National Institute for Health and Care Excellence

Final

Urinary tract infection (recurrent): antimicrobial prescribing guideline

Evidence review

October 2018

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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 the prevention of UTI in women (including pregnant women), men and children with recurrent UTI, who do not have a catheter. Lower UTI, acute pyelonephritis, and catheter-associated UTI are covered in separate evidence reviews.

Recurrent UTI includes recurrence of lower UTIs (cystitis) and/or upper UTIs (acute pyelonephritis), but repeated pyelonephritis should prompt further investigation. See NICE antimicrobial prescribing guidelines on lower UTI and acute pyelonephritis for background information.

Recurrent UTIs are repeated UTIs with a frequency of at least 3 UTIs in the last year or 2 UTIs in the last 6 months (European Association of Urology (EAU) guidelines on urological infections [2017]). This may be due to relapse or reinfection:

- Relapse is recurrent UTI with the same strain of organism. Relapse is the likely cause if UTI recurs within a short period (for example within 2 weeks) after treatment.
- Reinfection is recurrent UTI with a different strain or species of organism. Reinfection is the likely cause if UTI recurs more than 2 weeks after treatment.

The number of recurrences that is regarded as clinically significant depends on the risks of infection and the impact of UTI on the person (EAU guideline [2017]). Lower UTI (cystitis) recurs within a year in 25 to 50% of women, usually as reinfections (rather than relapses) (NICE clinical knowledge summary – UTI (lower) - women).

Recurrent UTIs are common in women. Risk factors in young and pre-menopausal women include sexual intercourse, new sexual partner, mother with a history of UTI and history of UTI as a child. In post-menopausal and elderly women, risk factors include history of UTI before menopause, urinary incontinence, atrophic vaginitis due to oestrogen deficiency, increased post-void urine volume, and urine catheterisation and functional status deterioration in elderly institutionalised women (EAU guideline [2017]).

Some people (mainly women) may be able to identify 1 or more triggers that often brings on a UTI. These triggers may vary for different people, and include sexual intercourse, going for long walks and wearing occlusive underwear.

Risk factors that may predispose men to recurrent UTIs include abnormalities of urinary tract function or structure, incomplete bladder emptying and immunosuppression (NICE clinical knowledge summary – UTI (lower) - men).

Risk factors for recurrent UTI in children include abnormalities of urinary tract function or structure, for example vesicoureteric reflux, spinal abnormalities and constipation; dysfunctional elimination syndrome; and infection or irritation of the genital area that prevents regular voiding (NICE clinical knowledge summary – UTI - children).

The diagnosis of recurrent UTI should be confirmed by urine culture. Extensive routine investigations such as cystoscopy and imaging are not routinely recommended, but may be performed in some circumstances such as when renal calculi or outflow obstruction is suspected (EAU guideline [2017]).

The management of suspected community-acquired bacterial urinary tract infection in adults aged 16 years and over is covered in the NICE quality standard on urinary tract infection in

adults (2015). 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 includes a placeholder statement on the treatment of recurrent UTI, which is an area of care that has been prioritised by the Quality Standards Advisory Committee but for which no source guidance was currently available. A placeholder statement indicates the need for evidence-based guidance to be developed in this area.

The NICE guideline on urinary tract infection in under 16s (2007) defines recurrent UTI in children as:

- 2 or more episodes of UTI with acute pyelonephritis/upper UTI, or
- 1 episode of UTI with acute pyelonephritis plus 1 or more episode of UTI with cystitis/lower UTI, or
- 3 or more episodes of UTI with cystitis/lower UTI.

The NICE guideline on urinary tract infection in under 16s (2007) makes recommendations on the diagnosis of UTI in infants and children. 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 (2013). Infants and children who have had recurrent UTIs should undergo ultrasound (within 6 weeks) (see the NICE guideline on urinary tract infection in under 16s (2007) for more information).

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.

1.2 Managing infections that require antibiotics

In most cases, managing a UTI will require antibiotic treatment, but antibiotics should only be started when there is clear evidence of infection. Antibiotic prophylaxis may also be an option in people with recurrent UTI, to reduce the risk of recurrent infections. The NICE guideline on urinary tract infection in under 16s (2017) recommends that antibiotic prophylaxis may be considered in infants and children with recurrent UTI.

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 UTI include paracetamol or non-steroidal anti-inflammatory drugs, cranberry products and urine alkalinising agents. Other strategies have also been used to reduce the risk of recurrent infections. These include avoiding known risk factors, behavioural changes (for example, reducing fluid intake, habitual and post-coital delayed urination and wearing occlusive underwear), probiotics, cranberry products and D-mannose (see Clinical effectiveness).

1.2.2 Back-up antibiotic prescribing strategies

The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) recommends that if the person has been given a back-up antibiotic 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 with recurrent UTI 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 with recurrent UTI, the NICE clinical knowledge summary on UTI (lower) – men suggests that men are advised about measures that may reduce the risk of recurrent UTIs, such as to maintain sufficient fluid intake (at least 2 litres per day) to avoid dehydration. 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.

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. All infants and children 3 months or older with recurrent UTI should be assessed by a paediatric specialist.

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.

The NICE clinical knowledge summary on UTI (lower) - women suggests routinely referring the following women with recurrent UTIs:

- who have a risk factor for an abnormality of the urinary tract
- who are immunocompromised or who have diabetes
- who have a known abnormality of their renal tract who might benefit from surgical correction
- who have not responded to preventive treatments.

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).

For men with recurrent UTI, the NICE clinical knowledge summary on UTI (lower) – men suggests that alternative conditions such as urethritis are considered. At least 50% of men

with recurrent UTI will have prostate involvement, 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. 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.

Treatment failure (due to relapse or reinfection) is more likely in men with risk factors for complications (see NICE antimicrobial prescribing guideline on UTI: acute pyelonephritis). Prognosis partly depends on whether any underlying cause can be treated or removed, such as urinary stone extraction. For men with suspected urological cancer an urgent 2-week referral should be arranged. A non-urgent referral for bladder cancer should be considered in men aged 60 years and over with recurrent or persistent unexplained UTI (NICE clinical knowledge summary – UTI (lower) – men).

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. These references were screened using their titles and abstracts and 133 full text references were obtained and assessed for relevance. Thirty-eight full text 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%.

Thirteen of the 38 references were prioritised by the committee as the best available evidence and were included in this evidence review (see appendix F: included studies). The methods for identifying, selecting and prioritising the best available evidence are described in the interim process guide.

The 25 references that were not prioritised for inclusion are listed in appendix I: studies not prioritised. Also see appendix E: evidence prioritisation for more information on study selection.

The remaining 95 references were excluded. These are listed in appendix J: excluded studies with reasons for their exclusion.

Four further systematic reviews were identified following stakeholder consultation and an updated search (May 2018). Luis et al. (2017) is a systematic review and Ledda et al. (2017) is an RCT both covering cranberry products, however, both studies were deprioritised as another systematic review also identified following stakeholder consultation on the same intervention was prioritised (Fu et al. [2017)]; see appendix I: studies not prioritised). Fu et al. conducted a meta-analysis comparing cranberry products with placebo or no treatment in non-pregnant women. A third systematic review (Roshdibonab et al. [2017)]) conducted the same comparison in children and was also included in the guideline. The remaining 15 references identified in the updated search 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
Probiotics (lactobacillus)					
Grin et al. 2013 Systematic review. Multiple countries. Follow-up up to 12 months	n=294 (5 RCTs)	Premenopausal women with history of UTI, defined as one or more UTIs within the last 12 months	Lactobacillus (pessaries or oral; in 3 studies lactobacillus given after a course of antibiotics), for prophylaxis	Placebo	Incidence of recurrent urinary tract infections
Schwenger et al. 2015 Systematic review. Multiple countries. Follow-up up to 28 days	n=735 (9 RCTs and quasi-RCTs)	Adults and children with history of at least 1 UTI or current UTI, 1 study in healthy women (some studies included children with VUR)	Probiotics in any formulation for prophylaxis	Placebo Antibiotics	Symptomatic bacterial urinary tract infection
D-Mannose					
Kranjcec et al. 2014 RCT Croatia Follow-up 6 months	n=308	Non-pregnant women with history of UTI, defined as at least 2 UTIs in the last 6 months and/or 3 UTIs in the last year	Oral d-mannose for prophylaxis	Antibiotic (nitrofurantoin) No treatment	Number of women experiencing a urinary tract infection
Cranberry products					
Fu et al. 2017 Systematic review Multiple countries 6 to 12 months follow up	n=1498 (7 RCTs)	Generally healthy non-pregnant women with a history of UTI	Cranberry products (juice, tablets and powder capsules) for prophylaxis	Placebo or no treatment	Number of women experiencing a urinary tract infection
Jepson et al. 2012 Systematic review. Multiple countries. Follow-up up to 12 months	n=4,473 (24 RCTs)	Adults susceptible to UTI including: people with a history of recurrent lower UTI (defined as more than	Cranberry products (juice, concentrate, capsules, or tablets) for prophylaxis	Placebo, no treatment, water, methenamine hippurate, antibiotics or lactobacillus	Number (incidence) of confirmed urinary tract infection

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
		2 episodes in the last year); pregnant women; older people, people with cancer or spinal injury/neuropathic bladder and children with first or subsequent UTI			
Roshdibonab et al. 2017 Multiple countries 3 to 17 months follow up	n=794 (10 RCTs)	Children with history of UTI	Cranberry juice or capsules for prophylaxis	Placebo or antibiotics	Number of urinary tract infections
Beerepoot et al. 2011 RCT Netherlands Follow-up up to 15 months	n=221	Premenopausal women with a history of recurrent UTI, defined as at least 3 self-reported UTIs in the last year	Cranberry capsules for prophylaxis	Antibiotic (co-trimoxazole)	Number of symptomatic urinary tract infections over 12 months Proportion of patients with at least 1 symptomatic urinary tract infection during 12 months of prophylaxis use Median time to the first symptomatic urinary tract infection
Uberos et al. 2012 RCT Spain Follow-up up to 12 months	n=192	Children 1 month to 13 years, with a history of recurrent UTI (defined as at least 2 episodes in the last 6 months), VUR of any degree or renal pelvic dilation associated with UTI	Cranberry syrup for prophylaxis	Antibiotic (trimethoprim)	Number of urinary tract infection and safety
Abbreviations: RCT, Randomised controlled trial; VUR, Vesicoureteral reflux					

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

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Oestrogens					
Perrotta et al. 2008 Systematic review. Multiple countries Follow-up up to 4 years	n=3,345 (9 RCTs)	Post-menopausal women	Oral oestrogens, with or without progestogens; or vaginal oestrogens, delivered by vaginal ring, vaginal pessaries, vaginal tablets	Placebo or antibiotics	Women with recurrent urinary tract infections Urinary tract infections Time until recurrence Number of urinary infections/person/year

Table 3: Summary of included studies: antimicrobials

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Antibiotics versus placebo or no treatment					
Albert et al. 2004 Systematic review Multiple countries. Follow-up not clearly reported	n=1,120 (19 RCTs)	Non-pregnant women (both pre- and post-menopausal women) with at least 2 UTIs in the last year	Antibiotics of various classes administered for at least 6 months	Placebo, antibiotics or another pharmacological non-antibiotic treatment	Number of recurrences per patient-year using 1) microbiological criteria and 2) clinical criteria Proportion of patients who had severe side effects Proportion of patients who had mild side effects
Dai et al. 2010 Systematic review Multiple countries Follow-up varied according to study	n=1,093 (7 RCTS)	Children with or without VUR	Antibiotics of various classes	Placebo	Deterioration of renal scars
Muller et al. 2017 Systematic review	n=3,052 (26 RCTs)	Adults and children (authors conducted a mixed analysis of studies in adults,	Nitrofurantoin	Placebo	Occurrence of urinary tract infection

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Multiple countries. Follow-up varied according to study		children or both); the ages of participants involved were not reported consistently, if at all.			Mild adverse effects Emergence of resistance
Schneeberger al. 2015 Systematic review US Follow-up until delivery	n=200 (1 RCT)	Pregnant women with history of 1 or more UTIs before or during pregnancy	Nitrofurantoin and close monitoring	Close monitoring alone	Recurrent urinary tract infection before birth (recurrent pyelonephritis, recurrent cystitis) Preterm birth (less than 37 weeks) Small for gestational age
Williams and Craig 2011 Systematic review Multiple countries. Follow-up varied according to study	n=1,557 (12 RCTs)	Children (without VUR), however studies in which less than 50% of the population had VUR (any grade) were included.	Antibiotics of various classes	Placebo	Recurrence of urinary tract infections Microbial resistance to prophylactic drug Adverse events Withdrawals due to adverse events
Antibiotics versus other antibiotics					
Muller et al. 2017 Systematic review Multiple countries. Follow-up varied according to study	n=3,052 (26 RCTs)	Adults and children (authors conducted a mixed analysis of studies in adults, children or both); the ages of participants involved were not reported consistently, if at all.	Nitrofurantoin	Different antibiotic classes: • Beta-lactams • Quinolones • Co-trimoxazole • Trimethoprim • Methenamine hippurate	Occurrence of urinary tract infection Mild adverse effects
Albert et al. 2004 Systematic review	n=1,120 (19 RCTs)	Non-pregnant women (both pre- and post-menopausal women)	Antibiotics of various classes		Number of recurrences per patient-year using 1) microbiological

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Multiple countries. Follow-up not clearly reported		with at least 2 UTIs in the last year			criteria and 2) clinical criteria Proportion of patients who had severe side effects Proportion of patients who had mild side effects
Williams and Craig 2011 Systematic review Multiple countries. Follow-up varied according to study	n=1,557 (12 RCTs)	Children (without VUR), however studies in which less than 50% of the population had VUR (any grade) were included.	Antibiotics of various classes		Recurrence of urinary tract infections Microbial resistance to prophylactic drug Adverse events Withdrawals due to adverse events
Duration of antibiotic treatment (adults)					
Zhong et al. 2011 RCT China Follow-up12 months	n=68	Postmenopausal women	Antibiotic (continuous low-dose daily)	Antibiotic (intermittent patient-initiated single-dose)	Occurrence of urinary tract infection Conditions predisposing to antibiotic use Adverse events
Abbreviations: RCT, Randomised controlled trial; VUR, vesicoureteral reflux					

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

3.1.1 Lactobacillus (probiotic) in non-pregnant women

The evidence review for lactobacillus is based on 2 meta-analyses (Grin et al. 2013 and Schwenger et al. 2015). The studies cover lactobacillus compared with placebo, and lactobacillus compared with antibiotics.

Lactobacillus versus placebo

The evidence review for lactobacillus versus placebo is based on Grin et al. 2013 (5 RCTs, n=294), which included studies in premenopausal women with a history of prior urinary tract infection (UTI) (defined as 1 or more UTIs within the last 12 months prior to entry to the study). In 2 studies included in the meta-analysis, participants received a course of lactobacillus following a UTI treated with antimicrobials until the infection cleared. Four studies treated the women with vaginal pessaries containing lactobacillus, the remaining study used a lactobacillus drink preparation. The strains of *Lactobacillus spp.* included across the studies were: *L. rhamnosus* GR-1, *L. fermentum* B-54, *L. casei v rhamnosus* LCR35, *L. rhamnosus* GG, and *L. crispastus* CTV-05. The composition of the different preparations varied among the different studies. The pessaries were administered daily, 5 days a week or twice a week. The length of treatment ranged from 5 days to 12 months. Length of follow-up was also inconsistent between studies, ranging from 4 weeks to 12 months.

The populations included in the studies were mostly premenopausal adult women. Only 1 study reported the age range of included participants; their ages ranged from 18 to 50 years old. Most studies included in the meta-analysis defined UTI with microbiological criteria that ranged from 10^3 colony forming units per millilitre (CFU/mL) to 10^5 CFU/mL. In some studies, women were already receiving antibiotic treatment for their UTI and, in 1 study the women were healthy and had no infection.

Lactobacillus spp. did not significantly reduce the risk of recurrent UTIs in premenopausal women when compared with placebo (5 RCTs, n=194: 29.9% versus 34.7%; risk ratio [RR] 0.85 95% CI 0.58 to 1.25; low quality evidence). When authors restricted the analysis to studies that only used 'effective strains' of lactobacillus (as defined by the authors), results were statistically significant (2 RCTs, n=127, 16.1% versus 32.3%: RR 0.51, 95% CI 0.26 to 0.99; NNT 7 [95% CI 4 to 64]; moderate quality evidence).

Lactobacillus versus antibiotics

The evidence review for lactobacillus versus antibiotics is based on a single RCT (NAPRUTI Study II 2006) reported within a systematic review (Schwenger et al. 2015). The 'Non-antibiotic versus Antibiotic Prophylaxis for Recurrent Urinary Tract Infections' (NAPRUTI) study compared *Lactobacillus spp.* (*L. rhamnosus* GR-1 and *L. reuteri* RC-14) with co-trimoxazole as prophylaxis for the prevention of UTIs in postmenopausal women with recurrent UTIs. Patients randomised to receive lactobacillus took 1 capsule containing at least 10^9 CFUs of *L. rhamnosus GR-1* and *L. reuteri RC-14* twice a day and 1 placebo capsule at night for 12 months. Patients

randomised to receive co-trimoxazole took a 480 mg tablet at night, and 1 placebo capsule twice a day for 12 months.

Schwenger et al. (2015) defined the rate of UTIs in each treatment group as the number of patients experiencing at least 1 UTI, not the number of UTIs in a treatment group.

There was no significant difference in the number of symptomatic infections between women treated with lactobacillus and those treated with antibiotics (1 RCT, n=223: 74.8% versus 66.7%; RR 1.12, 95% CI 0.95 to 1.33; low quality evidence).

Sensitivity analysis was conducted to determine the effect of imputing data (participants with missing data were assumed to have negative outcomes, known as worst case scenario), or ignoring missing data on the reported outcome. When a worst case scenario was applied for those randomised to the lactobacillus treatment group, there was a significant increase in the number of symptomatic bacterial UTIs seen in this group compared with those receiving antibiotics (1 RCT, n=223: 79.1% versus 66.7%; RR 1.19 95% CI 1.01 to 1.4; NNT 8 [95% CI 5 to 114]; moderate quality evidence). However, when a worst case scenario was applied for antibiotics, there was a significant increase in the number of symptomatic bacterial UTIs seen in this group compared with those receiving lactobacillus (1 RCT, n=223: 74.8% versus 89.8%; RR 0.83 95% CI 0.74 to 0.94; NNT 7 [95% CI 4.0 to 19.0]; moderate quality evidence).

3.1.2 D-Mannose in non-pregnant women

The evidence review for D-mannose is based on 1 RCT (Kranjcec et al. 2014, n=308) comparing D-mannose (200 ml of 1% solution once daily in the evening) with no treatment, or an antibiotic (nitrofurantoin 50 mg once daily in the evening). Kranjcec et al. (2014) included non-pregnant women who presented with current UTI and a history of recurrent UTI. The authors defined the latter as 2 episodes in the last 6 months or 3 episodes in the last year. Authors based the diagnosis of UTI on a microbiological assessment ($\geq 10^3$ CFUs per ml) as well as lower urinary tract symptoms such as dysuria, frequency and urgency. All women in the study took antibiotics (ciprofloxacin 500 mg twice a day) for 1 week for their current UTI. The median age was between 48 and 52 years, and 47.4% of participants were postmenopausal. The authors assessed effectiveness as the number of participants presenting with 1 recurrent UTI during the study period.

D-mannose versus no treatment

D-mannose was significantly more effective in preventing recurrent UTI in non-pregnant women compared with no treatment over the 6-month study period (Kranjcec et al. 2014, n=205: 14.6% versus 60.8%; RR 0.24, 95% CI 0.15 to 0.39; NNT 3 [95% CI 2 to 3]; high quality evidence).

D-mannose versus antibiotic

D-mannose did not show a significant benefit in reducing recurrent UTIs in non-pregnant women when compared with antibiotics (nitrofurantoin 50 mg a day) over the 6-month study period (Kranjcec et al. 2014, n=206: 14.6% versus 20.4%; RR 0.71, 95% CI not stated, calculated by NICE as 95% CI 0.39 to 1.31; low quality evidence).

3.1.3 Cranberry products

The evidence review for cranberry products is based on 1 systematic review (Jepson et al. 2012,) and 2 RCTs (Beerepoot et al. 2011 and Uberos et al. 2012). The 2 RCTs provided evidence on antimicrobial resistance (see section 5). Across all publications included, authors defined recurrent UTI as 3 episodes of infection in the last 12 months or 2 episodes of infection in the last 6 months. Participants received cranberry products either in liquid form (juice or syrup) or solid form (capsules or tablets). Cranberry products were compared with placebo, no treatment or antibiotics.

Two further systematic reviews were identified following stakeholder consultation and an updated search. Fu et al. (2017) conducted a meta-analysis comparing cranberry products with placebo or no treatment in non-pregnant women and Roshdibonab et al. (2017) conducted the same comparison in children.

Cranberry products in women

Two systematic reviews (Jepson et al. 2012 and Fu et al. 2017) and 1 RCT (Beerepoot et al. 2011) assessed the efficacy of cranberry products for preventing UTIs in women. The studies included women with recurrent or previous UTI. Age groups varied across the studies from young women to elderly women and not all studies specified whether pregnant women were excluded. The main outcome of interest was reduction of recurrent UTIs, defined as participants with 1 or more UTI, or repeat symptomatic UTI.

Cranberry products versus placebo or no treatment

Jepson et al. (2012) identified 4 RCTs that compared cranberry products (juice, syrup or tablets) with matched placebo or no treatment. The concentration of cranberry products as well as the frequency of administration varied across the studies. The age of women also varied across the studies from 21 to 72 years. Across the studies, authors used microbiological criteria and symptoms to assess UTIs. Some studies required $>10^4$ CFUs/ml in a sample, and others $\geq 10^5$ CFUs/ml in a sample.

Jepson et al. 2012 found that prophylactic cranberry products for 3, 6 or 12 months did not show a significant benefit in the number of women who had one or more UTI during follow up (4 RCTs, n=594: 19.9% versus 22.8%; RR 0.74, 95% CI 0.42 to 1.31; very low quality evidence) when compared with placebo or no treatment.

Evidence identified following stakeholder consultation

Fu et al. (2017) compared cranberry in either juice or capsule form, for preventing UTIs in non-pregnant women, with a follow up of 6 to 12 months. Age of participants varied from 21 to 72 years old. The included studies differed in their definition of UTI, with most trials defining UTI through the presence of symptoms, and 4 requiring confirmed bacteriuria of varying thresholds. This data adds an additional 4 unique RCTs to the Jepson et al. (2012) analysis, including a total of 501 additional participants. Furthermore, 3 of the RCTs included in Fu et al. (2017), are also included in Jepson et al. (2012), while 1 RCT included in Jepson et al. (2012) is not included in Fu et al. (2017).

Cranberry juice or capsules significantly reduced the incidence of UTI in non-pregnant women, diagnosed either by symptom presence or culture confirmation, compared with placebo or no treatment (7 RCTs, n=1498: 20.7% versus 26.5%; RR 0.74, 95% CI 0.55 to 0.98; very low quality evidence). When restricted to UTIs

confirmed by culture, this difference was not significantly significant (5 RCTs, n=912: 19.8% versus 24.0%; RR 0.71, 95% CI 0.45 to 1.12; very low quality evidence).

Cranberry juice did not significantly reduce the incidence of UTI, diagnosed either by symptom presence or culture confirmation, compared with placebo or no treatment (6 RCTs, n= 1272: 22.0% versus 26.6%; RR 0.79, 95% CI 0.59 1.06, very low quality evidence). However, cranberry tablets did significantly reduce incidence of UTI compared with placebo (2 RCTs, n= 276: 13.5% versus 28.0%; RR 0.48, 95% CI 0.29 to 0.79; low quality evidence).

Cranberry products versus antibiotics

Jepson et al. 2012 identified 2 RCTs that compared cranberry products (tablets 500 mg) with antibiotics (trimethoprim 100 mg or co-trimoxazole 480 mg). The frequency of administration varied across the studies. The age of women varied across the studies, with 1 study recruiting women aged 45 years and older, and the other study including premenopausal women who were older than 18 years. It was unclear whether pregnant women were excluded. Both RCTs used microbiologic criteria to confirm UTIs. One study required $>10^4$ CFUs/ml in a urine sample while the other required $\geq 10^5$ CFUs/ml. The duration of the studies was 6 or 12 months.

Prophylactic cranberry products did not show a significant benefit in reducing recurrent UTIs in women (2 RCTs, n=344: 51.1% versus 40.4%; RR 1.31, 95% CI 0.85 to 2.02; moderate quality evidence) when compared with antibiotics (trimethoprim or co-trimoxazole).

Cranberry products versus placebo or no treatment in pregnant women

One systematic review (Jepson et al. 2012) assessed the efficacy of cranberry products for preventing UTIs pregnant women, which included 2 studies of cranberry products (juice) compared with matched placebo or water. No data were identified for comparisons with antibiotics. The authors did not provide details on whether pregnant women had previous or current UTIs. One study was available as abstract only and did not include information on diagnosis of UTI or treatment length. The authors of the second study confirmed UTI using microbiological criteria ($>10^8$ CFUs per ml of single organism) and symptoms such as dysuria, frequency or urgency. The length of this study was 5 to 7 months. The main outcome reported was the reduction of recurrent UTIs, defined as participants with 1 or more UTI, or repeat symptomatic UTI.

Prophylactic cranberry products did not show a significant benefit in reducing recurrent UTIs in pregnant women (Jepson et al. 2012, 2 RCTs, n=674: 56.6% versus 55.6%; RR 1.04, 95% CI 0.93 to 1.17; moderate quality evidence) when compared with placebo or no treatment. No other relevant outcomes were reported.

Cranberry products versus placebo or no treatment in elderly men and women

One systematic review (Jepson et al. 2012) assessed the efficacy of cranberry products for preventing UTIs in older people (men and women), which included 2 RCTs. These RCTs covered whether cranberry products (juice or capsules) were more effective than matched placebo or no treatment in adults aged 60 years and over. In 1 study, patients took 300 ml cranberry juice or matched placebo juice. It was unclear whether this was taken once a day or more frequently. In the other study patients took a 650 mg cranberry capsule once or twice a day. The studies included people who were either admitted to acute medicine for the elderly assessment, rehabilitation units for elderly people, or lived in care facilities. One study only

included elderly people with dementia. Both RCTs used microbiologic criteria and symptoms to confirm UTI. One study required >10^4 CFUs/ml in a urine sample while the other required ≥10^8 CFUs/ml. No data were identified for comparisons with antibiotics. The main outcome reported was participants with 1 or more UTI at follow up, measured using urine culture.

Prophylactic cranberry products did not show a significant benefit in reducing recurrent UTIs in older people (men and women) when compared with placebo or no treatment during a 6-month treatment period (2 RCTs, n=413: 9.7% versus 12.6%; RR 0.75, 95% CI 0.39 to 1.44; very low quality evidence).

Cranberry products in children

Two systematic reviews (Jepson et al. 2012 and Roshdibonab et al. 2017) assessed the efficacy of cranberry products for preventing UTIs in children. The included studies covered whether cranberry products were more effective than placebo or no treatment, or antibiotics. The main outcome reported was reduction of recurrent UTI defined as participants with 1 or more UTI or repeated symptomatic UTI.

Cranberry products versus placebo or no treatment

Jepson et al. (2012) identified 2 RCTs comparing cranberry products (concentrate or juice) with matched placebo or no treatment. One publication included only girls aged 3 to 14 years with an average age of 7 years and 6 months. The other publication did not specify the sex or ages of the children. The authors of 1 publication used symptoms and microbiological criteria (> 10^8 CFUs per ml) to diagnose UTI, whereas the other publication did not specify diagnostic criteria.

Prophylactic cranberry products did not show a significant benefit in reducing recurrent UTIs in children over the 6-month study period (2 RCTs, n=309: 16.3% versus 29.5%; RR 0.48, 95% CI 0.19 to 1.22; low quality evidence) when compared with placebo or no treatment.

Evidence identified following stakeholder consultation

Roshdibonab et al. (2017) included 8 RCTs comparing cranberry taken daily in juice or capsule form, with placebo for recurrent UTI in children, with 2 to 12 month follow up. Children were aged between 1 to 13 years, with UTI diagnosed by positive urine culture in all studies. Two of the RCTs included in the meta-analysis included children with catheters. This data includes an additional 6 RCTs to the Jepson et al. (2012) analysis, including a total of 262 additional participants. The 2 RCTs included in Jepson et al. (2012) for this population are also included in Roshdibonab et al. (2017).

Children using cranberry juice or capsules showed a significant reduction in incidence of culture confirmed UTI compared with children taking placebo (8 RCTs, n= 571: OR 0.31, 95% CI 0.21 to 0.46; very low quality evidence).

Cranberry products versus antibiotics

Jepson et al. (2012) identified 1 RCT comparing cranberry products (syrup) with antibiotics (trimethoprim 8 mg/kg). The authors included children between 1 month and 13 years, and mean ages ranged from 28.3 to 30.7 months. Children either presented with recurrent UTI (2 or more infections in 6 months), vesicoureteric reflux of any degree, pyelic ectasia or hydronephrosis, or anatomical kidney disorder.

Jepson et al. 2012 found that prophylactic cranberry products did not show a significant benefit in reducing recurrent UTIs in children (1 RCT, n=192: 10.7% versus 15.4%; RR 0.69, 95% CI 0.32 to 1.51; low quality evidence) when compared with antibiotics (trimethoprim) over the 6-month study period.

3.2 Non-antimicrobial pharmacological interventions

3.2.1 Oestrogens in post-menopausal women

The evidence review for oestrogens (with or without progestogens) is based on 1 systematic review of 9 RCTs (Perrotta et al. 2008, n=3,345). The author's objective was to examine the efficacy of oestrogen in decreasing the rate of recurrent urinary tract infection (UTI) in postmenopausal women and its safety. All studies within the systematic review included post-menopausal women with recurrent UTI (defined as 3 episodes of infection in the last 12 months or 2 episodes of infection in the last 6 months). The systematic review included comparisons of oral oestrogen versus placebo, vaginal oestrogen versus placebo, and vaginal oestrogen versus oral antibiotics. The main efficacy outcome was reduction in recurrent UTI.

Oral oestrogens compared with placebo

Perrotta et al. (2008) identified 4 RCTs that reported on the efficacy of oral oestrogens compared with placebo in post-menopausal women. These included 1 large study (n=2,654) with a duration of up to 4 years, and 3 smaller studies (fewer than 100 participants each) with durations of 12 weeks or 6 months. The age of women varied across the studies, with the large study recruiting participants less than 80 years of age, while another study reported mean age of 88 years. In the large study the oestrogen preparation also contained a progestogen. There was no significant reduction in recurrent UTI when oral oestrogen was compared with placebo (4 RCTs, n=2,798: 11.3% versus 10.4%; RR 1.08, 95% CI 0.88 to 1.33; moderate quality evidence).

Vaginal oestrogens compared with placebo or no treatment

Perrotta et al. (2008) identified 2 small RCTs that reported on the efficacy of vaginal oestrogens compared with placebo or no treatment. The trials differed in the administration method of oestrogens and comparator used. One RCT compared an oestrogen-releasing vaginal ring with no treatment while the other compared topically applied vaginal oestrogen cream with placebo cream. The age of the participants was not reported, and the results were presented separately for each study, not pooled in a meta-analysis. Oestrogen administered via a vaginal ring (Estring) showed a statistically significant benefit for reducing recurrent UTI compared with no treatment during the 36 week study period (1 RCT, n=108: 50.9% versus 80%; RR 0.64, 95% CI 0.47 to 0.86; NNT 4 [95% CI 3 to 9]; moderate quality evidence). Similarly, oestrogen administered topically (oestriol cream) showed a significant reduction in recurrent UTI when compared with placebo during an 8-month study period (1 RCT, n=93: 16% versus 62.8%; RR 0.25 95% CI 0.13 to 0.5; NNT 3 [95% CI 2 to 4]; high quality evidence).

Vaginal oestrogens versus antibiotics

Perrotta et al. (2008) identified 2 RCTs that reported on the efficacy of vaginal oestrogens (pessary or cream) compared with oral antibiotics (nitrofurantoin or ofloxacin). Both studies included post-menopausal women. However, ages or

diagnostic criteria for UTI were not specified. Perrotta et al. (2008) presented the results of the studies separately as the authors felt that results could not be pooled due to high heterogeneity. There were significantly more UTIs at the end of the 9-month study period with vaginal oestrogens delivered via pessary compared with nitrofurantoin 100 mg a day (1 RCT, n=171; 67.4% versus 51.8%; RR 1.3, 95% CI 1.01 to 1.68; low quality evidence). In contrast, vaginal oestrogen cream (premarin cream) was significantly more effective than ofloxacin 600 mg a day in reducing recurrent UTI at the end of the 3-month study period (1 RCT, n=42; 7.4% versus 80%; RR 0.09 95% CI 0.02 to 0.36; NNT 2 [95% CI 2 to 2] ; low quality evidence). This benefit only lasted as long as participants were on prophylaxis, with no benefit seen 2 months after stopping (1 RCT, n=42; 7.4% versus 13.3%; RR 0.56 95% CI 0.09 to 3.55; very low quality evidence).

3.3 Antimicrobials in non-pregnant women

The evidence review for antimicrobials in non-pregnant women is based on 1 systematic review (Albert et al. 2004), and 1 RCT (Zhong et al. 2011). The included studies assessed antibiotics compared with placebo, and the duration of antibiotic treatment.

3.3.1 Antibiotics compared with placebo

Albert et al. (2004) included 10 RCTs comparing antibiotics with placebo (n=1,120), assessing the efficacy and safety of antibiotic prophylaxis to prevent recurrent urinary tract infection (UTI) in adult non-pregnant women. Participants were included if they had experienced at least 2 episodes of uncomplicated UTI in the previous year, and were aged over 14 years old. The authors performed sensitivity analysis, excluding trials that had different inclusion criteria or tested different prophylaxis schedules.

In 8 RCTs, antibiotic prophylaxis was given for 6 months, and in 2 RCTs it was given for 12 months. The antibiotic dose regimens used in the studies included: ciprofloxacin 125 mg post-coital (women were instructed to take ciprofloxacin as a single dose after sexual intercourse), co-trimoxazole 40/200 mg daily, cephalexin 125 mg daily, nitrofurantoin 50 mg daily, nitrofurantoin 100 mg daily, norfloxacin 200 mg daily and cinoxacin 250 mg daily). In all studies, prophylaxis was stopped in each case of recurrent infection. Recurrence was defined as the presence of bacteriuria and the clinical symptoms of UTI.

Antibiotic prophylaxis, when compared with placebo, significantly reduced the recurrence of UTI during the prophylactic period of 6 to 12 months, when using microbiological criteria (10 RCTs, n=372: 12.3% versus 65.5%; RR 0.21 95% CI 0.13 to 0.34; NNT 2 [95% CI 2 to 3]; high quality evidence) and clinical criteria (7 RCTs, n=257: 7.4% versus 51.2%; RR 0.15 95% CI 0.08 to 0.28; NNT 3 [95% CI 2 to 3]; high quality evidence). However, this effect was diminished when recurrence was reported after the prophylactic period (2 RCTs, n=70: 52.3% versus 57.7%; RR 0.82 95% CI 0.44 to 1.53; very low quality evidence).

3.3.2 Choice of antibiotic

Although Albert et al. (2004) reported outcomes for studies which compared different antibiotic choices, these studies were included in a larger meta-analysis (Muller et al. 2017), which is described in section 3.5.2 of this evidence review.

3.3.3 Antibiotic dosing and course length

Zhong et al. (2011) (n=83) compared the efficacy and safety of intermittent single-dose antibiotic prophylaxis versus continuous antibiotic prophylaxis over 12 months. The study included postmenopausal women who had experienced 3 or more UTIs within a 12-month period. The average number of UTIs prior to entry was approximately 5 infections in the previous year, in both treatment groups. Participants took antibiotics either continuously over the study period or used single-dose antibiotics whenever they were exposed to conditions that might trigger UTI. These conditions were determined from the women's experience and included working or walking for a long time, sexual intercourse, travelling, or micturition delay. It was unclear whether women took their intermittent antibiotics before or after exposure to triggers for UTI. The choice of antibiotic (nitrofurantoin, norfloxacin, ciprofloxacin, amoxicillin, co-trimoxazole, cefaclor or cefuroxime) in both groups was done on a case by case basis and depended on the woman's previous use of antibiotics and the outcome of an antimicrobial susceptibility test. Dose varied by antibiotic but was the same for an individual antibiotic. Diagnosis of UTI was based on microscopic pyuria in a urine test.

The authors reported the number of episodes of UTI per year, the number of episodes per year per patient as well as the number of patients having 1, 2, 3, and up to 12 episodes per year. There was no statistically significant difference between the intermittent single-dose and continuous treatment regimens (Zhong et al. 2011, n=68: 80.6% versus 70.3%; RR and 95% CI not stated; calculated by NICE as RR 1.15 95% CI 0.87 to 1.51; moderate quality evidence).

One study in Albert et al. 2004 (Melekos et al. 1997), compared ciprofloxacin 125 mg taken as a single dose immediately after sexual intercourse, and ciprofloxacin taken as a single dose at night. The study was conducted in pre-menopausal women aged 18 to 45, who were sexually active and had ≥3 documented lower UTIs in the last 12 months. They found no significant difference in the number of women experiencing at least one microbiological recurrence whilst on prophylaxis (1 RCT, n=135: 2.9% versus 3.1%; RR 0.93 95% CI 0.13 to 6.4; low quality evidence), or the number of women experiencing at least one clinical recurrence whilst on prophylaxis (1 RCT, n=135: 5.7% versus 4.6%; RR 1.24 95% CI 0.29 to 5.32; low quality evidence). Authors noted no significant difference between groups, in the microbiological recurrence after the prophylactic period (low quality evidence).

3.4 Antimicrobials in pregnant women

The evidence review for antimicrobials in pregnant women is based on 1 systematic review (Schneeberger et al. 2015). This review covers whether antibiotics are more effective than clinical surveillance alone (no treatment) in preventing recurrent urinary tract infection (UTI). Schneeberger et al. (2015) planned to assess the effectiveness of pharmacological and non-pharmacological interventions for the prevention of recurrent UTI in pregnant women. However, only a single RCT was identified as meeting the inclusion criteria, which compared a continuous course of nitrofurantoin and close monitoring until delivery, with close monitoring alone.

3.4.1 Nitrofurantoin compared with no treatment (monitoring alone)

Pregnant women who were admitted to hospital with a clinical diagnosis of acute pyelonephritis were included into the study. Clinical diagnosis included the presence of costovertebral angle and 2 of the following symptoms: temperature ≥101°F, pyuria, or bacteriuria (>10^3 gram-negative organisms per ml). Women randomised to receive

antibiotics were given nitrofurantoin 50 mg three times a day for the remainder of the pregnancy in conjunction with close monitoring. Monitoring was defined as fortnightly visits to the clinic until the 36th week of pregnancy, after which time they were seen weekly until delivery. Urine tests were also conducted at each visit.

Nitrofurantoin significantly reduced the incidence of asymptomatic bacteriuria in pregnant women when compared with monitoring alone (1 RCT, n=102: 32.6% versus 59.3%; RR 0.55 0.95% CI 0.34 to 0.89; NNT 4 [95% CI 3 to 13]; moderate quality evidence). However, nitrofurantoin did not significantly reduce recurrent pyelonephritis (n=167: 7.3% versus 8.2%; RR 0.89, 95% CI 0.31 to 2.53; low quality evidence) or recurrent UTI (n=167: 2.4% versus 8.2%; RR 0.3, 95% CI 0.06 to 1.38; low quality evidence) in pregnant women. Furthermore, nitrofurantoin did not show any additional benefit compared with monitoring alone for the following outcomes: number of preterm births <37 weeks, birthweight, 5 minute Apgar score <7, and miscarriage (very low to low quality evidence).

3.4.2 Choice of antibiotic

No evidence from systematic reviews or RCTs was identified.

3.4.3 Antibiotic dosing and course length

No evidence from systematic reviews or RCTs was identified.

3.5 Antimicrobials in adults and children (mixed population analysis)

The evidence review for antimicrobials in men, women and children is based on 1 systematic review (Muller et al. 2017). This study did not stratify analysis by gender or age, but reported overall outcomes. Most studies included had a mixed gender population in either adults or children. The included studies cover antibiotics versus placebo and antibiotics versus other antibiotics.

3.5.1 Antibiotics compared with placebo

Nitrofurantoin versus placebo

Muller et al. (2017), which included 26 RCTs (n=3,052), assessed the effectiveness of nitrofurantoin (various doses: 100 mg a day, 100mg twice a day, 100 three times a day, 75 mg a day, 50 mg a day or 50 mg twice a day, 1mg/kg (children aged 2 to 18 years), 1.5 mg/kg (children, age not reported), 2 mg/kg (children aged 2 to 12 years)), given as long-term prophylaxis (defined as greater than 14 days), for the primary or secondary prevention of urinary tract infection (UTI) in men, non-pregnant women (pre- or post-menopausal) and children (predominantly female children). The authors did not define primary or secondary prophylaxis. Most included studies recruited people with recurrent UTI; however, the study specific definition of recurrent UTI was not reported. A few studies conducted in children included children with neurogenic bladder requiring catheterisation. The ages of children included in the individual studies was not reported in all studies, or reported in a consistent manner. The duration of antibiotic prophylaxis varied among studies, and ranged from 5 weeks to 24 months. Muller et al. (2017) also assessed short-term prophylaxis (defined as 3 to 14 days). However, the studies included looked at surgical prophylaxis which is not relevant to this evidence review.

Nitrofurantoin when given as primary or secondary long-term prophylaxis (for 5 weeks to 24 months) significantly reduced the occurrence of UTI in adults and children compared with placebo or no treatment (8 RCTs, n=491: 22.5% versus 59%; RR 0.38, 95% CI 0.28 to 0.50; NNT 3 [95% CI 3 to 4]; low quality evidence).

One controlled trial included in Muller et al. (2017) which could not be included in the meta-analysis (due to lack of randomisation) compared nitrofurantoin, methenamine hippurate and no treatment in older men and women. Those who were allocated to receive no treatment received almost twice as many antibiotic courses than any other groups (no results were reported, only described narratively).

3.5.2 Choice of antibiotic

Muller et al. (2017) assessed the effectiveness of nitrofurantoin compared with a range of other antibiotics (amoxicillin, penicillin, pivmecillinam, cefaclor, cefixime, cinoxacin, norfloxacin, co-trimoxazole, trimethoprim, methenamine hippurate) and stratified the analysis according to antibiotic class. The duration of antibiotic prophylaxis varied among studies, and ranged from 3 months to 24 months.

Nitrofurantoin compared with other antibiotics (overall)

There was no significant difference between nitrofurantoin and other antibiotics in reducing the incidence of recurrent UTI in adults and children (22 RCTs, n=1,319: 23.3% versus 26.1%; RR 0.93, 95% CI 0.69 to 1.26; very low quality evidence).

Nitrofurantoin versus methenamine hippurate

Using nitrofurantoin as prophylaxis for the prevention of recurrent UTI significantly reduced the incidence of UTI in adults and children compared with methenamine hippurate (2 RCTs, n=196: 35.8% versus 51.2%; RR 0.60, 95% CI 0.43 to 0.85; NNT 7 [95% CI 4 to 102]; low quality evidence).

Nitrofurantoin versus trimethoprim

There was no significant difference between nitrofurantoin and trimethoprim in reducing the incidence of UTI in adults or children (5 RCTs, n=350: 22.5% versus 29.3%; RR 0.81, 95% CI 0.38 to 1.71; very low quality evidence).

Nitrofurantoin versus co-trimoxazole

There was no significant difference between nitrofurantoin and co-trimoxazole in reducing the incidence of UTI in adults or children (4 RCTs, n=81: 12% versus 8.9%; RR 1.42, 95% CI 0.17 to 12.0; very low quality evidence).

Nitrofurantoin versus beta-lactam antibiotics

There was no significant difference between nitrofurantoin and or beta-lactam antibiotics in reducing the incidence of recurrent UTI in adults and children (5 RCTs, n=249: 16.5% versus 22.4%; RR 0.84, 95% CI 0.49 to 1.44; very low quality evidence).

Nitrofurantoin versus quinolones

There was no significant difference between nitrofurantoin and quinolones in reducing the incidence of recurrent UTI in adults and children (3 RCTs, n=186: 29.8% versus 14.7%; RR 2.26, 95% CI 0.73 to 7; very low quality evidence).

3.5.3 Antibiotic dosing and course length

Muller et al. (2017) conducted a meta-analysis to assess the effect of different nitrofurantoin dosing regimens for long-term prophylaxis in adult participants (100 mg daily, 75 mg daily, 50 mg daily and 50 mg twice daily). The studies used to calculate the effect of dose on the incidence of urinary tract infections were not reported by Muller et al. (2017), neither were they identifiable from the supplementary material. They reported no significant differences between the different regimens (absolute figures not reported; p=0.08, I^2 =53%; unable to give GRADE quality rating).

3.6 Antimicrobials in children

The evidence review for antimicrobials in children is based on 2 systematic reviews (Dai et al. 2010, and Williams and Craig 2011). The included studies cover antibiotics versus placebo and antibiotics versus other antibiotics. Some studies included a small proportion of children diagnosed with vesicoureteric reflux, but most excluded children with grades 4 and 5, or recruited only those with milder/less symptomatic grades (1-3), which typically resolved in most children without intervention.

3.6.1 Antibiotics compared with placebo

Williams and Craig (2011), which included 5 RCTs (n=1,069), assessed the efficacy of antibiotic prophylaxis compared with placebo in children with recurrent urinary tract infection (UTI). Not all the included studies had clear inclusion and exclusion criteria, and the authors pointed out that it is likely that children were misclassified in the individual studies due to the poor inclusion criteria, and this may impact upon the generalisability of the overall findings. The ages of children included in the studies varied, with 1 study including children from birth to 18 years, and in other studies no age range was reported. The definition of recurrent UTI was not consistent across the studies. However, 1 of the studies included in the review excluded children with a history of urinary tract infection. The length of prophylaxis also differed between studies, with the majority of children receiving antibiotics for at least 6 months. In 2 studies, the length of prophylaxis was not reported. The antibiotics used were nitrofurantoin (50 mg daily [children weighing >20 kg], 25 mg daily [children weighing <20 kg], and co-trimoxazole [trimethoprim 2 mg/kg/daily and sulfamethoxazole 10 mg/kg/daily]. Studies which had a population of children in which more than 50% were diagnosed with any grade of vesicoureteral reflux were excluded from the systematic review.

Antibiotic prophylaxis did not significantly reduce the recurrence of symptomatic UTI compared with placebo or no treatment (4 RCTs, n=1,024: 10.5% versus 17.2%; RR 0.75, 95% CI 0.36 to 1.53; very low quality evidence). This did not change when the analysis was restricted to studies that only included children without vesicoureteral reflux (3 RCTs, n=491: 7.3% versus 13.8%; RR 0.56 95% CI 0.15 to 2.12; very low quality evidence). There was no significant difference in the rate of antimicrobial resistance to the prophylactic antibiotic in children who received antibiotics compared with placebo (Williams and Craig 2011, 2 RCTs, n=118: 35.3% versus 16.4%; RR 2.4, 95% CI 0.62 to 9.26; very low quality evidence). Similarly, antibiotics offered no significant benefit over the use of placebo or no treatment in the number of repeat positive cultures obtained in children (very low quality evidence).

Another systematic review (Dai et al. 2010) also assessed the effect of long-term antibiotic prophylaxis in children (aged less than 18 years old) for the prevention of recurrent UTI. Long-term prophylaxis was defined by the authors as antibiotics given for at least 2 months. Children with or without vesicoureteral reflux of various grades

were included in the studies. Six out of 7 studies compared co-trimoxazole with placebo for a duration of 3 to 24 months.

Antibiotics did not significantly reduce the rate of deteriorated renal scars in children when compared with placebo or no treatment (Dai et al. 2010, 7 RCTs, n=1,093: 2.9% versus 3.5%; RR 0.95 95% CI 0.51 to 1.78; very low quality evidence).

3.6.2 Choice of antibiotic

Williams and Craig (2010) assessed the choice of antibiotics for prophylactic use in the prevention of recurrent UTI in children.

Nitrofurantoin versus trimethoprim

Nitrofurantoin (1 to 1.5 mg/kg daily) significantly reduced the risk of obtaining a repeat positive culture at the end of prophylaxis (6 months) compared with trimethoprim (2–3 mg/kg daily) in children being treated to prevent recurrent UTI (1 RCT, n=60: 20% versus 61.7%; RR 0.3, 95% CI 0.2 to 0.6; NNT 3 [95% CI 2 to 8]; moderate quality evidence).

Nitrofurantoin versus co-trimoxazole

Nitrofurantoin (1 to 2 mg/kg daily) significantly reduced the recurrence of symptomatic UTI at 6 months compared with co-trimoxazole (2 mg/kg daily) (1 RCT, n=132: 25.8% versus 45.5%; RR 0.57, 95% CI 0.35 to 0.92; NNT 6 [95% CI 3 to 27]; very low quality evidence).

Nitrofurantoin versus cefixime

Nitrofurantoin (1 mg/kg daily) did not reduce the risk of obtaining a repeat positive culture at the end of prophylaxis (6 to 12 months) compared with cefixime (2 mg/kg daily; 1 RCT, n=57: 10% versus 7.4%; risk difference 0.03 95% CI -0.12 to 0.17; moderate quality evidence).

3.6.3 Antibiotic dosing and course length

No evidence from systematic reviews or RCTs was identified.

4 Safety and tolerability

Details of safety and tolerability outcomes from studies included in the evidence review are shown in appendix H: 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 Probiotics (lactobacillus)

No safety data were reported for lactobacillus compared with placebo. Schwenger et al. (2015) assessed the effect of probiotic prophylaxis for the prevention of recurrent urinary tract infection (UTI) in adults (men and non-pregnant women) and children compared with antibiotics. Safety data were described in 4 studies included in the review, however they were not pooled in the analysis (justification not provided). A single study (NAPRUTI Study II 2006) compared probiotics with antibiotics, and showed there is no significant difference in the number of adverse events experienced by those who receive antibiotics compared with those who receive probiotics (1 RCT, n=152: 5.6% versus 11.8%; RR and 95% CI not stated; calculated by NICE as RR 0.47, 95% CI 0.20 to 1.12; low quality evidence). In the same study, there is no significant difference between the proportions of participants who experienced at least 1 adverse event having received probiotics compared with those who received antibiotics (1 RCT, n= 152: 52.8% versus 58.3%; RR and 95% CI not stated; calculated by NICE as RR 0.91 95% CI 0.73 to 1.13; low quality evidence). Another study included in the review (Stapleton et al. 2011), reported that a single participant withdrew from treatment in the lactobacillus group due to a lack of efficacy.

4.1.2 D-Mannose

Kranjcec et al. (2014) assessed the safety of D-mannose compared with an antibiotic (nitrofurantoin) in non-pregnant women who presented with current UTI and a history of recurrent UTI. While Kranjcec et al. (2014) included a no treatment study arm, no adverse events were reported for these participants.

D-mannose versus placebo or no treatment

No relevant evidence was identified.

D-mannose versus antibiotic

D-mannose significantly reduced adverse events, such as diarrhoea, nausea, and vaginal burning, in non-pregnant women when compared with nitrofurantoin (n=206: 7.8% versus 28.2%; RR 0.28, 95% CI 0.13 to 0.57; NNH 5 [95% CI 4 to 10]; high quality evidence).

4.1.3 Cranberry

Jepson et al. 2012 assessed the safety of prophylactic cranberry products (24 RCTs, n=4,473) comparing cranberry products with placebo or no treatment, or antibiotics. The authors pooled safety data (any gastrointestinal effect) across several adult subgroups including women, and elderly women and men. Data on children were not available.

Cranberry products versus placebo or no treatment

Prophylactic cranberry products in comparison with placebo or no treatment did not significantly affect the incidence of any gastrointestinal adverse events (4 RCTs, n=597: 3% versus 3.3%; RR 0.83, 95% CI 0.31 to 2.27; low quality evidence).

Cranberry products versus antibiotics

Prophylactic cranberry products in comparison with antibiotics did not significantly affect the incidence of gastrointestinal adverse events (2 RCTs, n=344: 9.6% versus 12.0%; RR 0.78, 95% CI 0.42 to 1.42; low quality evidence).

4.2 Non-antimicrobial pharmacological interventions

4.2.1 Oestrogens

Hormone replacement therapy (HRT) increases the risk of venous thromboembolism, stroke, endometrial cancer (reduced by a progestogen), breast cancer, and ovarian cancer; there is an increased risk of coronary heart disease in women who start combined HRT more than 10 years after menopause (MHRA Drug Safety Update, November 2015; British National Formulary [BNF], December 2017). Before prescribing HRT, health professionals should consider carefully the potential benefits and risks for every woman. The minimum effective dose of HRT should be used for the shortest duration (MHRA Drug Safety Update, November 2015). The endometrial safety of long-term or repeated use of topical vaginal oestrogens is uncertain; treatment should be reviewed at least annually, with special consideration given to any symptoms of endometrial hyperplasia or carcinoma (BNF August 2018).

Perrotta et al. (2008) identified 2 small RCTs that reported on the safety of oral oestrogens compared with placebo. Adverse events reported in these RCTs were breast tenderness or discomfort, or vaginal bleeding or spotting. There were significantly more adverse events with oral oestrogen compared with placebo (Perrotta et al. 2008, 2 RCTs, n=104; 23.5% versus 3.8%; RR 5.11, 95% CI 1.39 to 18.76; NNH 5 [95% CI 3 to 14]; high quality evidence).

Perrotta et al. (2008) also identified 2 RCTs that reported on the safety of vaginal oestrogens compared with placebo. Safety results were reported in 2 ways, as pooled analysis and RCT-based results. Overall, results suggested that vaginal oestrogen was associated with more adverse events (vaginal bleeding, nonphysiologic discharge, vaginal irritation, burning, or itching) when compared with placebo (2 RCTs, n=201: 23.3% versus 5.1%; RR 4.57, 95% CI 1.81 to 11.5; NNH 5 [95% CI 3 to 11]; low quality evidence). Furthermore, there were significantly more adverse events (burning, itching, or vaginal bleeding) with vaginal oestrogen compared with oral antibiotics (Perrotta et al. 2008, 2 RCTs, n=216: 16.4% versus 0%; RR 12.86, 95% CI 1.75 to 94.29; NNH 6 [95% CI 4 to 10]; moderate 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 therapy 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 should 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

A systematic review (Albert et al. 2004) assessed the safety of antibiotic prophylaxis for the prevention of recurrent UTI in non-pregnant women.

Antibiotic prophylaxis did not significantly increase the incidence of severe side effects compared with placebo (10 RCTs, n=420: 4% versus 2.1%; RR 1.58, 95% CI 0.47 to 5.28; low quality evidence). However, antibiotics did increase the incidence of 'other side effects' (defined as non-serious side effects such vagina itching and nausea) compared with placebo (10 RCTs, n=420: 15.1% versus 7.7%; RR 1.78, 95% CI 1.06 to 3.00; NNH 13 [95% CI 7 to 70]; low quality evidence).

One RCT included in the systematic review (Melekos et al. 1997) found no significant difference in the number of non-serious side effects, between premenopausal women who took ciprofloxacin (125 mg) as a single dose immediately after sexual intercourse, or once daily at night (1 RCT, n=135: 5.7% versus 13.8%; RR 0.41 95% CI 0.13 to 1.28; low quality evidence).

Zhong et al. (2011) (n=83) found that intermittent single-dose antibiotics significantly reduced the incidence of adverse events compared with continuous antibiotics (n=73: 63.6% versus 92.5%; RR and 95% CI not stated; calculated by NICE as RR 0.69 95% CI 0.52 to 0.9; NNH 3 [95% CI 2 to 9]; moderate quality evidence).

4.3.2 Antibiotics in pregnant women

No evidence was identified regarding the safety of antibiotic prophylaxis in pregnant women.

4.3.3 Antibiotics in adults and children

Muller et al. (2017) assessed the safety of nitrofurantoin, given as long-term prophylaxis (defined as greater than 14 days) for the primary or secondary prevention of UTI in men, non-pregnant women (pre- or post-menopausal) and children (predominantly female children).

Overall, the use of nitrofurantoin as prophylaxis (for at least 3 months) for recurrent UTI, significantly increased the risk of experiencing mild (not defined) adverse effects compared with other antibiotics (amoxicillin, penicillin, pivmecillinam, cefaclor, cefixime, cinoxacin, norfloxacin, co-trimoxazole, trimethoprim, or methenamine hippurate) (22 RCTs n=1,205: 30.6% versus 11.7%; RR 2.24 95% CI 1.77 to 2.83; NNH 5 [95% CI 4 to 6]; low quality evidence).

When specific antibiotics were compared, there were significantly more mild adverse effects with nitrofurantoin compared with beta-lactams (5 RCTs, n=275: 25% versus 12.2%; RR 1.99, 95% CI 1.19 to 3.32; NNH 7 [95% CI 4 to 28]; very low quality evidence); trimethoprim (4 RCTs, n=330: 42% versus 14.6%; RR 2.20 95% CI 1.51 to 3.20; NNH 3 [95% CI 2 to 4]; moderate quality evidence); and methenamine hippurate (2 RCTs, n=196: 35.8% versus 7%; RR 4.22, 95% CI 2.06 to 8.67; NNH 3 [95% CI 2 to 6]; moderate quality evidence).

However, when nitrofurantoin was compared with quinolones or co-trimoxazole, there were no significant differences in the number of mild adverse effects (very low quality evidence).

4.3.4 Antibiotics in children

Williams and Craig (2011) assessed the safety of antibiotic prophylaxis in comparison with placebo or no treatment in children with recurrent UTI. Antibiotics did not significantly affect the incidence of adverse events reported (2 RCTs, n=914: 3.8% versus 2.4%; RR 2.31, 95% CI 0.03 to 170.67; very low quality evidence) or the number of withdrawals due to adverse events (2 RCTs, n=576: 1.4% versus 3.5%; RR 0.40, 95% CI 0.13 to 1.26; very low quality evidence).

Nitrofurantoin significantly reduced the incidence of adverse events compared with trimethoprim (1 RCT, n=60: 25.8% versus 62.1%; RR 0.42, 95% CI 0.21 to 0.81; NNH 2 [95% CI 1 to 8]; low quality evidence).

Nitrofurantoin significantly increased the incidence of adverse events compared with cefixime (1 RCT, n=120: 61.7% versus 28.3%; risk difference 2.18, 95% CI 1.39 to 3.41; NNH 3 [95% CI 2 to 6]; moderate quality evidence).

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.

5.1 Antimicrobial resistance in the included studies

5.1.1 Cranberry products

Beerepoot et al. (2011) (n=221) reported that *E. coli* isolates from women receiving co-trimoxazole showed antibiotic resistance for amoxicillin, trimethoprim, and co-trimoxazole at 1 month prophylaxis (70% resistance). This reduced at 1 and 3 months after stopping prophylaxis, returning to baseline at 12 months. *E. coli* isolates from women receiving cranberry products did not show antibiotic resistance. However, prophylactic cranberry products did reduce the development of antibiotic resistance in premenopausal women compared with prophylaxis with co-trimoxazole (moderate quality evidence).

Uberos et al. 2016 (n=192) found that cranberry products did not show a significant benefit in reducing the development of antibiotic resistance in children (n=192; narrative results reported; moderate quality evidence). This study included an unknown proportion of children with vesicoureteral reflux.

5.1.2 Antibiotic prophylaxis

Muller et al. (2017) reported resistance data from 1 RCT (n=15) comparing nitrofurantoin prophylaxis with placebo in children. Weekly urine cultures showed *E. coli* cultures were replaced over time by resistant strains including *Klebsiella* and *Pseudomonas* spp., in children receiving nitrofurantoin prophylaxis, and this change

was not seen in children receiving placebo. However, there were no reports of infection from resistant strains (low quality evidence).

Another RCT included in the systematic review (n= 130) compared nitrofurantoin and trimethoprim prophylaxis in children. At baseline, 9% (6/67) of children randomised to nitrofurantoin carried nitrofurantoin resistant strains, which decreased to 7% (4/60) during prophylaxis. 8% (5/63) of children randomised to trimethoprim carried trimethoprim resistant strains at baseline, which increased to 47% (28/60) throughout prophylaxis (very low quality evidence).

6 Other considerations

6.1 Resource impact

6.1.1 Antibiotic prophylaxis

Recommended antibiotics (nitrofurantoin, trimethoprim, amoxicillin and cefalexin) are available as generic formulations, but there is currently no generic formulation of pivmecillinam, 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 (for example, with antibiotic prophylaxis). See the NICE guideline on medicines adherence).

6.3 Regulatory status

6.3.1 Oestrogens

A range of oral and vaginal oestrogens (for example, estradiol), with or without progestogens, are available for use in managing menopausal symptoms and prevention of osteoporosis. See the summaries of product characteristics for information on licensed indications of individual medicines. None are specifically licensed for preventing recurrent urinary tract infections, so use for this indication would be off label. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

6.3.2 Antibiotics

Amoxicillin is not licensed for preventing UTIs, so use for this indication would be off label. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

7 Terms used in the guideline

7.1.1 Vesicoureteric reflux

Vesicoureteric reflux occurs when there is damage to the valve between the bladder and the ureters (tubes which carry urine away from the kidney into the bladder), causing it to no longer working properly. This means that urine may flow backwards, and sometimes reach as far back as the kidneys. This is problematic when the urine is infected with bacteria, as the infection can reach the kidneys, and result in a very severe urinary tract infection otherwise known as acute pyelonephritis, or worse. This is common in children (1 in 100), and can lead to multiple urinary tract infections. Most children with the condition, find that it resolves as they get older without intervention.

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 Quality standard QS90: Urinary tract infections in adults (2015) • NICE Clinical knowledge summary on UTI (lower) – women • NICE Clinical knowledge summary on UTI (lower) – men • NICE clinical knowledge summary on UTI - children • European Association of Urology guidelines on urological infections (2017)
Safety netting	What safety netting advice is needed for managing the infection?	• NICE clinical knowledge summary on UTI (lower) - women • NICE clinical knowledge summary on UTI (lower) - men

Key area	Key question(s)	Evidence sources
		• 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 • MHRA Drug Safety Update (November 2015) • British National Formulary (BNF) (August 2018)
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 CG160: Fever in under 5s: assessment and initial management (2017) • NICE clinical knowledge summary on diarrhoea – antibiotic associated • BNF (August 2018)
	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

Key area	Key question(s)	Evidence sources
	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 • NICE guideline NG15: Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015)European surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report (2016) • Chief medical officer (CMO) report (2011)
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)
Regulatory status	What is the regulatory status of interventions for managing the infection or symptoms?	• Summary of product characteristics • General Medical Council's Good practice in prescribing and managing medicines and devices (2013)

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2 # Appendix B: Review protocol

Review protocol for recurrent urinary tract infections			Notes
I	Review question	What pharmacological (antimicrobial and non-antimicrobial) and non-pharmacological interventions are effective in managing recurrent urinary tract infections (UTIs)?	• antimicrobial includes antibiotics (treatment and prophylaxis) • non-antimicrobial includes analgesia and cranberry products • search will include terms for recurrent 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 interventions in managing recurrent UTIs to address antimicrobial resistance. In line with the major goals of antimicrobial stewardship. This includes interventions that lead prescribers to: • optimise therapy 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

Review protocol for recurrent urinary tract infections			Notes
			• 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 recurrent UTIs (lower or upper) of any severity. The definition of 'recurrence' of UTI varies: • 2 UTIs in 6 months or ≥3 UTIs in 1 year in non-pregnant women (Source: PHE guidance: definition has also been applied to all women). • 2 or more UTIs in a 3-month period in men aged 16 years and over (Source: CKS) In children (NICE CG54) • 2 or more episodes of UTI with acute pyelonephritis/upper UTI or • 1 episode of UTI with acute pyelonephritis/upper UTI plus 1 or more episode of UTI with cystitis/lower UTI, or 3 or more episodes of UTI with cystitis/lower UTI This review protocol includes recurrent UTI (defined by any of the above criteria) in non-pregnant and pregnant women, men and children. Consideration will be given to	• Subgroups of interest, those: • with protected characteristics under the Equality Act 2010. • with true allergy • pregnant women • men • children (possible age groups) • older people (frailty, care home resident, dementia) • people with 'complicated[1]' lower UTI • people with upper UTI • people with risk factors[2] for increased resistance

[1] 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)

[2] 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)

Review protocol for recurrent urinary tract infections			Notes
		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.	
V	Eligibility criteria – intervention(s)/ exposure(s)/ prognostic factor(s)	The review will include studies which include: • Non-pharmacological interventions[3]. • Non-antimicrobial pharmacological interventions[4]. • Antimicrobial pharmacological interventions[5]. For the treatment of recurrent UTI 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).	Limited to those interventions commonly in use (as agreed by the committee)
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. • Other antimicrobial pharmacological interventions.	

[3] Non-pharmacological interventions include: no intervention, watchful waiting, delayed prescribing, self-care prevention (avoiding bubble bath, appropriate wiping etc.)

[4] Non-antimicrobial pharmacological interventions include: analgesics, NSAIDs, cranberry products, barley, D-mannose

[5] Antimicrobial pharmacological interventions include: delayed (back-up) prescribing, standby or rescue therapy, prophylaxis (including post-coital and rotation of antibiotics) 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

Review protocol for recurrent urinary tract infections			Notes
VII	Outcomes and prioritisation	a) Clinical outcomes such as: • mortality • infection cure rates (number or proportion of people with resolution of symptoms at a given time point, incidence of escalation of treatment) • time to clinical cure (mean or median time to resolution of illness) • reduction in symptoms (duration or severity) • rate of complications with or without treatment • safety, tolerability, and adverse effects. b) Thresholds or indications for antimicrobial treatment (which people are most, or least likely to benefit from antimicrobials) c) Changes in antimicrobial resistance patterns, trends and levels as a result of treatment. d) Patient-reported outcomes, such as medicines adherence, patient experience and patient satisfaction. e) Ability to carry out activities of daily living. f) Service user experience. g) Health and social care related quality of life, including long-term harm or disability. h) Health and social care utilisation (including length of stay, planned and unplanned contacts). The Committee considered which outcomes should be prioritised when multiple outcomes are reported (critical and important outcomes). Additionally, the Committee were asked to consider what clinically important features of study design may be important for this condition (for example length of study follow-up, treatment	The committee have agreed that the following outcomes are critical: • reduction in number of recurrent[6] episodes • 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 and deterioration in renal function) 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)

[6] Recurrence may be due to underlying causes which require further investigation (for example stones, less usual pathogens etc)
[7] Ascending infection leading to pyelonephritis, renal failure or sepsis, and in pregnancy, pre-term labour developmental delay or cerebral palsy in the infant and foetal death. In men, prostate involvement. Also urinary stones, risk of blood infections (bacteraemia), renal abscess, renal scarring in children, neonatal sepsis.

Review protocol for recurrent urinary tract infections			Notes
		failure/recurrence, important outcomes of interest such as sequela or progression to more severe illness).	• an individual's risk factors for resistance and choice of antibiotic 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 review 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 • in relation to antimicrobial resistance, non-UK papers.	

Review protocol for recurrent urinary tract infections			Notes
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 screening/ selection/ analysis	All references from the database searches will be downloaded, de-duplicated and screened on title and abstract against the criteria above. 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 and included 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; 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 2006 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.	

Review protocol for recurrent urinary tract infections			Notes
		• 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 please 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	Standard study checklists will be used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual.The risk of	

Review protocol for recurrent urinary tract infections			Notes
	outcome/ study level	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 section 6.4 of Developing NICE guidelines: the manual	
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, selective reporting bias	For details please see the interim process guide (2017)	
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	A multidisciplinary committee developed the guideline. The committee was convened by NICE and chaired by Dr Tessa Lewis in line with section 3 of Developing NICE guidelines: the manual.	

Review protocol for recurrent urinary tract infections			Notes
	authors and guarantor	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.	

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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 Methenamine hippurate Gentamicin Amikacin Tobramycin	Lines 21-84

	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 Delayed treatment Prescribing times Antibiotic prophylaxis	Lines 141-160
Self Care	Self management Self care secondary prevention Catheter removal	Lines 162-176
Systematic Reviews	Meta analysis	Lines 185-199

	Systematic Reviews Reviews	
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

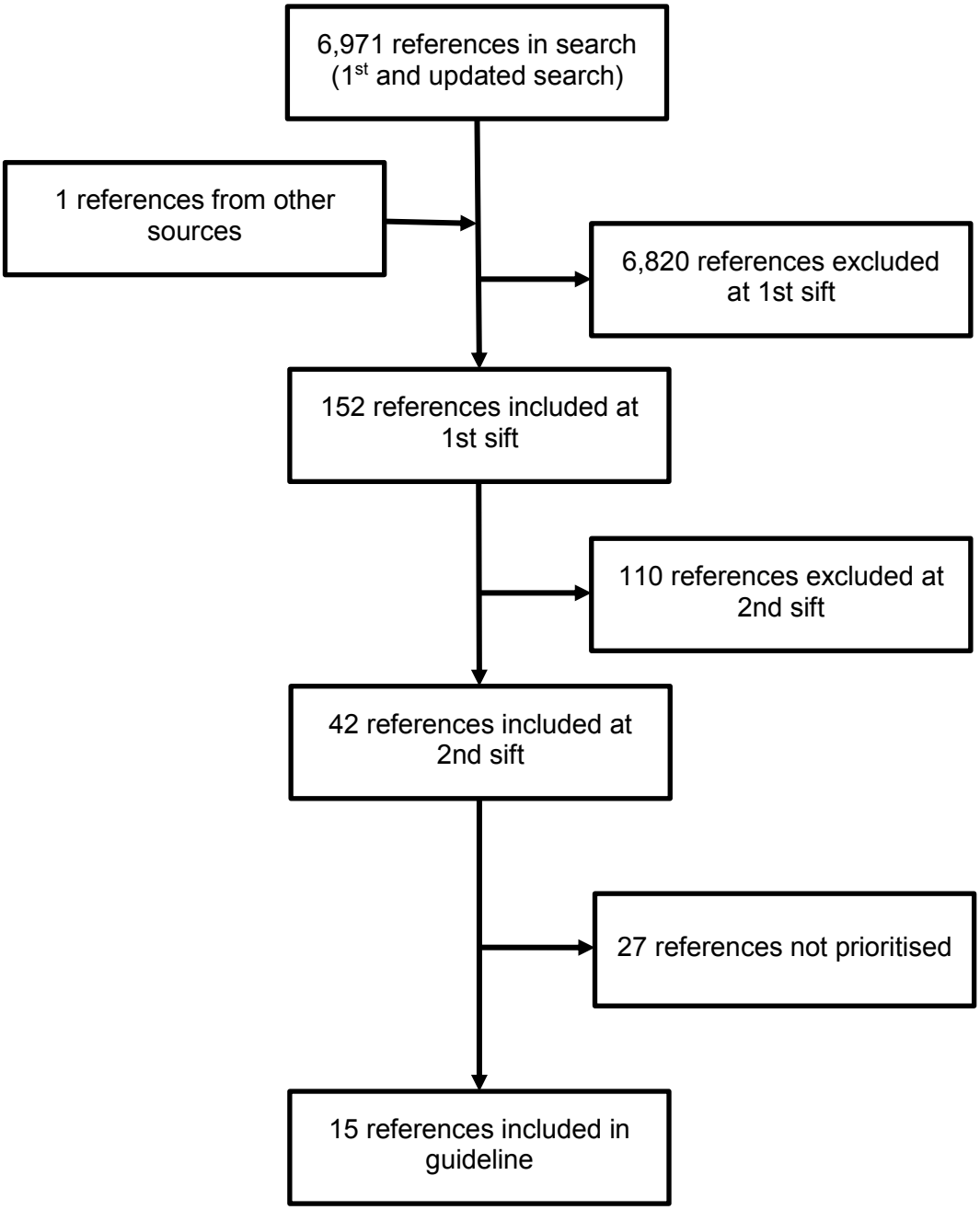
157	Inappropriate prescribing/	1695
158	or/155-157	4764914
159	154 and 158	221871
160	151 or 159	292655
161	20 and 160	15345
162	Self Care/ or self medication/	32883
163	((self or selves or themsel*) adj4 (care or manag*)).ti,ab.	33223
164	Secondary Prevention/	17180
165	Hygiene/	14900
166	Baths/	4966
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
261 limit 260 to (letter or historical article or comment or editorial or news)	867
262 260 not 261	20072

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?				
Lactobacillus	Grin et al. 2013 Schwenger et al. 2015	-	Beerepoot et al. 2013	Stapleton et al. 2011
D-Mannose	Kranjcec et al. 2014	-	-	Porru et al. 2014
Cranberry products	Fu et al. 2017 Jepson et al. 2012 Roshdibonab et al. 2017	Beerepoot et al. 2011 Uberos et al. 2012	Beerepoot et al. 2013 Luis et al. 2017 Wang et al. 2012	Afshar et al. 2012 Bailey et al. 2007 Barbosa-Cesnik et al. 2011 Bianco et al. 2012 Bosmans et al. 2014 Caljouw et al. 2014 Ferrara et al. 2009 Ledda et al. 2015 Maki et al. 2016 McMurdo et al. 2009 Salo et al. 2012 Sengupta et al. 2011 Singh et al. 2016 Stapleton et al. 2012 Takahashi et al. 2013 van den Hout et al. 2014
Which non-antimicrobial pharmacological interventions are effective?				
Oestrogens	Perrotta et al. 2008	-	Beerepoot et al. 2013	-
Is antibiotic prophylaxis effective?				
Antibiotic prophylaxis versus placebo	Albert et al. 2004 Muller et al. 2017 Williams and Craig 2011	-	Mathew 2010 Mori et al. 2009 Price et al. 2016	Norinder et al. 2006

Key questions	Included studies[1]		Studies not prioritised[2]	
	Systematic reviews	RCTs	Systematic reviews	RCTs
	Schneeberger et al. 2012			
Which antibiotic prophylaxis is most effective?				
Antibiotic prophylaxis versus different antibiotic prophylaxis	Dai et al. 2010 Williams and Craig 2011	-	Albert et al. 2004	Antachopoulos et al. 2016
What is the optimal dosage, duration and route of administration of antibiotic prophylaxis?				
Dosage	-	-	-	-
Course length	Albert et al. 2004	Zhong et al. 2011	-	-
Route of administration	-	-	-	-

[1] See appendix F for full references of included studies
[2] See appendix I for full references of not-prioritised studies, with reasons for not prioritising these studies

Appendix F: Included studies

Albert X, Huertas I, Pereiro II, Sanfelix J, Gosalbes V, and Perrota C (2004) Antibiotics for preventing recurrent urinary tract infection in non-pregnant women. The Cochrane database of systematic reviews (3), CD001209

Beerepoot Marielle A. J, ter Riet, Gerben, Nys Sita, van der Wal, Willem M, de Borgie, Corianne A J. M, de Reijke, Theo M, Prins Jan M, Koeijers Jeanne, Verbon Annelies, Stobberingh Ellen, and Geerlings Suzanne E (2011) Cranberries vs antibiotics to prevent urinary tract infections: a randomized double-blind noninferiority trial in premenopausal women. Archives of internal medicine 171(14), 1270-8

Dai B, Liu Y, Jia J, and Mei C (2010) Long-term antibiotics for the prevention of recurrent urinary tract infection in children: a systematic review and meta-analysis. Archives of disease in childhood 95(7), 499-508

Fu Z, Liska D, Talan D., Chung M. Cranberry Reduces the Risk of Urinary Tract Infection Recurrence in Otherwise Healthy Women: A Systematic Review and Meta-Analysis. Journal of Nutrition. 2017; 147(12):2282-2288

Grin Peter M, Kowalewska Paulina M, Alhazzan Waleed, and Fox-Robichaud Alison E (2013) Lactobacillus for preventing recurrent urinary tract infections in women: meta-analysis. The Canadian journal of urology 20(1), 6607-14

Jepson RG, Williams G, and Craig JC (2012) Cranberries for preventing urinary tract infections. The Cochrane database of systematic reviews 10, CD001321

Kranjcec Bojana, Papes Dino, and Altarac Silvio (2014) D-mannose powder for prophylaxis of recurrent urinary tract infections in women: a randomized clinical trial. World journal of urology 32(1), 79-84

Muller A E, Verhaegh E M, Harbarth S, Mouton J W, and Huttner A (2017) Nitrofurantoin's efficacy and safety as prophylaxis for urinary tract infections: a systematic review of the literature and meta-analysis of controlled trials. Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases,

Perrotta C, Aznar M, Mejia R, Albert X, and Ng C W (2008) Oestrogens for preventing recurrent urinary tract infection in postmenopausal women. The Cochrane database of systematic reviews (2), CD005131

Roshdibonab F, Mohammadbager FazlJoo S, Torbati M, Mohammadi Gh, Asadloo M, Noshad H. The Role of Cranberry in Preventing Urinary Tract Infection in Children; a Systematic Review and Meta-Analysis. Int J Pediatr 2017; 5(12): 6457-68. DOI: 10.22038/ijp.2017.27041.2327

Schneeberger Caroline, Geerlings Suzanne E, Middleton Philippa, and Crowther Caroline A (2015) Interventions for preventing recurrent urinary tract infection during pregnancy. The Cochrane database of systematic reviews 11, CD009279

Schwenger Erin M, Tejani Aaron M, and Loewen Peter S (2015) Probiotics for preventing urinary tract infections in adults and children. The Cochrane database of systematic reviews (12), CD008772

Uberos J, Nogueras-Ocana M, Fernandez-Puentes V, Rodriguez-Belmonte R, Narbona-Lopez E, Molina-Carballo A, and Munoz-Hoyos A (2012) Cranberry syrup vs trimethoprim in

the prophylaxis of recurrent urinary tract infections among children: A controlled trial. Open Access Journal of Clinical Trials 4, 31-38

Williams G, and Craig JC (2011) Long-term antibiotics for preventing recurrent urinary tract infection in children. The Cochrane database of systematic reviews (3), CD001534

Zhong Y H, Fang Y, Zhou J Z, Tang Y, Gong S M, and Ding X Q (2011) Effectiveness and safety of patient initiated single-dose versus continuous low-dose antibiotic prophylaxis for recurrent urinary tract infections in postmenopausal women: a randomized controlled study. The Journal of international medical research 39(6), 2335-43

Appendix G: Quality assessment of included studies

G.1 Lactobacillus

Table 4: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Grin et al. 2013
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
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 – lactobacillus preparations are available in the UK
Were all important outcomes considered?	No – only a single outcome was reported
Are the benefits worth the harms and costs?	See GRADE profiles

Table 5: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Schwenger et al. 2015
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
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?	No - only a single outcome was reported
Are the benefits worth the harms and costs?	See GRADE profiles

G.2 D-Mannose

Table 6: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Kranjcec et al. 2014
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?	Unclear[a]
Were the groups similar at the start of the trial?	Yes
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
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
[a] Not specified	

G.3 Cranberry products

Table 7: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Jepson et al. 2012
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
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

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

Study reference	Fu et al. 2018
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
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

Table 9: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Roshidibonab et al. 2018
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
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

Table 10: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Beerepoot et al. 2011	Uberos et al. 2012
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?	Yes	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]

[a] Patient population included children with vesicoureteral reflux (VUR)

G.4 Oestrogens

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

Study reference	Perrotta 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
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.5 Antimicrobials in non-pregnant women

Table 12: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Albert et al. 2004	Muller et al. 2017
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?	No	No
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 [a]	Yes [a]
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 [b]	Unclear [b]
Were all important outcomes considered?	Yes [c]	Yes [c]
Are the benefits worth the harms and costs?	See GRADE profiles	

[a] 9 studies could not be pooled in a meta-analysis due to uncommon features in the individual studies
[b] Not all the antibiotics reviewed are available for use in the UK
[c] The review planned to assess a number of outcomes, but there was no evidence available for all outcomes

Table 13: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Zhong et al. 2011[a]
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?	Unclear
Were the groups similar at the start of the trial?	Yes
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
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

[a] Summary statistics, risk ratio, and 95% confidence interval (CI) not reported; calculated by NICE

G.6 Antimicrobials in pregnant women

Table 14: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Schneeberger et al. 2015
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
If the results of the review have been combined, was it reasonable to do so?	N/A
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.7 Antimicrobials in a mixed population of adults and children

Table 15: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Muller et al. 2017
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?	Unclear[a]
Did the review's authors do enough to assess the quality of the included studies?	Yes
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?	No[b]
Are the benefits worth the harms and costs?	See GRADE profiles

Study reference	Muller et al. 2017
[a] Studies were included if they were controlled trials, evaluating oral doses of nitrofurantoin. The majority of studies included were randomised (81%), with a small proportion double-blinded (27%). [b] The study did not report all the secondary outcomes they planned *a priori*.	

G.8 Antimicrobials in children

Table 16: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Dai et al. 2010	Williams and Craig 2011
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	Yes
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	No[b]
Are the benefits worth the harms and costs?	See GRADE profiles	
[a] Most studies did not report a clear inclusion and exclusion criteria for participants entry into the study; it was possible for patients to be misclassified, there was also significant heterogeneity despite the use of a random effects model. [b] Not all planned outcomes were reported; and in some studies 'repeat positive urine culture' was reported instead of the recurrence of urinary tract infection		

Appendix H: GRADE profiles

H.1 Lactobacillus

Table 17: GRADE profile – lactobacillus versus placebo in premenopausal women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lactobacillus	Placebo	Relative (95% CI)	Absolute		
Risk of recurrent urinary tract infection (follow-up 1-12 months)												
5[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	44/147 (29.9%)	51/147 (34.7%)	RR 0.85 (0.58 to 1.25)	52 fewer per 1000 (from 146 fewer to 87 more)	⊕⊕OO LOW	CRITICAL
Risk of recurrent urinary tract infection - sensitivity analysis of only effective strains of lactobacillus[3] (follow-up 1-12 months)												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	10/62 (16.1%)	21/65 (32.3%)	RR 0.51 (0.26 to 0.99)	158 fewer per 1000 (from 239 fewer to 3 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CI, confidence interval; RR, risk ratio												

[1] Grin et al. 2013
[2] Downgraded 1 level – at a minimal important difference of 25%, data are consistent with no meaningful difference, appreciable harm or appreciable benefit
[3] Effective strains of lactobacillus as defined by study authors
[4] Downgraded 1 level – at a minimal important difference of 25%, data are consistent with no meaningful difference or appreciable harm with placebo

Table 18: GRADE profile – lactobacillus versus 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	Lactobacillus	Co-trimoxazole	Relative (95% CI)	Absolute		
Symptomatic bacterial urinary tract infection												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	serious[3]	none	86/115 (74.8%)	72/108 (66.7%)	RR 1.12 (0.95 to 1.33)	80 more per 1000 (from 33 fewer to 220 more)	⊕⊕OO LOW	CRITICAL
Symptomatic bacterial urinary tract infection - worst case scenario probiotics												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[3]	none	91/115 (79.1%)	72/108 (66.7%)	RR 1.19 (1.01 to 1.4)	127 more per 1000 (from 7 more to 267 more)	⊕⊕⊕O MODERATE	CRITICAL
Symptomatic bacterial urinary tract infection - worst case scenario antibiotics												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[4]	none	86/115 (74.8%)	97/108 (89.8%)	RR 0.83 (0.74 to 0.94)	153 fewer per 1000 (from 234 fewer to 54 fewer)	⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lactobacillus	Co-trimoxazole	Relative (95% CI)	Absolute		
No. of people experiencing at least 1 adverse event												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	66/125 (52.8%)	74/127 (58.3%)	NICE analysis: RR 0.91 (0.73 to 1.13)[5]	52 fewer per 1000 (from 157 fewer to 76 more)	⊕⊕OO LOW	CRITICAL
Number of adverse events												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	7/125 (5.6%)	15/127 (11.8%)	NICE analysis: RR 0.47 (0.2 to 1.12)[5]	63 fewer per 1000 (from 94 fewer to 14 more)	⊕⊕OO LOW	CRITICAL

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

[1] Schwenger et al. 2015 (NAPRUTI Study II 2006)
[2] Downgraded 1 level - high risk of attrition bias
[3] Downgraded 1 level – at a minimal important difference of 25%, data are consistent with no meaningful difference or appreciable harm with lactobacillus
[4] Downgraded 1 level – at a minimal important difference of 25%, data are consistent with no meaningful difference or appreciable harm with co-trimoxazole
[5] RR and 95% CI not reported, calculated by NICE assuming an intention-to-treat analysis was done

H.2 D-mannose in non-pregnant women

Table 19: GRADE profile – D-mannose versus no treatment

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	D-mannose	No treatment	Relative (95% CI)	Absolute		
Participants with recurrent urinary tract infection												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	15/103 (14.6%)	62/102 (60.8%)	RR 0.24 (0.15 to 0.39)[2]	462 fewer per 1000 (from 517 fewer to 371 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

Abbreviations: CI, Confidence interval; N/A, Not applicable; RR, Relative risk

[1] Kranjcec et al. 2014
[2] 95% confidence interval not stated; intervals calculated by NICE

Table 20: GRADE profile – D-mannose versus antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	D-mannose	Antibiotics	Relative (95% CI)	Absolute		
Participants with recurrent urinary tract infection												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	D-mannose	Antibiotics	Relative (95% CI)	Absolute		
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	very serious[2]	none	15/103 (14.6%)	21/103 (20.4%)	RR 0.71 (0.39 to 1.31)[3]	59 fewer per 1000 (from 124 fewer to 63 more)	⊕⊕OO LOW	CRITICAL
Adverse events												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	8/103 (7.8%)	29/103 (28.2%)	RR 0.28 (0.13 to 0.57)[3]	203 fewer per 1000 (from 245 fewer to 121 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

Abbreviations: CI, Confidence interval; N/A, Not applicable; RR, Relative risk

[1] Kranjcec et al. 2014
[2] Downgraded 2 levels - at a minimal important difference of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[3] 95% confidence interval not stated; calculated by NICE

H.3 Cranberry products

Table 21: GRADE profile – cranberry products versus placebo or no treatment in women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cranberry products	Placebo or no treatment	Relative (95% CI)	Absolute		
Participants with one or more UTI at follow-up												
4[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	very serious[3]	none	64/322 (19.9%)	62/272 (22.8%)	RR 0.74 (0.42 to 1.31)	59 fewer per 1000 (from 132 fewer to 71 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: UTI, urinary tract infection; CI, Confidence interval; N/A, Not applicable; RR, Relative risk

[1] Jepson et al. 2012
[2] Downgraded 1 level – heterogeneity >50%
[3] Downgraded 2 levels - at a minimal important difference of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Data from study identified following consultation

Table 22: GRADE profile – cranberry products versus placebo or no treatment in women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cranberry	Placebo or no treatment	Relative (95% CI)	Absolute		
Incidence of urinary tract infection (symptom or culture confirmed) (follow-up 6 to 12 months)												
7[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	165/796 (20.7%)	186/702 (26.5%)	RR 0.74 (0.55 to 0.98)	69 fewer per 1000 (from 5 fewer to 119 fewer)	⊕OOO VERY LOW	CRITICAL
Incidence of urinary tract infection (culture confirmed) (follow-up 6 to 12 months)												
5[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	100/504 (19.8%)	98/408 (24.0%)	RR 0.71 (0.45 to 1.12)	70 fewer per 1000 (from 132 fewer to 29 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, confidence interval; RR, relative risk												

[1] Fu et al. 2017
[2] Downgraded 1 level - all studies have high or unclear risk of bias in at least 1 quality assessment domain, as reported by study authors
[3] Downgraded 1 level - heterogeneity ≥50%
[4] Downgraded 1 level - at minimal important difference of 25%, data are consistent with no meaningful difference or appreciable harm with placebo

Table 23: GRADE profile – cranberry juice versus placebo or no treatment in women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cranberry juice	Placebo or no treatment	Relative (95% CI)	Absolute		
Incidence of urinary tract infection (symptom or culture confirmed) (follow-up 6 to 12 months)												
6[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	146/663 (22.0%)	162/609 (26.6%)	RR 0.79 (0.59 to 1.06)	56 fewer per 1000 (from 109 fewer to 16 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, confidence interval; RR, relative risk												

[1] Fu et al. 2017
[2] Downgraded 1 level - all studies have high or unclear risk of bias in at least 1 quality assessment domain, as reported by study authors
[3] Downgraded 1 level - heterogeneity ≥50%
[4] Downgraded 1 level - at minimal important difference of 25%, data are consistent with no meaningful difference or appreciable harm with placebo

Table 24: GRADE profile – cranberry tablets or capsules versus placebo in women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cranberry tablets or capsules	Placebo	Relative (95% CI)	Absolute		
Incidence of urinary tract infection (symptom or culture confirmed) (follow-up 6 to 12 months)												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	18/133 (13.5%)	40/143 (28.0%)	RR 0.48 (0.29 to 0.79)	145 fewer per 1000 (from 199 fewer to 59 fewer)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI, confidence interval; RR, relative risk												

[1] Fu et al. 2017
[2] Downgraded 1 level all studies have high or unclear risk of bias in at least 1 quality assessment domain, as reported by study authors
[3] Downgraded 1 level at minimal important difference of 25%, data are consistent with no meaningful difference or appreciable harm with placebo

Table 22: GRADE profile – cranberry products versus antibiotics in women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cranberry products	Antibiotics	Relative (95% CI)	Absolute		
Repeat symptomatic urinary tract infection												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	91/178 (51.1%)	67/166 (40.4%)	RR 1.31 (0.85 to 2.02)	125 more per 1000 (from 61 fewer to 412 more)	⊕⊕⊕O MODERATE	CRITICAL
Development of antibiotic resistance - premenopausal women												
1[3]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[4]	none	N=221		E. coli isolates from women receiving co-trimoxazole showed antibiotic resistance for amoxicillin, trimethoprim, and trimethoprim-sulfamethoxazole at 1 month prophylaxis (70% resistance). This reduced at 1 month and 3 months after stopping of prophylaxis, returning to baseline at 12 months. E. coli isolates from women receiving cranberry products did not show antibiotic resistance.		⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CI, Confidence interval; N/A, Not applicable; RR, Relative risk												

[1]Jepson et al. 2012
[2]Downgraded 1 level - at a minimal important difference of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[3] Beerepoot et al. 2011
[4] Downgraded 1 level – not assessable

Table 23: GRADE profile – cranberry products versus placebo or no treatment in pregnant women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cranberry products	Placebo or no treatment	Relative (95% CI)	Absolute		
Participants with one or more UTI at follow-up												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	184/325 (56.6%)	194/349 (55.6%)	RR 1.04 (0.93 to 1.17)	22 more per 1000 (from 39 fewer to 94 more)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CI, Confidence interval; N/A, Not applicable; RR, Relative risk												

[1] Jepson et al. 2012
[2] Downgraded by 1 level - high drop-out rate across the studies

Table 24: GRADE profile – cranberry products versus placebo or no treatment in elderly women and men

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cranberry products	Placebo or no treatment	Relative (95% CI)	Absolute		
Participants with one or more UTI at follow-up												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	20/207 (9.7%)	26/206 (12.6%)	RR 0.75 (0.39 to 1.44)	32 fewer per 1000 (from 77 fewer to 56 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, Confidence interval; N/A, Not applicable; RR, Relative risk												

[1] Jepson et al. 2012
[2] Downgraded by 1 level - high drop-out rate across the studies
[3] Downgraded 2 levels - at a 95% confidence interval, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 25: GRADE profile – cranberry products versus placebo or no treatment in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cranberry products	Placebo or no treatment	Relative (95% CI)	Absolute		
Adverse events - any gastrointestinal effect												
4[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	10/328 (3%)	9/269 (3.3%)	RR 0.83 (0.31 to 2.27)	6 fewer per 1000 (from 23 fewer to 42 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI, Confidence interval; N/A, Not applicable; RR, Relative risk												

[1] Jepson et al. 2012

[2] Downgraded 2 levels - at a minimal important difference of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 26: GRADE profile – cranberry products versus antibiotics in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cranberry products	Antibiotics	Relative (95% CI)	Absolute		
Adverse events – gastrointestinal												
2[i]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[ii]	none	17/178 (9.6%)	20/166 (12.0%)(	RR 0.78 (0.42 to 1.42)	27 fewer per 1000 (from 70 fewer to 51 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI, Confidence interval; N/A, Not applicable; RR, Relative risk												

[1] Jepson et al. 2012
[2] Downgraded 1 level – heterogeneity >50%
[3] Downgraded 1 level - at a minimal important difference of 25%, data are consistent with no meaningful difference or appreciable harm with placebo or no treatment

Table 27: GRADE profile – cranberry products versus placebo or no treatment in children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cranberry products	Placebo or no treatment	Relative (95% CI)	Absolute		
Participants with one or more UTI at follow-up												
2[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	25/153 (16.3%)	46/156 (29.5%)	RR 0.48 (0.19 to 1.22)	153 fewer per 1000 (from 239 fewer to 65 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI, Confidence interval; N/A, Not applicable; RR, Relative risk												

[1]Jepson et al. 2012

[2] Downgraded 2 levels - at a minimal important difference of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Data from study identified following consultation

Table 31: GRADE profile – cranberry products versus placebo in children

Quality assessment							No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cranberry	Placebo	Relative (95% CI)		
Incidence of urinary tract infection (culture confirmed) (follow-up 2 to 12 months)											
8[1]	randomised trials	serious[2]	serious[3]	serious[4]	serious[5]	none	n =293	n =278	OR 0.31 (0.21 to 0.46)[6]	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, confidence interval; OR, odds ratio											

[1] Roshdibonab et al. 2017
[2] Downgraded 1 level - 5 of the included studies have high or unclear risk of bias in at least 1 quality assessment criteria domain, as reported by study authors
[3] Downgraded 1 level - heterogeneity ≥50%
[4] Downgraded 1 level - 2 of the included studies included people with catheters
[5] Downgraded 1 level - not assessable
[6] Relative risk could be calculated by NICE as the data is not available

Table 28: GRADE profile – cranberry products versus antibiotics in children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cranberry products	Antibiotics	Relative (95% CI)	Absolute		
Repeat symptomatic urinary tract infection												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	8/75 (10.7%)	18/117 (15.4%)	RR 0.69 (0.32 to 1.51)	48 fewer per 1000 (from 105 fewer to 78 more)	⊕⊕OO LOW	CRITICAL
Development of antibiotic resistance												
1[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	N=192		No differences between the treatment branches were observed in the rate of percentage of resistance to amoxicillin or co-trimoxazole (χ2 = 2.7; P-value not significant and χ2 = 0.3; P-value not significant, respectively).		⊕⊕⊕O MODERATE	CRITICAL

[1] Jepson et al. 2012
[2] Downgraded 2 levels - at a minimal important difference of 25%, data are consistent with no meaningful difference, appreciable harm or appreciable benefit
[3] Uberos et al. 2012
[4] Downgraded 1 level - not assessable

H.4 Oestrogens in post-menopausal women

Table 29: GRADE profile – oral oestrogen versus placebo or no treatment

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral oestrogen	Placebo	Relative (95% CI)	Absolute		
Urinary tract infection at the end of the treatment period												
4[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	157/1389 (11.3%)	147/1409 (10.4%)	RR 1.08 (0.88 to 1.33)	8 more per 1000 (from 13 fewer to 34 more)	⊕⊕⊕O MODERATE	CRITICAL
All adverse events												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/51 (23.5%)	2/53 (3.8%)	RR 5.11 (1.39 to 18.76)	155 more per 1000 (from 15 more to 670 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Abbreviations: CI, Confidence interval; N/A, Not applicable; RR, Relative risk												

[1] Perrotta et al. 2010
[2] Downgraded 1 level - at a minimal important difference of 25%, data are consistent with no meaningful difference or appreciable harm with oral oestrogen

Table 30: GRADE profile – vaginal oestrogen versus placebo or no treatment

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaginal oestrogen	Placebo/no treatment	Relative (95% CI)	Absolute		
Urinary tract infection at the end of the treatment period (estradiol-releasing silicone vaginal ring [Estring] vs no treatment)												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[2]	none	27/53 (50.9%)	44/55 (80%)	RR 0.64 (0.47 to 0.86)	288 fewer per 1000 (from 424 fewer to 112 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Urinary tract infection at the end of the treatment period (topically applied intravaginal oestriol cream vs placebo)												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	8/50 (16%)	27/43 (62.8%)	RR 0.25 (0.13 to 0.5)	471 fewer per 1000 (from 546 fewer to 314 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Any adverse event												
2[1]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	serious[2]	none	24/103 (23.3%)	5/98 (5.1%)	RR 4.57(1.81 to 11.5)	190 more per 1000 (from 17 fewer to 1000 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI, Confidence interval; N/A, Not applicable; RR, Relative risk												

[1] Perrotta et al. 2010
[2] Downgraded 1 level - at a minimal important difference of 25%, data are consistent with no meaningful difference or appreciable harm with no treatment
[3] Downgraded 1 level - heterogeneity > 50%

Table 31: GRADE profile – vaginal oestrogen versus oral antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaginal oestrogen	Oral antibiotics	Relative (95% CI)	Absolute		
Urinary tract infection at the end of the treatment period (oestriol-containing vaginal pessary vs oral antibiotics)												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	serious[3]	none	58/86 (67.4%)	44/85 (51.8%)	RR 1.3 (1.01 to 1.68)	155 more per 1000 (from 5 more to 352 more)	⊕⊕OO LOW	CRITICAL
Urinary tract infection at the end of the treatment period (Vaginal oestrogens [intravaginal premarin cream] vs oral antibiotics)												
1[1]	randomised trials	very serious[4]	N/A	no serious indirectness	no serious imprecision	none	2/27 (7.4%)	12/15 (80%)	RR 0.09 (0.02 to 0.36)	728 fewer per 1000 (from 784 fewer to 512 fewer)	⊕⊕OO LOW	CRITICAL
Urinary tract infection 2 months after treatment												
1[1]	randomised trials	very serious[4]	N/A	no serious indirectness	very serious[5]	none	2/27 (7.4%)	2/15 (13.3%)	RR 0.56 (0.09 to 3.55)	59 fewer per 1000 (from 121 fewer to 340 more)	⊕OOO VERY LOW	CRITICAL
Adverse events												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	19/116 (16.4%)	0/100 (0%)	RR 12.86 (1.75 to 94.29)	-	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI, Confidence interval; N/A, Not applicable; RR, Relative risk

[1] Perrotta et al. 2010
[2] Downgraded 1 level - large drop-out rate (29%)
[3] Downgraded 1 level - at a minimal important difference of 25%, data are consistent with no meaningful difference or appreciable harm with vaginal oestrogen
[4] Downgrade 2 levels - small study, 2:1 randomisation, relative short treatment duration compared to other studies (3 months), unclear why antibiotic treatment would result in 80% recurrent UTI
[5] Downgraded 2 levels - at a minimal important difference of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[6] Downgraded 1 level - very wide CI interval

H.5 Antimicrobials in non-pregnant women

Table 32: GRADE profile – antibiotics versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic	Placebo	Relative (95% CI)	Absolute		
Patients with at least one microbiological recurrence during prophylaxis												
10[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	24/195 (12.3%)	116/177 (65.5%)	RR 0.21 (0.13 to 0.34)	518 fewer per 1000 (from 570 fewer to 433 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Patients with at least one clinical recurrence during prophylaxis												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic	Placebo	Relative (95% CI)	Absolute		
7[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/136 (7.4%)	62/121 (51.2%)	RR 0.15 (0.08 to 0.28)	436 fewer per 1000 (from 471 fewer to 369 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Patients with at least one microbiological recurrence after prophylaxis												
2[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	very serious[3]	none	23/44 (52.3%)	15/26 (57.7%)	RR 0.82 (0.44 to 1.53)	104 fewer per 1000 (from 323 fewer to 306 more)	⊕OOO VERY LOW	CRITICAL
Severe side effects												
10[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	9/225 (4%)	4/195 (2.1%)	RR 1.58 (0.47 to 5.28)	12 more per 1000 (from 11 fewer to 88 more)	⊕⊕OO LOW	CRITICAL
Other side effects (non-serious side effects)												
10[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[4]	none	34/225 (15.1%)	15/195 (7.7%)	RR 1.78 (1.06 to 3.00)	60 more per 1000 (from 5 more to 154 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI, Confidence interval; RR, Relative risk												

[1] Albert et al. 2004
[2] Downgraded 1 level – heterogeneity > 50%
[3] Downgraded 2 levels – at a minimal important difference of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[4] Downgraded 1 level – at a minimal important difference of 25%, data are consistent with no meaningful difference or appreciable harm with antibiotics

Table 33: GRADE profile – single-dose versus continuous antibiotic prophylaxis in postmenopausal women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intermittent patient-initiated single dose antibiotics	Continuous antibiotics	Relative (95% CI)	Absolute		
Patients with at least 1 recurrent urinary tract infection												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[2]	none	25/31 (80.6%)[3]	26/37 (70.3%)[3]	No summary statistic reported NICE analysis RR 1.15 (0.87 to 1.51)[4]	105 more per 1000 (from 91 fewer to 358 more)	⊕⊕⊕O MODERATE	CRITICAL
Any adverse events												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[5]	none	21/33 (63.6%)[3]	37/40 (92.5%)[3]	No summary statistic reported NICE analysis RR 0.69 (0.52 to 0.9)[4]	287 fewer per 1000 (from 444 fewer to 93 fewer)	⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intermittent patient-initiated single dose antibiotics	Continuous antibiotics	Relative (95% CI)	Absolute		
Abbreviations: CI, Confidence interval; N/A, Not applicable; RR, Relative risk												

[1] Zhong et al. 2011
[2] Downgraded 1 level - at a minimal important difference of 25%, data are consistent with no meaningful difference appreciable harm with intermittent patient-initiated single dose antibiotics
[3] Summary statistics not stated; calculated by NICE
[4] Risk ratio and 95% confidence interval not stated; calculated by NICE
[5] Downgraded 1 level - at a minimal important difference of 25%, data are consistent with no meaningful difference or appreciable harm with continuous antibiotics

Table 34: GRADE profile – single-dose versus continuous antibiotic prophylaxis in pre-menopausal women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Post coital ciprofloxacin	Continuous ciprofloxacin	Relative (95% CI)	Absolute		
Patients with at least one microbiological recurrence during prophylaxis												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	very serious[2]	none	2/70 (2.9%)	2/65 (3.1%)	RR 0.93 (0.13 to 6.4)	2 fewer per 1000 (from 27 fewer to 166 more)	⊕⊕OO LOW	CRITICAL
Patients with at least one clinical recurrence during prophylaxis												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	very serious[2]	none	4/70 (5.7%)	3/65 (4.6%)	RR 1.24 (0.29 to 5.32)	11 more per 1000 (from 33 fewer to 199 more)	⊕⊕OO LOW	CRITICAL
Other side effects (non-serious side effects)												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	very serious[2]	none	4/70 (5.7%)	9/65 (13.8%)	RR 0.41 (0.13 to 1.28)	82 fewer per 1000 (from 120 fewer to 39 more)	⊕⊕OO LOW	CRITICAL
Patients with at least one microbiological recurrence after prophylaxis												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	very serious[2]	none	25/70 (35.7%)	21/65 (32.3%)	RR 1.11 (0.69 to 1.77)	36 more per 1000 (from 100 fewer to 249 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI, Confidence interval; N/A, Not applicable; RR, Relative risk												

[1] Albert et al. 2004 (Melekos et al. 1998)
[2] Downgraded 2 levels - at a minimal important difference of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

H.6 Antimicrobials in pregnant women

Table 35: GRADE profile – nitrofurantoin and close monitoring versus close monitoring

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nitrofurantoin and close surveillance	Close surveillance alone	Relative (95% CI)	Absolute		
Recurrent pyelonephritis												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	very serious[2]	none	6/82 (7.3%)	7/85 (8.2%)	RR 0.89 (0.31 to 2.53)	9 fewer per 1000 (from 57 fewer to 126 more)	⊕⊕OO LOW	CRITICAL
Recurrent urinary tract infection (cystitis)												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	very serious[2]	none	2/82 (2.4%)	7/85 (8.2%)	RR 0.3 (0.06 to 1.38)	58 fewer per 1000 (from 77 fewer to 31 more)	⊕⊕OO LOW	CRITICAL
Asymptomatic bacteriuria in women with 90% clinical attendance												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[3]	none	14/43 (32.6%)	35/59 (59.3%)	RR 0.55 (0.34 to 0.89)	267 fewer per 1000 (from 392 fewer to 65 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Preterm birth (<37 weeks)												
1[1]	randomised trials	no serious risk of bias	N/A	no serious indirectness	very serious[2]	none	7/73 (9.6%)	6/74 (8.1%)	RR 1.18 (0.42 to 3.35)	15 more per 1000 (from 47 fewer to 191 more)	⊕⊕OO LOW	CRITICAL
Birthweight (g) (Better indicated by higher values)												
1[1]	randomised trials	serious[4]	N/A	no serious indirectness	serious[5]	none	71	76	MD 113 lower (327.2 lower to 101.2 higher)		⊕⊕OO LOW	CRITICAL
5-min Apgar score <7												
1[1]	randomised trials	serious[4]	N/A	no serious indirectness	very serious[2]	none	2/73 (2.7%)	1/74 (1.4%)	RR 2.03 (0.19 to 21.87)	14 more per 1000 (from 11 fewer to 282 more)	⊕OOO VERY LOW	CRITICAL
Miscarriages												
1[1]	randomised trials	serious[4]	N/A	no serious indirectness	very serious[2]	none	3/82 (3.7%)	1/85 (1.2%)	RR 3.11 (0.33 to 29.29)	25 more per 1000 (from 8 fewer to 333 more)	⊕OOO VERY LOW	CRITICAL

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

[1] Schneeberger et al. 2015
[2] Downgraded 2 levels - at a minimal important difference of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[3] Downgraded 1 level - at a 95% confidence interval, data are consistent with no meaningful difference, appreciable benefit with nitrofurantoin
[4] Downgraded 1 level -it is unclear how the lack of blinding would have led to a under or over estimation of effect
[5] Downgraded 1 level – at a minimal important difference of 0.5 standard deviation of the close surveillance arm, data are consistent with no meaningful difference or appreciable benefit with close surveillance alone

H.7 Antimicrobials in a mixed population of adults and children

Table 36: GRADE profile – nitrofurantoin versus placebo in adults and children

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		
Occurrence of urinary tract infection												
8[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	38/169 (22.5%)	190/322 (59%)	RR 0.38 (0.28 to 0.5)	366 fewer per 1000 (from 425 fewer to 295 fewer)	⊕⊕OO LOW	CRITICAL
Abbreviations: N/A ,not applicable; CI, confidence interval: RR, risk ratio												

[1] Muller et al. 2017
[2] Downgraded 1 level - high risk of bias associated with the lack of randomisation in 3 studies; randomisation was unclear in 3 studies.
[3] Downgraded by 1 level - one study included patients with spinal cord injury, another study included children with neurogenic bladder

[5] Downgraded by 1 level – not assessable

Table 37: GRADE profile – nitrofurantoin versus antibiotics in adults and children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nitrofurantoin	Antibiotics	Relative (95% CI)	Absolute		
Occurrence of urinary tract infection												
22[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	119/511 (23.3%)	211/808 (26.1%)	RR 0.93 (0.68 to 1.26)	18 fewer per 1000 (from 84 fewer to 68 more)	⊕OOO VERY LOW	CRITICAL
Mild adverse effects												
22[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious	none	154/503 (30.6%)	82/702 (11.7%)	RR 2.24 (1.77 to 2.83)	145 more per 1000 (from 90 more to 214 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI, confidence interval: RR, risk ratio												

[1] Muller et al. 2017
[2] Downgraded 2 levels - majority of evidence was to be of high risk of bias, which is likely to affect the measurement of the outcome
[3] Downgraded 2 levels – at a minimal important difference of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 38: GRADE profile – nitrofurantoin versus methenamine hippurate in adults and children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nitrofurantoin	Methenamine hippurate	Relative (95% CI)	Absolute		
Occurrence of urinary tract infection												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	24/67 (35.8%)	66/129 (51.2%)	RR 0.60 (0.43 to 0.85)	205 fewer per 1000 (from 292 fewer to 77 fewer)	⊕⊕OO LOW	CRITICAL
Mild side effects												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	24/67 (35.8%)	9/129 (7%)	RR 4.22 (2.06 to 8.67)	225 more per 1000 (from 74 more to 535 more)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CI, confidence interval: RR, risk ratio												

[1] Muller et al. 2017
[2] Downgraded by 1 level as majority of evidence has high risk of bias, which is likely to affect the measurement of the outcome
[3] Downgraded 1 level – at a 95% confidence interval, data are consistent with no meaningful difference or appreciable harm with methenamine hippurate

Table 39: GRADE profile – nitrofurantoin versus trimethoprim in adults and children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nitrofurantoin	Trimethoprim	Relative (95% CI)	Absolute		
Occurrence of urinary tract infection												
5[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	very serious[4]	none	32/142 (22.5%)	61/208 (29.3%)	RR 0.81 (0.38 to 1.71)	56 fewer per 1000 (from 182 fewer to 208 more)	⊕OOO VERY LOW	IMPORTANT
Mild adverse effects												
4[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	58/138 (42%)	28/192 (14.6%)	RR 2.20 (1.51 to 3.2)	175 more per 1000 (from 74 more to 321 more)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CI, confidence interval: RR, risk ratio												

[1] Muller et al. 2017
[2] Downgraded by 1 level as majority of evidence has high risk of bias
[3] Downgraded 1 level – heterogeneity > 50%
[4] Downgraded 2 levels – at a minimal important difference of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 40: GRADE profile – nitrofurantoin versus co-trimoxazole in adults and children

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		
Occurrence of urinary tract infection												
4[1]	randomised trials	very serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	3/25 (12%)	5/56 (8.9%)	RR 1.42 (0.17 to 12)	37 more per 1000 (from 74 fewer to 982 more)	⊕OOO VERY LOW	CRITICAL
Mild adverse effects												
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	very serious[4]	none	1/6 (16.7%)	1/13 (7.7%)	RR 2.17 (0.16 to 29.1)	90 more per 1000 (from 65 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, confidence interval: RR, risk ratio												

[1] Muller et al. 2017
[2] Downgraded by 1 level as majority of evidence has high risk of bias
[3] Downgraded by 1 level as one study included children with vesicoureteral reflux
[4] Downgraded 2 levels – at a minimal important difference of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 41: GRADE profile – nitrofurantoin versus beta-lactams in adults and children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nitrofurantoin	Beta-lactams	Relative (95% CI)	Absolute		
Occurrence of urinary tract infection												
5[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	19/115 (16.5%)	30/134 (22.4%)	RR 0.84 (0.49 to 1.44)	36 fewer per 1000 (from 114 fewer to 99 more)	⊕OOO VERY LOW	CRITICAL
Mild adverse effects												
5[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	32/128 (25%)	18/147 (12.2%)	RR 1.99 (1.19 to 3.32)	121 more per 1000 (from 23 more to 284 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, confidence interval: RR, risk ratio												

[1] Muller et al. 2017
[2] Downgraded 1 level - majority of evidence has very high risk of bias
[3] Downgraded 2 levels – at a minimal important difference of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[4] Downgraded 1 level – at a minimal important difference of 25%, data are consistent with no meaningful difference or appreciable harm with nitrofurantoin

Table 42: GRADE profile – nitrofurantoin versus quinolones in adults and children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nitrofurantoin	Quinolones	Relative (95% CI)	Absolute		
Occurrence of urinary tract infection												
3[1]	randomised trials	very serious[2]	serious[3]	serious[4]	very serious[5]	none	25/84 (29.8%)	15/102 (14.7%)	RR 2.26 (0.73 to 7)	185 more per 1000 (from 40 fewer to 882 more)	⊕OOO VERY LOW	CRITICAL
Mild adverse effects												
3[1]	randomised trials	very serious[2]	serious[3]	serious[4]	very serious[5]	none	24/112 (21.4%)	19/118 (16.1%)	RR 1.37 (0.79 to 2.36)	60 more per 1000 (from 34 fewer to 219 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, confidence interval: RR, risk ratio												

[1] Muller et al. 2017
[2] Downgraded by 1 level as majority of evidence has high risk of attrition bias, which is likely to affect the measurement of the outcome
[3] Downgraded 1 level – heterogeneity > 50%
[4] Downgraded 1 level as nitrofurantoin was compared to cinoxacin (not available in the UK), in 2 of the studies
[5] Downgraded 2 levels – at a minimal important difference of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

H.8 Antimicrobials in children

Table 43: GRADE profile – antibiotic versus placebo or no treatment

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic	Placebo or no treatment	Relative (95% CI)	Absolute		
Recurrence of symptomatic urinary tract infection - no vesicoureteral reflux												
3[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	very serious[5]	none	20/273 (7.3%)	30/218 (13.8%)	RR 0.56 (0.15 to 2.12)	61 fewer per 1000 (from 117 fewer to 154 more)	⊕OOO VERY LOW	CRITICAL
Recurrence of symptomatic urinary tract infection												
4[1]	randomised trials	serious[2]	serious[3]	serious[4]	very serious[5]	none	58/553 (10.5%)	81/471 (17.2%)	RR 0.75 (0.36 to 1.53)	43 fewer per 1000 (from 110 fewer to 91 more)	⊕OOO VERY LOW	CRITICAL
Repeat positive culture												
4[1]	randomised trials	serious[2]	very serious[3]	serious[4]	serious[6]	none	43/270 (15.9%)	76/197 (38.6%)	RR 0.31 (0.08 to 1.18)	266 fewer per 1000 (from 355 fewer to 69 more)	⊕OOO VERY LOW	CRITICAL
Microbial resistance to prophylactic drug												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic	Placebo or no treatment	Relative (95% CI)	Absolute		
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[5]	none	18/51 (35.3%)	11/67 (16.4%)	RR 2.4 (0.62 to 9.26)	230 more per 1000 (from 62 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
All adverse events												
2[1]	randomised trials	serious[2]	very serious[3]	serious[4]	very serious[5]	none	19/499 (3.8%)	10/415 (2.4%)	RR 2.31 (0.03 to 170.67)	32 more per 1000 (from 23 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Withdrawal due to adverse events												
2[1]	randomised trials	serious[2]	no serious inconsistency	serious[4]	very serious[5]	none	4/288 (1.4%)	10/288 (3.5%)	RR 0.40 (0.13 to 1.26)	21 fewer per 1000 (from 30 fewer to 9 more)	⊕OOO VERY LOW	CRITICAL
Rate of new or deteriorated renal scars												
7[7]	randomised trials	serious[2]	no serious inconsistency	serious[4]	very serious[5]	none	17/578 (2.9%)	18/515 (3.5%)	RR 0.95 (0.51 to 1.78)	2 fewer per 1000 (from 17 fewer to 27 more)	⊕OOO VERY LOW	CRITICAL
Emergence of resistance												
1[8]	randomised trials	serious[9]	N/A	no serious indirectness	serious[10]	none	n=15		*E. coli* cultures were replaced over treatment by resistant strains in children receiving nitrofurantoin, but not in children receiving placebo.		⊕⊕OO LOW	CRITICAL
Abbreviations: CI, confidence interval: RR, risk ratio:, N/A, not applicable												

[1] Williams and Craig 2011
[2] Downgraded by 2 levels due to a very high risk of bias - lack of randomisation, lack of blinding, selective reporting of outcomes
[3] Downgraded 1 level – heterogeneity > 50%
[4] Downgraded by 1 level as most studies did not report a clear inclusion and exclusion criteria for participants entry into the study; it was possible for patients to be misclassified
[5] Downgraded 2 levels – at a minimal important difference of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[6] Downgraded 1 level – at a minimal important difference of 25%, data are consistent with no meaningful difference or appreciable harm with placebo
[7] Dai et al. 2010
[8] Muller et al. 2017
[9] Downgraded 1 level - high risk of bias associated with the lack of randomisation in 3 studies and randomisation was unclear in 3 studies included in systematic review; unclear which studies this is relevant to
[10] Downgraded 1 level – not assessable

Table 44: GRADE profile – Nitrofurantoin versus trimethoprim

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nitrofurantoin	Trimethoprim	Relative (95% CI)	Absolute		
Repeat positive culture												
1[1]	randomised trials	no serious risk of bias	N/A	serious[2]	no serious imprecision	none	12/60 (20%)	37/60 (61.7%)	RR 0.3 (0.2 to 0.6)	432 fewer per 1000 (from 493 fewer to 247 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events												
1[1]	randomised trials	no serious risk of bias	N/A	serious[2]	serious[3]	none	8/31 (25.8%)	18/29 (62.1%)	RR 0.42 (0.21 to 0.81)	360 fewer per 1000 (from 490 fewer to 118 fewer)	⊕⊕OO LOW	CRITICAL
Emergence of resistance												
1[4]	randomised trials	serious[5]	N/A	serious[6]	serious[7]	none	n=67	n=63	Resistance rates linked to nitrofurantoin prophylaxis reduced (9% to 7%; quality not accessible) whereas rates associated with trimethoprim prophylaxis increased (8% to 47%)		⊕⊕OO VERY LOW	CRITICAL
Abbreviations: N/A, not applicable; CI, confidence interval: RR, risk ratio												

[1] Williams and Craig 2011
[2] Downgraded by 1 level as 30 children had vesicoureteral reflux or significant structural abnormalities
[3] Downgraded 1 level – at a minimal important difference of 25%, data are consistent with no meaningful difference or appreciable harm with trimethoprim
[4] Muller et al. 2017
[5] Downgraded 1 level - high risk of bias associated with the lack of randomisation in 3 studies and randomisation was unclear in 3 studies included in systematic review; unclear which studies this is relevant to
[6] Downgraded by 1 level - study included children with neurogenic bladder
[7] Downgraded 1 level – not assessable

Table 45: GRADE profile – Nitrofurantoin versus co-trimoxazole

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		
Recurrence of symptomatic urinary tract infection												
1[1]	randomised trials	serious[2]	N/A	serious[3]	serious[4]	none	17/66 (25.8%)	30/66 (45.5%)	RR 0.57 (0.35 to 0.92)	195 fewer per 1000 (from 295 fewer to 36 fewer)	⊕OOO VERY LOW	CRITICAL

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		
Microbial resistance to prophylactic drugs												
2[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	10/29 (34.5%)	45/67 (67.2%)	RR 0.54 (0.31 to 0.92)	309 fewer per 1000 (from 463 fewer to 54 fewer)	⊕OOO VERY LOW	CRITICAL
Abbreviations: N/A, not applicable; CI, confidence interval: RR, risk ratio												

[1] Williams and Craig 2011
[2] Downgraded 2 levels - a very high risk of bias - lack of randomisation, lack of blinding, selective reporting of outcomes
[3] Downgraded 1 level – classification of children was unclear
[4] Downgraded 1 level – at a minimal important difference of 25%, data are consistent with no meaningful difference or appreciable harm with co-trimoxazole

Table 46: GRADE profile – Nitrofurantoin versus cefixime

Quality assessment							No of patients		Effect (95% CI)	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nitrofurantoin	Cefixime			
Repeat positive culture											
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	no serious imprecision	none	3/30 (10%)	2/27 (7.4%)	Risk difference 0.03 (-0.12 to 0.17)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events											
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	no serious imprecision	none	37/60 (61.7%)	17/60 (28.3%)	Risk difference 2.18 (1.39 to 3.41)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: N/A, not applicable; CI, confidence interval: RR, risk ratio											

[1] Williams et al. 2011
[2] Downgraded 1 level - most studies did not report a clear inclusion and exclusion criteria for participants entry into the study; it was possible for patients to be misclassified, not all planned outcomes were reported

[1]Jepson et al. 2012
[2] Downgraded 2 levels - at a minimal important difference of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Appendix I: Studies not-prioritised

Study reference	Reason
Afshar K, Stothers L, Scott H, and MacNeily A E (2012) Cranberry juice for the prevention of pediatric urinary tract infection: a randomized controlled trial. The Journal of urology 188(4 Suppl), 1584-7	This RCT does not provide additional evidence that adds to the evidence from a prioritised systematic review
Antachopoulos Charalampos, Ioannidou Maria, Tratselas Athanasios, Iosifidis Elias, Katragkou Aspasia, Kadiltzoglou Paschalis, Kollios Konstantinos, and Roilides Emmanuel (2016) Comparison of cotrimoxazole vs. second-generation cephalosporins for prevention of urinary tract infections in children. Pediatric nephrology (Berlin, and Germany) 31(12), 2271-2276	This RCT does not provide additional evidence that adds to the evidence from a prioritised systematic review
Bailey David T, Dalton Carol, Joseph Daugherty, F, and Tempesta Michael S (2007) Can a concentrated cranberry extract prevent recurrent urinary tract infections in women? A pilot study. Phytomedicine : international journal of phytotherapy and phytopharmacology 14(4), 237-41	This RCT does not provide additional evidence that adds to the evidence from a prioritised systematic review
Barbosa-Cesnik Cibele, Brown Morton B, Buxton Miatta, Zhang Lixin, DeBusscher Joan, and Foxman Betsy (2011) Cranberry juice fails to prevent recurrent urinary tract infection: results from a randomized placebo-controlled trial. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 52(1), 23-30	RCT included in a systematic review that has been prioritised
Beerepoot M A. J, Geerlings S E, van Haarst, E P, van Charante, N Mensing, ter Riet, and G (2013) Nonantibiotic prophylaxis for recurrent urinary tract infections: a systematic review and meta-analysis of randomized controlled trials. The Journal of urology 190(6), 1981-9	A higher quality systematic review has been prioritised (Perrotta et al. 2011)
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),	This RCT does not provide additional evidence that adds to the evidence from a prioritised systematic review
Bianco L, Perrelli E, Towle V, Ness Ph, and Juthani-Mehta M (2012) Pilot randomized controlled dosing study of cranberry capsules for reduction of bacteriuria plus pyuria in female nursing home residents. Journal of the American Geriatrics Society 60(6), 1180-1	This RCT does not provide additional evidence that adds to the evidence from a prioritised systematic review
Bosmans JE, Beerepoot MA, Prins JM, ter Riet G, and Geerlings SE (2014) Cost-effectiveness of cranberries vs antibiotics to prevent urinary tract infections in premenopausal women: a randomized clinical trial. PloS one 9(4), e91939	No or fewer critical outcomes reported
Caljouw Monique A. A, van den Hout, Wilbert B, Putter Hein, Achterberg Wilco P, Cools Herman J. M, and Gussekloo Jacobijn (2014) Effectiveness of cranberry capsules to prevent urinary tract infections in vulnerable older persons: a double-blind randomized placebo-controlled trial in long-term care facilities. Journal of the American Geriatrics Society 62(1), 103-10	This RCT does not provide additional evidence that adds to the evidence from a prioritised systematic review
Ferrara Pietro, Romaniello Luciana, Vitelli Ottavio, Gatto Antonio, Serva Martina, and Cataldi Luigi (2009) Cranberry juice for the prevention of recurrent urinary tract infections: a randomized controlled trial in children. Scandinavian journal of urology and nephrology 43(5), 369-72	RCT included in a systematic review that has been prioritised

Study reference	Reason
Ledda A, Bottari A, Luzzi R, Belcaro G, Hu S, Dugall M, Hosoi M, Ippolito E, Corsi M, Gizzi G, Morazzoni P, Riva A, Giacomelli L, and Togni S (2015) Cranberry supplementation in the prevention of non-severe lower urinary tract infections: a pilot study. European review for medical and pharmacological sciences 19(1), 77-80	A higher quality systematic review has been prioritised (Fu et al. 2017)
Luís, Â, Domingues F and Pereira L. Can Cranberries Contribute to Reduce the Incidence of Urinary Tract Infections? A Systematic Review with Meta-Analysis and Trial Sequential Analysis of Clinical Trials. The Journal of Urology. Sept 2017;198(3):614–621	A higher quality systematic review has been prioritised (Fu et al. 2017)
Maki Kevin C, Kaspar Kerrie L, Khoo Christina, Derrig Linda H, Schild Arianne L, and Gupta Kalpana (2016) Consumption of a cranberry juice beverage lowered the number of clinical urinary tract infection episodes in women with a recent history of urinary tract infection. The American journal of clinical nutrition 103(6), 1434-42	This RCT does not provide additional evidence that adds to the evidence from a prioritised systematic review
Mathew JL. Antibiotic prophylaxis following urinary tract infection in children: a systematic review of randomized controlled trials. Indian pediatrics. 2010 Jul 1;47(7):599-605.	A higher quality systematic review has been prioritised (Williams and Craig 2011)
McMurdo Marion E. T, Argo Ishbel, Phillips Gabby, Daly Fergus, and Davey Peter (2009) Cranberry or trimethoprim for the prevention of recurrent urinary tract infections? A randomized controlled trial in older women. The Journal of antimicrobial chemotherapy 63(2), 389-95	RCT included in a systematic review that has been prioritised
Mori et al. 2009, Antibiotic prophylaxis for children at risk of developing urinary tract infection: a systematic review. Acta paediatrica (Oslo, and Norway : 1992) 98(11), 1781-6	A higher quality systematic review has been prioritised (Williams and Craig 2011)
Norinder Birgit Stattin, Norrby Ragnar, Palmgren Ann-Chatrin, Hollenberg Sofia, Eriksson Ulla, and Nord Carl Erik (2006) Microflora changes with norfloxacin and pivmecillinam in women with recurrent urinary tract infection. Antimicrobial agents and chemotherapy 50(4), 1528-30	This RCT does not provide additional evidence that adds to the evidence from a prioritised systematic review
Porru D, Parmigiani A, Tinelli C, Barletta D, Choussos D, Di Franco C, Bobbi V, Bassi S, Miller O, Gardella B, Nappi R E, Spinillo A, and Rovereto B (2014) Oral D-mannose in recurrent urinary tract infections in women: A pilot study. Journal of Clinical Urology 7(3), 208-213	This RCT does not provide additional evidence that adds to the evidence from a prioritised systematic review
Price Jameca Renee, Guran Larissa A, Gregory W Thomas, and McDonagh Marian S (2016) Nitrofurantoin vs other prophylactic agents in reducing recurrent urinary tract infections in adult women: a systematic review and meta-analysis. American journal of obstetrics and gynecology 215(5), 548-560	A higher quality systematic review has been prioritised (Muller et al. 2017)
Salo Jarmo, Uhari Matti, Helminen Merja, Korppi Matti, Nieminen Tea, Pokka Tytti, and Kontiokari Tero (2012) Cranberry juice for the prevention of recurrences of urinary tract infections in children: a randomized placebo-controlled trial. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 54(3), 340-6	This RCT does not provide additional evidence that adds to the evidence from a prioritised systematic review
Sengupta K, Alluri K V, Golakoti T, Gottumukkala G V, Raavi J, Kotchrlakota L, Sigalan S C, Dey D, Ghosh S, and Chatterjee A (2011) A randomized, double blind, controlled, dose dependent clinical trial to evaluate the efficacy of a proanthocyanidin standardized whole cranberry (Vaccinium macrocarpon) powder on infections of the urinary tract. Current Bioactive Compounds 7(1), 39-46	This RCT does not provide additional evidence that adds to the evidence from a prioritised systematic review

Study reference	Reason
Singh Iqbal, Gautam Lokesh Kumar, and Kaur Iqbal R (2016) Effect of oral cranberry extract (standardized proanthocyanidin-A) in patients with recurrent UTI by pathogenic E. coli: a randomized placebo-controlled clinical research study. International urology and nephrology 48(9), 1379-86	This RCT does not provide additional evidence that adds to the evidence from a prioritised systematic review
Stapleton Ann E, Au-Yeung Melissa, Hooton Thomas M, Fredricks David N, Roberts Pacita L, Czaja Christopher A, Yarova-Yarovaya Yuliya, Fiedler Tina, Cox Marsha, and Stamm Walter E (2011) Randomized, placebo-controlled phase 2 trial of a Lactobacillus crispatus probiotic given intravaginally for prevention of recurrent urinary tract infection. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 52(10), 1212-7	RCT included in a systematic review that has been prioritised
Stapleton Ann E, Dziura James, Hooton Thomas M, Cox Marsha E, Yarova-Yarovaya Yuliya, Chen Shu, and Gupta Kalpana (2012) Recurrent urinary tract infection and urinary Escherichia coli in women ingesting cranberry juice daily: a randomized controlled trial. Mayo Clinic proceedings 87(2), 143-50	This RCT does not provide additional evidence that adds to the evidence from a prioritised systematic review
Takahashi Satoshi, Hamasuna Ryoichi, Yasuda Mitsuru, Arakawa Soichi, Tanaka Kazushi, Ishikawa Kiyohito, Kiyota Hiroshi, Hayami Hiroshi, Yamamoto Shingo, Kubo Tatsuhiko, and Matsumoto Tetsuro (2013) A randomized clinical trial to evaluate the preventive effect of cranberry juice (UR65) for patients with recurrent urinary tract infection. Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy 19(1), 112-7	This RCT does not provide additional evidence that adds to the evidence from a prioritised systematic review
van den Hout WB, Caljouw MA, Putter H, Cools HJ, and Gussekloo J (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	No or fewer critical outcomes reported
Wang Chih-Hung, Fang Cheng-Chung, Chen Nai-Chuan, Liu Sot Shih-Hung, Yu Ping-Hsun, Wu Tao-Yu, Chen Wei-Ting, Lee Chien-Chang, and Chen Shyr-Chyr (2012) Cranberry-containing products for prevention of urinary tract infections in susceptible populations: a systematic review and meta-analysis of randomized controlled trials. Archives of internal medicine 172(13), 988-96	A higher quality systematic review has been prioritised (Jepson et al. 2012)

Appendix J: Excluded studies

Study reference	Reason for exclusion
Altarac Silvio, and Papes Dino (2014) Use of D-mannose in prophylaxis of recurrent urinary tract infections (UTIs) in women. BJU international 113(1), 9-10	Publication/study type (literature review)
Aydin A, Ahmed K, Zaman I, Khan M S, and Dasgupta P (2015) Recurrent urinary tract infections in women. Obstetrical and Gynecological Survey 70(10), 621-622q2	Publication/study type (literature review)
Beerepoot Maj, Ter Riet G, Nys S, Wal Wm, Borgie Cajm, Reijke Tm, Prins Jm, Koeijers J, Verbon A, Stobberingh E E, and Geerlings S E (2012) Predictive value of Escherichia coli susceptibility in strains causing asymptomatic bacteriuria for women with recurrent symptomatic urinary tract infections receiving prophylaxis. Clinical Microbiology and Infection. 1;18(4).	Publication/study type
Beversdorf D Q, Galloway H S, Foster Sr, R T, and Tatum P E (2011) Preventing recurrent urinary tract infections in a woman with dementia. Clinical Geriatrics 19(11), 33-35	Unable to source study
Bleidorn Jutta, Hummers-Pradier Eva, Schmiemann Guido, Wiese Birgitt, and Gagyor Ildiko (2016) Recurrent urinary tract infections and complications after symptomatic versus antibiotic treatment: follow-up of a randomised controlled trial. German medical science : GMS e-journal 14, Doc01	Publication/study type (retrospective long-term follow-up analysis)
Bonetta A, Derelli R, and Pierro F (2011) Cranberry extracts reduce urinary tract infections during radiotherapy for prostate adenocarcinoma. Anticancer research 31(5), 1849-1850	Unable to source study
Braga Luis H, Pemberton Julia, Heaman Jessie, DeMaria Jorge, and Lorenzo Armando J (2014) Pilot randomized, placebo controlled trial to investigate the effect of antibiotic prophylaxis on the rate of urinary tract infection in infants with prenatal hydronephrosis. The Journal of urology 191(5 Suppl), 1501-7	Not a relevant study
Brandstrom P (2011) The swedish reflux trial. Pediatric nephrology (Berlin, and Germany) 26(9), 1733	Not relevant population
Brandström P, Jodal U, Sillén U, and Hansson S (2011) The Swedish reflux trial: review of a randomized, controlled trial in children with dilating vesicoureteral reflux. Journal of pediatric urology 7(6), 594-600	Not relevant population
Brandstrom P, and Hansson S (2013) Growth in children with dilating VUR-a follow up of the swedish reflux trial. Pediatric nephrology (Berlin, and Germany) 28(8), 1391	Not relevant population
Canning D A (2010) Antibiotic prophylaxis and recurrent urinary tract infection in children. Journal of Urology 184(5), 2135	Unable to source study
Cayley Jr, and W E (2013) Are cranberry products effective for the prevention of urinary tract infections?. American Family Physician 88(11), 745-746	Publication/study type (commentary)
Cote J, Caillet S, Doyon G, Sylvain JF, and Lacroix M (2010) Bioactive compounds in cranberries and their biological properties. Critical reviews in food science and nutrition 50(7), 666-79	Not a relevant study
Damiano Rocco, Quarto Giuseppe, Bava Ilaria, Ucciero Giuseppe, De Domenico, Renato, Palumbo Michele I, and Autorino Riccardo (2011) Prevention of recurrent urinary tract infections by intravesical administration of hyaluronic acid and chondroitin sulphate: a placebo-controlled randomised trial. European urology 59(4), 645-51	Poor relevance against search terms (intervention)

Study reference	Reason for exclusion
Damiano R, Quarto G, Bava I, Ucciero G, De Domenico, R, Palumbo M I, and Autorino R (2011) Erratum: Prevention of recurrent urinary tract infections by intravesical administration of hyaluronic acid and chondroitin sulphate: A placebo-controlled randomised trial (European Urology (2011) 59 (645-651)). European Urology 60(1), 193	Poor relevance against search terms (intervention)
Dessi A, Atzei A, and Fanos V (2011) Cranberry in children: Prevention of recurrent urinary tract infections and review of the literature. Brazilian Journal of Pharmacognosy 21(5), 807-813	Publication/study type (literature review)
De Vita, Davide, and Giordano Salvatore (2012) Effectiveness of intravesical hyaluronic acid/chondroitin sulfate in recurrent bacterial cystitis: a randomized study. International urogynecology journal 23(12), 1707-13	Poor relevance against search terms (intervention)
De Vita, Davide, Antell Henrik, and Giordano Salvatore (2013) Effectiveness of intravesical hyaluronic acid with or without chondroitin sulfate for recurrent bacterial cystitis in adult women: a meta-analysis. International urogynecology journal 24(4), 545-52	Poor relevance against search terms (intervention)
Dieter A A (2015) Cranberry capsules (2 taken twice daily for an average 38 days) reduce the risk of postoperative urinary tract infection in women undergoing benign gynaecological surgery involving intraoperative catheterisation. Evidence-Based Medicine 20(4), 137	Publication/study type (commentary)
Donabedian H (2006) Nutritional therapy and infectious diseases: a two-edged sword. Nutrition journal 5, 21	Not a relevant study
Dotis J, Printza N, Stabouli S, Pavlaki A, Samara S, and Papachristou F (2014) Efficasy of cranberry capsules to prevent recurences of urinary tract infections. Pediatric nephrology (Berlin, and Germany) 29(9), 1793-4	Unable to source study
Duenas-Garcia O F, Sullivan G, Hall C D, Flynn M K, and O'Dell K (2016) Pharmacological agents to decrease new episodes of recurrent lower urinary tract infections in postmenopausal women. A systematic review. Female Pelvic Medicine and Reconstructive Surgery 22(2), 63-69	Not a relevant study
Durham Spencer H, Stamm Pamela L, and Eiland Lea S (2015) Cranberry Products for the Prophylaxis of Urinary Tract Infections in Pediatric Patients. The Annals of pharmacotherapy 49(12), 1349-56	Publication/study type (literature review)
Edmonson M Bruce, and Eickhoff Jens C (2017) Weight Gain and Obesity in Infants and Young Children Exposed to Prolonged Antibiotic Prophylaxis. JAMA pediatrics 171(2), 150-156	Not relevant population
Eells Samantha J, McKinnell James A, and Miller Loren G (2011) Daily cranberry prophylaxis to prevent recurrent urinary tract infections may be beneficial in some populations of women. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 52(11), 1393-5	Publication/study type (commentary)
Epp Annette, Larochelle Annick, Lovatsis Danny, Walter Jens-Erik, Easton William, Farrell Scott A, Girouard Lise, Gupta Chander, Harvey Marie-Andree, Robert Magali, Ross Sue, Schachter Joyce, Schulz Jane A, Wilkie David, Ehman William, Domb Sharon, Gagnon Andree, Hughes Owen, Konkin Jill, Lynch Joanna, Marshall Cindy, Society of, Obstetricians, Gynaecologists of, and Canada (2010) Recurrent urinary tract infection. Journal of obstetrics and gynaecology Canada : JOGC	Publication/study type (literature review)

Study reference	Reason for exclusion
= Journal d'obstetrique et gynecologie du Canada : JOGC 32(11), 1082-101	
Espino M, Areses R, Meseguer Cg, Pena A, Melgosa M, Ruperez M, Mitjavilla M, and Albillos Jc (2012) Antibiotic prophylaxis inhighdegree vesicoureteral reflux. Prospective, randomized and multicentric study. Preliminary results. Pediatric nephrology (Berlin, and Germany) 27(9), 1648-9	Publication/study type (commentary)
Falakaflaki B, Fallah R, Jamshidi Mr, Moezi F, and Torabi Z (2007) Comparison of nitrofurantoin and trimethoprim-sulphamethoxazole for long-term prophylaxis in children with recurrent urinary tract infections. International Journal of Pharmacology 3(2), 179-82	Not relevant population
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 (literature review)
Fernández-Puentes V, Uberos J, Rodríguez-Belmonte R, Nogueras-Ocaña M, Blanca-Jover E, and Narbona-López E (2015) Efficacy and safety profile of cranberry in infants and children with recurrent urinary tract infection. Anales de pediatria (barcelona, and spain : 2003) 82(6), 397-403	Unable to source
Flower Andrew, Wang Li-Qiong, Lewith George, Liu Jian Ping, and Li Qing (2015) Chinese herbal medicine for treating recurrent urinary tract infections in women. The Cochrane database of systematic reviews (6), CD010446	Does not reflect usual UK practice
Fonseca Fernando F, Tanno Fabio Y, and Nguyen Hiep T (2012) Current options in the management of primary vesicoureteral reflux in children. Pediatric clinics of North America 59(4), 819-34	Not relevant population
Foxman B, Cronenwett AE, Spino C, Berger MB, and Morgan DM (2015) Cranberry juice capsules and urinary tract infection after surgery: results of a randomized trial. American journal of obstetrics and gynecology 213(2), 194.e1-8	Not relevant population
Foxman Betsy, Cronenwett Anna E. W, Spino Cathie, Berger Mitchell B, and Morgan Daniel M (2015) Cranberry juice capsules and urinary tract infection after surgery: results of a randomized trial. American journal of obstetrics and gynecology 213(2), 194.e1-8	Duplicate
Fromentin E, Vostalova J, Vidlar A, Galandakova A, Vrbkova J, Ulrichova J, Student V, and Simanek V (2014) A randomized, double-blind, placebo-controlled clinical trial to investigate the efficacy of cranberry fruit powder (Pacran) in the prevention of recurrent urinary tract infection in women. FASEB journal 28(1 suppl. 1),	Abstract only
Gallien P, and Reymann Jm (2008) Cranberry for prevention of urinary tract infections in multiple sclerosis patients. ClinicalTrials gov (www clinicaltrials gov) (accessed 4 November 2010),	Publication/study type (study registration)
Gallien Philippe, Amarenco Gerard, Benoit Nicolas, Bonniaud Veronique, Donze Cecile, Kerdraon Jacques, de Seze, Marianne, Denys Pierre, Renault Alain, Naudet Florian, and Reymann Jean Michel (2014) Cranberry versus placebo in the prevention of urinary infections in multiple sclerosis: a multicenter, randomized, placebo-controlled, double-blind trial. Multiple sclerosis (Houndmills, Basingstoke, and England) 20(9), 1252-9	Not relevant population
Garin Eduardo H, Olavarria Fernando, Garcia Nieto, Victor , Valenciano Blanca, Campos Alfonso, and Young Linda (2006)	Not relevant population

Study reference	Reason for exclusion
Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. Pediatrics 117(3), 626-32	
Gautam L, Singh I, Gautam Lk, Kaur Ir, Rai S, and Joshi Mk (2014) Effect of oral cranberry extract (standardised proanthocyanidin-a) on the uropathogenic bacteria in urine of patients with subclinical/recurrent uti: A randomised placebo controlled clinical study. Indian journal of urology 30, S152	Abstract only
Gupta A (2007) Cranberry and Prevention of UTI - A Comprehensive Approach. http://www.clinicaltrials.gov,	Publication/study type (study registration)
Gucuk Adnan, Burgu Berk, Gokce Ilker, Mermerkaya Murat, and Soygur Tarkan (2013) Do antibiotic prophylaxis and/or circumcision change periurethral uropathogen colonization and urinary tract infection rates in boys with VUR?. Journal of pediatric urology 9(6 Pt B), 1131-6	Not a relevant study
Gupta K, and Trautner B W (2013) Diagnosis and management of recurrent urinary tract infections in non-pregnant women. BMJ (Online) 346(7910), f3140	Publication/study type (literature review)
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	Not a relevant study
Hari P, Sarin Y K, and Mathew J L (2014) Antimicrobial prophylaxis for children with vesicoureteral reflux. Indian Pediatrics 51(7), 571-574	Not relevant population
Hari Pankaj, Hari Smriti, Sinha Aditi, Kumar Rakesh, Kapil Arti, Pandey Ravindra Mohan, and Bagga Arvind (2015) Antibiotic prophylaxis in the management of vesicoureteric reflux: a randomized double-blind placebo-controlled trial. Pediatric nephrology (Berlin, and Germany) 30(3), 479-86	Not relevant population
Higgs R (2010) Pediatrics: Modest effect of prophylactic antibiotics on UTI in children. Nature Reviews Urology 7(1), 5	Publication/study type (commentary)
Hodson E M, Wheeler D M, Vimalchandra D, Smith G H, and Craig J C (2007) Interventions for primary vesicoureteric reflux. The Cochrane database of systematic reviews (3), CD001532	Not relevant population
Jepson RG, Mihaljevic L, and Craig J (2000) Cranberries for preventing urinary tract infections. The Cochrane database of systematic reviews (2), CD001321	Updated systematic review available
Jepson RG, Mihaljevic L, and Craig J (2001) Cranberries for preventing urinary tract infections. The Cochrane database of systematic reviews (3), CD001321	Updated systematic review available
Jepson RG, Mihaljevic L, and Craig J (2004) Cranberries for preventing urinary tract infections. The Cochrane database of systematic reviews (2), 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
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
Jodal Ulf, Smellie Jean M, Lax Hildegard, and Hoyer Peter F (2006) Ten-year results of randomized treatment of children with severe vesicoureteral reflux. Final report of the International	Not relevant population

Study reference	Reason for exclusion
Reflux Study in Children. Pediatric nephrology (Berlin, and Germany) 21(6), 785-92	
Juthani-Mehta Manisha, Van Ness, Peter H, Bianco Luann, Rink Andrea, Rubeck Sabina, Ginter Sandra, Argraves Stephanie, Charpentier Peter, Acampora Denise, Trentalange Mark, Quagliarello Vincent, and Peduzzi Peter (2016) Effect of Cranberry Capsules on Bacteriuria Plus Pyuria Among Older Women in Nursing Homes: A Randomized Clinical Trial. JAMA 316(18), 1879-1887	Not relevant population
LaPlante K L, Gill C M, and Rowley D (2017) Cranberry capsules for bacteriuria plus pyuria in nursing home residents. JAMA - Journal of the American Medical Association 317(10), 1078	Publication/study type (commentary)
Larcombe James (2015) Urinary tract infection in children: recurrent infections. BMJ clinical evidence 2015,	Publication/study type (Review of systematic reviews/RCTs)
Lee B B, Simpson J M, Craig J C, and Bhuta T (2007) Methenamine hippurate for preventing urinary tract infections. The Cochrane database of systematic reviews (4), CD003265	Not relevant population
Lee Linda C, Lorenzo Armando J, and Koyle Martin A (2016) The role of voiding cystourethrography in the investigation of children with urinary tract infections. Canadian Urological Association journal = Journal de l'Association des urologues du Canada 10(5-6), 210-214	Not a relevant study
Lee Seung Joo, Shim Yoon Hee, Cho Su Jin, and Lee Jung Won (2007) Probiotics prophylaxis in children with persistent primary vesicoureteral reflux. Pediatric nephrology (Berlin, and Germany) 22(9), 1315-20	Not relevant population
Lee Seung Joo, and Lee Jung Won (2015) Probiotics prophylaxis in infants with primary vesicoureteral reflux. Pediatric nephrology (Berlin, and Germany) 30(4), 609-13	Not relevant population
Ledda A, Bottari A, Luzzi R, Belcaro G, Hu S, Dugall M, Hosoi M, Ippolito E, Corsi M, Gizzi G, Morazzoni P, Riva A, Giacomelli L, and Togni S (2015) Cranberry supplementation in the prevention of non-severe lower urinary tract infections: a pilot study. European review for medical and pharmacological sciences 19(1), 77-80	Publication/study type (observational study)
Leo V, Cappelli V, Massaro Mg, Tosti C, and Morgante G (2017) Evaluation of the effects of a natural dietary supplement with cranberry, Noxamicina® and D-mannose in recurrent urinary infections in perimenopausal women. Minerva ginecologica 69(4), 336-341	Non-English language
Lo V, Wah Y, and Maggio L (2011) Antibiotic prophylaxis to prevent recurrent UTI in children. American Family Physician 84(2), 3-4	Publication/study type (commentary)
Long Elliot, Colquhoun Samantha, and Carapetis Jonathan R (2006) Antibiotic prophylaxis for the prevention of recurrent urinary tract infections in children. Advances in experimental medicine and biology 582, 243-9	Publication/study type (book article)
Lorenzo A J, and Braga L H. P (2013) Use of cranberry products does not appear to be associated with a significant reduction in incidence of recurrent urinary tract infections. Evidence-Based Medicine 18(5), 181-182	Publication/study type (commentary)
Mattoo Tej K (2007) Medical management of vesicoureteral reflux--quiz within the article. Don't overlook placebos. Pediatric nephrology (Berlin, and Germany) 22(8), 1113-20	Not a relevant study

Study reference	Reason for exclusion
Mattoo Tej K, Chesney Russell W, Greenfield Saul P, Hoberman Alejandro, Keren Ron, Mathews Ranjiv, Gravens-Mueller Lisa, Ivanova Anastasia, Carpenter Myra A, Moxey-Mims Marva, Majd Massoud, Ziessman Harvey A, and Investigators Rivur Trial (2016) Renal Scarring in the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) Trial. Clinical journal of the American Society of Nephrology : CJASN 11(1), 54-61	Not relevant population
Mazokopakis Elias E, Karefilakis Christos M, and Starakis Ioannis K (2009) Efficacy of cranberry capsules in prevention of urinary tract infections in postmenopausal women. Journal of alternative and complementary medicine (New York, and N.Y.) 15(11), 1155	Publication/study type (commentary)
Mohseni Mohammad-Javad, Aryan Zahra, Emamzadeh-Fard Sahra, Paydary Koosha, Mofid Vahid, Joudaki Hasan, and Kajbafzadeh Abdol-Mohammad (2013) Combination of probiotics and antibiotics in the prevention of recurrent urinary tract infection in children. Iranian journal of pediatrics 23(4), 430-8	Not relevant population
Mutlu Hatice, and Ekinci Zelal (2012) Urinary tract infection prophylaxis in children with neurogenic bladder with cranberry capsules: randomized controlled trial. ISRN pediatrics 2012, 317280	Not relevant population
Naber Kurt G, Cho Yong-Hyun, Matsumoto Tetsuro, and Schaeffer Anthony J (2009) Immunoactive prophylaxis of recurrent urinary tract infections: a meta-analysis. International journal of antimicrobial agents 33(2), 111-9	Does not reflect usual UK practice
Nachum Z, Braverman M, Letova Ygz, Salim R, and Chazan B (2015) The effect of preventive antibiotic treatment in the postpartum period on urinary tract infection (UTI) rate in women treated during pregnancy for recurrent UTI e a prospective randomized controlled study. American journal of obstetrics and gynecology 212(1 suppl. 1), S399-s400	Abstract only
Nagler Evi Vt, Williams Gabrielle, Hodson Elisabeth M, and Craig Jonathan C (2011) Interventions for primary vesicoureteric reflux. The Cochrane database of systematic reviews (6), CD001532	Not a relevant population
Nct (2008) Prospective, randomized, double-blind, placebo-controlled study on parallel groups evaluating the efficacy and safety of cranberry (Vaccinium Macrocarpon) in prevention of urinary tract infections in multiple sclerosis patients. clinicaltrials.gov/ct2/show/NCT00280592,	Publication/study type (trial registration)
Nct (2008) Cranberry for UTI prevention in residents of long term care facilities (PACS). clinicaltrials.gov/ct2/show/NCT00596635,	Publication/study type (trial registration)
Nct, and Sumit D (2014) A Clinical Trial to Determine the Extent to Which Probiotic Therapy Reduces Side Effects of Antibiotic Prophylaxis in Pediatric Neurogenic Bladder Patients With a History of Recurrent Urinary Tract Infections. Http://clinicaltrials.gov/show/NCT02044965,	Publication/study type (trial registration)
Nelson Caleb P, Hoberman Alejandro, Shaikh Nader, Keren Ron, Mathews Ranjiv, Greenfield Saul P, Mattoo Tej K, Gotman Nathan, Ivanova Anastasia, Moxey-Mims Marva, Carpenter Myra A, and Chesney Russell W (2016) Antimicrobial Resistance and Urinary Tract Infection Recurrence. Pediatrics 137(4),	Not relevant population
Neveus Tryggve, Brandstrom Per, Linner Tina, Jodal Ulf, and Hansson Sverker (2012) Parental experiences and preferences regarding the treatment of vesicoureteral reflux. Scandinavian journal of urology and nephrology 46(1), 26-30	Not a relevant study

Study reference	Reason for exclusion
Nordenstrom Josefin, Holmdahl Gundela, Brandstrom Per, Sixt Rune, Stokland Eira, Sillen Ulla, and Sjostrom Sofia (2016) The Swedish infant high-grade reflux trial: Study presentation and vesicoureteral reflux outcome. Journal of pediatric urology ,	Not relevant population
Nordenstrom J, Sillen U, Holmdahl G, Linner T, Stokland E, and Sjostrom S (2016) The Swedish Infant High-grade Reflux Trial - Bladder function. Journal of pediatric urology ,	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 relevant population
Ostrovsky D A (2017) Cranberry Capsules do not Appear to Reduce Bacteriuria and Pyuria in Elderly Women Residing in Nursing Homes. Explore 13(3), 226-227	Publication/study type (literature review)
Perez-Gaxiola G (2011) Review: Antibiotic prophylaxis may not prevent recurrent symptomatic urinary tract infection in children. Archives of Disease in Childhood: Education and Practice Edition 96(5), 198	Abstract only
Pouwels Koen B, Visser Sipke T, and Hak Eelko (2013) Effect of pravastatin and fosinopril on recurrent urinary tract infections. The Journal of antimicrobial chemotherapy 68(3), 708-14	Poor relevance against search terms (interventions)
British Medical Journal Publishing Group (2013) Prevention of recurrent urinary tract infections in women. Drug and therapeutics bulletin 51(6), 69-72	Publication/study type (literature review)
Rego L L, Glazer C S, and Zimmern P E (2016) Risks of long-term use of nitrofurantoin for urinary tract prophylaxis in the older patient. Urological Science 27(4), 193-198	Publication/study type (literature review)
Salo J, Kontiokari T, Helminen M, Korppi M, Nieminen T, Pokka T, and Uhari M (2010) Randomized trial of cranberry juice for the prevention of recurrences of urinary tract infections in children. Clinical microbiology and infection 16(Suppl 2), S385-s386	Unable to source
Schaeffer Anthony J, Greenfield Saul P, Ivanova Anastasia, Cui Gang, Zerin J Michael, Chow Jeanne S, Hoberman Alejandro, Mathews Ranjiv I, Mattoo Tej K, Carpenter Myra A, Moxey-Mims Marva, Chesney Russell W, and Nelson Caleb P (2016) Reliability of grading of vesicoureteral reflux and other findings on voiding cystourethrography. Journal of pediatric urology ,	Not a relevant study
Seideman C, Lotan Y, and Palmer L (2015) Cost effectiveness of antimicrobial prophylaxis for children in the RIVUR trial. Journal of urology 193(4 suppl. 1), e665	Not relevant population
Sen Ayan (2006) Recurrent cystitis in non-pregnant women. Clinical evidence (15), 2558-64	Publication/study type (review of systematic reviews and RCTs)
Shaikh Nader, Hoberman Alejandro, Keren Ron, Gotman Nathan, Docimo Steven G, Mathews Ranjiv, Bhatnagar Sonika, Ivanova Anastasia, Mattoo Tej K, Moxey-Mims Marva, Carpenter Myra A, Pohl Hans G, and Greenfield Saul (2016) Recurrent Urinary Tract Infections in Children With Bladder and Bowel Dysfunction. Pediatrics 137(1),	Not relevant population
Shmuely H, Ofek I, Weiss EI, Rones Z, and Houri-Haddad Y (2012) Cranberry components for the therapy of infectious disease. Current opinion in biotechnology 23(2), 148-52	Not a clinical study
Stepanova N, Kruglikov V, Lebid L, and Kolesnyk M (2013) Oral lactobacilli vs antibiotic prophylaxis for recurrent urinary tract infections in premenopausal women. European Urology, and Supplements 12(1), e892	Publication/study type (literature review)

Study reference	Reason for exclusion
Sumukadas D, Davey P, and McMurdo M E. T (2009) Recurrent urinary tract infections in older people: The role of cranberry products. Age and Ageing 38(3), 255-257	Publication/study type (commentary)
Sung Jennifer, and Skoog Steven (2012) Surgical management of vesicoureteral reflux in children. Pediatric nephrology (Berlin, and Germany) 27(4), 551-61	Not relevant population
Takahashi S (2012) Prevention of acute uncomplicated cystitis by cranberry juice. International journal of urology 19, 410	Abstract only
Takvani A, Gokani C, and Malaviya P (2015) Vesicoureteric reflux-a prospective study of 11 years. European Urology, and Supplements 14(2), e505-e505a	Not a relevant study
Thomas J (2011) Cranberry juice fails to prevent recurring urinary tract infections. Australian Journal of Pharmacy 92(1092), 81	Abstract only
Uberos J, Rodrguez-Belmonte R, Fernndez-Puentes V, Narbona-Lpez E, Molina-Carballo A, and Munoz-Hoyos A (2010) Cranberry syrup vs. trimethoprim in the prophylaxis of recurrent urinary infection: A double-blind randomized clinical trial. Acta paediatrica 99(Suppl 462), 48	Abstract only
Uberos J, Fernandez-Puentes V, Molina-Oya M, Rodriguez-Belmonte R, Ruiz-Lopez A, Tortosa-Pinto P, Molina-Carballo A, and Munoz-Hoyos A (2012) Urinary excretion of phenolic acids by infants and children: a randomised double-blind clinical assay. Clinical medicine insights. Pediatrics 6, 67-74	Not a relevant study
Uehara Shinya, Monden Koichi, Nomoto Koji, Seno Yuko, Kariyama Reiko, and Kumon Hiromi (2006) A pilot study evaluating the safety and effectiveness of Lactobacillus vaginal suppositories in patients with recurrent urinary tract infection. International journal of antimicrobial agents 28 Suppl 1, S30-4	Abstract only
Vasileiou I, Katsargyris A, Theocharis S, and Giaginis C (2013) Current clinical status on the preventive effects of cranberry consumption against urinary tract infections. Nutrition research (New York, and N.Y.) 33(8), 595-607	Publication/study type (literature review)
Vicariotto Franco (2014) Effectiveness of an association of a cranberry dry extract, D-mannose, and the two microorganisms Lactobacillus plantarum LP01 and Lactobacillus paracasei LPC09 in women affected by cystitis: a pilot study. Journal of clinical gastroenterology 48 Suppl 1, S96-101	Publication/study type (observational study)
Vidlar A, Vostalova J, Vacek J, Kosina P, Vrbkova J, Ulrichova J, Student V, and Simanek V (2011) The effect of cranberry (Vaccini um macrocarpon) on the recurrence urinary tract infection in women. European Urology, and Supplements 10(9), 622	Abstract only
Vostalova Jitka, Vidlar Ales, Simanek Vilim, Galandakova Adela, Kosina Pavel, Vacek Jan, Vrbkova Jana, Zimmermann Benno F, Ulrichova Jitka, and Student Vladimir (2015) Are High Proanthocyanidins Key to Cranberry Efficacy in the Prevention of Recurrent Urinary Tract Infection?. Phytotherapy research : PTR 29(10), 1559-67	Publication/study type (literature review)
Wald E (2010) Antibiotic prophylaxis can prevent recurrent infection in children with urinary tract infections. Journal of Pediatrics 156(5), 856-857	Abstract only
Wan KS, Liu CK, Lee WK, Ko MC, and Huang CS (2016) Cranberries for Preventing Recurrent Urinary Tract Infections in Uncircumcised Boys. Alternative therapies in health and medicine 22(6), 20-23	Not relevant intervention

Study reference	Reason for exclusion
Williams GJ, Lee A, and Craig JC (2001) Long-term antibiotics for preventing recurrent urinary tract infection in children. The Cochrane database of systematic reviews (4), CD001534	Updated systematic review available
Williams GJ, Wei L, Lee A, and Craig JC (2006) Long-term antibiotics for preventing recurrent urinary tract infection in children. The Cochrane database of systematic reviews (3), CD001534	Updated systematic review available
Williams GJ, Craig JC, and Carapetis JR (2013) Preventing urinary tract infections in early childhood. Advances in experimental medicine and biology 764, 211-8	Publication/study type (literature review)