National Institute for Health and Care Excellence

Final

Urinary tract infection (lower): antimicrobial prescribing guideline

Evidence review

October 2018

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

ISBN: 978-1-4731-3120-0

Contents

Contents **4**
1 Context **7**
1.1 Background 7
1.2 Managing infections that require antibiotics 9
1.2.1 Self-care 9
1.2.2 Back-up prescribing strategies 9
1.2.3 Antibiotic prescribing strategies 9
1.3 Safety netting advice 10
1.4 Symptoms and signs of a more serious illness or condition (red flags) 11
2 Evidence selection **12**
2.1 Literature search 12
2.2 Summary of included studies 12
3 Clinical effectiveness **20**
3.1 Non-pharmacological interventions in adults 20
3.1.1 Cranberry products 20
3.1.2 Other non-pharmacological interventions 20
3.2 Non-antimicrobial pharmacological interventions in adults 21
3.2.1 Oral analgesia 21
3.3 Antimicrobials in non-pregnant women 22
3.3.1 Natural history of lower urinary tract infections 22
3.3.2 Antibiotic prescribing strategies 23
3.3.3 Antibiotics compared with placebo 24
3.3.4 Choice of antibiotic 25
3.3.5 Antibiotic dosing and course length 28
3.4 Antimicrobials in pregnant women 29
3.4.1 Antibiotic prescribing strategies 29
3.4.2 Antibiotics compared with placebo or no treatment 29
3.4.3 Choice of antibiotics 30
3.4.4 Antibiotic dosing and course length 31
Direct comparisons of different antibiotic course lengths 32
3.5 Antimicrobials in older people 33
3.5.1 Antibiotic prescribing strategies 33
3.5.2 Antibiotics compared with placebo or no treatment 33
3.5.3 Choice of antibiotic 33
3.5.4 Antibiotic dosing and course length 33
3.6 Antimicrobials in men 35
3.7 Antimicrobials in children 35
3.7.1 Antibiotic prescribing strategies 35
3.7.2 Antibiotics compared with placebo 35

3.7.3 Choice of antibiotic ... 35
3.7.4 Antibiotic dosing and course length ... 36
4 Safety and tolerability ... 37
4.1 Non-pharmacological interventions ... 37
4.1.1 Cranberry products ... 37
4.1.2 Other non-pharmacological interventions ... 37
4.2 Non-antimicrobial pharmacological interventions ... 37
4.2.1 Oral analgesia ... 37
4.3 Antimicrobials ... 38
4.3.1 Antibiotics in non-pregnant women ... 38
4.3.2 Antibiotics in pregnant women ... 40
4.3.3 Antibiotics in older people ... 41
4.3.4 Antibiotics in children ... 41
5 Antimicrobial resistance ... 42
6 Other considerations ... 43
6.1 Resource impact ... 43
6.1.1 Antibiotics ... 43
6.2 Medicines adherence ... 43
7 Terms used in the guideline ... 44
7.1.1 Apgar score ... 44
Appendices ... 45
Appendix A: Evidence sources ... 45
Appendix B: Review protocol ... 49
Appendix C: Literature search strategy ... 56
Appendix D: Study flow diagram ... 68
Appendix E: Evidence prioritisation ... 69
Appendix F: Included studies ... 71
Appendix G: Quality assessment of included studies ... 73
G.1 Cranberry products ... 73
G.2 Oral analgesia ... 73
G.3 Antibiotics in non-pregnant women ... 74
G.4 Antibiotics in pregnant women ... 75
G.5 Antibiotics in older people ... 76
G.6 Antibiotics in children ... 77
Appendix H: GRADE profiles ... 78
H.1 Cranberry products ... 78
H.2 Oral analgesia ... 81
H.3 Antibiotic prescribing strategies in non-pregnant women ... 85
H.4 Antibiotics in non-pregnant women ... 89
H.5 Antibiotics in pregnant women ... 102
H.6 Antibiotics in older people ... 109

H.7 Antibiotics in children **114**
Appendix I: Studies not prioritised **119**
Appendix J: Excluded studies **123**

1 Context

1.1 Background

Urinary tract infection (UTI) is a non‑specific term that refers to infection anywhere in the urinary tract. This evidence review covers lower UTI (also known as cystitis), which is infection of the bladder, and asymptomatic bacteriuria (clinically significant levels of bacteria in the urine >10^5 colony forming units [CFU]/mL), without physical signs of infection), in women (including pregnant women), men, older people and children. Acute pyelonephritis, recurrent UTIs, and catheter-associated UTIs are covered in separate evidence reviews.

Acute, uncomplicated cystitis is a benign infection that usually resolves in a few days. A UK primary care study found that in women with suspected cystitis and at least moderately severe symptoms (Little et al. 2009), symptoms resolved after an average of 3.3 days in women treated with an antibiotic to which the pathogen was sensitive, 4.7 days in women treated with an antibiotic to which the pathogen was resistant, and 4.9 days in women with infection not treated with an antibiotic.

UTIs are usually caused by bacteria from the gastrointestinal tract entering the urethra and ascending into the bladder. The most common causative pathogen in uncomplicated UTIs, in 70 to 95% of cases, is *Escherichia coli* (*E. coli*). *Staphylococcus saprophyticus* accounts for 5 to 10% of cases and occasionally other Enterobacteriaceae, such as *Proteus mirabilis* and *Klebsiella* species are isolated.

Symptoms and signs of lower UTIs include (NICE clinical knowledge summary on UTI (lower) - women and UTI (lower) - men:

- urinary frequency, urgency or strangury (the feeling of needing to pass urine despite having just done so)
- dysuria (pain or discomfort on passing urine)
- urine that is offensive smelling, cloudy, or contains blood
- constant lower abdominal ache
- non-specific malaise, such as aching all over, nausea, tiredness and cold sweats
- urge incontinence.

Typical features may be absent in frail, older people (men and women) living in nursing homes (with or without catheters). Atypical symptoms may be present, such as new-onset or worsening fever, chills, rigors, nausea and vomiting, general malaise, increased confusion, or new onset delirium. For people with loin pain and/or fever, acute pyelonephritis should be suspected and the person managed accordingly (see NICE antimicrobial prescribing guideline on acute pyelonephritis).

Additional or alternative symptoms and signs in infants and children include fever, vomiting, lethargy, irritability, poor feeding and changes to continence (NICE guideline on urinary tract infection in under 16s).

A definitive diagnosis of UTI requires laboratory urine culture to determine the presence of clinically significant bacteriuria. This takes a few days to be reported and to avoid delays, management of suspected lower UTI is often based on an assessment of symptoms and urine dipstick testing.

The European Association of Urology guidelines recommend that the diagnosis of uncomplicated cystitis (which they define as acute, sporadic or recurrent cystitis limited to non-pregnant, premenopausal women with no known anatomical and functional abnormalities within the urinary tract or comorbidities) can be made with a high probability based on a focused history of lower urinary tract symptoms and the absence of vaginal

discharge or irritation. They recommend that urine dipstick testing is a reasonable alternative to culture for diagnosis of uncomplicated cystitis. However, urine cultures are recommended in the following situations:

- suspected acute pyelonephritis
- symptoms that do not resolve or recur within 2 to 4 weeks after the completion of treatment
- women who present with atypical symptoms
- pregnant women
- men with suspected UTI.

The NICE clinical knowledge summary on UTI (lower) - women suggests sending urine for culture and sensitivity from all women with a suspected UTI associated with visible or non-visible haematuria; and from all women with a suspected UTI during pregnancy (before empirical antibiotic treatment is started and 7 days after antibiotic treatment has been completed as a test of cure).

The NICE guideline on urinary tract infection in under 16s makes recommendations on the diagnosis of UTI in infants and children. The guideline recommends:

- Infants and children presenting with unexplained fever of 38°C or higher should have a urine sample tested after 24 hours at the latest.
- Infants and children with an alternative site of infection should not have a urine sample tested. When infants and children with an alternative site of infection remain unwell, urine testing should be considered after 24 hours at the latest.
- Infants and children with symptoms and signs suggestive of UTI should have a urine sample tested for infection.

All infants younger than 3 months with suspected UTI should be referred to paediatric specialist care and a urine sample should be sent for urgent microscopy and culture. These infants should be managed in accordance with the recommendations for this age group in the NICE guideline on fever in under 5s. For infants and children 3 months or older but younger than 3 years, urgent microscopy and culture is the preferred method for diagnosing UTI and this should be used where possible. For children 3 years or older, dipstick testing is diagnostically as useful as microscopy and culture, and can safely be used (see the NICE guideline on urinary tract infection in under 16s for more details).

Uncomplicated cystitis should be differentiated from asymptomatic bacteriuria, where there is significant bacteriuria but no symptoms or signs of infection. Asymptomatic bacteriuria is not an infection but a commensal colonisation, which should not be treated and therefore should not be screened for, except if it is considered a risk factor in clearly defined situations, such as in pregnant women and prior to urological procedures breaching the mucosa (European Association of Urology guidelines on urological infections 2017).

The NICE clinical knowledge summary on UTI (lower) - women suggests screening pregnant women for asymptomatic bacteriuria on the first antenatal visit by sending urine for culture. If asymptomatic bacteriuria is found, send a second urine sample for culture, and if this confirms asymptomatic bacteriuria, treat with antibiotics.

Three randomised controlled trials (RCTs) provided data about causative organisms in lower UTI in non-pregnant women in this evidence review (see Clinical effectiveness). No data on causative organisms of lower UTI were found for pregnant women, older people or children. *Escherichia coli* (*E. coli*) was the main causative organism in most studies although rates varied from 55.2% to 80%. The data are limited by variation in method of diagnosis (dipstick testing or midstream urine analysis) and no or low growth of organisms in some studies which may explain some of the variation. Other commonly reported pathogens included *Staphylococcus spp.* (2.6% to 4.9%), *Klebsiella spp.* (1.0% to 8.3%), *Proteus spp.* (0.6% to 7%) and Enterococci spp. (1.1% to 4.0%).

The management of suspected community-acquired bacterial UTI in adults aged 16 years and over is covered in the NICE quality standard on urinary tract infection in adults. This includes women who are pregnant, people with indwelling catheters and people with other diseases or medical conditions such as diabetes. The quality standard was developed to contribute to a reduction in emergency admissions for acute conditions that should not usually require hospital admission, and improvements in health-related quality of life. It does not make any quality statements around antibiotic treatment of complicated UTI, but includes 7 statements that describe high-quality care for adults with UTI.

1.2 Managing infections that require antibiotics

In most cases, managing lower UTI will require antibiotic treatment, but antibiotics should only be started when there is clear evidence of infection. For some people with lower UTI, delaying antibiotic treatment to see if symptoms will resolve without antibiotic treatment may be an option.

1.2.1 Self-care

The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) recommends that people should be given verbal advice and written information that they can take away about how to manage their infection themselves at home with self-care if it is safe to do so.

Self-care options that have been used to relieve symptoms in lower UTI include paracetamol or non-steroidal anti-inflammatory drugs, cranberry products and urine alkalinising agents. However, there is no or limited evidence for these interventions (see Clinical effectiveness).

1.2.2 Back-up prescribing strategies

The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population recommends that if the person has been given a back-up (delayed) prescription, they should be told:

- How to self-care to manage their symptoms.
- What the antimicrobials would be used for, if needed.
- How to recognise whether they need to use the antimicrobials, and if so:
    - how to get them
    - when to start taking or using them
    - how to take them.

1.2.3 Antibiotic prescribing strategies

The NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) recommends that when antimicrobials are prescribed, prescribers should:

- Consider supplying antimicrobials in pack sizes that correspond to local (where available) and national guidelines on course lengths.
- Follow local (where available) or national guidelines on prescribing the shortest effective course, the most appropriate dose, and route of administration.
- Undertake a clinical assessment and document the clinical diagnosis (including symptoms) in the patient's record and clinical management plan.
- Document in the patient's records (electronically wherever possible):
    - the reason for prescribing an antimicrobial
    - the plan of care as discussed with the patient, their family member or carer (as appropriate), including the planned duration of any treatment.

- Take into account the benefits and harms for an individual patient associated with the particular antimicrobial, including:
  - possible interactions with other medicines or any food and drink
  - the patient's other illnesses, for example, the need for dose adjustment in a patient with renal impairment
  - any drug allergies (these should be documented in the patient's record)
  - the risk of selection for organisms causing healthcare associated infections, for example, *C. difficile*.
- Document in the patient's records the reasons for any decision to prescribe outside local (where available) or national guidelines.

The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) recommends that resources and advice should be available for people who are prescribed antimicrobials to ensure they are taken as instructed at the correct dose, via the correct route, for the time specified. Verbal advice and written information that people can take away about how to use antimicrobials correctly should be given, including:

- not sharing prescription-only antimicrobials with anyone other than the person they were prescribed or supplied for
- not keeping them for use another time
- returning unused antimicrobials to the pharmacy for safe disposal and not flushing them down toilets or sinks.

1.3 Safety netting advice

The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) recommends that safety netting advice should be shared with everyone who has an infection (regardless of whether or not they are prescribed or supplied with antimicrobials). This should include:

- how long symptoms are likely to last with and without antimicrobials
- what to do if symptoms get worse
- what to do if they experience adverse effects from the treatment
- when they should ask again for medical advice.

The NICE clinical knowledge summary on UTI (lower) - women suggests advising all women to seek medical attention if they:

- develop fever or loin pain, because of suspected acute pyelonephritis, or
- do not respond to treatment with the first-choice antibiotic, because this may be due to a resistant organism.

For men, if hospital admission is not needed and empirical antibiotics are started, follow up should be arranged, for example after 48 hours, to check the response to treatment and the urine culture results. If symptoms persist after antibiotic treatment, referral for specialist urological assessment may be needed (NICE clinical knowledge summary on UTI (lower) - men).

The NICE guideline on urinary tract infection in under 16s (2007) recommends that all infants younger than 3 months with suspected UTI should be referred immediately to paediatric specialist care. For infants and children 3 months or older with cystitis/lower UTI, parents or carers should be advised to bring the infant or child for reassessment if they are still unwell 24 to 48 hours after antibiotic treatment was started, at which point urine culture should be done if this has not already been carried out.

1.4 Symptoms and signs of a more serious illness or condition (red flags)

Complications of lower UTI include ascending infection leading to pyelonephritis, renal failure, and sepsis.

In pregnancy, asymptomatic bacteriuria can lead to pyelonephritis; and symptomatic UTI has been associated with developmental delay or cerebral palsy in the infant, and foetal death. For women with visible or non-visible haematuria an urgent 2-week wait referral should be arranged if a urological cancer is suspected (NICE clinical knowledge summary on UTI (lower) – women).

In men, prostate involvement is common, which may lead to complications such as prostatic abscess or chronic bacterial prostatitis. Urinary stones are also a possibility, more likely with *Proteus mirabilis* infection which is associated with stone formation in the renal collecting ducts (NICE clinical knowledge summary on UTI (lower) - men). Emergency admission to hospital is recommended if a man with a suspected lower UTI is severely unwell with symptoms or signs suggestive of urosepsis (for example nausea and vomiting, confusion, tachypnoea, tachycardia, or hypotension). If hospital admission is not needed and empirical antibiotics are started, follow up should be arranged, for example after 48 hours, to check the response to treatment and the urine culture results. If symptoms persist after antibiotic treatment, referral for specialist urological assessment may be needed.

In children, UTIs can lead to renal scarring, but more often this is preceded by acute pyelonephritis rather than cystitis, and it is more common in children with vesicoureteral reflux. UTIs in childhood have also been associated with hypertension (if there is severe or bilateral renal scarring) and renal insufficiency or failure (if febrile UTIs are treated late). (NICE clinical knowledge summary on UTI - children).

2 Evidence selection

A range of evidence sources are used to develop antimicrobial prescribing guidelines. These fall into 2 broad categories:

- Evidence identified from the literature search (see section 2.1 below)
- Evidence identified from other information sources. Examples of other information sources used are shown in the interim process guide (2017).

See appendix A: evidence sources for full details of evidence sources used.

2.1 Literature search

A literature search was developed to identify evidence for the effectiveness and safety of interventions for managing all urinary tract infections (UTIs) (see appendix C: literature search strategy for full details). The literature search identified 6,695 references. Three additional references were identified by the committee. These references were screened using their titles and abstracts and 188 full text references were obtained and assessed for relevance. Forty-five references of systematic reviews and randomised controlled trials (RCTs) were assessed as relevant to the guideline review question (see appendix B: review protocol). Ten percent of studies were screened to establish inter-rater reliability, and this was within the required threshold of 90%.

The methods for identifying, selecting and prioritising the best available evidence are described in the interim process guide. Nineteen of the 45 references were prioritised by the committee as the best available evidence and were included in this evidence review (see appendix F: included studies).

The 26 references that were not prioritised for inclusion are listed in appendix I: not prioritised studies. Studies that assessed Chinese herbal medicines were not prioritised by the committee. Also see appendix E: evidence prioritisation for more information on study selection.

The remaining 143 references were excluded. These are listed in appendix J: excluded studies with reasons for their exclusion.

See also appendix D: study flow diagram.

2.2 Summary of included studies

A summary of the included studies is shown in tables 1 to 3. Details of the study citation can be found in appendix F: included studies. An overview of the quality assessment of each included study is shown in appendix G: quality assessment of included studies.

Table 1: Summary of included studies: non-pharmacological interventions

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Cranberry products					
Wing et al. 2015 RCT. USA. Double-blind Length of follow-up not reported	n=49	Healthy pregnant women (12 to 16 weeks), with non-anomalous foetuses, seeking prenatal care. Pre-treatment urine cultures were conducted to exclude presence of ASB. N.B. aim of study was to prevent ASB, which if becomes a symptomatic urinary tract infection has potentially fatal neonatal consequences,	TheraCran cranberry capsule, 2 capsules daily for 6 months (containing 32-34 mg proanthocyandin; equivalent to 250mL cranberry juice cocktail).	Placebo capsules (no cranberry ingredients)	Compliance Tolerability: Gastrointestinal intolerance Preterm delivery <37 week
Wing et al. 2008 RCT. USA. Double-blind Follow-up not clearly reported, but at least 18 months	n=188	Pregnant women (less than 16 weeks gestation) presenting initially for prenatal care. Pre-treatment urine cultures were conducted to exclude presence of ASB. N.B. aim of study was to prevent ASB, which if becomes a symptomatic urinary	One 240 mL bottle of low-calorie cranberry juice (27%; mean proanthocyanidin concentration of 106 mg per bottle) at breakfast and dinner, until delivery	One 240 mL bottle of placebo juice breakfast and dinner. One cranberry juice drink – breakfast and one placebo drink-dinner	Incidence of ASB Incidence of urinary tract infection Incidence of pyelonephritis

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
		tract infection has potentially fatal neonatal consequences,			
Abbreviations: RCT, Randomised controlled trial; ASB, Asymptomatic bacteriuria					

Table 2: Summary of included studies: non-antimicrobial pharmacological interventions

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Ibuprofen versus antibiotic					
Bleidorn et al. 2010 RCT. Germany. Double-blind Follow-up 28 days	n=80	Women aged 18 to 85 years, with at least one symptom of urinary tract infection (dysuria, frequency and without complicating factors)	Ibuprofen 400 mg three times a day for 3 days	Ciprofloxacin 250mg twice a day capsules, plus 1 placebo capsule a day for 3 days	Number of people with a symptom score of 0 on day 4
Gágyor et al.2015 RCT. Germany. Double-blind Follow-up 28 days	n=494	Women aged 18 to 65 years, with symptoms of urinary tract infection	Ibuprofen 400 mg three times a day for 3 days, plus one sachet of placebo granules	Fosfomycin 3g single dose sachet, plus placebo tablets times a day for 3 days	Total number of courses of antibiotics on days 0-28 Burden of symptom days (days 0-7)
Abbreviations: RCT, Randomised controlled trial					

Table 3: Summary of included studies: antimicrobials

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Back-up antibiotics					
Little et al. 2010 RCT. UK. Open-label (justified). Follow-up ranged from 35 to 968 days.	n=309	Non-pregnant woman women aged 18 – 70 years, presenting with suspected urinary tract infection.	5 comparisons: • Empirical antibiotics (immediate) • Back-up antibiotics • Symptom score (antibiotics offered if score >2)		Mean frequency symptom severity Duration of moderately bad symptoms (days) Mean unwell symptom severity

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
			• Dipstick (antibiotics offered if nitrites present, or leucocytes and blood detected) • Midstream urine (symptomatic treatment until microbiology results available and antibiotics targeted to results)		Number of people who used antibiotics Time to second consultation
Antibiotics versus placebo					
Ferry et al. 2004 RCT. Sweden Double-blind Follow-up 7 weeks	n=1,143	Non-pregnant women aged 18 years and older with symptoms of lower urinary tract infection: urgency, dysuria, suprapubic pain or loin pain.	3 regimens of pivmecillinam: • 200 mg three times a day, for 7 days; • 200 mg twice a day, for 7 days; • 400 mg twice a day, for 3 days	Placebo	Natural course Clinical course Bacteriological course
Falagas et al. 2009 Meta-analysis Follow-up varied according to the study	n=1,407 5 RCTs)	Non-pregnant women with clinically and microbiologically (with either a positive dipstick test and/or a positive urine culture), documented lower urinary tract infection	5 intervention arms: • pivmecillinam • nitrofurantoin • co-trimoxazole/ofloxacin • co-trimoxazole/ amoxicillin • co-trimoxazole	Placebo	Clinical success Clinical cure Microbiological success Microbiological reinfection Total adverse events
Kazemier et al. 2015 RCT. Netherlands. Double blind. Follow-up 6 weeks post-partum	n=85	Pregnant women (between 16 and 22 weeks' gestation) with asymptomatic bacteriuria	Nitrofurantoin 100 mg twice a day for 5 days	Placebo	Pyelonephritis Preterm birth <34 weeks
Smaill et al. 2015 Systematic review Multiple countries Follow-up varied according to the study	n=1998 (14 RCTs)	Pregnant women (at any stage), with asymptomatic bacteriuria	Different classes of antibiotics including sulphonamide, sulfasymazine, tetracycline,	Placebo or no treatment	All major congenital malformations

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
			methenamine mandelate, methenamine hippurate, nitrofurantoin and penicillin		
Zalmanovici-Trestioreanu et al. 2015 Systematic review Multiple countries Follow-up varied according to study	n=1,614 (9 RCTs)	Non-pregnant women aged up to 60 years, with asymptomatic bacteriuria	Different classes of antibiotics including trimethoprim, co-trimoxazole, amoxicillin, nitrofurantoin, ampicillin, cefaclor and tobramycin.	Placebo or no treatment	Proportion of patients who develop symptomatic UTI Proportion of patients with complications Any adverse event Death
Antibiotics versus other antibiotics					
Falagas et al. 2010 Systematic review Multiple countries Follow-up varied according to the study	n=3138 (27 RCTs)	Patients of any age with microbiologically confirmed case of cystitis	Fosfomycin 3g single dose	Other antibiotics	Complete cure and/or complete improvement at the end of treatment
Fitzgerald et al. 2012 Systematic review. Multiple countries. Follow-up varied according to study	n=1,116 (16 RCTs)	Children aged 0 to 18 years, with bacteriologically proven lower urinary tract infection (at least one culture of a known urinary pathogen, $>10^5$ CFU/mL). Review included studies in children with first time or recurrent urinary tract infection	2 comparisons: • Trimethoprim versus co-trimoxazole • Cefadroxil versus ampicillin		Persistent bacteriuria Persistent symptoms Reinfection Recurrence
Guinto et al. 2010 Systematic review	n=1,140 (5 RCTs)	Pregnant women with asymptomatic bacteriuria	Antibiotics of different classes (with different routes of administration or different dosing schedules)		Symptomatic infection, including pyelonephritis Persistent infection

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Multiple countries Follow-up according to the study					Recurrent infection Switch to another antibiotic
Rafalsky et al. 2006 Systematic review Multiple countries Follow-up varied according to the study	n=7,535 (11 RCTs)	Non-pregnant women aged 16 years and above, with uncomplicated acute cystitis	Quinolones	Other quinolones	Clinical response Bacteriological response Overall success Adverse events
Zalmanovici-Trestioreanu et al. 2010 Systematic review Multiple countries Follow-up varied according to study	n=6,016 (21 RCTs)	Non-pregnant healthy women aged 16 to 65 years, with uncomplicated urinary tract infection	Different classes of antibiotics (excluded quinolones) including amoxicillin, co-amoxiclav, nitrofurantoin, trimethoprim and co-trimoxazole.		Symptomatic and bacteriological cure at short and long-term follow-up Resistance development Adverse events and complications
Duration of antibiotic treatment					
Fitzgerald et al. 2012 Systematic review. Multiple countries. Follow-up varied according to study	n=1,116 (16 RCTs)	Children aged 0 to 18 years, with bacteriologically proven lower urinary tract infection (at least one culture of a known urinary pathogen, $>10^5$ CFU/mL). Review included studies in children with first time or recurrent urinary tract infection	Single-dose (or single-day) antibiotics	Standard-dose antibiotics	Persistent bacteriuria Persistent symptoms Reinfection Recurrence
Guinto et al. 2010 Systematic review Multiple countries Follow-up according to the study	n=1,140 (5 RCTs)	Pregnant women with asymptomatic bacteriuria	Single dose nitrofurantoin	7-day course of nitrofurantoin	Symptomatic infection, including pyelonephritis Persistent infection Recurrent infection Switch to another antibiotic

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Lutters et al. 2008 Systematic review. Multiple countries. Follow-up varied according to study	n=1,644 (15 RCTs)	Older people (women) aged 60 years and over, with acute uncomplicated urinary tract infection	3 comparisons: • single dose antibiotic • short course antibiotic (3 to 6 days) • longer course antibiotic (7 to 14 days) (where evidence available)		Clinical treatment failure: persistence of urinary symptoms, as study defined.
Michael et al. 2003 Systematic review Multiple countries Follow-up varied according to study	n=652 (10 RCTs)	Children aged three months to 18 years with culture proven urinary tract infection	Short course antibiotic (2 to 4 days) (single dose courses were excluded)	Longer course antibiotic (7 to 14 days)	Persisting clinical symptoms at the end of treatment Significant bacteriuria recurrent urinary tract infection after treatment (one month or more after completing treatment)
Milo et al. 2005 Systematic review Multiple countries Follow-up varied according to study	n=9605 (32 RCTs)	Non-pregnant women with lower urinary tract infection (men were included, but limited evidence found [<10%])	Short course antibiotic (3 days)	Longer course antibiotic (5 to 10 days)	Bacteriological cure, and recurrence Symptomatic cure, and recurrence
Smaill et al. 2015 Systematic review Multiple countries Follow-up varied according to the study	As described above				
Widmer et al. 2015 Systematic review Multiple countries Follow-up varied according to the study	n=1,622 (13 RCTs)	Pregnant women with asymptomatic bacteriuria	4 comparisons: • Single dose antibiotic (including one-day treatment with divided doses)	Each other (where evidence available)	Maternal cure rate defined as the woman having a negative culture following initial treatment for asymptomatic bacteriuria

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
			• Short course antibiotic (4 to 7 days) • Longer course antibiotic (14 days) • Continuous antibiotic (treatment continued until delivery)		
Abbreviations: RCT, Randomised controlled trial					

3 Clinical effectiveness

Full details of clinical effectiveness are shown in appendix H: GRADE profiles. The main results are summarised below.

3.1 Non-pharmacological interventions in adults

The main results are summarised below for non-pharmacological interventions in healthy pregnant women, preventing future episodes of asymptomatic bacteriuria or uncomplicated urinary tract infection (UTI). No systematic reviews or randomised controlled trials (RCTs) were identified in non-pregnant women, men, older people and children.

3.1.1 Cranberry products

The evidence review for cranberry products is based on 2 RCTs, (Wing et al. 2008 and Wing et al. 2015) in pregnant women. Both studies were conducted in healthy pregnant women, who otherwise had no indication or risk of asymptomatic bacteriuria or UTI. The included studies looked at cranberry capsules or cranberry juice drinks in pregnant women of less than 16 weeks gestation. The dose of proanthocyanidin within the capsules and juice drink, which is considered to be the active ingredient, was reported as equivalent as the same researchers conducted both studies (approximately 32-34 mg of proanthocyanidin).

One double blind RCT (Wing et al. 2008) assessed the efficacy of cranberry juice drink compared with placebo juice drink, when used to prevent UTI in healthy pregnant women. Wing et al. (2008) found no significant difference between the cranberry juice groups compared to the placebo group in the incidence of UTI or incidence of asymptomatic bacteriuria, incidence of pyelonephritis, preterm delivery <37 weeks, babies born with low birth weight, 1 min Apgar score <7, or admission to neonatal intensive care unit (NICU) (very low quality evidence).

One double blind RCT (Wing et al. 2015) assessed the safety and tolerability of cranberry capsules, when used to prevent UTI in healthy pregnant women. Wing et al. (2015) found that 25% of the participants had a history of UTI (p-value not reported). There was no significant difference in the number of babies born with a 1 min Apgar score <7, in those treated with cranberry capsules compared to placebo (1 RCT, n=33, 21.4% versus 0%; RR and 95% CI not stated, calculated by NICE as RR 9.33 95% 0.52 to 167.36; very low quality evidence).

There was no significant difference in preterm delivery (<37 weeks) rates, the number of babies born with low birth weight (< 2500g) or the number of admissions to a neonatal intensive care unit in those treated with cranberry capsules compared with placebo.

Overall, there were no significant differences in maternal or neonatal outcomes reported in both studies.

No systematic reviews or RCTs were identified that provided data on cranberry products for UTI in men, non-pregnant women and children.

3.1.2 Other non-pharmacological interventions

No systematic reviews or RCTs were identified that provided data on other non-pharmacological interventions in adults or children with uncomplicated UTI.

3.2 Non-antimicrobial pharmacological interventions in adults

3.2.1 Oral analgesia

The evidence review for oral analgesia is based on 2 RCTs (Bleidorn et al. 2010 and Gágyor et al. 2015) in non-pregnant women with lower urinary tract infection (UTI), defined as having at least one of the following symptoms: dysuria, frequency, urgency or foul smelling urine. The age of the study populations ranged from 18-65 years. Both studies used a 5 point symptom score scale (adapted from the scale described by Ferry et al. (2004), which included symptoms of dysuria, frequency, suprapubic pain and loin pain, to assess the severity of symptoms. Scores ranged from 0 (not at all) to 4 (very strong), with possible scores ranging from 0 to 12.

Ibuprofen compared with ciprofloxacin

One double-blind RCT (n=80) assessed the effectiveness of ibuprofen compared with ciprofloxacin (Bleidorn et al. 2010). The majority of women in the study had a positive dipstick result (86% in ibuprofen group; 91% in the ciprofloxacin group) and, a positive urine culture (86% in the ibuprofen group; 80% in the ciprofloxacin groups). The mean symptom severity was comparable between groups. Participants received either ibuprofen 400 mg three times a day or ciprofloxacin 250mg twice a day and 1 placebo tablet a day. Treatment was given for 3 days.

Ibuprofen was not significantly different to ciprofloxacin, in increasing symptom resolution four days after the start of treatment, for the management of lower UTI in non-pregnant women (1 RCT, n=69: 58.3% versus 51.5%; RR and 95% CI not stated, calculated by NICE as RR 1.13 95% CI 0.74 to 1.74; very low quality evidence), or 7 days after (1 RCT, n=69: 1 RCT, n=69: 75% versus 60.6%; RR and 95% CI not stated, calculated by NICE as RR 1.24 95% CI 0.89 to 1.73; low quality evidence). There was no significant difference between both groups in the total symptom score up to 7 days after the start of treatment (low quality evidence), severity of dysuria between both groups at day 4 and day 7 (low quality evidence). Furthermore, there was no significant difference between groups in the need for a second prescription up to 9 days following intervention (low quality evidence).

Ibuprofen compared with fosfomycin

One double-blind RCT assessed the effectiveness of ibuprofen compared with fosfomycin (Gágyor et al. 2015). Gágyor et al. (2015) found that up to 1 in 5 women had a UTI in the past year, in both the ibuprofen and antibiotic groups (17% versus 23%, p value not reported). The majority of women in the study had a positive dipstick test (85% in ibuprofen group; 83% in the fosfomycin groups) and a positive urine culture (76% in the ibuprofen and 77% in the fosfomycin groups respectively).Both groups were similar in mean symptom severity (Gágyor et al. 2015, mean (SD): ibuprofen group – 6.0 (2.2) versus antibiotic group - 6.1(2.5), p-value not reported).

Using ibuprofen to manage lower UTI significantly increased the number of non-pregnant women who eventually went on to use antibiotics after initial treatment, compared with those who were treated with fosfomycin (1 RCT n= 484: 31.1% versus 12.3%; RR and 95% CI not stated, calculated by NICE as RR 2.52 95% CI 1.72 to 3.70; NNT 6 [95% CI 4 to 9]; high quality evidence). Women using ibuprofen to manage their symptoms, were more likely to report a higher symptom burden over

the first 7 days after the start of their treatment, compared with fosfomycin (1 RCT, n=484: mean difference 5.3 95% CI 3.5 to 7.0; moderate quality evidence).

Women using ibuprofen were less likely to experience a recurrent UTI between days 15-28 of follow up, than if they were initially treated with fosfomycin (1 RCT, n=484: 5.8% versus 11.1%; RR and 95% CI not stated, calculated by NICE as RR 0.52 95% CI 0.28 to 0.97; NNT 19 [95% CI 10 to 272]; moderate quality evidence). The authors noted that this result could be because the baseline risk of having a recurrent UTI was greater in the fosfomycin group, as more women had experienced a UTI in the past year. There was no significant difference between groups in the number of women who experienced pyelonephritis during a 12 month period (low quality evidence).

When the analysis was restricted to women who were microbiologically confirmed to have a UTI (defined as having a positive urine culture prior to the start of treatment), overall there were significantly fewer antibiotic courses taken by women who were initially treated with ibuprofen compared with fosfomycin (1 RCT, n=360: 0.49 (ibuprofen) versus 1.18 (fosfomycin) antibiotic treatment courses per patient; moderate quality evidence). Likewise, when the analysis was restricted to those who did not have a microbiologically confirmed UTI (defined as negative urine culture prior to the start of treatment), overall there were significantly fewer antibiotic courses taken by those who received ibuprofen compared with fosfomycin (1 RCT, n=111: 0.10 (ibuprofen) versus 1.11 (fosfomycin) antibiotic treatment courses per patient; moderate quality evidence). However, this effect was driven mostly by the randomisation process, rather than the effect of the treatment itself.

3.3 Antimicrobials in non-pregnant women

The evidence review for antimicrobials in non-pregnant women is based on 4 systematic reviews (Falagas et al. 2009, Falagas et al. 2010, Rafalsky et al. 2006 and Zalmanovici-Trestioreanu et al. 2010) and 2 RCTs (Ferry et al. 2004 and Little et al. 2010). The included studies cover the natural history of urinary tract infection (UTI), back-up antibiotic prescribing, antibiotics versus placebo, and antibiotics versus other antibiotics. The studies were conducted in non-pregnant women aged 12 to 84 years old, with varying symptom severity reported across the studies.

3.3.1 Natural history of lower urinary tract infections

One RCT (Ferry et al. 2004; n=1,143, 288 women received placebo) assessed the natural history of lower UTI in non-pregnant women. The ‘natural course’ of UTI was defined as the spontaneous eradication of both symptoms and bacteriuria. The most common symptoms in the study population were urgency and dysuria. Each symptom was scored from a range of 0 (none) to 3 (severe), and added together, with possible total scores ranging from 0 to 12. The mean symptom score at baseline was 1.8 in the antibiotic group and 0.9 in the placebo groups (standard deviation not reported; p-value not reported). The mean duration of symptoms across both groups was 10 days (± 19.5 days, p-value not reported).

At 7 days after randomisation (results were presented in a graph):

- approximately 75% (216/288) of women in the placebo group did not report symptoms of suprapubic and loin pain (at inclusion, 60% reported suprapubic pain and 40% loin pain) (very low quality evidence)

- approximately 45% (130/288) of women in the placebo group did not report urgency and dysuria (most common symptoms at inclusion) (very low quality evidence)
- approximately 28% (81/288) of women in the placebo group were symptom free irrespective of infecting pathogen (very low quality evidence).

However, approximately 39% (111/288) of women dropped out of the study by the second follow-up visit and were subsequently treated with antibiotics. Of the remaining 166 patients in the placebo group, 54% (90/166) were completely symptom free at 5 to 7 weeks. Further analysis stratified by causative pathogen showed that of those infected by *Escherichia coli* or *Staphylococci* had lower rates of symptom resolution (n=266: numerical data not reported; very low quality evidence).

Ferry et al. (2004) found that 47% (46/97) of the women with a high bacterial count (n=97; ≥ 10^5 CFU/mL) at the start of the study were spontaneously 'cured' (produced a negative urine culture [<10^3 CFU/mL]) after 8 to 10 days of treatment (very low quality evidence). However, 40% (39/97) of the women with a high bacterial count at baseline, still had raised counts 7 days after treatment with placebo (very low quality evidence). The authors reported that women aged 55 years and over were more likely to have a positive urine culture than those aged 18 to 24 years (n=97: 22% versus 13% respectively, p-value not reported; very low quality evidence).

3.3.2 Antibiotic prescribing strategies

One RCT (Little et al. 2010; n=309) compared 5 different antibiotic prescribing strategies (immediate antibiotics, back-up antibiotics and 3 targeted antibiotics groups), for managing symptoms of lower UTI in non-pregnant women:

- Immediate antibiotics (trimethoprim 200 mg twice a day for 3 days; cefaclor or cefalexin if allergic to trimethoprim).
- Empirical back-up antibiotics (women were advised to drink plenty, and offered a back-up antibiotic prescription if symptoms did not improve after 48 hours; women could either pick up the prescription from the front desk or take away a prescription).
- Targeted antibiotics based on a positive result on midstream urine analysis (women were offered symptomatic treatment until results of the analysis were available).
- Targeted antibiotics based on positive dipstick result (if nitrite or both leucocytes and a trace of blood were present, women were offered antibiotics immediately).
- Targeted antibiotics based on a symptom score (two or more of urine cloudiness, urine smell, nocturia, or dysuria).

All groups were controlled for variation in self-help advice amongst the different general practitioners. Women requiring immediate antibiotics prior to randomisation or had symptoms suggestive of pyelonephritis (fever and vomiting) were excluded from the study. Women who were over 75 years or had dementia, or were experiencing psychosis, were also excluded. The women included in the study had a mean age of 39 to 45 years and moderate symptoms on average (mean score of 1.7 to 1.8, on a scale of 0=no problem, 1=mild problem, 2=moderately bad problem, 3=severe problem) at baseline. The majority of women included in the study (80% to 90%) had experienced a previous episode of cystitis (time period not specified). Despite strict inclusion criteria, only 66% of women who were randomised to receive a midstream urine analysis test, had a confirmed UTI. The proportion of women with a confirmed UTI was not reported in the other treatment arms. Urine culture was mandatory in only 1 intervention group, however women in other groups were tested

according to the doctor's discretion and preferences; the proportion of women who had a urine culture ranged from 23% to 89% (p<0.001). Similarly, the use of dipstick testing varied significantly between the different treatment groups, with women randomised to receive antibiotics based on the result of dipstick testing being the highest (50% to 95%; p<0.001). Women randomised to receive immediate antibiotics were used as the control for the study.

Clinical outcomes

There was no significant difference between the 4 alternative antibiotic prescribing strategies (back-up prescription, midstream urine analysis testing, dipstick testing and symptom severity score based prescription) compared to immediate antibiotic prescribing in mean frequency symptom severity reported 2 to 4 days after seeing the health professional (1 RCT, n=309: p=0.177; very low to low quality evidence); duration of moderately bad symptom days (1 RCT, n=309 p=0.369; very low quality evidence); or time to re-consultation (next appointment after initial appointment; 1 RCT, n=309 p=0.345; very low quality evidence).

Antibiotic usage outcomes

Little et al. (2010) found that women prescribed immediate antibiotics were significantly more likely to use antibiotics compared to women prescribed: back-up antibiotics (RR 1.25, 95% CI 1.07 to 1.46 [NICE analysis]; very low quality evidence), antibiotics based on midstream urine analysis (RR 1.20, 95% CI 1.03 to 1.38 [NICE analysis]; very low quality evidence) or antibiotics based on dipstick testing (RR 7.25, 95% CI 1.51 to 34.87 [NICE analysis]; very low quality evidence). There was no significant difference in the number of people who used antibiotics between those prescribed immediate antibiotics and those prescribed antibiotics based on symptom severity scores (RR 3.35, 95% CI 0.65 to 17.31 [NICE analysis]; very low quality evidence).

Women prescribed immediate antibiotics were significantly less likely to wait 48 hours before taking antibiotics compared to women prescribed: back-up antibiotics (RR 0.16, 95% CI 0.07 to 0.38 [NICE analysis]; low quality evidence), antibiotics based on midstream urine analysis (RR 0.20, 95% CI 0.08 to 0.48 [NICE analysis]; low quality evidence) or antibiotics based on dipstick testing (RR 0.21, 95% CI 0.07 to 0.64 [NICE analysis]; low quality evidence). There was no significant difference in the number of people who waited 48 hours before using antibiotics between those prescribed immediate antibiotics and those prescribed antibiotics based on symptom severity scores (RR 0.39, 95% CI 0.13 to 1.20 [NICE analysis]; very low quality evidence).

Little et al. (2010) found that despite randomisation, all groups delayed starting their antibiotic course by at least 24 hours (very low quality evidence). However, a delay of more than 48 hours was associated with a longer duration of moderately bad symptoms (very low quality evidence).

3.3.3 Antibiotics compared with placebo

A systematic review (Falagas et al. 2009; 5 RCTs, n=1,407) assessed the effectiveness of antibiotics in managing symptoms of uncomplicated lower UTI in non-pregnant women with uncomplicated cystitis, compared with placebo. The age of the included women varied across the studies, ranging from 15 to 75 years. Most women were reported to have mild to moderate symptoms. Only studies which

confirmed the presence of a UTI (either with a positive dipstick or positive culture) were included in the review.

The antibiotics used in the studies included: pivmecillinam, nitrofurantoin, cefixime, co-trimoxazole, ofloxacin and amoxicillin. In 2 included studies women were randomised to 3 intervention arms where the same antibiotic was given at 3 different doses. Varying antibiotic course lengths were used in the included studies: in 2 RCTs women received a single dose of antibiotic; in 1 RCT women received a 3 day course; and in 2 RCTs women received a 7-day course. In all studies, women in the placebo group received placebo for the same duration as the antibiotic group.

Antibiotics significantly increased the proportion of women having complete symptom resolution after treatment for a lower UTI, compared with placebo (4 RCTs, n= 1,062; 61.8% versus 25.7%; RR and 95% CI not stated, calculated by NICE as RR 2.26 95% CI 1.79 to 2.86; NNT 3 [95% CI 3 to 4]; high quality evidence). Antibiotics also significantly increased the proportion of women who had microbiological success (negative urine culture) at the end of treatment (3 RCTs, n=967; 90% versus 33.3%; RR and 95% CI not stated, calculated by NICE as RR 2.49 95% CI 1.64 to 3.78; NNT 2 [95% CI 2 to 2]; moderate quality evidence), however this effect was no longer significant after the end of treatment (NICE analysis; low quality evidence). Antibiotics significantly reduced the number of women experiencing microbiological reinfection or relapse after the end of treatment compared with placebo (5 RCTs, n=742; 15.8% versus 41.6%; RR and 95% CI not stated, calculated by NICE as RR 0.42 95% CI 0.28 to 0.64). The incidence of pyelonephritis did not differ significantly between those who received antibiotics or placebo (2 RCTs, n= 742; 0.21% versus 0.75%; RR and 95% CI not stated, calculated by NICE as RR 0.42 95% CI 0.05 to 3.37; low quality evidence).

3.3.4 Choice of antibiotic

Three systematic reviews assessed the effectiveness of different antibiotic regimens in non-pregnant women with uncomplicated lower UTI (Falagas et al. 2010, Rafalsky et al. 2006 and Zalmanovici-Trestioreanu et al. 2010). The age of the women ranged from 16 to 65 years and they were otherwise healthy, although co-morbidities were not reported. Women with a history of UTI or more than 2 UTIs in the past year were excluded.

One systematic review of 9 RCTs (Zalmanovici-Trestioreanu et al. 2010; n=1,614) assessed the effectiveness of various antibiotic classes including: co-trimoxazole, beta-lactams, nitrofurantoin and quinolones. Studies where more than 30% of women did not have a bacteriologically confirmed UTI were excluded from the review. The authors defined symptomatic cure as the absence of urinary symptoms, whilst bacteriological cure was defined as a negative culture result.

Nitrofurantoin compared with beta-lactams

Nitrofurantoin was not significantly different to beta-lactams when used for the treatment of lower UTI in non-pregnant women (Zalmanovici-Trestioreanu et al. 2010). There was no significant difference between treatment groups in short term symptomatic score (1 RCT, n=51: 92.9% versus 78.3%, RR 1.19, 95% CI 0.93 to 1.51; low quality evidence); short-term bacteriological cure (2 RCTs, n=170: 90.9% versus 88.5%. RR 1.09, 95% CI 0.75 to 1.58; very low quality evidence); or long-term bacteriological cure (2 RCTs, n=143: 87.9% versus 88.2%; RR 0.97, 95% CI 0.86 to 1.09; moderate quality evidence).

Nitrofurantoin compared with co-trimoxazole

Nitrofurantoin was not significantly different to co-trimoxazole when used for the treatment of lower UTI in non-pregnant women (Zalmanovici-Trestioreanu et al. 2010). There was no significant difference between treatment groups in short-term symptomatic score (3 RCTs, n=733: 89.8% versus 90.3%; RR 0.99, 95% CI 0.95 to 1.04; high quality evidence), or long-term symptomatic cure (2 RCTs, n=675: 90.2% versus 89.1%; RR 1.01, 95% CI 0.94 to 1.09; high quality evidence). There was no significant difference between nitrofurantoin and co-trimoxazole in short-term or long-term bacteriological cure (low to high quality evidence).

Beta-lactams compared with co-trimoxazole

Beta-lactams were not significantly different to co-trimoxazole in the treatment of lower UTI in non-pregnant women (Zalmanovici-Trestioreanu et al. 2010). There was no significant difference in short-term symptomatic cure (2 RCTs, n=176: 93% versus 97.8%; RR 0.95, 95% CI 0.81 to 1.12; low quality evidence), or long-term symptomatic cure (2 RCTs, n=138: 89.4% versus 84.7%; RR 1.06, 95% CI 0.93 to 1.21; moderate quality evidence). There was no significant difference between groups in the number of women reporting short-term or long-term bacteriological cure (low to moderate quality evidence).

Quinolones compared with beta-lactams

Quinolones were not significantly different to beta-lactams when used for the treatment of lower UTI in non-pregnant women (Zalmanovici-Trestioreanu et al. 2010). There was no significant difference between treatment groups in short-term symptomatic score (2 RCTs n=1,192: 90.8% versus 81.6%; RR 1.15, 95% CI 0.99 to 1.32; low quality evidence), or long-term symptomatic cure (1 RCT, n=675: 91.4% versus 90.8%; RR 1.01, 95% CI 0.96 to 1.05; high quality evidence). There was a significant increase in the number of women experiencing short term bacteriological cure who were treated with quinolone compared to a beta-lactam, however this effect was no longer significant in the long term (very low to moderate quality evidence). There was no significant difference between quinolones and beta-lactams in the number of women developing pyelonephritis (very low quality evidence).

Quinolones compared with co-trimoxazole

Quinolones were not significantly different to co-trimoxazole when used for the treatment of lower UTI in non-pregnant women (Zalmanovici-Trestioreanu et al. 2010). There was no significant difference in the number of women experiencing short-term symptomatic cure (5 RCTs, n=927: 95.1% versus 93.8%; RR 1.00, 95% CI 0.97 to 1.03; high quality evidence), or long-term symptomatic cure (1 RCT, n=614: 90% versus 90.6%; RR 0.99, 95% CI 0.94 to 1.05; high quality evidence). Likewise, there was no significant difference between treatment groups in short-term or long-term bacteriological cure (high quality evidence), or the number of women that developed pyelonephritis (very low quality evidence).

Quinolone compared with another quinolone

One systematic review of 11 RCTs (Rafalsky et al. 2006; n=7,535) assessed the effectiveness of different quinolones including ciprofloxacin, ofloxacin and levofloxacin compared with each other. The review only included studies where women had a positive urine culture (≥10^3 CFU/mL) and the presence of pyuria (defined as ≥10 leukocytes/mm^3), or a positive urine culture of ≥10^4 CFU/mL, in

addition to physical symptoms suggestive of a lower UTI. The authors defined cure or improvement at the test-of-cure visit, rate of eradication or rate of relapse, for the following comparisons.

Ciprofloxacin compared with ofloxacin

Ciprofloxacin (200mg daily) was not significantly different to ofloxacin (400 mg daily) when used for the treatment of lower UTI in non-pregnant women. There was no significant difference between treatment groups in clinical success (defined as cure or improvement) (1 RCT, n=45: 93.4% versus 96.1%; RR 0.97, 95% CI 0.93 to 1.01; moderate quality evidence), or microbiological eradication (1 RCT, n=458: 94.3% versus 97.4%; RR 0.97, 95% CI 0.93 to 1.01; moderate quality evidence). There was no significant difference between conventional ciprofloxacin and ofloxacin in the number of women who did not get re-infected or experience a microbiological relapse (moderate quality evidence).

Levofloxacin compared with ofloxacin

Levofloxacin (250mg daily) was not significantly different to ofloxacin (400 mg daily) when used for the treatment of lower UTI in non-pregnant women. There was no significant difference between treatment groups in cure (1 RCT, n=321: 86.6% versus 89%; RR 0.97, 95% CI 0.9 to 1.06; high quality evidence), or microbiological eradication (1 RCT, n=404: 96.1% versus 93.5%; RR 1.03, 95% CI 0.98 to 1.08; high quality evidence). There was no significant difference between levofloxacin and ofloxacin in the number of women who experienced microbiological relapse (high quality evidence).

Standard-release ciprofloxacin compared with extended-release ciprofloxacin

Standard-release ciprofloxacin (500 mg daily) was not significantly different to extended-release ciprofloxacin (500 mg daily) when used for the treatment of lower UTI in non-pregnant women. There was no significant difference between treatment groups in clinical success (defined as cure or improvement) (1 RCT, n=418: 92.7% versus 95.5%; RR 0.97, 95% CI 0.93 to 1.02; moderate quality evidence), or microbiological eradication (1 RCT, n=422: 93.7% versus 94.5%; RR 0.99, 95% CI 0.95 to 1.04; moderate quality evidence). There was no significant difference between conventional ciprofloxacin and extended-release ciprofloxacin in the number of women who did not get re-infected or experience a microbiological relapse (moderate quality evidence).

All doses were reported as a total daily dose. Rafalsky et al (2006) also reported other comparators of quinolone based drugs not licensed in the UK. The results of the comparisons have not been reported but are consistent with the evidence reported.

Fosfomycin (single dose) compared with other antibiotics

One systematic review of 27 RCTs (Falagas et al. 2010; n=3,138) assessed the effectiveness of a single 3 g dose of fosfomycin compared with other antibiotics including: ciprofloxacin, nitrofurantoin, trimethoprim, pefloxacin, cefalexin, pipemidic acid, and norfloxacin. The review included studies in which the women were microbiologically confirmed, or there was clinical suspicion of cystitis (described as the presence of symptoms suggestive of a UTI with or without pyuria, in combination with a positive urine culture).

Fosfomycin was not significantly different to other antibiotics in increasing the number of non-pregnant women experiencing clinical cure after an active UTI (9 RCTs, n=1,565: 85% versus 86.7%; RR 1.00, 95% CI 0.97 to 1.03 (NICE analysis); moderate quality evidence), or in increasing the number of non-pregnant women reporting eradication of the infection (12 RCTs, n=1,774: 84.6% versus 82.3%; RR 1.03, 95% CI 0.98 to 1.08; moderate quality evidence). There was also no significant difference between fosfomycin and other antibiotics in the following outcomes: clinical improvement, microbiological relapse or microbiological reinfection.

3.3.5 Antibiotic dosing and course length

One systematic review of 32 RCTs (Milo et al. 2005; n=9,605) assessed the effectiveness of 3 day antibiotic courses compared with courses of 5 to 10 days. In 6 of the included studies (n=1,356), men were also included (representing up to 10% of the study population), but it was not possible to separate out these data. The majority of women were aged 16 to 65 years; however 14 studies included women aged 65 years and over. No evidence was identified that compared antibiotics used at a different frequency of dosing in non-pregnant women.

Across all the included studies, participants were required to have a positive urine culture of $>10^5$ CFU/mL in voided midstream urine or obtained through a urinary catheter (women with an indwelling catheter were excluded). However, in 4 studies a lower threshold was used ($>10^4$ CFU/mL in 2 studies, $>10^3$ CFU/mL in 1 study, and $>10^2$ CFU/mL in 1 study). Participants were excluded if there were symptoms or signs of an upper UTI (costovertebral pain or tenderness, fever, or positive blood cultures).

Stratified analyses were conducted between studies that compared the same antibiotic at different course lengths, or different antibiotics at different course lengths. Pre-specified subgroup analyses were conducted in different antibiotic classes: quinolones, beta lactams, and co-trimoxazole for bacteriological failure outcomes.

There was no significant difference between antibiotics given for 3 days compared with antibiotics (all comparisons: same or different antibiotic), given for 5 to 10 days for the treatment of uncomplicated lower UTI in non-pregnant women, for the following outcomes (all ITT analysis):

- short-term symptomatic failure (2 to 15 days from the end of treatment) (17 RCTs, n=5,029: 21.2% versus 22.1%; RR 0.98, 95% CI 0.88 to 1.10; moderate quality evidence)
- long-term symptomatic failure (4 to 10 weeks from the end of treatment) (10 RCTs, n=3,910: 37.4% versus 35.6%; RR 1.07, 95% CI 0.99 to 1.16; high quality evidence)
- short-term bacteriological failure (2 to 15 days from the end of treatment) (20 RCTs, n=4,163: 18.1% versus 19.5%; RR 0.92, 95% CI 0.80 to 1.06; moderate quality evidence)
- development of pyelonephritis (8 RCTs, n= 582: 0.69% versus 0%; RR 3.04. 95% CI 0.32 to 28.93; very low quality evidence).

However, long term bacteriological failure (4 to 10 weeks from the end of treatment) was significantly higher with antibiotics given for 3 days compared with antibiotics given for 5 to 10 days (13 RCTs, n=2,943: RR 1.19, 95% CI 1.06 to 1.35; low quality evidence).

All the above results were consistent when the analyses were limited to studies which compared the same antibiotic given for 3 days or 5 to 10 days (very low to moderate evidence).

In a subgroup analysis of quinolones, 3-day treatment was associated with significantly more women experiencing short-term bacteriological failure compared with 5 to 10 days treatment (6 RCTs, n=1,614: 7.6% versus 5.1%; RR 1.47, 95% CI 1.01 to 2.16; low quality evidence). However, there was no significant difference in long-term bacteriological failure (moderate quality evidence).

In a subgroup analysis of beta-lactam antibiotics, there were no significant difference in short term (7 RCTs, n=798: 12.3% versus 11.5%: RR 1.11 95% CI 0.76 to 1.63; very low quality evidence) or long term (3 RCTs, n= 421: 35.4% versus 28.2%: RR 1.26 95% CI 0.96 to 1.65; low quality evidence) bacteriological failure incidence between 3-day and 5 to 10-day courses.

In a subgroup analysis of co-trimoxazole, 3-day treatment was associated with significantly more women experiencing short-term bacteriological failure compared with treatment for 5 to 10 days (5 RCTs, n=734: 8.7% versus 4.3%; RR 1.86, 95% CI 1.04 to 3.34 NNT 23 [95% CI 13 to 122]; very low quality evidence). However, there was no significant difference for long-term bacteriological failure (low quality evidence).

3.4 Antimicrobials in pregnant women

The evidence review for antimicrobials in pregnant women is based on 3 systematic reviews (Guinto et al. 2010, Smaill et al. 2015 and Widmer et al. 2015) and 1 RCT (Kazemier et al. 2015). Pregnant women in the included studies were diagnosed with asymptomatic bacteriuria, and were excluded if they presented with symptomatic urinary tract infection (UTI). Asymptomatic bacteriuria is the absence of specific urinary symptoms that are typical of a UTI, but with the presence of causative organisms in the urine in amounts that are suggestive of an infection.

3.4.1 Antibiotic prescribing strategies

No evidence was identified that compared different antibiotic prescribing strategies in pregnant women.

3.4.2 Antibiotics compared with placebo or no treatment

A systematic review (Smaill et al. 2015; 14 RCTs, n=2,000) and 1 RCT (Kazemier et al. 2015; n=248) assessed the effectiveness of antibiotics in the treatment of asymptomatic bacteriuria in pregnant women, compared with placebo or no treatment.

In Smaill et al. (2015), women were reported to have asymptomatic bacteriuria at an antenatal screening appointment as defined in the studies, and were included at any stage of pregnancy. Typical methods of diagnosis were 1 or more repeated samples showing $>10^5$ CFU/mL on either a clean-catch sample or midstream urine test, on at least 1 or more subsequent antenatal screening appointments. The causative organism was *E. coli* in most women, but 1 study specifically recruited women in which Group B streptococci was the causative organism. The inclusion criteria included studies which compared antibiotics with placebo or no treatment, but this was not presented separately in the analysis. The antibiotics used among the various studies included: sulphonamides, sulfamethoxazole, methenamine hippurate, methenamine mandelate, nitrofurantoin, penicillin, and ampicillin.

Antibiotics significantly reduced the incidence of persistent bacteriuria when compared with placebo or no treatment (4 RCTs, n=596: 20.3% versus 66.3%; RR 0.3, 95% CI 0.18 to 0.53; NNT 2 [95% CI 2 to 3]; low quality evidence). There was also a significant reduction in the number of preterm births (before 37 weeks) (2 RCTs, n=242: 5.8% versus 22.1%; RR 0.27, 95% CI 0.11 to 0.62; NNT 7 [95% CI 4 to 13]; moderate quality evidence). Significantly fewer women also developed pyelonephritis with antibiotics compared with placebo or no treatment (11 RCTs, n=1,932: 5.6% versus 20.8%; RR 0.23, 95% CI 0.13 to 0.41; NNT 7 [95% CI 6 to 9]; moderate quality evidence). However, there was no difference in serious adverse neonatal outcomes (very low quality evidence).

Kazemier et al (2015) (n=248) compared nitrofurantoin with placebo in pregnant women with asymptomatic bacteriuria. Asymptomatic bacteriuria was diagnosed using dipstick and culture test (>10^5 CFU/mL). Women who were eligible but decided not to participate in the study (i.e. received no treatment), were combined with the placebo group in the study's analysis. There were no significant differences between nitrofurantoin and placebo for preventing the development of a UTI which required antibiotics (n=248: 10.0% versus 20.2%; RR and 95% CI not stated, calculated by NICE as RR 0.50, 95% CI 0.19 to 1.3; very low quality evidence) or pyelonephritis (n=248: 2.5% versus 2.4%; RR and 95% CI not stated, calculated by NICE as RR 0.00, 95% CI 0.12 to 8.67; very low quality evidence). There was also no effect on preterm birth (before 34 weeks) (n=248: 2.5% versus 5.8%%; calculated by NICE as RR 0.43, 95% CI 0.06 to 3.24; very low quality evidence), but more women given nitrofurantoin had non-spontaneous onset of labour compared with placebo (n=248: 35% versus 21.2%; RR and 95% CI not stated, calculated by NICE as RR 1.65, 95% CI 1.01 to 27.2; very low quality evidence). Nitrofurantoin when compared with placebo did not affect neonatal outcomes, such as babies born with a small birthweight for their gestational age (<10^{th} percentile), perinatal death, and admission to a neonatal intensive care unit (very low quality evidence).

3.4.3 Choice of antibiotics

A systematic review of 5 RCTs (Guinto et al. 2010; n=1,140) assessed the effectiveness of different antibiotic regimens in pregnant women with asymptomatic bacteriuria (10^5 CFU/mL using clean-catch urine or midstream urine). There was some variation in the population of the individual RCTs: 1 study excluded women with physical symptoms of a UTI, 1 study excluded women who had received antibiotics since the first midstream urine test, and another study excluded women with a history of treatment for UTI during pregnancy. The gestational age of the women ranged from 14 to 32 weeks. The included studies compared fosfomycin (single dose) with cefuroxime (5-day course) or pivmecillinam (7-day course) with ampicillin (7-day course).

There was no significant difference between fosfomycin (single dose) and cefuroxime (5-day course) in persistent infection rates (1 RCT; n=84: 6.8% versus 5%; RR 1.36, 95% CI 0.24 to 7.75; very low quality evidence), or the incidence of shifting to other antibiotics (1 RCT; n=84: 0% versus 12.5%, RR 0.08, 95% CI 0.00 to 1.45; very low quality evidence). Similarly, there was no significant difference between pivmecillinam (7-day course) and ampicillin (7-day course) in persistent infection rates after 2 weeks (1 RCT; n=65: 12.5% versus 12.1%, RR 1.03, 95% CI 0.28 to 3.78; very low quality evidence), or persistent infection after 6 weeks (1 RCT; n=54: 24.1% versus 36%, RR 0.67, 95% CI 0.29 to 1.54; very low quality evidence). Pivmecillinam and ampicillin were also similar when comparing incidence of recurrent infection.

Note that persistent infection was defined as a repeat urine culture with the same organisms present after treatment had stopped. Recurrent infection was defined as a repeat positive urine culture, after the first infection had resolved after treatment.

Guinto et al (2010) also reported comparisons with antibiotics not available in the UK: pivampicillin/pivmecillinam versus cefalexin, and cycloserine versus sulphadimidine. None of the comparisons showed differences between the antibiotics.

3.4.4 Antibiotic dosing and course length

The evidence review of antibiotic course length in pregnant women diagnosed with asymptomatic bacteriuria is based on 3 systematic reviews (Guinto et al. 2010, Smaill et al. 2015 and Widmer et al. 2015). No evidence was identified that compared antibiotics used at a different frequency of dosing in pregnant women.

Different antibiotic course lengths compared with placebo

Smaill et al. (2015) assessed the effectiveness of antibiotics compared with placebo or no treatment. The antibiotics used included: sulphonamides, nitrofurantoin, methenamine hippurate, penicillin and ampicillin. However, if the main analyses showed significant heterogeneity, the authors also performed pre-specified subgroup analyses for based on treatment duration (single dose, short course of 3 to 7 days, intermediate course of 3 to 6 weeks, and continuous treatment until delivery) for those outcomes The authors performed subgroup analyses for pyelonephritis, preterm births, and birthweight less than 2,500 g.

Single-dose sulphonamide compared with placebo

Single-dose sulphonamide significantly reduced the development of pyelonephritis in pregnant women when compared with placebo (1 RCT, n=173: 10.3% versus 23.3%, RR 0.44, 95% CI 0.21 to 0.92; NNT 7 [95% CI 5 to 52]; low quality evidence). However, there was no effect on the number of babies born with a birthweight of less than 2,500 g when single-dose sulphonamide was compared with placebo (1 RCT, n=413: 7.7% versus 11.8%, RR 0.65, 95% CI 0.36 to 1.18; low quality evidence).The effect of single-dose sulphonamide on pre-term births was not reported.

Short course (3 to 7 days) compared with placebo or no treatment

Short-course (3 to 7 days) antibiotics did not significantly reduce the development of pyelonephritis in pregnant women when compared with placebo or no treatment (3 RCTs, n=483: 3.8% versus 13.3%, RR 0.31, 95% CI 0.09 to 1.16; low quality evidence). However, short-course penicillin significantly reduced the number of preterm births (<37 weeks) when compared with placebo (1 RCT, n=69: 5.4% versus 37.5%; RR 0.14, 95% CI 0.03 to 0.6; NNT 4 [95% CI 2 to 8]; moderate quality evidence). The effect of short-course antibiotics on birthweight was not reported.

Intermediate course (3 to 6 weeks) compared with placebo or no treatment

There was a significant reduction in the development of pyelonephritis with an intermediate course (3 to 6 weeks) of antibiotics compared with placebo or no treatment (2 RCTs, n=433: 3.3% versus 19.6%; RR 0.17, 95% CI 0.08 to 0.37; NNT 7 [95% CI 5 to 10]; moderate quality evidence). However, there was no effect on the number of babies born with a birthweight of less than 2,500 g when an intermediate course was compared with placebo (1 RCT, n=275: 11.3% versus 10.3%, RR 1.09, 95% CI 0.55 to 2.14; very low quality evidence).

Continuous antibiotics compared with placebo or no treatment

Continuous treatment with antibiotics significantly reduced the development of pyelonephritis when compared with placebo or no treatment (5 RCTs, n=843: 6.6% versus 25.6%; RR 0.16, 95% CI 0.04 to 0.57; NNT 6 [95% CI 5 to 8]; low quality evidence). It also reduced the number of preterm births (<37 weeks) (1 RCT, n=173: 6.0% versus 16.7%; RR 0.36, 95% CI 0.14 to 0.95; NNT 10 [95% CI 5 to 72]; low quality evidence), and the number of babies born with a birthweight of less than 2,500 g (4 RCTs, n=746: 8.3% versus 15.6%; RR 0.54, 95% CI 0.33 to 0.87; NNT 14 [95% CI 9 to 38]; low quality evidence) when compared with placebo or no treatment.

Direct comparisons of different antibiotic course lengths

Widmer et al. (2015) (13 RCTs, n=1,622) compared the effectiveness of single-dose antibiotics with short-course (4 to 7 days) antibiotics. A 'single dose' of antibiotics included antibiotics given in divided doses over a single day (such as amoxicillin 250 mg three times a day for 1 day), or a single larger dose (such as amoxicillin 3 g to be taken at once). Women were diagnosed using the following criteria: urine culture (5 studies); midstream urine culture (3 studies); clean-catch urine (1 study). Most studies required that women had a bacterial count of $>10^5$ CFU/mL with the same organism at 2 consecutive antenatal appointments. One study included in the systematic review (Brumfitt et al. 1982) reported that 24% of their study participants were symptomatic, despite inclusion criteria. In another study (Bailey et al. 1983), the intervention group were more likely to have had a history of UTI compared with the control group (50% versus 35%).

The authors of the review conducted pre-specified subgroup analyses because there was significant heterogeneity. The subgroup categories were comparison of the same antibiotic, and comparison between different antibiotics. The direction of results did not differ between the main and the subgroup analyses. The antibiotics used as a single dose included: amoxicillin, trimethoprim (with or without a sulphonamide), nitrofurantoin, fosfomycin and ampicillin.

Single dose compared with a short course (4 to 7 days)

There was no significant difference between single-dose antibiotics and short-course antibiotics in the number of women who reported no cure at the end of follow-up (13 RCTs, n=1,502: 23.2% versus 16.6%; RR 1.28, 95% CI 0.87 to 1.88; very low quality evidence), experienced recurrent asymptomatic bacteriuria (8 RCTs, n= 445: 18.5% versus 16.9%; RR 1.13 95% CI 0.77 to 1.66; very low quality evidence); developed pyelonephritis (2 RCTs, n=102: 9.3% versus 2.1%, RR 3.09, 95% CI 0.54 to 17.55; very low quality evidence), or had a preterm delivery (3 RCTs, n=804: 10.8% versus 9.1%, RR 1.17, 95% CI 0.77 to 1.78; moderate quality evidence).

However, single-dose antibiotics significantly increased the number of babies born with a low birthweight when compared with short-course (4 to 7 days) antibiotics (1 RCT, n=714: 13.2% versus 8.0%; RR 1.65, 95% CI 1.06 to 2.57; NNT 20 [95% CI 11 to 144]; moderate quality evidence).

Single-dose nitrofurantoin compared with a longer course (7 days) of nitrofurantoin

In Guinto et al. (2010), single-dose nitrofurantoin significantly increased the number of women with persistent infection compared with short-course (7 days) nitrofurantoin (1 RCT, n=741: 24.3% versus 13.8%; RR 1.76, 95% CI 1.29 to 2.40; NNT 10 [95% CI 7 to 21]; high quality evidence). There was no significant difference between single-dose and short-course antibiotics in the number of women who developed a

symptomatic infection at 2 weeks or prior to delivery, as well as preterm delivery (low to moderate quality evidence).

3.5 Antimicrobials in older people

The evidence review for antimicrobials in older people is based on 2 systematic reviews (Lutters et al. 2008 and Zalmanovici-Trestioreanu et al. 2015). The included studies covering the choice of antibiotic and duration of antibiotic treatment. Both reviews included studies conducted in older people, mostly older women, aged 55 years and older.

3.5.1 Antibiotic prescribing strategies

No evidence was identified that compared different antibiotic prescribing strategies in older people.

3.5.2 Antibiotics compared with placebo or no treatment

Zalmanovici et al. (2015) (9 RCTs, n=1,614) assessed the effectiveness of antibiotics compared with placebo or no treatment in institutionalised participants or outpatients with asymptomatic bacteriuria. Studies conducted in younger adults were also included in the systematic review (people aged 20 to 65 years in 1 RCT, people aged 18 to 40 years in 1 RCT, and people aged 16 years and older in 1 RCT). One RCT included in the systematic review was conducted specifically in people with diabetes with asymptomatic bacteriuria. Most of the evidence presented was based on female participants. However, 1 study included a mixed population, whereas another study was conducted solely in male participants. People with indwelling urinary catheters or the inability to pass urine were excluded.

The antibiotics included in the studies were amoxicillin, co-amoxiclav, nitrofurantoin, trimethoprim, co-trimoxazole, ciprofloxacin, norfloxacin, ofloxacin, amifloxacin, cefadroxil, cefpodixime proxetil, cefuroxime axetil, pivmecillinam, nalidixic acid, and ritipenem acoxil.

Antibiotics did not show a significant benefit in reducing symptomatic UTI when compared with placebo or no treatment in older people with asymptomatic bacteriuria (5 RCTs, n=1,046: 40.6% versus 20.3%; RR 1.11, 95% CI 0.51 to 2.43; very low quality evidence). However, antibiotics did significantly increase the number of participants with bacteriological cure when compared with placebo or no treatment (9 RCTs, n=1,154: 61% versus 17%; RR 2.67, 95% CI 1.85 to 3.85; NNT 3 [95% CI 2 to 3]; high quality evidence).

3.5.3 Choice of antibiotic

No evidence was identified that assessed antibiotic choice in older people.

3.5.4 Antibiotic dosing and course length

Lutters et al. (2008) (15 RCTs, n=1,644 participants) investigated the effectiveness of different antibiotic course lengths in older people (women) with UTI. No evidence was identified that compared antibiotics used at a different frequency of dosing in older people.

The antibiotics included in the studies were trimethoprim, fosfomycin, cefalexin sulfamethiazole, norfloxacin, ofloxacin, ciprofloxacin, pefloxacin, lomefloxacin, pipemidic acid, and temafloxacin.

Single-dose compared with a short course (3 to 6 days)

Up to 2 weeks after treatment stopped, participants treated with single-dose antibiotics had a statistically higher incidence of persistent UTI than participants treated with short-course antibiotics (5 RCTs, n=356: 22.1% versus 10.3%; RR 2.01, 95% CI 1.05 to 3.84; NNT 9 [95% CI 6 to 24]; low quality evidence). However, there was no difference in the long term (>2 weeks after treatment stopped) (5 RCTs, n=356: 28.9% versus 21.1%; RR 1.18, 95% CI 0.59 to 2.32; very low quality evidence). There was no significant difference between single-dose and short-course antibiotics in the reinfection rate, acceptability, or number of women reporting clinical failure (persistence of symptoms) (very low to moderate quality evidence).

Single-dose compared with a long course (7 to 14 days)

Up to 2 weeks after treatment stopped, participants treated with single-dose antibiotics had a statistically higher incidence of persistent UTI than participants treated with long-course antibiotics (6 RCTs, n=628: 11.9% versus 5.7%; RR 1.93, 95% CI 1.01 to 3.70; NNT 17 [95% CI 10 to 56]; low quality evidence). However, there was no difference in the long term (>2 weeks after treatment stopped) (5 RCTs, n=523: 19.6% versus 15.3%; RR 1.28, 95% CI 0.68 to 5.57; low quality evidence). There was no difference between single-dose and long-course antibiotics in the number of women reporting clinical failure (persistence of symptoms) (low quality of evidence).

Single-dose compared with a short or long course (3 to 14 days)

Lutters et al. (2008) combined the short-course and long-course treatment groups and compared them to single-dose treatment. There was no difference in persistent UTI up to 2 weeks after treatment stopped with single-dose compared with short or long-course treatment (8 RCTs, n=809: 12.2% versus 7.6%: RR 1.51, 95% CI 0.92 to 2.49; low quality evidence), or in the long term (>2 weeks after treatment stopped) (5 RCTs, n=521: 19.5% versus 16.6%; RR 1.14, 95% CI 0.8 to 1.63; low quality evidence). There was also no difference in clinical failure or acceptability (low quality evidence).

Short course (3 to 6 days) compared with a long course (7 to 14 days)

There was no significant difference between short-course and long-course antibiotics in the incidence of persistent UTI up to 2 weeks after treatment stopped (3 RCTs, n= 431: 16.1% versus 22.7%; RR 0.85, 95% CI 0.29 to 2.47; very low quality evidence) or in the long term (>2 weeks after treatment stopped) (3 RCTs, n=470: 25.9% versus 31.8%; RR 1.00 95% 0.12 to 8.57; very low quality evidence). There was also no difference between short-course and long-course antibiotics in clinical failure (persistence of symptoms), in reinfection rate, or acceptability (very low to low quality evidence).

3 days compared with 5 days

There was no significant difference between 3-day and 5-day antibiotic courses in the incidence of persistent UTI (1 RCT, n=26: 58.3% versus 21.4%; RR 2.72, 95% CI 0.90 to 8.27; low quality evidence). There was also no difference between 3-day and 5-day antibiotic courses for clinical failure (very low quality evidence).

3.6 Antimicrobials in men

No evidence was identified on antibiotic prescribing strategies or antibiotics in men with lower urinary tract infection (UTI). In 1 systematic review (Milo et al. 2005), 6 of the included studies (n=1,356) included data in men, representing up to 10% of the study population (see section 3.3.4).

3.7 Antimicrobials in children

The evidence review for antimicrobials in children is based on 2 systematic reviews (Michael et al. 2003 and Fitzgerald et al. 2012). The included studies cover the choice of antibiotic and duration of antibiotic treatment. Both study populations consisted of children aged 0 to 18 years, with bacteriologically proven urinary tract infection (UTI). Fitzgerald et al. (2012) included studies with children who had either their first UTI or recurrent infections. No evidence was identified on antibiotic versus placebo or back-up prescribing in children with uncomplicated lower UTI.

3.7.1 Antibiotic prescribing strategies

No evidence was identified that compared different antibiotic prescribing strategies in children with lower UTI.

3.7.2 Antibiotics compared with placebo

No evidence was identified that compared antibiotics with placebo in children with lower UTI.

3.7.3 Choice of antibiotic

One systematic review (Fitzgerald et al. 2012: 16 RCTs, n=1,116 children) assessed the choice of antibiotic in children with uncomplicated lower UTI. The ages of the children included in the studies ranged from 6 months to 18 years. Two RCTs included in the review had a significant proportion of children (51 to 52%) with recurrent UTI. In one study, 90% of the participants were sexually active (ages ranged from 12 to 18 years, with a mean age of 16.5 years). The remaining studies were conducted in children with uncomplicated lower UTI. The inclusion criteria was the same across all the included studies: bacteriologically confirmed UTI (defined as $\geq 10^5$ CFU/mL) and non-systemic symptoms of a lower UTI (including dysuria and frequency of urination).

The effect of trimethoprim (10 days) was similar to the effect of co-trimoxazole (10 days) for reducing persistent symptoms of lower UTI (1 RCT, n= 59: 6.7% versus 0%; RR 4.84, 95% CI 0.24 to 96.7; very low quality evidence). There was also no difference in persistent bacteriuria or recurrence between trimethoprim (10 days) and co-trimoxazole (10 days) (very low quality evidence). Likewise, the effects of cefadroxil (10 days) and ampicillin (10 days) were comparable for persistent symptoms of lower UTI (RCT, n=32: 0% versus 6.3%: RR 0.33 95% CI 0.01 to 7.62; very low quality evidence) and persistent bacteriuria (very low quality evidence).

Fitzgerald et al. (2012) reported other comparisons for antibiotics not available in the UK. The results were non-significant and consistent with those reported above.

3.7.4 Antibiotic dosing and course length

Two systematic reviews (Fitzgerald et al. 2012 and Michael et al. 2013) assessed the effectiveness of antibiotic course length in children with symptoms of lower UTI.

Fitzgerald et al. 2012 (16 RCTs, n=1,116 children) compared single-dose with short-course (3 to 7 days) or long-course (10 to 14 days) antibiotics, as well as comparing short-course with long-course antibiotics. Most studies compared 2 different antibiotics. The included studies investigated different antibiotics such as amikacin, amoxicillin, ampicillin, cefadroxil, ceftriaxone, cefalexin, cephalosporins, co-trimoxazole, fosfomycin, gentamicin, netilmicin, nitrofurantoin, pivmecillinam, sulfamethoxazole, sulfisoxazole, and trimethoprim. The main outcome in the included studies was persistent bacteriuria. Only a few studies reported persistent symptoms or recurrence.

Michael et al. 2013 (10 RCTs, n=652 children) compared short-course antibiotics (2 to 4 days) with a longer course (7 to 14 days), for up 15 months after stopping treatment. The ages of the children included in the studies ranged from 3 months to 18 years. The majority of studies included children with symptomatic or asymptomatic UTI (not defined). Children who had recurrent UTI, or a recent UTI (<3 months) were excluded. Within each included study, the authors compared different course lengths of the same antibiotic. Included studies investigated different antibiotics such as amoxicillin, cefuroxime, co-trimoxazole, nalidixic acid, nitrofurantoin, sulfamethoxazole, and trimethoprim. Outcomes included persistent infection, recurrence, and structural abnormalities.

Single-dose compared with a short (3 to 7 days) or long course (10 to 14 days)

In Fitzgerald et al. 2012, there was no significant reduction in the number of children with persistent bacteriuria when single-dose antibiotics were compared with short-course (3 to 7 days) antibiotics (2 RCTs, n=145: 28% versus 20%; RR 1.3, 95% CI 0.65 to 2.62; very low quality evidence). However, single dose antibiotics were associated with significantly more children experiencing persistent bacteriuria, than a longer course of antibiotics (10 days) (6 RCTs, n=228: 23.9% versus 10.4%; RR 2.01 95% CI 1.06 to 3.8; NNT 8 [95% CI 5 to 27]; very low quality evidence). There was also no difference between single-dose and long-course (10 days) antibiotics for persistent symptoms (1 RCT, n=30: 6.3% versus 21.4%; RR 0.29 95% CI 0.03 to 2.5; very low quality evidence).

Short course compared with a longer course

In Fitzgerald et al. 2012, there was no significant difference between short-course (3 to 7 days) and long-course (10 to 14 days) antibiotics in the number of children with persistent bacteriuria (3 RCTs, n=265: 21.3% versus 18.6%; RR 1.09, 95% CI 0.67 to 1.76; very low quality evidence). Course length did not affect the rate of reinfection or recurrence (very low quality evidence).

Michael et al. 2013 found that short-course (2 to 4 days) antibiotics and longer-course (7 to 14 days) antibiotics had a similar effect on the number of children with UTI at the end of treatment (Michael et al. 2003, 8 RCTs, n=4,223: 14.7% versus 14.1%; RR 1.06, 95% CI 0.64 to 1.76; very low quality evidence), at 1 to 3 months after treatment, at 3 to 15 months after treatment, and at 1 to 15 months after the end of treatment (very low quality evidence). There was also no significant difference in the rate of recurrence of UTI, persistence of bacteriuria, persistent bacteriuria based on normal and abnormal imaging, or resistance to antibiotics (very low to moderate quality evidence).

4 Safety and tolerability

Details of safety and tolerability outcomes from studies included in the evidence review are shown in appendix G: GRADE profiles. The main results are summarised below.

See the summaries of product characteristics, British National Formulary (BNF) and BNF for children (BNF-C) for information on contraindications, cautions and adverse effects of individual medicines, and for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breastfeeding.

4.1 Non-pharmacological interventions

4.1.1 Cranberry products

One double blind RCT (Wing et al. 2015) of cranberry products for the prevention of asymptomatic bacteriuria in healthy pregnant women assessed the efficacy of cranberry capsules compared with placebo capsules. Wing et al. 2015 found no significant difference between cranberry capsules and placebo in gastrointestinal intolerance (1 RCT, n=39: 76.5% versus 54.5%, p=0.2; NICE analysis: RR 1.40 95% CI 0.88 to 2.23; very low quality evidence).

4.1.2 Other non-pharmacological interventions

No evidence on safety and tolerability was found for other non-pharmacological interventions in non-pregnant women, men or children with lower urinary tract infection (UTI).

4.2 Non-antimicrobial pharmacological interventions

4.2.1 Oral analgesia

Paracetamol and non-steroidal anti-inflammatory drugs, such as ibuprofen are widely used to treat pain and fever. All NSAIDs should be used with caution in older people; in people with allergic disorders; in people with coagulation defects, uncontrolled hypertension, heart failure, and cardiovascular disease; and in people with a history gastrointestinal ulceration or bleeding, or inflammatory bowel disease. Side effects include gastro-intestinal disturbances, hypersensitivity reactions (particularly rashes, angioedema, and bronchospasm), and fluid retention (BNF August 2018).

The NICE guideline on fever in under 5s: assessment and initial management recommends that either paracetamol or ibuprofen can be considered in children with fever who appear distressed. However, these should not be used with the sole aim of reducing body temperature in children with fever. Paracetamol or ibuprofen should be continued only as long as the child appears distressed. Considering a change to the other agent is recommended if the child's distress is not alleviated, but giving both agents simultaneously is not recommended. Alternating these agents should only be considered if the distress persists or recurs before the next dose is due.

One RCT (Gágyor et al. 2015) assessed the safety of ibuprofen compared with fosfomycin in non-pregnant women with uncomplicated lower UTI. There was no significant difference in the number of adverse events experienced by non-pregnant women who used ibuprofen or fosfomycin for the management of their lower UTI (1

RCT n=484: 17.4% versus 23.5%; RR and 95% CI not stated, calculated by NICE as RR 0.74, 95% CI 0.52 to 1.06; moderate quality evidence). There was also no significant difference in the number of serious adverse events reported between groups (low quality evidence), or the number of adverse events thought to be drug related (low quality evidence).

4.3 Antimicrobials

Antibiotic-associated diarrhoea is estimated to occur in 2 to 25% of people taking antibiotics, depending on the antibiotic used (NICE clinical knowledge summary [CKS]: diarrhoea – antibiotic associated).

About 10% of the general population claim to have a penicillin allergy; this has often been because of a skin rash that occurred during a course of penicillin in childhood. Fewer than 10% of people who think they are allergic to penicillin are truly allergic. Therefore, penicillin allergy can potentially be excluded in 9% of the population. People with a history of immediate hypersensitivity to penicillins may also react to cephalosporins and other beta-lactam antibiotics. The most common side effect with penicillins is diarrhoea, which can also cause antibiotic-associated colitis. Diarrhoea is most common with broad-spectrum penicillins (such as amoxicillin and co-amoxiclav) (BNF August 2018).

Quinolones, including ciprofloxacin, cause arthropathy in the weight-bearing joints of immature animals and are generally not recommended in children or young people who are growing (BNF August 2018).

Nitrofurantoin should be used with caution in those with renal impairment. Adults (especially the elderly) and children on long-term treatment should be monitored for liver function and pulmonary symptoms, with nitrofurantoin discontinued if there is a deterioration in lung function (BNF August 2018).

Trimethoprim has a teratogenic risk in the first trimester of pregnancy (folate antagonist), and manufacturers advise avoidance during pregnancy (BNF August 2018).

Co-trimoxazole is currently under restriction for use in the UK. It is advised that it only be used in UTI where there is bacteriological evidence of sensitivity to co-trimoxazole. Co-trimoxazole should be used with caution in those with asthma, or people with blood disorders, GP6D deficiency or infants under 6 weeks (except for treatment or prophylaxis of pneumocystis pneumonia) (BNF August 2018).

4.3.1 Antibiotics in non-pregnant women

Falagas et al. (2009) assessed the effectiveness of antibiotics, compared with placebo, in managing the symptoms of UTI in non-pregnant women. Antibiotics caused significantly more adverse events than placebo (4 RCTs, n=1068: 19.2% versus 12.9%; RR and 95% CI not stated, calculated by NICE as RR 1.49, 95% CI 1.06 to 2.08; moderate quality evidence). However there was no significant difference between antibiotics and placebo in the number of women having to withdraw from treatment due to adverse effects (low quality evidence).

Zalmonovici et al. (2010) compared the safety of different antibiotics in non-pregnant women with uncomplicated lower UTI for the following comparisons:

Quinolones compared with co-trimoxazole

There was no significant difference between quinolones and co-trimoxazole in the number of adverse events (7 RCTs, n=1277: 30.9% versus 31.3%; RR 0.95, 95% CI 0.71 to 1.29; very low quality evidence) or the number of women who discontinued treatment due to an adverse event (3 RCTs, n=1063: 1.3% versus 4.1%; RR 0.37 95% CI 0.12 to 1.14; low quality evidence).

Beta-lactams compared with co-trimoxazole

There was no significant difference between those treated with beta-lactams or co-trimoxazole in the number of adverse events reported (2 RCTs, n=184: 22.6% versus 26.1%; RR 0.76, 95% 0.46 to 1.27; very low quality evidence) or the number of women discontinuing treatment due to an adverse event (2 RCTs, n=184: 4.3% versus 2.9%; RR 1.53, 95% CI 0.28 to 8.26; very low quality evidence).

Nitrofurantoin compared with beta-lactams

There was no significant difference between those treated with nitrofurantoin or beta-lactams in the number of adverse events reported (1 RCT, n=132: 42.9% versus 27.2%; RR 1.58, 95% CI 0.97 to 2.5; low quality evidence) or the number of women discontinuing treatment due to an adverse event (1 RCT, n=132: 0% versus 4.3%; RR 0.24, 95% CI 0.01 to 4.36); very low quality evidence).

Quinolones compared with beta-lactams

There was no significant difference between those treated with quinolones or beta-lactams in the number of adverse events reported (4 RCTs, n=1,501: 28.9% versus 29.3%; RR 0.90, 95% CI 0.61 to 1.33; very low quality evidence) or the number of women discontinuing treatment due to an adverse event (4 RCTs, n=1,501: 1.6% versus 0.79%; RR 1.96, 95% CI 0.74 to 5.3; low quality evidence).

Nitrofurantoin compared with co-trimoxazole

There was no significant difference between those treated with nitrofurantoin or co-trimoxazole in the number of adverse events reported (3 RCTs, n=921: 27.6% versus 28.8%; RR 0.96, 95% CI 0.79 to 1.17; high quality evidence) or the number of women discontinuing treatment due to an adverse event (4 RCTs, n=921: 2.6% versus 3.9%; RR 0.69, 95% CI 0.34 to 1.41; low quality evidence).

Quinolone compared with another quinolone

Rafalsky et al. (2006) compared the safety of different quinolone antibiotics in non-pregnant women with uncomplicated lower UTI for the following comparisons:

There was no significant difference between those treated with ciprofloxacin or ofloxacin when used for the treatment of lower UTI in non-pregnant women, in the number of adverse events reported (1 RCT, n=458: 39.5% versus 49.1%; RR 0.34 95% CI 0.01 to 8.21; very low quality evidence), or the number of women treated with ciprofloxacin, discontinuing treatment due to an adverse event, compared with those who received ofloxacin (1 RCT, n=458: 0.88% versus 0.43%; RR 2.02 95% CI 0.18 to 22.09; very low quality evidence).

There was no significant difference between those treated with levofloxacin (250 mg daily) or ofloxacin (400 mg daily) in the number of adverse events reported (1 RCT, n=591: 33.2% versus 32.8%; RR 1.01 95% CI 0.81 to 1.28; moderate quality

evidence) or the number of women experiencing serious adverse events (1 RCT, n=591: 0.3% versus 2.0%; RR 0.16 95% CI 0.02 to 1.35; low quality evidence).

There was no significant difference between those treated with standard-release ciprofloxacin (500 mg daily) or extended-release ciprofloxacin (500 mg daily) in the number of women discontinuing from treatment (1 RCT, n=891: 0.45% versus 0.45%; RR 1.01 95% CI 0.14 to 7.12; very low quality evidence) or the number of adverse events (1 RCT, n=891: 23.5% versus 27.3%; RR 0.86, 95% CI 0.69 to 1.08; low quality evidence).

Fosfomycin (single dose) compared with other antibiotics

Falagas et al. (2010) compared the safety of fosfomycin to other antibiotics, in the treatment of UTI in non-pregnant women. Fosfomycin was not significantly different to other antibiotics in the number of adverse events experienced by women seeking treatment for an acute lower UTI (13 RCTs, n=2,298: 9.3% versus 7.3%; RR 1.25, 95% CI 0.83 to 1.88; low quality evidence) or in the number of women withdrawing from treatment due to adverse effects of the treatment (2 RCTs, n=2,379: 1.9% versus 2.1%; RR 2.01 95% CI 0.05 to 80.21; very low quality evidence).

Milo et al. (2005) investigated the effectiveness of a 3-day antibiotic course compared with a longer course (5 to 10 days) in non-pregnant women with UTI. They found a significant reduction in the number of women reporting adverse events during treatment in women who received a 3-day course of antibiotics compared with a 5- to 10-day course (29 RCTs, n=7,617: 16.3% versus 20.6%; RR 0.83, 95% CI 0.74 to 0.93; NNH 23 [95% CI 16 to 39]; very low quality evidence), adverse events requiring withdrawal (24 RCTs, n=6,177: 1.5% versus 3.2%; RR 0.51, 95% CI 0.28 to 0.91; NNH 60 [95% CI 41 to 109]; very low quality evidence), and gastrointestinal adverse effects (24 RCTs, n=6,973: 6.7% versus 8.5%; RR 0.81, 95% CI 0.67 to 0.97; NNH 57 [95% CI 33 to 204]; very low quality evidence). Restricting the analysis to studies that compared a 3-day course with a longer course of the same antibiotic did not affect the results.

4.3.2 Antibiotics in pregnant women

One systematic review (Smaill et al. 2015) and one RCT (Kazemier et al. 2015) assessed the effectiveness of antibiotics compared with placebo or no treatment in pregnant women. However neither study reported adverse event data.

Guinto et al. (2010) assessed the efficacy and safety of different antibiotics in the management of asymptomatic bacteriuria in pregnant women. The authors did not report the total number of adverse events for any of the antibiotic comparison groups included. However, they reported specific adverse events as well as premature stopping of treatment. Because the antibiotics in the included studies varied widely, Guinto et al. (2010) presented a suite of comparisons for adverse events.

Pivmecillinam significantly increased the number of women reporting vomiting when compared with ampicillin (1 RCT, n=65: 43.8% versus 9.1%; RR 4.81, 95% CI 1.53 to 15.17; NNH 2 [95% CI 1 to 6]; very low quality evidence). It also increased the number of women who had to prematurely stop treatment when compared with ampicillin (1 RCT, n=65: 28.1% versus 3%; RR 9.28, 95% CI 1.25 to 69.13; NNH 4 [95% CI 2 to 11]; very low quality evidence). There was no difference between pivmecillinam and ampicillin in the number of participants reporting diarrhoea (very low quality evidence)

Fosfomycin did not change the number of women who reported adverse effects, such as allergy or pruritus, compared with cefuroxime (very low quality evidence). And a single dose of nitrofurantoin did not change the number of women reporting nausea when compared with a 7-day course of nitrofurantoin (moderate quality evidence).

Guinto et al. (2010) also conducted subgroup analyses for clinical outcomes stratified by course length. However, the subgroup analysis did not report any adverse event data.

Widmer et al. (2015) assessed the effectiveness and safety of different antibiotic course lengths in the management of asymptomatic bacteriuria in pregnant women. The antibiotics in the analysis included: amoxicillin, trimethoprim (with or without a sulphonamide), nitrofurantoin, fosfomycin and ampicillin. Single-dose antibiotics significantly reduced the number of women experiencing side effects when compared with short-course (4 to 7 days) antibiotics (Widmer et al. 2015, 12 RCTs, n=1,460: 13.1% versus 19.4%; RR 0.70, 95% CI 0.56 to 0.88; NNH 16 [95% CI 10 to 40]; very low quality evidence). This was true for subgroup analyses including comparisons with the same antibiotic in the 2 arms, and with different antibiotics in the two arms.

4.3.3 Antibiotics in older people

Zalmanovici-Trestioreanu et al. (2015) assessed the safety of antibiotics, compared with placebo or no treatment, in the management of asymptomatic bacteriuria in older people. Antibiotics increased the incidence of adverse events when compared with placebo or no treatment (Zalmanovici-Trestioreanu et al. 2015, 4 RCTs, n=921: 4% versus 1%; RR 3.77, 95% CI 1.40 to 10.15; NNH 31 [95% CI 19 to 82]; high quality evidence). There was no difference in the rate of complications or death (low quality evidence).

Lutters et al. (2008) investigated the safety of different antibiotic course lengths in older people with UTI. Antibiotic course length, such as single-dose, short-course, or long-course, had no effect on adverse events, or on the number of withdrawals due to adverse events (very low to low quality evidence).

4.3.4 Antibiotics in children

No evidence of safety outcomes in children with lower UTI was identified.

5 Antimicrobial resistance

The consumption of antimicrobials is a major driver for the development of antibiotic resistance in bacteria, and the 3 major goals of antimicrobial stewardship are to:

- optimise therapy for individual patients
- prevent overuse, misuse and abuse, and
- minimise development of resistance at patient and community levels.

The NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) recommends that the risk of antimicrobial resistance for individual patients and the population as a whole should be taken into account when deciding whether or not to prescribe an antimicrobial.

When antimicrobials are necessary to treat an infection that is not life-threatening, a narrow-spectrum antibiotic should generally be first choice. Indiscriminate use of broad-spectrum antibiotics creates a selective advantage for bacteria resistant even to these 'last-line' broad-spectrum agents, and also kills normal commensal flora leaving people susceptible to antibiotic-resistant harmful bacteria such as *C. difficile*. For infections that are not life-threatening, broad-spectrum antibiotics (for example, co-amoxiclav, quinolones and cephalosporins) need to be reserved for second-choice treatment when narrow-spectrum antibiotics are ineffective (CMO report 2011).

The ESPAUR report 2016 reported that antimicrobial consumption declined significantly between 2014 and 2015, with community prescribing from general and dental practice decreasing by more than 6%. Antibiotic prescribing in primary care in 2015 is at the lowest level since 2011, with broad-spectrum antibiotic use (antibiotics that are effective against a wide range of bacteria) continuing to decrease in primary care.

Urinary tract infections (UTI) are most commonly caused by *E. coli* (recorded in more than half of all the mandatory surveillance reports for *E. coli* bacteraemia when foci of infection are reported). Better management of UTIs is seen as a potential intervention to reduce the incidence of *E. coli* bacteraemia. The ESPAUR report 2016 states that between 2010 and 2014 the rate of bloodstream infections caused by *E. coli* and *Klebsiella pneumoniae* increased by 15.6% and 20.8% respectively. Between 2014 and 2015 the number of cases continued to increase; *E. coli* bloodstream infections increased by a further 4.6% and K. pneumoniae increased by 9%.

The ESPAUR report 2016 notes that across England trimethoprim resistance in Gram-negative UTI ranges from 16.3% to 66.7%, with 86% of Clinical Commissioning Groups (CCGs) having resistance rates above 25%.

Falagas et al. (2009) assessed the efficacy of antibiotics compared to placebo, in managing symptoms of UTI. They found no significant difference in the emergence of resistance, in the antibiotic group compared with the placebo group (5 RCTs, n=962: absolute figures not reported; OR 0.33 95% CI 0.40 to 2.70; low quality evidence).

6 Other considerations

6.1 Resource impact

6.1.1 Antibiotics

There is potential for resource savings if a back-up antibiotic prescription strategy is used in non-pregnant women with lower urinary tract infection (UTI) (see section 3.3.2).

Recommended antibiotics (nitrofurantoin, trimethoprim, amoxicillin, cefalexin and fosfomycin) are available as generic formulations, but there is currently no generic formulation of pivmecillinam, although the cost is comparable to other generic antibiotics, see Drug Tariff for costs.

Nitrofurantoin 25mg/5ml oral suspension is more expensive than other oral suspensions, such as trimethoprim 50mg/5ml. The cost of a 300 ml bottle of nitrofurantoin is £446.95 compared with £4.87 for a 100 ml bottle of trimethoprim (Drug Tariff, September 2018).

6.2 Medicines adherence

Medicines adherence may be a problem for some people with medicines that require frequent dosing (for example, some antibiotics) or longer treatment duration (NICE guideline on medicines adherence (2009).

Lutters et al. (2008) reported the acceptability (little or not satisfied with treatment) of various antibiotic course lengths in older people with lower UTI. They found no significant difference in acceptability (little or no satisfaction with treatment) between those who received a single dose of antibiotics compared to short-course antibiotics (1 RCT, n=158: 3.8% versus 12.7%; RR 0.30 95% CI 0.09 to 1.06; moderate quality evidence). However, there was a significant difference between those who received a single dose of antibiotics compared to a long-course antibiotics (1 RCT, n=388: 45.2% versus 62.3%; RR 0.73 95% CI 0.60 to 0.88; moderate quality evidence). There was no difference in acceptability between those who received a single dose of antibiotics compared to a short- or a long-course antibiotic (2 RCTs, n=546: 33.3% versus 47.8%; RR 0.58 95% CI 0.27 to 1.25; low quality evidence).

7 Terms used in the guideline

7.1.1 Apgar score

The appearance, pulse, grimace, activity and respiration (APGAR) score is a tool used to determine the condition of a new-born infant. The score is taken at a minute after birth, 5, 10 and sometimes 15 minutes after birth. It assesses the baby's ability to cope with the process of delivery, and thrive outside of the womb. The score ranges 0 to 10, where higher scores are better. Most babies score between 8 and 10 on the first assessment, however those with lower score most likely improve at later assessments. A consistently low Apgar score may be indicative of severe, long term impairments.

Appendices

Appendix A: Evidence sources

Key area	Key question(s)	Evidence sources
Background	• What is the natural history of the infection? • What is the expected duration and severity of symptoms with or without antimicrobial treatment? • What are the most likely causative organisms? • What are the usual symptoms and signs of the infection? • What are the known complication rates of the infection, with and without antimicrobial treatment? • Are there any diagnostic or prognostic factors to identify people who may or may not benefit from an antimicrobial?	• NICE guideline CG160: Fever in under 5s: assessment and initial management (2017) • NICE guideline NG15: Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) • NICE guideline NG63: Antimicrobial stewardship: changing risk-related behaviours in the general population (2017) • NICE guideline CG54: Urinary tract infection in under 16s: diagnosis and management (updated 2017) • NICE guideline NG76: Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence (2009) • NICE Clinical knowledge summary on UTI (lower) – women • NICE Clinical knowledge summary on UTI (lower) – men • European Association of Urology guidelines on urological infections 2017 • Little et al. 2009
Safety netting	• What safety netting advice is needed for managing the infection?	• NICE clinical knowledge summary on UTI (lower) - women

Key area	Key question(s)	Evidence sources
		• NICE clinical knowledge summary on UTI (lower) - men • NICE guideline CG54: Urinary tract infection in under 16s: diagnosis and management (updated 2017)
Red flags	• What symptoms and signs suggest a more serious illness or condition (red flags)?	• NICE clinical knowledge summary on UTI (lower) - women • NICE clinical knowledge summary on UTI (lower) - men • NICE clinical knowledge summary on UTI - children
Non-pharmacological interventions	• What is the clinical effectiveness and safety of non-pharmacological interventions for managing the infection or symptoms?	• Evidence review - see appendix F for included studies
Non-antimicrobial pharmacological interventions	• What is the clinical effectiveness and safety of non-antimicrobial pharmacological interventions for managing the infection or symptoms?	• Evidence review - see appendix F for included studies
Antimicrobial prescribing strategies	• What is the clinical effectiveness and safety of antimicrobial prescribing strategies (including back-up prescribing) for managing the infection or symptoms?	• Evidence review - see appendix F for included studies
Antimicrobials	• What is the clinical effectiveness and safety of antimicrobials for managing the infection or symptoms?	• Evidence review - see appendix F for included studies • NICE guideline NG15: Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) • NICE guideline CG160: Fever in under 5s: assessment and initial management (2017) • MHRA safety information • British National Formulary (BNF) (August 2018)

Key area	Key question(s)	Evidence sources
	• Which people are most likely to benefit from an antimicrobial?	• Evidence review - see appendix F for included studies
	• Which antimicrobial should be prescribed if one is indicated (first, second and third line treatment, including people with drug allergy)?	• Evidence review - see appendix F for included studies
	• What is the optimal dose, duration and route of administration of antimicrobials?	• Evidence review - see appendix F for included studies • BNF (August 2018) • BNF for children (BNF-C) (August 2018) • Summary of product characteristics
Antimicrobial resistance	• What resistance patterns, trends and levels of resistance exist both locally and nationally for the causative organisms of the infection • What is the need for broad or narrow spectrum antimicrobials? • What is the impact of specific antimicrobials on the development of future resistance to that and other antimicrobials?	• Evidence review - see appendix F for included studies • European surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report (2016) • Chief medical officer (CMO) report (2011) • NICE guideline NG76: Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence (2009)
Resource impact	• What is the resource impact of interventions (such as escalation or de-escalation of treatment)?	• Evidence review - see appendix F for included studies • Drug Tariff (September 2018)
Medicines adherence	• What are the problems with medicines adherence (such as when longer courses of treatment are used)?	• Evidence review - see appendix F for included studies • NICE guideline NG76: Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence (2009)

Key area	Key question(s)	Evidence sources
Regulatory status	• What is the regulatory status of interventions for managing the infection or symptoms?	• Summary of product characteristics

Appendix B: Review protocol

Review protocol for lower uncomplicated urinary tract infection			Notes
I	Review question	What pharmacological (antimicrobial and non-antimicrobial) and non-pharmacological interventions are effective in managing lower urinary tract infections (UTIs)?	• antimicrobial includes antibiotics • non-antimicrobial includes analgesia, cranberry products and urine alkalinizing agents. • search will include terms for lower urinary tract infections
II	Types of review question	Intervention questions will primarily be addressed through the search.	These will, for example, also identify natural history in placebo groups and causative organisms in studies that use laboratory diagnosis, and relative risks of differing management options.
III	Objective of the review	To determine the effectiveness of prescribing and other management interventions in managing lower UTIs, in line with the major goals of antimicrobial stewardship. This includes interventions that lead prescribers to: • optimise outcomes for individuals • reduce overuse, misuse or abuse of antimicrobials. All of the above will be considered in the context of national antimicrobial resistance patterns where available, if not available committee expertise will be used to guide decision-making.	The secondary objectives of the review of studies will include: • indications for prescribing an antimicrobial (for example 'red flags' and illness severity), thresholds for treatment and individual patient factors affecting choice of antimicrobial • indications for no or delayed antimicrobial • indications for non-antimicrobial interventions • antimicrobial choice, optimal dose, duration (specifically length of treatment) and route for specified antimicrobial(s) • the natural history of the infection

IV	Eligibility criteria – population/ disease/ condition/ issue/ domain	Population: Adults and children (aged 72 hours and older) with lower UTIs of any severity. Lower UTIs are a result of infections of the bladder (cystitis) or urethra. This review protocol includes lower UTI in non-pregnant and pregnant women, men and children. Consideration will be given to differing management in subgroups based on age, gender, pregnancy, complicating factors and risk of resistance. Studies that use, for example, symptoms or signs (prognosis), clinical diagnosis or microbiological methods for diagnosing the condition will be included.	Subgroups of interest, those: • with protected characteristics under the Equality Act 2010 • with true allergy • women with 'simple/uncomplicated[1]' lower UTI • pregnant women • men • children (possible age groups) • older people (frailty, care home resident, dementia) • asymptomatic bacteriuria • people with 'complicated[2]' lower UTI • people with risk factors for increased resistance[3]
V	Eligibility criteria – intervention(s)/ exposure(s)/ prognostic factor(s)	The review will include studies which include: • Non-pharmacological interventions[4] • Non-antimicrobial pharmacological interventions[5] • Antimicrobial pharmacological interventions[6]	Limited to those interventions commonly in use (as agreed by the committee)

[1] Uncomplicated UTI: infection of the urinary tract by a usual pathogen in a person with a normal urinary tract and with normal kidney function (Source: CKS)
[2] Complicated UTI: UTI with one or more factors that predispose to persistent infection, recurrent infection or treatment failure, such as abnormal urinary tract, virulent organism, impaired host defences (diabetes mellitus, immunocompromised) or impaired renal function (Source: CKS)
[3] Risk factors for increased resistance include: care home resident, recurrent UTI, previous hospitalisation, unresolving urinary symptoms, recent travel to country with increased resistance, previous UTI resistant to antibiotics (previous antibiotic use [trimethoprim]) (Source PHE management of infection guidance)
[4] Non-pharmacological interventions include: no intervention, watchful waiting, delayed prescribing
[5] Non-antimicrobial pharmacological interventions include: analgesics and NSAIDs, cranberry products and urine alkalinizing agents.
[6] Antimicrobial pharmacological interventions include: delayed (back-up) prescribing, standby or rescue therapy, narrow or broad spectrum, single, dual or triple therapy, escalation or de-escalation of treatment. Antibiotics included in the search include those named in current guidance (plus the class to which they belong) plus other antibiotics agreed by the committee

		For the treatment of lower UTIs in primary, secondary or other care settings (for example walk-in-centres, urgent care, and minor ailment schemes) either by prescription or by any other legal means of supply of medicine (for example, patient group direction).	
VI	Eligibility criteria – comparator(s)/ control or reference (gold) standard	Any other plausible strategy or comparator, including: • Placebo or no treatment • Non-pharmacological interventions • Non-antimicrobial pharmacological interventions • Antimicrobial pharmacological interventions	
VII	Outcomes and prioritisation	Clinical outcomes such as: a) mortality b) infection cure or improvement in symptoms (duration or severity) c) recurrence d) complications e) adverse events. Patient reported outcomes such as medicines adherence, patient experience and patient satisfaction. Health and social care-related quality of life such as ability to carry out activities of daily living. Health and social care utilisation such as length of stay, antimicrobial use and re-consultation rates.	The committee have agreed that the following outcomes are critical: • reduction in symptoms (duration or severity) for example difference in time to substantial improvement • time to clinical cure (mean or median time to resolution of illness) • rate of complications[7] (including mortality) with or without treatment, including escalation of treatment • health and social care utilisation (including length of stay, ITU stays, planned and unplanned contacts). • thresholds or indications for antimicrobial treatment (which people are most, or least likely to benefit from antimicrobials) • an individual's risk factors for resistance and choice of antibiotic

[7] Ascending infection leading to pyelonephritis, renal failure or sepsis, and in pregnancy, developmental delay or cerebral palsy in the infant and foetal death. Also recurrent infection, prostate involvement in men, urinary stones

			The committee have agreed that the following outcomes are important: • patient-reported outcomes, such as medicines adherence, patient experience • changes in antimicrobial resistance patterns, trends and levels as a result of treatment
VIII	Eligibility criteria – study design	The search will look for: • Systematic reviews of randomised controlled trials (RCTs) • RCTs If insufficient evidence is available progress to: • Controlled trials • Systematic reviews of non-randomised controlled trials • Non-randomised controlled trials • Observational and cohort studies • Pre and post intervention studies (before and after) • Time series studies	Committee to advise the NICE project team on the inclusion of information from other condition specific guidance and on whether to progress due to insufficient evidence.
IX	Other inclusion exclusion criteria	The scope sets out what the guidelines will and will not include (exclusions). Further exclusions specific to this guideline include: non-English language papers, studies that are only available as abstracts • for antimicrobial resistance non-UK papers.	
X	Proposed sensitivity/ sub-group analysis, or meta-regression	The search may identify studies in population subgroups (for example adults, older adults, children (those aged under 18 years of age), and people with co-morbidities or characteristics that are protected under the Equality Act 2010 or in the NICE equality impact assessment). These will be analysed within these categories to enable the production of management recommendations.	
XI	Selection process – duplicate	All references from the database searches will be downloaded, de-duplicated and screened on title and abstract against the criteria above.	

	screening/ selection/ analysis	A randomly selected initial sample of 10% of records will be screened by two reviewers independently. The rate of agreement for this sample will be recorded, and if it is over 90% then remaining references will screened by one reviewer only. Disagreement will be resolved through discussion. Where abstracts meet all the criteria, or if it is unclear from the study abstract whether it does, the full text will be retrieved. If large numbers of papers are identified at full text, the Committee may consider prioritising the evidence for example, evidence of higher quality in terms of study type or evidence with critical or highly important outcomes.	
XII	Data management (software)	Data management will be undertaken using EPPI-reviewer software. Any pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome.	
XIII	Information sources – databases and dates	Medline; Medline in Process; Embase; PubMed; Cochrane database of systematic reviews (CDSR); Database of abstracts of effectiveness (DARE) (legacy); Cochrane Central Register of Controlled Trials (CENTRAL); Health Technology Assessment (HTA) database; Clinicaltrials.gov • All the above to be searched from 2000 to present day. • Filters for systematic reviews, RCTs and comparative studies to be applied, unless numbers without filters are low • Searches to be limited to studies reported in English. • Animal studies and conference abstracts to be excluded Medicines and Healthcare products Regulatory Agency (MHRA) website; European Medicines Agency (EMA) website; U.S. Food and Drug Administration (FDA) website; Drug Tariff; MIMs • The above to be searched for advice on precautions, warnings, undesirable effects of named antimicrobials.	
XIV	Identify if an update	Not applicable at this time.	
XV	Author contacts	Web: https://www.nice.org.uk/guidance/indevelopment/gid-apg10002 Email: infections@nice.org.uk	

XVI	Highlight if amendment to previous protocol	For details please see the interim process guide (2017).	
XVII	Search strategy – for one database	For details see appendix C.	
XVIII	Data collection process – forms/ duplicate	GRADE profiles will be used, for details see appendix H.	
XIX	Data items – define all variables to be collected	GRADE profiles will be used, for details see appendix H.	
XX	Methods for assessing bias at outcome/study level	Standard study checklists will be used to critically appraise individual studies. For details please see the interim process guide (2017). The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/	
XXI	Criteria for quantitative synthesis (where suitable)	For details please see the interim process guide (2017).	
XXII	Methods for analysis – combining studies and exploring (in)consistency	For details please see the interim process guide (2017).	
XXIII	Meta-bias assessment – publication bias,	For details please see the interim process guide (2017).	

	selective reporting bias		
XXIV	Assessment of confidence in cumulative evidence	For details please see the interim process guide (2017).	
XXV	Rationale/ context – Current management	For details please see the introduction to the evidence review in the guideline.	
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by NICE and chaired by Dr Tessa Lewis in line with the interim process guide (2017). Staff from NICE undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.	
XXVII	Sources of funding/support	Developed and funded by NICE.	
XXVIII	Name of sponsor	Developed and funded by NICE.	
XXIX	Roles of sponsor	NICE funds and develops guidelines for those working in the NHS, public health, and social care in England.	

Appendix C: Literature search strategy

1 Search format

The search strategy has been designed to cover four UTI protocols and it takes the following format:

Urinary Tract Infections

AND (Named Antibiotics OR Classes of Antibiotics OR Pain Relief OR NSAIDs OR Cranberry Products OR Alkalinising agents OR Bladder instillations OR Drinking Fluids OR Prescribing Strategies OR Self Care OR Catheter Removal)

AND (Systematic Reviews OR Randomised Controlled Trials OR Observational Studies)

AND Limits

Note there is an additional search in this format:

Named Antibiotics AND Drug Resistance AND Limits

2 Overview of search results

	No. of hits in MEDLINE	Position in the strategy
Search without any limits	65,619	Line 178
Search with limits	14,263	Line 184
Search with limits and Systematic Reviews	2,428	Line 200
Search with limits and RCTs (not SRs)	2,230	Line 217
Search with limits and Observational Studies (not SRs or RCTs)	3,795	Line 240
Search with limits (without SRs, RCTs, Observational)	5,810	Line 241
Named Antibiotics AND Drug Resistance	48,201	Line 257
Named Antibiotics AND Drug Resistance with Limits	20,072	Line 262

3 Contents of the search strategy

Main concepts	Coverage	Position in strategy
Urinary Tract Infections	Urinary tract infections Cystitis Vesico-ureteral reflux Pyelonephritis Catheter-Related Infections Bacteriuria Urosepsis Urethritis	Lines 1-20
Named Antibiotics	Trimethoprim Nitrofurantoin Fosfomycin	Lines 21-84

	Methenamine hippurate Gentamicin Amikacin Tobramycin Amoxicillin Ampicillin Co-amoxiclav Pivmecillinam Cefalexin Cefotaxime Cefixime Ceftriaxone Ciprofloxacin Ofloxacin Colistin Ertapenem Doxycycline Septrin Chloramphenicol Tazocin Aztreonam Temocillin Tigecycline Vancomycin Teicoplanin Linezolid Cefuroxime Cefradine Ceftazidime Levofloxacin	
Classes of Antibiotics	Aminoglycosides Penicillins Cephalosporins Quinolones Carbapenems Tetracyclines	Lines 86-93
Pain Relief	Paracetamol Ibuprofen Naproxen Codeine Diclofenac Analgesics Non-steroidal anti-inflammatory drugs	Lines 96-111
Non-pharmaceutical products	Cranberry products Barley products D-Mannose	Lines 113-119
Alkalinising agents	Potassium citrate Sodium citrate Sodium bicarbonate	Lines 121-127
Bladder instillations	Chlorhexidine solution Sodium chloride solution	Lines 129-133
Drinking Fluids	Fluid therapy Drinking water, beverages, fluids or liquids	Lines 135-139
Prescribing Strategies	Watchful waiting No intervention Active surveillance	Lines 141-160

	Delayed treatment Prescribing times Antibiotic prophylaxis	
Self Care	Self management Self care secondary prevention Catheter removal	Lines 162-176
Systematic Reviews	Meta analysis Systematic Reviews Reviews	Lines 185-199
Randomised Controlled Trials	RCTs Controlled Clinical Trials Cross over studies	Lines 201-215
Observational Studies	Observational Study Epidemiologic Studies Case-Control Studies Cohort Studies Cross-Sectional Studies Controlled Before-After Studies	Lines 218-238
Limits	2006-Current Exclude Animal studies Exclude letters, editorials and letters	Lines 179-184
Additional search	Drug resistance	Lines 242-262

4 Key to search operators

/	Medical Subject Heading (MeSH) term
Exp	Explodes the MeSH terms to retrieve narrower terms in the hierarchy
.ti	Searches the title field
.ab	Searches the abstract field
*	Truncation symbol (searches all word endings after the stem)
adj*n*	Adjacency operator to retrieve records containing the terms within a specified number (*n*) of words of each other

5 Search strategy for MEDLINE

Database(s): **Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

#	Searches	Results
1	exp urinary tract/	406398
2	exp urinary tract infections/	42175
3	exp cystitis/	8814
4	vesico-ureteral reflux/	7753
5	exp pyelonephritis/	14154
6	exp Urinary Calculi/	32650
7	Urethritis/	4483

8	Catheters, Indwelling/	17219
9	Urinary Catheters/	530
10	Urinary Catheterization/	13329
11	Catheter-Related Infections/	3344
12	Catheter Obstruction/	139
13	(UTI or CAUTI or RUTI or cystitis* or bacteriuria* or pyelonephriti* or pyonephrosi* or pyelocystiti* or pyuri* or VUR or urosepsis* or uroseptic* or urosepses* or urethritis*).ti,ab.	38919
14	((urin* or renal* or kidney*) adj1 (system* or tract* or calculus or calculi* or stone* or sepsis*)).ti,ab.	82884
15	((bladder* or genitourin* or genito urin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) adj3 (infect* or bacteria* or microbial* or block* or obstruct* or catheter* or inflamm*)).ti,ab.	87091
16	((upper or lower) adj3 urin*).ti,ab.	21980
17	(bladder* adj3 (ulcer* or ulcus)).ti,ab.	151
18	(schistosomiasis adj3 (haematobia or hematobia or urin*)).ti,ab.	966
19	((vesicorenal* or vesicoureteral* or vesicoureteric* or vesico renal* or vesico ureteral* or vesico ureteric* or bladder* or cystoureteral* or ureter* or urether* or nephropathy*) adj3 (backflow* or reflux*)).ti,ab.	7989
20	or/1-19	576113
21	Trimethoprim/	6280
22	(Trimethoprim* or Monotrim*).ti,ab.	14565
23	Nitrofurantoin/	2517
24	(Nitrofurantoin* or Genfura* or Macrobid*).ti,ab.	2980
25	Fosfomycin/	1685
26	(Fosfomycin* or Phosphomycin* or Fosfocina* or Monuril* or Monurol* or Fomicyt*).ti,ab.	2378
27	Methenamine/	1045
28	(Methenamine* or hexamine* or hippurate* or Hiprex*).ti,ab.	2411
29	Gentamicins/	17268
30	(Gentamicin* or Cidomycin*).ti,ab.	21976
31	Amikacin/	3751
32	(amikacin* or Amikin*).ti,ab.	8118
33	Tobramycin/	3973
34	(tobramycin* or Nebcin*).ti,ab.	6203

35	Amoxicillin/	8654
36	(Amoxicillin* or Amoxil*).ti,ab.	12541
37	Ampicillin/	12932
38	ampicillin*.ti,ab.	20478
39	Amoxicillin-Potassium Clavulanate Combination/	2301
40	(co-amoxiclav* or Coamoxiclav* or Amox-clav* or Amoxicillin-Clavulanic Acid* or Amoxicillin-Potassium Clavulanate Combination* or Amoxi-Clavulanate* or Clavulanate Potentiated Amoxycillin Potassium* or Clavulanate-Amoxicillin Combination* or Augmentin*).ti,ab.	13396
41	Amdinocillin Pivoxil/	205
42	(pivmecillinam* or Pivamdinocillin* or Selexid*).ti,ab.	268
43	Cefalexin/	1974
44	(Cefalexin* or Cephalexin* or Keflex*).ti,ab.	2605
45	Cefotaxime/	5101
46	cefotaxime*.ti,ab.	7488
47	Cefixime/	711
48	(cefixime* or Suprax*).ti,ab.	1438
49	Ceftriaxone/	5210
50	(ceftriaxone* or Rocephin*).ti,ab.	8834
51	Ciprofloxacin/	11578
52	(Ciprofloxacin* or Ciproxin*).ti,ab.	21632
53	Ofloxacin/	5795
54	(ofloxacin* or Tarivid*).ti,ab.	6236
55	Colistin/	3071
56	(Colistin* or Colistimethate* or Colimycin* or Coly-Mycin* or Colymycin* or Colomycin* or Promixin*).ti,ab.	4291
57	(Ertapenem* or Invanz*).ti,ab.	1135
58	Doxycycline/	8515
59	(Doxycycline* or Efracea* or Periostat* or Vibramycin*).ti,ab.	11268
60	Trimethoprim, Sulfamethoxazole Drug Combination/	6306
61	(Septrin* or Co-trimoxazole* or Cotrimoxazole* or Sulfamethoxazole Trimethoprim Comb* or Trimethoprim Sulfamethoxazole Comb*).ti,ab.	5497
62	Chloramphenicol/	18958
63	(Chloramphenicol* or Cloranfenicol* or Kemicetine* or Kloramfenikol*).ti,ab.	24993

64	Piperacillin/	2423
65	(Tazocin* or Piperacillin* or Tazobactam*).ti,ab.	6222
66	Aztreonam/	1336
67	(Aztreonam* or Azactam*).ti,ab.	2743
68	(Temocillin* or Negaban*).ti,ab.	237
69	(Tigecycline* or Tygacil*).ti,ab.	2337
70	Vancomycin/	11836
71	(Vancomycin* or Vancocin*).ti,ab.	22446
72	Teicoplanin/	2067
73	(Teicoplanin* or Targocid*).ti,ab.	3233
74	Linezolid/	2421
75	(Linezolid* or Zyvox*).ti,ab.	4568
76	Cefuroxime/	2037
77	(Cefuroxime* or Cephuroxime* or Zinacef* or Zinnat* or Aprokam*).ti,ab.	3919
78	Cefradine/	540
79	(Cefradine* or Cephradine* or Nicef*).ti,ab.	699
80	Ceftazidime/	3461
81	(Ceftazidime* or Fortum* or Tazidime*).ti,ab.	7727
82	Levofloxacin/	2708
83	(Levofloxacin* or Evoxil* or Tavanic*).ti,ab.	6119
84	or/21-83	214218
85	20 and 84	18255
86	exp aminoglycosides/	142346
87	exp penicillins/	76761
88	exp cephalosporins/	39233
89	exp quinolones/	41144
90	exp Carbapenems/	8711
91	exp Tetracyclines/	44511
92	(Aminoglycoside* or Penicillin* or Cephalosporin* or Quinolone* or Carbapenem* or Tetracycline*).ti,ab.	120900
93	or/86-92	359234
94	20 and 93	22544

95	Anti-Infective Agents, Urinary/	2557
96	Acetaminophen/	15854
97	(paracetamol* or acetaminophen* or Panadol* or perfalgan* or calpol*).ti,ab.	20775
98	Ibuprofen/	7581
99	(ibuprofen* or arthrofen* or ebufac* or rimafen* or brufen* or calprofen* or feverfen* or nurofen* or orbifen*).ti,ab.	11191
100	Naproxen/	3730
101	(Naproxen* or Naprosyn* or Stirlescent*).ti,ab.	5450
102	Codeine/	4237
103	(codeine* or Galcodine*).ti,ab.	4407
104	Diclofenac/	6823
105	(Diclofenac* or Voltarol* or Dicloflex* or Econac* or Fenactol* or Volsaid* or Enstar* or Diclomax* or Motifene* or Rhumalgan* or Pennsaid*).ti,ab.	9698
106	(nsaid* or analgesic*).ti,ab.	87160
107	((nonsteroid* or non steroid*) adj3 (anti inflammator* or antiinflammator*)).ti,ab.	34162
108	analgesics/	43460
109	exp analgesics, non-narcotic/	299959
110	analgesics, short-acting/	8
111	or/96-110	400073
112	20 and 111	10492
113	Vaccinium macrocarpon/	645
114	(cranberry* or cranberries* or vaccinium macrocarpon*).ti,ab.	1247
115	Hordeum/	8153
116	(barley* or hordeum*).ti,ab.	15407
117	Mannose/	8489
118	(mannose* or d-mannose* or dmannose*).ti,ab.	24493
119	or/113-118	45484
120	20 and 119	1500
121	potassium citrate/	245
122	(potassium citrate* or Effercitrate*).ti,ab.	546
123	(sodium citrate* or Cymalon* or Cystocalm* or Micolette* or Micralax*).ti,ab.	2644
124	sodium bicarbonate/	4205

125	(sodium bicarbonate* or S-Bicarb* or SodiBic* or Thamicarb* or Polyfusor*).ti,ab.	5477
126	((alkalizer* or alkalinisation* or alkalinization* or alkalinising or alkalinizing) adj3 (drug* or agent* or therap*)).ti,ab.	191
127	or/121-126	10890
128	20 and 127	1049
129	Chlorhexidine/	7123
130	((chlorhexidine or sodium chloride*) adj3 (solution* or diluent* or instillation* or intravesical*)).ti,ab.	3327
131	Administration, Intravesical/	3418
132	(bladder* adj3 (instillat* or drug admin*)).ti,ab.	540
133	or/129-132	13618
134	20 and 133	1976
135	Drinking/ or Drinking Behavior/	19308
136	Fluid therapy/	17515
137	exp Beverages/	114331
138	((water* or fluid* or liquid* or beverage* or drinks) adj3 (consumption* or consume* or consuming* or intake* or drink* or hydrat* or rehydrat*)).ti,ab.	80871
139	or/135-138	210996
140	20 and 139	6845
141	watchful waiting/	2278
142	Antibiotic Prophylaxis/	11779
143	"no intervention*".ti,ab.	6125
144	(watchful* adj2 wait*).ti,ab.	2077
145	(wait adj2 see).ti,ab.	1225
146	(active* adj2 surveillance*).ti,ab.	5705
147	(expectant* adj2 manage*).ti,ab.	2738
148	((prescription* or prescrib*) adj4 ("red flag" or strateg* or appropriat* or inappropriat* or unnecessary or defer* or delay* or no or non or behaviour* or behavior* or optimal or optimi* or reduc* or decreas* or declin* or rate* or improv* or postcoital* or postcoitus* or postsex* or postintercourse* or post coital* or post coitus* or post sex* or post intercourse* or night* or nocturnal* or prophylaxis* or prophylactic* or prevent* or preoperative* or pre operative* or perioperative* or peri operative* or postoperative* or post operative*)).ti,ab.	25168

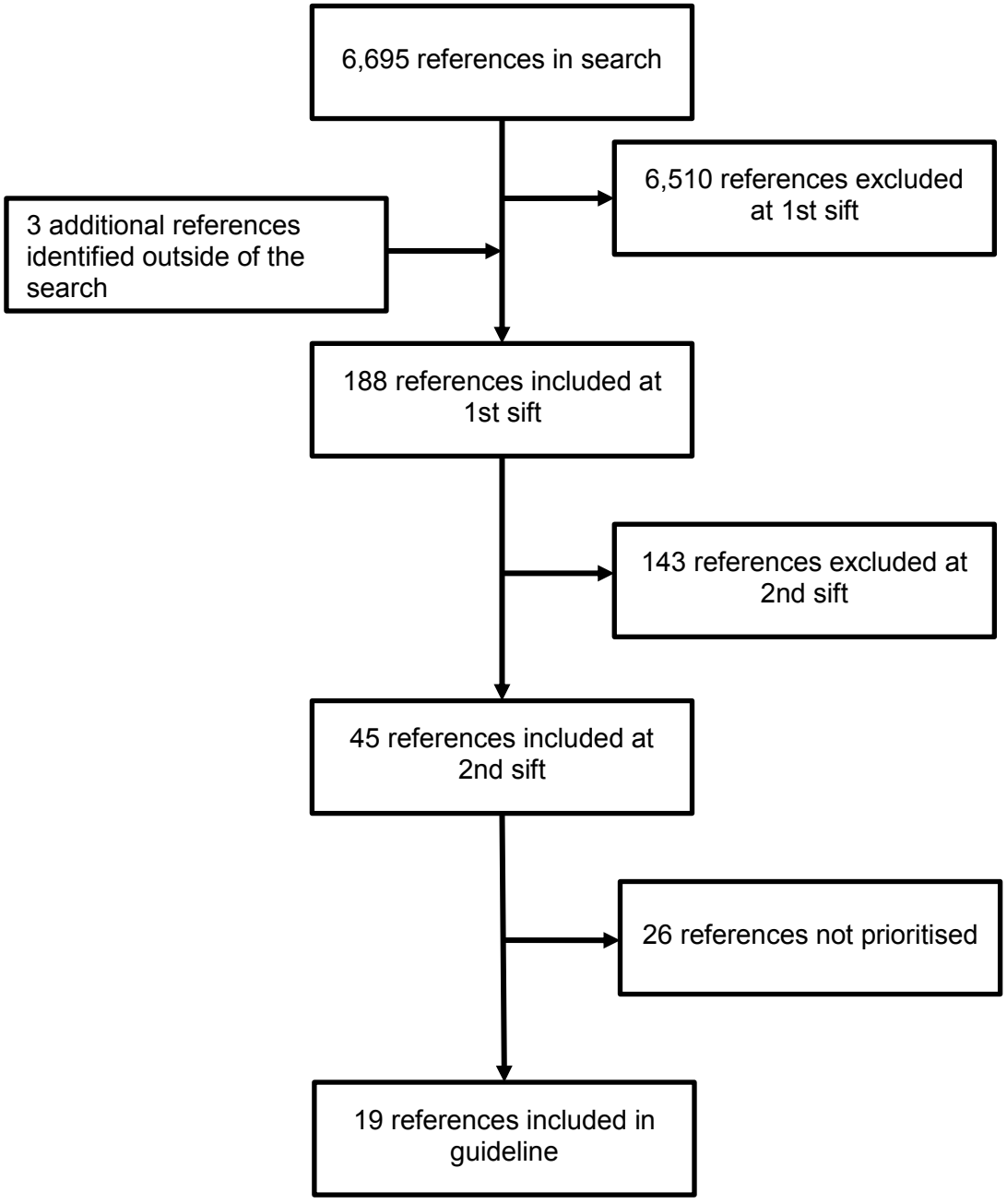
149	((misuse* or "mis-use*" or overuse* or "over-use*" or "over-prescri*" or abuse*) adj4 (bacter* or antibacter* or anti-bacter* or "anti bacter*" or antimicrobial or anti-microbial or "anti microbial" or antibiot* or anti-biot* or "anti biot*")).ti,ab.	1761
150	((delay* or defer*) adj3 (treat* or therap* or interven*)).ti,ab.	26341
151	or/141-150	82704
152	anti-infective agents/ or exp anti-bacterial agents/ or exp anti-infective agents, local/	844581
153	(antibacter* or anti-bacter* or antibiot* or anti-biot* or antimicrobial* or anti-microbial*).ti,ab.	401551
154	152 or 153	1017858
155	(postcoital* or postcoitus* or postsex* or postintercourse* or post coital* or post coitus* or post sex* or post intercourse* or night* or nocturnal* or delay* or defer* or back-up* or backup* or immediate* or rapid* or short* or long* or standby or "stand by" or rescue or escalat* or "de-escalat*" or (prescribing adj strateg*) or "red flag*" or prevent* or prophylaxis* or prophylactic*).ti,ab.	4758691
156	Coitus/	6880
157	Inappropriate prescribing/	1695
158	or/155-157	4764914
159	154 and 158	221871
160	151 or 159	292655
161	20 and 160	15345
162	Self Care/ or self medication/	32883
163	((self or selves or themsel*) adj4 (care or manag*)).ti,ab.	33223
164	Secondary Prevention/	17180
165	Hygiene/	14900
166	Baths/	4966
167	Soaps/	2343
168	((postcoital* or postcoitus* or postsex* or postintercourse* or post coital* or post coitus* or post sex* or post intercourse* or postmicturit* or micturit* or postmicturat* or micturat* or urinat* or defecat* or toilet* or lavatory or lavatories or perineal* or perineum*) adj3 (prophylaxis* or prophylactic* or treatment* or wipe* or wiping or hygiene* or hygienic* or clean* or douche* or douching* or bath* or soap* or wash* or shower*)).ti,ab.	1611
169	(second* adj3 prevent*).ti,ab.	21506
170	or/162-169	112930
171	20 and 170	1919

172	or/8-10	29047
173	Device Removal/	10427
174	172 and 173	753
175	(Catheter* adj3 (care* or removal* or removing* or remove* or "take* out" or "taking out" or change* or changing* or clean* or wash* or bath* or hygiene* or hygienic*)).ti,ab.	10138
176	174 or 175	10561
177	20 and 176	5423
178	85 or 94 or 95 or 112 or 120 or 128 or 134 or 140 or 161 or 171 or 177	65619
179	limit 178 to yr="2006 -Current"	21429
180	limit 179 to english language	19392
181	Animals/ not (Animals/ and Humans/)	4291504
182	180 not 181	15047
183	limit 182 to (letter or historical article or comment or editorial or news)	784
184	182 not 183	14263
185	Meta-Analysis.pt.	74747
186	Meta-Analysis as Topic/	15461
187	Network Meta-Analysis/	34
188	Review.pt.	2230816
189	exp Review Literature as Topic/	9193
190	(metaanaly* or metanaly* or (meta adj3 analy*)).ti,ab.	109466
191	(review* or overview*).ti.	389897
192	(systematic* adj5 (review* or overview*)).ti,ab.	109630
193	((quantitative* or qualitative*) adj5 (review* or overview*)).ti,ab.	7343
194	((studies or trial*) adj2 (review* or overview*)).ti,ab.	36022
195	(integrat* adj3 (research or review* or literature)).ti,ab.	8769
196	(pool* adj2 (analy* or data)).ti,ab.	22123
197	(handsearch* or (hand adj3 search*)).ti,ab.	7550
198	(manual* adj3 search*).ti,ab.	4715
199	or/185-198	2487695
200	184 and 199	2428
201	Randomized Controlled Trial.pt.	448607
202	Controlled Clinical Trial.pt.	91938

203 Clinical Trial.pt.	508233
204 exp Clinical Trials as Topic/	304614
205 Placebos/	34193
206 Random Allocation/	89847
207 Double-Blind Method/	143336
208 Single-Blind Method/	23779
209 Cross-Over Studies/	40867
210 ((random* or control* or clinical*) adj3 (trial* or stud*)).ti,ab.	1003782
211 (random* adj3 allocat*).ti,ab.	28603
212 placebo*.ti,ab.	189958
213 ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).ti,ab.	153095
214 (crossover* or (cross adj over*)).ti,ab.	74298
215 or/201-214	1721840
216 184 and 215	2933
217 216 not 200	2230
218 Observational Studies as Topic/	1959
219 Observational Study/	31517
220 Epidemiologic Studies/	7369
221 exp Case-Control Studies/	834068
222 exp Cohort Studies/	1623327
223 Cross-Sectional Studies/	234990
224 Controlled Before-After Studies/	218
225 Historically Controlled Study/	97
226 Interrupted Time Series Analysis/	243
227 Comparative Study.pt.	1770190
228 case control*.ti,ab.	102767
229 case series.ti,ab.	52479
230 (cohort adj (study or studies)).ti,ab.	133481
231 cohort analy*.ti,ab.	5462
232 (follow up adj (study or studies)).ti,ab.	43245
233 (observational adj (study or studies)).ti,ab.	70390
234 longitudinal.ti,ab.	186074

235	prospective.ti,ab.	454707
236	retrospective.ti,ab.	381342
237	cross sectional.ti,ab.	245513
238	or/218-237	3929955
239	184 and 238	5469
240	239 not (200 or 216)	3795
241	184 not (200 or 216 or 240)	5810
242	exp Drug Resistance, Bacterial/	72249
243	exp Drug Resistance, Multiple/	28752
244	((bacter* or antibacter* or anti-bacter* or "anti bacter*") adj4 (resist* or tolera*)).ti,ab.	34156
245	((antibiot* or anti-biot* or "anti biot*") adj4 (resist* or tolera*)).ti,ab.	42316
246	(multi* adj4 drug* adj4 (resist* or tolera*)).ti,ab.	12134
247	(multidrug* adj4 (resist* or tolera*)).ti,ab.	38335
248	(multiresist* or multi-resist* or "multi resist*").ti,ab.	6214
249	((microb* or antimicrob* or anti-microb* or "anti microb*") adj4 (resist* or tolera*)).ti,ab.	22368
250	(superbug* or super-bug* or "super bug*").ti,ab.	448
251	Superinfection/	1644
252	(superinvasion* or super-invasion* or "super invasion*" or superinfection* or super-infection* or "super infection*").ti,ab.	5185
253	R Factors/	4157
254	"r factor*".ti,ab.	3648
255	(resist* factor* or "r plasmid*" or resist* plasmid*).ti,ab.	5218
256	or/242-255	180317
257	84 and 256	48201
258	limit 257 to yr="2006 -Current"	25203
259	limit 258 to english language	23256
260	259 not 181	20939

Appendix D: Study flow diagram



Appendix E: Evidence prioritisation

Key questions	Included studies[1]		Studies not prioritised[2]	
	Systematic reviews	RCTs	Systematic reviews	RCTs
Which non-pharmacological interventions are effective?				
Cranberry	–	Wing et al. 2008 Wing et al. 2015	Dante et al. 2013 Jepson et al. 2009	Madden et al. 2015
Urinary alkalisation	–	–	O'Kane et al. 2016	–
Which non-antimicrobial pharmacological interventions are effective?				
Ibuprofen	–	Bleidorn et al. 2010 Gágyor et al. 2015	–	–
Which antibiotic prescribing strategies are effective (including back-up antibiotics)?				
Delayed antibiotics	–	Little et al. 2010	de Bont et al. 2015	
Is an antibiotic effective?				
Antibiotics versus placebo	Falagas et al. 2009 Smaill et al. 2015 Zalmanovici-Trestioreanu et al. 2015	Ferry et al. 2004 Kazemier et al. 2015	Fasugba et al. 2015	Bryce et al. 2016 Cai et al. 2012 Cai et al. 2015 Costelloe et al. 2010 Ferry et al. 2007
Which antibiotic is most effective?				
Antibiotics versus different antibiotics	Falagas et al. 2010 Fitzgerald et al. 2012 Guinto et al. 2010 Rafalsky et al. 2006 Zalmanovici-Trestioreanu et al. 2010	–	Angelescu et al. 2016 Dull et al. 2014 Falagas et al. 2010 Falagas et al. 2014 Huttner et al. 2015 Knotterus et al. 2012	Ceran et al. 2010 Gupta et al. 2007 Vachhani et al. 2015
What is the optimal dosage, duration and route of administration of antibiotic?				

Key questions	Included studies[1]		Studies not prioritised[2]	
	Systematic reviews	RCTs	Systematic reviews	RCTs
Dosage	–	–	–	–
Course length	Fitzgerald et al. 2012 Guinto et al. 2010 Lutters et al. 2008 Michael et al. 2003 Milo et al. 2005 Smaill et al. 2015 Widmer et al. 2015	–		Bayrak et al. 2007 Estebanez et al. 2009 Gupta et al. 2007 Haghighi et al. 2010 Hooton et al. 2012 Lumbiganon et al. 2009 Usta et al. 2011

Appendix F: Included studies

Bleidorn Jutta, Gágyor Ildiko, Kochen Michael M, Wegscheider Karl, and Hummers-Pradier Eva (2010) Symptomatic treatment (ibuprofen) or antibiotics (ciprofloxacin) for uncomplicated urinary tract infection?--results of a randomized controlled pilot trial. BMC medicine 8, 30

Falagas ME, Kotsantis IK, Vouloumanou EK, and Rafailidis PI (2009) Antibiotics versus placebo in the treatment of women with uncomplicated cystitis: a meta-analysis of randomized controlled trials.. The Journal of infection 58(2), 91-102

Falagas Matthew E, Vouloumanou Evridiki K, Togias Antonios G, Karadima Maria, Kapaskelis Anastasios M, Rafailidis Petros I, and Athanasiou Stavros (2010) Fosfomycin versus other antibiotics for the treatment of cystitis: a meta-analysis of randomized controlled trials. The Journal of antimicrobial chemotherapy 65(9), 1862-77

Ferry SA, Holm SE, Stenlund H, Lundholm R, and Monsen TJ (2004) The natural course of uncomplicated lower urinary tract infection in women illustrated by a randomized placebo controlled study.. Scandinavian journal of infectious diseases 36(4), 296-301

Fitzgerald Anita, Mori Rintaro, Lakhanpaul Monica, and Tullus Kjell (2012) Antibiotics for treating lower urinary tract infection in children. The Cochrane database of systematic reviews (8), CD006857

Gágyor Ildiko, Bleidorn Jutta, Kochen Michael M, Schmiemann Guido, Wegscheider Karl, and Hummers-Pradier Eva (2015) Ibuprofen versus fosfomycin for uncomplicated urinary tract infection in women: randomised controlled trial. BMJ (Clinical research ed.) 351, h6544

Guinto Valerie T, De Guia , Blanca , Festin Mario R, and Dowswell Therese (2010) Different antibiotic regimens for treating asymptomatic bacteriuria in pregnancy. The Cochrane database of systematic reviews (9), CD007855

Kazemier Brenda M, Koningstein Fiona N, Schneeberger Caroline, Ott Alewijn, Bossuyt Patrick M, de Miranda , Esteriek , Vogelvang Tatjana E, Verhoeven Corine J. M, Langenveld Josje, Woiski Mallory, Oudijk Martijn A, van der Ven , Jeanine E M, Vlegels Manita T. W, Kuiper Petra N, Feiertag Nicolette, Pajkrt Eva, de Groot , Christianne J M, Mol Ben W. J, and Geerlings Suzanne E (2015) Maternal and neonatal consequences of treated and untreated asymptomatic bacteriuria in pregnancy: a prospective cohort study with an embedded randomised controlled trial. The Lancet. Infectious diseases 15(11), 1324-33

Little P, Moore M V, Turner S, Rumsby K, Warner G, Lowes J A, Smith H, Hawke C, Leydon G, Arscott A, Turner D, and Mullee M (2010) Effectiveness of five different approaches in management of urinary tract infection: randomised controlled trial. BMJ (Clinical research ed.) 340, c199

Lutters Monika, and Vogt-Ferrier Nicole B (2008) Antibiotic duration for treating uncomplicated, symptomatic lower urinary tract infections in elderly women. The Cochrane database of systematic reviews (3), CD001535

Michael M, Hodson EM, Craig JC, Martin S, and Moyer VA (2003) Short versus standard duration oral antibiotic therapy for acute urinary tract infection in children. The Cochrane database of systematic reviews (1), CD003966

Milo G1, Katchman EA, Paul M, Christiaens T, Baerheim A, and Leibovici L (2005) Duration of antibacterial treatment for uncomplicated urinary tract infection in women. The Cochrane database of systematic reviews(2), CD004682

Rafalsky V, Andreeva I, and Rjabkova E (2006) Quinolones for uncomplicated acute cystitis in women. The Cochrane database of systematic reviews (3), CD003597

Smaill Fiona M, and Vazquez Juan C (2015) Antibiotics for asymptomatic bacteriuria in pregnancy. Cochrane Database of Systematic Reviews (8),

Widmer M, Lopez I, Gülmezoglu AM, Mignini L, Roganti A. Duration of treatment for asymptomatic bacteriuria during pregnancy. The Cochrane Library. 2015 Jan 1.

Wing Deborah A, Rumney Pamela J, Preslicka Christine W, and Chung Judith H (2008) Daily cranberry juice for the prevention of asymptomatic bacteriuria in pregnancy: a randomized, controlled pilot study. The Journal of urology 180(4), 1367-72

Wing Deborah A, Rumney Pamela J, Hindra Sasha, Guzman Lizette, Le Jennifer, and Nageotte Michael (2015) Pilot Study to Evaluate Compliance and Tolerability of Cranberry Capsules in Pregnancy for the Prevention of Asymptomatic Bacteriuria. Journal of alternative and complementary medicine (New York, and N.Y.) 21(11), 700-6

Zalmanovici Trestioreanu, Anca , Green Hefziba, Paul Mical, Yaphe John, and Leibovici Leonard (2010) Antimicrobial agents for treating uncomplicated urinary tract infection in women. The Cochrane database of systematic reviews (10), CD007182

Zalmanovici Trestioreanu, Anca , Lador Adi, Sauerbrun-Cutler May-Tal, and Leibovici Leonard (2015) Antibiotics for asymptomatic bacteriuria. The Cochrane database of systematic reviews 4, CD009534

Appendix G: Quality assessment of included studies

G.1 Cranberry products

Table 4: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Wing et al. 2008	Wing et al. 2015
Did the trial address a clearly focused issue?	Yes	Yes
Was the assignment of patients to treatments randomised?	Yes	Yes
Were patients, health workers and study personnel blinded?	Yes	Yes
Were the groups similar at the start of the trial?	Unclear[a]	Unclear[a,d]
Aside from the experimental intervention, were the groups treated equally?	No[b]	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	No[c]	No[c]
How large was the treatment effect?	See GRADE profiles	
How precise was the estimate of the treatment effect?	See GRADE profiles	
Can the results be applied in your context? (or to the local population)	Unclear[c]	Yes

[a] Women in the placebo group had a greater proportion of women classified as gravida 1 or 2.
[b] Some subjects were followed up for longer due to poor tolerance, but not well reported.
[c] Significant dropout (>10%), contributing to attrition bias and unable to determine whether this has led to over/underestimation of effect; not ITT analysis.
[d] Non-significant differences in ethnicity, co-morbid conditions, smokers, alcohol use and drug use.

G.2 Oral analgesia

Table 5: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Bleidorn et al. 2010	Gágyor et al. 2015
Did the trial address a clearly focused issue?	Yes	Yes
Was the assignment of patients to treatments randomised?	Yes	Yes
Were patients, health workers and study personnel blinded?	Yes	Yes
Were the groups similar at the start of the trial?	No[a]	Yes
Aside from the experimental intervention, were the groups treated equally?	Yes	Yes

Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes	Yes
How large was the treatment effect?	See GRADE profiles	
How precise was the estimate of the treatment effect?	See GRADE profiles	
Can the results be applied in your context? (or to the local population)	Yes	Yes
[a] Significant differences in previous episodes of urinary tract infection and mean score of impairment at inclusion, between both groups		

G.3 Antibiotics in non-pregnant women

Table 6: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Milo et al. 2005	Zalmanovici-Trestioreanu et al. 2015	Zalmanovici-Trestioreanu et al. 2010	Falagas et al. 2010	Falagas et al. 2009	Rafalsky et al. 2006
Did the review address a clearly focused question?	Yes	Yes	Yes	Yes	Yes	Yes
Did the authors look for the right type of papers?	Yes	Yes	Yes	Yes	Yes	Yes
Do you think all the important, relevant studies were included?	Yes	Yes	Yes	Yes	Yes	Yes
Did the review's authors do enough to assess the quality of the included studies?	Yes	Yes	Yes	Yes	Yes	Yes
If the results of the review have been combined, was it reasonable to do so?	Yes	Yes	Yes	Yes	Yes	Yes
What are the overall results of the review?	See GRADE profiles					
How precise are the results?	See GRADE profiles					
Can the results be applied to the local population?	Yes	Yes	Yes	Unclear[a]	Yes	Yes
Were all important outcomes considered?	Yes	Yes	Yes	Yes	Yes	Yes
Are the benefits worth the harms and costs?	See GRADE profiles					
[a] Only data in non-pregnant women was represented in forest plots, therefore unable to assess other outcomes reported in different populations described in the review.						

Table 7: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Ferry et al. 2004	Falagas et al. 2009	Little et al. 2010
Did the trial address a clearly focused issue?	Yes	Yes	Yes
Was the assignment of patients to treatments randomised?	Unclear[a]	Yes	Yes
Were patients, health workers and study personnel blinded?	Unclear[a]	Yes	No
Were the groups similar at the start of the trial?	Unclear[b]	Yes	Yes
Aside from the experimental intervention, were the groups treated equally?	Yes	Yes	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	No[c]	Yes	Yes
How large was the treatment effect?	See GRADE profiles		
How precise was the estimate of the treatment effect?	See GRADE profiles		
Can the results be applied in your context? (or to the local population)	Yes	Yes	Yes
Were all clinically important outcomes considered?	Yes	Yes	Yes
Are the benefits worth the harms and costs?	See GRADE profiles		

[a] Authors report blinding however method of randomisation/allocation not reported

[b] Baseline characteristics were not reported

[c] Significant dropout (>10%), contributing to attrition bias and unable to determine whether this has led to over/underestimation of effect; not Intention to treat analysis

G.4 Antibiotics in pregnant women

Table 8: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Guinto et al. 2010	Smaill et al. 2015	Widmer et al. 2015
Did the review address a clearly focused question?	Yes	Yes	Yes
Did the authors look for the right type of papers?	Yes	Yes	Yes
Do you think all the important, relevant studies were included?	Yes	Yes	Yes
Did the review's authors do enough to assess the quality of the included studies?	Yes	Yes	Yes
If the results of the review have been combined, was it reasonable to do so?	Yes	Yes	Yes
What are the overall results of the review?	See GRADE profiles		

Study reference	Guinto et al. 2010	Smaill et al. 2015	Widmer et al. 2015
How precise are the results?	See GRADE profiles		
Can the results be applied to the local population?	Yes	Yes	Yes
Were all important outcomes considered?	Yes	Yes	Yes
Are the benefits worth the harms and costs?	See GRADE profiles		

Table 9: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Kazemier et al. 2015
Did the trial address a clearly focused issue?	Yes
Was the assignment of patients to treatments randomised?	Yes
Were patients, health workers and study personnel blinded?	Yes
Were the groups similar at the start of the trial?	No[a]
Aside from the experimental intervention, were the groups treated equally?	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes[b]
How large was the treatment effect?	See GRADE profiles
How precise was the estimate of the treatment effect?	See GRADE profiles
Can the results be applied in your context? (or to the local population)	Yes
Were all clinically important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See GRADE profiles
[a] Current smoker status was significantly different between the nitrofurantoin group (8%) and placebo group (11%), p=0.004 [b] Study reported results according to an intention to treat analysis	

G.5 Antibiotics in older people

Table 10: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Lutters et al. 2008
Did the review address a clearly focused question?	Yes
Did the authors look for the right type of papers?	Yes
Do you think all the important, relevant studies were included?	Yes
Did the review's authors do enough to assess the quality of the included studies?	Yes

Study reference	Lutters et al. 2008
If the results of the review have been combined, was it reasonable to do so?	Yes
What are the overall results of the review?	See GRADE profiles
How precise are the results?	See GRADE profiles
Can the results be applied to the local population?	Yes
Were all important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See GRADE profiles

G.6 Antibiotics in children

Table 11: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Fitzgerald et al. 2012	Michaels et al. 2003
Did the review address a clearly focused question?	Yes	Yes
Did the authors look for the right type of papers?	Yes	Yes
Do you think all the important, relevant studies were included?	Yes	Unclear[b]
Did the review's authors do enough to assess the quality of the included studies?	Yes	Yes
If the results of the review have been combined, was it reasonable to do so?	Yes	Yes
What are the overall results of the review?	See GRADE profiles	
How precise are the results?	See GRADE profiles	
Can the results be applied to the local population?	Unclear[a]	Unclear[a]
Were all important outcomes considered?	Yes	Yes
Are the benefits worth the harms and costs?	See GRADE profiles	

[a] All of the studies were rated unclear risk of bias; most of evidence was very low to low quality evidence
[b] Data limits of the search meant they did not identify studies published prior to 2006

Appendix H: GRADE profiles

H.1 Cranberry products

Table 12: GRADE profile – cranberry capsules versus placebo in pregnant women with asymptomatic bacteriuria

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cranberry capsules	Placebo	Relative (95% CI)	Absolute		
Tolerability (follow-up 7 months; assessed with: Gastrointestinal intolerance[1])												
1[2]	randomised trials	serious[3]	N/A	serious[4]	serious[5]	none	13/17 (76.5%)	12/22 (54.5%)	No summary statistic reported NICE analysis RR 1.40 (0.88 to 2.23)[6]	218 more per 1000 (from 65 fewer to 671 more)	⊕OOO VERY LOW	CRITICAL
Compliance (medicines adherence) (follow-up 7 months; assessed with: Achieved at least 75% compliance)												
1[2]	randomised trials	serious[3]	N/A	serious[4]	very serious[7]	none	11/16 (68.8%)	17/22 (77.3%)	No summary statistic reported NICE analysis RR 0.89 (0.6 to 1.33)[6]	85 fewer per 1000 (from 309 fewer to 255 more)	⊕OOO VERY LOW	CRITICAL
Preterm delivery <37 week (follow-up 7 months)												
1[2]	randomised trials	serious[3]	N/A	serious[4]	very serious[7]	none	1/14 (7.1%)	2/19 (10.5%)	No summary statistic reported NICE analysis RR 0.68 (0.07 to 6.76)[6]	34 fewer per 1000 (from 98 fewer to 606 more)	⊕OOO VERY LOW	CRITICAL
Low birth weight <2500g (follow-up 7 months)												
1[2]	randomised trials	serious[3]	N/A	serious[4]	very serious[7]	none	1/14 (7.1%)	1/19 (5.3%)	No summary statistic reported NICE analysis RR 1.36 (0.09 to 19.88)[6]	19 more per 1000 (from 48 fewer to 994 more)	⊕OOO VERY LOW	CRITICAL
1 min Apgar score <7 (follow-up 7 months)												
1[2]	randomised trials	serious[3]	N/A	serious[4]	very serious[7]	none	3/14 (21.4%)	0/19 (0%)	No summary statistic reported NICE analysis RR 9.33 (0.52 to 167.36)[6]	-	⊕OOO VERY LOW	CRITICAL
5 min Apgar score <9 (follow-up 7 months)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cranberry capsules	Placebo	Relative (95% CI)	Absolute		
1[2]	randomised trials	serious[3]	N/A	serious[4]	very serious[7]	none	2/14 (14.3%)	0/19 (0%)	No summary statistic reported NICE analysis RR 6.67 (0.34 to 128.86)[6]	-	⊕OOO VERY LOW	CRITICAL
Admission to neonatal intensive care unit (follow-up 7 months)												
1[2]	randomised trials	serious[3]	N/A	serious[4]	very serious[7]	none	2/14 (14.3%)	1/19 (5.3%)	No summary statistic reported NICE analysis RR 2.71 (0.27 to 27.05)[6]	90 more per 1000 (from 38 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI, Confidence interval; N/A, Not applicable; RR, Risk ratio

[1] Gastrointestinal intolerance included: nausea, constipation, vomiting, heartburn, loss of appetite, diarrhoea and, stomach ache
[2] Wing et al. 2015
[3] Downgraded 1 level - high dropout rate may influence the outcome
[4] Downgraded 1 level - 25% of the study population had a history of urinary tract infection
[5] Downgraded 1 level - at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with cranberry capsules
[6] Calculated by NICE
[7] Downgraded 2 levels - at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 13: GRADE profile – cranberry juice drink versus placebo juice drink in pregnant women with asymptomatic bacteriuria

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cranberry juice	Placebo	Relative (95% CI)	Absolute		
Incidence of urinary tract infection (follow-up 6 weeks)												
1[1]	randomised trials	very serious[2]	N/A	serious[3]	very serious[4]	none	4/58 (6.9%)	7/63 (11.1%)	p=0.71 Incidence ratio in cranberry juice group 0.59 (0.22 to1.60), placebo group - 1.0. NICE analysis RR 0.62 (0.19 to 2.01)[5]	42 fewer per 1000 (from 90 fewer to 112 more)	⊕OOO VERY LOW	CRITICAL
Incidence of asymptomatic bacteriuria (follow-up 6 weeks)												
1[1]	randomised trials	very serious[2]	N/A	serious[3]	very serious[4]	none	-	-	Incidence ratio in cranberry juice group 0.43 (0.14 to1.39), placebo group - 1.0. NICE analysis couldn't be performed as absolute figures were not reported		⊕OOO VERY LOW	CRITICAL
Incidence of Pyelonephritis (follow-up 6 weeks; assessed with: add incidence ratio)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cranberry juice	Placebo	Relative (95% CI)	Absolute		
1[1]	randomised trials	very serious[2]	N/A	serious[3]	very serious[4]	none	2/58 (3.4%)	1/63 (1.6%)	No summary statistic reported NICE analysis RR 2.17 (0.2 to 23.33)[5]	19 more per 1000 (from 13 fewer to 354 more)	⊕OOO VERY LOW	CRITICAL
Preterm delivery <37 week (follow-up 6 weeks)												
1[1]	randomised trials	very serious[2]	N/A	serious[3]	very serious[4]	none	6/55 (10.9%)	4/57 (7%)	No summary statistic reported NICE analysis RR 1.55 (0.46 to 5.21)[5]	39 more per 1000 (from 38 fewer to 295 more)	⊕OOO VERY LOW	CRITICAL
Preterm delivery <34 week (follow-up 6 weeks)												
1[1]	randomised trials	very serious[2]	N/A	serious[3]	very serious[4]	none	2/58 (3.4%)	2/67 (3%)	Only p-value reported p=0.73 NICE analysis RR 1.16 (0.17 to 7.94)[5]	5 more per 1000 (from 25 fewer to 207 more)	⊕OOO VERY LOW	CRITICAL
Low birth weight (follow-up 6 weeks)												
1[1]	randomised trials	very serious[2]	N/A	serious[3]	very serious[4]	none	4/58 (6.9%)	2/63 (3.2%)	Only p-value reported p=0.72 NICE analysis RR 2.17 (0.41 to 11.42)[5]	37 more per 1000 (from 19 fewer to 331 more)	⊕OOO VERY LOW	CRITICAL[8]
1 min Apgar score <7 (follow-up 6 weeks)												
1[1]	randomised trials	very serious[2]	N/A	serious[3]	very serious[4]	none	3/53 (5.7%)	2/57 (3.5%)	Only p-value reported p=0.52 NICE analysis RR 1.61 (0.28 to 9.28)[5]	21 more per 1000 (from 25 fewer to 291 more)	⊕OOO VERY LOW	CRITICAL
5 min Apgar score <9 (follow-up 6 weeks)												
1[1]	randomised trials	very serious[2]	N/A	serious[3]	very serious[4]	none	4/58 (6.9%)	5/63 (7.9%)	Only p-value reported p=1.0 NICE analysis RR 0.79 (0.22 to 2.78)[5]	17 fewer per 1000 (from 62 fewer to 141 more)	⊕OOO VERY LOW	CRITICAL
Admission to neonatal intensive care unit (follow-up 6 weeks)												
1[1]	randomised trials	very serious[2]	N/A	serious[3]	very serious[4]	none	3/53 (5.7%)	6/57 (10.5%)	Only p-value reported p=0.51 NICE analysis RR 0.54 (0.14 to 2.04)[5]	48 fewer per 1000 (from 91 fewer to 109 more)	⊕OOO VERY LOW	CRITICAL
Compliance rates (follow-up 6 weeks)												
1[1]	randomised trials	very serious[2]	N/A	serious[3]	very serious[4]	none	3/58 (5.2%)	6/63 (9.5%)	Only p-value reported p=0.45 NICE analysis RR 0.54 (0.14 to 2.07)[5]	44 fewer per 1000 (from 82 fewer to 102 more)	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cranberry juice	Placebo	Relative (95% CI)	Absolute		
Abbreviations: CI, Confidence interval; N/A, Not applicable; RR, Risk ratio												

[1] Wing et al. 2008
[2] Downgraded 2 levels - very serious methodological flaws, including high attrition and different baseline characteristics of intervention and comparator group
[3] Downgraded by 1 level - PICO did not fully reflect that stated in the review protocol
[4] Downgraded 2 levels - at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[5] Calculated by NICE
[6] Downgraded 1 level - at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with cranberry

H.2 Oral analgesia

Table 14: GRADE profile – ibuprofen versus fosfomycin in non-pregnant women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ibuprofen	Fosfomycin	Relative (95% CI)	Absolute		
Women on antibiotics for urinary tract infection during follow-up (follow-up 12 months)												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	75/241 (31.1%)	30/243 (12.3%)	MD 18.8 higher (11.6 to 25.9 higher) p<0.001 NICE analysis RR 2.52 (1.72 to 3.7)[2]	188 more per 1000 (from 89 more to 333 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Mean symptom burden day 0-4 (follow-up 12 months; Better indicated by lower values)												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[3]	none	241	243	MD 3.0 higher (1.9 to 4.2 higher) Ibuprofen: mean (SD) 13.1 (7.1), fosfomycin: mean (SD) 10.1 (5.9); p<0.001.		⊕⊕⊕O MODERATE	CRITICAL
Mean symptom burden day 0-7 (follow-up 12 months; Better indicated by lower values)												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[3]	none	241	243	MD 5.3 higher (3.5 to 7 higher) Ibuprofen, mean (SD) 17.3 (11.0); fosfomycin, mean (SD) 12.1 (8.2); p<0.001.		⊕⊕⊕O MODERATE	CRITICAL
Serious adverse effects, probably drug related (follow-up 12 months)												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	very serious[4]	none	1/241 (0.41%)	0/243 (0%)	MD 0.4 higher (0.4 lower to 1.2 higher) p=0.32 NICE analysis RR 3.02 (0.12 to 73.88)[2]		⊕⊕OO LOW	CRITICAL
Patients reporting serious adverse events (follow-up 12 months)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ibuprofen	Fosfomycin	Relative (95% CI)	Absolute		
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	very serious[4]	none	4/241 (1.7%)	0/243 (0%)	MD 0.4 higher (0.4 lower to 1.2 higher) p=0.6 NICE analysis RR 9.07 (0.49 to 167.63)[2]		⊕⊕OO LOW	CRITICAL
Patients reporting adverse events (follow-up 12 months)												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[3]	none	42/241 (17.4%)	57/243 (23.5%)	MD 6.0 lower (13.2 lower to 1.1 higher) p=0.12 NICE analysis RR 0.74 (0.52 to 1.06)[2]	61 fewer per 1000 (from 113 fewer to 14 more)	⊕⊕⊕O MODERATE	CRITICAL
All recurrent urinary tract infection until day 28 (follow-up 12 months)												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	very serious[4]	none	27/241 (11.2%)	34/243 (14%)	MD 2.8 lower (8.7 lower to 3.1 higher) p=0.41 NICE analysis RR 0.80 (0.5 to 1.28)[2]	28 fewer per 1000 (from 70 fewer to 39 more)	⊕⊕OO LOW	CRITICAL
Recurrence of urinary tract infection (day 15 - 28) (follow-up 12 months)												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[5]	none	14/241 (5.8%)	27/243 (11.1%)	MD 5.3 lower (10.2 to 0.4 lower) p=0.049 NICE analysis RR 0.52 (0.28 to 0.97)[2]	53 fewer per 1000 (from 3 fewer to 80 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Pyelonephritis (follow-up 12 months)												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	very serious[4]	none	5/241 (2.1%)	1/243 (0.41%)	MD 1.7 higher (0.3 lower to 3.6 higher) p=0.12 NICE analysis RR 5.04 (0.59 to 42.83)[2]	17 more per 1000 (from 2 fewer to 172 more)	⊕⊕OO LOW	CRITICAL
Febrile urinary tract infection (day 0 to 7) (follow-up 12 months)												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	very serious[4]	none	3/241 (1.2%)	0/243 (0%)	MD 1.2 higher (0.2 lower to 2.6 higher)p=0.12 NICE analysis RR 7.06 (0.37 to 135.91)[2]	-	⊕⊕OO LOW	CRITICAL
Patients without worsening symptoms at day 4 (follow-up 12 months)												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[6]	none	91/234 (38.9%)	129/229 (56.3%)	Only p value reported p<0.001 NICE analysis RR 0.69 (0.57 to 0.84)[2]	175 fewer per 1000 (from 242 fewer to 99 fewer)	⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ibuprofen	Fosfomycin	Relative (95% CI)	Absolute		
Patients without worsening symptoms at day 7 (follow-up 12 months)												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[7]	none	163/232 (70.3%)	129/229 (56.3%)	Only p value reported p=0.004 NICE analysis RR 1.25 (1.08 to 1.44)[2]	141 more per 1000 (from 45 more to 248 more)	⊕⊕⊕O MODERATE	CRITICAL
Mean activity impairment assessment day 0 to 7 (follow-up 12 months; Better indicated by lower values)												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[3]	none	241	243	MD 10.8 higher (7.1 to 14.6 higher) Ibuprofen: mean (SD) 30.3 (24.5), fosfomycin: mean (SD) 19.5 (16.7); p<0.001.		⊕⊕⊕O MODERATE	CRITICAL
Antibiotic treatment course per patient (women with positive urine culture) (follow-up 12 months; Better indicated by lower values)												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[8]	none	360		MD 58.5 lower (49.8 to 67 lower) Ibuprofen: 0.49 antibiotic treatment courses per patient, fosfomycin: 1.18 antibiotic treatment courses per patient; p<0.001.		⊕⊕⊕O MODERATE	CRITICAL
Antibiotic treatment course per patient (women with negative urine culture) (follow-up 12 months; Better indicated by lower values)												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[8]	none	111		MD 90.7 lower (74.3 to 99.9 lower) Ibuprofen: 0.10 antibiotic treatment courses per patient, fosfomycin: 1.11 antibiotic treatment courses per patient; p<0.001.		⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI, confidence interval; MD, mean difference; RR, risk ratio; N/A, Not applicable

[1] Gágyor et al. 2015
[2] Calculated by NICE
[3] Downgraded 1 level - at a default minimal important difference (MID) of 0.5 SD of comparator (fosfomycin), data are consistent with no meaningful difference or appreciable harm with fosfomycin
[4] Downgraded 2 levels - at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[5] Downgraded 1 level – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with fosfomycin
[6] Downgraded 1 level – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with fosfomycin
[7] Downgraded 1 level – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with ibuprofen
[8] Downgraded 1 level – not assessable

Table 15: GRADE profile – ibuprofen versus ciprofloxacin in non-pregnant women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ibuprofen	Ciprofloxacin	Relative (95% CI)	Absolute		
Symptom resolution at day 4 (follow-up mean 28 days)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ibuprofen	Ciprofloxacin	Relative (95% CI)	Absolute		
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	very serious[3]	none	21/36 (58.3%)	17/33 (51.5%)	Only p value reported p =0.744 NICE analysis RR 1.13 (0.74 to 1.74)[4]	67 more per 1000 (from 134 fewer to 381 more)	⊕OOO VERY LOW	CRITICAL
Symptom resolution at day 7 (follow-up 28 days)												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	serious[5]	none	27/36 (75%)	20/33 (60.6%)	Only p value reported p=0.306 NICE analysis RR 1.24 (0.89 to 1.73)[4]	145 more per 1000 (from 67 fewer to 442 more)	⊕⊕OO LOW	CRITICAL
Total symptom course at day 4 (follow-up 28 days; Better indicated by lower values)												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	serious[5]	none	39	38	MD 0.3 lower (1.1 lower to 0.5 higher)[4] Ibuprofen, mean (SD) – 1 (1.42); ciprofloxacin, mean (SD) – 1.3 (1.9); p = 0.406		⊕⊕OO LOW	CRITICAL
Total symptom course at day 7 (follow-up 28 days; Better indicated by lower values)												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	serious[6]	none	36	33	MD 0.1 higher (0.41 lower to 0.61 higher)[4] Ibuprofen, mean (SD) – 0.7 (1.26), ciprofloxacin, mean (SD) – 0.6 (0.86); p = 0.816		⊕⊕OO LOW	CRITICAL
Second prescription day 0 to 9 (follow-up 28 days)												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	serious[7]	none	12/36 (33.3%)	6/33 (18.2%)	Only p value reported p=0.247 NICE analysis RR 1.83 (0.78 to 4.33)[4]	151 more per 1000 (from 40 fewer to 605 more)	⊕⊕OO LOW	CRITICAL
Severity of dysuria at day 4 (follow-up 28 days; Better indicated by lower values)												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	serious[5]	none	36	33	MD 0.10 lower (0.48 lower to 0.28 higher)[4] Ibuprofen, mean (SD) – 0.4 (0.69), ciprofloxacin, mean (SD) – 0.5 (0.91); p-value 0.508		⊕⊕OO LOW	CRITICAL
Severity of dysuria at day 7 (follow-up 28 days; Better indicated by lower values)												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	serious[6]	none	36	33	MD 0.10 higher (0.17 lower to 0.37 higher)[4] Ibuprofen, mean (SD) – 0.3 (0.72), ciprofloxacin, mean (SD) – 0.2 (0.39); p-value 0.279		⊕⊕OO LOW	CRITICAL

Abbreviations: CI, confidence interval; MD, mean difference; RR, risk ratio; N/A, not applicable

[1] Bleidorn et al. 2010
[2] Downgraded 1 level - differences between groups at baseline despite randomisation.
[3] Downgraded 2 levels - at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[4] Calculated by NICE
[5] Downgraded 1 level - at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with ibuprofen
[6] Downgraded 1 level – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with ciprofloxacin
[7] Downgraded 1 level – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with ibuprofen

H.3 Antibiotic prescribing strategies in non-pregnant women

Table 16: GRADE profile – Immediate antibiotic prescribing versus other prescribing strategies for urinary tract infection in non-pregnant women (clinical outcomes)

Quality assessment							Effect					Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate antibiotic prescription[1]	Back-up antibiotic prescription	Midstream urine analysis[2]	Dipstick[3]	Symptom severity score[4]		
Mean frequency symptom severity (2 to 4 days after seeing the health professional) (mean difference; 95% CI)													
1[5]	randomised trials	serious risk of bias[6]	N/A	serious[7]	no serious imprecision	none	2.15 (SD 1.18) N=66	2.11 (−0.04; −0.47 to 0.40) N=62	-	-	-	⊕⊕OO LOW	CRITICAL
1[5]	randomised trials	serious risk of bias[6]	N/A	serious[7]	no serious imprecision	none	2.15 (SD 1.18) N=66	-	2.08 (−0.07; −0.51 to 0.37) N=54	-	-	⊕⊕OO LOW	CRITICAL
1[5]	randomised trials	serious risk of bias[6]	N/A	serious[7]	serious[8]	none	2.15 (SD 1.18) N=66	-	-	1.74 (−0.40; −0.85 to 0.04) N=58	-	⊕OOO VERY LOW	CRITICAL
1[5]	randomised trials	serious risk of bias[6]	N/A	serious[7]	serious[8]	none	2.15 (SD 1.18) N=66	-	-	-	1.77 (−0.38; −0.79 to 0.04) N=69	⊕OOO VERY LOW	CRITICAL
Duration of moderately bad symptoms in days (incidence ratio ;95% CI													
1[5]	randomised trials	serious risk of bias[6]	N/A	serious[7]	serious[9]	none	1[10] N=66	1.12 (0.85 to 1.47) N=62	-	-	-	⊕OOO VERY LOW	CRITICAL
1[5]	randomised trials	serious risk of bias[6]	N/A	serious[7]	serious[11]	none	1[10] N=66	-	1.21 (0.92 to 1.61) N=54	-	-	⊕OOO VERY LOW	CRITICAL
1[5]	randomised trials	no serious risk of bias[6]	N/A	serious[7]	serious[12]	none	1[10] N=66	-	-	0.91 (0.68 to 1.22) N=58	-	⊕OOO VERY LOW	CRITICAL

Quality assessment							Effect					Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate antibiotic prescription[1]	Back-up antibiotic prescription	Midstream urine analysis[2]	Dipstick[3]	Symptom severity score[4]		
1[5]	randomised trials	no serious risk of bias[6]	N/A	serious[7]	serious[13]	none	1[10] N=66	-	-	-	1.11 (0.85 to 1.44) N=69	⊕OOO VERY LOW	CRITICAL
Mean unwell symptom severity (mean difference; 95% CI)													
1[5]	randomised trials	serious risk of bias[6]	N/A	serious[7]	serious[8]	none	1.60 (SD 1.30) N=66	1.43 (−0.18; −0.65 to 0.30) N=62	-	-	-	⊕OOO VERY LOW	CRITICAL
1[5]	randomised trials	serious risk of bias[6]	N/A	serious[7]	no serious imprecision	none	1.60 (SD 1.30) N=66	-	1.66 (0.05; −0.44 to 0.55) N=54	-	-	⊕⊕OO LOW	CRITICAL
1[5]	randomised trials	serious risk of bias[6]	N/A	serious[7]	serious[8]	none	1.60 (SD 1.30) N=66	-	-	1.32 (−0.28; −0.77 to 0.20) N=58	-	⊕OOO VERY LOW	CRITICAL
1[5]	randomised trials	serious risk of bias[6]	N/A	serious[7]	serious[8]	none	1.60 (SD 1.30) N=66	-	-	-	1.26 (−0.35; −0.80 to 0.11) N=69	⊕OOO VERY LOW	CRITICAL
Time to re-consultation (hazard ratio; 95% CI)													
1[5]	randomised trials	serious risk of bias[6]	N/A	serious[7]	serious[9]	none	1 N=66	0.60 (0.35 to 1.05) N=62	-	-	-	⊕OOO VERY LOW	CRITICAL
1[5]	randomised trials	serious risk of bias[6]	N/A	serious[7]	very serious[14]	none	1 N=66	-	0.81 (0.47 to 1.39) N=54	-	-	⊕OOO VERY LOW	CRITICAL
1[5]	randomised trials	serious risk of bias[6]	N/A	serious[7]	very serious[14]	none	1 N=66	-	-	0.98 (0.58 to 1.65) N=58	-	⊕OOO VERY LOW	CRITICAL
1[5]	randomised trials	serious risk of bias[6]	N/A	serious[7]	serious[15]	none	1 N=66	-	-	-	0.73 (0.43 to 1.22) N=69	⊕OOO VERY LOW	CRITICAL
Net effect on symptom duration of delaying antibiotic use by >48 hours (incidence ratio; 95% CI)[16]													
1[5]	randomised trials	serious risk of bias[6]	N/A	serious[7]	serious[17]	none	1 N=66	1.22 (0.88 to 1.68) N=62	-	-	-	⊕OOO VERY LOW	CRITICAL

Quality assessment							Effect					Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate antibiotic prescription[1]	Back-up antibiotic prescription	Midstream urine analysis[2]	Dipstick[3]	Symptom severity score[4]		
1[5]	randomised trials	serious risk of bias[6]	N/A	serious[7]	serious[18]	none	1 N=66	-	1.73 (1.22 to 2.44) N=54	-	-	⊕OOO VERY LOW	CRITICAL
1[5]	randomised trials	serious risk of bias[6]	N/A	serious[7]	serious[19]	none	1 N=66	-	-	1.20 (0.78 to 1.85) N=58	-	⊕OOO VERY LOW	CRITICAL
1[5]	randomised trials	serious risk of bias[6]	N/A	serious[7]	very serious[14]	none	1 N=66	-	-	-	0.96 (0.59 to 1.57) N=69	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval; N/A – not applicable; SD – standard deviation													

[1] Immediate antibiotic group was used as the reference control group
[2] Symptomatic treatment until microbiology results available from midstream urinary analysis and then antibiotics targeted according to results
[3] Antibiotics offered if nitrites or leucocytes and a trace of blood were detected in dipstick test
[4] Antibiotics offered if two or more of urine cloudy on examination, urine offensive smell on examination, patient's report of moderately severe dysuria, or patient's report of nocturia
[5] Little et al. 2010
[6] Downgraded 1 level – immediate antibiotics were given to people in any treatment group when there was strong patient expectations and discretion was given to healthcare professionals to provide a dipstick test or midstream urine test in any group; study was open label but could not be blinded due to the nature of the interventions
[7] Downgraded 1 level - the majority of the women included in the study had a history of previous episodes of lower urinary tract infection
[8] Downgraded 1 level - at a default minimal important difference (MID) of 0.5 of SD of immediate antibiotic prescription arm, data are consistent with no meaningful difference or appreciable harm with immediate antibiotics
[9] Downgraded 1 level – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with back-up antibiotic prescription
[10] The average duration of symptoms rated as moderately bad or worse with immediate antibiotics was 3.5 days.
[11] Downgraded 1 level – at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with midstream urine analysis
[12] Downgraded 1 level – at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with immediate antibiotic prescription
[13] Downgraded 1 level – at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with symptom severity score
[14] Downgraded 2 levels – at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable harm or appreciable benefit[14]
[15] Downgraded 1 level –at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with symptom severity score
[16] Measured by comparison of each treatment group to immediate antibiotics
[17] Downgraded 1 level – at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with delaying antibiotics by 48 hours in the back-up prescription group
[18] Downgraded 1 level – at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with delaying antibiotics by 48 hours in the midstream urine analysis group
[19] Downgraded 1 level - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with delaying antibiotics by 48 hours in the dipstick group

Table 17: Grade profile - Immediate antibiotic prescribing versus other prescribing strategies for urinary tract infection in non-pregnant women (antibiotic use outcomes)

Quality assessment							No of patients					Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate antibiotics	Back-up antibiotics	Midstream urine analysis[1]	Dipstick[2]	Symptom severity score[3]	Relative (95% CI) Absolute		
No of people who used antibiotics														
1[4]	randomised trials	serious risk of bias[5]	N/A	serious[6]	seirous[7]	none	58/60 (97%)	41/53 (77%)	-	-	-	NICE analysis RR 1.25 (1.07 to 1.46)	VERY LOW ⊕OOO	CRITICAL
1[4]	randomised trials	serious risk of bias[5]	N/A	serious[6]	serious[7]	none	58/60 (97%)	-	38/47 (81%)	-	-	NICE analysis RR 1.20 (1.03 to 1.38)	VERY LOW ⊕OOO	CRITICAL
1[4]	randomised trials	serious risk of bias[5]	N/A	serious[6]	serious[8]	none	58/60 (97%)	-	-	40/50 (80%)	-	NICE analysis RR 7.25 (1.51 to 34.87)	VERY LOW ⊕OOO	CRITICAL
1[4]	randomised trials	serious risk of bias[5]	N/A	serious[6]	very serious[9]	none	58/60 (97%)	-	-	-	52/58 (90%)	NICE analysis RR 3.35 (0.65 to 17.31)	VERY LOW ⊕OOO	CRITICAL
Number of people that waited at least 48 hours before taking antibiotics														
1[4]	randomised trials	serious risk of bias[5]	N/A	serious[6]	no serious imprecision	none	5/60 (8%)	28/53 (53%)	-	-	-	NICE analysis RR 0.16 (0.07 to 0.38)	LOW ⊕⊕OO	CRITICAL
1[4]	randomised trials	serious risk of bias[5]	N/A	serious[6]	no serious imprecision	none	5/60 (8%)	-	20/47 (43%)	-	-	NICE analysis RR 0.20 (0.08 to 0.48)	LOW ⊕⊕OO	CRITICAL
1[4]	randomised trials	serious risk of bias[5]	N/A	serious[6]	no serious imprecision	none	5/60 (8%)	-	-	15/50 (30%)	-	NICE analysis RR 0.21 (0.07 to 0.64)	LOW ⊕⊕OO	CRITICAL
1[4]	randomised trials	serious risk of bias[5]	N/A	serious[6]	serious[10]	none	5/60 (8%)	-	-	-	11/58 (19%)	NICE analysis RR 0.39 (0.13 to 1.20)	VERY LOW ⊕OOO	CRITICAL
Time to antibiotic use (length of delay)														
1[5]	randomised trials	serious risk of bias[5]	N/A	serious[6]	serious[11]	none	1.19 days	2.21 days	2.18 days	1.43 days	1.40 days	-	VERY LOW ⊕OOO	CRITICAL

Abbreviations: CI, Confidence interval; N/A, not applicable; RR, risk ratio

[1] Symptomatic treatment until microbiology results available from midstream urinary analysis and then antibiotics targeted according to results
[2] Antibiotics offered if nitrites or leucocytes and a trace of blood were detected in dipstick test
[3] Antibiotics offered if two or more of urine cloudy on examination, urine offensive smell on examination, patient's report of moderately severe dysuria, or patient's report of nocturia
[4] Little et al. 2010
[5] Downgraded 1 level – immediate antibiotics were given to people in any treatment group when there was strong patient expectations and discretion was given to healthcare professionals to provide a dipstick test or midstream urine test in any group; study was open label but could not be blinded due to the nature of the interventions
[6] Downgraded 1 level - the majority of the women included in the study had a history of previous episodes of lower urinary tract infection
[7] Downgraded 1 level – at a minimal important difference (MID) of 25%, data is consistent with no meaningful difference or appreciable harm with immediate antibiotics

[8] Downgraded 1 level – confidence intervals are very wide
[9] Downgraded 2 levels – at a minimal important difference (MID) of 25%, data is consistent with no meaningful difference, appreciable benefit or appreciable harm
[10] Downgraded 1 level – at a minimal important difference (MID) of 25%, data is consistent with no meaningful difference or appreciable benefit with symptom severity based prescribing
[11] Downgraded 1 level – not assessable

H.4 Antibiotics in non-pregnant women

Table 18: GRADE profile – antibiotics versus placebo in non-pregnant women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics	Placebo	Relative (95% CI)	Absolute		
Clinical cure (complete symptom resolution)												
4[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	481/778 (61.8%)	73/284 (25.7%)	OR 4.67 (2.34 to 9.35) NICE analysis RR 2.26 (1.79 to 2.86)	324 more per 1000 (from 203 more to 478 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Clinical success (improvement of symptoms)												
4[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	none	495/778 (63.6%)	85/284 (29.9%)	OR 4.81 (2.51 to 9.35) NICE analysis RR 1.98 (1.36 to 2.88)	293 more per 1000 (from 108 more to 563 more)	⊕⊕⊕O MODERATE	CRITICAL
Microbiological success (negative urine culture) at the end of treatment												
3[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	none	641/712 (90%)	85/255 (33.3%)	OR 10.67 (2.96 to 38.43) NICE analysis RR 2.49 (1.64 to 3.78)	497 more per 1000 (from 213 more to 927 more)	⊕⊕⊕O MODERATE	CRITICAL
Microbiological success (negative urine culture) after the end of treatment												
3[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	516/603 (85.6%)	80/135 (59.3%)	OR 5.38 (1.63 to 17.77) NICE analysis RR 1.79 (0.99 to 3.22)	468 more per 1000 (from 6 fewer to 1000 more)	⊕⊕OO LOW	CRITICAL
Microbiological reinfection or relapse after the end of treatment												
5[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	none	106/670 (15.8%)	72/173 (41.6%)	OR 0.27 (0.13 to 0.55) NICE analysis RR 0.42 (0.28 to 0.64)	241 fewer per 1000 (from 300 fewer to 150 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Total adverse events												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics	Placebo	Relative (95% CI)	Absolute		
4[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	147/765 (19.2%)	39/303 (12.9%)	RR 1.64 (1.1 to 2.44) NICE analysis RR 1.49 (1.06 to 2.08)	63 more per 1000 (from 8 more to 139 more)	⊕⊕⊕O MODERATE	CRITICAL
Withdrawals due to adverse events												
3[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	9/722 (1.2%)	2/285 (0.7%)	OR 1.57 (0.31 to 7.93) NICE analysis RR 1.53 (0.32 to 7.37)	4 more per 1000 (from 5 fewer to 45 more)	⊕⊕OO LOW	CRITICAL
Incidence of pyelonephritis												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	1/477 (0.21%)	2/265 (0.75%)	OR 0.33 (0.04 to 2.70) NICE analysis RR 0.42 (0.05 to 3.37)	4 fewer per 1000 (from 7 fewer to 18 more)	⊕⊕OO LOW	CRITICAL
Emergence of resistance (follow-up 3-90 days)												
5[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[6]	none	n=173		OR 1.32 (0.50 to 3.48)[7]		⊕⊕OO LOW	CRITICAL

Abbreviations: CI – confidence interval; OR – odds ratio; RR – risk ratio

[1] Falagas et al. 2009
[2] Downgraded 1 level – heterogeneity > 50%
[3] Downgraded 1 level – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with antibiotics
[4] Downgraded 1 level – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with antibiotics
[5] Downgraded 2 levels – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[6] Downgraded 1 level – not assessable
[7] Relative risk could not be calculated by NICE as the original data could not be identified,

Table 19: GRADE profile – Quinolone versus co-trimoxazole in non-pregnant women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quinolone	Co-trimoxazole	Relative (95% CI)	Absolute		
Short-term symptomatic cure												
5[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	557/586 (95.1%)	320/341 (93.8%)	RR 1 (0.97 to 1.03)	0 fewer per 1000 (from 28 fewer to 28 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Long-term symptomatic cure												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quinolone	Co-trimoxazole	Relative (95% CI)	Absolute		
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	370/411 (90%)	184/203 (90.6%)	RR 0.99 (0.94 to 1.05)	9 fewer per 1000 (from 54 fewer to 45 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Short-term bacteriological cure												
7[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	725/765 (94.8%)	438/488 (89.8%)	RR 1.03 (1 to 1.07)	27 more per 1000 (from 0 more to 63 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Long-term bacteriological cure												
6[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	507/571 (88.8%)	261/313 (83.4%)	RR 1.06 (1 to 1.12)	50 more per 1000 (from 0 more to 100 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Resistance development												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/91 (2.2%)	3/69 (4.3%)	RR 0.64 (0.05 to 8.62)	16 fewer per 1000 (from 41 fewer to 331 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation due to adverse event												
3[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	9/700 (1.3%)	15/363 (4.1%)	RR 0.37 (0.12 to 1.14)	26 fewer per 1000 (from 36 fewer to 6 more)	⊕⊕OO LOW	CRITICAL
Adverse event												
7[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	280/905 (30.9%)	179/572 (31.3%)	RR 0.95 (0.71 to 1.29)	16 fewer per 1000 (from 91 fewer to 91 more)	⊕OOO VERY LOW	CRITICAL
Complications: Pyelonephritis												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	very serious[3]	none	11/20 (55%)	11/23 (47.8%)	RR 1.03 (0.06 to 16.2)	14 more per 1000 (from 450 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, confidence interval; RR, relative risk; N/A, not applicable												

[1] Zalmanovici-Trestioreanu et al. 2010
[2] Downgraded 1 level – most of the studies are low quality as reported by study authors
[3] Downgraded 2 levels – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[4] Downgraded 1 level – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with co-trimoxazole

Table 20: GRADE profile – beta-lactam versus co-trimoxazole in non-pregnant women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta-lactam	Co-trimoxazole	Relative (95% CI)	Absolute		
Short-term symptomatic cure												
2[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	80/86 (93%)	88/90 (97.8%)	RR 0.95 (0.81 to 1.12)	49 fewer per 1000 (from 186 fewer to 117 more)	⊕⊕OO LOW	CRITICAL
Long-term symptomatic cure												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta-lactam	Co-trimoxazole	Relative (95% CI)	Absolute		
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	59/66 (89.4%)	61/72 (84.7%)	RR 1.06 (0.93 to 1.21)	51 more per 1000 (from 59 fewer to 178 more)	⊕⊕⊕O MODERATE	CRITICAL
Short-term bacteriological cure												
5[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	189/212 (89.2%)	167/177 (94.4%)	RR 0.95 (0.88 to 1.04)	47 fewer per 1000 (from 113 fewer to 38 more)	⊕⊕OO LOW	CRITICAL
Long-term bacteriological cure												
5[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	147/174 (84.5%)	121/137 (88.3%)	RR 0.97 (0.87 to 1.08)	26 fewer per 1000 (from 115 fewer to 71 more)	⊕⊕⊕O MODERATE	CRITICAL
Resistance development												
3[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/150 (0.67%)	2/109 (1.8%)	RR 0.55 (0.09 to 3.42)	8 fewer per 1000 (from 17 fewer to 44 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation due to adverse event												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	5/115 (4.3%)	2/69 (2.9%)	RR 1.53 (0.28 to 8.28)	15 more per 1000 (from 21 fewer to 211 more)	⊕OOO VERY LOW	CRITICAL
Adverse events												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	26/115 (22.6%)	18/69 (26.1%)	RR 0.76 (0.46 to 1.27)	63 fewer per 1000 (from 141 fewer to 70 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval; RR – relative risk												

[1] Zalmanovici-Trestioreanu et al. 2010
[2] Downgraded 1 level - most of the studies are low quality, as reported by study authors
[3] Downgraded 1 level – heterogeneity > 50%
[4] Downgraded 2 levels – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 21: GRADE profile – nitrofurantoin versus beta-lactam in non-pregnant women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nitrofurantoin	Beta-lactam	Relative (95% CI)	Absolute		
Short-term symptomatic cure												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	serious[3]	none	26/28 (92.9%)	18/23 (78.3%)	RR 1.19 (0.93 to 1.51)	149 more per 1000 (from 55 fewer to 399 more)	⊕⊕OO LOW	CRITICAL
Short-term bacteriological cure												
2[1]	randomised trials	serious[2]	serious[4]	no serious indirectness	very serious[5]	none	60/66 (90.9%)	92/104 (88.5%)	RR 1.09 (0.75 to 1.58)	80 more per 1000 (from 221 fewer to 513 more)	⊕OOO VERY LOW	CRITICAL
Long-term bacteriological cure												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nitrofurantoin	Beta-lactam	Relative (95% CI)	Absolute		
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	51/58 (87.9%)	75/85 (88.2%)	RR 0.97 (0.86 to 1.09)	26 fewer per 1000 (from 124 fewer to 79 more)	⊕⊕⊕O MODERATE	CRITICAL
Discontinuation due to adverse event												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	very serious[5]	none	0/42 (0%)	4/92 (4.3%)	RR 0.24 (0.01 to 4.36)	33 fewer per 1000 (from 43 fewer to 146 more)	⊕OOO VERY LOW	CRITICAL
Adverse event												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	serious[6]	none	18/42 (42.9%)	25/92 (27.2%)	RR 1.58 (0.97 to 2.56)	158 more per 1000 (from 8 fewer to 424 more)	⊕⊕OO LOW	CRITICAL

Abbreviations: CI – confidence interval; N/A – not applicable; RR – relative risk

[1] Zalmanovici-Trestioreanu et al. 2010
[2] Downgraded 1 level - most of the studies are low quality, as reported by study authors
[3] Downgraded 1 level – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with nitrofurantoin
[4] Downgraded 1 level – heterogeneity > 50%
[5] Downgraded 2 levels – at minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[6] Downgraded 1 level – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with nitrofurantoin

Table 22: GRADE profile – Quinolone versus beta-lactam in non-pregnant women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quinolone	Beta-lactam	Relative (95% CI)	Absolute		
Short-term symptomatic cure												
2[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	540/595 (90.8%)	487/597 (81.6%)	RR 1.15 (0.99 to 1.32)	122 more per 1000 (from 8 fewer to 261 more)	⊕⊕OO LOW	CRITICAL
Long-term symptomatic cure												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	318/348 (91.4%)	297/327 (90.8%)	RR 1.01 (0.96 to 1.05)	9 more per 1000 (from 36 fewer to 45 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Short-term bacteriological cure												
5[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	561/636 (88.2%)	460/653 (70.4%)	RR 1.22 (1.13 to 1.31)	155 more per 1000 (from 92 more to 218 more)	⊕⊕⊕O MODERATE	CRITICAL
Long-term bacteriological cure												
2[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	very serious[4]	none	216/260 (83.1%)	196/237 (82.7%)	RR 0.9 (0.61 to 1.32)	83 fewer per 1000 (from 323 fewer to 265 more)	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quinolone	Beta-lactam	Relative (95% CI)	Absolute		
Resistance development												
1[1]	randomised trials	serious[5]	N/A	no serious indirectness	very serious[4]	none	2/155 (1.3%)	5/156 (3.2%)	RR 0.4 (0.08 to 2.04)	19 fewer per 1000 (from 29 fewer to 33 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation due to adverse event												
4[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	12/743 (1.6%)	6/758 (0.79%)	RR 1.98 (0.74 to 5.3)	8 more per 1000 (from 2 fewer to 34 more)	⊕⊕OO LOW	CRITICAL
Adverse events												
4[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	very serious[4]	none	218/743 (29.3%)	219/758 (28.9%)	RR 0.9 (0.61 to 1.33)	29 fewer per 1000 (from 113 fewer to 95 more)	⊕OOO VERY LOW	CRITICAL
Complications: Pyelonephritis												
1[1]	randomised trials	serious[5]	N/A	no serious indirectness	very serious[4]	none	0/162 (0%)	2/160 (1.3%)	RR 0.20 (0.01 to 4.08)	10 fewer per 1000 (from 12 fewer to 38 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI – confidence interval; N/A – not applicable; RR – relative risk

[1] Zalmanovici-Trestioreanu et al. 2010
[2] Downgraded 1 level – heterogeneity > 50%
[3] Downgraded 1 level – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with fluoroquinolone
[4] Downgraded 2 levels – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[5] Downgraded 1 level - most of the studies are low quality, as reported by study authors

Table 23: GRADE profile – nitrofurantoin versus co-trimoxazole in non-pregnant women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nitrofurantoin	Co-trimoxazole	Relative (95% CI)	Absolute		
Short-term symptomatic cure												
3[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	335/371 (90.3%)	325/362 (89.8%)	RR 0.99 (0.95 to 1.04)	9 fewer per 1000 (from 45 fewer to 36 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Long-term symptomatic cure												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	156/173 (90.2%)	147/165 (89.1%)	RR 1.01 (0.94 to 1.09)	9 more per 1000 (from 53 fewer to 80 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Short-term bacteriological cure												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nitrofurantoin	Co-trimoxazole	Relative (95% CI)	Absolute		
4[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	292/339 (86.1%)	295/329 (89.7%)	RR 0.97 (0.87 to 1.08)	27 fewer per 1000 (from 117 fewer to 72 more)	⊕⊕OO LOW	CRITICAL
Long-term bacteriological cure												
3[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	166/199 (83.4%)	160/196 (81.6%)	RR 1.01 (0.9 to 1.13)	8 more per 1000 (from 82 fewer to 106 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Resistance development												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	very serious[4]	none	0/38 (0%)	1/40 (2.5%)	RR 0.35 (0.01 to 8.35)	16 fewer per 1000 (from 25 fewer to 184 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation due to adverse event												
3[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	12/456 (2.6%)	18/465 (3.9%)	RR 0.69 (0.34 to 1.41)	12 fewer per 1000 (from 26 fewer to 16 more)	⊕⊕OO LOW	CRITICAL
Adverse events												
3[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	126/456 (27.6%)	134/465 (28.8%)	RR 0.96 (0.79 to 1.17)	12 fewer per 1000 (from 61 fewer to 49 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Abbreviations: CI, confidence interval; N/A, not applicable; RR, risk ratio

[1] Zalmanovici-Trestioreanu et al. 2010
[2] Downgraded 1 level - most of the studies are low quality, as reported by study authors
[3] Downgraded 1 level – heterogeneity > 50%
[4]Downgraded 2 levels – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 24: GRADE profile – ciprofloxacin versus ofloxacin in non-pregnant women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ciprofloxacin 200 mg daily	Ofloxacin 400 mg daily	Relative (95% CI)	Absolute		
Clinical efficacy - clinical success												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	no serious imprecision	none	211/226 (93.4%)	222/231 (96.1%)	RR 0.97 (0.93 to 1.01)	29 fewer per 1000 (from 67 fewer to 10 more)	⊕⊕⊕O MODERATE	CRITICAL
Microbiological efficacy – Eradication												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	no serious imprecision	none	215/228 (94.3%)	224/230 (97.4%)	RR 0.97 (0.93 to 1.01)	29 fewer per 1000 (from 68 fewer to 10 more)	⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ciprofloxacin 200 mg daily	Ofloxacin 400 mg daily	Relative (95% CI)	Absolute		
Microbiological efficacy - Patients without reinfection												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	no serious imprecision	none	215/228 (94.3%)	224/230 (97.4%)	RR 0.98 (0.96 to 1)	19 fewer per 1000 (from 39 fewer to 0 more)	⊕⊕⊕O MODERATE	CRITICAL
Microbiological efficacy - Patients without relapse												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	no serious imprecision	none	214/228 (93.9%)	210/230 (91.3%)	RR 1.03 (0.98 to 1.08)	27 more per 1000 (from 18 fewer to 73 more)	⊕⊕⊕O MODERATE	CRITICAL
Safety - discontinuation of treatment due to adverse events												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	very serious[3]	none	2/228 (0.88%)	1/230 (0.43%)	RR 2.02 (0.18 to 22.09)	4 more per 1000 (from 4 fewer to 92 more)	⊕OOO VERY LOW	CRITICAL
Safety - any adverse events												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	very serious[3]	none	90/228 (39.5%)	113/230 (49.1%)	RR 0.34 (0.01 to 8.21)	324 fewer per 1000 (from 486 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval; N/A – not applicable; RR – risk ratio												

[1] Rafalsky et al. 2006
[2] Downgraded 1 level – high dropout rate that would influence the outcome
[3] Downgraded 2 levels – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 25: GRADE profile – levofloxacin versus ofloxacin in non-pregnant women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levofloxacin 250 mg daily	Ofloxacin 400 mg daily	Relative (95% CI)	Absolute		
Clinical efficacy - cure												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	136/157 (86.6%)	146/164 (89%)	RR 0.97 (0.9 to 1.06)	27 fewer per 1000 (from 89 fewer to 53 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Microbiological efficacy – eradication												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	196/204 (96.1%)	187/200 (93.5%)	RR 1.03 (0.98 to 1.08)	28 more per 1000 (from 19 fewer to 75 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Microbiological efficacy - patients without relapse												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	193/204 (94.6%)	186/200 (93%)	RR 1.02 (0.97 to 1.07)	19 more per 1000 (from 28 fewer to 65 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levofloxacin 250 mg daily	Ofloxacin 400 mg daily	Relative (95% CI)	Absolute		
Safety - serious adverse events												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	very serious[2]	none	1/298 (0.34%)	6/293 (2%)	RR 0.16 (0.02 to 1.35)	17 fewer per 1000 (from 20 fewer to 7 more)	⊕⊕OO LOW	CRITICAL
Safety - any adverse events												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[3]	none	99/298 (33.2%)	96/293 (32.8%)	RR 1.01 (0.81 to 1.28)	3 more per 1000 (from 62 fewer to 92 more)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CI – confidence interval; N/A – not applicable; RR – risk ratio												

[1] Rafalsky et al. 2006
[2] Downgraded 2 levels – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[3] Downgraded 1 level – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with levofloxacin

Table 26: GRADE profile – standard-release ciprofloxacin versus extended-release ciprofloxacin in non-pregnant women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Standard-release ciprofloxacin 500 mg daily	Extended-release ciprofloxacin 500 mg daily	Relative (95% CI)	Absolute		
Clinical efficacy - clinical success												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	no serious imprecision	none	204/220 (92.7%)	189/198 (95.5%)	RR 0.97 (0.93 to 1.02)	29 fewer per 1000 (from 67 fewer to 19 more)	⊕⊕⊕O MODERATE	CRITICAL
Microbiological efficacy – eradication												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	no serious imprecision	none	209/223 (93.7%)	188/199 (94.5%)	RR 0.99 (0.95 to 1.04)	9 fewer per 1000 (from 47 fewer to 38 more)	⊕⊕⊕O MODERATE	CRITICAL
Microbiological efficacy - patients without reinfection												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	no serious imprecision	none	145/149 (97.3%)	139/141 (98.6%)	RR 0.99 (0.94 to 1.05)	10 fewer per 1000 (from 59 fewer to 49 more)	⊕⊕⊕O MODERATE	CRITICAL
Microbiological efficacy - patients without relapse												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	no serious imprecision	none	106/114 (93%)	104/110 (94.5%)	RR 0.98 (0.92 to 1.05)	19 fewer per 1000 (from 76 fewer to 47 more)	⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Standard-release ciprofloxacin 500 mg daily	Extended-release ciprofloxacin 500 mg daily	Relative (95% CI)	Absolute		
Safety - discontinuation of treatment												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	very serious[3]	none	2/447 (0.45%)	2/444 (0.45%)	RR 1.01 (0.14 to 7.12)	0 more per 1000 (from 4 fewer to 28 more)	⊕OOO VERY LOW	CRITICAL
Any adverse event												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	serious[4]	none	105/447 (23.5%)	121/444 (27.3%)	RR 0.86 (0.69 to 1.08)	38 fewer per 1000 (from 84 fewer to 22 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI, confidence interval; N/A, not applicable; RR, risk ratio												

[1] Rafalsky et al. 2006
[2] Downgraded 1 level – high dropout rate that would influence the outcome
[3] Downgraded 2 levels – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[4] Downgraded 1 level – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with extended-release ciprofloxacin

Table 27: GRADE profile – fosfomycin versus other antibiotics in non-pregnant women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fosfomycin	Other antibiotics	Relative (95% CI)	Absolute		
Clinical cure												
9[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	673/792 (85%)	670/773 (86.7%)	RR: 1.00 (0.96 to 1.03) NICE analysis RR 1 (0.97 to 1.03)	0 fewer per 1000 (from 26 fewer to 26 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical improvements												
4[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	54/476 (11.3%)	50/474 (10.5%)	RR: 1.00 (0.98 to1.03) NICE analysis RR 1.1 (0.77 to 1.57)	11 more per 1000 (from 24 fewer to 60 more)	⊕⊕OOO LOW	CRITICAL
Microbiological success (eradication)												
12[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	794/939 (84.6%)	687/835 (82.3%)	RR: 1.02 (0.96, 1.03) NICE analysis RR 1.03 (0.98 to 1.08)	25 more per 1000 (from 16 fewer to 66 more)	⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fosfomycin	Other antibiotics	Relative (95% CI)	Absolute		
Microbiological relapse												
8[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	32/427 (7.5%)	37/401 (9.2%)	RR: 0.84 (0.50, 1.39) NICE analysis RR 0.84 (0.5 to 1.39)	15 fewer per 1000 (from 46 fewer to 36 more)	⊕OOO VERY LOW	CRITICAL
Microbiological reinfection												
7[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	34/389 (8.7%)	23/359 (6.4%)	RR: 1.26 (0.77, 2.02) NICE analysis RR 1.26 (0.77 to 2.06)	17 more per 1000 (from 15 fewer to 68 more)	⊕⊕OO LOW	CRITICAL
No. of adverse events												
13[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	109/1168 (9.3%)	83/1130 (7.3%)	RR: 1.25 (0.83, 1.88) NICE analysis RR 1.25 (0.83 to 1.88)	18 more per 1000 (from 12 fewer to 65 more)	⊕⊕OO LOW	CRITICAL
Withdrawal due to an adverse event												
2[1]	randomised trials	no serious risk of bias	very serious[6]	no serious indirectness	very serious[4]	none	14/754 (1.9%)	16/775 (2.1%)	RR 2.01 (0.05 to 80.21) NICE analysis RR 2.01 (0.05 to 80.21)	14 more per 1000 (from 13 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval; N/A – not applicable; RR – risk ratio												

[1] Falagas et al. 2010
[2] Downgraded 1 level - most of the studies are low quality, as reported by study authors
[3] Downgraded 1 level – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with fosfomycin
[4] Downgraded 2 levels – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[5] Downgraded 1 level – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with fosfomycin
[6] Downgraded 1 level – heterogeneity > 50%

Table 28: GRADE profile – 3 day versus 5 to 10 day antibiotic courses in non-pregnant women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 day	5-10 day antibiotic course	Relative (95% CI)	Absolute		
Short term symptomatic failure (2-15 days from end of treatment): all antibiotic comparisons (ITT analysis)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 day	5-10 day antibiotic course	Relative (95% CI)	Absolute		
17[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	505/2378 (21.2%)	585/2651 (22.1%)	RR 0.98 (0.88 to 1.1)	4 fewer per 1000 (from 26 fewer to 22 more)	⊕⊕⊕O MODERATE	CRITICAL
Short term symptomatic failure (2-15 days from end of treatment): same antibiotic comparisons												
10[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	217/1216 (17.8%)	267/1253 (21.3%)	RR 1.02 (0.89 to 1.18)	4 more per 1000 (from 23 fewer to 38 more)	⊕⊕⊕O MODERATE	CRITICAL
Long term symptomatic failure (4 to 10 weeks): all antibiotic comparisons (ITT analysis)												
10[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	693/1851 (37.4%)	733/2059 (35.6%)	RR 1.07 (0.99 to 1.16)	25 more per 1000 (from 4 fewer to 57 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Long term symptomatic failure (4 to 10 weeks): same antibiotic comparisons												
10[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	378/1218 (31%)	343/1199 (28.6%)	RR 1.07 (0.95 to 1.2)	20 more per 1000 (from 14 fewer to 57 more)	⊕⊕⊕O MODERATE	CRITICAL
Short term bacteriological failure by antibiotic (2-15 days from end of treatment): all antibiotic comparisons (ITT analysis)												
20[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	367/2027 (18.1%)	416/2136 (19.5%)	RR 0.92 (0.8 to 1.06)	16 fewer per 1000 (from 39 fewer to 12 more)	⊕⊕⊕O MODERATE	CRITICAL
Short term bacteriological failure by antibiotic (2-15 days from end of treatment): same antibiotic comparisons												
20[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	167/1199 (13.9%)	167/1274 (13.1%)	RR 1.06 (0.87 to 1.29)	8 more per 1000 (from 17 fewer to 38 more)	⊕⊕OO LOW	CRITICAL
Short term bacteriological failure by antibiotic (2-15 days from end of treatment): same antibiotic comparisons – quinolones												
6[1]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[3]	none	62/815 (7.6%)	41/799 (5.1%)	RR 1.47 (1.01 to 2.16)	24 more per 1000 (from 1 more to 60 more)	⊕⊕OO LOW	CRITICAL
Short term bacteriological failure by antibiotic (2-15 days from end of treatment): same antibiotic comparisons – beta lactams												
7[1]	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[3]	none	47/382 (12.3%)	48/416 (11.5%)	RR 1.11 (0.76 to 1.63)	13 more per 1000 (from 28 fewer to 73 more)	⊕OOO VERY LOW	CRITICAL
Short term bacteriological failure by antibiotic (2-15 days from end of treatment): same antibiotic comparisons – co-trimoxazole												
5[1]	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[3]	none	29/334 (8.7%)	17/400 (4.3%)	RR 1.86 (1.04 to 3.34)	37 more per 1000 (from 2 more to 99 more)	⊕OOO VERY LOW	CRITICAL
Long term bacteriological failure (4 to 10 weeks from end of treatment): all antibiotic comparisons (ITT analysis)												
13[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	406/1435 (28.3%)	355/1508 (23.5%)	RR 1.19 (1.06 to 1.35)	45 more per 1000 (from 14 more to 82 more)	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 day	5-10 day antibiotic course	Relative (95% CI)	Absolute		
Long term bacteriological failure (4 to 10 weeks from end of treatment): same antibiotic comparisons												
10[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	265/1035 (25.6%)	221/1092 (20.2%)	RR 1.26 (1.08 to 1.47)	53 more per 1000 (from 16 more to 95 more)	⊕⊕OO LOW	CRITICAL
Long term bacteriological failure by antibiotic class (4 to 10 weeks from end of treatment): same antibiotic comparisons – quinolones												
4[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	118/580 (20.3%)	95/573 (16.6%)	RR 1.22 (0.95 to 1.56)	36 more per 1000 (from 8 fewer to 93 more)	⊕⊕⊕O MODERATE	CRITICAL
Long term bacteriological failure by antibiotic class (4 to 10 weeks from end of treatment): same antibiotic comparisons – beta lactams												
3[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	75/212 (35.4%)	59/209 (28.2%)	RR 1.26 (0.96 to 1.65)	73 more per 1000 (from 11 fewer to 183 more)	⊕⊕OO LOW	CRITICAL
Long term bacteriological failure by antibiotic class (4 to 10 weeks from end of treatment): same antibiotic comparisons – co-trimoxazole												
5[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	72/243 (29.6%)	67/310 (21.6%)	RR 1.32 (0.98 to 1.76)	69 more per 1000 (from 4 fewer to 164 more)	⊕⊕OO LOW	CRITICAL
Patients with any adverse events during treatment: all antibiotic comparisons												
29[1]	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	599/3682 (16.3%)	809/3935 (20.6%)	RR 0.83 (0.74 to 0.93)	35 fewer per 1000 (from 53 fewer to 14 fewer)	⊕OOO VERY LOW	CRITICAL
Patients with any adverse events during treatment: same antibiotic comparisons												
17[1]	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	280/1905 (14.7%)	379/1947 (19.5%)	RR 0.76 (0.63 to 0.92)	47 fewer per 1000 (from 72 fewer to 16 fewer)	⊕OOO VERY LOW	CRITICAL
Patients developed pyelonephritis: all antibiotic comparisons												
5[1]	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	very serious[4]	none	2/291 (0.69%)	0/291 (0%)	RR 3.04 (0.32 to 28.93)	-	⊕OOO VERY LOW	CRITICAL
Patients developed pyelonephritis: same antibiotic comparisons												
3[1]	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	very serious[4]	none	2/186 (1.1%)	0/195 (0%)	RR 3.04 (0.32 to 28.93)	-	⊕OOO VERY LOW	CRITICAL
Adverse events requiring the withdrawal of treatment: all antibiotic comparisons												
24[1]	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	46/2973 (1.5%)	103/3204 (3.2%)	RR 0.51 (0.28 to 0.91)	16 fewer per 1000 (from 23 fewer to 3 fewer)	⊕OOO VERY LOW	CRITICAL
Adverse events requiring the withdrawal of treatment: same antibiotic comparisons												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 day	5-10 day antibiotic course	Relative (95% CI)	Absolute		
13[1]	randomised trials	very serious[5]	serious[7]	no serious indirectness	serious[6]	none	16/1398 (1.1%)	57/1419 (4%)	RR 0.35 (0.12 to 0.98)	26 fewer per 1000 (from 35 fewer to 1 fewer)	⊕OOO VERY LOW	CRITICAL
Gastrointestinal adverse effects: all antibiotic comparisons												
24[1]	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	226/3357 (6.7%)	306/3616 (8.5%)	RR 0.81 (0.67 to 0.97)	16 fewer per 1000 (from 28 fewer to 3 fewer)	⊕OOO VERY LOW	CRITICAL
Gastrointestinal adverse effects: same antibiotic comparisons												
15[1]	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	114/1679 (6.8%)	153/1721 (8.9%)	RR 0.77 (0.61 to 0.97)	20 fewer per 1000 (from 35 fewer to 3 fewer)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval; ITT, Intention to treat analysis; RR – risk ratio												

[1] Milo et al. 2005
[2] Downgraded 1 level - most of the studies are low quality, as reported by study authors
[3] Downgraded 1 level - at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with a 3 day course of antibiotic
[4] Downgraded 2 levels - at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[5] Downgraded 2 levels - 'very serious' methodological flaws
[6] Downgraded 1 level – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with a 5-10 day course of antibiotic
[7] Downgraded 1 level - heterogeneity > 50%

H.5 Antibiotics in pregnant women

Table 29: GRADE profile – antibiotics versus no treatment for asymptomatic bacteriuria in pregnant women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics	No treatment	Relative (95% CI)	Absolute		
Development of pyelonephritis												
11[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	55/983 (5.6%)	197/949 (20.8%)	RR 0.23 (0.13 to 0.41)	160 fewer per 1000 (from 181 fewer to 122 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Preterm birth <37 weeks												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/120 (5.8%)	27/122 (22.1%)	RR 0.27 (0.11 to 0.62)	162 fewer per 1000 (from 297 fewer to 84 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Birthweight <2500 g												

6[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	63/729 (8.6%)	96/708 (13.6%)	RR 0.64 (0.45 to 0.93)	49 fewer per 1000 (from 75 fewer to 9 fewer)	⊕⊕OO LOW	CRITICAL
Birthweight (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	no serious imprecision	none	235	178	-	MD 61 higher (56.55 lower to 178.55 higher)	⊕⊕⊕O MODERATE	CRITICAL
Persistent bacteriuria												
4[1]	randomised trials	serious[2]	serious[4]	no serious indirectness	no serious imprecision	none	60/296 (20.3%)	199/300 (66.3%)	RR 0.30 (0.18 to 0.53)	464 fewer per 1000 (from 544 fewer to 312 fewer)	⊕⊕OO LOW	CRITICAL
Serious adverse neonatal outcome												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	very serious[5]	none	4/128 (3.1%)	2/145 (1.4%)	RR 2.27 (0.42 to 12.16)	18 more per 1000 (from 8 fewer to 154 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: N/A – not applicable; CI- confidence interval; RR – risk ratio												

[1] Smaill et al. 2015
[2] Downgraded 1 level - most of the studies are low quality, as reported by study authors
[3] Downgraded 1 level - at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with no treatment
[4] Downgraded 1 level - heterogeneity > 50%
[5] Downgraded 2 levels - at minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 30: GRADE profile – nitrofurantoin versus placebo for asymptomatic bacteriuria in pregnant women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Nitrofurantoin**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Pyelonephritis												
1[1]	randomised trials	very serious[2]	N/A	no serious indirectness	very serious[3]	none	1/40 (2.5%)	5/208 (2.4%)	Risk difference -0.4 (-3.6 to 9.4) NICE analysis RR 0 (0.12 to 8.67)[4]	24 fewer per 1000 (from 21 fewer to 184 more)	⊕OOO VERY LOW	CRITICAL
Preterm birth <34 weeks												
1[1]	randomised trials	very serious[2]	N/A	no serious indirectness	very serious[3]	none	1/40 (2.5%)	12/208 (5.8%)	Risk difference -1.5 (-15.3 to 18.5) NICE analysis RR 0.43 (0.06 to 3.24)[4]	33 fewer per 1000 (from 54 fewer to 129 more)	⊕OOO VERY LOW	CRITICAL
Maternal outcomes -urinary tract infections that require antibiotics												
1[1]	randomised trials	very serious[2]	N/A	no serious indirectness	very serious[3]	none	4/40 (10%)	42/208 (20.2%)	Risk difference -10.0 (-27.9 to 6.8) NICE analysis RR 0.50 (0.19 to 1.3)[4]	101 fewer per 1000 (from 164 fewer to 61 more)	⊕OOO VERY LOW	CRITICAL
Maternal outcomes - non spontaneous onset of labour												

1[1]	randomised trials	very serious[2]	N/A	no serious indirectness	very serious[5]	none	14/40 (35%)	44/208 (21.2%)	Risk difference 2.7 (-14.3 to 19.6) NICE analysis RR 1.65 (1.01 to 27.2)[4]	138 more per 1000 (from 2 more to 1000 more)	⊕OOO VERY LOW	CRITICAL
Neonatal outcomes - birthweight small for gestational age <10th percentile												
1[1]	randomised trials	very serious[2]	N/A	no serious indirectness	very serious[3]	none	1/40 (2.5%)	14/208 (6.7%)	Risk difference -5.7 (-22.5 to 11.3) NICE analysis RR 0.37 (0.05 to 2.75)[4]	42 fewer per 1000 (from 64 fewer to 118 more)	⊕OOO VERY LOW	CRITICAL
Neonatal outcomes - perinatal death												
1[1]	randomised trials	very serious[2]	N/A	no serious indirectness	very serious[3]	none	1/40 (2.5%)	2/208 (0.96%)	Risk difference 1.5 (-15.4 to 18.5) NICE analysis RR 0 (0.24 to 27.99)[4]	10 fewer per 1000 (from 7 fewer to 260 more)	⊕OOO VERY LOW	CRITICAL
Neonatal outcomes - admission to neonatal intensive care unit (NICU)												
1[1]	randomised trials	very serious[2]	N/A	no serious indirectness	very serious[3]	none	2/40 (5%)	5/208 (2.4%)	Risk difference 2.6 (-14.4 to 19.5) NICE analysis RR 2.08 (0.42 to 10.35)[4]	26 more per 1000 (from 14 fewer to 225 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: N/A – not applicable; CI- confidence interval; RR – risk ratio; NICU – neonatal intensive care unit												

[1] Kazemier et al. 2015
[2] Downgraded 2 levels - very serious methodological flaws: significant differences in baseline characteristics between intervention and comparator groups
[3] Downgraded 2 levels - at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[4] Calculated by NICE
[5] Downgraded 2 levels – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with nitrofurantoin; 95% confidence intervals are very wide

Table 31: GRADE profile – fosfomycin versus cefuroxime for asymptomatic bacteriuria in pregnant women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Fosfomycin**	**Cefuroxime**	**Relative (95% CI)**	**Absolute**		
Persistent infection												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	very serious[3]	none	3/44 (6.8%)	2/40 (5%)	RR 1.36 (0.24 to 7.75)	18 more per 1000 (from 38 fewer to 338 more)	⊕OOO VERY LOW	CRITICAL
Shift to another antibiotic												

1[1]	randomised trials	serious[2]	N/A	no serious indirectness	very serious[3]	none	0/44 (0%)	5/40 (12.5%)	RR 0.08 (0 to 1.45)	115 fewer per 1000 (from 125 fewer to 56 more)	⊕OOO VERY LOW	CRITICAL
Adverse effect: allergy or pruritus												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	very serious[3]	none	1/44 (2.3%)	0/40 (0%)	RR 2.73 (0.11 to 65.24)	-	⊕OOO VERY LOW	CRITICAL
Abbreviations: N/A – not applicable; CI – confidence interval; RR – risk ratio												

[1] Guinto et al. 2010
[2] Downgraded 1 level - high dropout rate that would influence the outcome
[3] Downgraded 2 levels - at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 32: GRADE profile – pivmecillinam versus ampicillin for asymptomatic bacteriuria in pregnant women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pivmecillinam**	**Ampicillin**	**Relative (95% CI)**	**Absolute**		
Persistent infection -after 2 weeks												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	very serious[3]	none	4/32 (12.5%)	4/33 (12.1%)	RR 1.03 (0.28 to 3.78)	4 more per 1000 (from 87 fewer to 337 more)	⊕OOO VERY LOW	CRITICAL
Persistent infection -after 6 weeks												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	very serious[3]	none	7/29 (24.1%)	9/25 (36%)	RR 0.67 (0.29 to 1.54)	119 fewer per 1000 (from 256 fewer to 194 more)	⊕OOO VERY LOW	CRITICAL
Recurrent infection												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	very serious[3]	none	2/32 (6.3%)	3/33 (9.1%)	RR 0.69 (0.12 to 3.85)	28 fewer per 1000 (from 80 fewer to 259 more)	⊕OOO VERY LOW	CRITICAL
Adverse effect: prematurely stopping treatment												
1[1]	randomised trials	very serious[4]	N/A	no serious indirectness	very serious[5]	none	9/32 (28.1%)	1/33 (3%)	RR 9.28 (1.25 to 69.13)	251 more per 1000 (from 8 more to 1000 more)	⊕OOO VERY LOW	CRITICAL
Adverse effect: vomiting												
1[1]	randomised trials	very serious[4]	N/A	no serious indirectness	serious[6]	none	14/32 (43.8%)	3/33 (9.1%)	RR 4.81 (1.53 to 15.17)	346 more per 1000 (from 48 more to 1000 more)	⊕OOO VERY LOW	CRITICAL
Adverse effect: diarrhoea												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	very serious[3]	none	1/32 (3.1%)	2/33 (6.1%)	RR 0.52 (0.05 to 5.41)	29 fewer per 1000 (from 58 fewer to 267 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: N/A – not assessable; CI – confidence interval; RR – risk ratio												

[1] Guinto et al. 2010
[2] Downgraded 1 level - high dropout rate that would influence the outcome
[3] Downgraded 2 levels - at a 95% confidence interval, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[4] Downgraded 2 levels - very serious methodological flaws
[5] Downgraded 2 levels – at a minimal important difference of 25%, data are consistent with no meaningful difference or appreciable harm with pivmecillinam; 95% confidence intervals are very wide
[6] Downgraded 1 level – 95% confidence intervals are very wide

Table 33: GRADE profile – different antibiotics course lengths versus no treatment for asymptomatic bacteriuria in pregnant women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic	No treatment	Relative (95% CI)	Absolute		
Development of pyelonephritis - single dose												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	serious[3]	none	9/87 (10.3%)	20/86 (23.3%)	RR 0.44 (0.21 to 0.92)	130 fewer per 1000 (from 184 fewer to 19 fewer)	⊕⊕OO LOW	CRITICAL
Development of pyelonephritis - short course (3-7 days)												
3[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	9/235 (3.8%)	33/248 (13.3%)	RR 0.32 (0.09 to 1.16)	90 fewer per 1000 (from 121 fewer to 21 more)	⊕⊕OO LOW	CRITICAL
Development of pyelonephritis - intermediate course (3-6 weeks)												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/209 (3.3%)	44/224 (19.6%)	RR 0.17 (0.08 to 0.37)	163 fewer per 1000 (from 181 fewer to 124 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Development of pyelonephritis - continuous treatment												
5[1]	randomised trials	serious[2]	serious[4]	no serious indirectness	no serious imprecision	none	30/452 (6.6%)	100/391 (25.6%)	RR 0.16 (0.04 to 0.57)	215 fewer per 1000 (from 246 fewer to 110 fewer)	⊕⊕OO LOW	CRITICAL
Preterm birth <37 weeks - short course (3-7 days)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/37 (5.4%)	12/32 (37.5%)	RR 0.14 (0.03 to 0.6)	322 fewer per 1000 (from 364 fewer to 150 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Preterm birth <37 weeks - continuous treatment												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	serious[3]	none	5/83 (6%)	15/90 (16.7%)	RR 0.36 (0.14 to 0.95)	107 fewer per 1000 (from 143 fewer to 8 fewer)	⊕⊕OO LOW	CRITICAL
Birthweight <2500 g - single dose												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	serious[3]	none	18/235 (7.7%)	21/178 (11.8%)	RR 0.65 (0.36 to 1.18)	41 fewer per 1000 (from 76 fewer to 21 more)	⊕⊕OO LOW	CRITICAL
Birthweight <2500 g - intermediate course (3-6 weeks)												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	very serious[5]	none	15/133 (11.3%)	15/145 (10.3%)	RR 1.09 (0.55 to 2.14)	9 more per 1000 (from 47 fewer to 118 more)	⊕OOO VERY LOW	CRITICAL
Birthweight <2500 g - continuous treatment												

4[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	30/361 (8.3%)	60/385 (15.6%)	RR 0.54 (0.33 to 0.87)	72 fewer per 1000 (from 104 fewer to 20 fewer)	⊕⊕OO LOW	CRITICAL
Abbreviations: N/A – not applicable; CI – confidence interval; RR – risk ratio												

[1] Smaill et al. 2015
[2] Downgraded 1 level - most of the studies are low quality, as reported by study authors
[3] Downgraded 1 level - at a minimal important difference of 25%, data are consistent with no meaningful difference or appreciable harm with no treatment
[4] Downgraded 1 level - heterogeneity > 50%
[5] Downgraded 2 levels - at a minimal important difference of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 34: GRADE profile – single dose versus short course (4 to 7 days) for asymptomatic bacteriuria in pregnant women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single dose	Short course (4-7 days)	Relative (95% CI)	Absolute		
No cure												
13[1]	randomised trials	very serious[2]	serious[3]	no serious indirectness	serious[4]	none	179/772 (23.2%)	121/730 (16.6%)	RR 1.28 (0.87 to 1.88)	46 more per 1000 (from 22 fewer to 146 more)	⊕OOO VERY LOW	CRITICAL
No cure - same antimicrobial agent												
10[1]	randomised trials	serious[5]	serious[3]	no serious indirectness	serious[4]	none	165/662 (24.9%)	107/624 (17.1%)	RR 1.34 (0.85 to 2.12)	58 more per 1000 (from 26 fewer to 192 more)	⊕OOO VERY LOW	CRITICAL
No cure - different antimicrobial agent												
3[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	none	14/110 (12.7%)	14/106 (13.2%)	RR 0.98 (0.49 to 1.95)	3 fewer per 1000 (from 67 fewer to 125 more)	⊕⊕OO LOW	CRITICAL
Recurrent asymptomatic bacteriuria												
8[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	43/232 (18.5%)	36/213 (16.9%)	RR 1.13 (0.77 to 1.66)	22 more per 1000 (from 39 fewer to 112 more)	⊕OOO VERY LOW	CRITICAL
Recurrent asymptomatic bacteriuria - same antimicrobial agent												
6[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	40/166 (24.1%)	34/147 (23.1%)	RR 1.12 (0.76 to 1.66)	28 more per 1000 (from 56 fewer to 153 more)	⊕OOO VERY LOW	CRITICAL
Recurrent asymptomatic bacteriuria - different antimicrobial agent (Copy)												
2[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[6]	none	3/66 (4.5%)	2/66 (3%)	RR 1.32 (0.23 to 7.46)	10 more per 1000 (from 23 fewer to 196 more)	⊕OOO VERY LOW	CRITICAL
Pyelonephritis												
2[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[6]	none	5/54 (9.3%)	1/48 (2.1%)	RR 3.09 (0.54 to 17.55)	44 more per 1000 (from 10 fewer to 345 more)	⊕OOO VERY LOW	CRITICAL
Preterm delivery												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single dose	Short course (4-7 days)	Relative (95% CI)	Absolute		
3[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	44/409 (10.8%)	36/395 (9.1%)	RR 1.17 (0.77 to 1.78)	15 more per 1000 (from 21 fewer to 71 more)	⊕⊕⊕O MODERATE	CRITICAL
Low birthweight												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[4]	none	48/364 (13.2%)	28/350 (8%)	RR 1.65 (1.06 to 2.57)	52 more per 1000 (from 5 more to 126 more)	⊕⊕⊕O MODERATE	CRITICAL
Side effects												
12[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[7]	none	97/738 (13.1%)	140/722 (19.4%)	RR 0.70 (0.56 to 0.88)	58 fewer per 1000 (from 85 fewer to 23 fewer)	⊕OOO VERY LOW	CRITICAL
Side effects - same antimicrobial agent												
9[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	95/628 (15.1%)	125/616 (20.3%)	RR 0.77 (0.61 to 0.97)	47 fewer per 1000 (from 79 fewer to 6 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Side effects - different antimicrobial agent												
3[1]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/110 (1.8%)	15/106 (14.2%)	RR 0.16 (0.04 to 0.58)	119 fewer per 1000 (from 136 fewer to 59 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: N/A, not applicable; CI, confidence interval; RR, risk ratio												

[1] Widmer et al. 2015
[2] Downgraded 2 levels - very serious methodological flaws
[3] Downgraded 1 level - heterogeneity > 50%
[4] Downgraded 1 level - at a minimal important difference of 25%, data are consistent with no meaningful difference or appreciable harm with single dose antibiotics
[5] Downgraded 1 level - most of the studies are of low quality
[6] Downgraded 2 levels - at a minimal important difference of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[7] Downgraded 1 level – at a minimal important difference of 25%, data are consistent with no meaningful difference or appreciable harm with short course antibiotics

Table 35: GRADE profile – 1-day nitrofurantoin versus 7-day nitrofurantoin for asymptomatic bacteriuria in pregnant women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1 day nitrofurantoin	7 day nitrofurantoin	Relative (95% CI)	Absolute		
Symptomatic infection at 2 weeks												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	very serious[2]	none	5/371 (1.3%)	7/370 (1.9%)	RR 0.71 (0.23 to 2.22)	5 fewer per 1000 (from 15 fewer to 23 more)	⊕⊕OO LOW	CRITICAL
Symptomatic infection prior to delivery												

1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	very serious[2]	none	10/354 (2.8%)	12/349 (3.4%)	RR 0.82 (0.36 to 1.88)	6 fewer per 1000 (from 22 fewer to 30 more)	⊕⊕OO LOW	CRITICAL
Persistent infection												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious impression	none	90/371 (24.3%)	51/370 (13.8%)	RR 1.76 (1.29 to 2.4)	105 more per 1000 (from 40 more to 193 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Adverse event: nausea												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[3]	none	23/375 (6.1%)	33/385 (8.6%)	RR 0.72 (0.43 to 1.2)	24 fewer per 1000 (from 49 fewer to 17 more)	⊕⊕⊕O MODERATE	CRITICAL
Preterm delivery												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[4]	none	39/354 (11%)	31/349 (8.9%)	RR 1.24 (0.79 to 1.94)	21 more per 1000 (from 19 fewer to 83 more)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: N/A – not applicable; CI – confidence interval; RR – risk ratio												

[1] Guinto et al. 2010
[2] Downgraded 2 levels - at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[3] Downgraded 1 level – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with a 7 day course of nitrofurantoin
[4] Downgraded 1 level - at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with a 1 day course of nitrofurantoin

H.6 Antibiotics in older people

Table 36: GRADE profile – antibiotics versus placebo or no treatment in older people with asymptomatic bacteriuria

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antibiotics**	**placebo or no treatment**	**Relative (95% CI)**	**Absolute**		
Symptomatic urinary tract infection												
5[1]	randomised trials	no serious risk of bias	very serious[2]	no serious indirectness	very serious[3]	none	225/554 (40.6%)	100/492 (20.3%)	RR 1.11 (0.51 to 2.43)	22 more per 1000 (from 100 fewer to 291 more)	⊕OOO VERY LOW	CRITICAL
Bacteriological cure												
9[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	305/496 (61.5%)	114/658 (17.3%)	RR 2.67 (1.85 to 3.85)	289 more per 1000 (from 147 more to 494 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Any adverse events												
4[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	21/506 (4.2%)	4/415 (0.96%)	RR 3.77 (1.4 to 10.15)	27 more per 1000 (from 4 more to 88 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Complications												

3[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	10/432 (2.3%)	12/382 (3.1%)	RR 0.78 (0.35 to 1.74)	7 fewer per 1000 (from 20 fewer to 23 more)	⊕⊕OO LOW	CRITICAL
Death												
6[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	49/387 (12.7%)	54/374 (14.4%)	RR 0.99 (0.7 to 1.41)	1 fewer per 1000 (from 43 fewer to 59 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI – confidence interval												

[1] Zalmanovici-Trestioreanu et al. 2015
[2] Downgraded 1 level – heterogeneity > 50%
[3] Downgraded 2 levels – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 37: GRADE profile – single dose versus short course (3 to 6 days) in older women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Single dose**	**Short-course (3 to 6 days)**	**Relative (95% CI)**	**Absolute**		
Persistent UTI: short term												
5[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	38/172 (22.1%)	19/184 (10.3%)	RR 2.01 (1.05 to 3.84)	104 more per 1000 (from 5 more to 293 more)	⊕⊕OO LOW	CRITICAL
Persistent UTI: long term												
3[1]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	11/38 (28.9%)	12/57 (21.1%)	RR 1.18 (0.59 to 2.32)	38 more per 1000 (from 86 fewer to 278 more)	⊕OOO VERY LOW	CRITICAL
Clinical failure (persistence of symptoms): short-term												
1[1]	randomised trials	serious[4]	N/A	no serious indirectness	very serious[5]	none	1/15 (6.7%)	0/8 (0%)	RR 1.69 (0.08 to 37.26)	-	⊕OOO VERY LOW	CRITICAL
Reinfection rate: short-term												
1[1]	randomised trials	serious[4]	N/A	no serious indirectness	very serious[5]	none	7/49 (14.3%)	10/47 (21.3%)	RR 0.67 (0.28 to 1.62)	70 fewer per 1000 (from 153 fewer to 132 more)	⊕OOO VERY LOW	
Reinfection rate: long-term												
1[1]	randomised trials	serious[4]	N/A	no serious indirectness	serious[3]	none	8/36 (22.2%)	3/38 (7.9%)	RR 2.81 (0.81 to 9.79)	143 more per 1000 (from 15 fewer to 694 more)	⊕⊕OO LOW	
Acceptability (little or no satisfaction with treatment)												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[6]	none	3/79 (3.8%)	10/79 (12.7%)	RR 0.30 (0.09 to 1.06)	89 fewer per 1000 (from 115 fewer to 8 more)	⊕⊕⊕O MODERATE	
Abbreviations: CI – confidence interval; UTI – urinary tract infection; N/A – not applicable												

[1] Lutters et al. 2008
[2] Downgraded 1 level - majority of studies low quality
[3] Downgraded 1 level - at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with single dose antibiotics
[4] Downgraded 1 level - majority of evidence rated unclear or high risk of bias
[5] Downgraded 2 levels - at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

[6] Downgraded 1 level – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with short-course antibiotics

Table 38: GRADE profile – single dose versus long course (7 to 14 days) in older women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single dose	Long course	Relative (95% CI)	Absolute		
Persistent UTI: short-term												
6[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	37/311 (11.9%)	18/317 (5.7%)	RR 1.93 (1.01 to 3.7)	53 more per 1000 (from 1 more to 153 more)	⊕⊕OO LOW	CRITICAL
Persistent UTI: long-term												
5[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	50/255 (19.6%)	41/268 (15.3%)	RR 1.28 (0.89 to 1.84)	43 more per 1000 (from 17 fewer to 129 more)	⊕⊕OO LOW	CRITICAL
Clinical failure (persistence of symptoms): short-term												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	very serious[4]	none	10/97 (10.3%)	5/91 (5.5%)	RR 1.94 (0.68 to 5.57)	52 more per 1000 (from 18 fewer to 251 more)	⊕⊕OO LOW	CRITICAL
Acceptability (little or no satisfaction with treatment)												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[5]	none	89/197 (45.2%)	119/191 (62.3%)	RR 0.73 (0.6 to 0.88)	168 fewer per 1000 (from 249 fewer to 75 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Adverse drug reactions												
3[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	20/305 (6.6%)	25/290 (8.6%)	RR 0.8 (0.45 to 1.41)	17 fewer per 1000 (from 47 fewer to 35 more)	⊕⊕OO LOW	CRITICAL
Discontinuation due to adverse reactions												
3[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/305 (0%)	1/290 (0.34%)	RR 0.33 (0.01 to 7.87)	2 fewer per 1000 (from 3 fewer to 24 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval; UTI – urinary tract infection; N/A – not applicable												

[1] Lutters et al. 2008
[2] Downgraded 1 level - majority of studies are low quality
[3] Downgraded 1 level - at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with single dose antibiotics
[4] Downgraded 2 levels - at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[5] Downgraded 1 level – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with long course antibiotics

Table 39: GRADE profile – single dose versus short course or long-course (3 to 14 days) in older women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single dose	Short-course or long-course treatment (3 to 14 days)	Relative (95% CI)	Absolute		
Persistent UTI: short term												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single dose	Short-course or long-course treatment (3 to 14 days)	Relative (95% CI)	Absolute		
8[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	49/401 (12.2%)	31/408 (7.6%)	RR 1.51 (0.92 to 2.49)	39 more per 1000 (from 6 fewer to 113 more)	⊕⊕OO LOW	CRITICAL
Persistent UTI: long term												
5[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	50/256 (19.5%)	44/265 (16.6%)	RR 1.14 (0.8 to 1.63)	23 more per 1000 (from 33 fewer to 105 more)	⊕⊕OO LOW	CRITICAL
Clinical failure (persistence of symptoms): short term												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	11/212 (5.2%)	5/199 (2.5%)	RR 1.91 (0.7 to 5.19)	23 more per 1000 (from 8 fewer to 105 more)	⊕⊕OO LOW	CRITICAL
Acceptability (little or no satisfaction with treatment)												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	92/276 (33.3%)	129/270 (47.8%)	RR 0.58 (0.27 to 1.25)	201 fewer per 1000 (from 349 fewer to 119 more)	⊕⊕OO LOW	CRITICAL
Adverse drug reactions												
3[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	20/305 (6.6%)	25/290 (8.6%)	RR 0.80 (0.45 to 1.41)	17 fewer per 1000 (from 47 fewer to 35 more)	⊕⊕OO LOW	
Discontinuation due to adverse reactions												
3[1]	randomised trials	serious[2]	serious[5]	no serious indirectness	very serious[4]	none	0/305 (0%)	1/290 (0.34%)	RR 0.33 (0.01 to 7.87)	2 fewer per 1000 (from 3 fewer to 24 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI – confidence interval; UTI – urinary tract infection

[1] Lutters et al. 2008
[2] Downgraded 1 level – majority of studies are low quality
[3] Downgraded 1 level – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with single dose antibiotics
[4] Downgrade 1 level – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[5] Downgraded 1 level - not assessable

Table 40: GRADE profile – short course (3 to 6 days) versus long course (7 to 14 days) in older women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short course	Long course	Relative (95% CI)	Absolute		
Persistent UTI: short-term												
3[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	very serious[4]	none	36/224 (16.1%)	47/207 (22.7%)	RR 0.85 (0.29 to 2.47)	34 fewer per 1000 (from 161 fewer to 334 more)	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short course	Long course	Relative (95% CI)	Absolute		
Persistent UTI: long-term												
3[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	64/247 (25.9%)	71/223 (31.8%)	RR 1.00 (0.12 to 8.57)	0 fewer per 1000 (from 280 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Clinical failure (persistence of symptom): short term												
4[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	30/199 (15.1%)	28/196 (14.3%)	RR 0.98 (0.62 to 1.54)	3 fewer per 1000 (from 54 fewer to 77 more)	⊕OOO VERY LOW	CRITICAL
Clinical failure (persistence of symptom): long term												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	serious[5]	none	29/119 (24.4%)	34/104 (32.7%)	RR 0.75 (0.49 to 1.13)	82 fewer per 1000 (from 167 fewer to 43 more)	⊕⊕OO LOW	CRITICAL
Reinfection rate short term												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	very serious[6]	none	10/119 (8.4%)	2/104 (1.9%)	RR 4.34 (0.98 to 19.49)	64 more per 1000 (from 0 fewer to 356 more)	⊕OOO VERY LOW	CRITICAL
Reinfection rate long term												
2[1]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[4]	none	23/212 (10.8%)	21/193 (10.9%)	RR 1.30 (0.42 to 4.01)	33 more per 1000 (from 63 fewer to 328 more)	⊕OOO VERY LOW	CRITICAL
Acceptability (little or no satisfaction with treatment)												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	very serious[4]	none	2/49 (4.1%)	5/43 (11.6%)	RR 0.35 (0.07 to 1.72)	76 fewer per 1000 (from 108 fewer to 84 more)	⊕⊕OO LOW	
Adverse drug reactions												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	very serious[4]	none	5/119 (4.2%)	5/104 (4.8%)	RR 0.87 (0.26 to 2.93)	6 fewer per 1000 (from 36 fewer to 93 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation due to adverse reactions												
2[1]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[4]	none	0/212 (0%)	4/194 (2.1%)	RR 0.11 (0.01 to 1.97)	18 fewer per 1000 (from 20 fewer to 20 more)	⊕OOO VERY LOW	CRITICAL
Mean number of adverse events per patient (day 9) (Better indicated by lower values)												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[7]	none	91	86	-	MD 0.90 lower (1.33 to 0.47 lower)	⊕⊕⊕O MODERATE	CRITICAL
Mean number of adverse events per patient (day 5) (Better indicated by lower values)												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[7]	none	91	86	-	MD 0.70 lower (1.09 to 0.31 lower)	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: UTI – urinary tract infection; CI – confidence interval; N/A – not applicable; RR – risk ratio; MD – mean difference

[1] Lutters et al. 2008
[2] Downgraded 1 level - majority of studies are low quality
[3] Downgraded 1 level - heterogeneity > 50%
[4] Downgraded 2 levels - at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[5] Downgraded 1 level - at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with long course antibiotics
[6] Downgraded 1 level – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with short course antibiotics; very wide confidence intervals
[7] Downgraded 1 level – at a minimal important difference (MID) of 0.5 standard deviation of control, data are consistent with no meaningful difference or appreciable harm with short course antibiotics

Table 45: GRADE profile – 3 days versus 5 days in older women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 days	5 days	Relative (95% CI)	Absolute		
Persistent UTI: short course (3 days after treatment)												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	serious[3]	none	7/12 (58.3%)	3/14 (21.4%)	RR 2.72 (0.9 to 8.27)	369 more per 1000 (from 21 fewer to 1000 more)	⊕⊕OO LOW	CRITICAL
Clinical failure (not recovered): short-term (3 days after treatment)												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	very serious[4]	none	3/12 (25%)	3/14 (21.4%)	RR 1.17 (0.29 to 4.74)	36 more per 1000 (from 152 fewer to 801 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval; UTI – urinary tract infection; N/A – not applicable; RR – risk ratio												

[1] Lutters et al. 2008
[2] Downgraded 1 level - majority of evidence is of low quality
[3] Downgraded 2 levels - at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with a 3 day course
[4] Downgraded 2 levels – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

H.7 Antibiotics in children

Table 41: GRADE profile – trimethoprim (10 days) versus co-trimoxazole (10 days) in children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Trimethoprim (10 days)	Co-trimoxazole (10 days)	Relative (95% CI)	Absolute		
Persistent bacteriuria												
1[1]	randomised trials	very serious[2]	N/A	no serious indirectness	very serious[3]	none	4/30 (13.3%)	2/29 (6.9%)	RR 1.93 (0.38 to 9.76)	64 more per 1000 (from 43 fewer to 604 more)	⊕OOO VERY LOW	CRITICAL
Persistent symptoms												
1[1]	randomised trials	very serious[2]	N/A	no serious indirectness	very serious[3]	none	2/30 (6.7%)	0/29 (0%)	RR 4.84 (0.24 to 96.66)	-	⊕OOO VERY LOW	CRITICAL
Recurrence												
1[1]	randomised trials	very serious[2]	N/A	no serious indirectness	very serious[3]	none	1/30 (3.3%)	0/29 (0%)	RR 2.90 (0.12 to 68.5)	-	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval; N/A – not applicable; RR – risk ratio												

[1] Fitzgerald et al. 2012
[2] Downgraded 2 levels – very serious methodological flaws
[3] Downgraded 2 levels – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 42: GRADE profile – cefadroxil (10 days) versus ampicillin (10 days) in children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cefadroxil (10 days)	Ampicillin (10 days)	Relative (95% CI)	Absolute		
Persistent bacteriuria												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	very serious[3]	none	0/16 (0%)	1/16 (6.3%)	RR 0.33 (0.01 to 7.62)	42 fewer per 1000 (from 62 fewer to 414 more)	⊕OOO VERY LOW	
Persistent symptoms												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	very serious[3]	none	0/16 (0%)	1/16 (6.3%)	RR 0.33 (0.01 to 7.62)	42 fewer per 1000 (from 62 fewer to 414 more)	⊕OOO VERY LOW	

Abbreviations: CI – confidence interval; N/A – not applicable; RR – risk ratio

[1] Fitzgerald et al. 2012
[2] Downgraded 2 levels - very serious methodological flaws
[3] Downgraded 2 levels – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 43: GRADE profile – single dose versus short course (3 to 7 days) in children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single dose	Short course (3-7 days)	Relative (95% CI)	Absolute		
Persistent bacteriuria												
2[1]	randomised trials	very serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	21/75 (28%)	14/70 (20%)	RR 1.3 (0.65 to 2.62)	60 more per 1000 (from 70 fewer to 324 more)	⊕OOO VERY LOW	CRITICAL
Recurrence												
2[1]	randomised trials	very serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	11/75 (14.7%)	7/70 (10%)	RR 1.5 (0.43 to 5.26)	50 more per 1000 (from 57 fewer to 426 more)	⊕OOO VERY LOW	CRITICAL
Re-infection												
1[1]	randomised trials	very serious[2]	N/A	serious[3]	very serious[4]	none	1/25 (4%)	5/20 (25%)	RR 0.16 (0.02 to 1.26)	210 fewer per 1000 (from 245 fewer to 65 more)	⊕OOO VERY LOW	CRITICAL

[1] Fitzgerald et al. 2012
[2] Downgraded 2 levels – very serious methodological flaws
[3] Downgraded 1 level - some children had a history of recurrent urinary tract infection
[4] Downgraded 2 levels – at a minimal important difference of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm t

Table 44: GRADE profile – single dose versus long course (10 days) in children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single-dose	Conventional 10 day treatment	Relative (95% CI)	Absolute		
Persistent bacteriuria (assessed with: Amoxicillin (4/6 studies))												
6[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	27/113 (23.9%)	12/115 (10.4%)	RR 2.01 (1.06 to 3.8)	105 more per 1000 (from 6 more to 292 more)	⊕OOO VERY LOW	CRITICAL
Persistent symptoms												
1[1]	randomised trials	very serious[2]	N/A	no serious indirectness	very serious[4]	none	1/16 (6.3%)	3/14 (21.4%)	RR 0.29 (0.03 to 2.5)	152 fewer per 1000 (from 208 fewer to 321 more)	⊕OOO VERY LOW	CRITICAL
Recurrence												
2[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	9/41 (22%)	6/38 (15.8%)	RR 1.38 (0.55 to 3.5)	60 more per 1000 (from 71 fewer to 395 more)	⊕OOO VERY LOW	CRITICAL
Persistent bacteriuria and symptoms												
1[1]	randomised trials	very serious[2]	N/A	no serious indirectness	very serious[4]	none	2/24 (8.3%)	1/22 (4.5%)	RR 1.83 (0.18 to 18.84)	38 more per 1000 (from 37 fewer to 811 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI – confidence interval; N/A – not applicable; RR – risk ratio

[1] Fitzgerald et al. 2012
[2] Downgraded 2 levels - very serious methodological flaws
[3] Downgraded 1 level - at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with a single dose of antibiotics
[4] Downgraded 1 level – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 45: GRADE profile – short course (3 to 7 days) versus long course (10 to 14 days) in children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short course (3-7 days)	Long course (10-14 days)	Relative (95% CI)	Absolute		
Persistent bacteriuria												
3[1]	randomised trials	very serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	29/136 (21.3%)	24/129 (18.6%)	RR 1.09 (0.67 to 1.76)	17 more per 1000 (from 61 fewer to 141 more)	⊕OOO VERY LOW	CRITICAL
Recurrence												
4[1]	randomised trials	very serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	25/163 (15.3%)	21/165 (12.7%)	RR 1.25 (0.74 to 2.13)	32 more per 1000 (from 33 fewer to 144 more)	⊕OOO VERY LOW	CRITICAL
Re-infection												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short course (3-7 days)	Long course (10-14 days)	Relative (95% CI)	Absolute		
2[1]	randomised trials	very serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	14/109 (12.8%)	15/102 (14.7%)	RR 0.88 (0.44 to 1.74)	18 fewer per 1000 (from 82 fewer to 109 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval; RR – risk ratio												

[1] Fitzgerald et al. 2012
[2] Downgraded 2 levels – very serious methodological flaws
[3] Downgraded 1 level - some children had history of recurrent urinary tract infection
[4] Downgraded 2 levels – at minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 50: GRADE profile – short course (2 to 4 days) versus longer course (7 to 14 days) in children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short duration	Standard duration	Relative (95% CI)	Absolute		
Urinary tract infection at end of treatment												
8[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	34/232 (14.7%)	27/191 (14.1%)	RR 1.06 (0.64 to 1.76)	8 more per 1000 (from 51 fewer to 107 more)	⊕OOO VERY LOW	CRITICAL
Urinary tract infection at 1 to 3 months after treatment												
6[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	19/138 (13.8%)	20/131 (15.3%)	RR 0.83 (0.46 to 1.47)	26 fewer per 1000 (from 82 fewer to 72 more)	⊕OOO VERY LOW	CRITICAL
Urinary tract infection at 3 to 15 months after treatment												
4[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	42/129 (32.6%)	35/109 (32.1%)	RR 1.05 (0.73 to 1.52)	16 more per 1000 (from 87 fewer to 167 more)	⊕OOO VERY LOW	CRITICAL
Urinary tract infection at 1 to 15 months after treatment												
10[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	62/267 (23.2%)	57/240 (23.8%)	RR 0.95 (0.70 to 1.29)	12 fewer per 1000 (from 71 fewer to 69 more)	⊕OOO VERY LOW	CRITICAL
Persistence of bacteriuria - sulphonamide containing antibiotics												
8[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	19/161 (11.8%)	19/128 (14.8%)	RR 0.80 (0.45 to 1.41)	30 fewer per 1000 (from 82 fewer to 61 more)	⊕OOO VERY LOW	CRITICAL
Persistence of bacteriuria - other antibiotics												
8[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	15/74 (20.3%)	8/63 (12.7%)	RR 1.72 (0.78 to 3.80)	91 more per 1000 (from 28 fewer to 356 more)	⊕⊕OO LOW	CRITICAL
Recurrence of urinary tract infection - sulphonamide containing antibiotics												
9[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	38/172 (22.1%)	33/155 (21.3%)	RR 0.96 (0.64 to 1.44)	9 fewer per 1000 (from 77 fewer to 94 more)	⊕OOO VERY LOW	CRITICAL
Recurrence of urinary tract infection - other antibiotics												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short duration	Standard duration	Relative (95% CI)	Absolute		
9[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	22/75 (29.3%)	22/68 (32.4%)	RR 0.93 (0.53 to 1.61)	23 fewer per 1000 (from 152 fewer to 197 more)	⊕OOO VERY LOW	CRITICAL
Persistence of bacteriuria and urinary tract imaging - Urinary tract infection with abnormal imaging												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	11/33 (33.3%)	13/27 (48.1%)	RR 0.71 (0.38 to 1.32)	140 fewer per 1000 (from 299 fewer to 154 more)	⊕OOO VERY LOW	CRITICAL
Persistence of bacteriuria and urinary tract imaging - Urinary tract infection with normal imaging												
2[1]	randomised trials	serious[2]	very serious[5]	no serious indirectness	very serious[3]	none	9/56 (16.1%)	8/38 (21.1%)	RR 0.99 (0.12 to 8.56)	2 fewer per 1000 (from 185 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Recurrence of urinary tract infection and urinary tract imaging - urinary tract infection with abnormal imaging												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	very serious[3]	none	1/7 (14.3%)	3/5 (60%)	RR 0.24 (0.03 to 1.67)	456 fewer per 1000 (from 582 fewer to 402 more)	⊕OOO VERY LOW	CRITICAL
Recurrence of urinary tract infection and urinary tract imaging - urinary tract infection with normal imaging												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	very serious[3]	none	1/24 (4.2%)	1/34 (2.9%)	RR 1.42 (0.09 to 21.55)	12 more per 1000 (from 27 fewer to 604 more)	⊕OOO VERY LOW	CRITICAL
Persistent bacteriuria: resistance to antibiotic												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[6]	none	8/18 (44.4%)	14/18 (77.8%)	RR 0.57 (0.32 to 1.01)	334 fewer per 1000 (from 529 fewer to 8 more)	⊕⊕⊕O MODERATE	CRITICAL
Recurrence of urinary tract infection: resistance to antibiotic												
3[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/28 (10.7%)	6/18 (33.3%)	RR 0.39 (0.12 to 1.29)	203 fewer per 1000 (from 293 fewer to 97 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI – confidence interval; RR – risk ratio

[1] Michael et al. 2003
[2] Downgraded 1 level - majority of evidence was rated unclear risk of bias by study authors
[3] Downgraded 2 levels – at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[4] Downgraded 1 level - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with short duration antibiotics
[5] Downgraded 2 levels - heterogeneity > 50%
[6] Downgraded 1 level - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with standard duration antibiotics

Appendix I: Studies not prioritised

Study reference	Reason for not prioritised
Angelescu Konstanze, Nussbaumer-Streit Barbara, Sieben Wiebke, Scheibler Fulop, and Gartlehner Gerald (2016) Benefits and harms of screening for and treatment of asymptomatic bacteriuria in pregnancy: a systematic review. BMC pregnancy and childbirth 16(1), 336	A higher quality systematic review has been prioritised (Smaill et al. 2015)
Bayrak Omer, Cimentepe Ersin, Inegol Ilknur, Atmaca Ali Fuat, Duvan Candan Iltemir, Koc Akif, and Turhan Nilgun Ozturk (2007) Is single-dose fosfomycin trometamol a good alternative for asymptomatic bacteriuria in the second trimester of pregnancy?. International urogynecology journal and pelvic floor dysfunction 18(5), 525-9	RCT included in a systematic review that has been prioritised (Falagas et al. 2010)
Bryce Ashley, Hay Alastair D, Lane Isabel F, Thornton Hannah V, Wootton Mandy, and Costelloe Ceire (2016) Global prevalence of antibiotic resistance in paediatric urinary tract infections caused by Escherichia coli and association with routine use of antibiotics in primary care: systematic review and meta-analysis. BMJ (Clinical research ed.) 352, i939	Lower quality systematic review (includes observational studies)
Cai Tommaso, Mazzoli Sandra, Mondaini Nicola, Meacci Francesca, Nesi Gabriella, D'Elia Carolina, Malossini Gianni, Boddi Vieri, and Bartoletti Riccardo (2012) The role of asymptomatic bacteriuria in young women with recurrent urinary tract infections: to treat or not to treat?. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 55(6), 771-7	RCT included in a systematic review that has been prioritised (Zalmanovici-Trestioreanu et al. 2015)
Cai Tommaso, Nesi Gabriella, Mazzoli Sandra, Meacci Francesca, Lanzafame Paolo, Caciagli Patrizio, Mereu Liliana, Tateo Saverio, Malossini Gianni, Selli Cesare, and Bartoletti Riccardo (2015) Asymptomatic bacteriuria treatment is associated with a higher prevalence of antibiotic resistant strains in women with urinary tract infections. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 61(11), 1655-61	A systematic review has been prioritised on study type as higher quality evidence, over this RCT (Falagas et al. 2009)
Ceran Nurgul, Mert Duygu, Kocdogan Funda Yuksel, Erdem Ilknur, Adalati Riza, Ozyurek Seyfi, and Goktas Pasa (2010) A randomized comparative study of single-dose fosfomycin and 5-day ciprofloxacin in female patients with uncomplicated lower urinary tract infections. Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy 16(6), 424-30	A systematic review has been prioritised on study type as higher quality evidence, over this RCT (Falagas et al. 2010)
Costelloe Ceire, Metcalfe Chris, Lovering Andrew, Mant David, and Hay Alastair D (2010) Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. BMJ (Clinical research ed.) 340, c2096	Lower quality systematic review (includes observational studies)
Dante G, Pedrielli G, Annessi E, and Facchinetti F (2013) Herb remedies during pregnancy: a systematic review of controlled clinical trials. The journal of maternal-fetal & neonatal medicine : the official journal of the European	No or fewer critical outcomes reported compared with prioritised RCTs

Study reference	Reason for not prioritised
Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, and the International Society of Perinatal Obstetricians 26(3), 306-12	
de Bont , Eefje G P. M, Alink Marleen, Falkenberg Famke C. J, Dinant Geert-Jan, and Cals Jochen W. L (2015) Patient information leaflets to reduce antibiotic use and reconsultation rates in general practice: a systematic review. BMJ open 5(6), e007612	No or fewer critical outcomes reported compared with prioritised RCT
Dull Ryan B, Friedman Stacey K, Risoldi Zara M, Rice Eric C, Starlin Richard C, and Destache Christopher J (2014) Antimicrobial treatment of asymptomatic bacteriuria in noncatheterized adults: a systematic review. Pharmacotherapy 34(9), 941-60	A higher quality systematic review has been prioritised (Zalmanovici-Trestioreanu et al. 2010)
Estebanez A, Pascual R, Gil V, Ortiz F, Santibanez M, Perez Barba, and C (2009) Fosfomycin in a single dose versus a 7-day course of amoxicillin-clavulanate for the treatment of asymptomatic bacteriuria during pregnancy. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology 28(12), 1457-64	RCT included in a systematic review that has been prioritised (Falagas et al. 2010)
Falagas Matthew E, Kastoris Antonia C, Kapaskelis Anastasios M, and Karageorgopoulos Drosos E (2010) Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum beta-lactamase producing, Enterobacteriaceae infections: a systematic review. The Lancet. Infectious diseases 10(1), 43-50	A higher quality systematic review has been prioritised (Falagas et al. 2010)
Falagas Matthew E, Lourida Panagiota, Poulikakos Panagiotis, Rafailidis Petros I, and Tansarli Giannoula S (2014) Antibiotic treatment of infections due to carbapenem-resistant Enterobacteriaceae: systematic evaluation of the available evidence. Antibiotics s and chemotherapy 58(2), 654-63	A higher quality systematic review has been prioritised (Falagas et al. 2010)
Fasugba Oyebola, Gardner Anne, Mitchell Brett G, and Mnatzaganian George (2015) Ciprofloxacin resistance in community- and hospital-acquired Escherichia coli urinary tract infections: a systematic review and meta-analysis of observational studies. BMC infectious diseases 15, 545	A higher quality systematic review has been prioritised (Falagas et al. 2009)
Ferry Sven A, Holm Stig E, Stenlund Hans, Lundholm Rolf, and Monsen Tor J (2007) Clinical and bacteriological outcome of different doses and duration of pivmecillinam compared with placebo therapy of uncomplicated lower urinary tract infection in women: the LUTIW project. Scandinavian journal of primary health care 25(1), 49-57	RCT included in a systematic review that has been prioritised (Falagas et al. 2009)
Gupta Kalpana, Hooton Thomas M, Roberts Pacita L, and Stamm Walter E (2007) Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. Archives of internal medicine 167(20), 2207-12	A systematic review has been prioritised on study type as higher quality evidence, over this RCT (Zalmanovici-Trestioreanu et al. 2010)
Haghighi B, Oskuilar H, Nejadi O, Etesam N, Mostafavi H, Alaghehbandan R, and Lari A R (2010) Comparison of 3-day and 7-day ciprofloxacin regimen for the treatment of uncomplicated urinary tract infection in women: A randomized double-blind clinical trial. Iranian Journal of Clinical Infectious Diseases 5(2), 70-74	A systematic review has been prioritised on study type as higher quality evidence, over this RCT (Milo et al. 2005)

Study reference	Reason for not prioritised
Hooton Thomas M, Roberts Pacita L, and Stapleton Ann E (2012) Cefpodoxime vs ciprofloxacin for short-course treatment of acute uncomplicated cystitis: a randomized trial. JAMA 307(6), 583-9	A systematic review has been prioritised on study type as higher quality evidence, over this RCT (Zalmanovici-Trestioreanu et al. 2010)
Huttner Angela, Verhaegh Els M, Harbarth Stephan, Muller Anouk E, Theuretzbacher Ursula, and Mouton Johan W (2015) Nitrofurantoin revisited: a systematic review and meta-analysis of controlled trials. The Journal of antimicrobial chemotherapy 70(9), 2456-64	A higher quality systematic review has been prioritised (Zalmanovici-Trestioreanu et al. 2010)
Jepson R G, Mihaljevic L, and Craig J C (2009) Cranberries for treating urinary tract infections. Cochrane Database of Systematic Reviews (4), no pagination	No RCTs met the systematic review inclusion criteria
Knottnerus Bart J, Grigoryan Larissa, Geerlings Suzanne E, Moll van Charante, Eric P, Verheij Theo J. M, Kessels Alphons G. H, ter Riet, and Gerben (2012) Comparative effectiveness of antibiotics for uncomplicated urinary tract infections: network meta-analysis of randomized trials. Family practice 29(6), 659-70	A systematic review has been prioritised on study type over this network meta-analysis (Zalmanovici-Trestioreanu et al. 2010)
Lumbiganon Pisake, Villar Jose, Laopaiboon Malinee, Widmer Mariana, Thinkhamrop Jadsada, Carroli Guillermo, Duc Vy, Nguyen , Mignini Luciano, Festin Mario, Prasertcharoensuk Witoon, Limpongsanurak Sompop, Liabsuetrakul Tippawan, Sirivatanapa Pannee, World Health Organization Asymptomatic Bacteriuria Trial, and Group (2009) One-day compared with 7-day nitrofurantoin for asymptomatic bacteriuria in pregnancy: a randomized controlled trial. Obstetrics and gynecology 113(2 Pt 1), 339-45	RCT included in a systematic review that has been prioritised (Widmer et al. 2015)
Madden Gregory R, Argraves Stephanie M, Van Ness, Peter H, and Juthani-Mehta Manisha (2015) Antibiotic susceptibility of urinary isolates in nursing home residents consuming cranberry capsules versus placebo. Infection control and hospital epidemiology 36(3), 356-7	No or fewer critical outcomes reported compared with prioritised RCTs
O'Kane Dermot B, Dave Sameer K, Gore Neel, Patel Farhaan, Hoffmann Tammy C, Trill Jeanne L, Del Mar , and Chris B (2016) Urinary alkalisation for symptomatic uncomplicated urinary tract infection in women. The Cochrane database of systematic reviews 4, CD010745	No RCTs met the systematic review inclusion criteria
Usta Taner A, Dogan Ozgur, Ates Ugur, Yucel Burak, Onar Zehra, and Kaya Erdal (2011) Comparison of single-dose and multiple-dose antibiotics for lower urinary tract infection in pregnancy. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 114(3), 229-33	A systematic review has been prioritised on study type as higher quality evidence, over this RCT (Widmer et al. 2015)
Vachhani Arpit Vallabhbhai, Barvaliya Manish, Naik Viren, Jha Pramod, and Tripathi Chandrabhanu (2015) Effectiveness and tolerability of short course co-trimoxazole, norfloxacin and levofloxacin in bacteriological cure of uncomplicated urinary tract infection in outpatient setting. An open label, parallel group, randomized controlled trial. Le infezioni in medicina : rivista periodica di	A systematic review has been prioritised on study type as higher quality evidence, over this RCT (Zalmanovici-Trestioreanu et al. 2010)

Study reference	Reason for not prioritised
eziologia, epidemiologia, diagnostica, and clinica e terapia delle patologie infettive 23(2), 155-60	

Appendix J: Excluded studies

Study reference	Reason for exclusion
Amador-Mulero L, Santiago Cb, Ferreiro-Garcia C, Fontan-Azpeitia M, Garcia-Diaz Mj, Garcia-Trabajo E, and Lorenzo-Frades R (2014) Effectiveness of red cranberries ingestion on urinary tract infections in pregnant women. [Spanish]. Matronas Profesion 15(2), 50-55	Non-English Language
Anonymous (2009) Empirical treatment of uncomplicated urinary tract infections (UTI) may be appropriate in some women. Drugs and Therapy Perspectives 25(2), 16-19	Abstract only
Anonymous (2012) Cranberry juice does not reduce urinary-tract infections. Australian Journal of Pharmacy 93(1102), 75	Abstract only
Anonymous (2012) Cranberry-containing products prevent urinary tract infections. Journal of the National Medical Association 104(9-10), 470	Abstract only
Anonymous (2013) Cranberries for preventing urinary tract infections (updated review). Prescriber 24(4), 20-20	Abstract only
Anonymous (2013) The Cochrane Database of Systematic Reviews - Issue 10 2013. Journal of Evidence-Based Medicine 6(4), 305-306	Not a clinical study
Anonymous (2016) Can ibuprofen reduce antibiotic prescriptions for uncomplicated UTIs?. Drug and Therapeutics Bulletin 54(4), 41	Abstract only
Anonymous (2016) Ibuprofen could provide alternative to antibiotics for uncomplicated utis. Clinical Pharmacist 8(2), no pagination	Not a clinical study
Aras Bekir, Kalfazade Nadir, Tugcu Volkan, Kemahli Eray, Ozbay Bedi, Polat Hakan, and Tasci Ali Ihsan (2008) Can lemon juice be an alternative to potassium citrate in the treatment of urinary calcium stones in patients with hypocitraturia? A prospective randomized study. Urological research 36(6), 313-7	Not relevant population
Arpit V, Jeet P, Viren N, Pramod J, and Chandrabhanu T (2014) Comparative study of cotrimoxazole versus norfloxacin versus levofloxacin in uncomplicated cases of lower urinary tract infection in adult patients at tertiary care hospital: A randomized controlled parallel group open label trial. Indian journal of pharmacology 46(7 suppl. 1), S9	Abstract only
Ayrim Aa, Turhan No, and Kafali H (2010) Single dose fosfomycin trometamol versus 5 day amoxicillin-clavulanate regimen for treatment of lower urinary tract infections in pregnant women. Turk Jinekoloji ve Obstetrik Dernegi Dergisi 7, 139	Abstract only
Bai Nan, Sun Chunguang, Wang Jin, Cai Yun, Liang Beibei, Zhang Lei, Liu Youning, and Wang Rui (2014) Ertapenem versus ceftriaxone for the treatment of complicated infections: a meta-analysis of randomized controlled trials. Chinese medical journal 127(6), 1118-25	Not relevant population
Barrons Robert, and Tassone Dan (2008) Use of Lactobacillus probiotics for bacterial genitourinary infections in women: a review. Clinical therapeutics 30(3), 453-68	Not a clinical study
Bates J, Thomas-Jones E, Kirby N, Pickles T, Thomas R, Bongard E, Gal M, Little P, Verheij T, Llor C, Cohen D, Francis N,	Abstract only

Study reference	Reason for exclusion
Hood K, and Butler C (2013) Effects of an optimised POCT guided diagnostic and treatment strategy for symptoms of uncomplicated UTI on use of appropriate antibiotics and uptake into primary care practice. Trials 14, 139dummy	
Beerepoot Maj, Ter Riet G, Nys S, Wal Wm, Borgie Cajm, Reijke Tm, Prins Jm, Koeijers J, Verbon A, Stobberingh Ee, and Geerlings Se (2013) Lactobacilli versus antibiotics to prevent urinary tract infections: A randomized, double-blind, noninferiority trial in postmenopausal women. [Dutch]. Nederlands tijdschrift voor geneeskunde 157(10),	Non-English language
Bjerrum Lars, Gahrn-Hansen Bente, and Grinsted Per (2009) Pivmecillinam versus sulfamethizole for short-term treatment of uncomplicated acute cystitis in general practice: a randomized controlled trial. Scandinavian journal of primary health care 27(1), 6-11	Does not reflect usual UK practice
Booth J, Agnew R, Tannenbaum C, and Hawthorne A (2013) Continence promotion workshop interventions for self-management of lower urinary tract symptoms in community living older women: A mixed methods pilot study. Neurourology and urodynamics 32(6), 794-5	Abstract only
Brown Christian T, Yap Tet, Cromwell David A, Rixon Lorna, Steed Liz, Mulligan Kathleen, Mundy Anthony, Newman Stanton P, van der Meulen , Jan , and Emberton Mark (2007) Self management for men with lower urinary tract symptoms: randomised controlled trial. BMJ (Clinical research ed.) 334(7583), 25	Duplicate reference
Brown Christian T, and Emberton Mark (2009) Self-management for men with lower urinary tract symptoms. Current urology reports 10(4), 261-6	Not relevant population
Chahine Elias B, Sourial Mariette, and Ortiz Raquel (2015) Ceftazidime/Avibactam: A New Antibiotic for Gram-Negative Infections. The Consultant pharmacist : the journal of the American Society of Consultant Pharmacists 30(12), 695-705	Poor relevance against search terms (population)
Coats Josh, Rae Nikolas, and Nathwani Dilip (2013) What is the evidence for the duration of antibiotic therapy in Gram-negative bacteraemia caused by urinary tract infection? A systematic review of the literature. Journal of global antimicrobial resistance 1(1), 39-42	Poor relevance against search terms (population)
Davis N F, Burke J P, Redmond E J, Elamin S, Brady C M, and Flood H D (2015) Trigonal versus extratrigonal botulinum toxin-A: a systematic review and meta-analysis of efficacy and adverse events. International urogynecology journal 26(3), 313-9	Not relevant population
DeAlleaume L, and Tweed E M (2006) When are empiric antibiotics appropriate for urinary tract infection symptoms? Journal of Family Practice 55(4), 338-342	Not a clinical study
Dovgan E, Rafalskiy V, Galkin V, and Malev I (2011) Cefixime vs. ciprofloxacin for short-term therapy of acute uncomplicated lower urinary tract infections in women. Basic & clinical pharmacology & toxicology 109, 127-8	Inappropriate or unclear methodology
Dovgan E, Rafalskiy V, Galkin V, and Malev I (2011) Efficacy and safety of 5-day therapy with cefixime versus ciprofloxacin for uncomplicated urinary tract infections in women: Randomised, Controlled study. Clinical microbiology and infection 17, S443	Abstract only

Study reference	Reason for exclusion
Drozdov Daniel, Schwarz Stefanie, Kutz Alexander, Grolimund Eva, Rast Anna Christina, Steiner Deborah, Regez Katharina, Schild Ursula, Guglielmetti Merih, Conca Antoinette, Reutlinger Barbara, Ottiger Cornelia, Buchkremer Florian, Haubitz Sebastian, Blum Claudine, Huber Andreas, Buergi Ulrich, Schuetz Philipp, Bock Andreas, Fux Christoph Andreas, Mueller Beat, and Albrich Werner Christian (2015) Procalcitonin and pyuria-based algorithm reduces antibiotic use in urinary tract infections: a randomized controlled trial. BMC medicine 13, 104	Does not reflect usual UK practice
Duane Sinead, Callan Aoife, Galvin Sandra, Murphy Andrew W, Domegan Christine, O'Shea Eamon, Cormican Martin, Bennett Kathleen, O'Donnell Martin, and Vellinga Akke (2013) Supporting the improvement and management of prescribing for urinary tract infections (SIMPle): protocol for a cluster randomized trial. Trials 14, 441	Not a clinical study
El Sakka, N , and Gould I M (2016) Role of old antibiotics in the management of urinary tract infection. Expert Review of Clinical Pharmacology 9(8), 1047-1056	Not a clinical study
Essadi F, and Elmehashi Mo (2010) Efficacy of cranberry juice for the prevention of urinary tract infections in pregnancy. Journal of maternal-fetal & neonatal medicine 23, 378	Abstract only
Faine B, Bell G, and Denning G (2011) Addressing antibiotic resistance: A randomized, controlled trial comparing short-course nitrofurantion versus ciprofloxacin for the treatment of acute uncomplicated cystitis. Annals of emergency medicine 58(4 suppl. 1), S220	Abstract only
Faine B, Bell G, and Denning G (2012) A pilot comparison of the efficacy of a 3-day course of nitrofurantoin versus 3-day ciprofloxacin in females with uncomplicated bacterial cystitis in the emergency department. Annals of emergency medicine 60(4 suppl. 1), S46	Abstract only
Fanos V, Atzei A, Zaffanello M, Piras A, and Cataldi L (2006) Cranberry and prevention of urinary tract infections in children. Journal of chemotherapy (Florence, and Italy) 18 Spec no 3, 21-4	Publication/study type (not an RCT)
Feld Leonard G, and Mattoo Tej K (2010) Urinary tract infections and vesicoureteral reflux in infants and children. Pediatrics in review 31(11), 451-63	Publication/study type (not an RCT)
Fitzgerald A, Lee C W, and Mori R (2007) Antibiotics for treating uncomplicated urinary tract infection in children. Cochrane Database of Systematic Reviews (4), no pagination	Publication/study type (comment only)
Flokas Myrto Eleni, Detsis Marios, Alevizakos Michail, and Mylonakis Eleftherios (2016) Prevalence of ESBL-producing Enterobacteriaceae in paediatric urinary tract infections: A systematic review and meta-analysis. The Journal of infection 73(6), 547-557	Publication/study type (observational)
Francis C, Mumford M, Strand M L, Moore E S, and Strand E A (2013) Timing of prophylactic antibiotic at cesarean section: a double-blinded, randomized trial. Journal of perinatology : official journal of the California Perinatal Association 33(10), 759-62	Poor relevance against search terms (population)
French L (2006) Urinary tract infection in women. Advanced Studies in Medicine 6(1), 24-29	Publication/study type (not an RCT)
Gagyor Ildiko, Haasenritter Jorg, Bleidorn Jutta, McIsaac Warren, Schmiemann Guido, Hummers-Pradier Eva, and Himmel Wolfgang (2016) Predicting antibiotic prescription after	Does not reflect usual UK practice

Study reference	Reason for exclusion
symptomatic treatment for urinary tract infection: development of a model using data from an RCT in general practice. The British journal of general practice : the journal of the Royal College of General Practitioners 66(645), e234-40	
Gagyor Ildiko, Hummers-Pradier Eva, Kochen Michael M, Schmiemann Guido, Wegscheider Karl, and Bleidorn Jutta (2012) Immediate versus conditional treatment of uncomplicated urinary tract infection - a randomized-controlled comparative effectiveness study in general practices. BMC infectious diseases 12, 146	Abstract only
Galkin Vv, Malev Iv, Dovgan Ev, Kozlov Sn, and Rafal'ski Vv (2011) [Efficacy and safety of cefixim and ciprofloxacin in acute cystitis (a multicenter randomized trial)]. Urologii?a? (Moscow, and Russia : 1999) (1), 13-6	Non-English language
Gallego-Vilar Daniel, Garcia-Fadrique Gonzalo, Povo-Martin Ivan, Salvador-Marin Manuel, and Gallego-Gomez Juan (2013) Maintenance of the response to dimethyl sulfoxide treatment using hyperbaric oxygen in interstitial cystitis/painful bladder syndrome: a prospective, randomized, comparative study. Urologia internationalis 90(4), 411-6	Poor relevance against search terms (population)
Garber M, Alverson B, and Burke M (2011) Should i prescribe antibiotics after draining an abscess in a young child? Should i pack his wound? Do i prescribe decolonizing measures? - Should i routinely prescribe antibiotic prophylaxis at discharge after UTI? - IV antibiotics in febrile UTI: How long is long enough? - Should i avoid steroids in wheezing patients whom i suspect also have bacterial pneumonia?. Hospital Pediatrics 1(1), 56-60	Not a relevant study
Garcia-Perdomo Herney Andres, Jimenez-Mejias Eladio, and Lopez-Ramos Hugo (2015) Efficacy of antibiotic prophylaxis in cystoscopy to prevent urinary tract infection: a systematic review and meta-analysis. International braz j urol : official journal of the Brazilian Society of Urology 41(3), 412-424	Poor relevance against search terms (intervention)
Giamarellos-Bourboulis Evangelos J, Mylona Vassiliki, Antonopoulou Anastasia, Tsangaris Iraklis, Koutelidakis Ioannis, Marioli Androniki, Raftogiannis Maria, Kopterides Petros, Lymberopoulou Korina, Mouktaroudi Maria, Papageorgiou Christos, Papaziogas Basileios, Georgopoulou Antonia-Panagiota, Tsaganos Thomas, Papadomichelakis Evangelos, Gogos Charalambos, Ladas Malvina, Savva Athina, Pelekanou Aimilia, Baziaka Fotini, Koutoukas Pantelis, Kanni Theodora, Spyridaki Aikaterini, Maniatis Nikolaos, Pelekanos Nikolaos, Kotsaki Antigone, Vaki Ilia, Douzinas Emmanuel E, Koratzanis Georgios, and Armaganidis Apostolos (2014) Effect of clarithromycin in patients with suspected Gram-negative sepsis: results of a randomized controlled trial. The Journal of antimicrobial chemotherapy 69(4), 1111-8	Not a relevant study
Gillespie Paddy, Callan Aoife, O'Shea Eamon, Duane Sinead, Murphy Andrew W, Domegan Christine, Galvin Sandra, and Vellinga Akke (2016) The cost effectiveness of the SIMPle intervention to improve antimicrobial prescribing for urinary tract infection in primary care. Journal of public health (Oxford, and England) ,	Not a clinical study
Goldberg Ori, Moretti Myla, Levy Amalia, and Koren Gideon (2015) Exposure to nitrofurantoin during early pregnancy and congenital malformations: a systematic review and meta-analysis.	Not a systematic review of RCTs

Study reference	Reason for exclusion
Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC 37(2), 150-6	
Grabein B, Graninger W, Rodriguez Bano, J , Dinh A, and Liesenfeld D B (2016) Intravenous fosfomycin-back to the future. Systematic review and meta-analysis of the clinical literature. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases ,	Not a relevant study
Green H, Rahamimov R, Gafter U, Leibovitci L, and Paul M (2011) Antibiotic prophylaxis for urinary tract infections in renal transplant recipients: a systematic review and meta-analysis. Transplant infectious disease : an official journal of the Transplantation Society 13(5), 441-7	Poor relevance against search terms (population)
Grigoryan Larissa, Trautner Barbara W, and Gupta Kalpana (2014) Diagnosis and management of urinary tract infections in the outpatient setting: a review. JAMA 312(16), 1677-84	Not a clinical study
Guirguis-Blake Janelle (2008) Cranberry products for treatment of urinary tract infection. American family physician 78(3), 332-3	Publication/study type (comment only)
Gupta A (2007) Cranberry and Prevention of UTI - A Comprehensive Approach. http://www.clinicaltrials.gov ,	Publication/study type (comment only)
Hamasuna Ryoichi, Tanaka Kazushi, Hayami Hiroshi, Yasuda Mitsuru, Takahashi Satoshi, Kobayashi Kanao, Kiyota Hiroshi, Yamamoto Shingo, Arakawa Soichi, Matsumoto Tetsuro, Japanese Research Group for, and U T I (2014) Treatment of acute uncomplicated cystitis with faropenem for 3 days versus 7 days: multicentre, randomized, open-label, controlled trial. The Journal of antimicrobial chemotherapy 69(6), 1675-80	Does not reflect usual UK practice
Handeland Maria, Grude Nils, Torp Torfinn, and Slimestad Rune (2014) Black chokeberry juice (Aronia melanocarpa) reduces incidences of urinary tract infection among nursing home residents in the long term--a pilot study. Nutrition research (New York, and N.Y.) 34(6), 518-25	Does not reflect usual UK practice
Harmsen Mirjam, Adang Eddy M. M, Wolters Rene J, van der Wouden , Johannes C, Grol Richard P. T. M, and Wensing Michel (2009) Management of childhood urinary tract infections: an economic modeling study. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 12(4), 466-72	Not a relevant study
Heidari Bateni, Zhoobin , Shahrokh Hossein, Salimi Hormoz, Safari Hossein, Tabatabai Meghdad, and Saedi Dariush (2014) Single-dose versus multiple-dose ciprofloxacin plus metronidazole prophylaxis in transrectal ultrasound-guided biopsy of the prostate: a randomized controlled trial. Acta medica Iranica 52(9), 664-70	Not a relevant study
Hidalgo Jose A, Vinluan Celeste M, and Antony Nishaal (2016) Ceftazidime/avibactam: a novel cephalosporin/nonbeta-lactam beta-lactamase inhibitor for the treatment of complicated urinary tract infections and complicated intra-abdominal infections. Drug design, and development and therapy 10, 2379-86	Not a clinical study
Higgs R (2010) Pediatrics: Modest effect of prophylactic antibiotics on UTI in children. Nature Reviews Urology 7(1), 5	Not a clinical study
Holm Anne, Cordoba Gloria, Sorensen Tina Moller, Jessen Lisbeth Rem, Siersma Volkert, and Bjerrum Lars (2015) Point of care susceptibility testing in primary care - does it lead to a more	Publication/study type (literature review)

Study reference	Reason for exclusion
appropriate prescription of antibiotics in patients with uncomplicated urinary tract infections? Protocol for a randomized controlled trial. BMC family practice 16, 106	
Hong Mai-Chi, Hsu Donald I, and Bounthavong Mark (2013) Ceftolozane/tazobactam: a novel antipseudomonal cephalosporin and beta-lactamase-inhibitor combination. Infection and drug resistance 6, 215-23	Not a relevant study
Howell A (2011) Cranberry works for UTI'S. Australian Journal of Pharmacy 92(1094), 10	Publication/study type (commentary)
Howell Amy, Souza Dan, Roller Marc, and Fromentin Emilie (2015) Comparison of the Anti-Adhesion Activity of Three Different Cranberry Extracts on Uropathogenic P-fimbriated Escherichia coli: a Randomized, Double-blind, Placebo Controlled, Ex Vivo, Acute Study. Natural product communications 10(7), 1215-8	Not a relevant study
Huang Pc, and Yang Hj (2007) A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Effect of Adjuvant Treatment With Compound Cranberry Extract Tablets (UmayC) in Acute Bacterial Cystitis. http://www.clinicaltrials.gov ,	Publication/study type (no data reported)
Jansaker Filip, Frimodt-Moller Niels, Bjerrum Lars, Dahl Knudsen, and Jenny (2016) The efficacy of pivmecillinam: 3 days or 5 days t.i.d against community acquired uncomplicated lower urinary tract infections - a randomized, double-blinded, placebo-controlled clinical trial study protocol. BMC infectious diseases 16(1), 727	Publication/study type (commentary)
Jenkins Timothy C, Irwin Amy, Coombs Letoynia, Dealleaume Lauren, Ross Stephen E, Rozwadowski Jeanne, Webster Brian, Dickinson L Miriam, Sabel Allison L, Mackenzie Thomas D, West David R, and Price Connie S (2013) Effects of clinical pathways for common outpatient infections on antibiotic prescribing. The American journal of medicine 126(4), 327-335.e12	Not relevant study
Jepson R G, and Craig J C (2008) Cranberries for preventing urinary tract infections. The Cochrane database of systematic reviews (1), CD001321	Updated systematic review available
Jepson Ruth G, and Craig Jonathan C (2007) A systematic review of the evidence for cranberries and blueberries in UTI prevention. Molecular nutrition & food research 51(6), 738-45	Updated systematic review available
Jia Bei, Lu Ping, Huang Wenxiang, Li Chongzhi, Huang Ailong, Zhou Xiangdong, Zhang Weili, Wu Guoming, and Zhang Genfu (2010) A multicenter, randomized controlled clinical study on biapenem and imipenem/cilastatin injection in the treatment of respiratory and urinary tract infections. Chemotherapy 56(4), 285-90	Does not reflect usual UK practice
Kartal Elif Doyuk, Yenilmez Aydin, Kiremitci Abdurrahman, Meric Hatice, Kale Metin, and Usluer Gaye (2006) Effectiveness of ciprofloxacin prophylaxis in preventing bacteriuria caused by urodynamic study: a blind, randomized study of 192 patients. Urology 67(6), 1149-53	Not a relevant study
Katz A, Efros M, Kaminetsky J, Herrlinger K, Chirouzes D, and Ceddia M (2014) A green and black tea extract benefits urological health in men with lower urinary tract symptoms. Therapeutic Advances in Urology 6(3), 89-96	Not a relevant study
Kawada Y, Ishihara S, Matsui T, Tsugawa M, Matsumoto T, Watanabe K, and Nakashima M (2008) [Comparative study on	Abstract only

Study reference	Reason for exclusion
sitafloxacin and levofloxacin in complicated urinary tract infections]. Japanese Journal of Chemotherapy 56(Suppl 1), 81-91	
Kazemier Bm, Koningstein Fn, Schneeberger C, Ott A, Bossuyt Pm, Miranda E, Vogelvang Te, Verhoeven Cjm, Langenveld J, Woiski M, Oudijk Ma, Reijnders Fjl, Ven Ajem, Vlegels Mtw, Kuiper Pn, Feiertag N, Mol Bwj, Groot Cjm, and Geerlings Se (2014) Maternal and neonatal consequences of asymptomatic bacteriuria in pregnancy-the ASB trial. Reproductive sciences (Thousand Oaks, and Calif.) 21(3 suppl. 1), 255a	Abstract only
Kazemier Brenda M, Schneeberger Caroline, De Miranda , Esteriek , Van Wassenaer , Aleid , Bossuyt Patrick M, Vogelvang Tatjana E, Reijnders Frans J. L, Delemarre Friso M. C, Verhoeven Corine J. M, Oudijk Martijn A, Van Der Ven , Jeanine A, Kuiper Petra N, Feiertag Nicolette, Ott Alewijn, De Groot , Christianne J M, Mol Ben Willem J, and Geerlings Suzanne E (2012) Costs and effects of screening and treating low risk women with a singleton pregnancy for asymptomatic bacteriuria, the ASB study. BMC pregnancy and childbirth 12, 52	Publication/study type (protocol)
Kim Jae Heon, Sun Hwa Yeon, Kim Tae Hyong, Shim Sung Ryul, Doo Seung Whan, Yang Won Jae, Lee Eun Jung, and Song Yun Seob (2016) Prevalence of antibiotic susceptibility and resistance of Escherichia coli in acute uncomplicated cystitis in Korea: Systematic review and meta-analysis. Medicine 95(36), e4663	Abstract only
Lavin-Alconero L, Rosso-Fernandez Cm, Barriga-Ribera A, Sojo-Dorado J, Palacios Z, Lopez-Hernandez I, Merino V, Camean M, Pascual A, and Rodriguez-Bano J (2015) Fosfomycin versus meropenem in bacteremic urinary tract infections caused by extended-spectrum betalactamase producing escherichia coli (Esbl-Ec): Forest study. Clinical therapeutics 37(8 suppl. 1), e34-e35	Abstract only
Larcombe James (2007) Urinary tract infection in children. BMJ clinical evidence 2007,	Publication/study type (commentary)
Lee Anne C. C, Quaiyum Mohammad A, Mullany Luke C, Mitra Dipak K, Labrique Alain, Ahmed Parvez, Uddin Jamal, Rafiqullah Iftekhar, DasGupta Sushil, Mahmud Arif, Koumans Emilia H, Christian Parul, Saha Samir, Baqui Abdullah H, Projahnmo Study, and Group (2015) Screening and treatment of maternal genitourinary tract infections in early pregnancy to prevent preterm birth in rural Sylhet, Bangladesh: a cluster randomized trial. BMC pregnancy and childbirth 15, 326	Not a relevant study
Letouzey V, Ulrich D, Demattei C, Alonso S, Huberlant S, Lavigne J P, de Tayrac , and R (2017) Cranberry capsules to prevent nosocomial urinary tract bacteriuria after pelvic surgery: a randomised controlled trial. BJOG : an international journal of obstetrics and gynaecology ,	Not a relevant study
Liu Y B, Lv X J, Yu R J, Qiu H M, Bai J L, Jiang N, Lin J M, Liu Y J, Yan H Y, Song S D, He P, Guo D Y, and Li X S (2014) Multicenter, double-blind, randomized clinical trial of parenterally administered Cefoselis versus Cefepime for the treatment of acute bacterial infections. European review for medical and pharmacological sciences 18(14), 2006-12	Does not reflect usual UK practice
Mangin D (2013) Review: Cranberry products do not reduce urinary tract infections in susceptible populations. Annals of Internal Medicine 158(10), JC11	Publication/study type (literature review)

Study reference	Reason for exclusion
Manzano Sergio, Bailey Benoit, Girodias Jean-Bernard, Galetto-Lacour Annick, Cousineau Jocelyne, and Delvin Edgard (2010) Impact of procalcitonin on the management of children aged 1 to 36 months presenting with fever without source: a randomized controlled trial. The American journal of emergency medicine 28(6), 647-53	Not a relevant study
Marild Staffan, Jodal Ulf, and Sandberg Torsten (2009) Ceftibuten versus trimethoprim-sulfamethoxazole for oral treatment of febrile urinary tract infection in children. Pediatric nephrology (Berlin, and Germany) 24(3), 521-6	Does not reflect usual UK practice
Matthews S James, and Lancaster Jason W (2011) Urinary tract infections in the elderly population. The American journal of geriatric pharmacotherapy 9(5), 286-309	Publication/study type (literature review)
Mayor S (2016) Cranberry capsules do not reduce urinary tract infections in older women, study finds. BMJ (Online) 355, no pagination	Abstract only
Mirone V, Fusco F, Taglialatela D, Verze P, Di Vito , C , Lotti T, Imbimbo C, Emeron Study, and Group (2009) Efficacy and safety of ciprofloxacin XR 1000 mg once daily versus ciprofloxacin 500 mg twice daily in the treatment of complicated urinary tract infections. Journal of chemotherapy (Florence, and Italy) 21(6), 651-60	Not relevant population
Mosley J F, Smith L L, Parke C K, Brown J A, Wilson A L, and Gibbs L V (2016) Ceftazidime-avibactam (Avycaz): For the treatment of complicated intra-abdominal and urinary tract infections. P and T 41(8), 479-483	Not a relevant study
Mospan Geoffrey A, and Wargo Kurt A (2016) 5-Day versus 10-Day Course of Fluoroquinolones in Outpatient Males with a Urinary Tract Infection (UTI). Journal of the American Board of Family Medicine : JABFM 29(6), 654-662	Not relevant population
Mostafa Safinaz, and Miller Brian J (2014) Antibiotic-associated psychosis during treatment of urinary tract infections: a systematic review. Journal of clinical psychopharmacology 34(4), 483-90	Publication/study type (systematic review includes observational studies)
Naber K G, Llorens L, Kaniga K, Kotey P, Hedrich D, and Redman R (2009) Intravenous doripenem at 500 milligrams versus levofloxacin at 250 milligrams, with an option to switch to oral therapy, for treatment of complicated lower urinary tract infection and pyelonephritis. Antibiotics s and chemotherapy 53(9), 3782-92	Does not reflect usual UK practice
Naber Kg, Niggemann H, and Stein G (2014) Nitroxoline for treatment of uncomplicated UTI: IPD meta-analysis of four controlled clinical studies. International journal of infectious diseases 21, 200-1	Abstract only
Nct (2009) Pilot study: Dosing study of cranberry capsules for the prevention of bacteriuria in nursing home residents. clinicaltrials.gov/ct2/show/NCT01033383 ,	Published study included in a prioritised systematic review
Nickavar A, and Sotoudeh K (2011) Treatment and prophylaxis in pediatric urinary tract infection. International Journal of Preventive Medicine 2(1), 4-9	Publication/study type (commentary)
Nicolle Lindsay, Anderson Peter A. M, Conly John, Mainprize Thomas C, Meuser Jamie, Nickel J Curtis, Senikas Vyta M, and Zhanel George G (2006) Uncomplicated urinary tract infection in women. Current practice and the effect of antibiotic resistance on	Publication/study type (literature review)

Study reference	Reason for exclusion
empiric treatment. Canadian family physician Medecin de famille canadien 52, 612-8	
Norg Roelf J. C, van de Beek, Kees, Portegijs Piet J. M, van Schayck, C P Onno, and Knottnerus J Andre (2006) The effectiveness of a treatment protocol for male lower urinary tract symptoms in general practice: a practical randomised controlled trial. The British journal of general practice : the journal of the Royal College of General Practitioners 56(533), 938-44	Not a relevant study
Opperman E A (2010) Cranberry is not effective for the prevention or treatment of urinary tract infections in individuals with spinal cord injury. Spinal cord 48(6), 451-6	Not a relevant population
Palou J, Angulo Jc, Ramón de Fata F, García-Tello A, González-Enguita C, Boada A, Sanz M, and en representación de los investigadores del ensayo clínico Mone (2013) [Randomized comparative study for the assessment of a new therapeutic schedule of fosfomycin trometamol in postmenopausal women with uncomplicated lower urinary tract infection]. Actas urologicas españolas 37(3), 147-55	Non-English language
Park J, Min K, and Kang D (2007) The efficacy and safety of a once-daily extended-release ciprofloxacin tablet for the empirical treatment of symptomatic uncomplicated cystitis in Korean women. [Korean]. Korean journal of urology 48(1), 35-9	Non-English language
Peng F-Y, Jia B, Tang J, Liu C-W, Huang W-X, Zhang W-L, Hu Z-L, Yan C-S, Wang J-G, Lu X-J, and Jiang N (2008) [A multicenter, randomized controlled, double-blind clinical trial of piperacillin/tazobactam(4:1) in the treatment of bacterial infections]. Chinese Journal of Antibiotics 33(2), 114-20	Non-English language
Pinto-Lopes R, Sousa-Pinto B, and Azevedo L F (2016) Single dose versus multiple dose of antibiotic prophylaxis in caesarean section: a systematic review and meta-analysis. BJOG : an international journal of obstetrics and gynaecology ,	Not a relevant study
Pitsouni Eleni, Alexiou Vangelis, Saridakis Vasilis, Peppas George, and Falagas Matthew E (2009) Does the use of probiotics/synbiotics prevent postoperative infections in patients undergoing abdominal surgery? A meta-analysis of randomized controlled trials. European journal of clinical pharmacology 65(6), 561-70	Not a relevant study
Pohl A (2007) Modes of administration of antibiotics for symptomatic severe urinary tract infections. The Cochrane database of systematic reviews (4), CD003237	Not a relevant population
Price E, Pallett A, Gilbert R D, and Williams C (2010) Microbiological aspects of the UK National Institute for Health and Clinical Excellence (NICE) guidance on urinary tract infection in children. The Journal of antimicrobial chemotherapy 65(5), 836-41	Not a relevant study type (commentary of guidance)
Rafal'ski Vv, Dovgan Ev, Kozyrev IuV, Gustovarova Ta, Khlybova Sv, Novoselova Av, Filippenko Ng, and Likhikh Dg (2013) [The efficacy and safety of cefixime and amoxicillin/clavulanate in the treatment of asymptomatic bacteriuria in pregnant women: a randomized, prospective, multicenter study]. Urologiia? (Moscow, and Russia : 1999) (5), 24, 26-8	Non-English language
Rafalskiy V, Dovgan E, Kozyrev Y, Gustovarova T, Khlybova S, Novoselova A, Filippenko N, and Lichich D (2012) Cefixime vs. amoxicillin/clavulanate in pregnant women with asymptomatic	Abstract only

Study reference	Reason for exclusion
bacteriuria: Multicentre randomised study. Clinical microbiology and infection 18, 425-6	
Rahardjo Harrina E, Tirtayasa Pande M. W, Afriansyah Andika, Parikesit Dyandra, and Akbar Muhammad I (2016) The Effectiveness of a Three Day Course Antibiotic Post-urodynamic Study in Preventing Lower Urinary Tract Infection. Acta medica Indonesiana 48(2), 84-90	Not a relevant study
Ramos Jorge A, Salinas Diego F, Osorio Johanna, and Ruano-Ravina Alberto (2016) Antibiotic prophylaxis and its appropriate timing for urological surgical procedures in patients with asymptomatic bacteriuria: A systematic review. Arab journal of urology 14(3), 234-9	Not a relevant study
Regal Randolph E, Pham Co Q. D, and Bostwick Thomas R (2006) Urinary tract infections in extended care facilities: preventive management strategies. The Consultant pharmacist : the journal of the American Society of Consultant Pharmacists 21(5), 400-9	Publication/study type (literature review)
Reglodi Dora, Kiss Peter, Horvath Gabriella, Lubics Andrea, Laszlo Eszter, Tamas Andrea, Racz Boglarka, and Szakaly Peter (2012) Effects of pituitary adenylate cyclase activating polypeptide in the urinary system, with special emphasis on its protective effects in the kidney. Neuropeptides 46(2), 61-70	Not a relevant study
Rosso-Fernandez Clara, Sojo-Dorado Jesus, Barriga Angel, Lavin-Alconero Lucia, Palacios Zaira, Lopez-Hernandez Inmaculada, Merino Vicente, Camean Manuel, Pascual Alvaro, Rodriguez-Bano Jesus, and Group Forest Study (2015) Fosfomycin versus meropenem in bacteraemic urinary tract infections caused by extended-spectrum beta-lactamase-producing Escherichia coli (FOREST): study protocol for an investigator-driven randomised controlled trial. BMJ open 5(3), e007363	Publication/study type (Study protocol)
Salvatorelli Nicola, Garcia-Larrosa Alejandro, Allegrini Alessandro, and Pavone Daniele (2016) A New Approach to the Treatment of Uncomplicated Cystitis: Results of a Randomized Placebo-Controlled Clinical Trial. Urologia internationalis 97(3), 347-351	Not a relevant intervention
Schaeffer E M (2012) Re: Cefpodoxime vs ciprofloxacin for short-course treatment of acute uncomplicated cystitis: A randomized trial. Journal of Urology 188(4), 1193-1194	Publication/study type (commentary)
Schaeffer E M (2013) Re: Lactobacilli vs antibiotics to prevent urinary tract infections: A randomized, double-blind, noninferiority trial in postmenopausal women. Journal of Urology 189(4), 1332-1333	Publication/study type (commentary)
Schmiemann Guido, Kniehl Eberhardt, Gebhardt Klaus, Matejczyk Martha M, and Hummers-Pradier Eva (2010) The diagnosis of urinary tract infection: a systematic review. Deutsches Arzteblatt international 107(21), 361-7	No relevant outcomes reported
Selekman R E, Allen I E, and Copp H L (2016) Determinants of practice patterns in pediatric UTI management. Journal of pediatric urology 12(5), 308.e1-308.e6	Not a relevant study
Senguttuvan P, and Jigy J (2014) Profile and outcome of pelviureteric junction obstruction. Open Urology and Nephrology Journal 7(1), 67-70	Not a relevant study

Study reference	Reason for exclusion
Senneby Erik, Petersson Ann-Cathrine, and Rasmussen Magnus (2015) Epidemiology and antibiotic susceptibility of aerococci in urinary cultures. Diagnostic microbiology and infectious disease 81(2), 149-51	Not a relevant study
Simoes e Silva, Ana Cristina, and Oliveira Eduardo Araujo (2015) Update on the approach of urinary tract infection in childhood. Jornal de pediatria 91(6 Suppl 1), S2-10	Abstract only
Singh Krishan P, Li Gang, Mitrani-Gold Fanny S, Kurtinecz Milena, Wetherington Jeffrey, Tomayko John F, and Mundy Linda M (2013) Systematic review and meta-analysis of antimicrobial treatment effect estimation in complicated urinary tract infection. Antibiotics s and chemotherapy 57(11), 5284-90	Not a relevant study
Sivathasan Niroshan, and Rakowski Krzysztof R (2011) Microscopy, culture, and sensitive management of uncomplicated urinary tract infections in adults in the primary care setting. Saudi medical journal 32(6), 559-62	Not a clinical study
Souverein D (2017) Effectiveness of fosfomycin versus nitrofurantoin in Dutch risk groups with cystitis: a pilot study (Uri-weg study) - Uri-weg study. Http://apps.who.int/trialsearch/trial2.aspx? Trialid=euctr2015-004297-14-nl ,	Unable to source study
Stamatiou K, Alevizos A, Petrakos G, Lentzas I, Papathanasiou M, Mariolis A, Panagopoulos P, and Sofras F (2007) Study on the efficacy of cefaclor for the treatment of asymptomatic bacteriuria and lower urinary tract infections in pregnant women with a history of hypersensitivity to penicillin. Clinical and experimental obstetrics & gynecology 34(2), 85-7	Inappropriate or unclear methodology
Stothers L, Brown P, Fenster H, Levine M, and Berkowitz J (2016) Dose response of cranberry in the treatment of lower urinary tract infections in women. Journal of urology 195(4 suppl. 1), e355	Abstract only
Sucher Allana J, Chahine Elias B, Cogan Peter, and Fete Matthew (2015) Ceftolozane/Tazobactam: A New Cephalosporin and beta-Lactamase Inhibitor Combination. The Annals of pharmacotherapy 49(9), 1046-56	Not a relevant study
Syahputra Fa, Rahardjo He, Islianti Pi, and Matondang Fa (2016) Efficacy of additional solifenacin succinate therapy for irritative symptoms in females with uncomplicated lower urinary tract infection (SoluTion): A randomized controlled trial. BJU international 117, 5	Abstract only
Thomas J (2011) Cranberry juice fails to prevent recurring urinary tract infections. Australian Journal of Pharmacy 92(1092), 81	Abstract only
Turner David, Little Paul, Raftery James, Turner Sheila, Smith Helen, Rumsby Kate, Mullee Mark, and group Utis (2010) Cost effectiveness of management strategies for urinary tract infections: results from randomised controlled trial. BMJ (Clinical research ed.) 340, c346	Not a relevant study
van den Hout , Wilbert B, Caljouw Monique A. A, Putter Hein, Cools Herman J. M, and Gussekloo Jacobijn (2014) Cost-effectiveness of cranberry capsules to prevent urinary tract infection in long-term care facilities: economic evaluation with a randomized controlled trial. Journal of the American Geriatrics Society 62(1), 111-6	Not a relevant study

Study reference	Reason for exclusion
van Nieuwkoop , Cees , van't Wout, Jan W, Assendelft Willem J. J, Elzevier Henk W, Leyten Eliane M. S, Koster Ted, Wattel-Louis G Hanke, Delfos Nathalie M, Ablij Hans C, Kuijper Ed J, Pander Jan, Blom Jeanet W, Spelt Ida C, van Dissel , and Jaap T (2009) Treatment duration of febrile urinary tract infection (FUTIRST trial): a randomized placebo-controlled multicenter trial comparing short (7 days) antibiotic treatment with conventional treatment (14 days). BMC infectious diseases 9, 131	Abstract only
Vellinga Akke, Galvin Sandra, Duane Sinead, Callan Aoife, Bennett Kathleen, Cormican Martin, Domegan Christine, and Murphy Andrew W (2016) Intervention to improve the quality of antimicrobial prescribing for urinary tract infection: a cluster randomized trial. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 188(2), 108-15	Not a relevant study
Vousden N, and Shennan A H (2009) 1 Day of nitrofurantoin was not as effective as 7 days for asymptomatic bacteriuria in pregnancy. Evidence-Based Medicine 14(4), 113	Abstract only
Wagenlehner Florian M, Sobel Jack D, Newell Paul, Armstrong Jon, Huang Xiangning, Stone Gregory G, Yates Katrina, and Gasink Leanne B (2016) Ceftazidime-avibactam Versus Doripenem for the Treatment of Complicated Urinary Tract Infections, Including Acute Pyelonephritis: RECAPTURE, a Phase 3 Randomized Trial Program. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 63(6), 754-62	Does not reflect usual UK practice
Wagenlehner Florian M, Umeh Obiamiwe, Steenbergen Judith, Yuan Guojun, and Darouiche Rabih O (2015) Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI). Lancet (London, and England) 385(9981), 1949-56	Not relevant population
Wang Xiaohui, Zhang Xiaoke, Zong Zhiyong, Yu Rujia, Lv Xiaoju, Xin Jianbao, Tong Chaohui, Hao Qinglin, Qin Zhiqiang, Xiong Ying, Liu Hong, Ding Guohua, Hu Chengping, Biapenem Study Collaborative, and Group (2013) Biapenem versus meropenem in the treatment of bacterial infections: a multicenter, randomized, controlled clinical trial. The Indian journal of medical research 138(6), 995-1002	Does not reflect usual UK practice
Whelan Peter (2006) Manage urinary tract infections. The Practitioner 250(1686), 38-passim	Abstract only
Whiting P, Westwood M, Bojke L, Palmer S, Richardson G, Cooper J, Watt I, Glanville J, Sculpher M, and Kleijnen J (2006) Clinical effectiveness and cost-effectiveness of tests for the diagnosis and investigation of urinary tract infection in children: a systematic review and economic model. Health technology assessment (Winchester, and England) 10(36), iii-154	Abstract only
Wing D, Rumney P, Preslicka C, and Chung J (2007) Cranberry for asymptomatic bacteriuria prevention in pregnancy. American journal of obstetrics and gynecology 197(6 Suppl 1), S73, Abstract no: 223	Abstract only
Wing Da, Rumney Pj, and Howell A (2008) Evaluation of bacterial anti-adhesion activity of urinary cranberry metabolites following daily ingestion for asymptomatic bacteriuria in pregnancy. 55th	Abstract only

Study reference	Reason for exclusion
Annual Meeting of the Society of Gynecologic Investigation, 2008 March 26-29, San Diego, and USA , 454	
Wing Da, Rumney Ppj, Hindra S, Le J, and Nageotte M (2015) Evaluation of compliance and tolerability of cranberry capsules in pregnancy for the prevention of asymptomatic bacteriuria in pregnancy. Reproductive sciences (Thousand Oaks, and Calif.) 22, 146a	Abstract only
Woodfield J C, Beshay N, van Rij, and A M (2009) A meta-analysis of randomized, controlled trials assessing the prophylactic use of ceftriaxone. A study of wound, chest, and urinary infections. World journal of surgery 33(12), 2538-50	Not a relevant population
Wu G, Abraham T, and Saad N (2014) Role of tigecycline for the treatment of urinary tract infections. Journal of Pharmacy Technology 30(3), 87-92	Not a relevant study
Yang Lu, Gao Liang, Chen Yongji, Tang Zhuang, Liu Liangren, Han Ping, Zeng Hao, Li Xiang, and Wei Qiang (2015) Prophylactic Antibiotics in Prostate Biopsy: A Meta-Analysis Based on Randomized Controlled Trials. Surgical infections 16(6), 733-47	Not a relevant study
Yang Lu, Tang Zhuang, Gao Liang, Li Tao, Chen Yongji, Liu Liangren, Han Ping, Li Xiang, Dong Qiang, and Wei Qiang (2016) The augmented prophylactic antibiotic could be more efficacious in patients undergoing transrectal prostate biopsy: a systematic review and meta-analysis. International urology and nephrology 48(8), 1197-207	Not a relevant study
Yang Stephen Shei-Dei, Chiang I Ni, Lin Chia-Da, and Chang Shang-Jen (2012) Advances in non-surgical treatments for urinary tract infections in children. World journal of urology 30(1), 69-75	Publication/study type (literature review)
Zheng L, Xu N, Cai Y-N, Feng P, Liu Y-J, Wang W, and Han X-F (2008) [A multicenter randomized controlled clinical study of pazufloxacin mesilate versus levofloxacin in the treatment of acute respiratory and urinary tract infections]. Chinese Journal of Antibiotics 33(3), 182-7	Non-English language