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Lower Urinary Tract Infections: Management, Outcomes and Risk Factors for Antibiotic Re-prescription in Primary Care

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SUMMARY

Background: Urinary tract infections (UTIs) are major drivers of antibiotic prescribing in primary care. Inappropriate antibiotic prescribing for UTIs likely drives antibiotic resistance. We aimed to describe current investigation and antibiotic treatment to examine opportunities for improved antimicrobial stewardship.
Methods: We identified a cohort of all patients with lower UTI diagnosis between 2011 and 2015 in the 390 primary care practices contributing data to ResearchOne in England. We examined investigation, antibiotic treatment and antibiotic re-prescription within 28 days according to guideline-defined patient groups. We assessed risk factors for re-prescription using mixed-effect logistic regression.
Findings: In total, 494,675 UTIs were diagnosed in 300,354 patients. Median age was 54 years, and 83.3% were women. Same-day antibiotic was prescribed for 85.7% of UTIs; 56.8% were treated with trimethoprim, and urine sampling was undertaken in 25.0%. The antibiotic re-prescription rate was low (17,430, 4.1%) and increased slightly over time in men (from 5.2% in 2011 to 6.2% in 2015). Overall, 21.1% of pre-prescription were for the same antibiotic. The percentage of adults with recurrent UTIs ranged from 1.0% in 18–64 year-old men to 2.6% in women ≥65 years. The risk of antibiotic re-prescription increased with age, calendar year, recent antibiotic prescribing and treatment with antibiotic other than trimethoprim or nitrofurantoin.
Interpretation: Most patients diagnosed with lower UTI in primary care receive same-day empirical antibiotics with little diversity in choice of agent. The antibiotic re-prescription rate is low. Microbiological investigation and re-prescription of the same antibiotic given for the initial episode happened in one quarter of UTIs.
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1. Introduction

Symptoms of urinary tract infection (UTIs) are a common reason for consultation in primary care, where most suspected episodes are managed. Uncomplicated lower UTIs generally resolve quickly and many are self-limiting [1], but 11% of women report to have experienced at least one UTI and 3% report to have experienced three or more UTIs in the previous year [2]. There are marked differences across four European countries in culture positivity, antibiotic prescribing and re-consultation, despite similarities in the presentation of UTI in primary care, the pathogens and antibiotic sensitivities [3]. The high incidence of UTI and tendency to recur leads to high healthcare costs [4].

UTIs are the second most common reason for antibiotic prescribing [5]. In the UK, recent national clinical guidelines recommend treatment of lower UTIs with narrow spectrum antibiotics, particularly nitrofurantoin or trimethoprim, when the risk of resistance is low (e.g. considering previous antibiotic use and previous urine culture and sensitivity results) [6]. Amoxicillin or oral cephalosporins are advised for second or third line therapy for pregnant women and children aged 3 months or more [6]. Choice of second line antibiotic therapy in adult men should be guided by culture results after considering alternative diagnoses to UTIs [6]. Antibiotic use, even in short courses, can alter the normal microbial composition of the gastrointestinal tract and the vagina [7], selecting for drug-resistant pathogens. Furthermore, a meta-analysis of five studies of UTIs managed in primary care found an increased risk of antibiotic resistance that persisted for up to one year and a higher risk associated with multiple courses of antibiotics [8]. Evidence of a dose–response between the number of courses of amoxicillin and trimethoprim and resistance also exists [9]. Antibiotic resistance is associated with higher morbidity, mortality and healthcare costs [10]. It is therefore important to avoid unnecessary antibiotic prescribing and to make appropriate choices to treat UTIs.

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Research in context

Evidence before this study

Urinary tract infections (UTIs) are major drivers of antibiotic prescribing in primary care. Inappropriate antibiotic prescribing for UTIs likely drives antibiotic resistance. PubMed was searched for publications reporting on treatment failure rates and risk factors in patients treated for lower urinary tract infection up to February 6, 2018. Search terms were ("urinary tract infections"[Mesh] AND ("treatment failure"[Mesh] OR (("therapy" OR "treatment" OR "therapeutics"[MeSH Terms]) AND response AND failure))) with no language restriction. Of 157 articles retrieved, 6 were identified as relevant. The most recent period studied was 2013–2017 in a multinational clinical trial including 513 women. Reported rates varied between 2% when failure requiring hospitalisation was studied in Taiwan, to 39% amongst women treated with fosfomycin in a multinational clinical trial in hospital units and outpatient services. Treatment failure was found to be associated with older age, pregnancy, diabetes, renal impairment, antibiotic choice and duration. We concluded that few studies have examined the frequency of, and risk factors for treatment failure across the spectrum of UTI, or described its management in the community.

Added value of this study

Most patients diagnosed with lower UTI in primary care (85.7%) receive same-day empirical antibiotic therapy with little treatment diversity, generally limited to trimethoprim and nitrofurantoin, reflecting national guidelines. Microbiological investigation was undertaken infrequently and had little impact on treatment. The antibiotic re-prescription rate was low (4.1%) but gradually increased over time and was seen on average in over 3000 patients each year. Re-prescription of the same antibiotic occurred surprisingly frequently.

Implications of all the available evidence

Guidelines for investigation of UTI are not being followed. Use of microbiological investigations currently has little impact on prescribing. There is a need to consider recent antibiotic use to prevent re-prescription of the same antibiotic.

This study aimed to describe current investigation, antibiotic treatment and antibiotic re-prescription rates (as a likely indicator of treatment failure) across the spectrum of all lower urinary tract infections (UTIs) managed in primary care in England, with reference to current guideline-defined groups of patients.

2. Methods

2.1. Study Design and Setting

We analysed a cohort of all patients attending primary care general practices contributing data to ResearchOne. ResearchOne is a healthcare research database containing de-identified clinical and administrative data drawn from the electronic patient health records held on The Phoenix Partnership (TPP) SystmOne clinical record system. ResearchOne was created by TPP in partnership with the University of Leeds and the UK Government's Technology Strategy Board. It contains approximately 28 million records from over 400 general practitioners' practices spread geographically throughout England and is updated from new data entered as part of routine clinical practice on TPP SystmOne. Primary care clinical data are coded using the Read code, version 3 classification system. Prescription data are coded using the British National Formulary and the Dictionary of Medicines and Drugs. Data quality checks are performed centrally to assess data integrity, quality and representativeness of the population in England (http://www.researchone.org/data/). The data extract analysed was created on 5 June 2017. The study period was from 1 January 2011 to 31 December 2015. For each patient, we analysed information from the general practice at which the patient had most recently been registered.

The study was approved by the ResearchOne Project Committee and the University of Leeds, Medicine and Health University Ethics Review Committee (MREC-18-005). No patients or public were involved in this research.

2.2. Study Participants

We identified all patients who had a lower UTI diagnostic code recorded during the study period. The diagnostic codes considered are shown in Table S1. Individuals were eligible for study inclusion if they were registered in a ResearchOne general practice for a minimum of 28 days before the date of UTI diagnosis. To ascertain the outcomes, a minimum of 10 days of post-UTI follow-up was also required. The eligibility for study inclusion ended on the earliest of the following dates: death, practice deregistration or last date of data collection from the practice.

2.3. Study Definitions

The diagnostic codes used to identify episodes of lower UTI are listed in Supplementary Table 1. To account for multiple consultations for the same episode of infection, we considered diagnostic codes recorded within 28 days of each other to be related to the same UTI episode (Supplementary Fig. 1A). The index date of a UTI episode was defined by the date of the first recorded UTI diagnostic code for that episode in the patient record [11,12]. We excluded episodes that started prior to 1st January 2011. Patients with UTI were grouped into 7 groups defined according to recent clinical guidelines [13] (Table 1).

To describe the proportion of patients who had a urine sample collected for culture or microscopy during the index episode, we identified Read codes for either requests or results that were recorded within 10 days of the UTI start date (Supplementary Table 2). To describe the number of patients who received antimicrobial therapy for UTI whilst allowing for delays related to microbiological diagnosis [14], we identified prescriptions for any oral antibiotic issued on the same day or within 3 days of the index UTI diagnosis (British National Formulary [BNF] chapter 1.5; Supplementary Table 3).

As in previous studies [15], we studied antibiotic re-prescription as a proxy measure of treatment effectiveness. We defined antibiotic re-prescription as the earliest prescription of a UTI-specific antibiotic for the same UTI episode between 4 and 28 days after the date of the initial antibiotic prescription (Supplementary Fig. 1B). These antibiotics included drugs recommended, or used for the treatment of UTIs in the UK, albeit not necessarily exclusively for this purpose (trimethoprim, nitrofurantoin, pivmecillinam, fosfomycin, ciprofloxacin, cephalexin, and co-amoxiclav). For sensitivity analyses, we also defined antibiotic re-prescription as the earliest occurrence of a new antibiotic prescription of a UTI-specific antibiotic between 6–28 days and 8–28 days after the initial antibiotic prescription. Information on antibiotic susceptibility, prescription duration and reason for antibiotic regimen were not available in this setting. Drug allergy and intolerance were discarded as a reason for re-prescription in this study.

2.4. Statistical Analysis

For each patient group, we described the number of UTI episodes recorded and patient characteristics on the date of diagnosis. We also

Table 1
Patient characteristics at diagnosis of lower urinary tract infection by patient group.

	Children <3mths	Children 3 mths-3 yrs	Children 4–15 yrs	Women 18–64 yrs	Men 18–64 yrs	Adults ≥65 yrs	Pregnant women	Catheter	All UTIs
No. of patients	120	8491	23,392	144,096	22,629	100,393	1306	33	300,354
Total no. of episodes	121	10,015	30,868	229,883	29,559	184,725	1352	34	494,675
Median no. of episodes per patient [IQR]	1 [1–1]	1 [1–2]	1 [1–2]	2 [1–4]	1 [1–2]	2 [1–5]	1 [2–3]	2 [1–4]	2 [1–4]
Median age in years [IQR]	NA	2 [2–3]	8 [5–11]	41 [29–53]	50 [40–58]	77 [71–84]	28 [24–32]	73 [63–83]	54 [31–73]
Women, n (%)	51 (42.2)	7645 (76.3)	26,366 (85.4)	NA	NA	137,572 (74.5)	NA	6 (17.7)	410,667 (83.0)
Ethnicity, n (%)									
White	53 (76.8)	6446 (83.9)	15,730 (72.2)	135,022 (73.4)	16,221 (70.8)	115,794 (83.1)	770 (67.1)	20 (83.3)	293,694 (76.9)
Black	1 (1.5)	83 (1.1)	312 (1.4)	2316 (1.3)	366 (1.6)	356 (0.3)	26 (2.3)	–	3493 (0.9)
Asian	8 (11.6)	728 (9.5)	2338 (10.7)	11,552 (6.3)	1558 (6.8)	2251 (1.6)	123 (10.7)	–	18,700 (4.9)
Other	7 (10.1)	423 (5.5)	3416 (15.7)	35,127 (19.1)	4758 (20.8)	20,920 (15.0)	229 (20.0)	4 (16.7)	66,004 (17.3)
Calendar year, n (%)									
2011	17 (14.1)	1701 (17.0)	5226 (16.9)	39,542 (17.2)	5317 (18.0)	32,571 (17.6)	255 (18.9)	–	86,033 (17.4)
2012	28 (23.1)	1881 (18.8)	5827 (18.9)	43,364 (18.9)	5698 (19.3)	35,404 (19.2)	252 (18.6)	–	93,903 (19.0)
2013	23 (19.0)	2023(20.2)	6224 (20.2)	46,328 (20.2)	6032 (20.4)	37,185 (20.1)	273 (20.2)	2 (5.9)	99,663 (20.2)
2014	32 (26.5)	2284 (22.8)	6814 (22.1)	49,893 (21.7)	6183 (20.9)	39,410 (21.3)	285 (21.1)	12 (35.3)	106,745 (21.6)
2015	21 (17.4)	2126 (21.2)	6777 (22.0)	50,756 (22.1)	6329 (21.4)	40,155 (21.7)	287 (21.2)	20 (58.8)	108,331 (21.9)
Prior antibiotic use, n (%)									
Prescribed in last year, n (%)	20 (16.5)	6060 (60.5)	16,699 (54.1)	146,582 (63.8)	16,102 (54.5)	138,900 (75.2)	793 (58.7)	24 (70.6)	329,980 (66.7)
Median time since last prior antibiotic in months [IQR]	0.6 [0.3–0.9]	4.0 [1.3–9.9]	6.2 [2.0–14.7]	4.9 [1.7–11.7]	4.4 [1.2–12.8]	2.8 [1.0–7.8]	4.9 [1.8–12.3]	1.8 [0.8–5.1]	3.9 [1.3–10.4]
Comorbidities, n (%)									
Cardiovascular diseases	–	3 (0.03)	12 (0.04)	5464 (2.4)	2699 (9.1)	58,535 (31.7)	1 (0.1)	14 (41.2)	66,733 (13.5)
Diabetes	–	4 (0.04)	132 (0.4)	12,502 (5.4)	3858 (13.1)	36,099 (19.5)	12 (0.9)	10 (29.4)	52,659 (10.7)
Asthma	1 (0.8)	237 (2.4)	3714 (12.0)	42,543 (18.5)	4359 (14.7)	24,777 (13.4)	236 (17.5)	2 (5.9)	77,463 (15.7)
COPD	–	1 (0.01)	3 (0.01)	19 (0.01)	7 (0.02)	124 (0.1)	–	–	155 (0.03)
Cancer	–	3 (0.03)	47 (0.2)	8076 (3.5)	1765 (6.0)	32,476 (17.6)	6 (0.4)	12 (35.3)	42,408 (8.6)
CKD stage 3–5	–	4 (0.04)	12 (0.04)	4355 (1.9)	1048 (3.6)	49,920 (27.0)	1 (0.1)	4 (11.8)	55,351 (11.2)

Note: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; UTI, urinary tract infection. Ethnicity was missing for 22.8% of episodes of UTI.

determined the proportion of episodes for which a urine sample for culture or microscopy was collected, the annual number of UTIs per patient and the proportion treated (antimicrobial therapy, first drug class and multiple antibiotics). Furthermore, we described the proportion of UTIs managed with antibiotic re-prescription each year and their treatment. For patients treated with antibiotics, we also described patient baseline characteristics according to whether they resulted in re-prescription or not, and investigated risk factors for antibiotic re-prescription using mixed effect logistic regression models with GP practice and patient level random effects to account for within patient correlation of events (i.e. all UTI episodes diagnosed for each patient were analysed) and heterogeneity between practices. A priori factors considered and included in adjusted regression models were risk factors for UTI reported in previous studies that were available and likely to be well coded: age (<10, 10-year groups between 10–79 and ≥80 years), sex, ethnicity (missing data recorded as a separate category), year of UTI diagnosis, diagnosed chronic comorbidities (cardiovascular diseases, diabetes, chronic obstructive pulmonary disease, asthma, cancer and chronic kidney disease of stage ≥3 recorded before the UTI episode), antibiotic/s use in last year (none, <1 month, 1 to <3 months, 3 to <6 months, 6 to <12 months), and the initial antibiotic prescribed. Statistical tests were 2-sided, and statistical significance was considered $p < 0.05$. All analyses were performed in Stata version 15.0 (StataCorp LP, College Station, TX, USA).

2.5. Role of the Funding Source

The study funder had no role in study design, data collection, analysis, interpretation, or writing up of the report. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

2.6. Data Statement

Access to raw data can be requested from the The Phoenix Partnership (TPP) SystmOne clinical system (http://www.researchone.org/data/).

3. Results

3.1. UTI Diagnosis and Patient Characteristics

During the study period, a total of 494,675 episodes were recorded as lower UTI in 300,354 patients registered in 390 general practices (mean 1.7 infections per person). Eighty-three per cent of episodes were in women (Table 1). Median age at diagnosis was 54 years (IQR 31–73). The highest frequency of UTIs occurred in women aged 18–64 years (46.5%) and the lowest amongst children of <3 months of age (9.1%). The overall mean annual number of UTI

episodes per person was 1 (SD = 0.40). The percentage of adults with only 1 UTI episode per year ranged from 79.2% in women aged ≥65 years to 91.0% in men aged 18–64 years (Fig. 1). The percentage of adults with ≥3 episodes per year (recurrent UTI) ranged from 1.0% in men aged 18–64 years to 2.6% in women aged ≥65 years.

An antibiotic prescription for any indication in the previous year was recorded for 66.7% of patients with UTIs. The median time since last prescribed antibiotic was 3.9 months (IQR 1.3–10.4), ranging from 0.6 for children of <3 months to 6.2 months for those aged 4–15 years. A penicillin (6% co-amoxiclav, 0.5% pivmecillinam, and 29.4% other penicillin), trimethoprim (26.2%) and nitrofurantoin (15.1%) were those most often prescribed. The most common comorbidities present at the time of UTI diagnosis were asthma (15.7%) and cardiovascular diseases (13.5%). Chronic kidney disease was also common in the eldest age group (26.1% of episodes with stage 3 renal disease). A urine sample for microscopy or culture was requested within 10 days for 25.0% of episodes (range between 9.1% in children of <3 months and 30.6% in 18- to 64-year-old men; Table 2).

3.2. Antibiotic Treatment

Antibiotics were prescribed on the same date of diagnosis for 85.7% of UTIs (range from 20.7% in children of <3 years to 89% in women aged 18–64 years). Only 17% of those who received antibiotics had a recorded urine testing within 10 days of diagnosis (range from 9.1% for the <3 year group to 30.6% for 18- to 64-year-old women). Overall, the most common antibiotics initially prescribed were trimethoprim (56.8%) and nitrofurantoin (23.9%; Fig. 2). Cephalexin was the most commonly prescribed antibiotic in pregnant women (30.4%) and the second most commonly prescribed in children aged <4 years (24.0% in those <3 months and 5.6% in those aged 3 months to 3 years). Multiple antibiotics were administered to 3543 (0.8%) patients. Six percent of UTI episodes diagnosed in pregnant women (n = 62) were treated with trimethoprim and the proportion of UTIs treated with co-amoxiclav varied between 4.3% in children aged 4–15 years (n = 1086) and 7.6% in men aged 18–64 years (n = 1830). Chronic kidney disease (of stage ≥3) was diagnosed in 9.4% of episodes treated with nitrofurantoin in women and 15.0% of those in men (in 0.6 of episodes in women and 1.9% of those in men with stage ≥4).

The ratio of trimethoprim to nitrofurantoin prescribing gradually decreased over the study period from 6317/1981 in 2011 to 7870/3481 in 2015 for men (28.1% decrease); and from 36,372/12,853 to 43,383/24,099 (35.7% decrease), respectively, in women (Supplementary Fig. 2). Amongst women ≥70 years old, the proportion of UTIs treated with trimethoprim slightly decreased over time, from 45.9% in 2011 to 43.4% in 2015. The absolute number of UTIs diagnosed in this patient group increased during the study period, from 8938 in 2011 to 10,264 in 2015. In men, this number also increased over time (from 2657 to 3314, respectively), but the proportion of episodes treated with trimethoprim remained stable during the study period (overall 40.2%).

3.3. Antibiotic Re-prescription

Antibiotic re-prescription occurred in 17,430 (4.1%) UTI episodes treated with antibiotics, ranging from 1.9% in children aged 4–15 years and in pregnant women, to 6.3% in adults aged ≥65 years. These re-prescription events were unrelated to antibiotic allergy or intolerance (data not shown). Antibiotic re-prescription occurred in 9859 (6.3%) episodes diagnosed in ≥65-year-old adults and increased slightly over time only in men (from 5.2% in 2011 to 6.2% in 2015). When defining antibiotic re-prescription using antibiotic prescribing windows of 6–28 and 8–28 days (instead of 4–28), re-prescription was observed in 14,972 (3.5%) and 11,912 (2.8%) of UTI episodes, respectively (Supplementary Table 4). Factors associated with antibiotic re-prescription are shown in Table 3. The risk increased with age, from 2.1% of episodes in patients <10 years to 6.9% of episodes in those aged ≥80 years (adjusted odds ratio [OR] = 0.97, 95%CI 0.84 to 1.12 for 10–19 years and 2.62, 95%CI 2.34 to 2.94 for those ≥80 years, compared with UTI episodes from patients aged <10 years; $p < 0.001$). Odds of infection was lower in women than in men (OR = 0.77, 95%CI 0.73 to 0.80; $p < 0.001$) and in non-white ethnic groups (OR = 0.61, 95%CI 0.45–0.83 for black; OR = 0.75, 95%CI 0.67–0.85 for Asian; compared to white). It was slightly higher in patients with comorbidities, including cancer (OR = 1.15, 95%CI 1.09 to 1.21; $p < 0.001$) and diabetes (OR = 1.12, 95%CI 1.07 to 1.18; $p < 0.001$). Odds of re-prescription increased with shorter time since prior antibiotic use, from 1.16 (95% CI 1.09 to 1.24) for 6–12 months to 3.35 (95%CI 3.19 to 3.53) for <1 month, compared with non-use in the previous year ($p < 0.001$). Initial treatment of the UTI with antibiotics other than trimethoprim was associated with a higher odds of re-prescription (OR = 1.18, 95%CI 1.10 to 1.27 for co-amoxiclav; OR = 1.56, 95%CI 1.30 to 1.86 for pivmecillinam; OR = 8.98, 95%CI 8.18 to 9.85 for multiple concomitant antibiotics; compared with trimethoprim) except for nitrofurantoin (OR = 0.96, 95%CI 0.92 to 1.00). Furthermore, the odds of re-prescription of any antibiotic increased over time (OR = 1.20, 95%CI 1.14 to 1.27 in 2015 compared with 2011; $p < 0.001$).

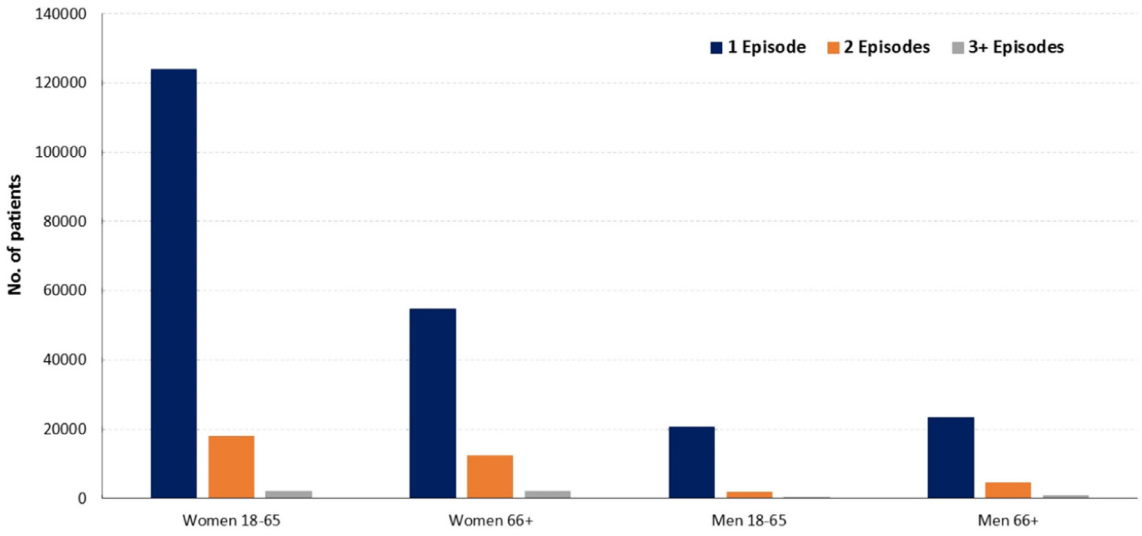

Fig. 1. Distribution of patients by the annual number of lower urinary tract infection episodes in adult women and men, Jan 2011–Dec 2015.

Table 2
Diagnosis and treatment of episodes of lower urinary tract infection by patient group.

	Children <3mth	Children				3mth–3 yrs	Children 4–15 yrs	Women 18–64 yrs	Men 18–64 yrs
Adults ≥65 yrs	Pregnant women	Catheter	All UTIs						
No. of patients	120	8491	23,392	144,096	22,629	100,393	1306	33	300,354
Total no. of episodes	121	10,015	30,868	229,883	29,559	184,725	1352	34	494,675
Urine testing within 10 days, n (%)	11 (9.1)	2624 (26.2)	9426 (30.5)	54,235 (23.6)	9036 (30.6)	45,978 (24.9)	301 (22.3)	7 (20.6)	123,409 (25.0)
No. of antibiotics prescribed, n (%)									
0	91 (75.2)	3034 (30.3)	5174 (16.8)	22,016 (9.6)	5209 (17.6)	28,634 (15.5)	316 (23.4)	17 (50.0)	65,414 (13.2)
1	29 (24.0)	6928 (69.2)	25,532 (82.7)	206,222 (89.7)	24,153 (81.7)	154,331 (83.6)	1031 (76.3)	17 (50.0)	425,399 (86.0)
2	1 (0.8)	51 (0.5)	160 (0.5)	1611 (0.7)	192 (0.7)	1723 (0.9)	5 (0.4)	–	3782 (0.8)
3+	–	2 (0.02)	2 (0.01)	34 (0.01)	5 (0.02)	37 (0.02)	–	–	80 (0.02)
Antibiotic prescribed on date of diagnosis, n (%)	25 (20.7)	6786 (67.8)	25,354 (82.1)	206,094 (89.7)	24,022 (81.3)	153,520 (83.1)	1008 (74.6)	17 (50.0)	423,967 (85.7)
Trimethoprim	13 (52.0)	4709 (69.4)	19,222 (75.8)	117,450 (57.0)	13,671 (56.9)	80,745 (52.6)	62 (6.2)	8 (47.1)	240,797 (56.8)
Nitrofurantoin	–	113 (1.7)	1242 (4.9)	53,954 (26.2)	4844 (20.2)	39,413 (25.7)	254 (25.2)	7 (41.2)	101,205 (23.9)
Cephalexin	6 (24.0)	380 (5.6)	1231 (4.9)	10,551 (5.1)	1039 (4.3)	8303 (5.4)	306 (30.4)	–	22,032 (5.2)
Co-amoxiclav	1 (4.0)	375 (5.5)	1086 (4.3)	7680 (3.7)	1813 (7.6)	8880 (5.8)	48 (4.8)	1 (5.9)	20,104 (4.7)
Ciprofoxacin	–	7 (0.1)	58 (0.2)	2353 (1.1)	1083 (4.5)	3671 (2.4)	–	–	7215 (1.7)
Pivmecillinam	–	1 (0.01)	18 (0.1)	626 (0.3)	76 (0.3)	1249 (0.8)	1 (0.1)	–	1985 (0.5)
Fosfomycin	–	–	–	10 (0.0)	2 (0.01)	42 (0.03)	–	–	54 (0.01)
Other	5 (20.0)	1157 (17.1)	2350 (9.3)	11,933 (5.8)	1321 (5.5)	9617 (6.3)	333 (33.0)	1 (5.9)	27,032 (6.4)
Multiple	–	44 (0.7)	147 (0.6)	1537 (0.8)	173 (0.7)	1600 (1.0)	–	–	3543 (0.8)
Antibiotic re-prescription[a], n (%)	1 (3.3)	167 (2.4)	475 (1.9)	5638 (2.7)	1143 (4.7)	9859 (6.3)	20 (1.9)	4 (23.5)	17,430 (4.1)
Antibiotic prescribed for treatment failure, n (%)									
Nitrofurantoin	–	19 (11.4)	122 (25.7)	2249 (39.9)	328 (28.8)	3134 (31.8)	7 (35.0)	1 (25.0)	5916 (33.9)
Trimethoprim	–	51 (30.5)	107 (22.5)	1078 (19.1)	262 (23.0)	2350 (23.8)	2 (10.0)	–	3873 (22.2)
Cephalexin	–	51 (30.5)	125 (26.3)	757 (13.4)	117 (10.3)	1336 (13.6)	9 (45.0)	–	2418 (13.9)
Co-amoxiclav	–	41 (24.6)	92 (19.4)	808 (14.3)	168 (14.7)	1402 (14.2)	2 (10.0)	2 (50.0)	2530 (14.5)
Ciprofloxacin	1 (100)	2 (1.2)	15 (3.2)	438 (7.8)	211 (18.5)	1020 (10.4)	–	1 (25.0)	1695 (9.7)
Pivmecillinam	–	–	5 (1.1)	133 (2.4)	21 (1.8)	289 (2.9)		–	448 (2.6)
Fosfomycin	–	–	–	8 (0.1)	3 (0.3)	22 (0.2)	–	–	33 (0.2)
Multiple	–	3 (1.8)	9 (1.9)	168 (3.0)	31 (2.7)	306 (3.1)	–	–	517 (3.0)

[a] The number of antibiotic re-prescriptions has been calculated for patients who were prescribed an antibiotic for the index urinary tract infection episode within 3 days of diagnosis. UTI, urinary tract infection.

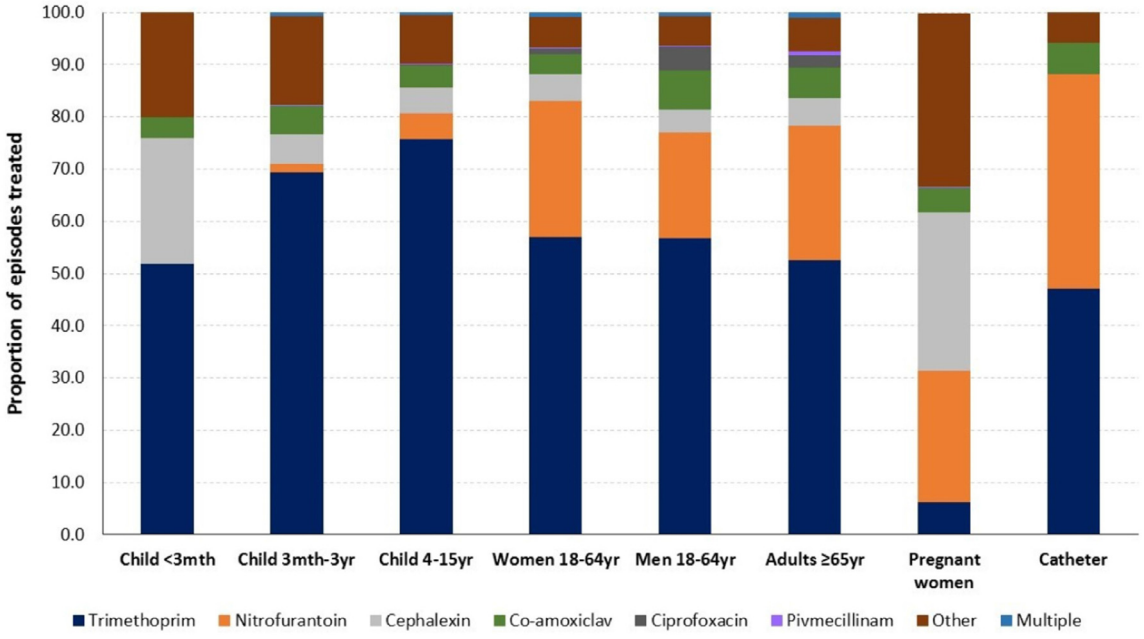

Fig. 2. Distribution of the proportion of lower urinary tract infection episodes by type of antibiotic initially prescribed and patient group amongst patients with prescribed antibiotic, Jan 2011–Dec 2015.

Table 3
Associations between patient characteristics at lower urinary tract infection diagnosis and antibiotic re-prescription amongst patients prescribed antibiotics.

	UTI with re-prescription (%)	UTI without re-prescription[a] (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
No. of episodes	17,430	411,831		
Sociodemographic characteristics				
Women	13,505 (77.5)	349,004 (84.7)	0.59 (0.57–0.62)	0.77 (0.73–0.80)
Age group, years				
<10	469 (2.7)	22,415 (5.4)	1	1
10–19	258 (2.6)	25,370 (6.2)	0.85 (0.74–0.97)	0.97 (0.84–1.12)
20–29	814 (4.7)	46,423 (11.3)	0.84 (0.75–0.95)	0.94 (0.83–1.07)
30–39	1050 (6.0)	44,498 (10.8)	1.13 (1.00–1.27)	1.26 (1.12–1.43)
40–49	1516 (8.7)	50,031 (12.2)	1.44 (1.28–1.61)	1.58 (1.40–1.77)
50–59	1856 (10.7)	49,531 (12.0)	1.80 (1.61–2.01)	1.81 (1.61–2.03)
60–69	3252 (18.7)	58,577 (14.2)	2.69 (2.42–2.99)	2.40 (2.15–2.69)
70–79	3819 (21.9)	58,089 (14.1)	3.22 (2.90–3.58)	2.59 (2.31–2.90)
≥80	4196 (24.7)	56,897 (13.8)	3.62 (3.26–4.02)	2.62 (2.34–2.94)
Ethnicity[b]				
White	10,943 (81.4)	243,684 (76.4)	1	1
Black	51 (0.4)	2973 (0.9)	0.43 (0.32–0.58)	0.61 (0.45–0.83)
Asian	369 (2.7)	15,997 (5.0)	0.58 (0.51–0.65)	0.75 (0.67–0.85)
Other	2089 (15.5)	56,471 (17.7)	0.88 (0.82–0.95)	0.91 (0.85–0.97)
Calendar year				
2011	2782 (16.0)	71,534 (17.4)	1	1
2012	3235 (18.6)	78,050 (19.0)	1.07 (1.01–1.13)	1.08 (1.02–1.15)
2013	3472 (19.9)	83,172 (20.2)	1.08 (1.02–1.14)	1.12 (1.05–1.18)
2014	3978 (22.8)	88,818 (21.6)	1.18 (1.12–1.25)	1.21 (1.15–1.28)
2015	3963 (22.7)	90,257 (21.9)	1.17 (1.11–1.24)	1.20 (1.14–1.27)
Median no. of episodes per patient [IQR]	3 [2–6]	2 [1–4]		
Prior antibiotic use				
None in prior year	3016 (17.3)	139,002 (33.8)	1	1
6–<12 months	1742 (10.0	65,925 (16.0)	1.23 (1.15–1.30)	1.16 (1.09–1.24)
3–<6 months	2119 (12.2)	64,301 (15.6)	1.53 (1.44–1.62)	1.37 (1.29–1.46)
1–<3 months	4368 (25.1)	83,734 (20.3)	2.37 (2.25–2.49)	1.93 (1.83–2.04)
<1 month	3.35 (3.19–3.53)	58,869 (14.3)	4.52 (4.31–4.74)	3.35 (1.00–1.11)
Comorbidities				
Cardiovascular disease	3737 (21.4)	50,884 (12.4)	2.01 (1.93–2.11)	1.05 (1.00–1.10)
Diabetes	2826 (16.2)	41,404 (10.1)	1.81 (1.72–1.90)	1.12 (1.07–1.18)
Asthma	2957 (17.0)	64,973 (15.8)	1.08 (1.03–1.13)	1.07 (1.02–1.13)
Cancer	2445 (14.0)	33,451 (8.1)	1.86 (1.77–1.97)	1.15 (1.09–1.21)
Chronic kidney disease stage 3–5	3107 (17.8)	42,375 (10.3)	1.94 (1.85–2.04)	1.05 (1.00–1.11)
Initial antibiotic prescribed				
Trimethoprim	7374 (45.2)	233,423 (57.3)	1	1
Nitrofurantoin	3777 (23.2)	97,428 (23.9)	1.20 (1.15–1.25)	0.96 (0.92–1.00)
Other	1384 (8.5)	25,702 (6.3)	1.77 (1.66–1.88)	1.48 (1.39–1.58)
Cephalexin	1045 (6.4)	20,987 (5.2)	1.50 (1.39–1.61)	1.15 (1.07–1.24)
Co-amoxiclav	1108 (6.8)	18,996 (4.7)	1.69 (1.57–1.81)	1.18 (1.10–1.27)
Ciprofloxacin	484 (3.0)	6731 (1.7)	1.95 (1.76–2.17)	1.17 (1.06–1.30)
Multiple	953 (5.9)	2590 (0.6)	13.18 (11.99–14.49)	8.98 (8.18–9.85)
Pivmecillinam	174 (1.1)	1811 (0.4)	2.79 (2.32–3.35)	1.56 (1.30–1.86)

Note: CKD, chronic renal disease; OR, adjusted odds ratios for associations with treatment response failure during the study period from mixed effect logistic regression models with general practice and patient level random effects; Wald test p-value for association was <0.001 for all factors except for cardiovascular (p = 0.07) and chronic kidney disease (p = 0.06). Intraclass correlation coefficients for patients and practices were 0.181 and 0.009, respectively.

[a] Urinary tract infections (UTIs) treated with antibiotics without re-prescription.

[b] Ethnicity was missing for 22.5% of UTI episodes.

Overall, the antibiotics more commonly re-prescribed were nitrofurantoin (33.9%) and trimethoprim (22.2%). Three percent of episodes (n = 516) were treated with multiple antibiotics. Furthermore, the index prescription and re-prescribed antibiotics were the same in 27.1% (pivmecillinam), 25.4% (nitrofurantoin), 22.4% (cephalexin), 20.0% (trimethoprim), 19.0% (ciprofloxacin) and 18.0% (co-amoxiclav) of cases (some patients were treated with more than 1 antibiotic). Patterns of antibiotic re-prescribing remained relatively stable over time except for cephalexin and pivmecillinam. The proportion of re-prescriptions with cephalexin decreased from 17.4% in 2011 to 13.5% in 2015 in women, and from 11.6% to 9.1%, respectively, in men. In contrast, the proportion treated with pivmecillinam increased over time from 1.4% in 2011 to 4.3% in 2015 in women, and from 1.0% to 3.8%, respectively, in men.

4. Discussion

In this large cohort of patients diagnosed with lower UTI in primary care practices in England, we found that the great majority (four out of five) received empirical antibiotic therapy on the day of diagnosis, and most (83%) had no evidence of urine sample collection for microbiological investigation in their electronic health records. Recent exposure to antibiotics was common in all patient groups and was associated with an increased risk of antibiotic re-prescription. In line with national guidelines, there was little diversity in treatment, which was generally limited to two antibiotics, trimethoprim and nitrofurantoin (24% and 56%, respectively). Antibiotic re-prescription was uncommon (4.1% of UTI episodes).

This study was based on the analysis of data collected as part of routine clinical primary care practice, and was therefore not specifically gathered for research purposes. We identified an unselected population of all patient groups diagnosed with lower UTI in ResearchOne primary care practices in England, which enabled us to describe the management and outcomes of all groups of patients identified in current clinical guidelines for the management of UTIs. We did not restrict the analysis to microbiologically confirmed episodes because our aim was to describe the real-world management in the primary care setting. We also did not investigate the role of

urinary dipstick examination, which is not coded in primary care. We classified UTIs according to guideline-defined patient groups and found a low number of UTIs in patients with catheters. It is possible that some infections diagnosed in patients with catheters were coded using generic diagnostic codes and were therefore classified in other patient groups (e.g. adults aged 65 years or above). The percentage of patients with recurrent UTIs (more than one episode per year) ranged from 9.0% for men aged 18–64 years to 20.8% for women aged ≥65 years, and the percentages with three or more episodes per year ranged from 1.0% to 2.6%, respectively. These figures are comparable with those found in a population-based survey conducted in England, which found that 3% of women aged >15 years reported at least three UTIs in the previous year [2]. A Canadian surveillance study also recorded that 14% of people with UTI had more than one episode of infection during a 2-year period [16]. The data therefore appear consistent with other relevant studies. A strength of our study is the longitudinal individual-patient data from 390 primary care practices geographically spread across England. This allowed the examination of temporal associations with prescribing. This risk factor analysis accounted for the diagnosis of multiple UTI episodes within patients and for the specific general practices in which the patients were treated. We were unable to account for antibiotic resistance per se and some factors that have been found to be associated with resistance, including recent hospital admissions (and antibiotics administered during admissions) [17], use of invasive procedures in health-care settings, or care home residence [17]. Furthermore, we were unable to evaluate dose–response associations because of the lack of information on antibiotic dose and duration in the dataset. In addition, our study did not exclude patients with other infections, so it is therefore impossible to completely rule out that some of the antibiotic prescriptions were administered to treat a concomitant non-UTI infection.

Overall, 86% of UTIs were treated with a same-day antibiotic prescription, reflecting routine clinical practice in primary care, with decisions likely based on the report of typical symptoms with or without findings of dipstick urine testing. The proportion of patients being offered delayed prescriptions or symptomatic treatment and follow-up [18] would seems to be low, and there may be more opportunity to reduce empirical therapy, as undertaken in the Netherlands [3]. Initial treatment comprised just 2 antibiotics, nitrofurantoin and trimethoprim, thus, prescribing in general follows national guidance for situation when the risk of resistance is considered to be low [6,13]. NICE considers administration of antibiotic therapy in the previous 3 months as a risk factor for trimethoprim resistance. In our study, the median time since last prior antibiotic prescription was 4 months.

Antibiotic resistance is a major threat to human health and calls for action to address this threat are widespread. The UK Chief Medical Officer's (CMO's) annual report 2011 highlighted the importance of antimicrobial resistance and the need to reduce its impact [11]. A five year antimicrobial resistance strategy was published in 2013 that proposed potential means of 'conserving and stewarding' the effectiveness of existing antimicrobial treatments [19]. A theoretical way of reducing the emergence and spread of antibiotic resistance is to introduce more variation (i.e. diversity) into antibiotic prescribing [20,21]. We have confirmed that there is little diversity in prescribing for UTIs, but introducing greater variety would oppose current clinical guidelines and prescribing practice.

A urine sample for microbiological investigation is recommended in all children under 3 months [22], all children under 16 [6], pregnant women [13] and all men [18]. An annual average increase in urine sampling for culture of 3% has been reported [23]. We found that microbiological investigation is not being carried out as recommended. However, even if microbiological examination and/or culture were coded for one in four of all episodes of UTI in patients older than 3 months, we cannot exclude lack of recording of this information by some GPs.

As in previous studies [1–4], we investigated antibiotic re-prescription as a measure of treatment effectiveness. Because this approach has limitations, we used different definitions of re-prescription (the earliest subsequent prescription of a UTI-specific antibiotic issued within 4–28 days after the initial antibiotic prescription in the primary analysis; and within 6–28 and 8–28 days in sensitivity analyses). However, because of lack of linkage to hospital and emergency services, we did not consider progression of UTI to pyelonephritis and sepsis in the definition of re-prescription and might have missed some events. The percentage of patients re-prescribed antibiotics after an index prescription for the same UTI episode was low (3–4%), but this still represents over 3000 patients each year. We also found evidence of a statistically significant, gradual increase in antibiotic re-prescription over the five years covered by the study. Previous studies have reported rates ranging between 2% when failure requiring hospitalisation was studied in a population-based study in Taiwan [24] to 39% amongst women treated with fosfomycin in a multinational randomised clinical trial [25]. In our study, the risk of antibiotic re-prescription was higher in older patients, men, those with white ethnicity, those recently prescribed antibiotics and those not treated with trimethoprim or nitrofurantoin. The random effects for patient and practice showed that there was only a small practice effect and a more substantial patient effect consistent with the development of resistance within patients. The median time between first and second date of antibiotic prescription was 11 days, which makes it unlikely that allergy/intolerance to the first prescription explained the second. This was confirmed by an analysis of recorded data on drug allergy and intolerance. One reason for antibiotic re-prescription might be infection with a resistant pathogen, the relationship between prior recent antibiotics and re-prescription supports this hypothesis. In men, the presence of prostatitis, might account for treatment failure. The association between white ethnicity and antibiotic re-prescribing suggests that there may be cultural health seeking behaviours affecting prescribing, which may warrant further investigation. Non-compliance with the index prescription is another possible reason for treatment failure, one that we could not assess. Indeed, in a population-based survey in England, 63% of women prescribed antibiotics for a recent UTI reported taking them as prescribed [2]. The risk factors for antibiotic re-prescribing identified in our cohort are consistent with those reported in studies of treatment response failure [26–28] and of antibiotic resistance in the community, including the higher risk of antibiotic-resistance [8,9,29,30] and multidrug resistance [31] associated with recent antibiotic exposure. A recent surveillance study based on the patient-level analysis of community urine isolates in Scotland also reported an increased risk of multidrug resistance associated with higher cumulative exposure to total antibiotic, nitrofurantoin and trimethoprim in the previous six months and with higher numbers of antibiotic classes prescribed in the previous year in adults [17]. This increase in risk remained after 7–9 months of any antibiotic exposure and 10–12 months of nitrofurantoin and trimethoprim use. Previous studies have also reported increased risk of antibiotic (multi)drug resistance in men [17,30], older patients [17,30] and in those with comorbidities [17]. Furthermore, in our study we found that antibiotic re-prescription was significantly less likely for UTI episodes treated with trimethoprim than for episodes treated with the other agents used, in spite of higher rates of resistance to trimethoprim (34% in 2012–2016) [32]. There are several possible explanations for this finding. Firstly, trimethoprim may be more effective than the other agents. Secondly, patients with less severe symptoms, or those who are more likely to have self-limiting conditions are being treated with trimethoprim making it look like trimethoprim is more effective. Thirdly, other antibiotics are being used for more challenging cases or those with genuinely resistant infections, increasing the risk of antibiotic re-prescription. The latter, seems less likely given the high percentage of patients treated with nitrofurantoin and low resistance rates to this agent. Another explanation is that nitrofurantoin is being used in patients with reduced renal function and is ineffective for pharmacokinetic reasons, a theory which is supported by the increased risk of re-prescription in chronic kidney disease. These findings warrant further investigation.

Over one in five episodes of antibiotic re-prescription in our study were treated with the same antibiotic as was initially prescribed. It is illogical to re-prescribe the same antibiotic when treatment failure is considered clinically and this also contradicts NICE recommendation [6]. This finding suggests (as this was a constant phenomenon across all antibiotics) that a substantial minority of practitioners tend to prescribe according to favoured agents despite a different choice being appropriate.

We analysed routinely collected data and found evidence of its validity when compared with other types of studies. For example, in a previous study in CPRD practices, trimethoprim was the most commonly prescribed antibiotic for community acquired UTI and accounted for 50% of prescriptions and prescriptions of nitrofurantoin increased between 2004 and 2014 [11]. In a prospective cohort study, antibiotic prescribing at initial primary care consultation was seen in 95.1% of women with suspected UTI aged $\geq$16 years in England, with most common antibiotics: 46.1% trimethoprim and 48.7% nitrofurantoin; and 14.5% subsequent antibiotic prescription (similar to ours when unrestricted to the UTI specific list) [3]. In a population-based home survey amongst 892 randomly selected women aged $\geq$16 years in England, 65% of participants with UTIs reported contacting their local general practice to seek care, and of those seen by a health professional, 25% had their urine sample sent for laboratory analysis and 74% were prescribed an antibiotic [2].

In conclusion, there are opportunities to optimise antibiotic prescribing for UTIs that could potentially reduce the risk of antibiotic resistance. Most patients currently diagnosed with lower UTI in primary care receive same-day antibiotic treatment, without microbiological investigation. There is little diversity in antibiotic treatment, which is generally limited to two agents, trimethoprim and nitrofurantoin, reflecting national guidelines. The rate of antibiotic re-prescription is low but is gradually increasing and requires further study. Approximately one in five patients with re-prescription receives the same antibiotic again. We recommend that practice is audited to drive down this proportion. Management of UTIs might need to consider recent antibiotic use to minimise development of antibiotic resistance to drugs used for first and second line therapy.

Contributors

Dr. MP-R had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics approval and data acquisition: JS. Study design: MP-R, RW, MHW, JS. Creation and validation of lists of diagnostic codes and algorithms to define infections and treatment response failure: MP-R, MHW, JS. Creation of cohort and covariates: MP-R. Drafting of manuscript: MP-R. Critical revision of the manuscript for important intellectual content: RW, MHW, JS. All authors approved the submission.

Declaration of Competing Interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work except from UK National Health Service Improvement. MW reports to have received personal fees from AiCuris, Allergan, Antabio, Astra Zeneca, Basilea, Bayer, the Medicine Company, Menarini, Motif Biosciences, Nabriva, Paratek, Pfizer, Phico Roche, Therapeutics Spero, and Tetraphase, outside the submitted work; as well as grants from Pfizer, Paratek, and Tetraphase, outside the submitted work.

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Appendix A. Supplementary Data

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References

[1] Foxman B. The epidemiology of urinary tract infection. Nat Rev Urol 2010;7(12):653–60.
[2] 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.
[3] Butler CC, Francis N, Thomas-Jones E, et al. Variations in presentation, management, and patient outcomes of urinary tract infection: a prospective four-country primary care observational cohort study. Br J Gen Pract 2017;67(665):e830–41.
[4] Foxman B, Barlow R, D'Arcy H, Gillespie B, Sobel JD. Urinary tract infection: self-reported incidence and associated costs. Ann Epidemiol 2000;10(8):509–15.
[5] Car J. Urinary tract infections in women: diagnosis and management in primary care. BMJ 2006;332(7533):94–7.
[6] National Institute for Health and Care Excellence (NICE). Urinary tract infection (lower): Antimicrobial prescribing. Clinical guideline [NG109] October 2018. Available from https://www.nice.org.uk/guidance/ng109; 2018.
[7] Tempera G, Furneri PM, Cianci A, Incognito T, Marano MR, Drago F. The impact of prulifloxacin on vaginal lactobacillus microflora: an in vivo study. J Chemother 2009;21(6):646–50.
[8] Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. BMJ 2010;340:c2096.
[9] Hillier S, Roberts Z, Dunstan F, Butler C, Howard A, Palmer S. Prior antibiotics and risk of antibiotic-resistant community-acquired urinary tract infection: a case-control study. J Antimicrob Chemother 2007;60(1):92–9.
[10] The Review on Antimicrobial Resistance. Antimicrobial resistance: Tackling a crisis for the health and wealth of nations; 2014.
[11] Ahmed H, Farewell D, Jones HM, Francis NA, Paranjothy S, Butler CC. Incidence and antibiotic prescribing for clinically diagnosed urinary tract infection in older adults in UK primary care, 2004-2014. PLoS One 2018;13(1):e0190521.
[12] McDonald HC, Pandya AG, Kimball AB. Dermatologic workforce on the Texas border: using burden on primary care as an outcome measure. Int J Dermatol 2013;52(4):506–7.
[13] McNulty C. Management and treatment of common infections. Antiobiotic guidance for primary care: For consultation and local adaptation London. 2017.
[14] Crellin E, Mansfield KE, Leyrat C, et al. Trimethoprim use for urinary tract infection and risk of adverse outcomes in older patients: cohort study. BMJ 2018;360:k341.
[15] Sanchez Garcia M. Early antibiotic treatment failure. Int J Antimicrob Agents 2009;34(Suppl. 3):S14–9.
[16] Laupland KB, Ross T, Pitout JD, Church DL, Gregson DB. Community-onset urinary tract infections: a population-based assessment. Infection 2007;35(3):150–3.
[17] Malcolm W, Fletcher E, Kavanagh K, et al. Risk factors for resistance and MDR in community urine isolates: population-level analysis using the NHS Scotland infection intelligence platform. J Antimicrob Chemother 2018;73(1):223–30.
[18] National Institute for Health and Care Excellence (NICE). Clinical knowledge summaries: Urinary tract infection (lower) - women Available from https://cks.nice.org.uk/urinary-tract-infection-lower-women#!scenario; 2015.
[19] Department of Health. In: Do Health, editor. UK five year antimicrobial resistance strategy 2013 to 2018; 2013.
[20] Abel zur Wiesch P, Kouyos R, Abel S, Viechtbauer W, Bonhoeffer S. Cycling empirical antibiotic therapy in hospitals: meta-analysis and models. PLoS Pathog 2014;10(6):e1004225.
[21] Baur D, Gladstone BP, Burkert F, et al. Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and Clostridium difficile infection: a systematic review and meta-analysis. Lancet Infect Dis 2017;17(9):990–1001.
[22] National Institute for Health and Care Excellence (NICE). Urinary tract infection in under 16s: diagnosis and management. Clinical guideline [CG54] September 2017 update. Available from https://www.nice.org.uk/guidance/cg54; 2017.
[23] O'Sullivan JW, Stevens S, Hobbs FDR, et al. Temporal trends in use of tests in UK primary care, 2000-15: retrospective analysis of 250 million tests. BMJ 2018;363:k4666.
[24] Lee MT, Lee SH, Chang SS, et al. Comparative effectiveness of different oral antibiotics regimens for treatment of urinary tract infection in outpatients: an analysis of national representative claims database. Medicine (Baltimore) 2014;93(28):e304.
[25] Huttner A, Kowalczyk A, Turjeman A, et al. Effect of 5-day nitrofurantoin vs single-dose fosfomycin on clinical resolution of uncomplicated lower urinary tract infection in women: a randomized clinical trial. JAMA 2018;319(17):1781–9.
[26] Goettsch WG, Janknegt R, Herings RM. Increased treatment failure after 3-days' courses of nitrofurantoin and trimethoprim for urinary tract infections in women: a population-based retrospective cohort study using the PHARMO database. Br J Clin Pharmacol 2004;58(2):184–9.
[27] Lawrenson RA, Logie JW. Antibiotic failure in the treatment of urinary tract infections in young women. J Antimicrob Chemother 2001;48(6):895–901.
[28] Singh N, Gandhi S, McArthur E, et al. Kidney function and the use of nitrofurantoin to treat urinary tract infections in older women. CMAJ 2015;187(9):648–56.
[29] Bryce A, Hay AD, Lane IF, Thornton HV, Wootton M, Costelloe C. Global prevalence of antibiotic resistance in paediatric urinary tract infections caused by Escherichia

coli and association with routine use of antibiotics in primary care: systematic review and meta-analysis. BMJ 2016;352:i939.
[30] Donnan PT, Wei L, Steinke DT, et al. Presence of bacteriuria caused by trimethoprim resistant bacteria in patients prescribed antibiotics: multilevel model with practice and individual patient data. BMJ 2004;328(7451):1297.
[31] Rossignol L, Maugat S, Blake A, et al. Risk factors for resistance in urinary tract infections in women in general practice: a cross-sectional survey. J Infect 2015;71(3):302–11.
[32] Public Health England. English surveillance programme for antimicrobial utilisation and resistance (ESPAUR). Report 2017. London: Public Health England; 2017.