94	0.91	0.97	<0.001
Previous number of days with symptoms	0 to 7		Reference category		
	8 to 14	0.76	0.51	1.13	0.043
	15 to 21	1.09	0.57	2.09	
	22 or more	0.56	0.27	1.16	
Number of times a urine infection had been treated in the past year	0		Reference category		
	1	0.66	0.46	0.95	0.002
	2	0.79	0.54	1.14	
	3 or more	0.53	0.37	0.75	
Prescribed antibiotic	No		Reference category		
	Yes	1.69	1.05	2.72	0.006
UTI	No		Reference category		
	Yes	1.03	0.77	1.38	0.542
Country	Wales	0.99	0.80	1.22	0.900
	England	0.97	0.80	1.18	0.770
	Spain	0.98	0.80	1.19	0.810
	The Netherlands	1.07	0.84	1.37	0.588

\*Model based on 457 participants. Countries compared to the overall average

### 2.3 Two-level Cox proportional hazards model of time to full recovery with countries compared to England (participants nested within practices)

Variable		Hazard Ratio	95% Confidence Interval		p-value
			Lower	Upper	
Age of participants at baseline		0.994	0.988	1.001	0.096
Clinician-rated symptom severity score		0.948	0.920	0.976	<0.001
Previous number of days with symptoms	0 to 7	Reference category			
	8 to 14	0.641	0.437	0.941	0.043
	15 to 21	0.996	0.548	1.810	
	22 or more	0.519	0.263	1.027	
Number of times a urine infection had been treated in the past year	0	Reference category			
	1	0.692	0.496	0.966	0.002
	2	0.840	0.604	1.170	
	3 or more	0.556	0.405	0.762	
Prescribed antibiotic	No	Reference category			
	Yes	1.894	1.199	2.993	0.006
UTI	No	Reference category			
	Yes	1.083	0.837	1.402	0.542
Country	England	Reference category			
	Wales	1.02	0.74	1.40	0.959
	Spain	1.00	0.74	1.37	
	The Netherlands	1.10	0.76	1.60	

\*Model based on 457 participants. Countries compared to The Netherlands

### 3. Time to resolution of moderately bad symptoms

#### 3.1 Univariable analyses

Variable type	Variable		n	Hazard Ratio	95% Confidence Interval		p-value	Retain in multivariable analysis
					Lower	Upper		
Case-mix	Participants age at baseline		551	1.00	1.00	1.00	0.794	No
Case-mix	Clinician-rated symptom severity score		543	0.95	0.93	0.97	<0.001	Yes
Case-mix	Number of days off work	0 day	258					No
		1 or more	35	0.98	0.68	1.41	0.892	
Case-mix	Previous number of days with symptoms	0 to 7 days	439				0.068	Yes
		8 to 14 days	62	0.80	0.61	1.07		
		15 to 21 days	23	0.67	0.42	1.08		
		22 days or more	222	0.65	0.40	1.05		
Case-mix	Leukocytes	Negative	80				0.584	No
		+	87	0.97	0.70	1.35		
		++	109	0.99	0.72	1.37		
		+++	169	1.14	0.85	1.51		
Case-mix	Nitrites	Negative	291				0.525	No
		Positive	169	0.94	0.76	1.15		
Case-mix	Protein	Negative	245				0.883	No
		Positive	186	1.02	0.82	1.25		
Case-mix	Blood	Negative	125				0.849	No
		Positive	217	1.02	0.81	1.29		
Case-mix	pH	5.0 to 7	323				0.928	No
		pH 7.5 to pH 8.5	28	0.98	0.66	1.46		
Case-mix	Cloudy urine	No	260				0.592	No
		Yes	207	1.06	0.87	1.28		
Case-mix	Offensive smell urine	No	320				0.023	No*
		Yes	148	0.79	0.64	0.97		
Case-mix	Temperature of participants at baseline		533	1.06	0.89	1.27	0.521	No
Case-mix	Diagnosed a urine infection in the past	No	86				0.002	yes
		Yes	445	0.69	0.54	0.87		
Case-mix	Number of urine infections treated in the past year	0	221				0.001	Yes
		1	88	0.76	0.58	0.99		
		2	85	0.69	0.53	0.90		
		3 or more	120	0.62	0.49	0.79		
Management	Performed a dipstick test	No	78				0.427	No
		Yes	471	1.12	0.85	1.47		

Management	Would have collected a urine sample under normal circumstances	No	282					No
		Yes	235	1.05	0.86	1.28	0.623	
Management	Prescribed antibiotic	No	56					No
		Yes	494	1.13	0.82	1.57	0.456	
Management	Organised follow-up	No	371					No
		Yes	169	0.84	0.67	1.05	0.122	
Exposure	UTI	No	307					Yes (exposure of interest)
		Yes	194	1.05	0.86	1.29	0.618	
Exposure	Wales		128	0.98	0.84	1.15	0.738	Yes (exposure of interest)
	England		169	1.01	0.88	1.16		
	Spain		150	1.08	0.93	1.25		
	Netherlands		104	0.93	0.79	1.11		

\*Due to the high number of missing responses in offensive smelling urine, this variable was not retained in the multivariable model



### 3.2 Two-level Cox proportional hazards model of time to resolution of moderately bad symptoms with countries compared to the overall average (participants nested within practices)

Variable		Hazard Ratio	95% Confidence Interval		p-value
			Lower	Upper	
Clinician-rated symptom severity score		0.955	0.932	0.979	<0.001
Previous number of days with symptoms	0 to 7 days	Reference category			
	8 to 14 days	0.781	0.576	1.059	0.0503
	15 to 21 days	0.687	0.411	1.149	
	22 days or more	0.573	0.343	0.957	
Number of times a urine infection had been treated in past year	0	Reference category			
	1	0.826	0.628	1.086	0.016
	2	0.724	0.543	0.966	
	3 or more	0.680	0.525	0.883	
UTI	No	Reference category			
	Yes	0.987	0.798	1.221	0.906
Country	Wales	1.101	0.922	1.314	0.640
	England	0.971	0.824	1.144	
	Spain	1.027	0.867	1.217	
	Netherlands	0.911	0.753	1.104	

\*Model based on 457 participants. Countries compared to the overall average

#### 4. Time to resolution of daytime frequency, nighttime frequency, and urgency

##### 4.1. Univariable analyses

Variable type	Variable	n	Hazard Ratio	95% Confidence Interval		p-value	Retain in multivariable analysis
				Lower	Upper		
Case-mix	Participants age at baseline	510	0.991	0.986	0.997	0.003	Yes
Case-mix	Clinician-rated symptom severity score	532	0.940	0.917	0.964	<0.001	Yes
Case-mix	Days off work	0 days					No
		1 or more days	0.911	0.601	1.379	0.658	
Case-mix	Previous number of days with symptoms	0 to 7 days				0.091	Yes
		8 to 14 days	0.740	0.530	1.032		
		15 to 21 days	0.818	0.487	1.374		
		22 or more	0.589	0.336	1.032		
Case-mix	Leukocytes	Negative				0.087	No*
		+	1.134	0.772	1.664		
		++	1.450	1.007	2.087		
		+++	1.436	1.031	1.999		
Case-mix	Nitrites	Negative				0.872	No
		Positive	0.981	0.780	1.234		
Case-mix	Protein	Negative				0.509	No
		Positive	0.923	0.728	1.170		
Case-mix	pH	5.0 to 7.0				0.478	No
		7.5 to 8.5	1.174	0.754	1.827		
Case-mix	Blood dipstick result	Negative				0.391	No
		Positive	1.126	0.859	1.477		
Case-mix	Cloudy urine	No				0.090	No*
		Yes	1.208	0.971	1.503		
Case-mix	Offensive smell urine	No				0.168	No
		Yes	0.850	0.674	1.071		
Case-mix	Temperature of participants at baseline	524	1.055	0.858	1.298	0.610	No
Case-mix	Diagnosed UTI in the last year	No				0.092	Yes
		Yes	0.794	0.608	1.038		
Case-mix	Number of UTI diagnosed in the last year	0				0.003	Yes
		1	0.846	0.637	1.124		
		2	0.722	0.536	0.973		
		3 or more	0.542	0.409	0.717		
Management	Performed a dipstick test	No					No

		Yes	463	0.826	0.612	1.113	0.209	
Management	Would have collected a urine sample under normal circumstances	No	274					No
		Yes	233	0.900	0.722	1.121	0.348	
Management	Prescribed antibiotic	No	54					No
		Yes	485	1.249	0.861	1.812	0.241	
Management	Organised follow-up	No	364					No
		Yes	165	0.916	0.718	1.169	0.482	
Exposure	UTI	No	302					No
		Yes	189	1.18	0.94	1.48	0.154	
Exposure	Wales		126	0.91	0.76	1.09	0.742	Yes
	England		168	1.03	0.88	1.21		
	Spain		145	1.07	0.90	1.26		
	Netherlands		101	1.00	0.83	1.20		

\*Due to the high number of missing responses regarding level of leukocytes and cloudy urine, these variables were not retained in the multivariable model.

**4.2. Two-level Cox proportional hazards model of time to resolution of daytime frequency, nighttime frequency, and urgency with countries compared to the overall average (participants nested within practices)**

Variable		Hazard Ratio	95% Confidence Interval		p-value
			Lower	Upper	
Participants age at baseline		0.99	0.99	1.00	0.026
Symptoms severity score		0.94	0.91	0.97	<0.001
Previous number of days with symptoms	0 to 7				<b>Reference category</b>
	8 to 14	0.77	0.54	1.09	0.248
	15 to 21	0.91	0.52	1.60	
	22 or more	0.63	0.35	1.14	
Number of time a urine infection had been treated in the past year	0				<b>Reference category</b>
	1	0.92	0.68	1.24	0.018
	2	0.78	0.56	1.08	
	3 or more	0.62	0.46	0.84	
UTI	No				<b>Reference category</b>
	Yes	1.13	0.89	1.44	0.324
Country	Wales	1.00	0.82	1.24	0.788
	England	1.06	0.89	1.28	
	Spain	1.04	0.86	1.25	
	Netherlands	0.90	0.73	1.12	

\*Model based on 447 participants. Countries compared to the overall average.

## 5- Relationship between time to recovery, antibiotic prescribing, and UTI

		Time to full recovery		
		UTI		
		Yes	No	Total
Prescribed antibiotic	Yes	178, 8 (5, 14)	270, 10 (6, 14)	494, 9 (5, 14)
	No	16, 12 (8, 14)	36, 14 (7, 14)	56, 14 (7, 14)
	Total	194, 9 (6, 14)	307, 10 (6, 14)	
		Time to resolution of moderately bad symptoms		
		UTI		
		Yes	No	Total
Prescribed antibiotic	Yes	178, 3 (3, 6)	270, 4 (2, 6)	494, 4 (2, 6)
	No	16, 3 (2.5, 5.5)	36, 4 (2, 8.5)	56, 3.5 (2, 8)
	Total	194, 3 (3, 6)	307, 4 (2, 6)	
		Time to resolution of daytime frequency, night time frequency, and urgency		
		UTI		
		Yes	No	Total
Prescribed antibiotic	Yes	173, 6 (4, 13)	267, 8 (5, 14)	485, 8.5 (5, 14)
	No	16, 9 (5, 14)	34, 9 (4, 14)	54, 7 (4, 14)
	Total	189, 8 (5, 14)	302, 7 (5, 14)	

\*n, Median (IQR)

## 6. Full search strategy for systematic review

OVID Medline Search Strategy (1946 to January week 3 2014);

1. exp Primary Health Care/
2. exp General Practice/
3. exp Family Practice/
4. exp Group Practice/
5. primary care.mp.
6. general practice.mp.
7. group practice.mp.
8. family practice.mp.
9. exp Physicians, Family/
10. exp Physician-Patient Relations/
11. primary healthcare.mp.
12. family physician\*.mp.
13. primary health care.mp.
14. general practi\*.mp.
15. family practi\*.mp.
16. family doctor\*.mp.
17. or/1-16
18. exp Urinary Tract Infections/
19. exp Bacteriuria/
20. exp Cystitis/
21. exp Cystitis, Interstitial/
22. exp Escherichia coli Infections/
23. exp Pyelonephritis/
24. bacteriuria.mp.
25. (urinary adj2 infection\*).tw.
26. (Urinary Tract Infection\* or UTI).mp.
27. cystitis.tw.
28. bladder infection\*.mp.
29. or/18-28
30. (Albania or Andorra or Armenia or Austria or Azerbaijan or Belarus or Belgium or Bosnia & Herzegovina or Bulgaria or Croatia or Cyprus or Czech Republic or Denmark or Estonia or Finland or France or Georgia or Germany or Greece or Hungary or Iceland or Ireland or Italy or Kosovo or Latvia or Liechtenstein or Lithuania or Luxembourg or Macedonia or Malta or Moldova or Monaco or Montenegro or The Netherlands or Norway or Poland or Portugal or Romania or Russia or San Marino or Serbia or Slovakia or Slovenia or Spain or Sweden or Switzerland or Turkey or Ukraine or United Kingdom or Vatican City or Holland or Great Britain or Britain or England or Scotland or Wales or UK or welsh or scottish or irish).tw.
31. 17 and 29 and 30
32. "Pregnancy"/
33. pregnan\*.mp.
34. exp Catheters/
35. or/32-34
36. 31 not 35
37. limit 36 to english language