

# Urinary tract infection (recurrent): antimicrobial prescribing

NICE guideline

Published: 31 October 2018

[www.nice.org.uk/guidance/ng112](https://www.nice.org.uk/guidance/ng112)

## Your responsibility

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

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

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

# Contents

|  |    |
|--|----|
| Overview .....   | 4  |
| Who is it for? .....                                   | 4  |
| Recommendations.....                                   | 5  |
| 1.1 Preventing recurrent urinary tract infections..... | 5  |
| 1.2 Self-care .....                                    | 11 |
| 1.3 Choice of antibiotic prophylaxis .....             | 12 |
| Terms used in the guideline .....                      | 15 |
| Recurrent urinary tract infection.....                 | 15 |
| Trigger .....  | 15 |
| Summary of the evidence.....                           | 16 |
| Self-care.....   | 16 |
| Oestrogens .....                                       | 21 |
| Antibiotic prophylaxis .....                           | 25 |
| Choice of antibiotic prophylaxis .....                 | 31 |
| Antibiotic dosing and course length.....               | 34 |
| Other considerations.....                              | 37 |
| Medicines adherence.....                               | 37 |
| Resource implications.....                             | 37 |
| Update information .....                               | 38 |

This guideline is the basis of QS90.

This guideline should be read in conjunction with NG109 and NG111.

## Overview

This guideline sets out an antimicrobial prescribing strategy for preventing recurrent urinary tract infections in children, young people and adults who do not have a catheter. It aims to optimise antibiotic use and reduce antibiotic resistance.

See a [2-page visual summary of the recommendations](#), including a table to support prescribing decisions.

There is also a [NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use](#).

## Who is it for?

- Health professionals
- People with recurrent urinary tract infection, their families and carers

# Recommendations

## 1.1 Preventing recurrent urinary tract infections

- 1.1.1 Manage an acute UTI as outlined in the [NICE guidelines on urinary tract infection \(lower\): antimicrobial prescribing](#) or [pyelonephritis \(acute\): antimicrobial prescribing](#).
- 1.1.2 Be aware that [recurrent UTI](#):
- includes lower UTI and upper UTI (acute pyelonephritis)
  - may be due to relapse (with the same strain of organism) or reinfection (with a different strain or species of organism)
  - is particularly common in women.
- 1.1.3 Give advice to people with recurrent UTI about behavioural and personal hygiene measures and self-care treatments (see the [recommendations on self-care](#)) that may help to reduce the risk of UTI.

## Referral and seeking specialist advice

- 1.1.4 Refer or seek specialist advice on further investigation and management for:
- men aged 16 years and over
  - people with recurrent upper UTI
  - people with recurrent lower UTI when the underlying cause is unknown
  - pregnant women
  - children and young people under 16 years in line with the [NICE guideline on urinary tract infection in under 16s](#)
  - people with suspected cancer in line with the [NICE guideline on suspected](#)

[cancer: recognition and referral.](#)

For a short explanation of why the committee made these recommendations, see the [evidence and committee discussion on antibiotic prophylaxis](#).

Full details of the evidence and committee's discussion are available in the [evidence review](#).

## Treatment for women with recurrent UTI who are not pregnant

### Oestrogen

- 1.1.5 Consider the lowest effective dose of vaginal oestrogen (for example, estriol cream) for postmenopausal women with recurrent UTI if behavioural and personal hygiene measures alone are not effective or not appropriate. Discuss the following with the woman to ensure shared decision-making:
- the severity and frequency of previous symptoms
  - the risk of developing complications from recurrent UTIs
  - the possible benefits of treatment, including for other related symptoms, such as vaginal dryness
  - the possible adverse effects such as breast tenderness and vaginal bleeding (which should be reported because it may require investigation)
  - the uncertainty of endometrial safety with long-term or repeated use
  - preferences of the woman for treatment with vaginal oestrogen.

Review treatment within 12 months, or earlier if agreed with the woman. In October 2018, this was an off-label use of vaginal oestrogen products. See [NICE's information on prescribing medicines](#).

- 1.1.6 Do not offer oral oestrogens (hormone replacement therapy) specifically to reduce the risk of recurrent UTI in postmenopausal women.

For a short explanation of why the committee made these recommendations, see the [evidence and committee discussion on oestrogens](#).

Full details of the evidence and committee's discussion are available in the [evidence review](#).

## Antibiotic prophylaxis

- 1.1.7 For women with recurrent UTI who are not pregnant, consider a trial of antibiotic prophylaxis only if behavioural and personal hygiene measures, and vaginal oestrogen (in postmenopausal women) are not effective or not appropriate.
- 1.1.8 For women with recurrent UTI who are not pregnant, ensure that any current UTI has been adequately treated then consider single-dose antibiotic prophylaxis for use when exposed to an identifiable [trigger](#) (see the [recommendations on choice of antibiotic prophylaxis](#)). Take account of:
- the severity and frequency of previous symptoms
  - the risk of developing complications
  - previous urine culture and susceptibility results
  - previous antibiotic use, which may have led to resistant bacteria
  - the woman's preferences for antibiotic use.
- 1.1.9 When single-dose antibiotic prophylaxis is given, give advice about:
- how to use the antibiotic
  - possible adverse effects of antibiotics, particularly diarrhoea and nausea
  - returning for review within 6 months
  - seeking medical help if there are symptoms of an acute UTI.

For a short explanation of why the committee made these recommendations, see the [evidence and committee discussion on antibiotic prophylaxis and antibiotic dosing and course length](#).

Full details of the evidence and committee's discussion are available in the [evidence review](#).

1.1.10 For women with recurrent UTI who are not pregnant and have had no improvement after single-dose antibiotic prophylaxis or have no identifiable triggers, ensure that any current UTI has been adequately treated then consider a trial of daily antibiotic prophylaxis (see the [recommendations on choice of antibiotic prophylaxis](#)). Take account of:

- any further investigations (for example, ultrasound) that may be needed to identify an underlying cause
- the severity and frequency of previous symptoms
- the risks of long-term antibiotic use
- the risk of developing complications
- previous urine culture and susceptibility results
- previous antibiotic use, which may have led to resistant bacteria
- the woman's preferences for antibiotic use.

1.1.11 When a trial of daily antibiotic prophylaxis is given, give advice about:

- the risk of resistance with long-term antibiotics, which means they may be less effective in the future
- possible adverse effects of long-term antibiotics
- returning for review within 6 months
- seeking medical help if there are symptoms of an acute UTI.



For a short explanation of why the committee made these recommendations, see the [evidence and committee discussion on antibiotic prophylaxis](#).

Full details of the evidence and committee's discussion are available in the [evidence review](#).

## Treatment for men and pregnant women with recurrent UTI

1.1.12 For men and pregnant women with recurrent UTI, ensure that any current UTI has been adequately treated then consider a trial of daily antibiotic prophylaxis (see the [recommendations on choice of antibiotic prophylaxis](#)) if behavioural and personal hygiene measures alone are not effective or not appropriate, with specialist advice. Take account of:

- any further investigations (for example, ultrasound) that may be needed to identify an underlying cause
- the severity and frequency of previous symptoms
- the risks of long-term antibiotic use
- the risk of developing complications
- previous urine culture and susceptibility results
- previous antibiotic use, which may have led to resistant bacteria
- the person's preferences for antibiotic use.

1.1.13 When a trial of daily antibiotic prophylaxis is given, give advice as in recommendation 1.1.11.

For a short explanation of why the committee made these recommendations, see the [evidence and committee discussion on antibiotic prophylaxis](#).

Full details of the evidence and committee's discussion are available in the [evidence review](#).

## Treatment for children and young people under 16 years with recurrent UTI

- 1.1.14 For children and young people under 16 years with recurrent UTI, ensure that any current UTI has been adequately treated then consider a trial of daily antibiotic prophylaxis (see the [recommendations on choice of antibiotic prophylaxis](#)) if behavioural and personal hygiene measures alone are not effective or not appropriate, with specialist advice. Take account of:
- underlying causes following specialist assessment and investigations
  - the uncertain evidence of benefit of antibiotic prophylaxis for reducing the risk of recurrent UTI and the rate of deterioration of renal scars
  - the severity and frequency of previous symptoms
  - the risks of long-term antibiotic use
  - the risk of developing complications
  - previous urine culture and susceptibility results
  - previous antibiotic use, which may have led to resistant bacteria
  - preferences for antibiotic use.
- 1.1.15 When a trial of daily antibiotic prophylaxis is given, give advice as in recommendation 1.1.11.

## Reassessment

- 1.1.16 Review antibiotic prophylaxis for recurrent UTI at least every 6 months, with the review to include:
- assessing the success of prophylaxis
  - discussion of continuing, stopping or changing prophylaxis (taking into account the person's preferences for antibiotic use and the risk of antimicrobial resistance)

- a reminder about behavioural and personal hygiene measures and self-care treatments (see the [recommendations on self-care](#)).

If antibiotic prophylaxis is stopped, ensure that people have rapid access to treatment if they have an acute UTI.

## 1.2 Self-care

### 1.2.1 Be aware that:

- Some women with recurrent UTI may wish to try D-mannose if they are not pregnant (the evidence for D-mannose was based on a study in which it was taken as 200 ml of 1% solution once daily in the evening). D-mannose is a sugar that is available to buy as powder or tablets; it is not a medicine.
- Some women with recurrent UTI may wish to try cranberry products if they are not pregnant (evidence of benefit is uncertain and there is no evidence of benefit for older women).
- Some children and young people under 16 years with recurrent UTI may wish to try cranberry products with the advice of a paediatric specialist (evidence of benefit is uncertain).

### 1.2.2 Advise people taking cranberry products or D-mannose about the sugar content of these products, which should be considered as part of the person's daily sugar intake.

### 1.2.3 Be aware that evidence is inconclusive about whether probiotics (lactobacillus) reduce the risk of UTI in people with recurrent UTI.

For a short explanation of why the committee made these recommendations, see the [evidence and committee discussion on self-care](#).

Full details of the evidence and committee's discussion are available in the [evidence review](#).

### 1.3 Choice of antibiotic prophylaxis

1.3.1 When prescribing antibiotic prophylaxis for recurrent UTI, take account of local antimicrobial resistance (AMR) data from Public Health England and:

- follow the recommendations in table 1 for people aged 16 years and over
- follow the recommendations in table 2 for children and young people under 16 years.

Table 1 People aged 16 years and over

| Treatment                             | Antibiotic prophylaxis and dosage   |
|---------------------------------------|---|
| <b>First-choice oral antibiotics</b>  | <b>Trimethoprim:</b><br>200 mg as a single dose when exposed to a trigger, or 100 mg at night<br>There is a teratogenic risk in first trimester of pregnancy (folate antagonist; <a href="#">BNF information on trimethoprim</a> ). The companies advise that it is contraindicated in pregnancy ( <a href="#">trimethoprim summary of product characteristics</a> )<br><b>Nitrofurantoin</b> (if estimated glomerular filtration rate is 45 ml/minute or more):<br>100 mg as a single dose when exposed to a trigger, or 50 mg to 100 mg at night<br>Avoid at term in pregnancy; may produce neonatal haemolysis ( <a href="#">BNF information on nitrofurantoin</a> ) |
| <b>Second-choice oral antibiotics</b> | <b>Amoxicillin</b> (off-label use):<br>500 mg as a single dose when exposed to a trigger, or 250 mg at night<br><b>Cefalexin:</b><br>500 mg as a single dose when exposed to a trigger, or 125 mg at night  |

See the [BNF](#) for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breastfeeding.

Choose antibiotics according to recent culture and susceptibility results where possible, with rotational use based on local policies. Select a different antibiotic for prophylaxis if treating an acute UTI.

For off-label use, see [NICE's information on prescribing medicines](#).

**Table 2 Children and young people under 16 years**

| Treatment   | Antibiotic prophylaxis and dosage   |
|---|---|
| <b>Choice for children under 3 months</b>   | Refer to paediatric specialist  |
| <b>First-choice oral antibiotics for children aged 3 months and over (specialist advice only)</b> | <p><b>Trimethoprim:</b></p> <p>3 months to 5 months, 2 mg/kg at night (maximum 100 mg per dose) or 12.5 mg at night</p> <p>6 months to 5 years, 2 mg/kg at night (maximum 100 mg per dose) or 25 mg at night</p> <p>6 years to 11 years, 2 mg/kg at night (maximum 100 mg per dose) or 50 mg at night</p> <p>12 years to 15 years, 100 mg at night</p> <p>There is a teratogenic risk in first trimester of pregnancy (folate antagonist; <a href="#">BNFC information on trimethoprim</a>). The companies advise that it is contraindicated in pregnancy (<a href="#">trimethoprim summary of product characteristics</a>)</p> <p><b>Nitrofurantoin</b> (if estimated glomerular filtration rate is 45 ml/minute or more):</p> <p>3 months to 11 years, 1 mg/kg at night</p> <p>12 years to 15 years, 50 mg to 100 mg at night</p> <p>Avoid at term in pregnancy; may produce neonatal haemolysis (<a href="#">BNFC information on nitrofurantoin</a>)</p> |
| <b>Second-choice oral antibiotics for children aged 3 months and over</b>                         | <p><b>Cefalexin:</b></p> <p>3 months to 15 years, 12.5 mg/kg at night (maximum 125 mg per dose)</p> <p><b>Amoxicillin</b> (off-label use):</p> <p>3 months to 11 months, 62.5 mg at night</p> <p>1 year to 4 years, 125 mg at night</p> <p>5 years to 15 years, 250 mg at night</p>   |

See the [BNF for children](#) (BNFC) for appropriate use and dosing in specific populations, for

example, hepatic and renal impairment.

Choose antibiotics according to recent culture and susceptibility results where possible, with rotational use based on local policies. Select a different antibiotic for prophylaxis if treating an acute UTI. If 2 or more antibiotics are appropriate, choose the antibiotic with the lowest acquisition cost.

The age bands apply to children of average size and, in practice, the prescriber will use the age bands in conjunction with other factors such as the severity of the condition and the child's size in relation to the average size of children of the same age.

For off-label use, see [NICE's information on prescribing medicines](#).

For a short explanation of why the committee made these recommendations, see the [evidence and committee discussion on choice of antibiotic prophylaxis and antibiotic dosing and course length](#).

Full details of the evidence and committee's discussions are available in the [evidence review](#).

# Terms used in the guideline

## Recurrent urinary tract infection

Recurrent urinary tract infection (UTI) in adults is defined as repeated UTI with a frequency of 2 or more UTIs in the last 6 months or 3 or more UTIs in the last 12 months ([European Association of Urology \[EAU\] guidelines on urological infections \[2017\]](#)).

Recurrent UTI is diagnosed in children and young people under 16 years if they have:

- 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.

See the [NICE guideline on urinary tract infection in under 16s](#).

## Trigger

Some people (mainly women) may be able to identify 1 or more triggers (for example, sexual intercourse) that often brings on a UTI. These triggers may vary for different people.

# Summary of the evidence

## Self-care

### Probiotics (lactobacillus)

- Lactobacillus did not significantly reduce the risk of recurrent infection in premenopausal women with a history of previous urinary tract infection (UTI; 1 or more episode in the past 12 months) compared with placebo (low quality evidence). This was based on a systematic review and meta-analysis of randomised controlled trials (RCTs; [Grin et al. 2013](#)). When the analysis was restricted to 2 RCTs with 'effective strains' of lactobacillus, there was a statistically significant difference (16.1% versus 32.3%: number needed to treat [NNT] 7 [range 4 to 64]; moderate quality evidence).
- In most studies lactobacillus was used following a UTI treated with antibiotics until the infection resolved. Lactobacillus pessaries were used in 4 RCTs and a drink preparation was used in 1 RCT.
- Evidence for lactobacillus compared with antibiotic prophylaxis (co-trimoxazole) in postmenopausal women with 1 or more previous UTI found, overall, no significant differences between treatment options (low quality evidence). This was based on 1 RCT included in a systematic review ([Schwenger et al. 2015](#)).
- No safety data were reported for lactobacillus compared with placebo. Data for lactobacillus compared with antibiotic were reported narratively, and the reason for not pooling data was unclear. One systematic review reported no significant difference in the number of people experiencing at least 1 adverse event with lactobacillus compared with antibiotics (Schwenger et al. 2015; low quality evidence).
- No systematic reviews or RCTs were identified that included data on lactobacillus in men or children.

### Cranberry products

- A range of cranberry products are available; a liquid preparation (juice or syrup), tablets or capsules were used in the included studies.



- Evidence for these products was identified in different populations (non-pregnant women, pregnant women, elderly men and women, and children), with some conflicting results.
- In women (unclear whether pregnant women were included) with a previous history of UTI, cranberry products used for up to 12 months did not significantly reduce the risk of recurrent infection (19.9% versus 22.8%) compared with placebo or no treatment (very low quality evidence). This was based on a systematic review and meta-analysis of RCTs ([Jepson et al. 2012](#)).
- However, a more recent systematic review and meta-analysis of RCTs ([Fu et al. 2017](#)) was identified following stakeholder consultation, which included additional data to Jepson et al. (2012). Cranberry products used for 6 to 12 months did significantly reduce the incidence of UTI in non-pregnant women with a previous history of UTI compared with placebo or no treatment (20.7% versus 26.5%; NNT 17 [range 9 to 68]; very low quality evidence). This significant reduction was not seen when UTIs were confirmed by urine culture (19.8% versus 24.0%; very low quality evidence).
- Subgroup analysis in Fu et al. (2017) found that cranberry juice used for 6 to 12 months did not reduce the incidence of UTI diagnosed by symptom presence or culture confirmation compared with placebo or no treatment (22.0% versus 26.6%; very low quality evidence); whereas cranberry tablets taken for 6 to 12 months did show a significant reduction in the incidence of UTI (13.5% versus 28.0%; NNT 7 [range 5 to 20]; low quality evidence). However, the analysis for cranberry tablets was based on much smaller numbers of participants.
- In elderly adults (men and women) with a previous history of UTI, cranberry products used for up to 12 months did not significantly reduce the risk of recurrent infection (9.7% versus 12.6%; moderate quality evidence) compared with placebo or no treatment ([Jepson et al. 2012](#)).
- In pregnant women with a previous history of UTI, cranberry products did not show a significant benefit in reducing recurrent UTI (56.6% versus 55.6%; moderate quality evidence) when compared with placebo or no treatment ([Jepson et al. 2012](#)).
- In children with a previous history of 1 or more UTIs or 'repeated symptomatic UTI', cranberry products used for up to 12 months did not significantly reduce the risk of recurrent infection compared with placebo or no treatment (16.3% versus 29.5%; low quality evidence; [Jepson et al. 2012](#)).
- However, a more recent systematic review and meta-analysis of RCTs ([Roshdibonab](#)

[et al. 2017](#)) was identified following stakeholder consultation, which included additional data to Jepson et al. (2012). Cranberry products used for up to 12 months did significantly reduce the incidence of UTI in children with recurrent UTI compared with placebo (odds ratio 0.31, 95% confidence interval 0.21 to 0.46; no absolute figures stated; very low quality evidence).

- When cranberry products were compared with antibiotics (trimethoprim or co-trimoxazole), there was no significant difference between groups in reducing the risk of recurrent infection in women (51.1% versus 40.4%; moderate quality evidence; Jepson et al. 2012). There was also no significant difference between cranberry products and antibiotics (trimethoprim) in reducing the risk of recurrent infection in children (10.7% versus 15.4%; low quality evidence; Jepson et al. 2012).
- Evidence for cranberry products reducing the risk of antimicrobial resistance compared with antibiotics was conflicting. Cranberry products reduced the risk in premenopausal women compared with antibiotic prophylaxis (co-trimoxazole) during a 12-month treatment period ([Beerepoot et al. 2011](#); moderate quality evidence). However, the risk was not reduced in children during a 12-month treatment period (including children with vesicoureteral reflux [VUR]; [Uberos et al. 2012](#); moderate quality evidence).
- There were no significant differences in gastrointestinal adverse events in adults treated with cranberry products compared with no treatment or antibiotics (Jepson et al. 2012; low quality evidence). Two further studies showed higher numbers of adverse events in adults given placebo compared with cranberry products and 1 further study showed similar numbers of adverse events between groups.
- No data were identified for adverse effects of cranberry products in children.

## D-mannose

- D-mannose (200 ml of 1% solution once daily in the evening) used for up to 6 months significantly reduced the risk of recurrent infection in non-pregnant women compared with no treatment (14.6% versus 60.8%, NNT 3 [range 2 to 3]; high quality evidence). This was based on 1 RCT in non-pregnant women presenting with a current UTI and a history of recurrent UTI ([Kranjcec et al. 2014](#)). All women were treated with ciprofloxacin 500 mg twice a day for 7 days for their current infection.
- There was no significant reduction in recurrent infection when D-mannose was compared with antibiotic prophylaxis (nitrofurantoin 50 mg a day) over the 6-month

study period (Kranjcec et al. 2014; low quality evidence).

- There were significantly fewer adverse events (such as diarrhoea, nausea and vaginal burning) with D-mannose compared with antibiotics in non-pregnant women (7.8% versus 28.2%, number needed to harm [NNH] 5 [range 4 to 10]; Kranjcec et al. 2014; high quality evidence).
- No systematic reviews or RCTs were identified that included data on D-mannose in pregnant women, men or children.

## Committee discussion on self-care

- Based on their experience, and the need to minimise inappropriate use of antibiotics, the committee agreed that people should be given advice about behavioural and personal hygiene measures to reduce the risk of UTI, such as:
  - drinking enough fluids to avoid dehydration
  - not delaying habitual and post-coital urination
  - wiping from front to back after defaecation
  - not douching or wearing occlusive underwear.

## Probiotics (lactobacillus)

- The committee discussed the evidence for the probiotic lactobacillus. While there was some evidence to support the use of 'effective strains', there was no information on which lactobacillus products were included in this analysis. They also noted the high drop-out rate in the study.
- Based on evidence, the committee agreed that people should be told that there is inconclusive evidence to recommend the use of lactobacillus to prevent recurrent UTIs.

## Cranberry products

- The committee recognised that cranberry products are used widely and discussed the very low quality evidence showing some benefit for reducing the risk of UTIs, specifically in non-pregnant women, and children and young people. They were also aware that there was no evidence to suggest benefit in older women. The committee also noted the conflicting evidence for cranberry products in reducing the risk of antimicrobial resistance.
- Taking account of the limitations of the evidence, and the need to minimise antimicrobial resistance, the committee agreed that some women who are not pregnant and some children and young people under 16 may wish to try cranberry products as a self-care treatment. However, due to safety concerns with delayed

treatment, particularly in children and young people, the committee agreed that cranberry products should only be considered in this population following advice from a paediatric specialist.

- The committee recognised that there was some evidence to suggest that cranberry juice was not significantly better than placebo in non-pregnant women, while cranberry capsules showed a significant benefit. However, due to significant limitations in the evidence the committee was not able to recommend a specific cranberry product.
- The committee discussed the sugar content of cranberry products, and based on their experience, agreed that people should be advised to take account of their daily sugar intake if using cranberry products.

### D-mannose

- The committee was aware of the mechanism of action of D-mannose, which is also in cranberry products.
- The committee noted evidence suggesting that D-mannose was effective in reducing the risk of recurrent UTI in non pregnant women, and noted the low NNT of 3 (range 2 to 3) over 6 months, compared with no treatment. However, this was based on 1 small RCT. The committee agreed to make a recommendation that some women who are not pregnant may wish to try D-mannose, as a self care treatment, noting the sugar content of this product which should be considered.

## Oestrogens

- Oral oestrogens (with or without progestogens) taken for up to 4 years did not significantly reduce the risk of recurrent infection in postmenopausal women with recurrent UTI compared with placebo (moderate quality evidence). This was based on a systematic review and meta-analysis of RCTs ([Perrotta et al. 2008](#)). Recurrent UTI was defined as 3 or more episodes in the past 12 months or 2 or more episodes in the past 6 months.
- Vaginal oestrogen cream (estriol cream 0.5 mg applied topically at night for 2 weeks

then twice weekly) for 8 months significantly reduced the risk of recurrent infection in postmenopausal women compared with placebo (16.0% versus 62.8%, NNT 3 [range 2 to 4]; high quality evidence). This was based on 1 RCT in the Perrotta et al. (2008) systematic review.

- Vaginal oestrogen cream was also significantly more effective than oral antibiotics (ofloxacin 600 mg a day) in reducing the risk of recurrent infection over a 3-month study period (7.4% versus 80.0%, NNT 2 [range 2 to 2]; low quality evidence). However, no difference was seen 2 months after treatment was stopped (very low quality evidence). This was based on 1 RCT included in the Perrotta et al. (2008) systematic review.
- Vaginal oestrogen administered via a vaginal ring in 12-week cycles, for a total of 36 weeks significantly reduced the risk of recurrent infection in postmenopausal women compared with placebo (50.9% versus 80.0%, NNT 4 [range 3 to 9]; Perrotta et al. 2008, moderate quality evidence).
- However, vaginal oestrogen administered via a pessary (used daily for 2 weeks then once every 2 weeks) significantly increased the risk of recurrent infection in postmenopausal women compared with an oral antibiotic (nitrofurantoin 100 mg a day) over a 9-month study period (67.4% versus 51.8%; Perrotta et al. 2008; low quality evidence).
- Oral oestrogens increased adverse events (such as breast tenderness and vaginal bleeding) in postmenopausal women compared with placebo (NNH 5 [range 3 to 14]; Perrotta et al. 2008; high quality evidence).
- Vaginal oestrogens did not significantly increase adverse events (such as breast tenderness and vaginal bleeding) in postmenopausal women compared with placebo or no treatment, but there was a significant increase in burning, itching or vaginal bleeding when compared with oral antibiotics (Perrotta et al. 2008; low to moderate quality evidence).
- Oestrogens (hormone replacement therapy [HRT]) increase the risk of venous thromboembolism (when taken orally), 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 ([Medicines and Healthcare products Regulatory Agency \[MHRA\] Drug Safety Update on HRT, September 2007](#) and [BNF information on sex hormones](#)). Before prescribing HRT, health professionals should consider carefully the potential benefits and risks for

every woman. See the [NICE guideline on menopause](#) for more information on using vaginal oestrogen for urogenital atrophy.

- Vaginal oestrogens should be used in the smallest effective amount, for the shortest duration to minimise systemic effects. 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 ([MHRA Drug Safety Update on HRT, September 2007](#) and [BNF information on sex hormones](#)). The [NICE guideline on menopause](#) recommends that women using vaginal oestrogen should report unscheduled vaginal bleeding to their GP.

## Committee discussion on oestrogens

- Based on evidence of a lack of effectiveness and taking account of MHRA safety advice, the committee agreed to not recommend oral oestrogens (HRT) specifically to prevent recurrent UTI in postmenopausal women.
- Based on evidence, the committee agreed that vaginal oestrogens were effective in reducing the risk of recurrent UTI in postmenopausal women, although this was based on small numbers of women and appears to diminish when the treatment is stopped. They noted the low NNTs for recurrent infection compared with placebo (NNT 3 [range 2 to 4] for topical cream; NNT 4 [range 3 to 9] for vaginal ring), and also when a topical cream was compared with antibiotics (NNT 2 [range 2 to 2]). However, oestrogen administered via a pessary was less effective than antibiotics.
- Based on evidence and their experience, the committee recognised the adverse effects of vaginal oestrogens (such as breast tenderness and vaginal bleeding), which may require additional investigations.
- The committee was aware of MHRA safety advice on the use of HRT; they agreed this was important for women and prescribers to discuss the possible harms of vaginal oestrogens, but that it should not prevent the safe use of an effective treatment for recurrent UTI.
- Vaginal oestrogens are not licensed for preventing recurrent UTI, although oestrogen deficiency is a known risk factor. The committee noted that there do not appear to be any effective, licensed, non-antimicrobial alternatives for preventing recurrent UTI in postmenopausal women.
- Based on evidence, their experience and data on antimicrobial resistance, the committee agreed that vaginal oestrogens could be considered for postmenopausal women with recurrent UTI, with review within 12 months, or earlier if agreed with the woman. The committee recognised that this was a preference-sensitive decision and the benefits and harms of vaginal oestrogens need to be discussed with the woman, taking account of other symptoms the woman may want to address, such as vaginal dryness. The committee agreed that, before vaginal oestrogen is given, women should be asked about their preferences and given advice about the possible risks and benefits, returning for



review and reporting unscheduled vaginal bleeding.

- The committee could not make any firm conclusions from the evidence or their experience about different vaginal oestrogen products. They agreed that this will need to be considered with the woman on an individual basis.

## Antibiotic prophylaxis

- The main complication of lower UTIs, including recurrent infections, is ascending infection leading to pyelonephritis. Most episodes of pyelonephritis are uncomplicated and result in no residual kidney damage. However, complications can include impaired renal function or renal failure, septicaemia and preterm labour in pregnancy ([NICE clinical knowledge summary on pyelonephritis](#)).
- In pregnancy, asymptomatic bacteriuria can lead to pyelonephritis; and symptomatic UTI has been associated with developmental delay or cerebral palsy in the infant, and fetal death ([NICE clinical knowledge summary on UTI \[lower\] – women](#)).
- In men with UTIs, prostate involvement is common, which may lead to complications such as prostatic abscess or chronic bacterial prostatitis, and urinary stones are a possibility ([NICE clinical knowledge summary on UTI \[lower\] – men](#)).
- In children, UTIs can lead to renal scarring, but more often this is preceded by acute pyelonephritis rather than cystitis. Renal scarring is more common in children with vesicoureteral reflux, where recurrent UTIs are more likely ([NICE clinical knowledge summary on UTI – children](#)).

## Efficacy of antibiotic prophylaxis

- Antibiotic prophylaxis for 6 to 12 months significantly reduced the risk of recurrent infection (using microbiological criteria) in non-pregnant women with recurrent UTI (2 or more 'uncomplicated' episodes in the past 12 months) compared with placebo (12.3% versus 65.5%, NNT 2 [range 2 to 3]; high quality evidence). This was based on a systematic review and meta-analysis ([Albert et al. 2004](#)). However, there was no significant difference when recurrent infections were reported after the period of prophylaxis (very low quality evidence).

- Antibiotic prophylaxis with nitrofurantoin for 5 weeks to 24 months significantly reduced the risk of recurrent infection in a mixed population of adults (including non-pregnant women and men) and children (mainly females) with recurrent UTI when compared with placebo or no treatment (22.5% versus 59.0%, NNT 3 [range 3 to 4]; low quality evidence). This was based on a systematic review and meta-analysis of RCTs ([Muller et al. 2017](#)).
- Antibiotic prophylaxis with nitrofurantoin 50 mg three times a day for the duration of pregnancy significantly reduced the risk of recurrent asymptomatic bacteriuria in pregnant women who were admitted to hospital with acute pyelonephritis (32.6% versus 59.3%, NNT 4 [range 3 to 13]) compared with no treatment (monitoring alone; moderate quality evidence). This was based on 1 RCT (n=102) included in a systematic review ([Schneeberger et al. 2015](#)). However, antibiotic prophylaxis did not significantly reduce the risk of recurrent UTI (including pyelonephritis) in pregnant women, or birth outcomes such as pre-term birth, low birthweight and miscarriage (Schneeberger et al. 2015; very low to low quality evidence).
- Antibiotic prophylaxis with nitrofurantoin or co-trimoxazole for at least 6 months (duration not reported in all studies) did not significantly reduce the risk of recurrent infection in children under 18 with recurrent UTI compared with placebo or no treatment (very low quality evidence). This was based on a systematic review and meta-analysis of RCTs ([Williams and Craig 2011](#)). Not all studies had clearly defined inclusion and exclusion criteria, and some had a small proportion of children with VUR. However, the result did not change when the analysis was restricted to studies that included children without VUR (very low quality evidence).
- Antibiotic prophylaxis for at least 2 months (co-trimoxazole in most studies) did not significantly reduce the rate of deteriorated renal scars in children under 18 years (with or without VUR) compared with placebo or no treatment (very low quality evidence). This was based on a systematic review and meta-analysis of RCTs ([Dai et al. 2010](#)).
- There was no significant difference in the rate of antimicrobial resistance antibiotic prophylaxis compared with placebo in children under 18 years (Williams and Craig 2011, very low quality evidence).

## Safety of antibiotic prophylaxis

- Antibiotic-associated diarrhoea occurs in 2 to 25% of people taking antibiotics,

depending on the antibiotic used ([NICE clinical knowledge summary on 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. See the [NICE guideline on drug allergy](#) for more information.
- Nitrofurantoin should be used with caution in those with renal impairment ([MHRA Drug Safety Update on nitrofurantoin, September 2014](#)). It should be avoided at term in pregnancy because it may produce neonatal haemolysis. Adults (especially older adults) and children on long-term therapy should be monitored for liver function and pulmonary symptoms ([BNF information on nitrofurantoin](#)).
- Trimethoprim has a teratogenic risk in the first trimester of pregnancy (folate antagonist; [BNF information on trimethoprim](#)). Manufacturers advise that trimethoprim is contraindicated in pregnancy ([trimethoprim summary of product characteristics](#)).
- In non-pregnant women, there was no significant difference in serious adverse effects with antibiotic prophylaxis compared with placebo, but there was a significant increase in the number of 'other adverse effects' (low quality evidence). This was based on a systematic review and meta-analysis of RCTs (NNH 13 [range 7 to 70]; Albert et al. 2004).
- In children, there was no significant difference in the incidence of adverse effects reported or the number of withdrawals due to adverse events with antibiotic prophylaxis compared with placebo or no treatment (Williams and Craig 2011; very low quality evidence).
- No systematic reviews or RCTs were identified that assessed the adverse effects of antibiotic prophylaxis in pregnant women.
- See the [summaries of product characteristics](#) for information on contraindications, cautions and adverse effects of individual medicines.

## Committee discussion on antibiotic prophylaxis

### People aged 16 years and over with recurrent UTI

- Based on evidence and their experience, the committee agreed that antibiotic prophylaxis was effective in reducing the risk of recurrent UTI in non-pregnant women, although this benefit was not seen after the treatment is stopped. They noted the low NNTs for recurrent infection compared with placebo (NNT 2 [range 2 to 3]). However, they also recognised the increased risk of harms with antibiotic prophylaxis compared with placebo.
- Based on evidence, the committee agreed that antibiotic prophylaxis was also effective in a mixed population of people with recurrent UTI, including pre- and postmenopausal women, men and children (NNT 3 [3 to 4]). However, interpretation of the evidence was more difficult due to variations in the populations studied and antibiotic choice, dosage and duration.
- The committee discussed the evidence specifically in pregnant women, which found that antibiotic prophylaxis was effective in reducing the risk of recurrent asymptomatic bacteriuria in pregnant women (NNT 4 [range 3 to 13]). However, they recognised that the study had a number of limitations. The study was small and not powered to show any benefit in preterm births. The population was pregnant women who were admitted to hospital with acute pyelonephritis. The committee noted that nitrofurantoin is not an appropriate choice of antibiotic to show benefit in this population. They were also aware that UTI has been associated with developmental delay or cerebral palsy in the infant, and fetal death.
- Taking account of the benefits and harms of antibiotic prophylaxis and the need to minimise antimicrobial resistance, the committee agreed that antibiotic prophylaxis could be considered in people aged 16 years and over with recurrent UTI, but only after other management options had been unsuccessful (behavioural and personal hygiene measures, managing any triggers and using non-antimicrobial treatments), if appropriate.
- The committee recognised the importance of reviewing antibiotic prophylaxis, and considered that up to every 6 months was reasonable based on possible adverse

effects of antibiotics, the risk of resistance with long-term antibiotics, the possible need for any further investigations if recurrence of UTIs continues, and to allow time to assess treatment success. People should also know to seek medical help if they experience symptoms of an acute infection despite taking prophylaxis.

- The committee discussed the importance of the review and were aware of other conditions where a specific date is included on the prescription to prompt review within 6 months.
- To reduce the risk of antimicrobial resistance, the committee agreed that at each review women should be reminded about self-care, and consideration should be given to either stopping, continuing or changing antibiotic prophylaxis (for example, from single-dose to daily prophylaxis). However the committee was not able to make specific recommendations about when to stop, continue or change antibiotic prophylaxis as it will depend on the circumstances of an individual person.
- Based on evidence that suggests antibiotic prophylaxis does not continue to be effective after stopping treatment, the committee agreed that if antibiotic prophylaxis was stopped, women should be able to access treatment rapidly if they have symptoms of an acute UTI.
- The committee recognised the limitations of the evidence on antibiotic prophylaxis in pregnant women and men, and the lack of evidence to support the use of non-antimicrobial treatments. Therefore, the committee agreed that it was appropriate to refer all pregnant women to an obstetrician if recurrent UTI is diagnosed during pregnancy. They also agreed that most men with recurrent UTI should be referred for further specialist urology investigation and management, taking an individualised approach that takes account of multimorbidity. The committee agreed that any decision to prescribe antibiotic prophylaxis in pregnant women or men should be under specialist advice.
- The committee also recognised the higher risks associated with recurrent upper UTIs (pyelonephritis), and agreed that it was appropriate to refer these people for further specialist investigation and management.

- The committee agreed that further consideration should be made for women with recurrent lower UTI if the underlying cause of recurrence was unknown or required further investigation. However, due to resource implications and the lower risk of complications for this population, the committee agreed that specialist advice should be sought, rather than specialist referral.
- The committee was aware of the recommendation in the [NICE guideline on suspected cancer: recognition and referral](#), which states that a non-urgent referral for bladder cancer should be considered for people over 60 with recurrent unexplained UTI.
- The committee also recognised the equality considerations for managing recurrent UTI in transgender people, due to anatomical differences between women and men.

### **Children and young people under 16 years with recurrent UTI**

- The committee was aware that the [NICE guideline on urinary tract infection in under 16s](#) makes recommendations on referring children and young people with recurrent UTI to a paediatric specialist for assessment and investigations.
- Based on evidence, the committee noted that antibiotic prophylaxis does not appear to be effective in reducing the risk of recurrent UTI in children. However, there was considerable uncertainty in the evidence (all very low quality).
- Based on their experience, the committee agreed that most cases of recurrent UTI in children and young people are due to a functional or structural abnormality of the urinary tract.
- Taking account of the uncertainty in the evidence and the need to minimise antimicrobial resistance from long-term antibiotic use, the committee agreed that antibiotic prophylaxis could be considered in children and young people under 16 years, but only under specialist advice when other management options have been unsuccessful. This would be an individualised decision following an assessment of underlying causes, taking into account the severity and frequency of previous symptoms and the risk of developing complications.

- The committee recognised the importance of reviewing antibiotic prophylaxis, and considered that every 6 months was reasonable. They agreed that the same principles for the review in adults apply to children and young people.

## Choice of antibiotic prophylaxis

- Antibiotic prophylaxis with nitrofurantoin (various doses: 100 mg a day, 75 mg a day, 50 mg a day or 50 mg twice a day) for at least 3 months significantly reduced the risk of recurrent infection in a mixed population of adults (including non-pregnant women and men) and children (mainly females) compared with methenamine hippurate (NNT 7 [range 4 to 102]; low quality evidence). However, there was no significant difference between nitrofurantoin and either trimethoprim, beta-lactams or quinolones (very low to low quality evidence). This was based on a systematic review and meta-analyses of RCTs ([Muller et al. 2017](#)).
- Antibiotic prophylaxis with nitrofurantoin (1 to 1.5 mg/kg daily) for 6 months significantly reduced the risk of having a positive urine culture at the end of the study period in children with recurrent UTI compared with trimethoprim (2 to 3 mg/kg daily; NNT 3 [range 2 to 8]) and reduced the risk of having a recurrent symptomatic UTI compared with co-trimoxazole (2 mg/kg daily; NNT 6 [range 3 to 27]; very low to moderate quality evidence). However, there was no difference with nitrofurantoin compared with cefixime (2 mg/kg daily; 6 to 12 months; moderate quality evidence). This was based on a systematic review of single RCTs ([Williams and Craig 2011](#)).
- Overall, antibiotic prophylaxis with nitrofurantoin (for at least 3 months) increased the risk of mild (not defined) adverse effects compared with other antibiotics in a mixed population of adults and children (30.6% versus 11.7%; NNH 5 [range 4 to 6]; Muller et al. 2017; low quality evidence). When specific antibiotics were compared, there were significantly more mild adverse effects with nitrofurantoin compared with beta-lactams (NNH 7 [range 4 to 28]), trimethoprim (NNH 3 [range 2 to 4]) and methenamine (NNH 3 [range 2 to 6]), but no difference between nitrofurantoin and quinolones or co-trimoxazole (Muller et al. 2017; very low to moderate quality evidence).
- In children, there were significantly fewer adverse events with nitrofurantoin compared with trimethoprim (NNH 2 [range 1 to 8]), but significantly more adverse events with

nitrofurantoin compared with cefixime (NNH 3 [range 2 to 6]; moderate quality evidence). This was based on a systematic review of single RCTs (Williams and Craig 2011).

- No systematic reviews or RCTs were identified that included data on the choice of antibiotic in pregnant women.



## Committee discussion on choice of antibiotic prophylaxis

- Based on evidence of no major differences in clinical effectiveness between classes of antibiotics, the committee agreed that the choice of antibiotic prophylaxis should largely be driven by minimising the risk of resistance. Resistant bacteria are a particular concern in UTIs and, where possible, any previous urine culture and susceptibility results, and antibiotic prescribing for UTI, should be checked and antibiotics chosen accordingly.
- Based on their experience and resistance data, the committee agreed that a different antibiotic should be selected for antibiotic prophylaxis if an acute UTI is being treated. They also recognised that rotational use of antibiotics may be needed, based on local policies.
- The committee discussed that, if antibiotic prophylaxis is needed to prevent 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 *Clostridium difficile*. Broad-spectrum antibiotics need to be reserved for second-choice treatment of non-life-threatening infections when narrow-spectrum antibiotics are ineffective.
- Based on evidence, their experience and resistance data, the committee agreed to recommend **trimethoprim** or **nitrofurantoin** (based on culture and susceptibility results) as first choice antibiotics for prophylaxis. These antibiotics have less effect on the normal intestinal microflora in gastrointestinal tract, which is particularly important when continuous antibiotic prophylaxis is used.
  - Trimethoprim should only be prescribed if a lower risk of resistance is likely, for example, if trimethoprim has not been used in the past 3 months, if previous urine culture results suggest trimethoprim susceptibility (but this was not used as treatment) and in younger women in areas where local epidemiology data suggest resistance is low. There is a higher risk of trimethoprim resistance with recent use and in older people in residential facilities. Trimethoprim is contraindicated in pregnant women.
  - Nitrofurantoin is not recommended for people with an estimated glomerular

filtration rate (eGFR) of less than 45 ml/minute. With long-term use, there is a lower risk of resistance of nitrofurantoin compared with trimethoprim, but this needs to be balanced against the increased harms, such as pulmonary fibrosis.

- The committee was aware that nitrofurantoin suspension is currently substantially more expensive than trimethoprim suspension and, if both antibiotics are appropriate, the one with the lowest acquisition cost should be chosen.
- Based on evidence, their experience and resistance data, the committee agreed to recommend **cefalexin** or **amoxicillin** (based on culture and susceptibility results) as second-choice antibiotics for prophylaxis.
  - Amoxicillin and cefalexin are broad spectrum antibiotics that have a similar spectrum of activity and can be used if bacteria are susceptible.
- Based on evidence that methenamine hippurate was less effective than antibiotic prophylaxis with nitrofurantoin, the committee was not able to make a recommendation on its use. They were also aware that methenamine hippurate is a medicine that is considered less suitable for prescribing ([BNF information on methenamine hippurate](#)).

## Antibiotic dosing and course length

- Single-dose antibiotic prophylaxis (used when exposed to conditions that may trigger a UTI) was not significantly different to daily antibiotic prophylaxis in the number of women with at least 1 recurrent infection over a 12-month study period in postmenopausal women with recurrent UTI (3 or more episodes in the past 12 months; 80.6% versus 70.3%; moderate quality evidence). This was based on 1 RCT ([Zhong et al. 2011](#)).
- The conditions for using the single-dose antibiotic were determined by the woman's experience, such as walking for a long time or sexual intercourse. The choice of antibiotic (nitrofurantoin, amoxicillin, co-trimoxazole, quinolones or cephalosporins) varied and was determined on a case by case basis, depending on the woman's previous antibiotic use and following an antibiotic susceptibility test.

- In 1 RCT (reported in a systematic review by [Albert et al. 2004](#)) single-dose ciprofloxacin (250 mg) taken immediately after sexual intercourse was as effective as a daily dose in non-pregnant women in reducing the risk of recurrent UTI during the period of prophylaxis (Albert et al. 2004; low quality evidence).
- There were significantly fewer adverse events with single-dose antibiotic prophylaxis compared with daily antibiotic prophylaxis (NNH 3 [range 2 to 9]; Zhong et al. 2011; moderate quality evidence).
- There was no significant difference in the number of non-serious adverse effects between those who took a single dose of ciprofloxacin (250 mg) immediately after sexual intercourse, or daily at night (Albert et al. 2004; low quality evidence).

## Committee discussions on antibiotic dosing and course length

- Based on evidence, the committee was aware that a range of doses and course lengths were used for daily antibiotic prophylaxis. The committee agreed that usual BNF doses for daily prophylaxis should be used. The duration of treatment needs to be determined on an individual basis with a review of treatment success within 6 months, to include discussion of a trial of stopping antibiotic prophylaxis as appropriate.
- The committee discussed the evidence for using single-dose antibiotic prophylaxis (including post-coital single-dose antibiotics) in non-pregnant women. The committee agreed that the single dose used when exposed to an identifiable trigger would be the same as a single treatment dose for a UTI.
- Based on evidence, their experience and antimicrobial resistance data, the committee agreed that single-dose prophylaxis was as effective as continuous prophylaxis, with fewer adverse effects in non-pregnant women with an identifiable trigger, and should be considered as the first option for antibiotic prophylaxis in this group of women. Prophylaxis needs to be tailored to an individual woman's personal triggers, and advice given about how to use the antibiotic. Antibiotics for single-dose prophylaxis would be kept at home to avoid unnecessary GP and pharmacy visits.
- No evidence from systematic reviews and RCTs was identified for using a course of antibiotics to keep at home for treating an acute UTI in people with recurrent UTIs (also known as stand-by antibiotics). The use of stand-by antibiotics could potentially lead to inappropriate antibiotic overuse in the absence of medical supervision, which would not reflect the principles of antimicrobial stewardship. Therefore, while the committee recognised that they may have a role in some specialist cases, they were not able to make a recommendation on their use.

## Other considerations

### Medicines adherence

Medicines adherence may be a problem for some people with medicines that require regular dosing or longer treatment duration (for example, continuous antibiotic prophylaxis). See the [NICE guideline on medicines adherence](#).

### Resource implications

Recommended antibiotics are available as generic formulations, see the [Drug Tariff](#) for costs.

Nitrofurantoin 25 mg/5 ml oral suspension is more expensive than other oral suspensions, such as trimethoprim 50 mg/5 ml. 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).

# Update information

## Minor updates since publication

**February 2019:** Minor corrections to one of the evidence summaries.

ISBN: 978-1-4731-3126-2

## Accreditation

