Improving antibiotic prescribing for older people with urinary tract infection in primary care

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This work has not previously been accepted in substance for any degree and is not concurrently submitted in candidature for any degree.

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Publications arising from the work in this thesis

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2. **Ahmed H**, Farewell D, 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

3. **Ahmed H**, Farewell D, Jones HM, Francis NA, Paranjothy S, Butler CC. Antibiotic prophylaxis and clinical outcomes among older adults with recurrent urinary tract infection: cohort study. Age and Ageing 2018; doi: 10.1093.

4. **Ahmed H**, Farewell D, Francis NA, Paranjothy S, Butler CC. Risk of adverse outcomes following urinary tract infection in older people with renal impairment: Retrospective cohort study using linked health record data. PLoS Medicine 2018. 15(9):e1002652.

5. **Ahmed H**, Farewell D, Francis NA, Paranjothy S, Butler CC. Choice of empirical antibiotic therapy and adverse outcomes in older adults with suspected urinary tract infection: cohort study. Open Forum Infectious Diseases 2019. 6(3):ofz039.

6. **Ahmed H**, Farewell D, Francis NA, Paranjothy S, Butler CC. Impact of antibiotic treatment duration on outcomes in 32,593 older men with suspected urinary tract infection: cohort study. Pharmacoepidemiology and Drug Safety 2019. DOI:10.1002/pds.4791

Presentations arising from the work in this thesis

1. Trends in the incidence of clinically diagnosed urinary tract infection in UK primary care. South West Society of Academic Primary Care. Cardiff, March 2016.

2. Using routinely collected data to understand the epidemiology and treatment of urinary tract infection in UK primary care. FARR Institute PhD Symposium. Manchester, April 2017.

3. Long-term antibiotic prophylaxis to prevent recurrent urinary tract infections in older people. General Practice Research on Infections Network conference. Oslo, October 2017.

4. Impact of antibiotic treatment duration on outcomes in older men with UTI in primary care. General Practice Research on Infections Network conference. Utrecht, October 2018.

5. Nitrofurantoin versus trimethoprim for UTI in older people with renal impairment. General Practice Research on Infections Network conference. Utrecht, October 2018.

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List of abbreviations

AKI	Acute kidney injury
ABU	Asymptomatic bacteriuria
CI	Confidence Interval
CPRD	Clinical Practice Research Datalink
eGFR	Estimated glomerular filtration rate
GP	General Practitioner
HR	Hazard ratio
IQR	Interquartile range
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NNT	Number Needed to Treat
NNH	Number Needed to Harm
OR	Odds ratio
SAIL	Secure Anonymised Information Linkage
THIN	The Health Improvement Network
UTI	Urinary tract infection

Note to the reader

As far as possible, I have written this thesis in the active voice. Using the active voice raised the issue of whether to use the first-person singular – 'I'– or first-person plural – 'we', with the former potentially distracting and less readable, but the latter seeming out of place in a PhD thesis where the work is the product of one person. I have elected to use the less distracting 'we' when talking about what I have done in the active voice to improve the readability of the text. However, for the record, I wish to make it clear that the use of 'we' in this thesis implies that 'I' have done something.

Summary

Urinary tract infection (UTI) is a common cause of morbidity, NHS use, and antibiotic prescribing in older people. However, few randomised trials or observational studies have explored the impact of different antibiotic prescribing strategies on UTI-related outcomes in older people. Routinely collected healthcare data provides an opportunity to investigate associations between different treatment approaches and outcomes efficiently and cost-effectively.

The aim of this thesis was to carry out epidemiological analyses of linked general practice, hospital, and mortality data from the Clinical Practice Research Datalink, to understand the impact of different antibiotic prescribing strategies on outcomes in older people with acute and recurrent UTI.

In chapter 4, we investigate the burden of clinically diagnosed UTI in older people in UK primary care and found that in a sample of adults aged ≥65, 21% present with at least one UTI over a 10-year period. We also found that choice and duration of antibiotic therapy improved over time. For example, between 2004 and 2014, nitrofurantoin prescribing increased, broad-spectrum antibiotic prescribing decreased, and there was an increase in the proportion of patients prescribed antibiotics for durations recommended by clinical guidelines. In chapters 5 and 7, we investigate associations between antibiotic choice and risk of treatment failure, hospitalisation and death. We

found that broad-spectrum antibiotics offer little benefit over nitrofurantoin, and nitrofurantoin is associated with better outcomes than trimethoprim in patients with renal impairment. Chapter 6 investigates the impact of short versus long course antibiotic treatment on UTI outcomes in older men and found that shorter durations of treatment are associated with higher rates of treatment failure but lower rates of acute kidney injury. Chapter 8 reports a systematic review and meta-analysis of randomised trials and found that the evidence for prophylactic antibiotics for recurrent UTI in older people is based on three studies of postmenopausal women. In chapter 9, we provide the only currently available data on outcomes in older men with recurrent UTI prescribed long-term antibiotic prophylaxis.

This thesis reports new evidence to support more prudent antibiotic prescribing for UTI in older people and highlights the need for more robust evidence to address challenges in diagnosis and treatment of UTI.

1 Introduction

In 2011, the Annual Report of the Chief Medical Officer to the UK Government focussed on infections and the rise of antimicrobial resistance (1). The report was instrumental in generating political interest in the global public health threat of antimicrobial resistance, and led to a National Institute of Health Research themed funding call. The research reported in this thesis was funded by that call and examines antibiotic prescribing for urinary tract infection (UTI) in older people, with the aim of generating new evidence that improves antibiotic use and ultimately helps to contain antibiotic resistance.

1.1 Urinary tract infection in older people

UTI refers to infection in the bladder, kidneys, or other part of urinary tract, most commonly cause by gram-negative bacteria ascending through the urethra. It can be classified according to the presence of fever, the anatomical location, or presence of factors that increase patients' susceptibility to UTI or UTI-related complications. Prevention and acute treatment of UTI is the commonest reason for antibiotic prescribing in older people (2, 3). UTIs can present with non-specific symptoms and signs in older people and there are concerns that this has led to over-diagnosis and over-treatment (4, 5). Urine culture is less useful because it is more difficult to get an uncontaminated sample from older people, and because the prevalence of asymptomatic bacteriuria increases with age (6). Therefore, an older person with acute confusion and significant bacterial growth in their urine culture may not have a UTI, but may be diagnosed and treated for a

UTI. However, under-treatment of UTI is also problematic and is thought to be a contributor to the increasing rates of blood-stream infection observed in older people in certain parts of England (7). UK hospital data suggest that the overall burden of UTI in older people has increased. The number of emergency admissions of older people with a primary diagnosis of UTI rose from 35,800 in 2001 to 107,300 in 2012, an increase of 200% (8). This is a substantial increase in burden, even if some of this increase is due to changes in coding practices.

1.2 Antibiotic resistance

The global threat of antibiotic resistance is well recognised, with an estimated 700,000 deaths attributed to antibiotic resistant infections annually (9). The estimated economic impact is expected to reach US$100 trillion by 2050 (9) . The European Antimicrobial Resistance Surveillance Network estimated that there were 671,689 antibiotic resistant infections across participating European countries between January 1st and December 31st 2015. These infections accounted for 33,110 deaths and 874,541 disability-adjusted life-years. The burden was highest in infants (age <1 year) and older people (age >65 years) (10).

Prior antibiotic exposure is the most widely studied risk factor for antibiotic resistance, with most studies reporting a greater than two-fold increase for the risk of antibiotic resistant infections in those previously exposed to antibiotics versus those unexposed (11). In primary care, prior prescribing of antibiotics for UTI increased the risk of antibiotic resistant urinary pathogens by four-fold in the subsequent 30 days and by two-fold at six-months (12). Therefore, co-ordinated actions to minimise antibiotic

resistance include antibiotic stewardship; prescribing antibiotics only when absolutely necessary and prescribing the most appropriate antibiotic, at the most appropriate dose and for the most appropriate duration (13). The aim is for more prudent prescribing to help preserve the effectiveness and value of existing antibiotics.

1.3 Rationale for this thesis

This thesis presents a series of complementary observational studies investigating antibiotic prescribing and subsequent outcomes in older people who presented to primary care with a suspected UTI. The overarching hypothesis is that variation in the choice and duration of antibiotic prescribing for UTI in older people is unwarranted and has little impact on their clinical outcomes. This presents an opportunity to improve the use of existing antibiotics by generating new evidence that could support more standardised and prudent prescribing.

We chose primary care as the setting as it is responsible for 90% of patient contacts and 75% of antibiotic prescribing in the UK NHS (14). We chose to study UTI because 75-90% of patients with suspected UTI are prescribed an empirical antibiotic without microbiological confirmation of infection or results of antibiotic susceptibilities, (15, 16) therefore presenting an opportunity to improve the choice of the initial empirical prescription. Furthermore, UTI accounts for about 15% of all antibiotic prescriptions in primary care, (17) so small changes in prescribing behaviour could have considerable impact at a population level. We chose older people (defined as age ≥65 years) for three reasons. First, because of data reporting a rise in UTI hospital admissions in this age group (13). Second, because clinical

guidelines excluded older people from most recommendations for the management of UTI (18, 19). Third, because the Chief Medical Officer's report stated that this age group would present the greatest growth in the burden of infectious disease and that, within this group, UTI was one of the three most important infection-related morbidities along with healthcare-associated infection and influenza (1).

1.4 Thesis outline

Figure 1.1 outlines the organisation of this thesis. Chapter 2 presents a literature review that appraises published studies reporting the incidence, diagnosis, clinical management and outcomes of older people with UTI. We highlight key evidence gaps and summarise how these informed the aims and objectives of this thesis. These are listed at the end of the chapter.

Chapter 3 describes the research methods. We justify the choice of data source and approach to data analysis, including methods used to adjust for confounding and other biases inherent in observational research.

Chapters 4-9 describe the results. We present detailed information regarding the background and methods for the results chapters in chapters 2 and 3. Therefore, we only briefly summarise the key points at the start of each results chapter to prevent unnecessary repetition. The discussion for each results chapter is presented in full. In chapter 4, we present the findings on trends in the incidence of UTI in primary care over a 10-year study period. We also report trends in antibiotic prescribing for UTI over this period. Chapters 5 and 6 focus on variation in antibiotic prescribing and impact on patient outcomes. We report associations between the choice

and duration of empirical antibiotic prescribing and several adverse outcomes. Chapter 7 examines if variation is warranted in patients with renal impairment, and investigates outcomes in patients prescribed trimethoprim versus nitrofurantoin by degree of kidney function. Chapters 8 and 9 focus on recurrent UTI and report a systematic review and meta-analysis of randomised trials of antibiotic prophylaxis versus non-antibiotic prophylaxis or placebo, and an observational study of prophylaxis versus no prophylaxis.

In chapter 10, we summarise the key findings. We appraise our research, and reflect on its strengths and weaknesses, and the lessons learnt. We also present implications for future research and practice.

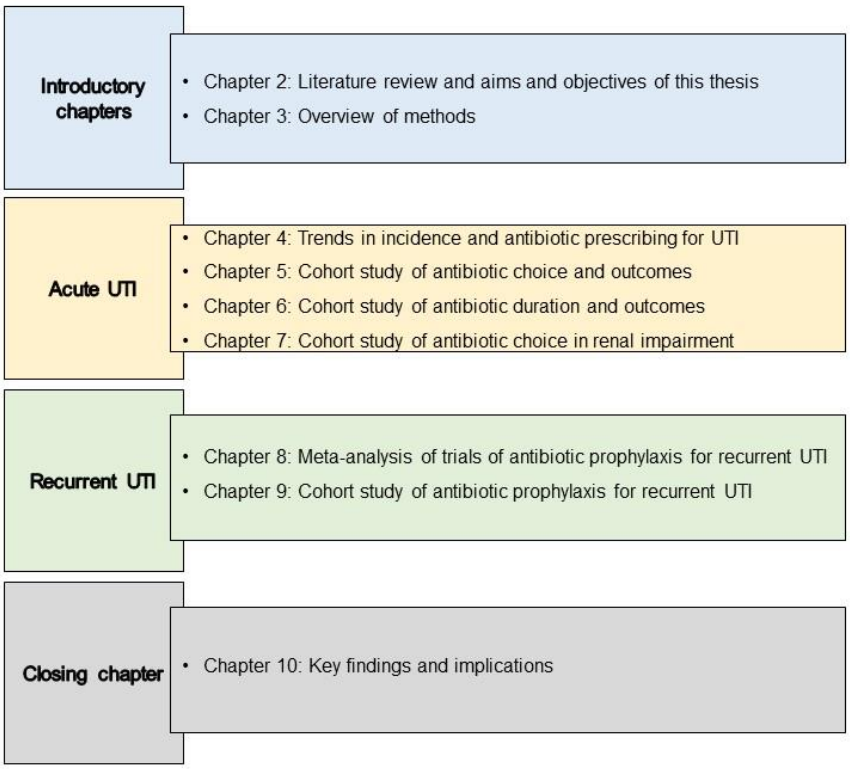


Figure 1.1. Organisation of chapters in this thesis.

2 Literature review

2.1 Introduction

This aim of this chapter is to present an overview of published evidence relevant to the objectives of this thesis, to highlight evidence gaps, and to contextualise the primary research studies presented in later chapters. We searched PubMed from January 1980 to April 2018 for English language studies reporting on UTI in older people in primary care using relevant search terms related to UTI (e.g., Urinary tract infection* OR cystitis) and older people (e.g., old* OR elder OR aged). We combined these terms with keywords for each specific objective, e.g., to identify studies reporting the incidence of UTI in older people, we combined the search terms related to UTI and older people with “incidence” OR “prevalence”. We used the same method to identify studies on antibiotic prescribing for UTI (search terms were “antibiotic* OR antimicrobial*”), diagnosis of UTI (search term was “diagnos*”), recurrent UTI (search term was “recurrent”), and renal impairment in UTI (search terms were “renal impairment OR acute kidney injury”). We screened titles and abstracts and removed studies that were not related to the clinical management of UTI in primary care. We reviewed full-text papers of the remaining studies to identify those for inclusion in this review. We included studies that were either directly relevant to the objectives of this thesis, or were important to help contextualise the background and rationale for the empirical studies in chapters 4-9. For objectives where no studies were identified, we re-searched but without

restricting to older people and identified relevant studies that included adults of any age. We clarify in the text whether the evidence presented comes from studies of older people or from adults of all ages. When reporting the studies, we present data from systematic reviews first (if available), then randomised trials (if they add additional information), and then observational studies (if they add additional information).

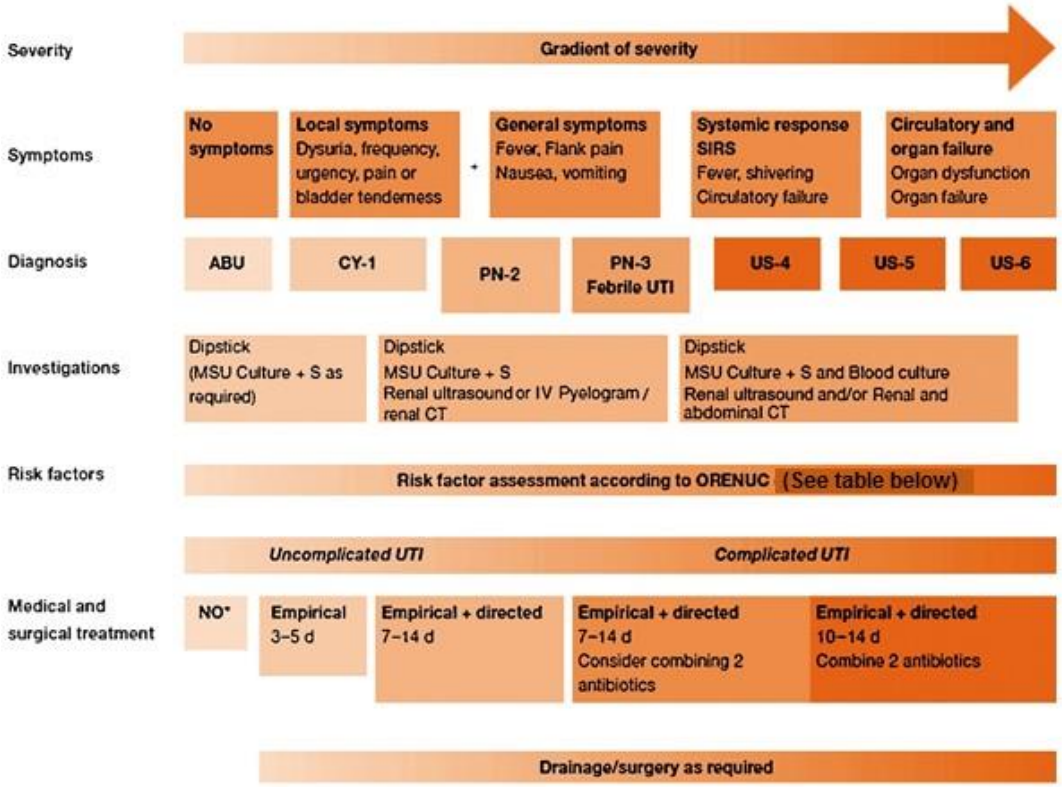
2.2 Definition and classification of UTI

UTI is an umbrella term that can refer to infection in the bladder (cystitis), kidneys (pyelonephritis), or other part of urinary tract. It can be classified according to the presence of fever (febrile versus non-febrile UTI), anatomical location (lower versus upper UTI), or presence of factors that increase patients' susceptibility to UTI or UTI-related complications (complicated versus uncomplicated) (20). The Infectious Disease Society of America and European Society for Microbiology and Infectious Diseases define uncomplicated lower UTI as cystitis occurring in non-pregnant, pre-menopausal women with no known relevant anatomical or functional abnormalities within the urinary tract, or comorbidities that could pre-dispose to UTI or UTI-related complications (18). Complicated lower UTI therefore includes UTI in men, pregnant or post-menopausal women, and in patients with relevant anatomical or functional abnormalities of the urinary tract, indwelling urinary catheters, renal diseases, and/or other concomitant immunocompromising diseases.

In 2011, the European Association of Urology argued that most UTIs are uncomplicated and the widely used definition of complicated UTI included many individuals with no excess risk of an adverse outcome (21). They

proposed a new classification of UTI that defined uncomplicated and complicated according to the severity of clinical presentation (from asymptomatic bacteriuria to sepsis), and number and severity of host risk factors for an adverse outcome (Figure 2.1) (22).

A consistent and widely accepted classification of UTI is important for clinical practice because most clinical guidelines restrict their recommendations to uncomplicated UTI. Therefore, clinicians may treat patients presenting with what they judge to be complicated UTI outside of these guidelines. Based on The Infectious Disease Society of America guidelines, this includes all men and all adults aged ≥65 years, and may partly explain the observed variation in antibiotic prescribing for UTI seen in this population.



Host risk factors in urinary tract infections categorized according to the ORENUC system		
Phenotype	**Category of risk factor**	**Examples of risk factors**
O	No known risk factor	Otherwise healthy premenopausal women
R	Risk factors for recurrent urinary tract infection but no risk of more severe outcome	Sexual behavior (frequency, spermicide)–Hormonal deficiency in postmenopause–Secretor type of certain blood groups–Well-controlled diabetes mellitus
E	Extraurogenital risk factors with risk of more severe outcome	Prematurity, newborn–Pregnancy–Male gender–Badly controlled diabetes mellitus–Relevant immunosuppression (not well defined)
N	Nephropathic diseases with risk of more severe outcome	Relevant renal insufficiency (not well defined)–Polycystic nephropathy–Interstitial nephritis (eg, due to analgesics)
U	Urologic risk factors with risk of more severe outcome, which can be resolved during therapy	Ureteral obstruction due to a ureteral stoneW–Well-controlled neurogenic bladder disturbances–Transient short-term external urinary catheter–Asymptomatic bacteriuria
C	Permanent urinary catheter and unresolvable urologic risk factors with risk of more severe outcome	Long-term external urinary catheter–Unresolvable urinary obstruction–Badly controlled neurogenic bladder disturbances

Figure 2.1. Classification of complicated and uncomplicated UTI as proposed by the European Association of Urology. ABU = asymptomatic bacteriuria; CT = computed tomography; CY = cystitis; IV = intravenous; MSU = midstream sample of urine; PN = pyelonephritis; US = urosepsis. Reproduced with permission from Smelov et al, European Urology Supplements (22), license number 4450771360815.

2.3 Incidence of UTI

Over a third of a random sample of 2424 females in England reported having had at least one UTI in their lifetime, and this varied by age group (16–34 years, 36%; 35–54 years, 42%; and 55+ years, 33%) (15). Published estimates of the incidence of UTI in *older* people vary in their design and methods. The Pittsburgh Good Health Study followed 417 adults aged ≥65 from July 1986 to June 1988 and estimated UTI incidence to be 10.9 episodes per 100 person-years in men, and 14.0 episodes per 100 person-years in women (23). They defined UTI as a presentation with urinary tract symptoms that included dysuria and urinary frequency but did not include confirmatory urine culture. These estimates are almost 20 years old and do not adequately reflect current population demographics or recent trends in health service use related to an aging population. However, the estimates are similar to those of the more recent Leiden 85-plus study (24). This study recruited 479 adults aged ≥85 and followed them for 4 years. UTI was defined by physician diagnosis and corroborating urine analysis. UTI incidence rates were 7.8 per 100 person-years in men and 12.8 per 100 person-years in women. The small sample size prevented meaningful analysis of trends over time.

UK based estimates are limited to a study of older patients with type 2 diabetes mellitus. McDonald and colleagues used the Clinical Practice Research Datalink (CPRD) to identify clinically diagnosed infections using clinical codes (25). They estimated UTI incidence to range from 2.94 (age 65-69) to 14.1 (age ≥85) episodes per 100 person-years in men, and 11.0 (age 65-69) to 22.3 (age ≥85) episodes per 100 person-years in women.

However, these estimates are likely to be higher than for the general population of older people due to the higher incidence of UTI in people with type 2 diabetes mellitus (26).

In summary, population-based estimates of UTI incidence in older people are limited to two studies from the USA and The Netherlands with follow-up of 2-4 years, and incidence estimates of 8-11 per 100 person years in older men, and 13-14 per 100 person years in older women (23, 24). UK estimates are more granular but are limited to older people with type 2 diabetes mellitus (25). Therefore, we still need reliable current population-based estimates of the incidence of UTI in older people, in a longitudinal sample that is large enough to identify trends over time and is generalisable to the UK over-65 population. These estimates will increase understanding of UTI burden, inform health service planning, and allowing prioritisation of resources for prevention and management.

2.4 Pathophysiology

The pathogenesis of UTI is described in detail in Figure 2.2. Most uncomplicated UTIs arise from microorganisms ascending through the urethra, although some microorganisms can reach the urinary tract by hematogenous or lymphatic spread (20). In adults of all ages, E. coli is the causative pathogen in 70–95% of uncomplicated UTIs, Staphylococcus in 5–10% and other Enterobacteriaceae, such as Proteus mirabilis and Klebsiella, in the remainder. The microbial spectrum of complicated UTIs is broader and includes species of Pseudomonas, Enterococcus, Staphylococcus, Serratia, and Providencia and fungi (20).

The microbiology of UTI in older adults is less well described. A Brazilian study of 598 women aged ≥65 presenting to primary care or nephrology outpatients with symptoms of UTI identified 99 urine cultures with bacterial growth of >100,000 colony-forming units/mL (27). The predominant bacterial species were E.coli (75%), Enterococcus (9%), Proteus mirabilis (6%), Klebsiela (5%), Staphylococcus (3%) and Citrobacter (1%). In contrast, a study of 171 US nursing home residents with suspected UTI found that E.coli was isolated in 54%, Proteus in 15%, Klebsiella in 14%, other Enterobacteraciaeae in 6%, Enterococcus in 4.5%, and Staphylococcus in 4% (28). However, this included samples with bacterial growth of a little as 10,000 colony-forming units/mL.

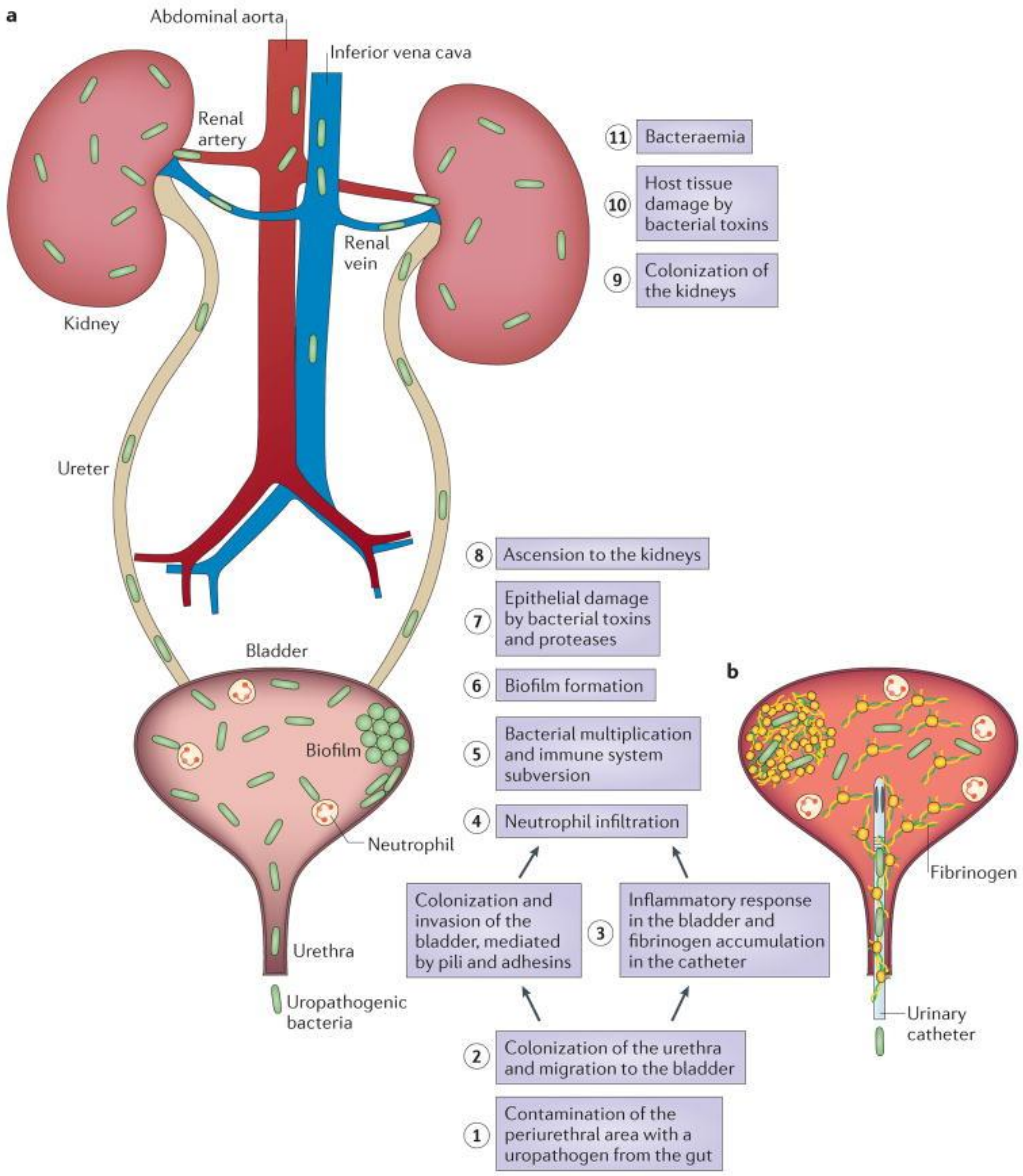


Figure 2.2. Pathogenesis of urinary tract infections.

a | Uncomplicated urinary tract infections (UTIs) begin when uropathogens that reside in the gut contaminate the periurethral area (step 1) and are able to colonize the urethra. Subsequent migration to the bladder (step 2) and expression of pili and adhesins results in colonization and invasion of the superficial umbrella cells (step 3). Host inflammatory responses, including neutrophil infiltration (step 4), begin to clear extracellular bacteria. Some bacteria evade the immune system, either through host cell invasion or through morphological changes that result in resistance to neutrophils, and these bacteria undergo multiplication (step 5) and biofilm formation (step 6). These bacteria produce toxins and proteases that induce host cell damage (step 7), releasing essential nutrients that promote

bacterial survival and ascension to the kidneys (step 8). Kidney colonization (step 9) results in bacterial toxin production and host tissue damage (step 10). If left untreated, UTIs can ultimately progress to bacteraemia if the pathogen crosses the tubular epithelial barrier in the kidneys (step 11). **b |** Uropathogens that cause complicated UTIs follow the same initial steps as those described for uncomplicated infections, including periurethral colonization (step 1), progression to the urethra and migration to the bladder (step 2). However, in order for the pathogens to cause infection, the bladder must be compromised. The most common cause of a compromised bladder is catheterization. Owing to the robust immune response induced by catheterization (step 3), fibrinogen accumulates on the catheter, providing an ideal environment for the attachment of uropathogens that express fibrinogen-binding proteins. Infection induces neutrophil infiltration (step 4), but after their initial attachment to the fibrinogen-coated catheters, the bacteria multiply (step 5), form biofilms (step 6), promote epithelial damage (step 7) and can seed infection of the kidneys (steps 8 and 9), where toxin production induces tissue damage (step 10). If left untreated, uropathogens that cause complicated UTIs can also progress to bacteraemia by crossing the tubular epithelial cell barrier (step 11). Reproduced with permission from Flores-Mireles et al, Nature Reviews Microbiology (20), license number 4450770317355.

2.5 Clinical guideline recommendations for UTI in older people

The Scottish Intercollegiate Guidelines Network (SIGN) produced the first comprehensive UK clinical guideline for the management of adult bacterial UTI in 2006 (29). SIGN presented their guidance as applicable to four groups: adult non-pregnant women, pregnant women, adult men, and people with indwelling urinary catheters. The guideline specifically stated that all adults aged ≥65 presenting with suspected UTI should have a full clinical assessment including measurement and recording of vital signs. There were no other recommendations specific to older adults but the following statements were applicable to this age-group:

1. No antibiotic treatment for men and non-pregnant women with asymptomatic bacteriuria,
2. All adult men (of any age) presenting with a UTI to have urine sampled and sent for culture,
3. All adult men and non-pregnant women with lower UTI to be treated with trimethoprim or nitrofurantoin as first-line,
4. All adult non-pregnant women (of any age) with lower UTI to be treated with three-day antibiotic therapy.

Shortly after publication of the SIGN guidelines, Public Health England (then known as the Health Protection Agency) published their first guideline for the management of UTI in November 2007 (30). Their guideline focused more on UTI diagnosis and discussed the challenges of accurate diagnosis of UTI in older people given the less specific symptoms and signs, the difficulties around urine sampling, and the prevalence of asymptomatic bacteriuria. They encouraged a more criteria-based approach to UTI diagnosis in older people. These two guidelines were the main sources of UTI management recommendations during the period of study in the empirical studies presented later in this thesis. Subsequent iterations of the Public Health England guideline increased the detail of the recommendations for diagnosing UTI in older adults. The current version (published April 2019) contains a comprehensive checklist of symptoms and signs needed to satisfy a diagnosis of UTI. There is also clear guidance to not use urine dipstick in older adults (to align with a national campaign to reduce unnecessary urine dipstick use in the frail elderly), and reminders to consider sepsis, delirium and other causes of the clinical presentation (31).

Public Health England recommend considering delayed antibiotics for older adults with mild symptoms but specific recommendations regarding antibiotic treatment are not made as these are presented in the current National Institute of Health and Care Excellence (NICE) guidance for antimicrobial prescribing for lower UTI. NICE published these guidelines in October 2018 and recommend nitrofurantoin or trimethoprim (if risk of trimethoprim resistance is low) as first-line antibiotic treatment for adult men and non-pregnant adult women (32). Second-line options include pivmecillinam and fosfomycin. NICE also produced guidance on the treatment of recurrent UTI in October 2018 (33). Key recommendations include:

1. Discussing with patients behavioural and hygiene measures that may reduce the risk of UTI recurrence,
2. Considering vaginal oestrogens for postmenopausal women with recurrent UTI in whom behavioural and hygiene measures are not effective,
3. Considering a trial of daily antibiotic prophylaxis in patients where the above measures have failed to reduce UTI incidence.

If prescribing daily antibiotic prophylaxis, NICE recommend trimethoprim or nitrofurantoin as first-line with a review of their effect at six months.

2.6 Diagnosis of UTI

Accurate diagnosis of UTI is challenging in older adults. One aim of accurate diagnosis is to help decide whether a specific treatment is required. In the case of UTI, that treatment would be antibiotics +/- additional supportive or symptomatic measures such as analgesics. The pathway to UTI diagnosis

in primary care usually involves patients consulting with symptoms and signs of illness, a clinical decision about whether or not to sample urine, perform point-of-care urinalysis, and send urine for laboratory microscopy and culture. This is followed by a decision to prescribe (or not prescribe) antibiotics, either empirically without microbiological confirmation of infecting organism or antibiotic susceptibilities, or following results of urine culture.

Few symptoms or signs are predictive of laboratory confirmed UTI in older people. A systematic review of 15 diagnostic studies of people aged ≥65 investigated the predictive value of 66 different symptoms and signs (34). Studies varied in quality, and in their definition of symptoms and signs, meaning that only a few symptoms and signs were appropriate for meta-analysis. Only one study included men. All studies used urine culture, either alone or in combination with symptoms and signs as the reference standard. Among studies that used urine culture *alone* as the reference standard, there was little discussion about the limitations of their approach given the prevalence of asymptomatic bacteriuria in this older population. Among studies that used signs or symptoms *and* urine culture as the reference standard, it was not clear how they dealt with the issue of index tests being part of the reference test. Almost all studies had missing reference test data (i.e. missing urine cultures). Pooled estimates from six studies identified the presence of new urinary incontinence (positive likelihood ratio 1.96) and dysuria (positive likelihood ratio 1.70) as predictive of the reference test. Incontinence, foul smelling urine and haematuria were predictors of the reference test in men, but not in women. Acute changes in functional status

were strong predictors of the reference test in both genders, but changes in cognition were not. Abnormal vital signs (fever, tachycardia and hypotension) were of limited value. Overall, the review highlights the methodological challenges of diagnostic accuracy studies of UTI in older people, especially given the lack of an ideal reference standard, and the clinical challenge of using symptoms and signs to select patients who may have a UTI and thus require urine sampling or antibiotic treatment.

In patients with appropriate symptoms, urine sampling and urinalysis +/- urine culture may help to support or refute the diagnosis of UTI. Two US studies investigated the reason for urine sampling in nursing home residents and found that factors most commonly associated with urine sampling requests were acute changes in cognition or function, change in the urine colour, odour, or sediment, and dysuria (35, 36). The diagnostic accuracy of urinalysis in older adults is unclear. A meta-analysis of four studies of older people conducted between 1990 and 1999 found that the presence of nitrites or leukocyte esterase on urinalysis had sensitivity and specificity for UTI of 82% and 71% respectively (37). More recent studies of older patients found that the negative predictive value for dipstick testing ranges from 92% to 100% (38-40). Given the variable test characteristics in older people, current thinking suggests that urinalysis should be performed in the community setting primarily to rule out a diagnosis of UTI (41).

Urine culture is currently used to confirm the presence of bacteriuria in patients with symptoms and signs of a UTI and thus support a diagnosis of UTI. Urine culture in older adults is less useful because of high rates of contaminated samples that may mask true positives and true negatives, and

make interpretation difficult. Interpretation of urine culture results is based on findings from studies conducted in the 1950s (42). Current guidance from Public Health England is that urine cultures with bacterial counts of ≥100,000 cfu/mL are indicative of infection, and counts below this usually indicate contamination. However, in specific patient groups, counts between 10,000 cfu/mL and 100,000 cfu/mL may also be significant. Furthermore, a pure isolate with counts between 10,000-100,000 cfu/mL should be evaluated based on clinical information or confirmed by repeat culture (43).

Urine cultures may be requested in patients without symptoms or signs of UTI and may show bacterial growth. Asymptomatic bacteriuria (ABU) is defined as the presence of bacteria in the urine in quantities of >100,000 cfu/mL in two consecutive urine specimens in women or one urine specimen in men, in the absence of clinical signs or symptoms suggestive of a UTI (44). The estimated prevalence of ABU is 6-10% in women and 5% in men older than 65, increasing to 20% in women and 10% in men over 85 (45). The prevalence is higher in institutionalized adults with estimates ranging from 25-50% for women and 15-35% for men (6). A systematic review and meta-analysis of seven randomised and two quasi-randomised trials (1614 participants, seven studies only included adults aged ≥65) found no difference in the development of symptomatic UTI, UTI-related complications or death in adults with ABU treated with antibiotics versus placebo or no treatment (46). Antibiotic treatment resulted in greater rates of bacteriological cure but with significantly more adverse events and thus had no overall clinical benefit. However, an estimated 45% of adults (of all ages) with ABU are thought to be treated with antibiotics, with isolation of

gram-negative pathogens, pyuria, nitrite positivity and female gender associated with greater odds of receiving treatment (47).

In summary, common reasons for requesting urine sampling in older people are acute changes in cognition or function, change in the urine colour, odour, or sediment, and dysuria (35, 36). Of these reasons, current evidence suggests only change in function and dysuria are associated with bacteriuria (36). Existing diagnostic studies are limited by the challenge of obtaining an uncontaminated urine sample, and the prevalence of asymptomatic bacteriuria in older people, both of which render urine culture an imperfect reference standard.

2.7 Antibiotic treatment of UTI

Most people with symptoms or signs suggestive of UTI receive antibiotic treatment. Analysis of data from the 2010-2011 US National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey found that same-day empirical antibiotics were prescribed to 65% of adults aged ≥65 presenting to ambulatory care with a possible UTI (48). There are no published UK data reporting empirical antibiotic prescribing rates for older adults with UTI. Analysis of UK primary care data for adults of all ages from The Health Improvement Network database found that 92% of patients presenting with suspected UTI were prescribed same-day empirical antibiotics (16). These patients were aged 14 and over and patients with co-morbidities were excluded. Lower prescribing rates were reported in a household survey of women aged 16 and over. Of those who had seen a healthcare professional for a UTI, 75% reported receiving an empirical same-day antibiotic prescription (15).

Although same-day antibiotic prescribing is the most common treatment strategy employed for patients presenting to primary care with suspected UTI, current NICE and Public Health England guidance suggests consideration of delayed prescribing for those with milder symptoms (32, 49). We did not identify any studies investigating the effect of delayed antibiotic prescribing for UTI in older people. Evidence for delayed prescribing in UTI comes from a trial of 309 women aged <75 presenting to primary care with suspected UTI who were randomised to receive immediate antibiotics, delayed antibiotics, or targeted antibiotics based on urine dipstick, culture, or a symptom score (50). Women in the delayed antibiotic group were advised to drink plenty, and offered a back-up antibiotic prescription if symptoms did not improve after 48 hours. There were no differences in mean symptom severity 2-4 days after presentation or mean symptom duration between women receiving immediate versus delayed antibiotics. However, there were differences in antibiotic use, with 97% of women in the immediate group using antibiotics versus 77% in the delayed group.

Despite the relatively high rates of antibiotic prescribing for patients with suspected UTI, few studies have quantified their benefits and harms in older adults. Only two (51, 52) of five (51-55) double-blind randomised trials of antibiotics versus placebo in women with urinary tract symptoms and bacteriuria included women over 65, and none included women over 85. We found no trials of antibiotics versus placebo for urinary tract infection in older men. Meta-analysis of the five trials in women found that antibiotics were more likely to result in clinical cure (1062 patients, odds ratio (OR) 4.81,

95% confidence interval (CI) 2.51-9.21) and microbiological eradication (967 patients, OR 10.67, 95% CI 2.96-38.43) (56). Furthermore, antibiotic treatment reduced microbiological reinfection or relapse by 73% (OR 0.27, 95% CI 0.13-0.55) but increased the odds of an adverse event by 64% (OR 1.64, 95% CI 1.10-2.44). It is unlikely that the benefits reported in these trials are directly generalisable to a primary care population of older people. Most primary care patients are prescribed antibiotics without microbiological confirmation of UTI and therefore rates of clinical and microbiological cure would differ. Also, the older primary care population may have more co-morbid conditions and long-term medication use than the trial participants and thus, may experience more adverse events, potentially shifting the risk-benefit balance reported in these trials.

In summary, immediate antibiotic prescribing is commonly used for patients presenting to primary care with suspected UTI. Delayed antibiotic prescribing may reduce antibiotic consumption without impacting on illness severity or duration, but the current evidence base is limited to one trial that did not include people aged over 70. Although meta-analysis of five trials found that antibiotics were more likely to result in clinical cure than placebo, only two of these included older adults and it remains unclear if the benefits seen are generalisable to a primary care population of older men and women.

2.8 Empirical antibiotic choice

Four systematic reviews summarised results from randomised trials comparing clinical outcomes in patients prescribed different antibiotics for UTI (57-60). Overall, no clinically important differences were found between

trimethoprim, nitrofurantoin, flouroquinolones, beta-lactams, and fosfomycin (57-59). Rashes were more common with beta-lactams and trimethoprim than other agents. Despite documented concerns, hypersensitivity reactions such as pulmonary fibrosis and hepatotoxicity were not observed in participants randomised to nitrofurantoin in 27 trials (59). One review also reported no clinically important differences between different flouroquinolones, but participants randomised to ciprofloxacin experienced less adverse events than other flouroquinolones (60). Only one further relevant trial was published since these reviews, comparing 5-day nitrofurantoin with single dose fosfomycin in women (median age 44, interquartile range (IQR) 31-64) (61). Women randomised to nitrofurantoin were more likely to report clinical cure at 28 days (70% v 50%). Rates of adverse events were low and similar between the two groups. However, despite 53 trials with over 20,000 participants, only four trials included women over 65, and no trials included men over 65. The trials that included women over 65 lacked age related sub-group analyses, meaning effects in this population remain relatively unknown.

2.9 Antibiotic treatment duration

A systematic review and meta-analysis of 15 randomised trials (1644 participants) compared outcomes in older patients prescribed different durations of antibiotic treatment for UTI (62). Single dose treatment was mostly inferior to short (3-6 days) and long (7-14 days) course treatment, and resulted in greater risk of persistent symptoms and re-infection two weeks after onset. Meta-analysis of four trials of 1210 older women showed that 3-6 days of treatment was similar to 7-14 days and resulted in no

significant differences in symptom duration, re-infection rates, adverse events or patient satisfaction (63-66) . None of these four trials included men and three had limitations in methodological quality due to inadequate reporting of allocation concealment, blinding, and outcome assessment (63, 64, 66). Overall, this review provides reasonable quality evidence supporting three-day antibiotic therapy for UTI in older women. We found no relevant trials published after the search dates for this review.

In contrast, there is far less evidence to guide antibiotic duration in older men. The clinical guideline recommendation of seven-day antibiotic therapy is largely based on expert consensus (19, 49, 67). Previous randomised trials investigating different antibiotic durations for UTI in men have focussed on febrile (68, 69) or complicated UTI (70, 71), where some men were recruited following hospital admission or diagnosed with prostatitis or pyelonephritis. One further study only included men with spinal cord injury (72). Therefore, these trials are not generalisable to the majority of older men with community-acquired UTI seen and treated in primary or ambulatory care settings. Furthermore, the shortest therapy duration investigated in these trials was 7-days. We identified only one observational study of short versus long course antibiotic therapy in older men with UTI (73). This study of US male Veterans found no difference in the rate of clinical recurrence between those prescribed >7-day therapy versus those prescribed ≤7 day therapy. However, this study used outpatient data only and therefore may have missed men where recurrence was diagnosed via a subsequent hospital admission. Therefore, the optimal duration of antibiotic therapy for UTI in older men remains unclear and there is a need

to understand if shorter courses are as safe and effective as 7-day courses in a primary care population.

2.10 Variation in antibiotic prescribing

There is variation in the choice of empirical antibiotic prescribing for patients presenting to primary care with a suspected UTI (74). Differences in clinical guideline recommendations for first-line empirical antibiotics may explain some of this variation. For example, UK guidelines generally recommend nitrofurantoin or trimethoprim for first-line empirical treatment of UTI, but Spanish guidelines include fosfomycin and flouroquinolones as acceptable first-line options (75). These differences were observed in the POETIC prospective observational study. This study described empirical antibiotic prescribing for 797 adult women (median age 45 years) presenting to primary care with suspected UTI in Wales, England, Spain and The Netherlands (74). In Wales, 76% of empirical antibiotic prescriptions were for trimethoprim, compared to 46% in England, 10% in The Netherlands and 0% in Spain. Fosfomycin comprised 75% of empirical prescriptions in Spain but was rarely used in the other three countries. Nitrofurantoin comprised 80% of empirical prescriptions in The Netherlands, 48% in England, 20% in Wales, and only 3% in Spain. Use of co-amoxiclav or flouroquinolones was low in Wales, England and The Netherlands, but higher in Spain. Importantly, the study found that differences in prescribing were not due to differences in severity of presentation or prevalence of co-morbidities, and had no impact on clinical recovery, suggesting the variation was unwarranted. However, this study included only younger women and it is

not known if similar variation in older adults with a higher prevalence of co-morbid conditions would impact on clinical outcomes.

Prescribing also varies between countries where clinical guidelines are similar. For example, UK guidelines are similar to those in the USA. Both currently recommend nitrofurantoin or trimethoprim as first-line treatments depending on patients' renal function and local resistance levels, followed by pivmecillinam or fosfomycin, with other agents reserved for situations where aforementioned antibiotics are inappropriate. However, recent US data suggest flouroquinolones account for around 50% of empirical prescriptions for UTI, trimethoprim-sulfamethoxazole for around 23%, nitrofurantoin for 24% and other antibiotics for the remaining 3% (76). There are no data specifically for older people, but age over 65 was associated with a 2.5 fold increase in the odds of receiving a flouroquinolone prescription (76). These data suggest differences in clinical guidelines are not the sole reason for variation in prescribing. Qualitative work suggested that primary care clinicians were more likely to consider second-line antibiotics for older patients, who were frail, had co-morbidities, and were judged to have more severe illness (77). The perceived aim of broad-spectrum antibiotic prescribing was to prevent treatment failure, worsening illness, and hospitalisation, events thought to be more likely if first-line antibiotics were prescribed for that clinical scenario. These findings are supported by quantitative analyses showing that increasing age and number of co-morbidities are associated with increased odds of overall antibiotic prescribing (78), and of broad-spectrum antibiotic prescribing (79).

In summary, antibiotic prescribing for UTI varies and this variation is not completely accounted for by differences in clinical guideline recommendations. There is no evidence to suggest that this variation results in better outcomes. Some of the variation may be accounted for by clinician behaviour and clinical judgement, with clinicians preferring broad-spectrum antibiotics in older frailer patients whom they judge to be more severely unwell.

2.11 Antibiotic prescribing for UTI in patients with renal impairment

Prescribing for UTI in renal impairment warrants additional discussion because the two commonly recommended first-line antibiotics, nitrofurantoin and trimethoprim, are not always appropriate. Numerous large observational studies have found an association between trimethoprim prescribing (with and without sulfamethoxazole) and hyperkalaemia, hospital admission for acute kidney injury, and sudden death (80-84). About 20% of older people in England have chronic kidney disease stages 3 to 5 (85) (Table 2.1) and this degree of renal impairment is associated with an increased risk of end-stage renal disease (86). Therefore, some variation in antibiotic prescribing for older people with UTI may be due to necessary avoidance of trimethoprim in patients judged to be at risk of a renal-related adverse event.

Table 2.1. Staging chronic kidney disease using the estimated glomerular filtration rate.

Estimated Glomerular Filtration Rate (ml/min/1.73m^2)	**chronic kidney disease stage**
≥90 Normal	1
60-89 Mild reduction related to normal range for a young adult	2
45-59 Mild to moderate reduction	3a
30-44 Moderate to severe reduction	3b
15-29 Severe reduction	4
<15 Kidney failure	5

Nitrofurantoin was contraindicated in patients with estimated glomerular filtration rates (eGFR) of below 60mls/min/1.73m^2 due to concerns about its efficacy. In 2014, a systematic review found little evidence to support the avoidance of nitrofurantoin in patients with renal impairment (87). The review found that the perceived reduced efficacy came from studies that had found a reduction in urinary nitrofurantoin excretion in patients with renal impairment compared to those with normal renal function, but had not assessed or reported the impact of this on clinical outcomes such as symptom resolution or microbiological eradication. Furthermore, a retrospective cohort study found no difference in treatment failure rates among women with renal impairment prescribed nitrofurantoin, versus

those with normal renal function (88). These studies prompted the UK Medicines and Healthcare products Regulation Authority to lower the threshold for nitrofurantoin use to an eGFR≥45 mls/min/1.73m^2. Since the updated guidance, one further retrospective cohort study compared outcomes in older women with a median eGFR of 38mls/min/1.73m^2, prescribed either nitrofurantoin or trimethoprim, and found no difference in risk of treatment failure or UTI hospitalisation. However, these studies did not include men, had a small number of outcome events and therefore wide confidence intervals around their effect estimates, did not use clinically relevant definitions for the severity of kidney disease, and lacked appropriate comparator groups. Therefore, there is still a need to evaluate outcomes following nitrofurantoin prescribing in older people with renal impairment to understand if avoidance is clinically warranted.

2.12 Recurrent UTI

The European Association of Urology define recurrent UTI as repeated UTI with a frequency of 2 or more in the last 6 months or 3 or more in the last 12 months (67) and this definition has been adopted by the upcoming NICE clinical guideline (33). Most research on recurrent UTI focusses on younger women. The incidence of recurrent UTI in women aged 18-64 in the USA between 2003 and 2011 was around 1 in a 1000 (89). The prevalence of recurrent UTI in older people is not known but point-prevalence surveys of antibiotic use in care homes have consistently found that UTI prevention is the most common reason for antibiotic prescribing (2, 3, 90, 91). The current NICE clinical guideline for recurrent UTI recommends that recurrence is initially managed through behavioural, hygiene and self-care measures

(33). Vaginal oestrogens could be considered for postmenopausal women. Antibiotic prophylaxis is recommended if the above measures are ineffective. Nitrofurantoin and trimethoprim are suggested first-line agents and their effect should be reviewed after six months.

2.13 Antibiotic prophylaxis for prevention of recurrent UTI

Clinical guidelines recommend long-term low-dose antibiotic prophylaxis for prevention of recurrent UTI (67, 92). A Cochrane systematic review and meta-analyses found that long-term low-dose antibiotic prophylaxis conferred a relative risk reduction of 79% in the proportion of women experiencing a microbiologically confirmed UTI, compared to placebo. However, these analyses included data from mostly small trials of younger women without co-morbidities and there is uncertainty around the generalisability of these findings to older adults (93). We identified four trials published since this review that assessed the effect of antibiotic prophylaxis on UTI recurrence (94-97). Trials only included women. Overall, antibiotic prophylaxis was more effective than oral Lactobacilli capsules (94) or vaginal oestrogens (95), less effective than oral D-mannose powder (96), and similar in effect to oral cranberry capsules (97). Only one trial assessed the impact of antibiotic prophylaxis on antibiotic resistance and found that after one month of trimethoprim-sulfamethoxazole prophylaxis, resistance to trimethoprim-sulfamethoxazole, trimethoprim, and amoxicillin increased from 20-40% to 80-95% in the feces and urine of asymptomatic women (94). After 12 months of prophylaxis, all urinary *E coli* isolates of asymptomatic women were resistant to trimethoprim-sulfamethoxazole and trimethoprim.

In summary, the existing evidence for use of antibiotic prophylaxis for older people with recurrent UTI has several gaps and limitations. First, there are no robust data to inform prophylactic antibiotic use in men. Second, trial findings in women were mixed, making it difficult to provide clear recommendations for clinical practice. Third, existing trials often excluded those with co-morbidities such as diabetes, thus limiting their generalizability. Finally, trials were underpowered to study important but rare events such as hospitalisation.

2.14 Non-antibiotic treatments for prevention and management of UTI

Given that the increasing threat of antimicrobial resistance is primarily driven by antibiotic consumption, non-antibiotic strategies to treat and prevent UTI warrant discussion. The most widely trialled non-antibiotic agent for treatment of acute uncomplicated UTIs are Non-Steroidal Anti-inflammatory Drugs (NSAIDs). A randomised trial of ibuprofen versus placebo in women aged 65-70 with suspected acute UTI found that ibuprofen had no impact on symptoms but did reduce consumption of delayed antibiotics (34.9% versus 51%) (98). Two non-inferiority trials found that ibuprofen and diclofenac were inferior to pivmecillinam and norfloxacin in terms of symptom severity and resolution and increased the number of women who developed pyelonephritis (99, 100). A randomised trial of ibuprofen versus fosfomycin also found that women in the ibuprofen arm had more severe symptoms for longer and more cases of pyelonephritis (101).

Several non-antibiotic agents have been studied to assess their effect on recurrent UTI. Cranberry juice was thought to reduce the number of

symptomatic UTIs, but the most recent Cochrane review of 24 studies with 4473 participants concluded that cranberry products compared to placebo provide no benefit in most population groups, and the benefit in some subgroups is likely to be very small (102). Vaginal oestrogens reduced the risk of UTI recurrence in postmenopausal women compared to placebo in two randomized trials with relative risks of 0.25 (95% CI, 0.13-0.50) and 0.64 (95% CI, 0.47-0.86), but increased the number of adverse events including vaginal bleeding (103). A recent randomized trial found that increasing fluid intake to 1.5 litres above their normal daily intake reduced the mean number of UTIs (3.2 in the usual care group versus 1.7 in the hydration group), and UTI-related antibiotic prescriptions (3.6 in the usual care group versus 1.9 in the hydration group) in premenopausal women with recurrent UTI over 12 months (104).

In summary, current evidence does not support the use of NSAIDs for treatment of acute UTI given the observed increase in cases of pyelonephritis. For prevention of recurrent UTI, there is insufficient evidence to support the use of cranberry products, but vaginal oestrogens may be beneficial for postmenopausal women and increased hydration seems promising as a simple and effective preventative measure, although the available trial only included premenopausal women.

2.15 Summary of evidence gaps

We identified several gaps in the published evidence that could be addressed to generate new knowledge that could improve antibiotic prescribing for UTI in older people. First, there are no current estimates of the incidence of UTI in UK primary care in a generalisable sample of older

people to inform service provision. Second, there are no data describing trends in antibiotic prescribing for UTI over time in the UK, which are necessary to understand whether practice aligns with the available evidence and guidance. Third, little is known about the association between different antibiotics prescribed for UTI and clinical outcomes. This is important to help understand if observed variation is clinically warranted, and related to better outcomes. Fourth, there are no data to inform the optimal duration of antibiotic treatment for UTI in older men. Could shorter courses be used safely? Fifth, currently available research has not fully evaluated outcomes following nitrofurantoin use in older people with renal impairment to help understand if avoidance of nitrofurantoin is clinically warranted. Finally, it is unclear if long-term antibiotic prophylaxis is beneficial for older people with recurrent UTI.

2.16 Aims and objectives of this thesis

The aim of this thesis was to generate new evidence that could improve antibiotic prescribing for UTI in older people.

Our specific objectives were to:

1. Describe trends in the incidence of UTI in older people in UK primary care over time.
2. Describe trends in antibiotic prescribing for UTI in older people in UK primary care over time.
3. Investigate associations between choice of empirical antibiotic and adverse outcomes in older people with UTI.

4. Investigate associations between the duration of antibiotic treatment and adverse outcomes in older men with UTI.
5. Investigate associations between nitrofurantoin prescribing and adverse outcomes in older people with UTI and renal impairment.
6. Systematically review and meta-analyse randomised trials comparing antibiotic prophylaxis versus non-antibiotic prophylaxis or placebo in older people with recurrent UTI.
7. Investigate outcomes associated with long-term antibiotic prophylaxis versus no antibiotic prophylaxis in older people with recurrent UTI

3 Overview of methods

This chapter provides an overview of the data source used in the quantitative primary research that addresses objectives 1-5, and objective 7. We also summarise the methodological approaches generic to these objectives. Methods specific to a single objective are presented in the relevant chapter. Strengths and limitations are also discussed in the relevant chapters, as these differed depending on the study objective.

3.1 Data source

We addressed the aforementioned research objectives through a series of retrospective cohort studies using routinely collected healthcare data. The strengths of using routinely collected healthcare data for research are dependent on the structure, function and coverage of the health system involved but include (105):

- Size and statistical power to address questions in under-studied populations and/or about rare exposures and outcomes.
- Longitudinal data to allow follow-up over time.
- Ability to address several inter-related questions relatively cheaply and efficiently.
- Ability to link data across health and other (e.g., social care) datasets to enable a more holistic understanding of disease determinants and outcomes.

- Findings may be more generalisable to the population of interest than those generated from clinical trials.

The main limitation of using routinely collected healthcare data is that it is not collected for research and is therefore subject to variation in its quality, completeness and recording methods (105). Diagnostic codes are open to interpretation and partly depend on the clinician's clinical judgement. Therefore, two clinicians could see patients who present with the same signs and symptoms but code their presentation differently. Furthermore, not all required variables will be measured or coded and therefore it is challenging to fully account for all sources of confounding.

In the UK, 98% of the population are registered with a General Practitioner (GP), and GPs are responsible for acute care in the community, long-term care for chronic illness, and for referring to and collating information from hospital specialists (106). Therefore, GP records are an important source of longitudinal data about patients' healthcare encounters.

There were four main sources of routinely collected GP data for researchers at the start of this project: The Clinical Practice Research Datalink (CPRD) (106), The Health Improvement Network database (THIN) (107), the QResearch database (108), and the Secure Anonymised Information Linkage databank (SAIL) (109). We chose the CPRD because:

- It had wider coverage and contained a greater number of patient records than THIN and SAIL.
- It was used more extensively than the other three databases, with an increasing number of published validation studies.

There were also some pragmatic considerations. For example, use of CPRD was covered by a Cardiff University license that included access to linked hospital admission and mortality data. Furthermore, data could be extracted using their online data portal and could be stored and processed on an office desktop computer. This was in contrast to SAIL where data could only be accessed and analysed in a secure web gateway which could increase processing time if using large data-sets. This was also in contrast to QResearch where linked hospital and mortality data could only be analysed on-site at the University of Nottingham.

3.2 The CPRD

The CPRD (formerly known as the General Practice Research Database) is a not-for-profit research service funded by the National Institute for Health Research and the Medicines and Healthcare products Regulatory Agency. It is owned by the UK Department of Health and contains the records of 11 million patients from 674 general practices across the UK (106). Linked hospital and death registration data are available for patients from approximately 50% of contributing English practices. A previous study of the incidence of lower respiratory tract infections and pneumonia identified records for 1,534,443 adults aged 65 and over in CPRD between 1997 and 2011, with linked data available for 916,128, (110) suggesting a sufficient sample for our proposed analyses.

Practices “opt-in” to contribute data to CPRD and can provide additional consent to allow CPRD to link their data at the patient-level with other datasets, including hospital and death registry data. Patients registered with a practice that contributes data to CPRD can “opt-out”, meaning that their

data would not be included in the practices CPRD contribution. Approximately 7% of the UK population are included in the CPRD and patients are broadly representative of the wider UK population in terms of age, gender and ethnicity (106). The CPRD holds data on demographics, clinical encounters and diagnoses, drug prescriptions, laboratory tests and referrals to specialists.

CPRD GP data are coded using the Read code system. Read codes were developed by Dr James Read and Abies Informatics Ltd in the early 1980s and recommended for national adoption across UK General Practice by the British Medical Association and the Royal College of General Practitioners in 1988 (111). Read codes are organised in three categories;

- Diagnoses – codes all begin with a uppercase letter, e.g., H33 (Asthma)
- Processes of care – codes all begin with a number, e.g., 65E (Influenza vaccination)
- Medication – codes all begin with a lowercase letter, e.g., bu25 (Aspirin 75mg tablets).

The coding system is hierarchical, with greater detail as you descend through the hierarchy (Table 3.1) (112).

Table 3.1. Example of the Read code hierarchy.

Read code	Description
C	Endocrine, nutritional, metabolic and immunity disorders
C1	Other endocrine gland diseases
C10	Diabetes mellitus
C10E	Type 1 diabetes mellitus
C10E7	Type 1 diabetes mellitus with retinopathy

CPRD provides participating practices guidelines that describe how to record significant clinical events in a patient's medical history. The raw data provided by each practice undergo extensive quality control and validity checks by a research team based at the Medicines and Healthcare products Regulatory Agency before release. These data are assessed by an 'up to standard' audit, confirming the reliability and accuracy of data recording in several key areas. Practices meeting this standard are included in the CPRD data warehouse. Patient-level data are also assessed, with patients considered 'acceptable' for inclusion in the CPRD if recorded data are internally consistent in four areas: age, sex, registration details, and event recording (106). Data are only available to researchers once they have met these quality checks on completeness and reliability and the CPRD deems them to be of the standard required for research purposes. Linked hospital and death registration data are available for patients from approximately 50% of contributing English practices. Of patients with linked data, around 67% are matched exactly on NHS number, gender, date of birth and

postcode, and a further 28% are matched exactly on NHS number, gender, and date of birth (113). Hospital diagnoses and causes of death are recorded using version 10 of the International Classification of Disease (ICD-10).

Although CPRD's size, longitudinal data, and linkage capabilities made it an appropriate and valuable resource for the objectives of this thesis, we identified several limitations with its use. First, we required linked data which restricted us to data from English practices only, potentially reducing the generalisability of the findings to other parts of the UK. Second, CPRD was subject to the same limitations and variations in data coding that apply to all routinely collected healthcare data as discussed earlier in this chapter. Third, CPRD recorded *prescribe*d medication, not dispensed or consumed medication and there no data to inform us of what proportion of medication prescribed in CPRD practices is dispensed or consumed. Fourth, CPRD does not record medication bought over the counter, important for some of the studies in this thesis where outcomes could differ if over the counter symptomatic treatments were used. Fifth, CPRD does not contain any microbiological data. This was an important limitation and warrants further discussion. Without microbiology data, we would not be able to:

1. Determine who had a laboratory-confirmed UTI.
2. Determine any antibiotic resistance-related outcomes.

Therefore, our cohort actually consisted of people presenting with *suspected* UTI. In some ways, this is more clinically relevant, as most people who present to primary care with urinary tract symptoms are

diagnosed with a UTI based on their clinical presentation. If we had microbiology data and restricted to those with a urine sample sent for culture, we would be restricting to a select group as urine sampling is only recommended for men, women with atypical symptoms, and those who have failed a course of treatment (29), and even within these groups there is variation amongst practitioners (114). However, the lack of microbiology data meant that we did not know if differences in outcomes between studied groups related to differences in accuracy of the diagnosis, or reflected differences in resistance rates of the presenting infection. Furthermore, we were unable to determine whether differences in treatment choices had an impact on future resistance – especially important for exposures like antibiotic duration where evidence for an impact on resistance is limited (115).

On balance, we decided that the strengths of using CPRD outweighed the limitations but were clear about the limitations in our interpretation and reporting.

3.3 CPRD data extraction

We submitted prospective study protocols and analysis plans to the CPRD Independent Scientific Advisory Committee for approval. Approvals were requested at three time-points over the course of the project:

January 2015: Trends in UTI incidence and antibiotic prescribing (chapter 4)

October 2015: Antibiotic prophylaxis for recurrent UTI (chapter 9)

June 2017: Outcomes following different antibiotic treatment strategies for UTI (chapters 5-7).

Due to the sequence above and the time-lag between each approval process, our analysis of UTI incidence (chapter 4) and our study of UTI prophylaxis (chapter 9), uses CPRD data from 2004-2014, and our analysis of UTI outcomes (chapters 5-7) uses data from 2010-2016.

We extracted CPRD GP data using the CPRD Gold web portal. For our analysis of UTI incidence (chapter 4) and our study of UTI prophylaxis (chapter 9), we extracted data on all CPRD patients who, between 2004 and 2014, were aged ≥65, had data deemed as "acceptable", were registered with a practice whose data were deemed "up-to-standard", and were eligible for data-linkage. Only patients registered with practices who had consented to data-linkage were eligible for linkage to hospital and death registry data. Previous research found that patients from practices who had consented to data-linkage were similar to those from practices without data-linkage in terms of age, gender, follow-up time and socioeconomic deprivation (110). The analyses presented in chapters 5-7 used data from 2010 to 2016, but all other data specifications were as above. CPRD provided linked hospital and death registry data for each study once the study specific protocol and analysis plans were approved.

3.4 Data processing

CPRD provides data in several separate tables. For example, the "Patient" table contains basic demographic data that includes year of birth, start of CPRD follow-up, and end of CPRD follow-up for patients who have died or

left their practice. The “clinical” table contains data on all patient-practice encounters, with date of encounter and a Read code describing the reason for the encounter. Some encounters relate to multiple Read codes, as the patients may have discussed several different issues and/or had several different examinations. Some encounters may not have an associated Read code if no data were entered. The “therapy” table contains data on all prescriptions issued and includes date of issue, a code to differentiate between repeat and acute prescriptions, and data about quantity and dose prescribed. The same patient can be identified across the different tables by their unique patient identifier. Tables were cleaned by systematically identifying implausible or missing values for each variable. Variables required for analysis were then generated and the tables were combined using merge functions in R as required for each analysis.

3.5 Identifying episodes of UTI in CPRD

The first task was to develop a method for identifying UTI episodes in CPRD data. CPRD does not contain microbiology data. Therefore, UTIs were identified using clinical codes and drug prescriptions only. To identify relevant codes, we firstly reviewed code lists from published studies that used a primary care database to investigate antibiotic prescribing or urinary tract infections in primary care (25, 116). Secondly, we used the CPRD data browser to identify all UTI-related codes. The data browser identifies all codes within CPRD that match a given search term, which can be a word or part of a word. For example, searching for “*urinary tract infection*” would identify “urinary tract infection”, and “recurrent urinary tract infection”, and “urinary tract infection – site not specified”. Thirdly, we identified all acute

trimethoprim prescriptions in CPRD issued between 2004 and 2014 and reviewed the clinical Read codes relating to the prescribing indication. In the UK, during this period, trimethoprim was used almost exclusively for treatment of UTI. We found that 10% of trimethoprim prescriptions were not associated with a clinical code, i.e., no indication was recorded, and 25% were associated with a non-specific code, e.g., “telephone encounter”, or “had a chat to patient”. The remaining 65% of prescriptions were associated with codes we had already identified using the code lists from published studies and the CPRD data browser. The final code list was checked by three practicing GPs to ensure codes were clinically relevant and sensible. However, we accepted that we may miss around a third of UTIs because of coding issues. This proportion was similar to research from the THIN database that found no clinical code associated with 13% of antibiotic prescriptions, and a non-specific code associated with 18%, resulting in the prescribing indication being present for only 69% of antibiotic prescriptions (17).

Whilst Read codes enabled identification of UTI-related consultations, we still needed to define distinct UTI episodes, based on incident UTIs, because codes occurring within a short time-frame of one another could represent multiple consultations for the same UTI-related episode. To the best of our knowledge, there are no widely accepted time points to define when re-presentation following UTI treatment should be regarded as a “relapse”, due to failed treatment and ongoing symptoms secondary to the initial infection, or “recurrence”, due to infection with a new or different organism. Previous observational research regarded codes occurring within

28 days of one another as belonging to the same illness episode and those occurring greater than 28 days apart as representing separate or distinct infections (25, 73, 110). We followed this approach to define UTI episodes.

For the study of UTI incidence (chapter 4), we wanted to maximise the chances of identifying episodes of UTI and reduce the chances of identifying asymptomatic bacteriuria. We therefore identified UTI episodes as follows: All potential episodes needed a record of a primary care consultation with Read codes indicating either a diagnosis of UTI or a clearly relevant symptom of UTI, for example, dysuria or urinary frequency. They then needed at least one of the following:

1. A same-day antibiotic prescription, suggesting a primary care clinically diagnosed and empirically treated UTI.
2. A same-day emergency hospital admission with an ICD-10 code for UTI, suggesting a primary care clinically diagnosed UTI confirmed in secondary care.
3. A same-day Read code indicating urine was sent for culture, *and* an antibiotic prescription within seven days, suggesting a primary care clinically suspected UTI, confirmed and treated following culture

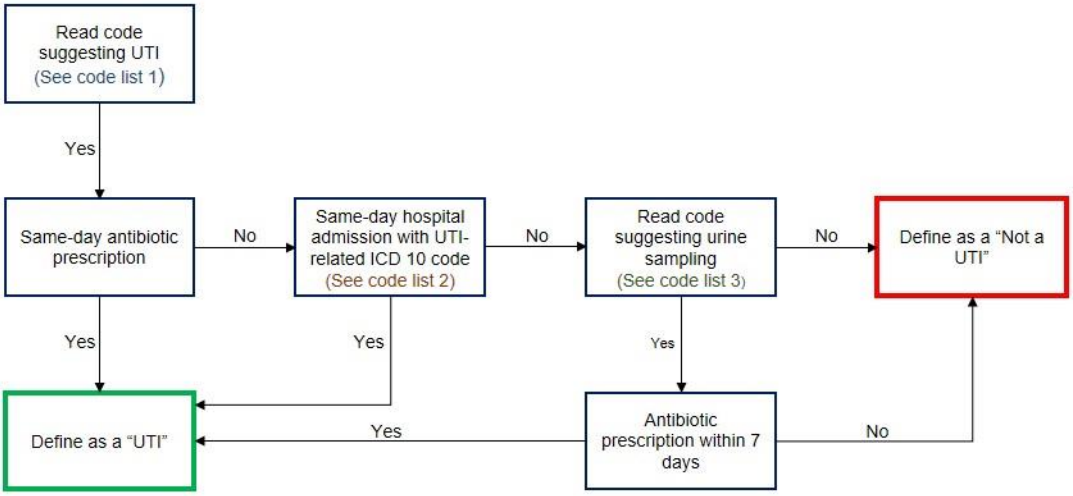
Figure 3.1 shows the flowchart and Read and ICD-10 codes used for case ascertainment via the above method.

For studies where we investigated outcomes of different antibiotic treatment strategies for UTI, UTI episodes were identified as those with a Read code indicating a diagnosis or clearly relevant symptom of UTI, (using the codes

in code list 1 in Figure 3.1), *and* a same-day antibiotic prescription, suggesting a primary care clinically diagnosed and empirically treated UTI.

We chose these definitions for UTI because clinical experience suggested that most older people presenting with suspected UTI would be prescribed antibiotics on the same day. This was partly supported by a study of the THIN database where 92% of patients aged over 14 presenting with symptoms suggestive of UTI received a same-day antibiotic (17). This study excluded patients with co-morbidities. Therefore, we felt the same-day prescribing rate would be higher in a sample of unselected older patients with comorbidities in whom the uncertainty around sepsis or poor prognosis would be greater. There were no data describing the prevalence of delayed prescribing in the older population and therefore we did not factor this in to our definitions as we felt its use was minimal during the study period.

For all studies, we excluded UTI episodes recorded within six months of registering at the practice, as these may represent historical events recorded at registration. We also excluded UTI episodes recorded within 14 days of a hospital discharge (identified from linked hospital data), as these may represent hospital-acquired infection, and the focus of our research was community-acquired UTI.



Code list 1

Read code	Code description
K190300	Recurrent urinary tract infection
K190.11	Recurrent urinary tract infection
1AG..00	Recurrent urinary tract infections
K190z00	Urinary tract infection, site not specified NOS
K190500	Urinary tract infection
K190400	Chronic urinary tract infection
K190.00	Urinary tract infection, site not specified
K15..00	Cystitis
K150.00	Acute cystitis
14D4.00	H/O: recurrent cystitis
K155.00	Recurrent cystitis
K15z.00	Cystitis NOS
K152z00	Other chronic cystitis NOS
K152y00	Chronic cystitis unspecified
K15y.00	Other specified cystitis
K15yz00	Other cystitis NOS
1J4..00	suspected UTI
1A53.11	C/O - loin pain
R090C00	Loin pain
1A55.00	Dysuria
1A...12	Urinary symptoms
K197.00	Haematuria
1A1..11	Frequency of micturition
1979	Suprapubic pain
1A12.00	Frequency of micturition
1AZ6.00	Lower urinary tract symptoms

Code list 2

Read code	Code description
4JJ..12	Mid-stream urine sample
4JJ..12	Mid-stream urine sample
461..11	MSU - general
4JJ2.00	MSU sent for bacteriology
4JJ2.00	MSU sent for bacteriology
4JJ1.00	MSU sent for C/S
4JJ1.00	MSU sent for C/S
4615	MSU sent to lab.
4615	MSU sent to lab.
46U..00	Urine culture
46U..00	Urine culture
46U8.00	Urine culture - Bacteria OS
4JJ..13	Urine for culture
4JJ..13	Urine for culture
46f3.00	Urine leucocyte test = ++
46f4.00	Urine leucocyte test = +++
46D..00	Urine microscopy - general
46DZ.00	Urine microscopy - general NOS
46G..00	Urine microscopy: cells
46X0.00	Urine nitrite positive
4146	Urine sample sent to Lab
4JJ3.00	Urine sent for culture
4JJ3.00	Urine sent for culture

Code list 3

ICD-10 code	Code description
N30.0	Acute cystitis
N30.9	Cystitis unspecified
N39.0	Urinary tract infection, site not specified

Figure 3.1. Flowchart and code lists used to ascertain UTI episodes for the UTI incidence study.

3.6 Estimating incidence of clinically diagnosed UTI

We calculated age and gender specific incidence rates and 95% confidence intervals (CIs) for clinically diagnosed community-acquired UTI each month from March 2004 to April 2014 by dividing the number of incident UTIs presenting to primary care by person-time at risk. Individuals were considered not at risk of an incident community acquired UTI if they were in hospital, for 14 days following a hospital discharge, and for periods of time following an incident UTI until they had 28 days without a UTI-related code. We multiplied calculated incident rates by 365 X 100 to transform from incidence per person-days at risk to incidence per 100 person-years at risk. Incidence rates were calculated for three age groups: 65-74, 75-84 and 85+ years.

We used joinpoint regression to model trends in incidence rates over time and identify the estimated location of any statistically significant change in the slope of a trend line (117). Joinpoint analysis identifies the best fit for inflexion points ("joinpoints") at which there is a significant change in trends using a series of permutation tests (118). In the UTI incidence study, joinpoint analysis was used to identify months (as the explanatory variable) at which significant changes in incidence rates occurred over the study period, and the size of these changes (as the percentage change in rate per year). A maximum of two joinpoints were allowed for each model we considered. This was the default value according to the number of observations in each model. We estimated the annual percentage change and 95% confidence intervals for each trend line.

3.7 Comparing outcomes following antibiotic treatment for UTI

In chapters 5-7 we report outcomes of different antibiotic treatment strategies for acute and recurrent UTI. The exposure variable in these studies was the antibiotic prescription (for example, the choice of antibiotic, or the prescription duration). The outcomes were adverse events that could be reliably ascertained from CPRD data and therefore were:

1. A record in the GP data of another UTI-related consultation (identified using the codes in code list 1 in Figure 3.1) with a same-day antibiotic prescription in the 14 days following the index event. This was regarded as a proxy for “treatment non-response” or “treatment failure”, that is, that the patient re-presented because of ongoing symptoms of UTI that had persisted despite the initial treatment, and were severe enough to warrant another course of treatment.
2. A record in the linked hospital data of a UTI-related hospitalisation in the 14 days following the index event. This included hospitalisations with ICD-10 codes for UTI or sepsis, and were regarded as an indication of worsening infection despite the initial treatment. The included codes were:

N30	Cystitis
N30.0	Acute cystitis
N30.8	Other cystitis
N30.9	Cystitis unspecified

N39.0	Urinary tract infection, site not specified
A41.5	Gram-negative sepsis NOS
A41.8	Other specified sepsis
A41.9	Sepsis, unspecified
A49.9	Bacteraemia NOS
R57.2	septic shock

3. A record in the linked hospital data of a hospitalisation with an acute kidney injury (AKI). AKI was ascertained from the following ICD-10 codes:

N17	Acute renal failure
N17.0	Acute renal failure with tubular necrosis
N17.1	Acute renal failure with acute cortical necrosis
N17.2	Acute renal failure with medullary necrosis
N17.8	Other acute renal failure
N17.9	Acute renal failure, unspecified
N19	Unspecified kidney failure

Hospitalisation for AKI was regarded as an indication of worsening systemic illness despite the initial treatment.

4. A record in the linked death registry data of death in the 28 days following the index event.

We chose to study a “treatment failure” related outcome as primary care clinicians had cited prevention of treatment failure as a reason for prescribing non-recommended antibiotics (77). We chose UTI-related hospitalisations because of the recently observed increase in hospitalisations for UTI (119) and for E.coli bacteraemia (7), with treatment failure of community-acquired UTI thought to be a contributory factor.

Hospitalisation for AKI was chosen for several reasons. AKI is more common in older adults, with around 5% of those aged over 70 experiencing an AKI hospitalisation each year in the UK, compared to around 1% of those aged 40-69 (120). AKI costs the NHS between £434 and £620 million each year (120). NICE defines AKI as a rise in serum creatinine of 26 micromols/litre or more within 48 hours, or a 50% or greater rise in serum creatinine occurring within 7 days (121).

NICE specifically recommends investigating for the presence of AKI in older people with acute illness, especially if suspected to have sepsis, a well-recognised risk factor for AKI (122, 123). In the context of UTI, AKI could be caused by the systemic effects of the infection (e.g., confusion or fever could disrupt fluid balance leading to dehydration), or by worsening infection and subsequent sepsis.

We chose 14 days for the treatment failure and hospitalisation outcomes to increase the likelihood that these events were related to the initial UTI. Longer time periods increase the likelihood that the outcome may have been influenced by an intervening event, e.g., if a 28 day period was used, a patient could have a UTI, recover, have a cardiac event and be hospitalised with AKI. We chose 28 days for the death outcome as the UTI could precipitate events (e.g., sepsis) which take some time to evolve before death.

3.8 Confounding variables

We considered multiple confounding variables that could be causes of both the antibiotic prescription (exposure) and outcome. We included age, gender, and Index of Multiple Deprivation score quintile. The Index of Multiple Deprivation is an area-level measure of deprivation covering different aspects of material deprivation including housing, employment, income, access to services, education, crime, and living environment (124). We also included a Charlson score - a weighted summary measure of comorbidity (125). To calculate a Charlson score, we used each included patients clinical data to identify whether they had a history of myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease, connective tissue disease, peptic ulcer disease, chronic liver disease, diabetes, AIDS, or cancer prior to their entry into the cohort, using a previously published list of Read codes (125). Absence of a relevent code was taken to mean absence of the condition of interest. The presence and severity of each condition was scored according pre-defined Charlson score methodology (125) resulting

in an overall summary score. We also adjusted for a recorded history of coronary heart disease, renal disease, and respiratory disease, as these variables were previously found to be associated with antibiotic prescribing (78, 79).

The presence or absence of prescriptions for angiotensin converting enzyme inhibitors, angiotensin receptor blockers and potassium-sparing diuretics were also included as confounders as these were previously shown to be associated with AKI hospitalisation in adults with UTI (83, 84, 126).

We also adjusted for potential confounders that we thought could influence the clinical decision about antibiotic prescribing and the outcomes under investigation. These included:

- Whether the patient was housebound,
- Whether the patient had a recorded diagnosis of dementia, liver disease, rheumatoid arthritis, or cancer,
- Whether the patient had urinary incontinence or an indwelling urinary catheter,
- An estimated glomerular filtration rate (eGFR) calculated using the modification of diet in renal disease study equation (127),
- Polypharmacy, defined as records indicating ≥5 long-term medications per month in the year prior to the incident UTI.

To determine polypharmacy, we identified each included patients repeat prescriptions for the 12 months prior to cohort entry. All medications were included as long as they were prescribed at least 3 times in the past 12

months and coded as a repeat prescription and not as an acute prescription. We divided the number of different medications prescribed over the 12 month period by 12 to get an estimate for the number of medications prescribed per month and defined those with ≥5 medications per month as polypharmacy, the most commonly used numerical definition of polypharmacy in the healthcare literature (128).

We can consider the potential impact of the described confounding variables on exposure and outcome using rheumatoid arthritis as an example. A patient with rheumatoid arthritis may be using immunosuppressant drugs and therefore be at greater risk of an adverse outcome such as sepsis. The prescribing clinician may recognise that the patients is at increased risk of an adverse outcome, and this may influence the choice or duration of antibiotic treatment prescribed This could also occur in patients with cancer. Similarly, patients with a reduced eGFR are at greater risk of an infection-related adverse outcome (129) and reduced eGFR could influence a prescriber's choice of antibiotic due to, for example, the contraindications described in section 2.10 relating to kidney disease and nitrofurantoin.

CPRD records sociodemographic variables and drug prescriptions with a high degree of reliability and completeness (106). However, recording of co-morbidities varies, with better recording of those for which GPs received financial incentives during the study period. A systematic review of 49 studies that investigated the accuracy of diagnostic coding in the CPRD by comparing CPRD diagnostic codes with a review of the patient's medical records found that CPRD diagnostic codes had a positive predictive value

of over 90% for conditions such as cerebrovascular disease, diabetes, or hip fracture (130). Overall, most long-term conditions were recorded accurately with positive predictive values of over 80%. However, there were no data validating confounding variables such as urinary incontinence or the presence of an indwelling urinary catheter, meaning that it was unclear as to how reliably we could ascertain them in the CPRD.

3.9 Methods to adjust for measured confounders

We adjusted for confounders in two ways. We included all potential confounders in mixed effects multivariable logistic regression models using the lme4 package in R (131). In these models, we included the general practice as a random effect to account for clustering by practice (132). We also used the confounding variables to generate a propensity-score and then did propensity-score matched analyses. The propensity score was the probability of receiving the exposure variable given the confounding variables. The aim of propensity score matching is to improve balance of baseline characteristics in comparison groups (133). We used nearest neighbour matching with no replacement using the MatchIt package in R (134). Nearest neighbour matching previously showed consistently good performance in simulation studies that compared it to full matching and inverse probability of treatment weighting in scenarios that varied the prevalence of the treatment and the strength of association between the covariates and treatment assignment (135). We assessed balance in measured baseline covariates between matched groups by visually inspecting jitter plots and histograms of covariate distribution before and after matching, and by calculating standardised mean differences for

covariates between groups. We regarded standardised mean differences of <0.1 as reflecting adequate balance (136).

We used other methods to better understand the impact of confounding in specific analyses, and describe these in the relevant chapters. All analyses were conducted in R version 3.2.1.

3.10 Patient and Public Involvement

This project had two patient and public involvement representatives from inception to completion. Both were recruited through Health and Care Research Wales' INVOLVE network and expressed an interest in a project about UTIs. They had personal experience of UTIs. One had a neurological condition that predisposed her to recurrent infections, and the other was a carer for someone with recurrent UTIs. They were involved in discussions about the research questions that formed this project and provided advice on all aspects of the project. We met at six-monthly intervals to discuss progress and obtain their feedback on project findings.

4 Trends in UTI incidence and antibiotic prescribing

This is the first empirical study in this thesis and presents data on incidence and antibiotic prescribing for UTI in older adults in primary care.

4.1 Background

UTI is an important cause of morbidity and antibiotic use in older adults. In the UK, most episodes of suspected UTI are managed in primary care. Despite the associated morbidity, there are few recent, robust, externally valid data describing trends in the incidence of UTI in UK primary care. A large prospective observational study with systematic urine sampling would provide estimates of the incidence of microbiologically confirmed UTI, but would be expensive and pose several challenges including recruitment, retention and collection of uncontaminated urine samples. It would also not reflect the true burden of UTI in primary care as many episodes are diagnosed and treated clinically, based on symptoms and signs, without microbiological confirmation. Therefore, we used the CPRD to estimate incidence rates of clinically diagnosed UTI in UK primary care and examine associated antibiotic prescribing. We investigated trends in the proportion of older adults prescribed a UTI-specific antibiotic (nitrofurantoin or trimethoprim), and the proportion prescribed antibiotics for durations recommended in clinical guidelines.

4.2 Methods

This was a retrospective cohort study. Patients were eligible for inclusion if, between 1st March 2004 and 31st March 2014, they were ≥65 years old, had linked hospital data and more than one day of CPRD follow-up. We excluded patients with temporary registrations or gaps in their data coverage. Patient follow-up began on the latest of study start date, the patient's 65th birthday or 28 weeks after the patient first registered at the practice. Follow-up ended at the earliest of study end date, death, or last day of available CPRD data. We identified UTI episodes using the flowchart and code lists in Figure 3.1. We used joinpoint regression to model trends in incidence rates over time and identify the estimated location of any significant change in the slope of a trend line. For individuals prescribed a same-day empirical antibiotic, we investigated gender-specific trends for antibiotic choice and duration. We used multilevel logistic regression to account for clustering within practices and modelled trends in:

1. The proportion of older adults prescribed a UTI-specific antibiotic (trimethoprim or nitrofurantoin).
2. The proportion of older adults prescribed antibiotics for the duration recommended by clinical guidelines (three days for women, seven days for men).

4.3 Results

There were 966,454 adults aged ≥65 with data of acceptable standard, linked hospital data, and at least one day of follow-up between 2004 and 2014, in the database. We excluded 34,509 (3.6%), resulting in a final study

population of 931,945 older adults (Figure 4.1). Table 4.1 shows the study population characteristics.

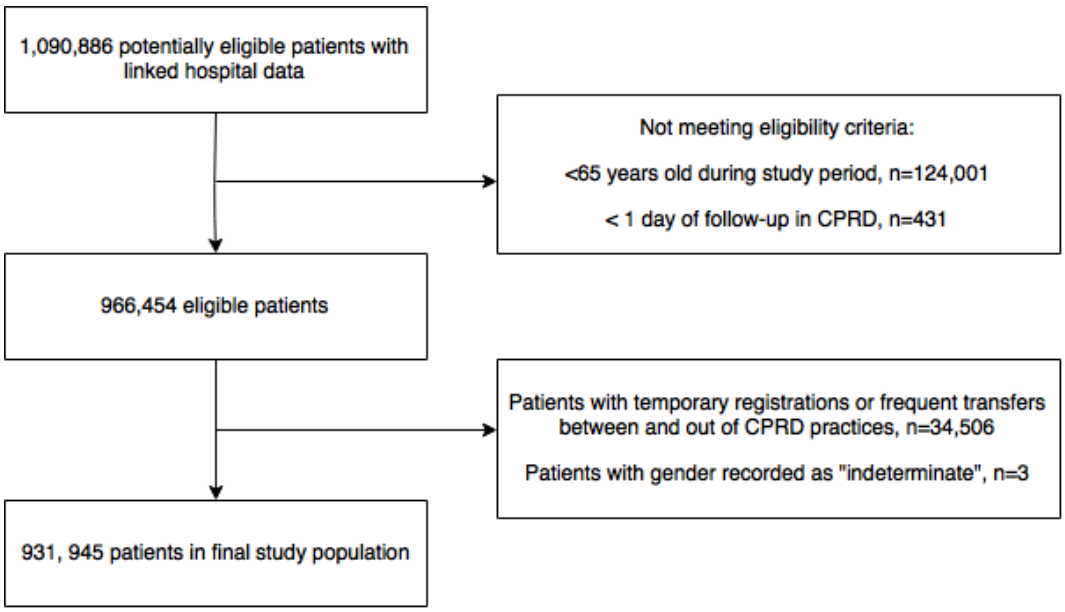


Figure 4.1. Flow of patients from initial identification in the database to final cohort.

Table 4.1. Characteristics of the study population.

	Number (%)
Total study population	931,945
Male	417,190 (45)
Female	514,755 (55)
Median (IQR) age at start of follow-up (years)	70.2 (65.0-78.2)
Median (IQR) age at end of follow-up (years)	77.1 (70.3-84.4)
Median (IQR) follow-up time (years)	5.0 (2.2-8.5)
Total follow-up time (person years)	4,857,433

4.3.1 Incidence by age and gender

Of 931,945 older adults, 196,358 (21%) had at least one UTI between 1st March 2004 and 31st March 2014. In this cohort of 196,358 patients, we identified 450,080 episodes of community-acquired UTI. Median number of episodes per person was 2 (IQR 1-4). Over 96% of episodes were identified by the presence of a diagnostic (e.g., “Urinary tract infection”) or symptomatic (e.g., “dysuria”) Read code and a same-day antibiotic prescription. Incidence of UTI increased with age and was higher in women. There was marked monthly variation in incidence for both men and women, but with no clear pattern or seasonal distribution.

The incidence of UTI in older men (episodes per 100 person-years at risk), increased between March 2004 and April 2014 from 2.81 (95% CI 2.48-3.15) to 3.05 (95% CI 2.56-3.54) in those aged 65-74, and 5.90 (95% CI 5.28-6.53) to 6.13 (95% CI 5.25-7.00) in those aged 75-84. The increase was most marked in those aged 85+, from 8.08 (95% CI 6.64-9.52) to 10.54 (95% CI 8.61-12.48). Joinpoint analyses showed an annual percentage

increase (APC) in incidence rates of 1.4% (95% CI 0.7-2.1) in those aged 65-74 (Figure 4.2). The APC for those aged 75-84 was 5.5% (95% CI 1.6-9.5) between March 2004 and September 2007, followed by a change in trend in September 2007 (95% CI May 2006 to January 2009), and then an APC of 1.1% (95% CI 0.0-2.2) between October 2007 and April 2014. The APC for those aged 85+ was 3.3% (95% CI 2.8-3.9).

The incidence of UTI in older women (episodes per 100 person-years at risk), increased between March 2004 and April 2014 from 9.03 (95% CI 8.44-9.61) to 10.96 (95% CI 10.05-11.87) in those aged 65-74, 11.35 (95% CI 10.62-12.07) to 14.34 (95% CI 13.13-15.54) in those aged 75-84, and 14.65 (95% CI 13.39-15.91) to 19.80 (95% CI 17.86-21.73) in those aged 85+. The APC for those aged 65-74 was 6.1% (95% CI 3.8-8.5) between March 2004 and November 2007, and 1.1% (95% CI 0.4-1.7) between December 2007 and April 2014 (Figure 4.3). The APC for those aged 75-84 was 8.8% (95% CI 6.6-11.2) between March 2004 and November 2006, and 3.2% (95% CI 2.7-3.6) between December 2006 and April 2014. The APC for those aged 85+ was 6.9% (95% CI 3.5-10.4) between March 2004 and February 2007, and 3.1% (95% CI 1.3-4.8) between March 2007 and April 2014. Estimated changes in trend for the 65-74, 75-84 and 85+ age groups occurred in December 2007 (95% CI May 2006 to April 2009), November 2006 (95% CI February 2006 to January 2008), and February 2007 (95% CI January 2006 to April 2009) respectively.

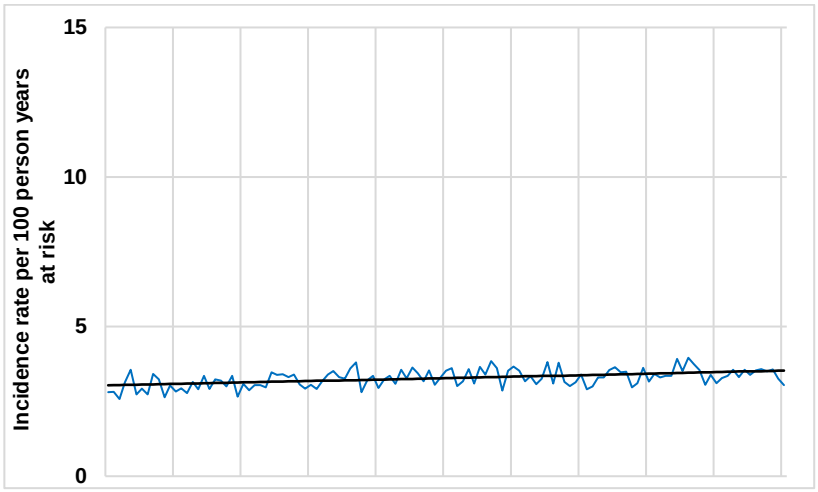


Figure 4.2a: Men aged 65-74. Statistically significant increase in incidence rate over time. The APC between 2004 and 2014 was 1.4% (95% CI 0.7-2.1).

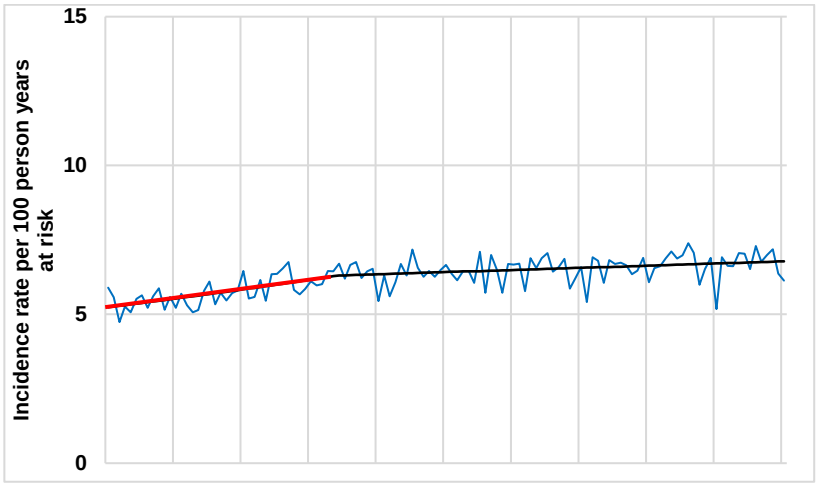


Figure 4.2b: Men aged 75-84. Estimated change in trend in September 2007. Statistically significant increase in incidence rate between 2004 and 2014. The APC between March 2004 and September 2007 was 5.5% (95% CI 1.6-9.5), and between October 2007 and April 2014 was 1.1% (95% CI 0.0-2.2).

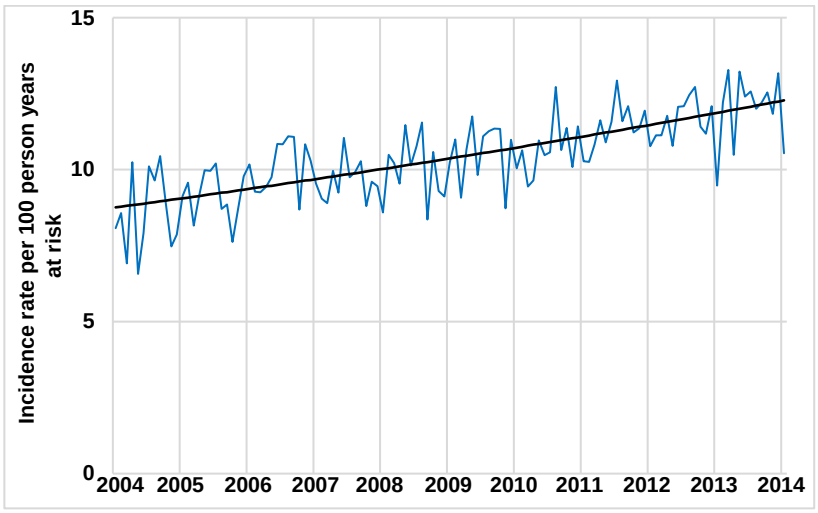


Figure 4.2c: Men aged 85+. Statistically significant increase in incidence rate between 2004 and 2014. The APC between 2004 and 2014 was 3.3% (95% CI 2.8-3.9).

APC = Annual Percentage Change. Observed monthly incidence represented by blue line. Joinpoint regression represented by red and black lines.

Figure 4.2. Joinpoint analyses of monthly age-specific community acquired urinary tract infection incidence rates for older men in UK primary care March 2004 – April 2014.

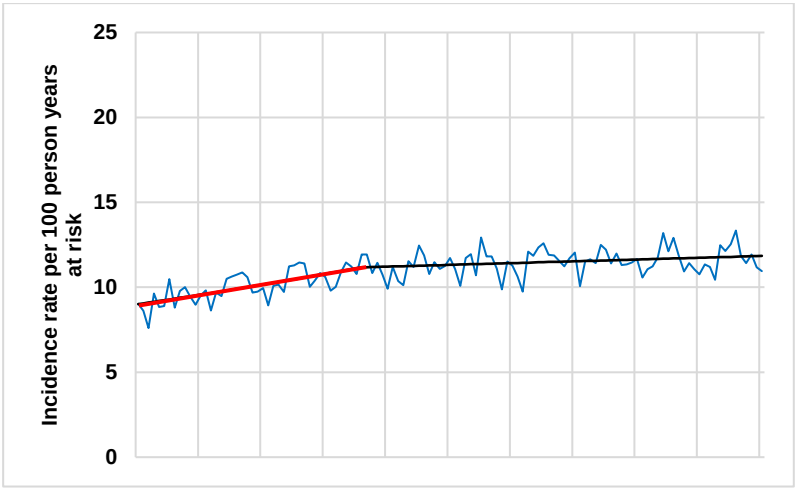


Figure 4.3a: Women aged 65-74. Estimated change in trend in November 2007. Statistically significant increase in incidence rate between 2004 and 2014. The APC between March 2004 and November 2007 was 6.1% (95% CI 3.8-8.5), and between December 2007 and April 2014 was 1.1% (95% CI 0.4-1.7).

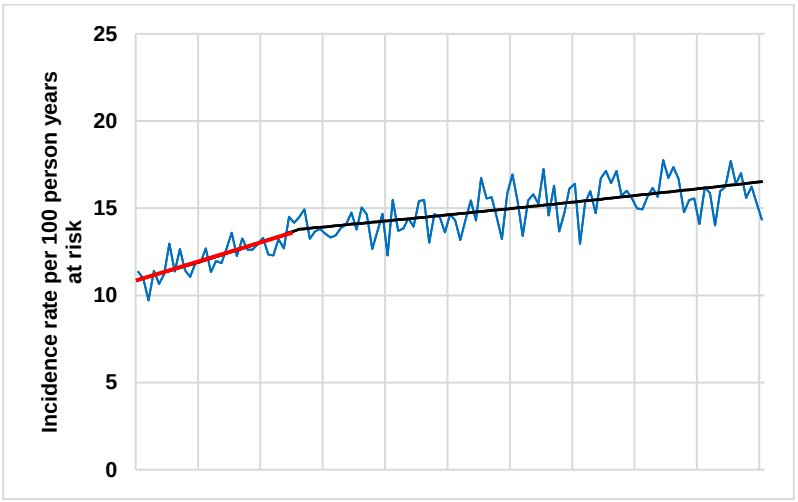


Figure 4.3b: Women aged 75-84. Estimated change in trend in November 2006. Statistically significant increase in incidence rate between 2004 and 2014. The APC between March 2004 and November 2006 was 8.8% (95% CI 6.6-11.2), and between December 2006 and April 2014 was 3.2% (95% CI 2.7-3.6).

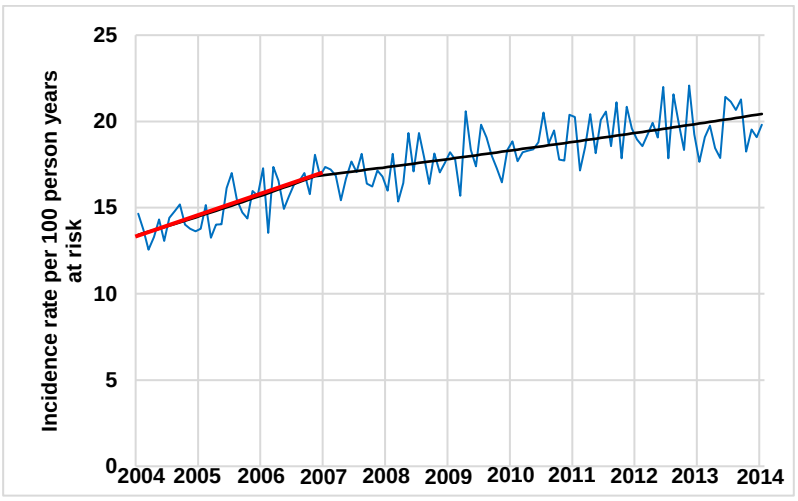


Figure 4.3c: Women aged 85+. Estimated change in trend in February 2007. Statistically significant increase in incidence rate between 2004 and 2014. The APC between March 2004 and February 2007 was 6.9% (95% CI 3.5-10.4), and between March 2007 and April 2014 was 3.1% (95% CI 1.3-4.8).

APC = Annual Percentage Change. Observed monthly incidence represented by blue line. Joinpoint regression represented by red and black lines.

Figure 4.3. Joinpoint analyses of monthly age-specific community acquired urinary tract infection incidence rates for older women in UK primary care March 2004 – April 2014.

4.3.2 Antibiotic choice

Trends in antibiotic choice were similar for older men and women (Figure 4.4 and Figure 4.5). Trimethoprim was consistently the most commonly prescribed antibiotic for community-acquired UTI, accounting for about 50% of all prescriptions. Prescriptions of broad-spectrum cephalosporins for UTI decreased markedly in men from 23.7% in 2004 to 4.1% in 2014, and women from 24.6% in 2004 to 5.5% in 2014. Quinolone use also decreased; in men from 12.2% in 2004 to 6% in 2014 and in women, from 6.2% in 2004 to 2.7% in 2014. Prescriptions of nitrofurantoin for community-acquired UTI increased markedly during the study period, rising from 5.5% of prescriptions for male UTI in 2004, to 22.3% in 2014, and from 6.2% of prescriptions for female UTI in 2004 to 27.9% in 2014. Use of other antibiotic groups remained relatively stable.

There was an increase in the proportion of older men prescribed a UTI-specific antibiotic (nitrofurantoin or trimethoprim) between March 2004 and April 2014, from 45% to 74%. Multi-level logistic regression model estimates suggest that a practice with UTI-specific prescribing one standard deviation below the mean would show an increase across the 10-year study period from 24% to 75%, and a practice with prescribing one standard deviation above the mean would show an increase from 67% to 95% (Table 4.2). Across the same period, there was also an increase in the proportion of older women prescribed a UTI-specific antibiotic, from 55% to 82%.

Model estimates suggest that a practice with UTI specific antibiotic prescribing one standard deviation below the mean would show an increase from 31% to 85% and a practice with prescribing one standard deviation above the mean would show an increase from 76% to 97% (Table 4.3).

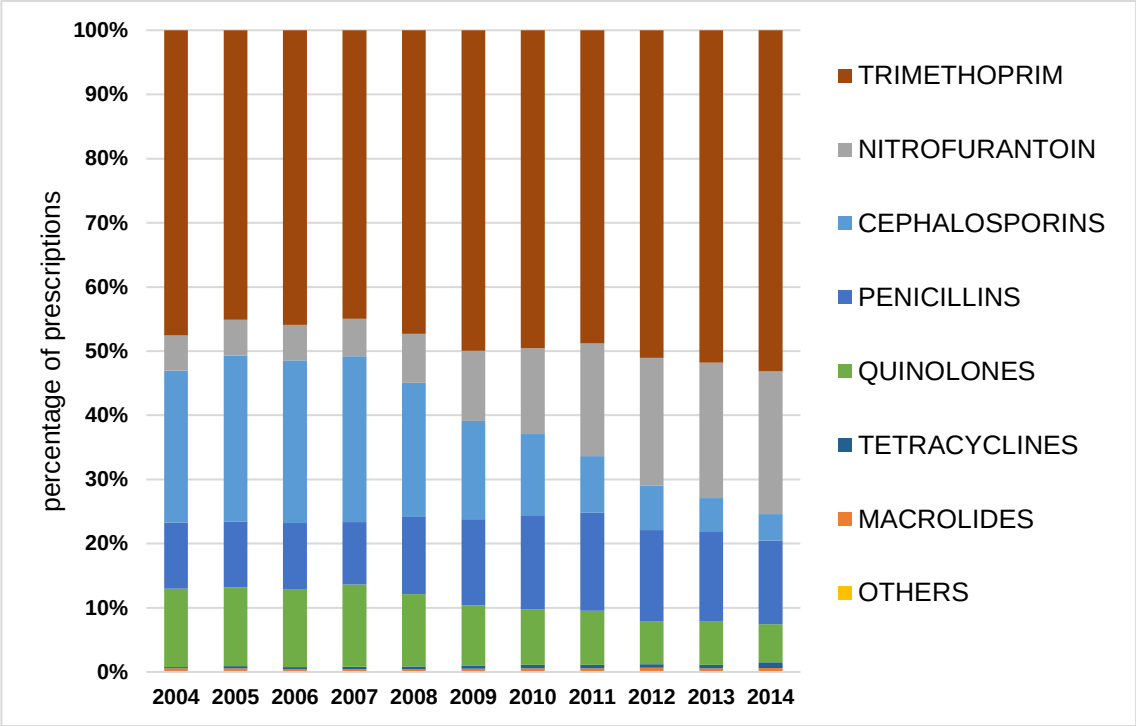


Figure 4.4. Antibiotic prescribing for community acquired UTI for older men by year and antibiotic group.

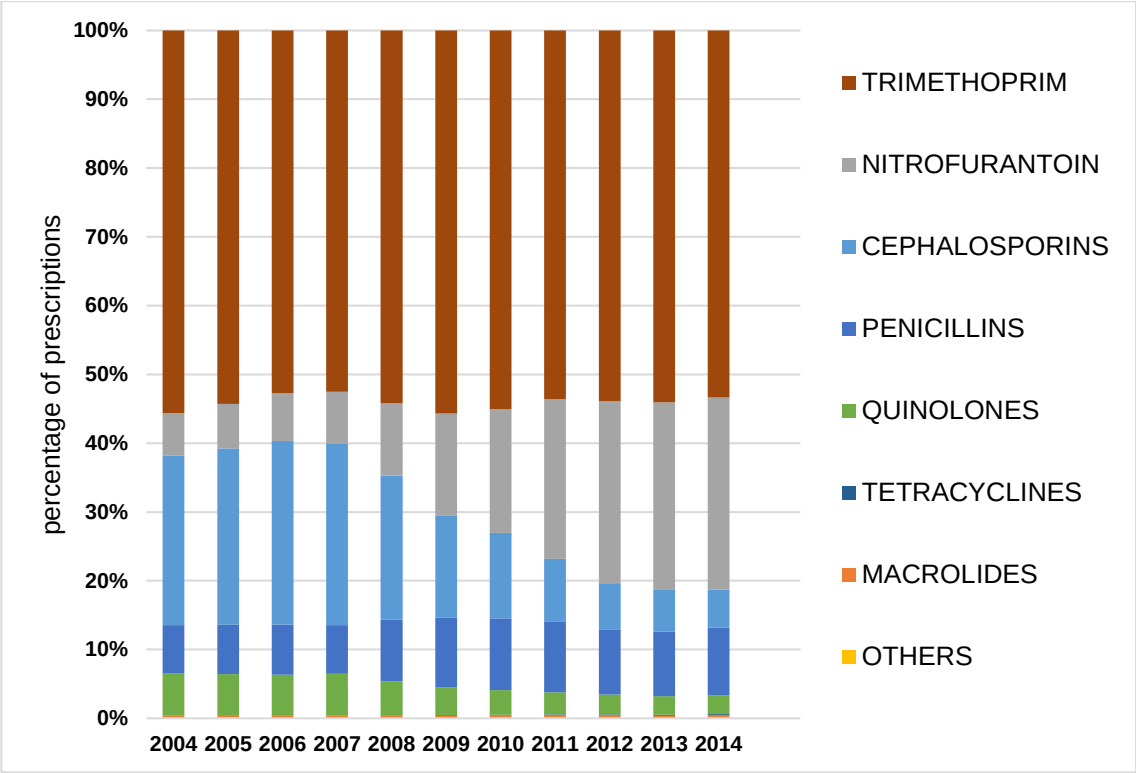


Figure 4.5. Antibiotic prescribing for community acquired UTI for older women by year and antibiotic group.

Table 4.2. Mixed multilevel model estimates for change in the proportion of older men prescribed a UTI-specific antibiotic between 2004-2014

Fixed effects	*Coefficient*	*Standard Error*	*z-value*	*p-value*
Intercept	-0.2024	0.05251	-3.854	<0.001
Time since 2004 (days)	0.0003368	0.00001695	19.870	<0.001
Random effects	*Standard Deviation*			
Practice	0.9317832			
Time since 2004 (days)	0.0002745			

*Generalised linear mixed model fit by maximum likelihood (Laplace approximation)

Table 4.3. Mixed multilevel model estimates for change in the proportion of older women prescribed a UTI-specific antibiotic between 2004-2014

Fixed effects	*Coefficient*	*Standard Error*	*z-value*	*p-value*
Intercept	0.1893026	0.0519098	3.647	<0.001
Time since 2004 (days)	0.0003631	0.0000172	21.110	<0.001
Random effects	*Standard Deviation*			
Practice	0.9704797			
Time since 2004 (days)	0.0003106			

*Generalised linear mixed model fit by maximum likelihood (Laplace approximation)

4.3.3 Antibiotic duration

There was an increase in the proportion of older men prescribed seven-day antibiotic therapy between 2004 and 2014, from 42% to 69% (Figure 4.6). This was accompanied by a reduction in the proportion of older men prescribed five-day antibiotic therapy, from 32% in 2004 to 14% in 2014. There was little change over time in the proportion of older men prescribed three-day or >7 day antibiotic therapy. Multi-level logistic regression model estimates suggest a practice with seven-day therapy prescribing one standard deviation below the mean would show an increase from 23% to 74%, and a practice with seven-day therapy prescribing one standard deviation above the mean would show a change from 64% to 94% (Table 4.4). Across the same period, there was also an increase in the proportion of older women prescribed three-day antibiotic therapy, from 15% to 26% (Figure 4.7). This was accompanied by a small reduction in the proportion of older women prescribed five-day therapy, from 29% in 2004 to 20% in 2014. There was little change over time in the proportion of women prescribed ≥7 day antibiotic therapy. Model estimates suggest that a practice with three-day therapy prescribing one standard deviation below

the mean would show a change from 4% to 31% and a practice with three-day therapy prescribing one standard deviation above the mean would show a change from 43% to 90% (Table 4.5).

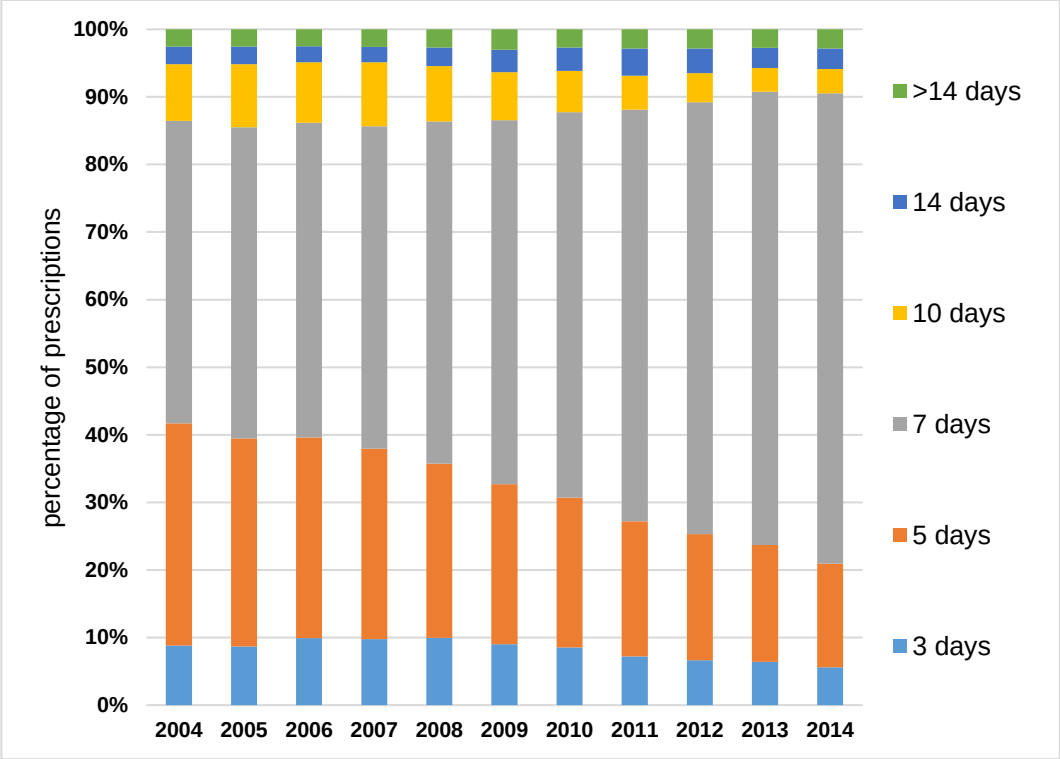


Figure 4.6. Duration of antibiotic prescription for community acquired UTI in older men.

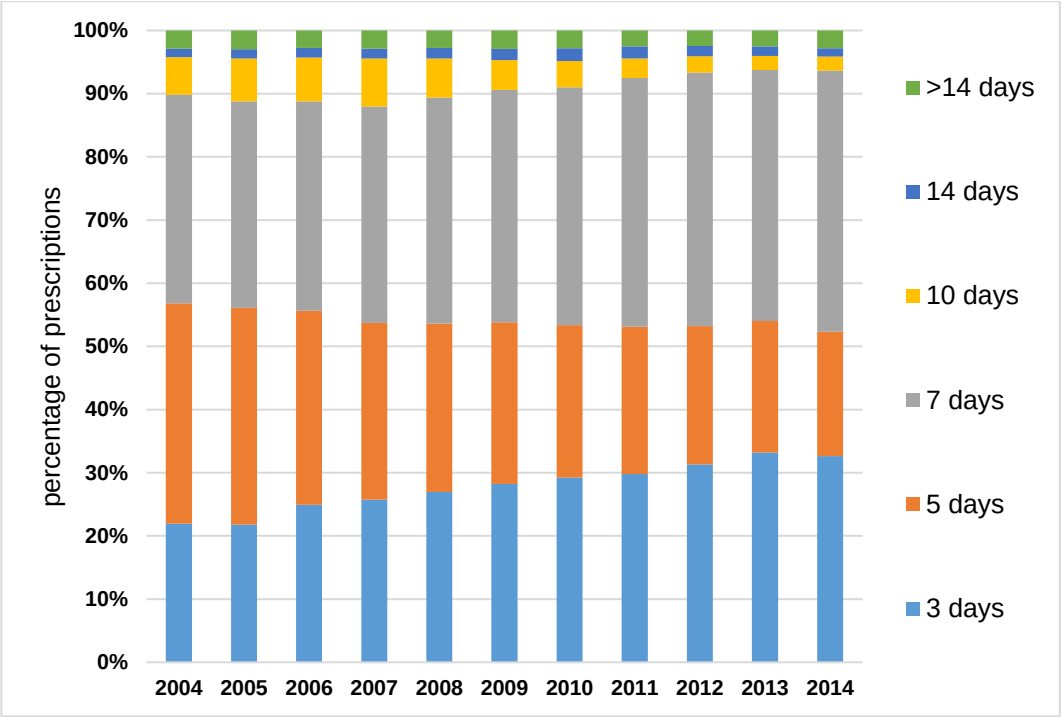


Figure 4.7. Duration of antibiotic prescription for community acquired UTI in older women.

Table 4.4.Mixed multilevel model estimates for change in the proportion of older men prescribed 7-day antibiotic treatment between 2004-2014

Fixed effects	*Coefficient*	*Standard Error*	*z-value*	*p-value*
Intercept	-0.3361	0.05087	-6.608	<0.001
Time since 2004 (days)	0.0003066	0.00001847	16.6	<0.001
Random effects	*Standard Deviation*			
Practice	0.896207			
Time since 2004 (days)	0.000306			

*Generalised linear mixed model fit by maximum likelihood (Laplace approximation)

Table 4.5.Mixed multilevel model estimates for change in the proportion of older women prescribed 3-day antibiotic treatment between 2004-2014

Fixed effects	*Coefficient*	*Standard Error*	*z-value*	*p-value*
Intercept	-1.751	0.07912	-22.135	<0.001
Time since 2004 (days)	0.0001947	0.00002557	7.615	<0.001
Random effects	*Standard Deviation*			
Practice	1.4830682			
Time since 2004 (days)	0.0004632			

*Generalised linear mixed model fit by maximum likelihood (Laplace approximation)

4.3.4 Additional analysis

Following peer-review of the above analyses by Reviewers at PLoS ONE, we examined whether the changing incidence of UTI was related to increasing age within each age-group. The Reviewers commented that although we reported age-specific incidence rates for UTI by 10-year age-groups, the mean age within these age-groups may have increased over time, and consequently the observed changes in incidence may be the result of increasing age. They requested that we calculate the mean age in each age-group at the start and end of the study period to examine whether this had changed (Table 4.6).

We found no evidence for a change in the mean age in any age-group across the study period, therefore decreasing the likelihood of increases in incidence being related to increasing age within our sample.

Table 4.6. Mean age in each age-group for each study year.

		Mean age (years) for each age-group for each study year										
	Age-group	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Men	65-74	69.2	69.2	69.2	69.2	69.2	69.1	69.1	69.0	69.0	69.0	69.0
	75-84	79.0	79.0	79.0	79.0	79.0	79.0	79.0	79.0	79.0	79.0	79.0
	85+	89.0	88.3	88.2	88.2	88.3	88.3	88.4	88.4	89.0	89.0	89.0
Women	65-74	69.3	69.4	69.4	69.3	69.3	69.2	69.2	69.1	69.0	69.0	69.0
	75-84	79.3	79.2	79.2	79.2	79.2	79.2	79.2	79.2	79.2	79.2	79.2
	85+	89.4	89.1	89.0	89.0	89.1	89.1	89.2	89.3	89.3	89.4	89.4

4.4 Discussion

This study is the first to provide age and gender-specific monthly incidence estimates of clinically diagnosed UTI derived from a large population-based sample. We identified monthly variation in incidence rates with an overall increasing incidence rate that was most marked for men over 85 and women over 75. About 20% of nearly one million older adults in our sample had at least one clinically diagnosed UTI in primary care over a 10-year period. The proportion of older adults prescribed nitrofurantoin or trimethoprim increased, as did the proportion of older men prescribed seven-day antibiotic therapy. The proportion of older women prescribed three-day antibiotic therapy also increased but three in four older women still received longer than three-day therapy suggesting on-going clinical uncertainty in this area. However, overall, these changes are encouraging and demonstrate improvements in guideline congruent prescribing.

4.4.1 Findings in context

Our incidence estimates are broadly consistent with those of the Pittsburgh Good Health Study (23) and the Leiden 85-plus study (24). In contrast to two previous studies, (137, 138) we did not identify any clear evidence of

seasonality. However, both previous studies included women of all ages. A more recent study examined UTI seasonality by age-group and found that UTI consultation incidence peaks between September and November for ages 14-69, but this seasonality progressively fades in older age groups, with no seasonality found in individuals aged 85+ (139).

We identified a change in incidence trend for older women occurring around 2007, with a reduction in the APC for incidence rates that followed this period. Reasons for this could include publication of the first two UK clinical guidelines on management of bacterial UTI in adults in 2006 and 2007. The SIGN guidelines provided evidence-based recommendations for diagnosis and treatment of UTI in adults (29). They did not provide recommendations specifically for older people, but they did highlight the prevalence of asymptomatic bacteriuria, and the evidence to show that antibiotic treatment for asymptomatic bacteriuria was more likely to cause harm than benefit. The Public Health England guidelines focussed on UTI diagnosis and made recommendations around urine sampling in older people (30). They discussed the importance of diagnosis based on combinations of specific signs and symptoms. This push towards criteria based diagnosis of UTI in older people was supported by a clinical trial published in 2005 that found UTI diagnosis based on a set of clinical criteria reduced antibiotic use (140, 141). Together, these publications may have had enough reach and impact to persuade clinicians to modify their approach towards UTI diagnosis in older people.

Our analyses demonstrated increasing incidence of UTI, especially in men over 85 and women over 75. This may represent over-diagnosis, reflecting

the increasing challenge of accurately diagnosing UTI in this population, or may represent an increase in true bacterial UTI, possibly due to the increasing prevalence of elderly multi-morbid individuals with greater susceptibility to infections. Further investigation is required to ascertain the reasons for this increase and to assess whether preventative or diagnostic interventions could effectively and safely reduce incidence and associated antibiotic use.

Guideline congruent antibiotic prescribing for community acquired UTI is improving, with increasing use of UTI-specific antibiotics. Prescribing of trimethoprim or nitrofurantoin for older men with UTI increased from 45% in 2004, to 74% in 2014. For older women, this increase was from 55% to 82%. The observed increases in trimethoprim and nitrofurantoin prescribing were accompanied by decreases in prescribing of cephalosporins, quinolones and co-amoxiclav. Despite limited empirical evidence for optimal antibiotic duration in older men, we observed greater adherence to prescribing of seven-day antibiotic therapy, which increased from 42% in 2004 to 69% in 2014. Three-day antibiotic prescribing for older women also increased, although not as dramatically, from 15% in 2004 to 26% in 2014. This was a surprising finding given that there is empirical trial evidence for optimal antibiotic duration for UTI in older women, with meta-analysis showing no difference in short (3 trials, N=431) or long-term (3 trials, N=470) outcomes between those treated with three days of antibiotics versus those treated with seven days (62). These results may be explained by findings from previous studies that report reasons for why clinician adherence to evidence based guidance for UTI is sub-optimal (142). This may be partly

due to conflicting recommendations in guidelines, (75) and partly due to clinical complexity and prognostic uncertainty associated with UTI in older adults (143, 144). Better understanding of these uncertainties around recovery and prognosis may help to improve adherence to three-day antibiotic therapy for older women. However, overall, these findings demonstrate improvements in evidence-based antibiotic prescribing for UTI in older adults and are an encouraging indicator of practice change.

4.4.2 Strengths and limitations

Our study used a large population-based sample to estimate UTI incidence trends. We sought to optimise the accuracy of our estimates by calculating days at risk for included individuals, and subtracted time at risk of hospital acquired infection from the denominator. We distinguished repeat consultations for the same infection from new incident infection by attributing codes within 28 days of one another to the same episode. This may have underestimated the incidence of UTI if some of these episodes were actually new incident UTIs. We did not have access to linked microbiological data and thus the UTI episodes are clinically diagnosed episodes rather than microbiologically confirmed, but as over 98% of these episodes were associated with a same-day antibiotic prescription, they are more likely to reflect the true burden of clinically diagnosed and empirically treated UTI in a primary care population. However, data used were recorded for clinical purposes and thus are prone to a degree of coding error, differential coding between clinicians, and confounding by indication. We also would not have captured incident UTIs where the antibiotic prescription was associated with a non-specific code (e.g., “patient reviewed”).

4.5 Conclusions

This population-based analysis of clinical records from nearly one million older adults has shown an increase in the incidence of clinically diagnosed UTI between 2004 and 2014. There is a clear need to better understand the reasons for the increasing incidence, and for interventions that improve prevention and diagnosis of UTI. Although antibiotic choice for UTI in primary care has improved, further improvements could arise through better understanding and addressing the reasons for the relatively low uptake of short-course therapy for older women.

5 Association between choice of empirical antibiotic prescription and adverse outcomes

In chapter 4, we described trends in antibiotic prescribing for UTI in older people in primary care. We found that the proportion of older patients with UTI prescribed nitrofurantoin or trimethoprim increased between 2004 and 2014. However, in 2014, 24% of older men and 19% of older women still received a prescription for an antibiotic other than nitrofurantoin or trimethoprim. In this chapter, we present analyses on whether prescribing these alternative antibiotics had an impact on the risk of treatment failure, UTI-related hospitalisation, or death, in the 14-28 days following the incident UTI.

5.1 Background

Nitrofurantoin and trimethoprim are narrow-spectrum antibiotics widely recommended for the treatment of UTI (18, 19). However, GPs may prescribe broad-spectrum antibiotics for some patients, especially if they are older or frail, have co-morbidities, or present with symptoms or signs of more severe illness (71). The perceived aim of broad-spectrum antibiotic prescribing is to prevent treatment failure, worsening illness, and hospitalisation, events thought to be more likely if narrow-spectrum antibiotics are prescribed for that clinical scenario (77).

Although randomised trials showed similar clinical cure rates between patients with UTI treated with nitrofurantoin or trimethoprim versus

flouroquinolones or cephalosporins (145-147), these trials only included young, healthy women and were underpowered to assess risk of important but rare outcomes such as UTI-related hospitalisation or death (58, 148). Previous observational studies compared trimethoprim-sulfamethoxazole with flouroquinolones, and sulfamethiazole with pivmecillinam and were either restricted to younger females, assessed treatment failure alone, or lacked clinical coding data to ascertain the indication for the antibiotic prescription (149, 150). Furthermore, trimethoprim-sulfamethoxazole, and sulfamethiazole are rarely used in UK primary care.

We therefore used the CPRD to investigate the risk of adverse outcomes in adults aged ≥65 prescribed empirical nitrofurantoin or trimethoprim versus other antibiotics commonly prescribed for suspected UTI in UK primary care. We had two aims. First, to Identify sociodemographic and clinical variables associated with broad-spectrum antibiotic prescribing (amoxicillin, cefalexin, ciprofloxacin or co-amoxiclav). Second, to assess whether amoxicillin, cefalexin, ciprofloxacin or co-amoxiclav were associated with a reduced risk of treatment failure, hospitalisation for UTI, sepsis or acute kidney injury (AKI), or death. If these antibiotics were associated with risks that were similar or higher than those of nitrofurantoin or trimethoprim, then this would support further reductions in their use, even in older, frailer, comorbid patients with more severe presenting features.

5.2 Methods

This was a retrospective cohort study. Patients were eligible for inclusion if, between 1st January 2010 and 31st December 2016, they were ≥65 years old, had linked hospital data and more than one day of CPRD follow-up. We

excluded patients with temporary registrations or gaps in their data coverage. Patient follow-up began on the latest of study start date, the patient's 65th birthday or 28 weeks after the patient first registered at the practice. Follow-up ended at the earliest of study end date, death, last day of available CPRD data, or 28 days after an incident UTI event. We identified eligible patients with a Read code indicating an incident primary care presentation with a suspected UTI (Code list 1 in Figure 3.1) and a same-day prescription code indicating empirical prescribing of a relevant antibiotic. We defined 'incident' as a consultation occurring in a patient without a UTI-related Read code or trimethoprim or nitrofurantoin prescription in the preceding 90 days. We used the first incident episode during each patient's follow-up period.

We used the recorded empirical antibiotic prescription as the exposure variable and used primary care demographic and clinical codes to describe baseline characteristics for each exposure group. We used multivariable logistic regression to estimate odds ratios (ORs) and 95% CIs for associations between demographic and clinical variables and broad-spectrum antibiotic prescribing for UTI. We then used mixed effects multivariable logistic regression to estimate ORs and 95% CIs for the risk of each adverse outcome with the general practice included as a random effect to account for clustering. The outcomes were re-consultation and re-prescription within 14 days following the incident UTI (proxy for treatment failure), hospitalisation for UTI, sepsis or AKI within 14 days following the incident UTI, and death within 28 days following the incident UTI. More

detail on the justification and ascertainment of these outcomes is provided in section 3.7.

We repeated the analyses using propensity-score matching to improve balance of baseline characteristics across the comparison groups. We first matched three patients with nitrofurantoin prescriptions to one patient with an amoxicillin prescription, and then repeated the process to compare nitrofurantoin with cefalexin, ciprofloxacin and co-amoxiclav. We then matched three patients with trimethoprim prescriptions to one patient with an amoxicillin prescription, and again repeated the process to compare trimethoprim with cefalexin, ciprofloxacin and co-amoxiclav.

5.3 Results

From a cohort of 795,484 patients aged 65 and over, we identified 123,607 (16%) with an incident UTI empirically treated with a relevant antibiotic (Figure 5.1). In this final cohort, 33,745 (27%) patients were male and the median age at time of incident UTI was 76 years (IQR 70-83). Trimethoprim was the most commonly prescribed antibiotic, accounting for 61% of all prescriptions, followed by nitrofurantoin (21%), cefalexin (6%), amoxicillin (5%), co-amoxiclav (4%) and ciprofloxacin (3%).

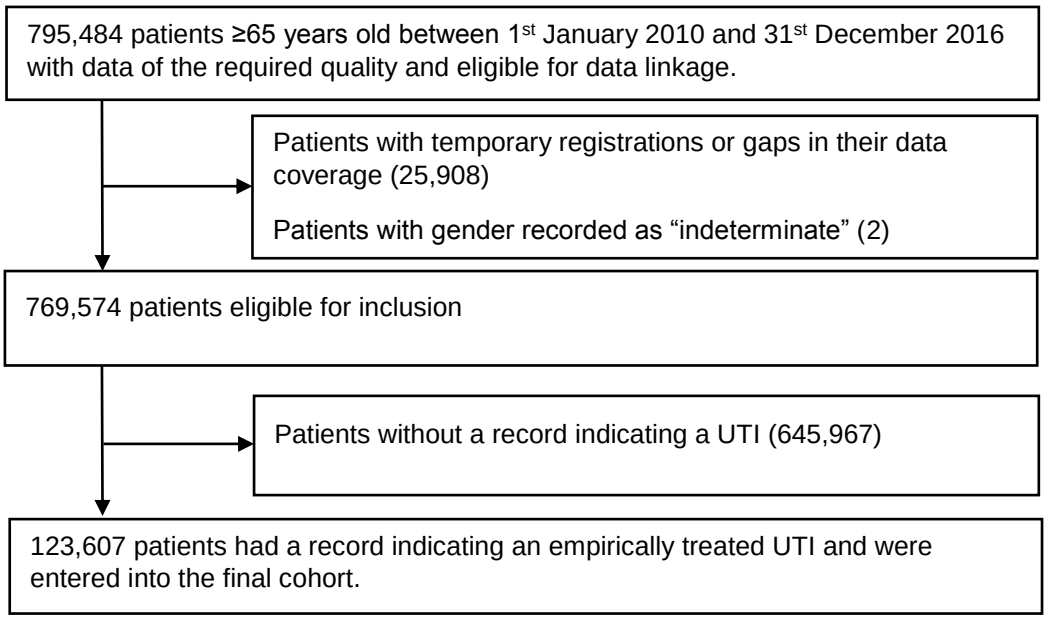


Figure 5.1. Flow of patients from initial identification in the database through to final cohort.

5.3.1 Baseline characteristics

There were differences in baseline characteristics across the antibiotic groups. For example, 55% of the ciprofloxacin group were male compared to 23% of the nitrofurantoin group and 26% of the trimethoprim group (Table 5.1). Compared to the nitrofurantoin and trimethoprim groups, greater proportions of the amoxicillin, cefalexin, ciprofloxacin and co-amoxiclav groups had co-morbidities, particularly ischaemic heart disease, heart failure, and renal disease. Around 3% of the nitrofurantoin and trimethoprim groups had a Charlson score of ≥6, compared to 5-6% of the other groups. The presence of rheumatoid arthritis (adjusted OR 1.34, 95% CI 1.23-1.46), a urinary catheter (adjusted OR 1.32, 95% CI 1.23-1.43), urinary incontinence (adjusted OR 1.10, 95% CI 1.06-1.15), liver disease (adjusted OR 1.30, 95% CI 1.08-1.55), and polypharmacy (adjusted OR 1.17, 95% CI 1.13-1.21), were all strongly associated with increased odds of a broad-

spectrum antibiotic prescription (amoxicillin, cefalexin, ciprofloxacin or co-amoxiclav, compared to nitrofurantoin or trimethoprim) (Table 5.2). Odds of a broad-spectrum antibiotic prescription also increased in a graded manner relative to increasing Charlson score and decreasing eGFR. Women had lower odds of a broad-spectrum antibiotic prescription than men, (adjusted OR 0.58, 95% CI 0.56-0.60), as did patients with dementia (compared to those without dementia; adjusted OR 0.91, 95% CI 0.85-0.97).

Table 5.1. Baseline characteristics by prescribed antibiotic. Values are numbers (%) unless otherwise stated.

	Amoxicillin	Cefalexin	Ciprofloxacin	Co-amoxiclav	Nitrofurantoin	Trimethoprim
N	6000 (4.6)	7546 (6.1)	3868 (3.1)	5516 (4.5)	25368 (20.5)	75309 (60.9)
Men	2028 (33.8)	2150 (28.5)	2115 (54.7)	2229 (40.4)	5930 (23.4)	19293 (25.6)
Mean (SD) age	78.2 (8.6)	77.5 (8.4)	76.5 (8.3)	77.6 (8.5)	76.5 (8.4)	76.8 (8.5)
Mean (SD) follow-up time (years)	4.6 (1.9)	4.2 (2.0)	4.5 (2.0)	4.2 (2.0)	4.6 (1.9)	4.7 (1.9)
Mean (SD) prescription duration (days)	7.8 (8.3)	8.2 (7.0)	7.6 (7.0)	8.3 (8.6)	6.6 (3.6)	6.4 (12.1)
Index of Multiple Deprivation decile						
1 or 2 (least deprived)	1418 (23.6)	1708 (22.6)	1056 (27.3)	1354 (24.5)	6850 (27.0)	18703 (24.8)
3 or 4	1384 (23.1)	1710 (22.7)	957 (24.7)	1401 (25.4)	6180 (24.4)	18191 (24.2)
5 or 6	1286 (21.4)	1722 (22.8)	850 (22.0)	1255 (22.8)	5214 (20.6)	16840 (22.4)
7 or 8	1079 (18.0)	1254 (16.6)	605 (15.6)	849 (15.4)	3970 (15.6)	12585 (16.7)
9 or 10 (most deprived)	833 (13.9)	1152 (15.3)	400 (10.3)	657 (11.9)	3154 (12.4)	8990 (11.9)
Housebound	271 (4.5)	41 (5.5)	136 (3.5)	265 (4.8)	929 (3.7)	2778 (3.7)
Respiratory disease	1388 (23.1)	1702 (22.6)	849 (21.9)	1198 (21.7)	5339 (21.0)	14592 (19.4)
Cardiac failure	389 (6.5)	516 (6.8)	212 (5.5)	347 (6.3)	1083 (4.3)	3352 (4.5)
Dementia	417 (7.0)	512 (6.8)	170 (4.4)	382 (6.9)	1439 (5.7)	4739 (6.3)
Peripheral vascular disease	337 (5.6)	488 (6.5)	252 (6.5)	321 (5.8)	1082 (4.3)	3307 (4.4)
Renal disease	1717 (28.6)	2243 (29.7)	1001 (25.9)	1499 (27.2)	5310 (20.9)	17378 (23.1)
Rheumatoid arthritis	233 (3.9)	297 (3.9)	108 (2.8)	188 (3.4)	900 (3.5)	1709 (2.3)
Cancer	922 (15.4)	1295 (17.2)	780 (20.2)	949 (17.2)	3889 (15.3)	10858 (14.4)
Stroke	733 (12.2)	886 (11.7)	392 (10.1)	673 (12.2)	2460 (9.7)	7115 (9.4)
Diabetes	1150 (19.2)	1474 (19.5)	783 (20.2)	1111 (20.1)	4234 (16.7)	12346 (16.4)
Liver disease	42 (0.7)	68 (0.9)	30 (0.8)	36 (0.7)	171 (0.7)	374 (0.5)
Ischaemic heart disease	1207 (20.1)	1602 (21.2)	821 (21.2)	1158 (21.0)	4290 (16.9)	12629 (16.8)
Urinary catheter	221 (3.7)	372 (4.9)	309 (8.0)	327 (5.9)	853 (3.4)	2015 (2.7)
Urinary incontinence	901 (15.0)	1199 (15.9)	471 (12.2)	867 (15.7)	3972 (15.7)	10414 (13.8)
Polypharmacy	2575 (42.9)	3299 (43.7)	1540 (39.8)	2376 (43.1)	9301 (36.7)	26019 (34.5)
eGFR						
60-90	3370 (56.2)	4168 (55.2)	2344 (60.6)	3170 (57.5)	16719 (65.9)	46341 (61.5)
45-59	1367 (22.8)	1749 (23.2)	811 (21.0)	1227 (22.2)	5237 (20.6)	16579 (22.0)
30-44	680 (11.3)	917 (12.2)	388 (10.0)	613 (11.1)	1815 (7.2)	6441 (8.6)
15-29	289 (4.8)	319 (4.2)	148 (3.8)	208 (3.8)	391 (1.5)	1312 (1.7)
<15	45 (0.8)	47 (0.6)	26 (0.7)	44 (0.8)	41 (0.2)	139 (0.2)
missing	249 (4.2)	346 (4.6)	151 (3.9)	254 (4.6)	1165 (4.6)	4497 (6.0)
Charlson score						
0	1652 (27.5)	2029 (26.9)	1073 (27.7)	1591 (28.8)	8845 (34.9)	26895 (35.7)
1	1259 (21.0)	1515 (20.1)	765 (19.8)	1098 (19.9)	5354 (21.1)	15060 (20.0)
2	1187 (19.8)	1406 (18.6)	773 (20.0)	1006 (18.2)	4755 (18.7)	14138 (18.8)
3	833 (13.9)	1070 (14.2)	535 (13.8)	769 (13.9)	3050 (12.0)	9107 (12.1)
4	466 (7.8)	658 (8.7)	313 (8.1)	437 (7.9)	1567 (6.2)	4844 (6.4)
5	308 (5.1)	428 (5.7)	197 (5.1)	305 (5.5)	955 (3.8)	2715 (3.6)
≥6	295 (4.9)	440 (5.8)	212 (5.5)	310 (5.6)	842 (3.3)	2550 (3.4)

Table 5.2. Association between baseline variables and broad-spectrum antibiotic prescribing.

	Number (%) in each group			
Variable	**Broad-spectrum N=22930**	**Narrow-spectrum N=100677**	**Adjusted OR (95% CI)***	**p-value**
Women	14408 (63.3)	75454 (74.9)	0.58 (0.56-0.60)	<0.001
Age group				
65-69 years	5059 (22.1)	25837 (25.7)	Reference	
70-74 years	4252 (18.5)	19496 (19.4)	1.04 (0.99-1.09)	0.144
75-79 years	4331 (18.9)	18778 (18.7)	1.02 (0.97-1.07)	0.406
80-84 years	4091 (17.8)	16012 (15.9)	1.07 (1.01-1.12)	0.011
85+ years	5197 (22.7)	20554 (20.4)	1.01 (0.96-1.06)	0.592
Index of multiple deprivation decile				
1 or 2 (least deprived)	5536 (24.1)	25553 (25.4)	Reference	
3 or 4	5452 (23.8)	24371 (24.2)	0.96 (0.91-1.02)	0.205
5 or 6	5113 (22.3)	22054 (21.9)	0.97 (0.92-1.04)	0.531
7 or 8	3787 (16.5)	16555 (16.4)	1.03 (0.96-1.10)	0.378
9 or 10 (most deprived)	3042 (13.3)	12144 (12.1)	1.07 (1.00-1.16)	0.042
Housebound	1089 (4.7)	3707 (3.7)	1.08 (1.00-1.16)	0.039
Respiratory disease	5137 (22.4)	19931 (19.8)	1.08 (1.03-1.13)	0.001
Heart failure	1464 (6.4)	4435 (4.4)	1.02 (0.95-1.10)	0.560
Dementia	1481 (6.5)	6178 (6.1)	0.91 (0.85-0.97)	0.005
Peripheral vascular disease	1398 (6.1)	4389 (4.4)	1.03 (0.96-1.10)	0.430
Renal disease	6460 (28.2)	22688 (22.5)	0.95 (0.89-1.02)	0.151
Rheumatoid arthritis	826 (3.6)	2609 (2.6)	1.34 (1.23-1.46)	<0.001
Cancer	3946 (17.2)	14747 (14.6)	1.02 (0.96-1.10)	0.427
Stroke	2684 (11.7)	9575 (9.5)	1.00 (0.95-1.07)	0.766
Type 2 diabetes mellitus	4518 (19.7)	16580 (16.5)	0.95 (0.90-1.01)	0.098
Liver disease	176 (0.8)	545 (0.5)	1.30 (1.08-1.55)	0.005
Ischaemic heart disease	4788 (20.9)	16919 (16.8)	1.01 (0.97-1.05)	0.674
Urinary catheter	1229 (5.4)	2868 (2.8)	1.32 (1.23-1.43)	<0.001
Urinary incontinence	3438 (15.0)	14386 (14.3)	1.10 (1.06-1.15)	<0.001
Polypharmacy	9790 (42.7)	35320 (35.1)	1.17 (1.13-1.21)	<0.001
eGFR				
60-90	13052 (56.9)	63060 (62.6)	Reference	
45-59	5154 (22.5)	21816 (21.7)	1.13 (1.08-1.17)	<0.001
30-44	2598 (11.3)	8256 (8.2)	1.41 (1.33-1.49)	<0.001
15-29	964 (4.2)	1703 (1.7)	2.39 (2.18-2.61)	<0.001
<15	162 (0.7)	180 (0.2)	3.49 (2.80-4.34)	<0.001
Charlson score				
0	6345 (27.7)	35740 (35.5)	Reference	
1	4637 (20.2)	20414 (20.3)	1.15 (1.09-1.21)	<0.001
2	4372 (19.1)	18893 (18.8)	1.11 (1.03-1.19)	0.006
3	3207 (14.0)	12157 (12.1)	1.16 (1.06-1.28)	0.002
4	1874 (8.2)	6411 (6.4)	1.18 (1.05-1.34)	0.007
5	1238 (5.4)	3670 (3.6)	1.29 (1.12-1.49)	<0.001
≥6	1257 (5.5)	3392 (3.4)	1.31 (1.11-1.55)	0.001

Green cells show characteristics associated with broad-spectrum prescribing at the p<0.01 level and with an effect size of >0.1.

*Odds ratio adjusted for gender, age, deprivation, co-morbidities, and Charlson score.

Broad-spectrum = amoxicillin, cefalexin, ciprofloxacin and co-amoxiclav.

Narrow-spectrum = nitrofurantoin and trimethoprim.

5.3.2 Re-consultation and re-prescription

In the 14 days following the incident UTI, 7598 (6.1%) patients re-consulted and were re-prescribed an antibiotic. Compared to nitrofurantoin, patients prescribed ciprofloxacin or co-amoxiclav had lower odds of re-consultation and re-prescription (adjusted OR for ciprofloxacin; 0.58, 95% CI 0.48-0.70, adjusted OR for co-amoxiclav; 0.86, 95% CI 0.74-0.99) (Table 5.3). Similarly, compared to trimethoprim, patients prescribed ciprofloxacin or co-amoxiclav had lower odds of re-consultation and re-prescription (adjusted OR for ciprofloxacin; 0.55, 95% CI 0.46-0.65, adjusted OR for co-amoxiclav; 0.81, 95% CI 0.71-0.93) (Table 5.4). Propensity-score matched analyses produced similar estimates, and also found a reduction in odds of re-consultation and re-prescription in patients prescribed cefalexin (OR compared to nitrofurantoin; 0.85, 95% CI 0.75-0.98, OR compared to trimethoprim; 0.80, 95% CI 0.70-0.91) (Table 5.5).

5.3.3 Hospitalisation for UTI

In the 14 days following the incident UTI, 2057 (1.7%) patients were hospitalised for a UTI. We found no significant difference in the odds of UTI hospitalisation between nitrofurantoin or trimethoprim and the other antibiotics.

5.3.4 Hospitalisation for sepsis

In the 14 days following the incident UTI, 179 (0.1%) patients were hospitalised for sepsis. Patients prescribed ciprofloxacin had greater odds of hospitalisation for sepsis compared to nitrofurantoin (adjusted OR 3.12,

95% CI 1.65 - 5.92), and trimethoprim (adjusted OR 2.60, 95% CI 1.51 - 4.49). Propensity-score matched analysis produced similar estimates.

5.3.5 Hospitalisation for AKI

In the 14 days following the incident UTI, 889 (0.7%) patients were hospitalised for AKI. Compared to nitrofurantoin, patients prescribed ciprofloxacin had greater odds of hospitalisation for AKI (adjusted OR 1.71 95% CI 1.18 - 2.48). We found a similar estimate in the propensity-score matched analyses but the OR was non-significant due to the smaller sample size that resulted from matching. Compared to trimethoprim, patients prescribed amoxicillin, cefalexin or co-amoxiclav had lower odds of hospitalisation for AKI. Adjusted ORs were 0.69 (95% CI 0.50-0.95) for amoxicillin, 0.50 (95% CI 0.36-0.70) for cefalexin, and 0.63 (95% CI 0.45-0.88) for co-amoxiclav. We found no significant difference in the odds of AKI hospitalisation between trimethoprim and ciprofloxacin. Propensity-score matched analyses produced similar estimates.

5.3.6 Death

In the 28 days following the incident UTI, 1029 patients (1.2%) died. Compared to nitrofurantoin, patients prescribed amoxicillin, cefalexin or co-amoxiclav were more likely to die, with ORs of 1.51 (95% CI 1.16-1.97) for amoxicillin, 1.41 (95% CI 1.10-1.82) for cefalexin, and 1.63 (95% CI 1.24-2.14) for co-amoxiclav. Patients prescribed amoxicillin, cefalexin or co-amoxiclav were also more likely to die when compared to trimethoprim, with ORs of 1.37 (95% CI 1.09-1.73) for amoxicillin, 1.28 (95% CI 1.02-1.60) for cefalexin, and 1.48 (95% CI 1.16-1.88) for co-amoxiclav. There was again

consistency between estimates from multivariable regression and propensity-score matching.

5.3.7 Sensitivity analyses

The association between patients prescribed ciprofloxacin or co-amoxiclav and lower odds of re-consultation and re-prescription could be due to the significantly increased rates of sepsis hospitalisation (ciprofloxacin) and death (co-amoxiclav) in these group, preventing patients' re-presenting to primary care. We therefore combined these three outcomes and found that 7.3% of patients prescribed nitrofurantoin or trimethoprim re-consulted or were hospitalised for sepsis or died, compared to 6.4% of patients prescribed ciprofloxacin or co-amoxiclav, with an adjusted OR for the combined outcome of 0.82 (95% CI 0.74-0.90).

Table 5.3. ORs and 95% CIs for outcomes in patients prescribed nitrofurantoin versus amoxicillin, cefalexin, ciprofloxacin or co-amoxiclav.

Re-consultation and re-prescription within 14 days	Number (%) of events	Crude OR	Adjusted OR* (95% CI)	p-value
Nitrofurantoin	1575 (6.2)	Reference	Reference	Reference
Amoxicillin	357 (6.0)	0.96	1.02 (0.90 - 1.16)	0.740
Cefalexin	409 (5.4)	0.87	0.96 (0.85 - 1.09)	0.540
Ciprofloxacin	134 (3.5)	0.54	0.58 (0.48 - 0.70)	<0.001
Co-amoxiclav	314 (5.7)	0.91	0.86 (0.74 - 0.99)	0.040
Hospitalised for UTI within 14 days				
Nitrofurantoin	398 (1.6)	Reference	Reference	Reference
Amoxicillin	105 (1.8)	1.12	0.92 (0.73 - 1.16)	0.477
Cefalexin	120 (1.6)	1.01	0.86 (0.69 - 1.06)	0.159
Ciprofloxacin	88 (2.3)	1.46	1.20 (0.92 - 1.56)	0.185
Co-amoxiclav	112 (2.0)	1.30	1.05 (0.83 - 1.34)	0.672
Hospitalised for sepsis within 14 days				
Nitrofurantoin	28 (0.1)	Reference	Reference	Reference
Amoxicillin	8 (0.1)	1.21	0.99 (0.44 - 2.20)	0.976
Cefalexin	17 (0.2)	2.04	1.76 (0.94 - 3.30)	0.078
Ciprofloxacin	16 (0.4)	3.76	3.12 (1.65 - 5.92)	<0.001
Co-amoxiclav	14 (0.3)	2.30	1.89 (0.98 - 3.65)	0.058
Hospitalised for AKI within 14 days				
Nitrofurantoin	117 (0.5)	Reference	Reference	Reference
Amoxicillin	43 (0.7)	1.56	1.13 (0.79 - 1.62)	0.489
Cefalexin	39 (0.5)	1.12	0.83 (0.57 - 1.20)	0.319
Ciprofloxacin	43 (1.1)	2.43	1.71 (1.18 - 2.48)	0.004
Co-amoxiclav	38 (0.7)	1.50	1.03 (0.71 - 1.51)	0.865
Death within 28 days				
Nitrofurantoin	202 (0.8)	Reference	Reference	Reference
Amoxicillin	89 (1.5)	1.88	1.51 (1.16 - 1.97)	0.002
Cefalexin	101 (1.3)	1.69	1.41 (1.10 - 1.82)	0.007
Ciprofloxacin	45 (1.2)	1.47	1.27 (0.90 - 1.78)	0.168
Co-amoxiclav	90 (1.6)	2.07	1.63 (1.24 - 2.14)	<0.001

*Odds ratios adjusted for age, Index of Multiple Deprivation score quintile, Charlson score, and the presence or absence of a Read code indicating coronary heart disease, renal disease, respiratory disease, type 2 diabetes mellitus, heart failure, peripheral arterial disease, and stroke, gender, dementia, liver disease, rheumatoid arthritis, cancer, urinary incontinence or a urinary catheter, and polypharmacy.

Table 5.4. ORs and 95% CIs for outcomes in patients prescribed trimethoprim versus amoxicillin, cefalexin, ciprofloxacin or co-amoxiclav.

Re-consultation and re-prescription within 14 days	Number (%) of events	Crude OR	Adjusted OR* (95% CI)	p-value
Trimethoprim	4809 (6.4)	Reference	Reference	Reference
Amoxicillin	357 (6.0)	0.93	0.97 (0.86 - 1.09)	0.570
Cefalexin	409 (5.4)	0.84	0.91 (0.82 - 1.02)	0.098
Ciprofloxacin	134 (3.5)	0.53	0.55 (0.46 - 0.65)	<0.001
Co-amoxiclav	314 (5.7)	0.88	0.81 (0.71 - 0.93)	0.002
Hospitalised for UTI within 14 days				
Trimethoprim	1234 (1.6)	Reference	Reference	Reference
Amoxicillin	105 (1.8)	1.07	0.88 (0.72 - 1.09)	0.250
Cefalexin	120 (1.6)	0.97	0.82 (0.68 - 1.00)	0.053
Ciprofloxacin	88 (2.3)	1.40	1.15 (0.90 - 1.47)	0.252
Co-amoxiclav	112 (2.0)	1.24	1.01 (0.82 - 1.26)	0.901
Hospitalised for sepsis within 14 days				
Trimethoprim	96 (0.1)	Reference	Reference	Reference
Amoxicillin	8 (0.1)	1.05	0.82 (0.39 - 1.72)	0.604
Cefalexin	17 (0.2)	1.77	1.47 (0.86 - 2.50)	0.161
Ciprofloxacin	16 (0.4)	3.25	2.60 (1.51 - 4.49)	<0.001
Co-amoxiclav	14 (0.3)	1.99	1.57 (0.89 - 2.79)	0.122
Hospitalised for AKI within 14 days				
Trimethoprim	609 (0.8)	Reference	Reference	Reference
Amoxicillin	43 (0.7)	0.89	0.69 (0.50 - 0.95)	0.022
Cefalexin	39 (0.5)	0.64	0.50 (0.36 - 0.70)	<0.001
Ciprofloxacin	43 (1.1)	1.38	1.04 (0.75 - 1.44)	0.831
Co-amoxiclav	38 (0.7)	0.85	0.63 (0.45 - 0.88)	0.007
Death within 28 days				
Trimethoprim	724 (1.0)	Reference	Reference	Reference
Amoxicillin	89 (1.5)	1.55	1.37 (1.09 - 1.73)	0.008
Cefalexin	101 (1.3)	1.40	1.28 (1.02 - 1.60)	0.030
Ciprofloxacin	45 (1.2)	1.21	1.15 (0.83 - 1.59)	0.397
Co-amoxiclav	90 (1.6)	1.71	1.48 (1.16 - 1.88)	0.001

*Odds ratios adjusted for age, Index of Multiple Deprivation score quintile, Charlson score, and the presence or absence of a Read code indicating coronary heart disease, renal disease, respiratory disease, type 2 diabetes mellitus, heart failure, peripheral arterial disease, and stroke, gender, dementia, liver disease, rheumatoid arthritis, cancer, urinary incontinence or a urinary catheter, and polypharmacy.

Table 5.5. Propensity-score matched analyses comparing outcomes between nitrofurantoin, trimethoprim and other antibiotics.

	Amoxicillin (n=5751) versus nitrofurantoin (n=17,253)		Cefalexin (n=7200) versus nitrofurantoin (n=21,600)		Ciprofloxacin (n=3717) versus nitrofurantoin (n=11,151)		Co-amoxiclav (n=5262) versus nitrofurantoin (n=15,786)	
Outcomes	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Re-consultation and re-prescription within 14 days	0.96 (0.82-1.13)	0.620	0.85 (0.75-0.98)	0.020	0.48 (0.38-0.61)	<0.001	0.77 (0.64-0.93)	0.006
Hospitalised for UTI within 14 days	0.86 (0.61-1.21)	0.393	0.96 (0.78-1.18)	0.673	0.84 (0.57-1.26)	0.408	0.94 (0.68-1.31)	0.731
Hospitalised for sepsis within 14 days	1.09 (0.49-2.45)	0.833	1.89 (1.03 - 3.47)	0.038	3.21 (1.59-6.50)	0.001	1.91 (0.98-3.73)	0.058
Hospitalised for AKI within 14 days	1.16 (0.81-1.68)	0.411	0.55 (0.23-1.31)	0.175	1.53 (0.49-4.79)	0.457	0.87 (0.40-1.90)	0.727
Death within 28 days	1.50 (1.16-1.94)	0.002	1.44 (1.12 – 1.85)	0.004	1.18 (0.83-1.68)	0.353	1.39 (0.93-2.07)	0.108
	Amoxicillin (n=5751) versus trimethoprim (n=17,253)		**Cefalexin (n=7200) versus trimethoprim (n=21,600)**		**Ciprofloxacin (n=3717) versus trimethoprim (n=11,151)**		**Co-amoxiclav (n=5262) versus trimethoprim (n=15,786)**	
Outcomes	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Re-consultation and re-prescription within 14 days	0.87 (0.75 – 1.01)	0.076	0.80 (0.70 – 0.91)	<0.001	0.54 (0.43 – 0.70)	<0.001	0.74 (0.62 – 0.89)	0.002
Hospitalised for UTI within 14 days	0.73 (0.52 – 1.01)	0.056	0.84 (0.68 – 1.03)	0.089	0.91 (0.61 – 1.36)	0.647	0.91 (0.66 – 1.26)	0.584
Hospitalised for sepsis within 14 days	1.04 (0.47 – 2.33)	0.917	0.32 (0.04 – 2.98)	0.319	3.21 (1.59 – 6.50)	0.001	3.01 (1.43 – 6.31)	0.004
Hospitalised for AKI within 14 days	0.58 (0.41 – 0.81)	0.002	0.22 (0.09 – 0.53)	<0.001	0.88 (0.29 – 2.72)	0.826	0.42 (0.20 – 0.91)	0.028
Death within 28 days	1.24 (0.97 – 1.60)	0.091	1.08 (0.75 – 1.56)	0.665	1.04 (0.74 – 1.47)	0.823	1.13 (0.76 – 1.67)	0.548

Variables included in the propensity score model were age, Index of Multiple Deprivation score quintile, Charlson score, and the presence or absence of a Read code indicating coronary heart disease, renal disease, respiratory disease, diabetes, heart failure, peripheral arterial disease, and stroke, gender, dementia, liver disease, rheumatoid arthritis, cancer, urinary incontinence or a urinary catheter, and polypharmacy.

Odds ratios estimated using a mixed effect logistic regression model with the general practice included as a random effect to account for clustering.

5.4 Discussion

Our results show that 6% of older adults empirically treated in primary care for a UTI re-consulted and were re-prescribed antibiotics, 2.5% were hospitalised for UTI, sepsis, or AKI, and 1% died. Patients with co-morbid conditions, polypharmacy and renal impairment had greater odds of broad-spectrum antibiotic prescribing. Patients prescribed ciprofloxacin or co-amoxiclav had lower odds of re-consultation and re-prescription. Patients prescribed ciprofloxacin had greater odds of sepsis hospitalisation, and those prescribed amoxicillin, cefalexin or co-amoxiclav had greater odds of death. These associations persisted in propensity-score matched analyses. Patients prescribed amoxicillin, cefalexin or co-amoxiclav had lower odds of hospitalisation for AKI when compared to trimethoprim, but not compared to nitrofurantoin. Overall, compared to nitrofurantoin, we found no evidence that amoxicillin, cefalexin, ciprofloxacin or co-amoxiclav were associated with a reduction in the risk of UTI-related hospitalisation or death.

5.4.1 Results in context

Previous research showed that age, gender, social deprivation and co-morbid conditions were associated with increased rates of overall antibiotic prescribing, and age, insurance status, clinical setting, and clinician specialty were associated with increased rates of broad-spectrum antibiotic prescribing (78, 79). We add to previous work by identifying other co-morbid conditions that are associated with broad-spectrum antibiotic prescribing for UTI. We found that generally worsening health, reflected by increasing Charlson score or lower eGFR, had a relatively graded association with the odds of broad-spectrum antibiotic prescribing for UTI. This confirms the

hypothesis generated from previous qualitative work that suggested primary care clinicians were more likely to prescribe broad-spectrum antibiotics to sicker, frailer patients, and furthers our understanding of prescribing behaviour in clinical practice (77).

Our findings suggest that patients prescribed ciprofloxacin or co-amoxiclav had lower odds of re-consultation and re-prescription, which may reflect lower odds of treatment failure. This was in contrast to previous trials that generally showed similar clinical cure rates between narrow and broad-spectrum agents (145-147). This association remained significant when we combined the re-consultation and re-prescription outcome with hospitalisation for sepsis or death, suggesting that, despite the higher rates of sepsis and death in the ciprofloxacin and co-amoxiclav group, there remain a group of patients who were less likely to experience treatment failure with these agents. However, patients in the nitrofurantoin and trimethoprim groups who re-consulted and received another antibiotic prescription may have done so because of an adverse event or intolerance, rather than for treatment failure.

Amoxicillin, cefalexin and co-amoxiclav were associated with lower odds of AKI hospitalisation compared to trimethoprim. There is a mechanistic explanation for this finding. Trimethoprim (and trimethoprim-sulfamethoxazole) increases the risk of hyperkalaemia in patients co-prescribed renin-angiotensin system drugs (84) and in older adults in general,(80) and thus, it is the hyperkalaemia that likely leads to an AKI-coded hospital admission. Ciprofloxacin was associated with an increased risk of AKI hospitalisation compared to nitrofurantoin, which supports

previous findings of a two-fold increase in the risk of AKI associated with fluoroquinolone use (151).

We found an increase in the odds of sepsis in patients prescribed ciprofloxacin. Almost 6% of the ciprofloxacin group had a Charlson score of ≥6 and 55% were male, compared to 3% and 24% of the nitrofurantoin group. Therefore, this finding may be because these patients were sicker or had more complicated infection that resulted in a degree of residual confounding. It may also relate to higher levels of prior fluoroquinolone exposure, previously shown to be associated with increased sepsis risk, possibly due to disruption of the gut microbiome and subsequent dysregulation of the immune response to infection (152).

Our finding of an increased risk of death in patients prescribed amoxicillin, cefalexin or co-amoxiclav is intriguing. There are several possible explanations. The antibiotics themselves may increase the risk of death, particularly in this cohort, many of whom had multiple co-morbidities and were prescribed multiple other drugs. This is not implausible; co-amoxiclav use is associated with acute liver injury, which may result in serious and protracted illness in elderly co-morbid patients (153). It may also be due to antimicrobial resistance. For example, the 2017 English Surveillance Programme for Antimicrobial Utilisation and Resistance report showed that 15% of community-acquired E.coli UTIs were resistant to co-amoxiclav, 10% to cefalexin, but only 2% to nitrofurantoin (Amoxicillin resistance was not reported) (14). However, this does not explain why co-amoxiclav or cefalexin had greater odds of death than trimethoprim, where resistance rates in England are around 30%. Therefore, some of these findings could

be due to residual confounding. Patients prescribed co-amoxiclav or cefalexin may have been less healthy, presented with more severe illness, and were therefore more likely to experience an adverse outcome irrespective of the prescribed antibiotic. Thus, it may be more appropriate to regard the exposure as a combination of patient and prescription factors, which is why we have related associations to the “patients prescribed cefalexin”, rather than the prescription alone.

5.4.2 Strengths and limitations

We used data from a general practice database that is broadly representative of the UK population (106). Cohort entry was dependent on presentation and empirical treatment of UTI in primary care, and thus reduced indication bias. We also reduced indication bias by repeating the analyses with propensity-score matching and achieving adequate balance of baseline characteristics across the groups.

Our study has some limitations. We attempted to capture patients presenting with UTI but had no microbiological data to support this. However, whilst a limitation, this may be more representative of clinical practice as highlighted by a survey of women in the UK that found that only around 25% of those who presented to their GP with urinary symptoms had urine sent for laboratory analysis (15). Our outcomes, particularly sepsis and AKI, relied on coding and were not microbiologically or biochemically confirmed. We were unable to determine precise reasons for re-consultation and re-prescription and acknowledge that not all of these events may have been due to treatment failure. Based on current definitions (18), some patients may have presented with ‘complicated’ UTI, for which the

recommended treatment includes some of the alternative antibiotics assessed. Therefore, we have not commented on the appropriateness (or not) of the prescribed agent. Our findings are based on prescriptions and not on dispensed or ingested drugs. Finally, despite our design, differential coding, indication bias and residual confounding may have affected our findings.

5.5 Implications

Our findings demonstrate the clinical burden and workload associated with UTI in older people. Around 16% of our cohort had at least one empirically treated UTI over a median follow-up of five years. There are around 12 million people aged 65 and over in the UK. Therefore, over 5 years, around two million may present with a UTI and receive an antibiotic prescription, of whom 115,000 may re-consult and receive another antibiotic prescription, 58,000 may be hospitalised for a UTI-related cause, and 20,000 may die. These estimates of UTI burden highlight the need for interventions that improve prevention and management in older people. The estimates for hospitalisation and mortality suggest that presenting to primary care with a suspected UTI may be an indicator of an increased risk of a short-term adverse event. This highlights the need for better diagnostic tests and processes that enable UTI to be reliably ruled in or out at the point of care, and, if ruled out, prompt assessment for other causes of the clinical presentation.

Our findings also highlight the challenges associated with selecting antibiotics for older patients with suspected UTI. Given the association with increased risk of AKI, we suggest trimethoprim prescribing is reduced in

older adults. Compared to nitrofurantoin, we found no evidence that prescribing amoxicillin, cefalexin, ciprofloxacin or co-amoxiclav reduced the risk of hospitalisation or death, suggesting that the perceived aim expressed by clinicians in previous qualitative work was not being achieved, and thus supporting further reductions in prescribing of these agents, even in frailer, sicker patients.

Future research should use qualitative methods to explore and understand reasons for continued use of broad-spectrum antibiotics for UTI in primary care. There is also a need for research that provides clinicians with information on which patients are most likely to benefit from broad-spectrum antibiotic use. This would ideally require a large-scale prognostic study with prospective data collected on structured case-report forms to ensure capture of variables that may had resulted in residual confounding in our study, for example, temperature, heart rate, self-reported severity of symptoms. A well-conducted prognostic study would widen understanding of which variables (either alone or in combination) best predict pre-specified adverse outcomes in patients with microbiologically confirmed UTI and help target antibiotics more appropriately.

5.6 Conclusions

A consistent finding in this study was that, compared to nitrofurantoin, patients prescribed ciprofloxacin or co-amoxiclav were less likely to re-consult and receive a further antibiotic prescription. This may reflect a reduced risk of treatment failure. Our analyses also suggested that patients prescribed ciprofloxacin were more likely to be hospitalised for sepsis and patients prescribed co-amoxiclav were more likely to die. Combining the re-

consultation and re-prescription outcome with hospitalisation for sepsis or death found that despite the higher rates of sepsis and death in the ciprofloxacin and co-amoxiclav group, some patients were still less likely to experience treatment failure with these agents. However, residual confounding, and the lack of microbiology data with which to ascertain resistance-related outcomes, significantly limit the conclusions that can be drawn from these findings.

6 Association between antibiotic prescription duration and adverse outcomes in older men

In chapter 4, we described trends in the duration of antibiotic treatment for UTI in older men in primary care. We found that the proportion of older men with UTI prescribed guideline congruent 7-day antibiotic treatment increased between 2004 and 2014. However, in 2014, 30% of older men with UTI received a prescription for a different duration. In this chapter, we present analyses on whether these different durations of antibiotic treatment had an impact on the risk of treatment failure, UTI-related hospitalisation, or death, in the 14-28 days following the incident UTI. We restricted these analyses to older *men* as this is where the evidence is lacking, unlike in older women, where meta-analyses of randomised trials support the recommended 3-day treatment period and thus, make it unlikely that observational data would add significantly to the current evidence base.

6.1 Background

Around 20% of all UTIs occur in men (154). The optimal duration of antibiotic treatment for UTI in older men is not known (155). Most clinical guidelines recommend seven days of antibiotic therapy (19, 49, 67) but this recommendation is largely based on expert consensus due to the lack of data in this area. Previous randomised trials investigating different antibiotic durations for UTI in men have focussed on febrile (68, 69) or complicated UTI (70, 71), or men with spinal cord injury (72), and are not generalizable

to the majority of men with community-acquired UTI seen and treated in primary care.

Antimicrobial stewardship policies and guidelines recommend prescribing the minimum duration of antibiotic therapy required for clinical resolution (115, 156). A recent observational study found no difference in the rate of clinical recurrence between US male Veterans with UTI prescribed long course (≥7 days) versus short course therapy (<7 days) (73). However, this study uses outpatient data alone, and may have missed men who were subsequently hospitalised with UTI-related emergencies such as sepsis or acute kidney injury.

We therefore used the CPRD to estimate risk of adverse outcomes in older men prescribed different durations of antibiotic treatment for UTI in primary care. Our aim was to assess whether short course therapy was associated with an increased risk of treatment failure, hospitalisation for UTI, sepsis or acute kidney injury (AKI), or death, to determine the potential for safe and effective reduction of antibiotic treatment duration.

6.2 Methods

This was a retrospective cohort study. Men were eligible for inclusion if, between 1st January 2010 and 31st December 2016, they were ≥65 years old, had linked hospital data and more than one day of CPRD follow-up. We excluded men with temporary registrations or gaps in their data coverage. Follow-up began on the latest of study start date, the patient's 65th birthday or 28 weeks after the patient first registered at the practice. Follow-up ended at the earliest of study end date, death, last day of available CPRD data, or

28 days after an incident UTI event. We identified eligible men with a Read code indicating an incident primary care presentation with a suspected UTI (code list 1 in Figure 3.1) and a same-day prescription code indicating empirical prescribing of a relevant antibiotic. We defined 'incident' as a consultation occurring in a patient without a UTI-related Read code or trimethoprim or nitrofurantoin prescription in the preceding 90 days. We used the first incident episode during each patient's follow-up period.

We used prescription data for daily dosing and total quantity prescribed to calculate duration of antibiotic prescriptions as a proxy for duration of treatment. We excluded prescriptions with durations >14 days as it is unlikely that these were prescribed for an acute UTI, and more likely that they reflected treatment for prostatitis. We also excluded prescription durations of 1, 2, 4, and 6 days, as together these represented <1% of all calculated durations and were potentially unreliable. The final exposure groups were 3, 5, 7 and 8-14 days.

We used primary care demographic and clinical codes to describe baseline characteristics for patients by prescription duration. First, we assessed the impact of different prescription durations by using multivariable logistic regression to estimate ORs and 95% CIs for the risk of each outcome in those prescribed 7-day therapy, compared to those prescribed 3, 5 or 8-14 days therapy. Outcomes were re-consultation and re-prescription within 14 days following the incident UTI (proxy for treatment failure), hospitalisation for UTI, sepsis or AKI within 14 days following the incident UTI, and death within 28 days following the incident UTI. More detail on the justification and ascertainment of these outcomes is provided in section 3.7.

Second, we compared outcomes in men prescribed 3-day versus 7-day therapy using propensity score matching to improve balance of baseline characteristics across comparison groups. We chose 7 days as the reference standard as it is currently the recommended treatment duration for male UTI in the UK, and 3 days as the comparator as it is a potentially acceptable and feasible shorter duration of therapy, given that 3-day therapy is widely used to treat UTI in women. Prescriptions for duration of 5 days or 8-14 days were not included in this analysis.

We used mixed effects models in in the multivariable logistic regression analysis and the propensity score matched analysis, with the general practice included as a random effect to account for clustering. We repeated the analyses restricting to men prescribed trimethoprim, the most commonly used antibiotic for UTI in the UK during the study period. Finally, we calculated an E-value for our estimated associations (157). The E-value is defined as the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the exposure and the outcome to fully explain away a specific exposure-outcome association, conditional on the measured covariates. A large E-value implies that considerable unmeasured confounding would be needed to explain away an effect estimate. A small E-value implies little unmeasured confounding would be needed to explain away an effect estimate.

6.3 Results

From a cohort of 360,640 men aged 65 and over with a median follow-up of 4.9 years (IQR 3.1-6.4), we identified 33,745 (9.4%) with an incident UTI treated with a relevant antibiotic (Figure 6.1). Of these, we were able to

assign an antibiotic prescription duration to 32,593 (96.6%) incident UTIs. The median age at the time of incident UTI was 77 years (IQR 70 - 83). In total, 1966 (6.0%) men were prescribed amoxicillin, 2002 (6.1%) ciprofloxacin, 2060 (6.3%) cefalexin, 2143 (6.6%) co-amoxiclav, 5724 (17.6%) nitrofurantoin, and 18,698 (57.4%) trimethoprim. Guideline concordant 7-day therapy was prescribed to 20,729 (63.6%) men, 3-day therapy to 2498 (7.7%), 5-day therapy to 6254 (19.2%), and 8-14 days to 3112 (9.5%). Baseline characteristics were broadly similar across the groups (Table 6.1).

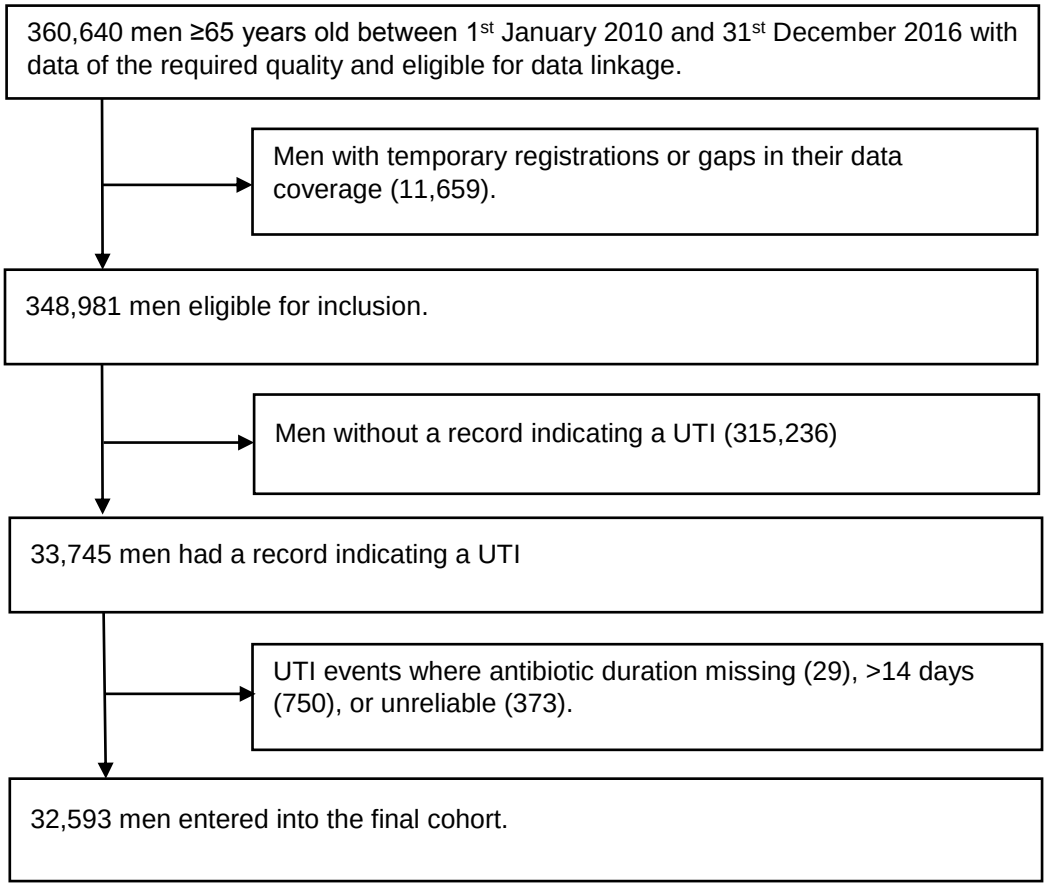


Figure 6.1. Flow of men from initial identification in the database to final cohort

Table 6.1. Baseline characteristics according to antibiotic prescription duration. Values are numbers (%) unless otherwise stated

	Antibiotic prescription duration			
	3 days	5 days	7 days	8-14 days
Number (%) of prescriptions	2498 (7.7)	6254 (19.2)	20729 (63.6)	3112 (9.5)
Mean (SD) age	77.4 (8.0)	77.7 (8.1)	76.9 (7.9)	76.7 (7.8)
Mean (SD) follow-up time (years)	4.6 (1.9)	4.5 (1.9)	4.6 (1.9)	4.6 (2)
Antibiotic choice				
Amoxicillin	12 (0.5)	512 (8.2)	1392 (6.7)	50 (1.6)
Cefalexin	60 (2.4)	262 (4.2)	1133 (5.5)	605 (19.4)
Ciprofloxacin	38 (1.5)	852 (13.6)	649 (3.1)	463 (14.9)
Co-amoxiclav	13 (0.5)	195 (3.1)	1843 (8.9)	92 (3.0)
Nitrofurantoin	241 (9.6)	802 (12.8)	3301 (15.9)	1380 (44.3)
Trimethoprim	2134 (85.0)	3631 (58.1)	12411 (59.9)	522 (16.8)
Index of multiple deprivation decile				
1 or 2 (least deprived)	527 (21.1)	1670 (26.7)	5217 (25.2)	890 (28.6)
3 or 4	552 (22.1)	1494 (23.9)	5016 (24.2)	764 (24.6)
5 or 6	599 (24.0)	1398 (22.4)	4568 (22.0)	655 (21.0)
7 or 8	427 (17.1)	945 (15.1)	3437 (16.6)	466 (15.0)
9 or 10 (most deprived)	393 (15.7)	747 (11.9)	2491 (12.0)	337 (10.8)
Housebound	101 (4.0)	251 (4.0)	641 (3.1)	107 (3.4)
Respiratory disease	478 (19.1)	1159 (18.5)	3934 (19.0)	629 (20.2)
Cardiac failure	178 (7.1)	438 (7.0)	1365 (6.6)	202 (6.5)
Dementia	160 (6.4)	399 (6.4)	1080 (5.2)	158 (5.1)
Peripheral vascular disease	218 (8.7)	573 (9.2)	1695 (8.2)	248 (8.0)
Renal disease	620 (24.8)	1560 (24.9)	4758 (23.0)	755 (24.3)
Rheumatoid arthritis	47 (1.9)	105 (1.7)	374 (1.8)	53 (1.7)
Cancer	486 (19.5)	1306 (20.9)	4225 (20.4)	689 (22.1)
Stroke	320 (12.8)	856 (13.7)	2542 (12.3)	370 (11.9)
Diabetes	576 (23.1)	1411 (22.6)	4659 (22.5)	677 (21.8)
Liver disease	17 (0.7)	36 (0.6)	122 (0.6)	23 (0.7)
Ischaemic heart disease	674 (27.0)	1622 (25.9)	5347 (25.8)	811 (26.1)
Urinary catheter	182 (7.3)	626 (10.0)	1783 (8.6)	325 (10.4)
Urinary incontinence	184 (7.4)	496 (7.9)	1393 (6.7)	225 (7.2)
Polypharmacy	1048 (42.0)	2462 (39.4)	7859 (37.9)	1123 (36.1)
Benign prostatic hyperplasia	760 (30.4)	1953 (31.2)	6341 (30.6)	1033 (33.2)
Prostate cancer	213 (8.5)	626 (10.0)	2071 (10.0)	331 (10.6)
eGFR				
60-90	1569 (62.8)	3909 (62.5)	13573 (65.5)	2016 (64.8)
45-59	514 (20.6)	1269 (20.3)	4101 (19.8)	600 (19.3)
30-44	223 (8.9)	563 (9.0)	1735 (8.4)	280 (9.0)
15-29	69 (2.8)	201 (3.2)	478 (2.3)	93 (3.0)
<15	19 (0.8)	48 (0.8)	74 (0.4)	11 (0.4)
missing	104 (4.2)	264 (4.2)	768 (3.7)	112 (3.6)
Charlson score				
0	657 (26.3)	1594 (25.5)	5819 (28.1)	836 (26.9)
1	484 (19.4)	1254 (20.1)	4067 (19.6)	579 (18.6)
2	512 (20.5)	1230 (19.7)	3958 (19.1)	613 (19.7)
3	334 (13.4)	902 (14.4)	2881 (13.9)	450 (14.5)
4	219 (8.8)	522 (8.3)	1759 (8.5)	258 (8.3)
5	141 (5.6)	351 (5.6)	1131 (5.5)	189 (6.1)
≥6	151 (6.0)	401 (6.4)	1114 (5.4)	187 (6.0)

6.3.1 Outcomes according to treatment duration

A total of 2007 (6.2%) men re-consulted and received another antibiotic prescription within 14 days following the incident UTI. Compared to 7-day therapy, there was a graded association between prescription duration and odds of re-consultation and re-prescription with adjusted ORs of 1.48 (95% CI 1.25-1.74) for 3-day therapy, 1.18 (95% CI 1.04-1.33) for 5-day therapy, and 0.80 (95% CI 0.67-0.96) for 8-14 day therapy (Table 6.2).

A total of 817 (2.5%) men were hospitalised for UTI, 89 (0.3%) hospitalised for sepsis, and 449 (1.4%) hospitalised for AKI within 14 days following the incident UTI. There were no significant associations between antibiotic prescription duration and hospitalisation for UTI or sepsis. Compared to 7-days, 3 and 8-14 day prescriptions were associated with reduced odds of hospitalisation for AKI (adjusted OR for 3-days 0.66, 95% CI 0.45-0.97, adjusted OR for 8-14 days 0.63, 95% CI 0.40-0.99). A total of 419 (1.3%) men died within 28 days of the incident UTI. There were no significant associations between antibiotic prescription duration and odds of death.

6.3.2 Propensity score matched comparison of 7-day versus 3-day therapy

We matched 2392 men prescribed 3-day therapy to 7182 men prescribed 7-day therapy. Inspection of jitter plots and histograms suggested matching had improved balance of covariates across the two groups. Standardised mean differences were all less than 0.1 (Table 6.3). 3-day therapy was associated with increased odds of re-consultation and re-prescription (OR

1.52, 95% CI 1.25-1.85) and reduced odds of hospitalisation for AKI (OR 0.62, 95% CI 0.42-0.93) (Table 6.4).

Table 6.2. Adjusted ORs and 95% CIs for each outcome by antibiotic prescription duration

Re-consultation and re-prescription within 14 days	Number of prescriptions	Number (%) of events	Crude OR	Adjusted OR* (95% CI)	p-value
7 days	20729	1225 (5.9)	Reference	Reference	Reference
3 days	2498	198 (7.9)	1.37	1.48 (1.25 - 1.74)	<0.001
5 days	6254	416 (6.7)	1.13	1.18 (1.04 - 1.33)	0.009
8-14 days	3112	168 (5.4)	0.91	0.80 (0.67 - 0.96)	0.020
Hospitalised for UTI within 14 days					
7 days	20729	543 (2.6)	Reference	Reference	Reference
3 days	2498	61 (2.4)	0.93	0.87 (0.66 - 1.15)	0.331
5 days	6254	147 (2.4)	0.89	0.82 (0.67 - 1.01)	0.063
8-14 days	3112	66 (2.1)	0.81	0.81 (0.61 - 1.08)	0.152
Hospitalised for sepsis within 14 days					
7 days	20729	53 (0.3)	Reference	Reference	Reference
3 days	2498	4 (0.2)	0.63	0.63 (0.22 - 1.75)	0.366
5 days	6254	13 (0.2)	0.81	0.63 (0.34 - 1.19)	0.159
8-14 days	3112	9 (0.3)	1.13	0.85 (0.38 - 1.90)	0.700
Hospitalised for AKI within 14 days					
7 days	20729	307 (1.5)	Reference	Reference	Reference
3 days	2498	30 (1.2)	0.82	0.66 (0.45 - 0.97)	0.033
5 days	6254	88 (1.4)	0.97	0.84 (0.66 - 1.08)	0.182
8-14 days	3112	24 (0.8)	0.53	0.63 (0.40 - 0.99)	0.047
Death within 28 days					
7 days	20729	252 (1.2)	Reference	Reference	Reference
3 days	2498	37 (1.5)	1.22	1.12 (0.78 - 1.61)	0.522
5 days	6254	89 (1.4)	1.17	1.01 (0.78 - 1.31)	0.917
8-14 days	3112	41 (1.3)	1.08	1.21 (0.83 - 1.78)	0.316

*Odds ratios adjusted for the choice of antibiotic, age, Index of Multiple Deprivation score quintile, Charlson comorbidity score, polypharmacy, and the presence or absence of a record indicating diabetes, dementia, coronary heart disease, stroke, cancer, heart failure, liver disease, renal disease, urinary incontinence, urinary catheter, benign prostatic hyperplasia, and prostate cancer.

Table 6.3. Baseline characteristics before and after propensity-score matching of men prescribed three versus seven days of antibiotics. Values are numbers (%) unless otherwise stated

	Before matching			After matching		
	3 days	7 days	SMD	3 days	7 days	SMD
Number (%) of prescriptions	2498 (7.7)	20729 (63.6)		2394 (25.0)	7182 (75.0)	
Mean (SD) age	77.4 (8.0)	76.9 (7.9)	0.071	77.5 (8.0)	77.4 (8.0)	0.008
Antibiotic choice						
Amoxicillin	12 (0.5)	1392 (6.7)	-0.887	12 (0.5)	39 (0.5)	-0.006
Cefalexin	60 (2.4)	1133 (5.5)	-0.202	57 (2.4)	166 (2.3)	0.005
Ciprofloxacin	38 (1.5)	649 (3.1)	-0.127	38 (1.6)	109 (1.5)	0.006
Co-amoxiclav	13 (0.5)	1843 (8.9)	-1.141	13 (0.5)	36 (0.5)	0.006
Nitrofurantoin	241 (9.6)	3301 (16.0)	-0.217	231 (9.6)	703 (9.8)	-0.005
Trimethoprim	2134 (85.4)	12411 (60.0)	0.727	2043 (85.3)	6129 (85.3)	0.000
IMD decile						
1 or 2 (least deprived)	527 (21.1)	5217 (25.2)		498 (20.8)	1497 (20.8)	
3 or 4	552 (22.1)	5016 (24.2)		529 (22.1)	1545 (21.5)	
5 or 6	599 (24.0)	4568 (22.0)		578 (24.1)	1703 (23.7)	
7 or 8	427 (17.1)	3437 (16.6)		408 (17.0)	1368 (19.0)	
9 or 10 (most deprived)	393 (15.7)	2491 (12.0)	0.147	381 (15.9)	1069 (14.9)	0.000
Housebound	101 (4.0)	641 (3.1)	0.052	100 (4.2)	296 (4.1)	0.003
Respiratory disease	478 (19.1)	3934 (19.0)	0.002	460 (19.2)	1371 (19.1)	0.003
Cardiac failure	178 (7.1)	1365 (6.6)	0.025	178 (7.4)	527 (7.3)	0.004
Dementia	160 (6.4)	1080 (5.2)	0.044	151 (6.3)	469 (6.5)	-0.009
Peripheral vascular disease	218 (8.7)	1695 (8.2)	0.018	213 (8.9)	622 (8.7)	0.008
Renal disease	620 (24.8)	4758 (23.0)	0.047	618 (25.8)	1764 (24.6)	0.029
Rheumatoid arthritis	47 (1.9)	374 (1.8)	-0.002	44 (1.8)	129 (1.8)	0.003
Cancer	486 (19.5)	4225 (20.4)	-0.022	476 (19.9)	1408 (19.6)	0.007
Stroke	320 (12.8)	2542 (12.3)	0.023	319 (13.3)	935 (13.0)	0.009
Diabetes	576 (23.1)	4659 (22.5)	0.020	576 (24.1)	1692 (23.6)	0.012
Liver disease	17 (0.7)	122 (0.6)	0.016	17 (0.7)	51 (0.7)	0.000
Ischaemic heart disease	674 (27.0)	5347 (25.8)	0.028	667 (27.9)	1983 (27.6)	0.006
Urinary catheter	182 (7.3)	1783 (8.6)	-0.053	174 (7.3)	498 (6.9)	0.013
Urinary incontinence	184 (7.4)	1393 (6.7)	0.018	175 (7.3)	512 (7.1)	0.007
Polypharmacy	1048 (42.0)	7859 (37.9)	0.086	1033 (43.1)	3080 (42.9)	0.005
Prostatic hyperplasia	760 (30.4)	6341 (30.6)	-0.006	743 (31.0)	2138 (29.8)	0.027
Prostate cancer	213 (8.5)	2071 (10.0)	-0.056	207 (8.6)	618 (8.6)	0.002
eGFR						
60-90	1569 (62.8)	13573 (65.5)		1569 (65.5)	4740 (66)	
45-59	514 (20.6)	4101 (19.8)		514 (21.5)	1558 (21.7)	
30-44	223 (8.9)	1735 (8.4)		223 (9.3)	685 (9.5)	
15-29	69 (2.8)	478 (2.3)		69 (2.9)	172 (2.4)	
<15	19 (0.8)	74 (0.4)		19 (0.8)	27 (0.4)	
missing	104 (4.2)	768 (3.7)	0.064	0 (0)	0 (0)	0.029
Charlson score						
0	657 (26.3)	5819 (28.1)		594 (24.8)	1894 (26.4)	
1	484 (19.4)	4067 (19.6)		463 (19.3)	1385 (19.3)	
2	512 (20.5)	3958 (19.1)		499 (20.8)	1423 (19.8)	
3	334 (13.4)	2881 (13.9)		328 (13.7)	1003 (14)	
4	219 (8.8)	1759 (8.5)		218 (9.1)	623 (8.7)	
5	141 (5.6)	1131 (5.5)		141 (5.9)	425 (5.9)	
≥6	151 (6.0)	1114 (5.4)	0.045	151 (6.3)	429 (6.0)	0.027

Table 6.4. Odds ratios and 95% CIs for each outcome in men matched on their propensity to receive a seven-day antibiotic prescription

	7 day prescriptions	3 day prescriptions		
Outcome	Number (%) of events	Number (%) of events	OR (95% CI)*	p-value
Re-consultation and re-prescription within 14 days	399 (5.6)	192 (8.0)	1.52 (1.25 - 1.85)	<0.001
Hospitalised for UTI within 14 days	209 (2.9)	59 (2.5)	0.81 (0.61 - 1.09)	0.179
Hospitalised for sepsis within 14 days	18 (0.3)	4 (0.2)	0.60 (0.20 - 1.75)	0.350
Hospitalised for AKI within 14 days	131 (1.8)	29 (1.2)	0.62 (0.42 - 0.93)	0.021
Death within 28 days	96 (1.3)	36 (1.5)	1.07 (0.73 - 1.57)	0.729

*Reference = 7 day prescription

Variables included in the propensity score model were choice of antibiotic, age, Index of Multiple Deprivation score quintile, Charlson comorbidity score, polypharmacy, and the presence or absence of a record indicating diabetes, dementia, coronary heart disease, stroke, cancer, heart failure, liver disease, renal disease, urinary incontinence, urinary catheter, benign prostatic hyperplasia, and prostate cancer.

Odds ratios estimated using a mixed effect logistic regression model with the general practice included as a random effect to account for clustering.

6.3.3 Sensitivity analyses

We repeated both analyses restricting to men who received trimethoprim and found that all ORs were consistent with our main analyses. We calculated E-values for the two significant associations in our propensity score matched analysis. The E-value was 2.4 for re-consultation and re-prescription, and 2.6 for AKI hospitalisation, suggesting any unmeasured confounder would require an OR of at least 2.4 for its association with antibiotic prescription duration and outcome, independent of measured confounders, to explain away the observed associations.

6.4 Discussion

We showed, for the first time, that in older men presenting to primary care with a UTI, 3-day antibiotic therapy was associated with a 52% increase in odds of re-consultation and re-prescription that could indicate treatment failure, but was not associated with increased odds of UTI-related hospitalisation or death. We also showed for the first time, an association between 3-day therapy and a 38% reduction in the odds of hospitalisation for AKI.

6.4.1 Results in context

A retrospective observational study of 33,336 index UTIs in US male Veterans found no difference in recurrence rates at 30 days between short and long duration antibiotic therapy (73). Similar to our study, inclusion was based on patients having a relevant diagnostic code and antibiotic prescription, without microbiological confirmation of UTI. However, this

study defined ‘short duration’ as ≤7 days, and 77% of the short duration group received 7-day therapy. Thus, their comparison was ≤7 days versus >7 days, and explains the discrepancy between our finding of increased odds of re-consulting and receiving another antibiotic prescription in short duration (3 or 5-day) versus long duration (7-day) therapy.

Our finding of an association between 3-day antibiotic therapy and reduced odds of AKI could be explained by trimethoprim prescribing. Trimethoprim is associated with hyperkalaemia and AKI in older adults (80), and was prescribed to 85% of men in our matched analysis. Therefore, reduced exposure in the 3-day group may have resulted in reduced rates of AKI.

Few randomised trials have investigated the potential for shorter duration of antibiotic treatment in men with UTI, and those that have focussed on more severe UTI. A Swedish trial of 114 men with febrile UTI showed similar clinical and microbiological cure rates between 14-day and 28-day antibiotic treatment (69). A randomised placebo controlled non-inferiority trial recruited men with febrile UTI from Dutch primary care and emergency departments, and showed 7-day antibiotic treatment was inferior to 14-day treatment in terms of clinical cure rates 10-18 days post UTI (68). In contrast, a US trial of men and women (39% men) with complicated UTI or acute pyelonephritis showed no difference in outcomes between those receiving 5-day versus 10-day antibiotic therapy (70). However, these trials recruited men with more severe UTI than that normally seen in a primary care setting. To the best of our knowledge, no trials have investigated the effect of short duration antibiotic therapy for men presenting to primary care

with symptoms suggestive of UTI, but without fever or other signs of ascending infection.

6.4.2 Strengths and limitations

We used data from a general practice database that is broadly representative of the UK population (106). Cohort entry was dependent on presentation and empirical treatment of UTI in primary care, and thus reduced indication bias. We also reduced indication bias by matching patients on their propensity to receive a 7-day prescription, and achieving adequate balance of covariates across treatment groups.

Our study has important limitations. We attempted to capture patients presenting with UTI but had no microbiological data to support this. However, whilst a limitation, this may also be more representative of clinical practice. Our estimates are based on *prescription* duration and may overestimate actual antibiotic consumption because prescriptions may not have been collected, and if collected, *consumed* antibiotics may have been less than the prescribed amount. Despite careful selection of codes used to identify eligible men, differential use of codes amongst clinicians means we may have included some men who had more complicated UTI or pyelonephritis. Although we found an increase in the rate of UTI-related re-consultation and re-prescription among men prescribed 3-day therapy, we were not able to assess the appropriateness of these events. Some of these events may represent 'treatment failure', but others may reflect unrealistic expectations about the speed of symptom resolution. Therefore, even if symptoms were recovering at a similar rate in those receiving short versus longer duration antibiotic therapy, a higher rate of re-consultation (and

further prescriptions) in those receiving shorter duration therapy may reflect an unrealistic belief that symptoms should have fully resolved by the end of the treatment course. A related limitation is that patients with seemingly "milder" symptoms may have been prescribed three-day therapy with planned follow-up, therefore introducing a degree of "detection bias" if symptoms were not completely resolved. Finally, despite our design, differential coding, indication bias and residual confounding may still have affected our findings. However, our E-values suggest residual confounders would need relatively strong associations between antibiotic duration and outcomes to alter the conclusions from our effect estimates.

6.5 Implications

Our findings suggest it may be possible to safely reduce the duration of antibiotic treatment to 3 days for older men presenting to primary care with a UTI. For patients, shorter duration treatment could mean better adherence and less side effects but a higher rate of treatment failure. Using the propensity score matched event rates and ORs in table 4, we estimate that treating 150 older men with 3-day instead of 7-day therapy, could result in four extra re-consultation and re-prescriptions (numbers needed to harm = 37) and one less AKI hospital admission (numbers needed to treat = 148) (158). For health services, there is potential for significant cost savings from prescription costs alone. The analysis in chapter 4 found that around 7% of a sample of roughly 400,000 men ≥65 were prescribed an antibiotic in primary care for UTI in 2014. Current UK population estimates suggest there are around 5.2 million men aged ≥65 (159). A 7% annual UTI rate equates to around 364,000 UTI events. Based on current prescribing costs reported

in the British National Formulary (3-day trimethoprim = £3.60, 7-day trimethoprim = £10.00, 7-day nitrofurantoin = £9.50), if all men were prescribed 3-days of trimethoprim instead of 7 days, and men who re-consulted were prescribed 7 days of nitrofurantoin, the UK health service could save around £2.2 million a year.

Future research should focus on an adequately powered randomised placebo controlled trial of 3 versus 7 day antibiotic treatment for older men presenting to primary care with a UTI. In line with recent thinking on trials of antibiotic stewardship interventions, the trial should include an efficacy and safety related co-primary outcome (160). Secondary outcomes should include patient reported outcome measures and measures of antibiotic resistance, especially as there is little evidence on whether shorter antibiotic courses affect the risk of subsequent antibiotic resistance. The trial may also offer an opportunity to include a third arm and test the recently debated strategy of symptom guided treatment versus 3 days versus 7 days, to see if antibiotic treatment is effective in those who stop once symptoms have resolved rather than completing the prescribed course (161).

6.6 Conclusions

Our findings suggest that there may be potential to safely reduce the antibiotic treatment duration for older men with UTI in primary care to three days. These findings should be interpreted with caution given the potential for residual confounding and other biases inherent in retrospective studies of routinely collected healthcare data. However, reducing antibiotic treatment duration to three days may reduce antibiotic burden and prescription costs but may also increase the risk of treatment failure. A

definitive randomised trial of short versus standard duration treatment is urgently needed to better understand the benefits and harms of this approach.

7 Association between nitrofurantoin prescribing and adverse outcomes in older people with renal impairment

In this chapter, we report analyses on whether nitrofurantoin is associated with increased risk of treatment failure, UTI-related hospitalisation, or death, in older people with UTI and a history of renal impairment.

7.1 Background

Nitrofurantoin and trimethoprim (alone or with sulfamethoxazole) are the two most commonly prescribed antibiotics for empirical treatment of UTIs and are recommended by clinical guidelines in the UK, USA, and Europe (18, 19). Nitrofurantoin use was initially limited to those with an eGFR ≥60mls/min/1.73m^2, due to concerns about poorer efficacy in patients with lower eGFRs. In 2014, a review of the evidence (87) and a retrospective cohort study (88) prompted the UK Medicines and Healthcare products Regulation Authority to lower the threshold for nitrofurantoin use to an eGFR≥45 mls/min/1.73m^2. However, outcomes following empirical nitrofurantoin prescribing in older adults with a UTI and an eGFR <60 mls/min/1.73m^2 are yet to be fully evaluated. We used data from the CPRD to estimate the risk of treatment failure, hospitalisation for UTI, sepsis or acute kidney injury (AKI), or death, in older patients with an eGFR<60 mls/min/1.73m^2 who were prescribed empirical nitrofurantoin versus

trimethoprim, to inform prescribing decisions and explore if nitrofurantoin prescribing is safe in patients with renal impairment.

7.2 Methods

This was a retrospective cohort study. Patients were eligible for inclusion if, between 1st January 2010 and 31st December 2016, they were ≥65 years old, had linked hospital data and more than one day of CPRD follow-up. We excluded patients with temporary registrations or gaps in their data coverage. Patient follow-up began on the latest of study start date, the patient's 65th birthday or 28 weeks after the patient first registered at the practice. Follow-up ended at the earliest of study end date, death, last day of available CPRD data, or 28 days after an incident UTI event. We identified eligible patients with a Read code indicating an incident primary care presentation with a suspected UTI (code list 1 in Figure 3.1), a same-day prescription code indicating empirical prescribing of nitrofurantoin or trimethoprim, and a creatinine record in the preceding 24 months. We defined 'incident' as a consultation occurring in a patient without a UTI-related Read code or trimethoprim or nitrofurantoin prescription in the preceding 90 days. We used the first incident episode during each patient's follow-up period.

We used the most recent serum creatinine value recorded in the 24 months preceding the incident UTI and data for patient age, gender and ethnicity to calculate an eGFR as per the Modification of Diet in Renal Disease (MDRD) Study equation (127). The choice of 24 months was pragmatic. We judged this to be a long enough period for a sufficient number of our cohort to have a creatinine measurement, but also short enough to reasonably represent a

patient's renal function at time of the index UTI. We categorised eGFRs as 45-59mls/min/1.73m^2, 30-44mls/min/1.73m^2, and <30mls/min/1.73m^2. To assess the impact of empirical trimethoprim versus nitrofurantoin prescribing, we used a range of demographic and clinical variables to match patients on their propensity to receive a trimethoprim prescription. We used nearest neighbour matching and matched three patients receiving trimethoprim with one patient receiving nitrofurantoin. We used mixed effects logistic regression to estimate ORs and 95% CIs for the risk of each adverse outcome, accounting for clustering within practices. Outcomes were re-consultation and re-prescription within 14 days following the incident UTI (proxy for treatment failure), hospitalisation for UTI, sepsis or AKI within 14 days following the incident UTI, and death within 28 days following the incident UTI. More detail on the justification and ascertainment of these outcomes is provided in section 3.7.

7.3 Results

From a cohort of 795,484 patients aged 65 and over, we identified 123,607 with an incident UTI empirically treated with a relevant antibiotic (Figure 7.1). Of these, 116,945 (95%) patients had a creatinine measurement recorded in the 24 months prior to the incident UTI, of whom 32,428 (28%) were male. The median age at time of incident UTI was 76 years (IQR 70-83). Almost one third of creatinine measurements were in the 90 days prior to the incident UTI. Median duration between most recent creatinine and UTI was 169 days (IQR 65-285). We excluded 76,112 patients with an eGFR ≥60. Of the remaining 40,833 patients with an eGFR <60, 26,970 (66.1%) had an eGFR of 45-59, 10,854 (26.6%) an eGFR of 30-44, and

3009 (7.3%) an eGFR of <15. In this cohort, 24,471 (60%) were prescribed trimethoprim and 7484 (18%) were prescribed nitrofurantoin. We matched 20,948 patients with an eGFR of 45-60 (15,711 prescribed trimethoprim, 5237 prescribed nitrofurantoin), 7260 with an eGFR of 30-44 (5445 prescribed trimethoprim, 1815 prescribed nitrofurantoin), and 1728 with an eGFR <30 (1296 prescribed trimethoprim, 432 prescribed nitrofurantoin). Inspection of jitter plots and histograms suggested matching had improved balance of covariates across trimethoprim versus nitrofurantoin groups. Standardised mean differences were all less than 0.1 (Table 7.1).

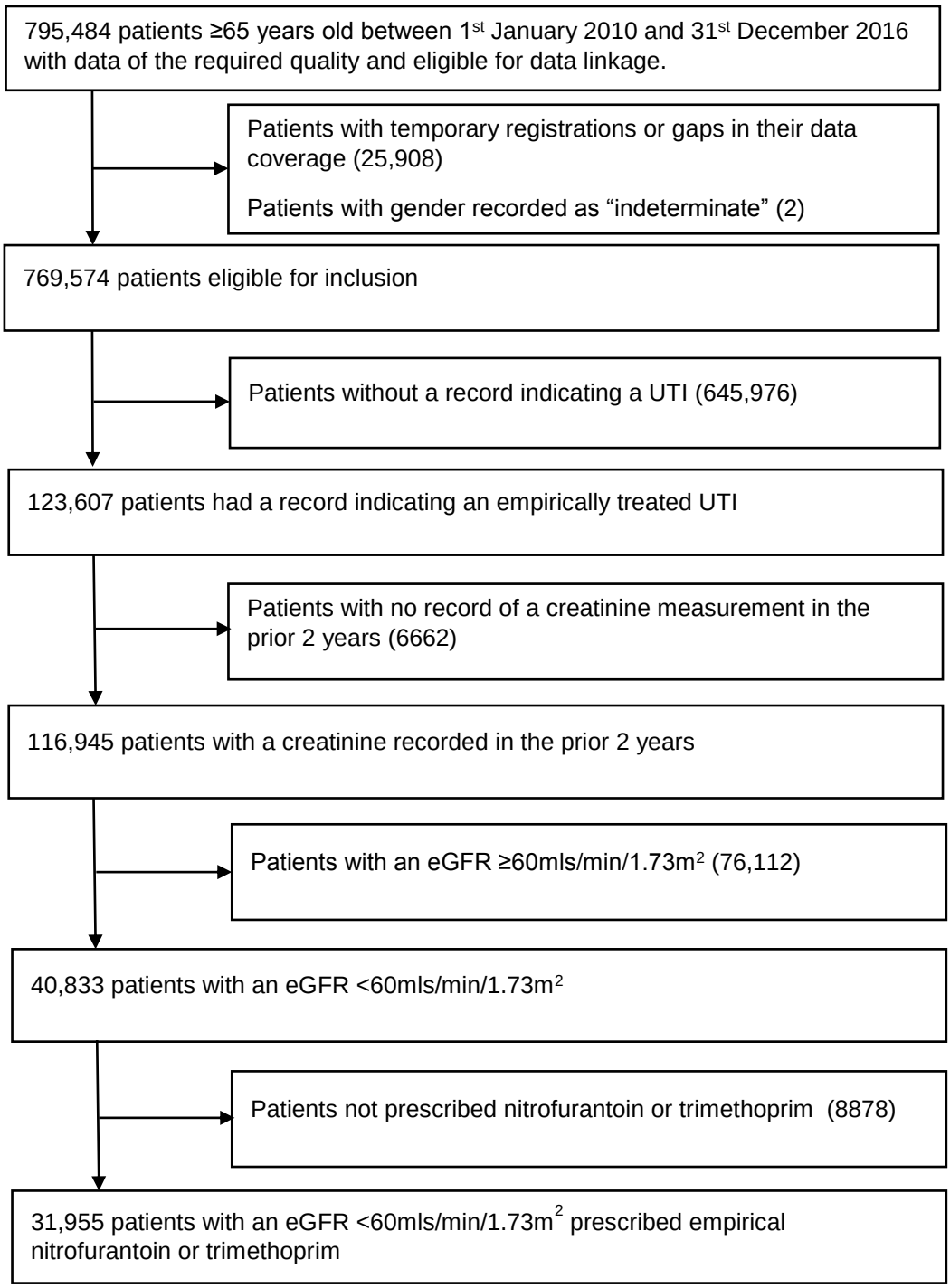


Figure 7.1. Flow of patients from initial identification in the database through to final cohort

Table 7.1. Balance of baseline characteristics across trimethoprim and nitrofurantoin groups following propensity score matching for patients with renal impairment.

Numbers are values (%) unless otherwise stated

	eGFR 45-60mls/min/1.73m^2			eGFR 30-44mls/min/1.73m^2			eGFR <30mls/min/1.73m^2		
	Trimethoprim	Nitrofurantoin	SMD*	Trimethoprim	Nitrofurantoin	SMD*	Trimethoprim	Nitrofurantoin	SMD*
N	15711	5237		5445	1815		1296	432	
Men	3421 (21.8)	1120 (21.4)	0.01	1201 (22.1)	414 (22.8)	-0.02	339 (26.2)	113 (26.2)	0.00
Mean (SD) age	78.9 (8.3)	78.8 (8.2)	-0.02	82.3 (7.9)	82.2 (8.0)	-0.01	83.4 (8.2)	83.4 (8.0)	0.00
Index of multiple deprivation decile									
1 or 2 (least deprived)	3746 (23.8)	1305 (24.9)		1162 (21.3)	360 (19.8)		281 (21.7)	93 (21.5)	
3 or 4	3807 (24.2)	1257 (24.0)		1219 (22.4)	466 (25.7)		297 (22.9)	95 (22.0)	
5 or 6	3488 (22.2)	1088 (20.8)		1229 (22.6)	394 (21.7)		286 (22.1)	100 (23.1)	
7 or 8	2711 (17.3)	867 (16.6)		986 (18.1)	301 (16.6)		231 (17.8)	79 (18.3)	
9 or 10 (most deprived)	1959 (12.5)	720 (13.7)	0.00	849 (15.6)	294 (16.2)	0.00	201 (15.5)	65 (15.0)	0.02
Housebound	637 (4.1)	206 (3.9)	-0.01	475 (8.7)	167 (9.2)	0.02	131 (10.1)	42 (9.7)	-0.01
Respiratory disease	3173 (20.2)	1115 (21.3)	0.00	1148 (21.1)	384 (21.2)	0.00	250 (19.3)	86 (19.9)	0.02
Cardiac failure	952 (6.1)	317 (6.1)	0.00	657 (12.1)	226 (12.5)	0.01	224 (17.3)	71 (16.4)	-0.02
Dementia	1111 (7.1)	361 (6.9)	-0.01	605 (11.1)	201 (11.1)	0.00	132 (10.2)	42 (9.7)	-0.02
Cancer	2389 (15.2)	853 (16.3)	0.03	924 (17)	314 (17.3)	0.01	229 (17.7)	74 (17.1)	-0.01
Stroke	1768 (11.3)	611 (11.7)	0.01	880 (16.2)	304 (16.7)	0.02	215 (16.6)	71 (16.4)	0.00
Diabetes	2890 (18.4)	956 (18.3)	0.00	1493 (27.4)	527 (29)	0.04	451 (34.8)	155 (35.9)	0.02
Ischaemic heart disease	3244 (20.6)	1098 (21)	0.01	1517 (27.9)	503 (27.7)	0.00	406 (31.3)	132 (30.6)	-0.02
Urinary catheter	406 (2.6)	176 (3.4)	0.00	240 (4.4)	112 (6.2)	0.07	93 (7.2)	29 (6.7)	-0.02
Urinary incontinence	2337 (14.9)	883 (16.9)	0.05	882 (16.2)	302 (16.6)	0.01	193 (14.9)	63 (14.6)	-0.01
Polypharmacy	6497 (41.4)	2262 (43.2)	0.04	3302 (60.6)	1117 (61.5)	0.02	877 (67.7)	294 (68.1)	0.01
Potassium-sparing diuretic	551 (3.5)	197 (3.8)	0.01	391 (7.2)	137 (7.5)	0.01	76 (5.9)	23 (5.3)	-0.02
Angiotensin-converting enzyme inhibitor	4364 (27.8)	1437 (27.4)	-0.01	1758 (32.3)	593 (32.7)	0.01	340 (26.2)	112 (25.9)	-0.01
Angiotensin-II receptor antagonist	2294 (14.6)	786 (15)	0.01	941 (17.3)	307 (16.9)	-0.01	220 (17.0)	79 (18.3)	0.03
Charlson score									
0	3802 (24.2)	1212 (23.1)		441 (8.1)	147 (8.1)		51 (3.9)	21 (4.9)	
1	2426 (15.4)	814 (15.5)		441 (8.1)	144 (7.9)		57 (4.4)	21 (4.9)	
2	3669 (23.4)	1256 (24)		1283 (23.6)	442 (24.4)		291 (22.5)	92 (21.3)	
3	2632 (16.8)	904 (17.3)		1237 (22.7)	381 (21.0)		276 (21.3)	93 (21.5)	
4	1561 (9.9)	490 (9.4)		894 (16.4)	273 (15.0)		229 (17.7)	79 (18.3)	
5	891 (5.7)	313 (6.0)		550 (10.1)	213 (11.7)		179 (13.8)	56 (13.0)	
≥6	730 (4.6)	248 (4.7)	0.02	599 (11.0)	215 (11.8)	0.02	213 (16.4)	70 (16.2)	-0.03

*Standardised Mean Difference

7.3.1 Re-consultation and re-prescription

In the 14 days following the incident UTI, 1334 (5.9%) patients prescribed trimethoprim and 436 (5.8%) patients prescribed nitrofurantoin re-consulted and received another antibiotic prescription. These proportions were similar across the three eGFR groups; 6.0% v 5.5% in those with an eGFR of 45-59, 5.8% v 6.4% in those with an eGFR of 30-44, and 5.7% v 6.7% in those with an eGFR of <30. Nitrofurantoin prescribing was associated with significantly lower odds of re-consultation and re-prescription in patients with eGFRs of 45-59 (OR 0.74, 95% CI 0.61-0.91), but no significant differences were found for the other eGFR groups (Table 7.2).

7.3.2 Hospitalisation for UTI

In the 14 days following the incident UTI, 529 (2.4%) patients prescribed trimethoprim and 185 (2.5%) patients prescribed nitrofurantoin were hospitalised for UTI. There were no significant differences between trimethoprim and nitrofurantoin for the odds of hospitalisation for UTI across the three eGFR groups.

7.3.3 Hospitalisation for sepsis

In the 14 days following the incident UTI, 47 (0.2%) patients prescribed trimethoprim and 10 (0.1%) patients prescribed nitrofurantoin were hospitalised for sepsis. There were no significant differences between trimethoprim and nitrofurantoin for the odds of hospitalisation for sepsis across the three eGFR groups.

7.3.4 Hospitalisation for AKI

In the 14 days following the incident UTI, 356 (1.6%) patients prescribed trimethoprim and 62 (0.8%) patients prescribed nitrofurantoin were hospitalised for AKI. Nitrofurantoin prescribing was consistently associated with reduced odds of hospitalisation for AKI across the three eGFR groups. The proportions of patients hospitalised for AKI in the trimethoprim versus nitrofurantoin groups were 0.8% v 0.5% in those with an eGFR of 45-59 (OR 0.62, 95% CI 0.40-0.94), 2.7% v 1.3% in those with an eGFR of 30-44 (OR 0.47, 95% CI 0.30-0.73), and 6.5% v 3.0% in those with an eGFR of <30 (OR 0.45, 95% CI 0.25-0.81).

7.3.5 Death

In the 28 days following the incident UTI, 321 (1.4%) patients prescribed trimethoprim and 91 (1.2%) patients prescribed nitrofurantoin died. Nitrofurantoin prescribing was associated with significantly lower odds of death in patients with eGFRs of 30-44 (OR 0.61, 95% CI 0.31-0.95), but no significant differences were found for the other eGFR groups.

7.3.6 Sensitivity analysis

We combined the hospitalisation and death outcomes to increase statistical power to detect these adverse outcomes but our findings were consistent with our main analysis (Table 7.3). Importantly, we did not detect any increase in odds of adverse outcomes in patients prescribed nitrofurantoin.

Table 7.2. Odds ratios and 95% confidence intervals for each outcome in propensity-score matched trimethoprim versus nitrofurantoin groups, across three eGFR categories.

eGFR 45-59	Trimethoprim group, n=15711	Nitrofurantoin group, n=5237		
	Number (%) of events	Number (%) of events	OR (95% CI)	p-value
Re-consultation and re-prescription within 14 days	942 (6.0)	290 (5.5)	0.74 (0.61-0.91)	0.004
Hospitalised for UTI within 14 days	288 (1.8)	105 (2.0)	1.09 (0.74-1.61)	0.648
Hospitalised for sepsis within 14 days	25 (0.2)	6 (0.72)	0.72 (0.30-1.76)	0.470
Hospitalised for AKI within 14 days	126 (0.8)	26 (0.5)	0.62 (0.40-0.94)	0.025
Death within 28 days	159 (1.0)	50 (1.0)	0.94 (0.69-1.30)	0.718
eGFR 30-44	Trimethoprim group, n=5445	Nitrofurantoin group, n=1815		
	Number (%) of events	Number (%) of events	OR (95% CI)	p-value
Re-consultation and re-prescription within 14 days	318 (5.8)	117 (6.4)	0.98 (0.71-1.33)	0.874
Hospitalised for UTI within 14 days	168 (3.1)	57 (3.1)	0.80 (0.44-1.47)	0.482
Hospitalised for sepsis within 14 days	14 (0.3)	2 (0.1)	0.43 (0.10-1.88)	0.262
Hospitalised for AKI within 14 days	146 (2.7)	23 (1.3)	0.47 (0.30-0.73)	<0.001
Death within 28 days	113 (2.1)	23 (1.3)	0.61 (0.39-0.95)	<0.001
eGFR <30	Trimethoprim group, n=1296	Nitrofurantoin group, n=432		
	Number (%) of events	Number (%) of events	OR (95% CI)	p-value
Re-consultation and re-prescription within 14 days	74 (5.7)	29 (6.7)	1.19 (0.76-1.85)	0.446
Hospitalised for UTI within 14 days	73 (5.6)	23 (5.3)	0.94 (0.58-1.53)	0.808
Hospitalised for sepsis within 14 days	8 (0.6)	2 (0.5)	0.75 (0.16-3.54)	0.715
Hospitalised for AKI within 14 days	84 (6.5)	13 (3.0)	0.45 (0.25-0.81)	0.008
Death within 28 days	49 (3.8)	18 (4.2)	1.11(0.64-1.93)	0.713

Variables included in the propensity score model were gender, age, Index of Multiple Deprivation score quintile, Charlson comorbidity score, polypharmacy, the presence or absence of a Read code indicating diabetes, dementia, coronary heart disease, stroke, cancer, heart failure, liver disease, urinary incontinence, urinary catheter, and prescribing of potassium-sparing diuretics, angiotensin converting enzyme inhibitors or angiotensin-II receptor blockers at the time of the index UTI.
Odds ratios estimated using a mixed effect logistic regression model with the general practice included as a random effect to account for clustering.

Table 7.3. Odds ratios and 95% confidence intervals for a combined "hospitalisation or death" outcome in propensity-score matched trimethoprim versus nitrofurantoin groups, across three eGFR categories.

eGFR	Number (%) of events* in trimethoprim group	Number (%) of events* in nitrofurantoin group	OR (95% CI)	p-value
45-59	491 (3.1)	157 (3.0)	0.96 (0.80-1.15)	0.645
30-44	329 (6.0)	82 (4.5)	0.48 (0.30-0.77)	0.002
<30	147 (11.0)	43 (10.0)	0.86 (0.60-1.24)	0.425

*Events from the following outcomes were combined: Hospitalisation for UTI, sepsis and AKI within 14 days and death within 28 days.

7.4 Discussion

Our results show that compared to trimethoprim, nitrofurantoin was associated with reduced odds of hospitalisation for AKI across all eGFR groups. We found no evidence of an association between nitrofurantoin and increased risk of any adverse event evaluated in our study.

7.4.1 Results in context

Two previous studies assessed trimethoprim and nitrofurantoin prescribing in patients with renal impairment. The first compared treatment failure rates in women with UTI prescribed nitrofurantoin according to renal function and found no difference across the eGFR groups (88). This study lacked a comparator group prescribed an alternative antibiotic, which makes it difficult to interpret their findings. The second compared outcomes in older women with a median eGFR of 38mls/min/1.73m^2, prescribed either nitrofurantoin or trimethoprim, and found no difference in risk of treatment failure or UTI hospitalisation (162). We compared nitrofurantoin with

trimethoprim across three eGFR groups, and found that nitrofurantoin was associated with lower odds of re-consultation and re-prescription in patients with eGFRs of 45-59. This difference could be explained by recent data showing that 34% of community-acquired E.coli UTIs in England are resistant to trimethoprim, compared to only 2.7% resistant to nitrofurantoin (14). However, rates of trimethoprim and nitrofurantoin resistance should be similar across eGFR groups, and therefore, why did we not find statistically significant differences between re-consultation and re-prescription rates in people with eGFRs <45? This could be due to less statistical power, as nitrofurantoin use was less common in these patients due to the advice to use with care in patients with eGFRs of 30-44 and to avoid in eGFRs <30. It may also be due to the possibility that nitrofurantoin efficacy was reduced in those with lower eGFRs but was offset by the high rates of trimethoprim resistance and thus resulted in apparent similar rates of re-consultation and re-prescription. However, it should be noted that the evidence for reduced nitrofurantoin efficacy in patients with renal impairment comes from several small studies that assessed urinary nitrofurantoin excretion, not clinical outcomes (87).

Our finding that nitrofurantoin was associated with a reduced risk of death in those with moderate renal impairment is consistent with previously reported estimates in studies that compared nitrofurantoin with amoxicillin in the general population (80, 126). We also found a previously unreported lower risk of AKI associated with nitrofurantoin use across all three eGFR groups of our cohort, that aligns with previous studies that found trimethoprim (with or without sulfamethoxazole) prescribing was associated

with an increased risk of hyperkalaemia, AKI and death compared to amoxicillin (80, 81, 83, 126). However, previous studies did not investigate associations by degree of renal impairment, providing little information to guide prescribing in this population.

7.4.2 Strengths and limitations

We used data from a general practice database that is broadly representative of the UK population, increasing the generalisability of our findings. This is the first study to investigate trimethoprim versus nitrofurantoin prescribing in renal impairment, using clinically relevant eGFR groups analogous to stages of CKD, and without excluding men. We also reduced indication bias by matching patients on their propensity to receive trimethoprim, and achieving adequate balance of covariates across the two groups.

Our study has important limitations. We attempted to capture patients presenting with UTI but had no microbiological data to support this. However, whilst a limitation, this may also be more representative of clinical practice. We were unable to investigate pulmonary/hepatic toxicity related to nitrofurantoin use due to the lack of reliable codes, and differential use of these codes by clinicians. However, two systematic reviews have shown that these toxicities are rare with short-term use (59, 163). We relied on a creatinine measurement from the 24 months prior to the UTI to estimate an eGFR, but this may not fully represent patients' current renal function. Finally, despite our design, differential coding, indication bias and residual confounding may still have affected our findings.

7.5 Implications

Current guidelines and the British National Formulary limit nitrofurantoin use to those with an eGFR >45mls/min/1.73m^2, although short courses can be used with care in those with eGFRs >30mls/min/1.73m^2 (19). We found no evidence to support this limitation, and actually found nitrofurantoin to be associated with a reduced risk of AKI compared to trimethoprim.

7.6 Conclusion

The recommendation to avoid nitrofurantoin in patients with an eGFR of <45mls/min/1.73m^2 has meant clinicians have to choose between trimethoprim or broad-spectrum agents to treat UTI in this patient group. However, previous work has shown increasing rates of bacterial resistance to trimethoprim and highlighted the need to avoid broad-spectrum antibiotics to help contain resistance. Our data suggest nitrofurantoin may be a suitable narrow spectrum treatment option in older patients with eGFRs <45mls/min/1.73m2. We found no associated increase in the risk of adverse outcomes but our findings are limited by the potential for residual confounding and the lack of data on nitrofurantoin-related lung and liver toxicity, and therefore should be interpreted with a degree of caution.

8 Antibiotic prophylaxis versus non-antibiotic prophylaxis or placebo for prevention of recurrent UTI in older people: systematic review and meta-analysis of randomised controlled trials

In chapters 5 to 7, we focussed on antibiotic treatment for acute UTI. In chapters 8 and 9, we will focus on long-term antibiotic prophylaxis for recurrent UTI. This chapter presents a systematic review and meta-analysis of randomised trials of antibiotic versus non-antibiotic prophylaxis for recurrent UTI in older people to widen understanding of the evidence base for this practice.

8.1 Background

Older men and women are commonly prescribed long-term antibiotic prophylaxis to prevent recurrent UTI (2, 3). The prevalence of prophylaxis use in community dwelling older adults is not known but the HALT-2 point prevalence survey of 1181 long-term care facilities in 19 European countries found that, between April and May 2013, 22% of 77,264 surveyed residents were prescribed antibiotic prophylaxis for UTI (164). Figures for the UK are higher. For example, in Northern Ireland, point prevalence surveys of care home residents found that 39.3% were prescribed antibiotic prophylaxis for UTI in November 2010 (n=585), and 46% in April 2011 (n=578) (2). Antibiotic use is a key driver of antibiotic resistance (12). Therefore,

antibiotic use must be justified by robust evidence, where the estimated benefit outweighs estimated harm.

Previous meta-analyses of 10 trials of 410 women showed antibiotic prophylaxis conferred a relative risk reduction of 79% in the proportion of women experiencing a microbiologically confirmed UTI, compared to placebo (93). However, these analyses included data from mostly small trials (sample sizes ranged from 27 to 60) of younger women (only 4 trials of 144 women included those aged over 65) without co-morbidities. There is uncertainty around the generalisability of these findings to older adults.

There are several important clinical uncertainties relating to long-term antibiotic prophylaxis in older adults with recurrent UTI, including effect on frequency of infective episodes, optimal duration of prophylaxis, adverse effects, risk of relapse following cessation of prophylaxis and effect on urinary antibiotic resistance. We therefore systematically reviewed randomised controlled trials comparing long-term antibiotic prophylaxis with placebo or non-antibiotic prophylaxis for preventing further episodes of UTI in older people. Our aim was to quantify the benefits and harms of long-term antibiotic prophylaxis for older adults, to better inform patients and clinicians during clinical decision-making.

8.2 Methods

We conducted a systematic review following guidance from the Cochrane handbook for systematic reviews of interventions for conduct and PRISMA guidelines for reporting (165).

The review protocol was prospectively registered on PROSPERO: (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015016628) registration number: PROSPERO 2015:CRD42015016628).

8.2.1 Data sources

We initially did a systematic search of Medline, Embase, CINAHL and the Cochrane Central Register of Controlled Trials from inception to March 2016 for English language randomised controlled trials. Our search strategy consisted of keywords and MESH terms for urinary tract infection and randomised trials (Figure 8.1). The search was repeated in April 2018 to identify any recently published eligible studies.

I conducted the first screening of potentially relevant records based on titles and abstracts. Due to time and resource constraints, these records were not screened by a second reviewer. The Cochrane Handbook for systematic reviews of interventions states in section 7.2.4 that "authors must first decide if more than one of them will assess the titles and abstracts of records retrieved from the search. Using at least two authors may reduce the possibility that relevant reports will be discarded" (166). We therefore acknowledge this issue in our limitations. The handbook also states that "It is most important that the final selection of studies into the review is undertaken by more than one author" and therefore I and another researcher independently performed the final selection of included trials based on full text evaluation. Reference lists of included studies and relevant systematic reviews were screened for further potentially relevant studies. Disagreements on which studies should or should not be included were resolved through discussion with the rest of the review team.

1. exp Urinary Tract Infections/

2. Urinary Tract Infection*.mp.

3. exp Cystitis/

4. (bladder adj infection*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

5. Bacteriuria.mp.

6. Pyuria.mp.

7. (recurrent adj urinary).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

8. UTI.mp.

9. exp Anti-Bacterial Agents/ or exp Antibiotic Prophylaxis/

10. antimicrobial*.mp.

11. randomized controlled trial.pt.

12. controlled clinical trial.pt.

13. randomized.ab.

14. placebo.ab.

15. clinical trials as topic.sh.

16. randomly.ab.

17. trial.ti.

18. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

19. 9 or 10

20. 18 and 19

21. 11 or 12 or 13 or 14 or 15 or 16 or 17

22. exp animals/ not humans.sh.

23. 21 not 22

24. 20 and 23

Figure 8.1. Medline search strategy

8.2.2 Study selection

We included only randomised controlled trials published in full (i.e., not abstracts) in English, comparing the effect of long-term antibiotic prophylaxis versus placebo or non-antibiotic prophylaxis on the rate of UTI in older adults with recurrent UTI. We defined “long-term antibiotics” as daily antibiotic dosing for at least six months, as clinical guidelines recommend reviewing patients after six-months of antibiotic prophylaxis to assess benefit (33). We defined “older adults” as women who were postmenopausal or over the age of 65, and men aged over 65. We used the National Institute of Health and Care Excellence clinical guideline definition of “recurrent UTI” - self-reported or clinically recorded history of two or more UTIs in six months, or three or more in 12 months (33).

We included studies recruiting adults of all ages and screened relevant results to assess whether reported data allowed estimates of effect size in our specified population of older adults. For data not presented in this format, we contacted authors if the study was published in the last ten years and if the mean or median age in any arm was greater than 50 years.

We excluded studies evaluating the effect of antibiotic prophylaxis in specific situations, e.g., post-catheterisation, post-surgery, in patients with spinal injuries or in those with structural renal tract abnormalities.

8.2.3 Outcome measures

Our primary outcome was the number of urinary tract infection recurrences per patient year during the prophylaxis period, defined microbiologically (>100,000 colony forming units of bacteria/ml of urine) and/or clinically (for example, dysuria, polyuria, loin pain, fever), or other measure of change in the frequency of UTI events during prophylaxis. We also aimed to assess the proportion of patients with severe (requiring withdrawal of treatment) and mild (not requiring withdrawal of treatment) adverse effects. Secondary outcomes included the proportion of patients who experienced at least one recurrence after the prophylaxis period, time to first recurrence, proportion of patients with antibiotic resistant micro-organisms in future urine samples, and quality of life.

8.2.4 Data extraction and quality assessment

We extracted study characteristics (setting, participants, intervention, control, funding source) and outcome data from included trials. We contacted two authors for sub-group data on postmenopausal women. One author replied and provided relevant outcome data. I and another member of the review team independently assessed the risk of bias of the included studies using the Cochrane Collaboration's risk of bias tool (167). Disagreements were resolved through discussion. We used RevMan version 5.3 to meta-analyse the data and generate forest plots.

8.2.5 Data synthesis and analysis

Outcomes measured in only one trial were reported narratively. Outcomes measured in more than one trial were synthesised quantitatively. We

estimated between trial heterogeneity using the I^2 statistic (168) and used random effects meta-analyses to estimate pooled risk ratios and 95% CIs (169). We undertook sensitivity analyses to examine treatment effects according to study quality and assessed the impact of including data from a potentially eligible trial where the study author did not reply to our request for data on older participants.

8.3 Results

From 6645 records, we identified 53 studies for full-text review (Figure 8.2). Four studies were eligible for inclusion (94-97). Two studies recruited only postmenopausal women (94, 95). Two studies recruited women of all ages but the median age was >50 years (96, 97). For these studies, we contacted authors requesting data for postmenopausal women, or if menopausal status not ascertained, for women aged over 65. We received data from one author and hence included three trials consisting of 594 postmenopausal women in our review (Table 8.1) (94-96). We did not identify any studies that included older men.

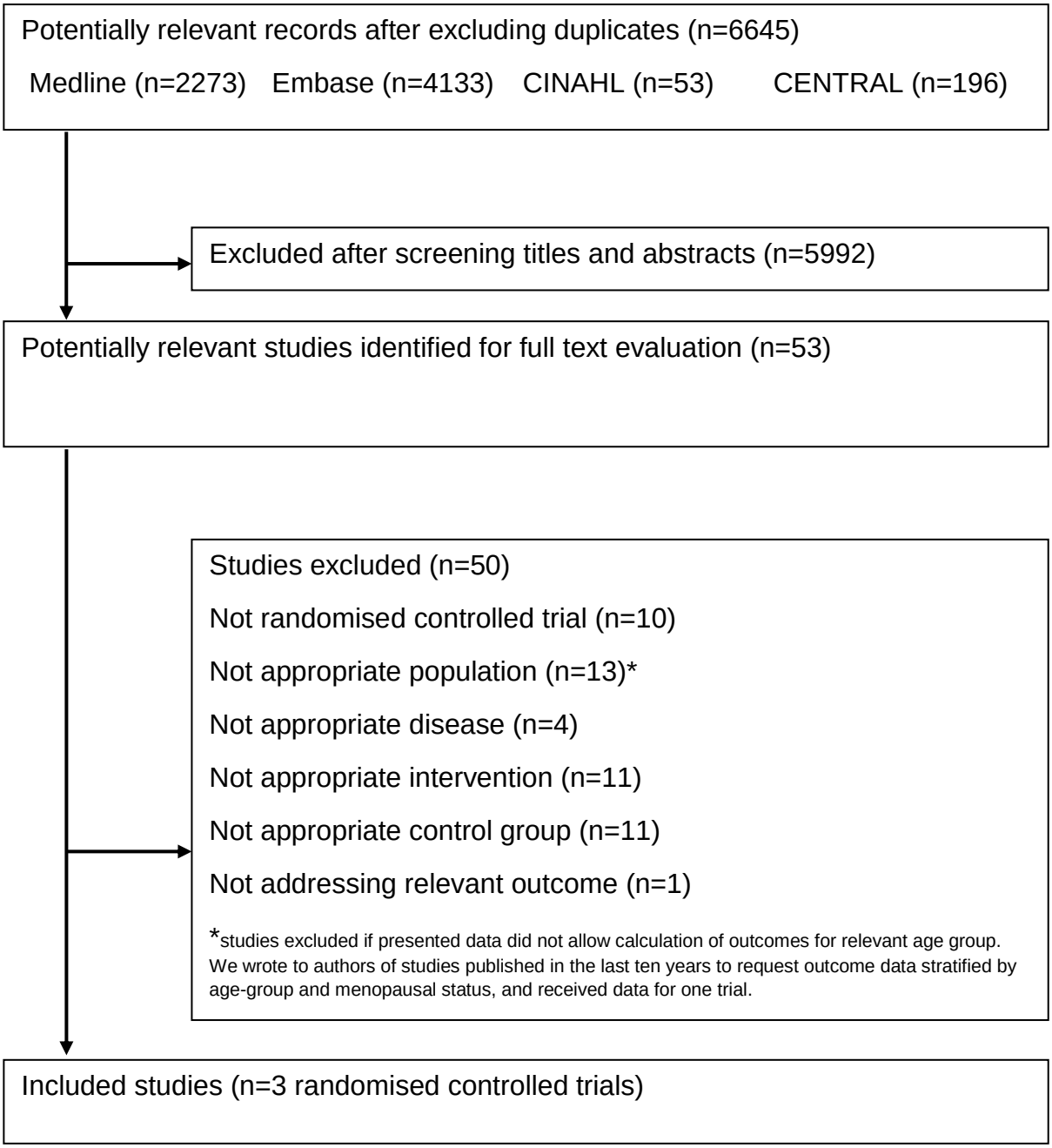


Figure 8.2. PRISMA flowchart

Table 8.1. Characteristics of included studies.

Study ID	Setting	N	Population	Intervention	Control	Confirmation of UTI	Outcomes
Raz 2003	Outpatient infection disease clinics in Northern Israel	150	Community dwelling postmenopausal women with recurrent UTI[‡]	Nitrofurantoin 100mg capsule at night for 9 months, with placebo vaginal pessary to mimic control group	Vaginal pessary containing 0.5mg Estriol daily for two weeks, then once a fortnight for nine months, with oral placebo capsules at night to mimic the intervention group	$>10^3$ colony forming units/mL bacteria in midstream urine	1.Number of women experiencing a recurrence during the prophylaxis period 2.Mean number of UTIs per woman during the prophylaxis period 3.Effects of oestrogens and antibiotics on vaginal mucosa, flora and pH 4.Mild and serious adverse events
Beerepoot 2012	Community setting in Amsterdam	238	Community dwelling postmenopausal women with a self-reported history of at least 3 UTIs in the preceding year	Trimethoprim-sulfamethoxazole 480mg tablet at night for 12 months, with placebo capsule twice daily	One capsule containing at least 10^9 colony forming units of *L rhamnosus GR-1* and *L reuteri RC-14* twice daily for 12 months, with placebo capsule at night	Symptoms +/- $>10^3$ colony forming units/mL bacteria in midstream urine	1.Number of women experiencing a recurrence during, and three months after the prophylaxis period 2.Mean number of UTIs per woman during the prophylaxis period 3.Median time to first recurrence during and after the prophylaxis period 4.Effects of lactobacilli and antibiotics on vaginal flora 5.Effects of lactobacilli and antibiotics on urinary and faecal antibiotic resistance 6.Mild and serious adverse events
Kranjcec 2014	Outpatients and primary care in Zabok, Croatia	206	Community dwelling women with self-reported recurrent UTI[‡]	Nitrofurantoin 50mg at night for six months	Two grams D-mannose powder diluted in 200mls water at night for six months OR No treatment	Symptoms and $>10^3$ colony forming units/mL bacteria in midstream urine	1.Number of women experiencing a recurrence during the prophylaxis period 2.Median time to first recurrence during the prophylaxis period 3.Adverse events

[‡] defined as two confirmed episodes of uncomplicated UTI in six months, or three in twelve months.

Trials were conducted in community and outpatient settings in Israel, Netherlands and Croatia. Only one trial included individuals with diabetes (94) and only one trial included individuals with renal impairment (96). Intervention arms consisted of 6 to 12 months of antibiotic prophylaxis. Control arms consisted of non-antibiotic prophylaxis with vaginal oestrogen pessaries (95), oral lactobacilli capsules (94), and D-mannose powder (96). One trial reported the number of urinary tract infection recurrences per patient year during the prophylaxis period (94). All trials reported the number of women experiencing a UTI during the prophylaxis period and frequency of adverse events. Only one trial assessed recurrence of UTI after the prophylaxis period (3 months) (89). One trial assessed effect on urinary and faecal bacterial resistance (89).

8.3.1 Risk of bias

Figure 8.3 summarises the risk of bias assessment. Allocation and randomisation details were poorly reported in two trials (95, 96). One trial was assessed as high risk for performance and detection bias; trial arms consisted of an oral antibiotic capsule or D-mannose powder diluted in 200mls water or no treatment with no use of placebo and did not report on blinding of outcome assessors (96). Only one trial reported a sample size calculation (95) . Overall, one trial was judged to be low risk of bias (94) and two trials unclear risk due to limited reporting of methods (95, 96).

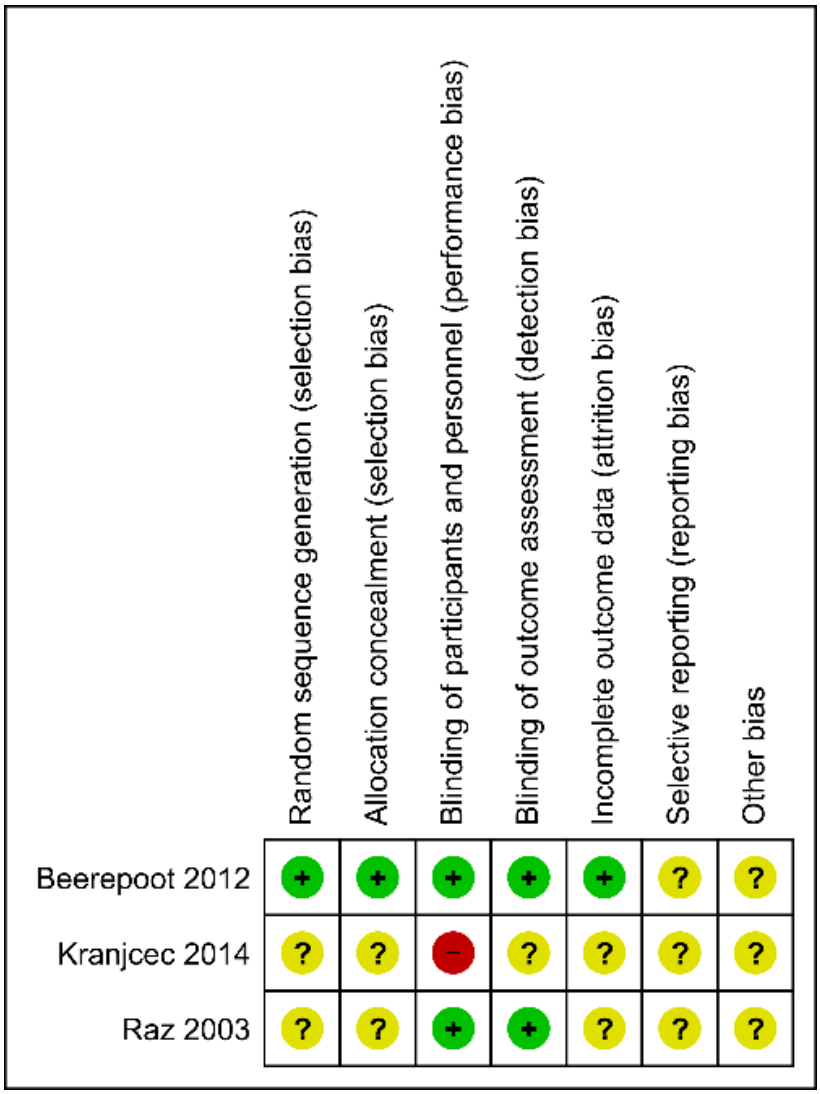


Figure 8.3. Summary of risk of bias assessment

8.3.2 Effect of long-term antibiotic prophylaxis on recurrent UTI

Compared to a capsule of Lactobacilli, prophylaxis with 480mg of trimethoprim-sulfamethoxazole for 12 months led to fewer microbiologically confirmed UTI episodes per patient year (mean number of episodes per year = 1.2 versus 1.8, mean difference 0.6, 95% CI 0.0-1.4, *p*=0.02). Prophylaxis with trimethoprim-sulfamethoxazole also led to less women experiencing a microbiologically confirmed UTI during prophylaxis (49.4% versus 62.9%; RR 0.79, 95% CI 0.63-1.0), and an increase in time to first

UTI (six months versus three months; log-rank *p*=0.02). There was no difference between arms in the mean number of microbiologically confirmed UTI episodes three months after cessation of prophylaxis (mean number of episodes = 0.1 versus 0.2, mean difference 0.0, 95% CI -0.1-0.3, *p*=0.64) (94) .

Compared to vaginal oestrogen pessaries, prophylaxis with 100mg of nitrofurantoin for nine months led to fewer women experiencing a UTI during prophylaxis (42.3% versus 64.6%; RR 0.65, 95% CI 0.8-0.90), and a lower mean number of UTIs per woman (0.6 episodes per woman versus 1.6 episodes per woman) (95).

Compared to D-mannose powder, prophylaxis with 50mg of nitrofurantoin for six months led to more postmenopausal women experiencing a UTI during prophylaxis (24% versus 19%, RR 1.24, 95% CI 0.57-2.69) (96).

Random effects meta-analysis (Figure 8.4) found that long-term antibiotic prophylaxis reduced the risk of a woman experiencing a UTI during the prophylaxis period (pooled RR 0.76, 95% CI 0.61-0.95) with about eight post-menopausal women needing treatment with long-term antibiotics to prevent one woman experiencing a UTI during the prophylaxis period (NNT=8.5).

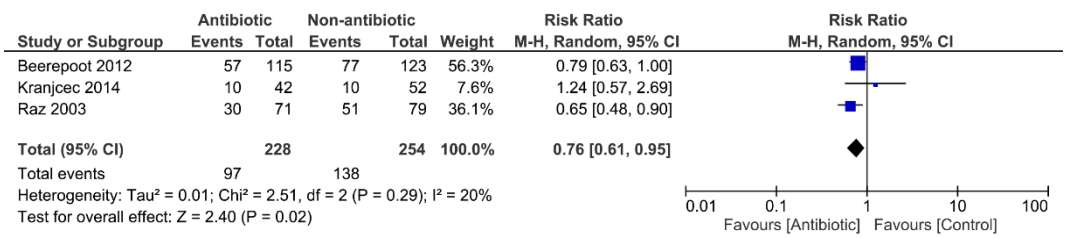


Figure 8.4. Forest plot showing results of meta-analysis for proportion of women experiencing a UTI during the prophylaxis period

8.3.3 Adverse events

Commonly reported side effects across the three trials included skin rash, gastrointestinal disturbance and vaginal symptoms. There were no statistically significant difference between odds of adverse events between trimethoprim-sulfamethoxazole and lactobacilli (94), or between nitrofurantoin and vaginal oestrogens (95). Risk of side effects with D-mannose powder were significantly lower than with nitrofurantoin (RR 0.28, 95% CI 0.13-0.57) (96). Overall, absolute numbers of serious adverse events or events resulting in treatment withdrawal were small.

We had data on mild adverse events (not resulting in treatment withdrawal) for all three trials. There was marked heterogeneity between trials for adverse events (I^2 = 86%).

Meta-analyses showed no statistically significant difference between antibiotics and control for overall risk of mild adverse events (RR 1.52, 95% CI 0.76-3.03) (Figure 8.5).

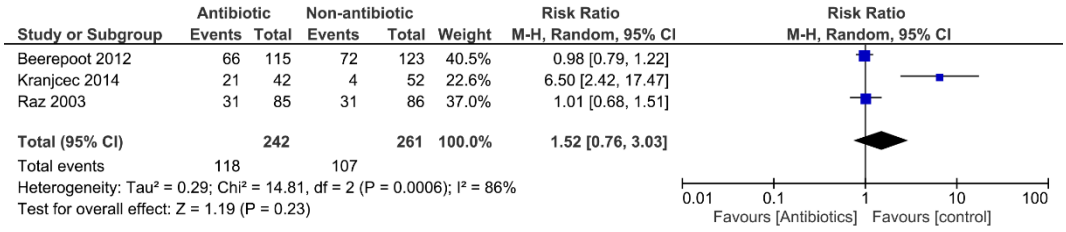


Figure 8.5. Forest plot showing results of meta-analysis for proportion of women experiencing mild side effect (treatment not withdrawn) during the prophylaxis period

We extracted data for serious adverse events (resulting in treatment withdrawal) for two trials. Meta-analyses showed no statistically significant

difference between antibiotics and control for overall risk of serious adverse events (RR 0.90, 95% confidence interval 0.31-2.66) (Figure 8.6).

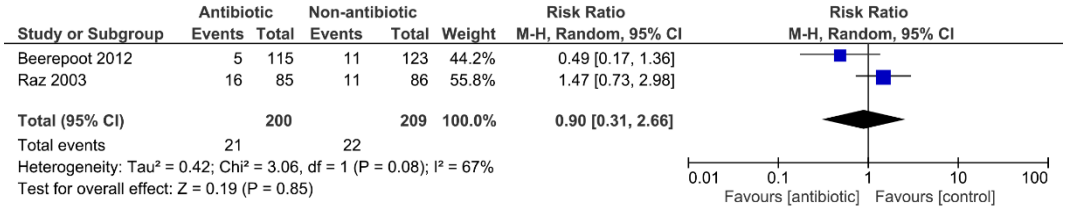


Figure 8.6. Forest plot showing results of meta-analysis for proportion of women experiencing a serious side effect (resulting in treatment withdrawal) during the prophylaxis period

8.3.4 Effect of long-term antibiotic prophylaxis on bacterial resistance

Compared with lactobacilli, women receiving 12 months prophylaxis with trimethoprim-sulfamethoxazole showed dramatic increases in the proportion of antibiotic resistant bacteria isolated from urine and faeces. For example, 20-40% of urinary and faecal E coli isolates were resistant to trimethoprim-sulfamethoxazole, trimethoprim and amoxicillin at baseline, increasing to 80-95% after one month of treatment. Over the 15 month follow-up period, resistance levels decreased following cessation of prophylaxis but remained above baseline levels (94).

8.3.5 Sensitivity analyses

We assessed the impact of removing the study at high risk of bias on the pooled effect size and direction (96). Removal made little difference to the meta-analysis for proportion of women experiencing a UTI during the prophylaxis period (RR 0.74, 95% CI 0.61-0.89). Removal did impact on the meta-analysis for proportion of women experiencing mild side effects during

the prophylaxis period, but overall difference between antibiotics and placebo did not reach statistical significance (RR 0.99, 95% CI 0.82-1.20).

We also pooled aggregate data from another potentially relevant study where authors did not respond to our request for data regarding postmenopausal women or women over 65 (97). This study compared 500mg of cranberry extract to 100mg trimethoprim taken at night for six months. However, adding aggregate data for the whole study population (women aged 45 and above) to our meta-analysis for the proportion of women experiencing a UTI during the prophylaxis period made little difference to risk estimates (RR 0.74, 95% CI 0.61-0.90).

8.4 Discussion

This systematic review assessed evidence from three European randomised trials reported between 2003 and 2014. Trials only included women. Compared to controls, long-term antibiotic prophylaxis reduced the risk of postmenopausal women experiencing a recurrent UTI during the prophylaxis period, without a statistically significant increase in risk of adverse events. Data from one trial found that long-term antibiotic prophylaxis led to a dramatic increase in urinary and faecal antibiotic resistance, and resulted in a reduction in UTI recurrence only during the treatment period, with no benefit apparent three months after cessation of prophylaxis (94). However, trials were small with relatively short follow-up and had limitations in design and reporting, with one trial judged high risk of bias.

8.4.1 Results in context

Meta-analysis of 10 randomised trials of women aged 18 and older found long-term antibiotics reduced the risk of UTI recurrence during the prophylaxis period by almost 80% (RR 0.21, 95% CI 0.13-0.34, NNT = 1.85) (93). Our analyses showed a smaller effect size and greater NNT for postmenopausal women, possibly due to more complex pathophysiology of recurrent UTI in this population. We did not identify a statistically significant increase in risk of adverse events associated with use of antibiotics. Adverse events are often poorly reported in trials (170), and we found heterogeneity for adverse events between trials. In addition, the studies included in this review compared long-term antibiotic prophylaxis with various non-antibiotic treatments and not placebo, and this may have influenced effect sizes for adverse events towards the null. We found small absolute numbers of serious adverse events, and cannot exclude the possibility of important effects being missed in these relatively small studies.

During two point prevalence surveys, almost half of all adults residing in a sample of care homes were prescribed antibiotics for prevention of recurrent UTI (2, 3). Based on three small trials, with relatively short follow-up periods and design limitations, our meta-analyses suggest that this widely practiced use of prophylaxis reduces risk of recurrence in older women. However, it is still unclear if these benefits extend to older men or frailer care home populations. These are important gaps in current evidence, especially given large-scale observational data showing 10% of older men who experience an acute UTI go on to have at least one recurrence (73).

Only one study followed up participants after cessation of prophylaxis and found that beneficial effects had ceased after 3 months (94). Previous studies of younger women have reported similar findings suggesting that prophylaxis only confers protection from recurrence during the active prophylaxis phase (93).

We found little data on the impact of long-term antibiotic prophylaxis on antibiotic resistance. Antibiotic use is associated with increased risk of resistance (12). Given the potential harms from acquiring an antibiotic resistant infection, the risk inferred by long-term antibiotic use is an important factor to consider with patients when making decisions about antibiotic prophylaxis.

8.4.2 Strengths and limitations

We conducted this review following prospective registration of a review protocol and in line with guidance from the Cochrane handbook for systematic reviews of interventions. The search strategies were comprehensive and supplemented with reviews of reference lists of relevant trials (94-97), systematic reviews (93, 103, 171) and clinical guidelines (18, 19, 92). Only one reviewer screened the initially identified records, raising the possibility of relevant records being missed. However, two reviewers independently performed final selection of studies into the review. We contacted authors where additional data were required for study inclusion. Due to resource constraints, we limited searches to English language and may have missed potentially relevant studies.

8.5 Implications

Based on the data analysed, a pragmatic approach is required when considering prescribing long-term antibiotic prophylaxis for older patients with recurrent UTI. Although long-term antibiotics may reduce the risk of UTI recurrence in women, this benefit diminishes upon cessation of treatment. Little is known about optimal prophylaxis period, long-term effects on health, risk of antibiotic resistant infections, effect in older men, effect in frail care home residents, or impact on important patient centred outcomes. These unknowns must be balanced against benefits and patient preferences.

Future research efforts on recurrent UTI should focus on improving the design and reporting of trials and developing a core set of outcomes to allow better synthesis of trial data. Antibiotic prophylaxis should be compared with non-antibiotic prophylaxis with some evidence of efficacy (such as vaginal oestrogens) rather than those with little or poor evidence of efficacy. Researchers should address unanswered questions regarding long-term effects, duration of use, adverse effects and antibiotic resistance.

8.6 Conclusion

There is ongoing uncertainty around the benefits and harms of long-term antibiotic prophylaxis in older men and frail care home residents with recurrent UTI. The effect of long-term antibiotic prophylaxis for older women with recurrent UTI was only assessed in three trials with a total of 594 women. Two of these trials had important limitations in their design. Therefore, prescribing long-term antibiotic prophylaxis to older women with recurrent UTI needs careful discussion between patient and clinician of the

ongoing uncertainties in the evidence. Although the existing evidence suggests that antibiotic prophylaxis reduces the risk of relapse, it also suggests a potential increase in urinary and faecal antibiotic resistance and rapidly diminished benefit once prophylaxis stops.

9 Association between long-term antibiotic prophylaxis and outcomes in older people with recurrent UTI

In chapter 8, we reported a systematic review and meta-analysis of the effect of antibiotic prophylaxis on outcomes in older people with recurrent UTI. We found that the evidence was limited to three small trials that only included postmenopausal women. In this chapter, we report analyses on associations between long-term antibiotic prophylaxis and UTI recurrence, acute antibiotic prescribing and hospitalisation, in older people with recurrent UTI.

9.1 Background

Clinical guidelines recommend several methods for preventing recurrent UTIs including avoidance of risk factors, vaginal oestrogens, immunoprophylaxis, or long-term low-dose antibiotic prophylaxis (67, 92). Our systematic review and meta-analysis of randomised trials found that long-term antibiotic prophylaxis reduced the risk of UTI recurrence in post-menopausal women during 6-12 months of follow-up. However, we identified several areas of uncertainty that need to be addressed to better inform clinical decision making around the use of long-term antibiotic prophylaxis in older adults with recurrent UTI. Firstly, there are no robust data to inform long-term antibiotic prophylaxis use in men. Secondly, trials in post-menopausal women often excluded those with co-morbidities, such as diabetes, thus limiting their generalizability to real-world older populations. Thirdly, previous studies were underpowered to study

important but rare events such as hospitalisation. Fourthly, no high quality trials have reported the comparative effects of different antibiotics used for prophylaxis of recurrent UTI.

An adequately powered, pragmatic, long-term randomised trial could address some of these uncertainties. However, given the challenges of recruitment and retention of older adults into clinical trials (172), and the associated costs and time scales, a trial may not be feasible. Epidemiological analysis of routinely collected large-scale healthcare data provides an opportunity to generate clinically useful evidence efficiently and cost-effectively. Therefore, we analysed data from anonymised linked health records of older adults with recurrent UTI to investigate gender-specific associations between long-term antibiotic prophylaxis and clinical outcomes, including hospitalisation, whilst accounting for comorbidities, and compare risk of each outcome by antibiotic class.

9.2 Methods

This was a retrospective cohort study using the CPRD. Patients were eligible for inclusion if, between 1st March 2004 and 31st December 2015, their data were of the quality required by CPRD, they were ≥65 years old, eligible for data-linkage with hospital admission data, and met the definition of recurrent UTI. We submitted the protocol and analysis plan for this study in 2016 and at that time the main clinical guideline for recurrent UTI was written by the Canadian Urological Association, who defined recurrent UTI as three or more uncomplicated incident UTIs in 12 months (92). We used this definition for our study. The recent NICE guideline for recurrent UTI use

a similar definition but also include people with 2 or more UTIs in the past 6 months (33).

Incident UTIs were identified using Read codes recorded by primary care clinicians or ICD-10 codes recorded in hospital admission data, as described in Figure 3.1 in chapter 3. Codes occurring within a short time-frame of one another could represent multiple consultations for the same UTI-related episode. Previous observational research regarded codes occurring within 28 days of one another as belonging to the same illness episode and those occurring greater than 28 days apart as representing separate or distinct infections (25, 73, 110). We therefore used this approach to distinguish repeat consultations for the same episode from incident episodes.

We excluded patients if they were temporary residents or had gaps in their data coverage. We also excluded those who had commenced a long-term antibiotic of interest prior to meeting the definition of recurrent UTI, those who met the definition of recurrent UTI but were prescribed long-term antibiotics other than those of interest to this study, and those with an exposure period of less than three months.

9.2.1 Exposures

The exposure of interest was prescription records indicating at least three consecutive months prescribing of trimethoprim, nitrofurantoin or cefalexin. We chose these antibiotics because:

1. Trimethoprim, nitrofurantoin and cefalexin were the only antibiotics recommended for long-term low-dose UTI prophylaxis by the British National Formulary during the study period.
2. Previous studies of care home residents in Northern Ireland and Wales found that trimethoprim and nitrofurantoin were the most common antibiotics prescribed for UTI prophylaxis (2, 173).
3. Including other long-term antibiotic prescriptions would risk assessing outcomes in patients where the prescription indication was not recurrent UTI, for example, long-term penicillins prescribed for recurrent cellulitis or prevention of infection in patients without a spleen.

To investigate associations between long-term antibiotic prophylaxis and outcomes, we partitioned patients' follow-up times into unexposed and exposed periods (Figure 9.1). Unexposed periods began from the day the patient met the definition of recurrent UTI to the earliest of, day of their first long-term antibiotic prescription, study end date (31st December 2015), death, or last day of available CPRD data. We identified long-term antibiotic prescriptions by searching for codes for nitrofurantoin, trimethoprim or cefalexin and restricting to those issued as a repeat prescription, rather than an acute prescription, using the "issueseq" variable in CPRD. These antibiotic are recommended to be taken once daily for UTI prophylaxis. Therefore, we used data on the quantity supplied to estimate the number of days of treatment covered by each prescription. We used these data to determine exposure periods and ensure that exposure periods contained at least three months of continuous long-term antibiotic prescriptions, allowing

up to seven days leeway at the end of each prescription for time to collect the next prescription. Exposed periods began from day of the first long-term antibiotic prescription to the earliest of, study end date (31st December 2015), death, or last day of available CPRD data, as a continuous period irrespective of whether there were periods when the prescribed long-term antibiotic was changed. Therefore, we regarded patients as exposed to long-term antibiotic prophylaxis from the day of their first prescription to the end of their follow-up. We estimated risk of each outcome during exposed versus unexposed periods.

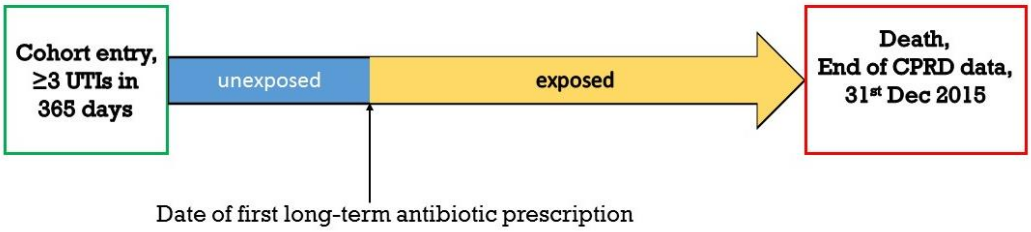


Figure 9.1. Partitioning of patient follow-up time according to exposure status.

To compare outcomes between the three specified antibiotics, we selected only those patients with an exposed period and partitioned their exposure period by the prescribed antibiotic (Figure 9.2). For example, a patient prescribed trimethoprim for six months and then nitrofurantoin for 9 months would have two exposure periods. For this analysis, follow-up began on the date of the first prescription and ended on the earliest of 90 days after the last prescription, date of the next exposure period, death, study end date, or last day of available CPRD data.

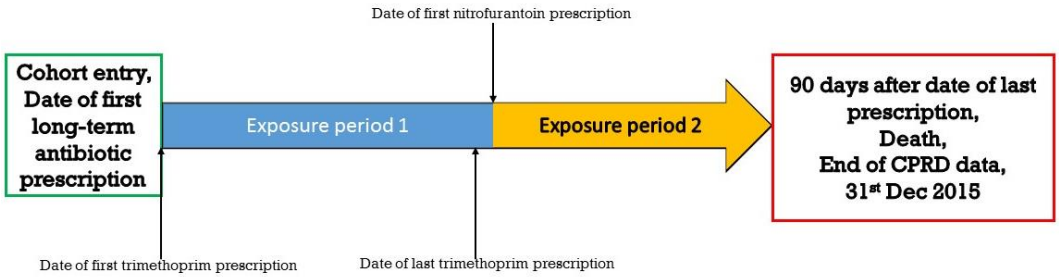


Figure 9.2. Partitioning exposure periods to compare different antibiotics prescribed for UTI prophylaxis.

9.2.2 Outcomes

The primary outcome was clinical recurrence, defined as a primary care record of symptoms or diagnoses indicating a UTI (using codes in code list 1 in Figure 3.1) and a same-day antibiotic prescription.

Secondary outcomes were all-cause primary care acute antibiotic prescribing, with one prescription equal to one event, UTI-related hospitalisation, ascertained from linked hospital data using relevant ICD-10 codes for UTI and cystitis (codes N30.0, N30.9, N39.0), and all-cause (emergency and elective) hospitalisation.

9.2.3 Statistical Analyses

We used primary care demographic and clinical codes to describe baseline characteristics for patients exposed and not exposed to long-term antibiotic prophylaxis, and, for those exposed, further described characteristics by antibiotic class. We used random effects Cox recurrent event models to estimate hazard ratios (HR) and 95% CIs for each outcome. To reduce indication bias, we used a shared frailty term to account for correlated multiple events per person. This approach introduces a random covariate into the model that induces dependence among the recurrent event times,

and describes the excess risk for distinct individuals whilst accounting for unmeasured heterogeneity that remains unexplained using observed covariates alone (174-176).

We adjusted for a range of potential confounding variables. These included age, Index of Multiple Deprivation score quintile, the presence or absence of a record indicating; diabetes, dementia, coronary heart disease, renal disease, stroke, cancer, heart failure, urinary incontinence and urinary catheter; polypharmacy, (defined as records indicating ≥5 long-term medications per months in the year prior to cohort entry), and a Charlson comorbidity score (125). We also used the most recent serum creatinine value recorded in the 24 months preceding the incident UTI and data for patient age, gender and ethnicity to calculate an eGFR as per the Modification of Diet in Renal Disease (MDRD) Study equation (127). We measured confounding variables using data inputted prior to the date of cohort entry, except for age, which was calculated at the time of each event.

We did several sensitivity analyses. The first was a pre-specified analysis where we selected only those patients with an unexposed *and* an exposed period and estimated risk of outcomes using a self-controlled case series design where each patient's unexposed period acted as their own control, thus reducing bias from between person residual confounding. We did a post-hoc analysis to assess robustness of associations between long-term antibiotic prophylaxis and outcomes, where we used data on time between prescriptions, number of tablets issued and prescribed dosage instructions to split exposed periods into "consistent exposure", "inconsistent exposure" and "post-exposure" periods and estimated risk of outcome for each period,

with the unexposed period as the reference. We also restricted analyses to only those prescribed the correct antibiotic dose defined as the dose recommended for UTI prophylaxis in adults by the BNF (50-100mg of nitrofurantoin at night, 100mg of trimethoprim at night, 125mg of cefalexin at night). Sensitivity analyses for the comparison between trimethoprim, nitrofurantoin and cefalexin included restricting to those prescribed the correct dose and those with only one exposure period.

9.3 Results

There were 966,454 patients aged ≥65 between 2004 and 2015 with data of the required quality and with linked hospital data, in the database. Of these, 931,945 (96%) met our initial eligibility criteria, and 25,276 (2.7%) had clinical records indicating recurrent UTI. Following further exclusions (Figure 9.3), we entered 19,696 patients from 393 primary care practices into our final cohort. 2737 (13.9%) of these patients had a period of exposure to long-term antibiotic prophylaxis, of whom 508 (18.6%) were men.

9.3.1 Baseline characteristics

Table 9.1 shows characteristics of included patients with recurrent UTI who were prescribed long-term antibiotic prophylaxis during their follow-up period (i.e., had a period of exposure) versus those who were not (i.e., remained unexposed). Characteristics were mostly similar except for higher proportions of patients with urinary incontinence and polypharmacy in those with a period of exposure. We adjusted for both these characteristics in our analyses. Baseline characteristics were also similar according to prescribed

antibiotic for those with exposure periods, except for a higher proportion of men in exposure periods with trimethoprim (21%) compared to nitrofurantoin (17%) or cefalexin (14%) (Table 9.2). Almost half of those exposed were initially prescribed trimethoprim. Over 20% of those exposed were prescribed their long-term antibiotic prophylaxis at a dose greater than that recommended for UTI prophylaxis by the British National Formulary (Table 9.3). Almost 50% of patients were prescribed long-term antibiotic prophylaxis for over two years.

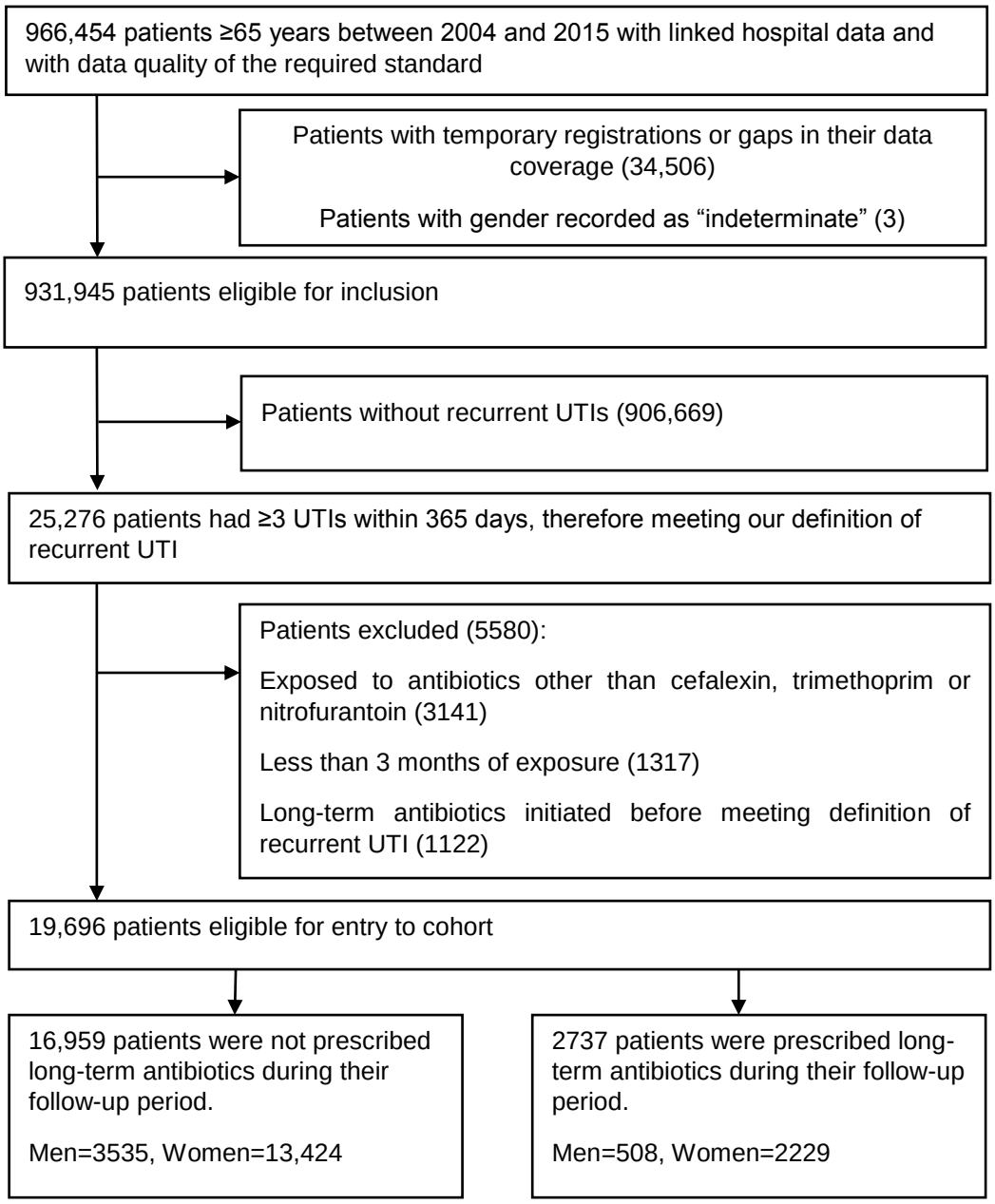


Figure 9.3. Flow of patients from initial identification in the database through to final cohort

Table 9.1. Characteristics of individuals with recurrent UTI prescribed long-term antibiotic prophylaxis versus those not prescribed long-term antibiotic prophylaxis. Values are numbers (%) unless otherwise stated

	Patients prescribed long-term antibiotic prophylaxis	Patients not prescribed long-term antibiotic prophylaxis
Total	2737	16959
Male	508 (18.6)	3535 (20.8)
Median (IQR) age at cohort entry	77.3 (71.4 – 84.0)	78.7 (72.3 – 85.1)
Median (IQR) follow-up time in days	1546 (877-2403)	826 (322-1650.5)
Index of multiple deprivation quintile:		
1 (least deprived)	661 (24.2)	3936 (23.2)
2	738 (27.0)	4441 (26.2)
3	606 (22.1)	3641 (21.5)
4	427 (15.6)	2876 (17.0)
5 (most deprived)	303 (11.1)	2048 (12.0)
missing	2 (0)	17 (0.1)
Housebound	108 (3.9)	816 (4.8)
Dementia	204 (7.4)	1268 (7.5)
Diabetes	475 (17.4)	2951 (17.4)
Coronary heart disease	587 (21.4)	3635 (21.4)
Congestive cardiac failure	130 (4.7)	1159 (6.8)
Renal Disease	492 (18.0)	3454 (20.4)
Stroke	344 (12.6)	2208 (13.0)
Urinary incontinence	630 (23.0)	3379 (19.9)
Urinary catheter	198 (7.2)	1248 (7.4)
Polypharmacy	1203 (44.0)	6935 (40.9)
eGFR:		
>90	156 (5.7)	1096 (6.5)
60-90	1101 (40.2)	6508 (38.4)
45-59	719 (26.3)	4547 (26.8)
30-44	362 (13.2)	2042 (12.0)
15-29	62 (2.3)	500 (2.9)
<15	6 (0.2)	74 (0.4)
missing	331 (12.1)	2192 (12.9)
Charlson score:		
0	887 (32.4)	5241 (30.9)
1	670 (24.5)	3804 (22.4)
2	488 (17.8)	3294 (19.4)
3	328 (12.0)	2122 (12.5)
4	179 (6.5)	1176 (6.9)
5	101 (3.7)	640 (3.8)
≥6	84 (3.1)	682 (4.0)

Table 9.2. Characteristics of patients according to antibiotic exposure period. Values are numbers (%) unless otherwise stated

	Trimethoprim	Nitrofurantoin	Cefalexin
Total	1559	1359	810
Male	329 (21.1)	230 (16.9)	116 (14.3)
Median (IQR) age at cohort entry	78.9 (73.1 - 85.5)	78.8 (73.5 - 85.1)	78.8 (73.4 - 84.9)
Median (IQR) follow-up time in days	319 (125.0 - 731.0)	314 (132.0 - 758.0)	400.5 (145.0 - 929.3)
Index of multiple deprivation quintile:			
1 (least deprived)	361 (23.2)	346 (25.5)	177 (21.9)
2	426 (27.3)	379 (27.9)	208 (25.7)
3	358 (23)	302 (22.2)	174 (21.8)
4	246 (15.8)	197 (14.5)	146 (18)
5 (most deprived)	168 (10.8)	133 (9.8)	105 (13)
missing	0 (0)	2 (0.1)	0 (0)
Housebound	66 (4.2)	39 (2.9)	33 (4.1)
Dementia	129 (8.3)	77 (5.7)	41 (5.1)
Diabetes	268 (17.2)	231 (17)	155 (19.1)
Coronary heart disease	333 (21.4)	295 (21.7)	167 (20.6)
Congestive cardiac failure	71 (4.6)	65 (4.8)	35 (4.3)
Renal Disease	280 (18)	226 (16.6)	155 (19.1)
Stroke	211 (13.5)	146 (10.7)	95 (11.7)
Urinary incontinence	364 (23.3)	320 (23.5)	196 (24.2)
Urinary catheter	129 (8.3)	83 (6.1)	52 (6.4)
Polypharmacy	668 (42.8)	584 (43)	369 (45.6)
eGFR:			
>90	87 (5.6)	74 (5.4)	32 (4)
60-90	615 (39.4)	591 (43.5)	294 (36.3)
45-59	419 (26.9)	344 (25.3)	229 (28.3)
30-44	204 (13.1)	168 (12.4)	135 (16.7)
15-29	41 (2.6)	19 (1.4)	22 (2.7)
<15	2 (0.1)	3 (0.2)	2 (0.2)
missing	191 (12.3)	160 (11.8)	96 (11.9)
Charlson score:			
0	504 (32.3)	459 (33.8)	254 (31.4)
1	374 (24)	327 (24.1)	202 (24.9)
2	285 (18.3)	246 (18.1)	156 (19.3)
3	194 (12.4)	149 (11)	95 (11.7)
4	96 (6.2)	92 (6.8)	46 (5.7)
5	58 (3.7)	47 (3.5)	30 (3.7)
≥6	48 (3.1)	39 (2.9)	27 (3.3)

Table 9.3. Initial choice, dose and duration of long-term antibiotic prophylaxis. Values are numbers (%) unless otherwise stated

	Men (n=508)	Women (n=2229)
Choice of antibiotic:		
Trimethoprim	282 (55.5)	1009 (45.3)
Nitrofurantoin	160 (31.5)	811 (36.4)
Cephalexin	66 (13.0)	409 (18.3)
Daily dose:		
As per BNF recommended dose	240 (47.2)	1104 (49.5)
Below recommended dose	0 (0)	2 (0.1)
Above recommended dose	109 (21.5)	498 (22.3)
Unable to calculate daily dose	159 (31.3)	625 (28.0)
Duration of treatment:		
3 months	5 (1.0)	17 (0.8)
4-6 months	53 (10.4)	217 (9.7)
7-12 months	102 (20.1)	355 (15.9)
13-18 months	70 (13.8)	320 (14.4)
19-24 months	57 (11.2)	214 (9.6)
>24 months	221 (43.5)	1106 (49.6)

9.3.2 Long-term antibiotic prophylaxis and risk of each outcome

Of 4043 men, 2750 men had 10,722 clinical recurrences diagnosed and treated in primary care. There were 9387 recurrences during unexposed periods and 1335 recurrences during exposed periods (Figure 9.4). Compared to unexposed periods, there was a statistically significant lower risk of clinical recurrence during periods of exposure to long-term antibiotic prophylaxis (adjusted HR 0.49, 95% CI 0.45-0.54). There was a 22% reduction in risk of UTI-related hospitalisation (adjusted HR 0.78, 95% CI 0.64-0.94) and a 46% reduction in risk of all-cause acute primary care antibiotic prescribing (adjusted HR 0.54, 95% CI 0.51-0.57). We found no significant association between long-term antibiotic prophylaxis and all-cause hospitalisation. Risk estimates were consistent across all sensitivity analyses (Table 9.4).

Of 15,653 women, 11,845 women had 60,124 clinical recurrences, with 51,748 recurrences during unexposed periods and 8376 recurrences during

exposed periods (Figure 9.4). Compared to unexposed periods, there were statistically significant lower risks of clinical recurrence (adjusted HR 0.57, 95% CI 0.55-0.59), and all-cause acute antibiotic prescribing (adjusted HR 0.61, 95% CI 0.59-0.62), during periods of exposure to long-term antibiotic prophylaxis. These estimates were consistent across all sensitivity analyses. There was a 19% increase in risk of UTI-related hospitalisation during periods of long-term antibiotic prophylaxis (adjusted HR 1.19, 95% CI 1.08 -1.31). However, when we re-assessed the risk of UTI-related hospitalisation in our sensitivity analysis using a self-controlled case series design, the direction of effect reversed, showing an 18% risk reduction, (adjusted HR 0.82, 95% CI 0.72-0.94) (Table 9.5). We found no significant association between long-term antibiotic prophylaxis and all-cause hospitalisation in our main analysis, but found an 8% risk increase in our self-controlled case series analysis (adjusted HR 1.08, 95% CI 1.02-1.15).

9.3.3 Comparing outcomes between trimethoprim, nitrofurantoin and cefalexin

There were 3728 exposure periods among 2737 patients, 1559 for trimethoprim, 1359 for nitrofurantoin and 810 for cefalexin. There were 2553 clinical recurrences among 853 patients during trimethoprim exposure, 2233 clinical recurrences among 707 patients during nitrofurantoin exposure, and 1679 clinical recurrences among 474 patients during cefalexin exposure. Compared to trimethoprim, exposure to nitrofurantoin or cefalexin was associated with a reduced risk of clinical recurrence (adjusted HR for nitrofurantoin 0.87, 95% CI 0.80-0.95, adjusted HR for cefalexin 0.70, 95% CI 0.64-0.77). There were no statistically significant

differences between trimethoprim and nitrofurantoin for any other outcome. Compared to trimethoprim, cefalexin exposure was associated with an 18% reduction in all-cause primary care acute antibiotic prescribing (adjusted HR 0.82, 95%CI 0.77-0.88), but was not statistically significantly associated with UTI-related hospitalisation or all-cause hospitalisation.

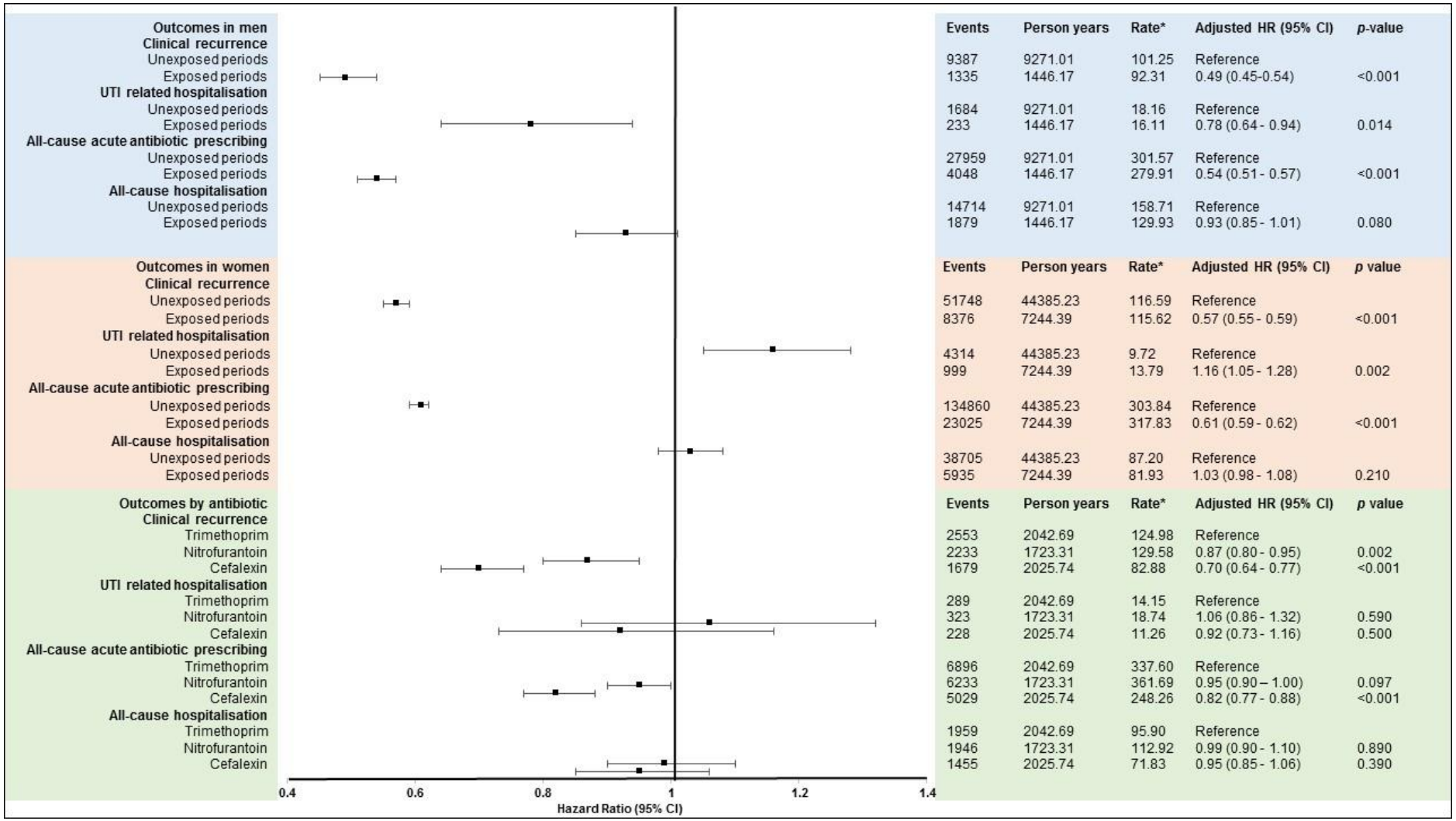


Figure 9.4. Number of events, person years of follow-up, and adjusted hazard ratios for each outcome

Table 9.4. Number of events, person years of follow-up and adjusted hazard ratios for main and sensitivity analyses in older men

									Self-controlled case series analysis						
	Events	Person-years	Rate[d]	Crude HR	Adjusted HR[a]	LCI[b]	UCI[c]	*P* value	Events	Person-years	Rate[d]	Adjusted HR	LCI[b]	UCI[c]	*P* value
Clinical recurrence															
Unexposed periods	9387	9271.01	101.25	R	R	R	R	R	1563	514.74	303.65	R	R	R	R
Exposed periods (main analysis)	1335	1446.17	92.31	0.47	0.49	0.45	0.54	<.001	1335	1446.17	92.31	0.31	0.28	0.34	<0.001
Consistent exposure periods	964	981.96	98.17	0.50	0.51	0.47	0.56	<.001							
Inconsistent exposure periods	161	179.94	89.47	0.37	0.42	0.34	0.51	<.001							
Post-exposure periods	210	284.27	73.87	0.38	0.45	0.38	0.53	<.001							
UTI-related hospitalisation															
Unexposed periods	1684	9271.01	18.16	R	R	R	R	R	139	514.74	27.00	R	R	R	R
Exposed periods (main analysis)	233	1446.17	16.11	0.77	0.78	0.64	0.94	0.01	233	1446.17	16.11	0.60	0.46	0.79	<0.001
Consistent exposure periods	156	981.96	15.89	0.75	0.74	0.59	0.92	0.01							
Inconsistent exposure periods	26	179.94	14.45	0.74	0.80	0.50	1.29	0.38							
Post-exposure periods	51	284.27	17.94	0.82	0.92	0.64	1.32	0.78							
Acute antibiotic prescribing															
Unexposed periods	27959	9271.01	301.57	R	R	R	R	R	3387	514.74	658.01	R	R	R	R
Exposed periods (main analysis)	4048	1446.17	279.91	0.53	0.54	0.51	0.57	<0.001	4048	1446.17	279.91	0.40	0.38	0.43	<0.001
Consistent exposure periods	2876	981.96	292.88	0.55	0.55	0.52	0.58	<0.001							
Inconsistent exposure periods	492	179.94	273.42	0.47	0.49	0.43	0.55	<0.001							
Post-exposure periods	680	284.27	239.21	0.51	0.54	0.49	0.60	<0.001							
All-cause hospitalisation															
Unexposed periods	14714	9271.01	158.71	R	R	R	R	R	744	514.74	144.54	R	R	R	R
Exposed periods (main analysis)	1879	1446.17	129.93	0.90	0.93	0.85	1.01	0.08	1879	1446.17	129.93	0.98	0.88	1.10	0.75
Consistent exposure periods	1323	981.96	134.73	0.93	0.92	0.84	1.01	0.08							
Inconsistent exposure periods	164	179.94	91.14	0.72	0.84	0.68	1.03	0.09							
Post-exposure periods	392	284.27	137.90	0.90	1.01	0.87	1.18	0.87							

Green cells indicate point estimates that are consistent across analyses, i.e., either all non-significant, or all in the same direction.

[a] Hazard ratio adjusted for age, deprivation score quintile, diabetes, dementia, coronary heart disease, renal disease, stroke, cancer, heart failure, urinary incontinence, urinary catheter; polypharmacy, and Charlson comorbidity score
[b] Lower confidence interval
[c] Upper confidence interval
[d] Rate is per 100 person years

Table 9.5. Number of events, person years of follow-up and adjusted hazard ratios for main and sensitivity analyses in older women

									Self-controlled case series analysis						
	Events	Person-years	Rate[d]	Crude HR	Adjusted HR[a]	LCI[b]	UCI[c]	*P* value	Events	Person-years	Rate[d]	Adjusted HR	LCI[b]	UCI[c]	*P* value
Clinical recurrence															
Unexposed periods	51748	44385.23	116.59	R	R	R	R	R	9753	3423.50	284.88	R	R	R	R
Exposed periods (main analysis)	8376	7244.39	115.62	0.55	0.57	0.55	0.59	<.001	8376	7244.39	115.62	0.34	0.33	0.36	<0.001
Consistent exposure periods	5298	4683.67	113.12	0.55	0.56	0.54	0.58	<.001							
Inconsistent exposure periods	1719	1229.40	139.82	0.59	0.64	0.60	0.69	<.001							
Post-exposure periods	1359	1331.32	102.08	0.52	0.58	0.54	0.62	<.001							
UTI-related hospitalisation															
Unexposed periods	4314	44385.23	9.72	R	R	R	R	R	565	3423.50	16.50	R	R	R	R
Exposed periods (main analysis)	999	7244.39	13.79	1.14	1.16	1.05	1.28	0.00	999	7244.39	13.79	0.82	0.72	0.94	0.005
Consistent exposure periods	606	4683.67	12.94	1.15	1.13	1.02	1.26	0.02							
Inconsistent exposure periods	172	1229.40	13.99	1.06	1.13	0.92	1.37	0.25							
Post-exposure periods	221	1331.32	16.60	1.20	1.29	1.09	1.53	0.00							
Acute antibiotic prescribing															
Unexposed periods	134860	44385.23	303.84	R	R	R	R	R	20647	3423.50	603.10	R	R	R	R
Exposed periods (main analysis)	23025	7244.39	317.83	0.60	0.61	0.59	0.62	<0.001	23025	7244.39	317.83	0.44	0.43	0.45	<0.001
Consistent exposure periods	14482	4683.67	309.20	0.59	0.60	0.58	0.61	<0.001							
Inconsistent exposure periods	4506	1229.40	366.52	0.61	0.63	0.60	0.66	<0.001							
Post-exposure periods	4037	1331.32	303.23	0.60	0.63	0.60	0.65	<0.001							
All-cause hospitalisation															
Unexposed periods	38705	44385.23	87.20	R	R	R	R	R	2898	3423.50	84.65	R	R	R	R
Exposed periods (main analysis)	5935	7244.39	81.93	1.05	1.03	0.98	1.08	0.21	5935	7244.39	81.93	1.08	1.02	1.15	0.013
Consistent exposure periods	3593	4683.67	76.71	1.00	1.00	0.96	1.04	0.84							
Inconsistent exposure periods	1012	1229.40	82.32	1.08	1.10	1.02	1.18	0.02							
Post-exposure periods	1330	1331.32	99.90	1.18	1.22	1.15	1.30	<0.001							

Green cells indicate point estimates that are consistent across analyses, i.e., either all non-significant, or all in the same direction.

[a] Hazard ratio adjusted for age, deprivation score quintile, diabetes, dementia, coronary heart disease, renal disease, stroke, cancer, heart failure, urinary incontinence, urinary catheter; polypharmacy, and Charlson comorbidity score
[b] Lower confidence interval
[c] Upper confidence interval
[d] Rate is per 100 person years

9.4 Discussion

We found reduced risks of clinical recurrence and all-cause acute antibiotic prescribing for older men and women with recurrent UTI during periods of long-term antibiotic prophylaxis. There was also a reduced risk of UTI-related hospitalisation in older men. These associations were consistent across several sensitivity analyses. We found an unexpected increased risk of UTI-related hospitalisation for women associated with exposure to long-term antibiotic prophylaxis, although the direction of effect reversed in our analysis that used individuals as their own controls. We therefore hypothesise that this inconsistent finding is due to residual unmeasured confounding that was unaccounted for in the main analyses. For example, women who received prophylaxis may have been less healthy than women who did not receive prophylaxis and thus at increased risk of hospitalisation irrespective of exposure. This may also explain the inconsistencies between findings for antibiotic prophylaxis and all-cause hospitalisation in women. Given the observed inconsistencies in risk estimates, these findings warrant further investigation. We also found that, compared to trimethoprim, nitrofurantoin and cefalexin were associated with a reduced risk of clinical recurrence, and cefalexin was associated with a reduced risk of all-cause acute antibiotic prescribing.

9.4.1 Results in context

To our knowledge, there are no rigorous randomised trials or observational studies investigating the effect of antibiotic prophylaxis in older men with recurrent UTI. One previous observational study found that around 13% of older men who experienced a UTI had at least one recurrence (73). Our analyses showed that only 13% of older men with recurrent UTI were prescribed long-term antibiotic

prophylaxis, but those that were had significantly lower rates of clinical recurrence, UTI-related hospitalisation and all-cause acute antibiotic prescribing. The low prescribing rates are likely due to male UTI being considered a more complicated infection and thus reluctance to prescribe until serious causes have been excluded, and also due to the dearth of empirical data to inform clinical practice.

Our finding of reduced risk of clinical recurrence for older women exposed to long-term antibiotic prophylaxis is consistent with findings from meta-analyses of post-menopausal women (177) and younger women (93). Our finding of an increased risk of UTI-related hospitalisation among women exposed to long-term antibiotic prophylaxis in our main analysis warrants further investigation. To the best of our knowledge, no previous observational research has reported on the association between antibiotic prophylaxis for UTI and UTI-related hospitalisation, and clinical trials of antibiotic prophylaxis in postmenopausal women did not assess hospitalisation as an outcome (177). Reversal of the risk estimates in our self-controlled analysis suggests that the initial finding was due to residual confounding but the study needs to be repeated in an independent data-set to address this uncertainty.

9.4.2 Strengths and limitations

To our knowledge, this study is the first to; provide robust data to inform the use of long-term antibiotic prophylaxis in older men with recurrent UTI; estimate risk of important clinical outcomes, including hospitalisation, in an unselected, real-world cohort of older adults with recurrent UTI; and provide estimates of comparative effectiveness of three antibiotics commonly used for UTI prophylaxis. This is a large study based on a representative sample of older

people with over 60,000 person years of follow-up. We used a strict definition of three clinically recorded incident UTI episodes in one year to define eligibility and limit indication bias. Clinical trials used self-report (94), primary care records (97), or were unclear about how they identified patients with a history of recurrent UTI (95, 96). Similar to previous database research on infections, we used Read and ICD-10 codes to identify UTI episodes and made allowances to distinguish repeat consultations for the same episode from incident episodes (25, 110). We used primary care records to ascertain exposure to long-term antibiotic prophylaxis. Recording of prescriptions issued in UK primary care has high levels of completeness, thus representing an accurate and reliable source of exposure data (178). We used clinically recorded diagnoses to adjust for a range of co-morbid conditions with previous research suggesting these are reliably coded in primary care records (130).

A limitation of our study is the use of clinical recurrence rather than microbiologically confirmed recurrence as the primary outcome. The main reason for this is that the CPRD does not contain microbiological data but, even if it did, urine sampling in UK primary care is highly variable and therefore less useful in a retrospective study. The lack of microbiology data also meant we were unable to investigate any impact on urinary bacterial antibiotic resistance. Our exposure data represented antibiotic prescribing, not antibiotic use. We were unable to investigate antibiotic related adverse events. A wide variety of codes could be used to record these events and it is difficult to reliably associate these codes with the prescribed antibiotic without a more detailed account of the clinical scenario. It is likely that residual confounding affected the findings regarding antibiotic prophylaxis and UTI-related hospitalisation in older women. Despite our

design, indication bias and residual confounding may also have affected other findings. However, there were few baseline differences between those unexposed to long-term antibiotic prophylaxis versus those exposed. Furthermore, we carried out several sensitivity analyses and interpreted inconsistent risk estimates cautiously, and within the constraints of the limitations inherent in observational study designs.

9.5 Implications

Clinicians should consider several factors when discussing the risks and benefits of long-term antibiotic prophylaxis in older women with recurrent UTI. Firstly, the evidence from this study and from previous trials, showing that long-term antibiotic prophylaxis reduces the risk of UTI recurrence. Secondly, trial evidence showing that long-term antibiotic prophylaxis does not significantly increase the risk of adverse events but does significantly increase the rate of urinary and fecal antimicrobial resistance. Thirdly, the findings from this study that suggest the association between antibiotic prophylaxis and the risk UTI-related hospitalisation is not clear. We suggest clinical guidelines make recommendations around antibiotic prophylaxis for recurrent UTI clearer, highlighting risks, benefits, and ongoing uncertainties, with clear guidance on appropriate patient selection and monitoring. We suggest recommending nitrofurantoin first-line for those with no contraindication.

Our analyses suggest older men with recurrent UTI could benefit from long-term antibiotic prophylaxis. We suggest clinicians consider long-term nitrofurantoin in selected older men with a clear history of recurrent UTI, following appropriate assessment for treatable functional or structural causes, and in light of the ongoing uncertainty about rates of adverse events and impact on antibiotic

resistance. In the absence of an adequately powered randomised trial, these study results provide the only robust data currently available to inform clinical practice in this area.

9.6 Conclusions

Antibiotic prophylaxis may reduce rates of recurrence and all-cause antibiotic prescribing in older people with recurrent UTI. They may also reduce UTI-related hospitalisations in older men but their effect on hospitalisations in older women requires further investigation, as does their impact on antibiotic resistance.

10 Main findings and implications for practice, policy and future research

The aim of the research reported in this thesis was to generate new evidence that could help towards more standardised and prudent antibiotic prescribing for UTI in older people. In this chapter, we summarise the main findings and discuss how they may inform clinical practice, policy and future research, and reflect on the strengths and limitations of the research.

10.1 Main findings

The main findings of this research are:

1. **21% of older people in this CPRD sample were clinically diagnosed with at least one UTI between 2004 and 2014, 96% of whom received a same-day empirical antibiotic prescription. In the 14-28 days following empirical antibiotic prescription for suspected UTI, 6% of older people in this sample re-consulted and received another antibiotic prescription, 2.5% were hospitalised for UTI, sepsis, or AKI, and 1% died.**

These findings highlight the impact of UTI-related clinical presentations on NHS workload. Population estimates suggest there are almost 12 million adults aged over 65 in the UK (159). We estimate that If 21% of adults in this age-group present at least once with a suspected UTI over the next 10 years, this will initially result in 2.5 million GP consultations and 2.4 million

antibiotic prescriptions. Following initial presentation, 145,000 older people will re-consult their GP and receive another antibiotic prescription, 60,000 will be hospitalised for UTI, sepsis, or AKI, and 24,000 will die. These may be conservative estimates given that the number of adults aged 65 and over in the UK are projected to increase to around 18 million, and the median number of UTI-related presentations in our sample was 2. However, these estimates are based on a sample where 96% were prescribed same-day empirical antibiotics. Previous work based on reviews of clinical guidelines and expert opinion suggests that ideally, 75-90% of people presenting with UTI should receive same-day antibiotics (179). Furthermore, coding issues meant our sample did not include about one-third of all possible UTI presentations. Therefore, including patients with a higher than expected empirical antibiotic prescribing rate, and not including people who were prescribed a UTI-specific antibiotic but were not coded accurately enough for inclusion, may have introduced bias and affected the generalisability of our findings.

Despite the aforementioned limitations, our work suggests that UTI-related presentations are an important source of NHS workload and antibiotic prescribing. There are several implications of these findings for clinical practice. First, older people need to be supported with evidence-based interventions that may safely prevent both UTI, and associated symptoms that are commonly mistaken for UTI. For example, recent randomised trial evidence found that increasing fluid intake by 1.5 litres of water a day in young women with recurrent UTIs, reduced the mean number of cystitis episodes from 3.2 to 1.7 per year, and mean number of antibiotic

prescriptions for UTI from 3.6 to 1.9 per year. Implementing this intervention in community-dwelling older people may be challenging, but implementation in care homes may be less difficult and may prevent a sizable proportion of UTIs given the high incidence in this population. Measures to prevent cystitis symptoms related to non-UTI causes may also help to reduce the proportion of patients who present with suspected UTI and consequently receive an antibiotic prescription. For example, older women may present with cystitis symptoms secondary to oestrogen deficiency. Randomised trials found that older women using vaginal oestrogen cream or pessaries had a 36-75% reduction in the relative risk of a UTI diagnosis, compared to placebo (103). Therefore, prevention of UTI and genitourinary symptoms commonly mistaken for UTI may be the most effective method of reducing unnecessary antibiotic prescribing for UTI, because once patients consult with these symptoms, most will receive an antibiotic prescription.

Second, there is a need for a shift in the diagnostic approach to UTI in older people. A total of 96% of older people who consulted with a suspected UTI received an empirical antibiotic prescription, presumably because the consulting clinician judged a UTI to be likely. Yet, the POETIC study (described in detail in section 2.9) found that of 726 women (mean age 45 years) presenting to GPs with suspected UTI, all of whom provided a mid-stream urine sample for microbiological analysis, 702 (88.5%) were prescribed antibiotics but only 259 (35.7%) had a microbiologically proven UTI (74). The diagnostic yield in older people may be lower because urine sampling may occur when they present with non-specific symptoms such as change in behaviour or falls. The potential for unnecessary antibiotic

prescribing may be greater because urine sampled for a non-specific clinical presentation may show bacterial growth that is actually asymptomatic bacteriuria but the interpreting clinician judges it as a UTI. Even if diagnostic yield in older people is similar to the POETIC study, up to 65% or 1.56 million of the projected 2.4 million antibiotic prescriptions for suspected UTI over the next 10 years may be unnecessary. Clinicians therefore need to adopt a more sceptical approach to UTI diagnosis in older people, with more consideration of alternate diagnoses that could explain the presenting symptoms, and better use of data that provide some insights into the predictive value of different symptoms, signs and bedside tests. However, the limitation of these data is that the performance of the symptoms, signs and bedside tests were most often assessed against urine culture, which is an imperfect reference standard.

Third, clinicians need to be supported to widen the use of delayed antibiotic prescribing as a potential management strategy for selected patients presenting with suspected UTI. Current NICE and Public Health England guidance suggests considering delayed prescribing for those with milder symptoms (32, 49), and previous research in younger women found delayed prescribed reduced antibiotic use compared to immediate prescribing without any important impact on symptoms severity or duration (50).

Given our findings, future research should develop and test interventions that may prevent UTI. For example, there is interest in immunoprophylaxis but its effect is not fully understood and further adequately powered randomised trials are needed (171). There is also a need for a programme of work around UTI diagnosis. A key limitation for UTI diagnostic accuracy

studies is the lack of an ideal reference standard. It may be time for a “back to basics” approach, to truly nail down what biochemical and microbiological features in urine reflect a UTI. Without addressing the current limitations of urine culture as a reference standard, future diagnostic studies will not add to the current limited evidence base. Finally, there is a need for randomised trials of delayed versus immediate antibiotic prescribing in older adults to understand if benefits seen in younger women are applicable to this population.

2. **Between 2004 and 2014, trimethoprim was prescribed to about 50% of older people with UTI with little change over time, Nitrofurantoin prescribing increased, and broad-spectrum antibiotic prescribing decreased. Outcomes were no better for patients empirically prescribed broad-spectrum antibiotics compared to those empirically prescribed nitrofurantoin. Over the same time period, the duration of antibiotic treatment prescribed also improved, with increases in guideline adherent 3-day treatment for older women and seven-day treatment for older men.**

These findings suggest a positive shift in antibiotic prescribing for UTI. Antibiotic stewardship campaigns and policies have encouraged a reduction in broad-spectrum antibiotic prescribing to reduce the impact of these agents on rates of antibiotic resistance. However, there is scope for further improvement given that around 20% of older adults in our sample received

a broad-spectrum antibiotic for suspected UTI. The prevalence of trimethoprim prescribing and the lack of change over time was an unexpected finding, especially given the increasing rates of trimethoprim resistance in the UK and concerns that sub-optimal treatment of trimethoprim-resistant UTIs may be a contributory factor to increasing rates of blood stream infections (7). The changes in antibiotic treatment duration were also encouraging, showing positive practice change that aligned with clinical guidelines and the antibiotic stewardship agenda.

The main implication for practice is that there is potential for further reductions in broad-spectrum antibiotic prescribing for UTI in older adults, especially given that we found no associated benefit compared to nitrofurantoin. Implications for policy makers include greater clarity on the definition of “complicated” and “uncomplicated” UTI, as perceived complicated UTI may be a driver of broad-spectrum antibiotic prescribing for UTI in older people. There is also potential to increase the proportion of older women prescribed three-day treatment, especially as previous meta-analyses found no clinically important differences in outcome between three and seven-day treatment (62). Policy makers could plan systematic antibiotic prescribing audit and feedback that includes choice and duration of prescribed antibiotics to allow practices to benchmark their prescribing with peers and identify specific outlying prescribing behaviours that may need amending. This peer-comparison intervention was found to effectively reduce inappropriate antibiotic prescribing for respiratory tract infections in a randomised trial set in primary care in the US (180). Open source data platforms such as openprescribing.net (https://openprescribing.net/) would

allow policy makers to provide such feedback quickly and inexpensively for all-cause antibiotic prescribing, but because these platforms have no data on the indication for the antibiotic prescription, other methods (such as CPRD data) would be required for UTI-specific prescribing.

Future research should aim to understand why some patients still receive prescriptions for broad-spectrum antibiotics, and develop and test complex interventions that further improve prescribing behaviour. Given the volume of antibiotics prescribed for UTI and the threat of antimicrobial resistance, there is a need for randomised trials of safe and effective non-antibiotic treatment for UTI. To date, trials of non-steroidal anti-inflammatory drugs have found them to be inferior to antibiotics (99, 101, 181), and trials of other agents, such as uva-ursi (182), are ongoing with final results awaited.

3. **Patients prescribed trimethoprim had a consistently greater risk of hospitalisation for AKI compared to patients prescribed other antibiotics.**

The analyses in this thesis confirm previous findings of an increased risk of acute kidney injury following trimethoprim prescribing. Several observational studies found an association between trimethoprim prescribing and hyperkalaemia, acute kidney injury, and sudden death, first in patients' co-prescribed medications affecting the renin-angiotensin system (81, 83, 84, 126), and more recently, in older patients irrespective of other prescribed medication (80). The implication of this finding for clinical

practice is that trimethoprim should be avoided in older people using medication that increases their risk of hyperkalaemia, for example, angiotensin-converting-enzyme inhibitors, aldosterone receptor blockers, potassium-sparing diuretics, and in those whose clinical presentation is suggestive of acute kidney injury. Implications for policy makers is to raise awareness amongst prescribers of this potentially serious adverse event, which is not mentioned in the recent NICE guideline on antimicrobial prescribing for UTI that recommends trimethoprim as a possible first-line therapy in patients at low-risk of resistance (183). Given that numerous studies have investigated this association, it is unlikely that further observational research will add significantly to the evidence base.

4. **Nitrofurantoin prescribing was not associated with worse outcomes in older people with renal impairment, and was actually associated with a reduction in the risk of AKI compared to trimethoprim.**

This is an important finding. Nitrofurantoin is a useful drug for UTI treatment. Previous research shows that only 1-2% of bacterial pathogens from UK community urine samples are resistant to nitrofurantoin (14), and nitrofurantoin-related serious adverse effects are rare (59). Concerns about poorer efficacy in patients with moderate or severe renal impairment led to warnings to avoid nitrofurantoin, resulting in prescriptions of alternate antibiotics. The most common antibiotic prescribed to older people with moderate or severe renal impairment and suspected UTI in our sample was

trimethoprim. However, previous research shows that 20-30% of bacterial pathogens from UK community urine samples are resistant to trimethoprim (14). Furthermore, as discussed previously, trimethoprim is associated with hyperkalaemia, which is more common in patients with renal impairment than those with normal renal function (184). Therefore, the lack of any evidence in our analyses to suggest reduced efficacy, the finding of a reduced rate of AKI hospitalisation, and the finding in previous research of low resistance rates, could increase healthcare professionals confidence in prescribing nitrofurantoin to older people with moderate or severe renal impairment. Our findings highlight the need for policy makers and guideline developers to re-appraise and clarify the evidence around the use of nitrofurantoin in older people with renal impairment and further support its use in this population. However, a limitation of our findings is the lack of microbiology data in our data-source, and therefore our inability to ascertain associations between nitrofurantoin and resistance-related outcomes.

5. **Only around 20-30% of older women were prescribed the recommended 3-day course of antibiotic treatment for UTI, with 40-50% receiving a prescription for ≥ 7-days.**

This was an unexpected finding. The clinical guideline recommendation of 3-day antibiotic therapy for uncomplicated UTI in women is supported by meta-analyses of randomised trials showing similar clinical outcomes between women prescribed 3-day versus 7-day antibiotic therapy (62, 185). One meta-analysis only included randomised trials in postmenopausal

women (62), thus increasing generalisability to the population studied in this thesis. However, clinicians may have prescribed 7-day antibiotic therapy because of uncertainty about whether the presenting features represented “uncomplicated” UTI, and concern about a poor outcome with 3-day therapy. Further uncertainty may have arisen from some clinical guidelines stating that their recommendations excluded older people (19). Therefore, the main implication of this finding for clinical practice is to clarify definitions of “uncomplicated” and “complicated” UTI to reduce uncertainty, and to include older people in recommendations in clinical guidelines. Future research efforts should aim to understand reasons for prescribing unnecessarily long courses of antibiotics and how best to address these to promote more prudent prescribing.

6. **3-day antibiotic treatment in older men with suspected UTI was associated with an increased risk of possible treatment failure, but a reduced risk of AKI hospitalisation compared to 7-day treatment.**

This finding warrants further investigation. There are potential benefits for patients and the NHS from safe and effective shorter treatment of UTI in older men. It is unclear from our data whether the higher rate of re-consultation and re-prescription amongst men receiving 3-day prescriptions was due to treatment failure, antibiotic side effects, or planned follow-ups. Furthermore, the lower rate of AKI hospitalisation amongst men receiving 3-day prescriptions may be due to residual confounding. Given the

limitations of these data, this finding should not affect clinical practice. However, the potential benefits associated with this finding support justification for a randomised trial of 3 versus 7-day antibiotic therapy for older men presenting to primary care with a UTI. Any such trial also presents an opportunity to generate new evidence for other uncertainties related to antibiotic prescribing. For example, the trial could include a third arm and test the recently debated strategy of symptom guided treatment versus 3 days versus 7 days, to see if antibiotic treatment is effective in those who stop once symptoms have resolved rather than completing the prescribed course (161). The trial could also generate new evidence on the effect of short versus long durations of antibiotic treatment on subsequent antibiotic resistance, highlighted by the National Institute of Health and Care Excellence as an area where further research is needed to widen understanding (115).

7. **Randomised trial evidence for the effect of long-term antibiotic prophylaxis for recurrent UTI in older people is limited to three small studies of postmenopausal women that lack data to draw firm conclusions about the impact of prophylaxis on UTI-related hospitalisations or antibiotic resistance.**

There is limited high quality randomised trial evidence to support the use of antibiotic prophylaxis for recurrent UTI in older people. Despite this, prophylaxis for recurrent UTI is the most common reason for antibiotic prescribing in care home residents (2, 3, 186). Our findings highlight

ongoing uncertainty around the use of antibiotic prophylaxis for recurrent UTI including the lack of evidence for its use in older men and the relatively little understanding of the impact on subsequent antibiotic resistant infections. The implications for clinical practice are to encourage thoughtful consideration of these limitations when discussing the benefits and harms or antibiotic prophylaxis with older people. Future research efforts should aim to test the effectiveness of antibiotic prophylaxis in adequately powered trials that include older men and care home residents, use a co-primary endpoint incorporating UTI recurrence rate and the acquisition of antibiotic resistant urinary pathogens, and consider long-term follow-up with routinely collected data to understand impact on rates of UTI-related hospitalisation, especially for bacteraemia.

8. **Antibiotic prophylaxis was associated with a reduced risk of UTI recurrence, hospitalisation, and all-cause acute antibiotic prescribing in older men.**

The study reported in chapter 9 was the first to investigate the use of antibiotic prophylaxis for recurrent UTI in older men. We found evidence of benefit that was consistent across several analyses. This study could inform prescribing of prophylaxis for older men, albeit with the normal caveats of observational data, and continued uncertainty around the impact of prophylaxis on antibiotic resistance. That said, to the best of our knowledge, there are no other data that can be drawn upon for this clinical scenario so clinicians could consider antibiotic prophylaxis for select older men with a

clear history of recurrent UTI, following appropriate assessment for treatable functional or structural causes.

10.2 Reflecting on the research in this thesis

This thesis arose from a desire to improve antibiotic prescribing for acute and recurrent UTI in older people. We wanted to know whether different antibiotic prescription strategies affected patient outcomes. We chose to do this using routinely collected healthcare data because this meant we could address several objectives efficiently and cost-effectively with adequate power to study the under-researched older population.

Two main limitations of our research were lack of microbiology data and the potential for residual confounding. The lack of microbiology data meant all comparisons were between patients with *suspected* UTI. Microbiology would have added additional value for two reasons; first, it would have allowed better understanding of whether patients with poor outcomes (e.g., death) actually had a confirmed UTI or not; second if would allowed study of antibiotic resistance related outcomes. Residual confounding is a key issue with observational data. We addressed measured confounders by adjusting in multivariable regression models and by matching on a propensity score. In the studies where we used propensity score matching, we achieved adequate balance of measured baseline characteristics. However, we were unable to address *unmeasured* confounders. Two patients with the same Read codes, may have presented with different symptoms and signs, had unrecorded differences in their general health, and therefore received different antibiotic prescriptions. Therefore, difference in their outcomes may have related to their general health or

presenting features rather than the antibiotic prescription. Potentially important unmeasured confounders include:

- Vital signs (e.g., temperature, heart rate) as indicators of the clinical severity of the presentation. More severe presentations may have prompted prescribing non-recommended antibiotics (e.g., broad-spectrum agents), and also contributed to poorer outcomes.
- Signs of complicated UTI, such as renal angle tenderness. This again would reflect a more severe presentation and could affect exposure and outcome in the same way as abnormal vital signs.
- Patient-reported symptom severity, again as an indicator of the clinical severity of presentation.
- A measure of frailty, as an indicator of the patient's general health. Frail patients may both be perceived to be at greater risk of an adverse outcome, and have a true greater risk of an adverse outcome, therefore potentially affecting the antibiotic prescribing decision and UTI-related outcome.
- Time of day, as antibiotic prescribing decisions may change as the day progresses, consistent with the hypothesis that decision fatigue progressively impairs clinicians' ability around ordering tests and treatments (187).

Because of the potential for unmeasured confounding, we were careful with the language we used and described associations as being between "patients who received a prescription for X", and the outcomes, rather than simply between prescription X and the outcome. We were also cautious with our interpretation of any findings.

There are potential measured confounders that were not adjusted for. We did not adjust for a history of recurrent UTI but this may affect antibiotic choice and duration and a patients risk of treatment failure. The relationship between antibiotic prescribing and AKI could be affected by non-steroidal anti-inflammatory (NSAID) medication use at the time of a UTI. We did not have data on over the counter NSAID use but could have adjusted for prescribed NSAID use. Other confounders of the relationship between antibiotic choice and AKI include metformin use, diarrhoea or vomiting, and dehydration, and these should have been appropriately adjusted for.

Another related limitation is that based on certain definitions, age alone would be enough to justify treating the patients in our sample as “complicated UTI”, and hence prescribing outside of the recommendations. Therefore, we did not comment on the appropriateness (or not) of the prescribed antibiotics but instead focussed on the impact of the antibiotic on the stated outcomes.

Given the above limitations, it is important to reflect on whether these data were appropriate for the objectives of this thesis. The benefits of these data include their size, generalisability, and reliability and completeness of recording of the prescriptions used as exposures in this thesis. Furthermore, addressing even one of the objectives of this thesis with a randomised trial would have been more expensive and taken longer than addressing all objectives using routinely collected data, especially given the huge challenges of recruiting and retaining older people in trials. The thesis aim was to generate new knowledge that could help to standardise antibiotic prescribing for UTI in older people and encourage more prudent prescribing,

and we believe that we have achieved that aim by showing, for example, the relative lack of benefit of broad-spectrum antibiotics compared to nitrofurantoin, and that avoiding nitrofurantoin in patients with renal impairment is unnecessary. Therefore, these data were appropriate even given the limitations we have acknowledged throughout this thesis.

Undertaking this thesis has provided several insights into the use of routinely collected data for research. The whole process was a huge learning curve that presented challenges in epidemiological research methods, data management and statistical programming. These data have huge potential but are most valuable for the right questions, for example estimating incidence or prevalence or comparing treatments where randomised trials are genuinely not feasible, or investigating drug safety. Although these data were an appropriate approach to the stated research, I quickly learnt the importance of understanding their strengths and weaknesses and how these affected interpretation of findings. There are also hugely valuable portions of CPRD data that are rarely used, for example, biochemical and haematological investigation results. Research questions that use these more objective variables are likely to be more appropriate for these data compared to questions that rely purely on Read codes, which can, at times, be subjective.

In hindsight, two ways in which the research in this thesis could have been improved are:

1. Less comparisons – for example, in chapter 5 (Associations between antibiotic choice and adverse outcomes), comparisons between

nitrofurantoin and cefalexin, ciprofloxacin and co-amoxiclav may have been more relevant, as these are the main broad-spectrum antibiotics prescribed in UK primary care and amoxicillin use for UTI is relatively rare.

2. Use of additional methods to account for unmeasured confounders, for example instrumental variable analysis. Finding a suitable instrument would have been challenging for some analyses but possible for others, for example in chapter 5, prior antibiotic prescription for UTI could have been used as a proxy instrument for physician prescribing preference.

10.3 Concluding remarks

This thesis presents new evidence on the burden and antibiotic management of acute and recurrent UTI in older people in UK primary care. Our findings have potential to contribute to better prescribing and the antimicrobial stewardship agenda and ultimately result in better outcomes for patients. Antibiotic prescribing for UTI has received far less attention than antibiotic prescribing for respiratory tract infection and this is highlighted by the observed reductions in prescribing for respiratory tract infections, compared with little change in prescribing for UTI (14). To improve the diagnosis and management of UTI in older people in the antibiotic stewardship era, we need better understanding of what clinical and microbiological features define a UTI, a better gold standard diagnostic test, trials of different prescription strategies and different non-antibiotic treatments, and a better understanding of the prognosis of UTI including the impact of UTI and the related inflammatory response on non-infectious

events. The research in this thesis, and the related peer-reviewed publications could serve as a stimulus for generating interest and funding for further work in this under-researched condition and population.

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Appendix

Published manuscripts