National Institute for Health and Care Excellence

Urinary tract infection (recurrent): antimicrobial prescribing

[B] Evidence review for the effectiveness of methenamine hippurate in the prevention of recurrent urinary tract infections (UTIs)

NICE guideline NG112

Evidence underpinning recommendations 1.2.8 to 1.2.11 and the recommendation for research in the NICE guideline

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Final

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1.1 Review question

What is the clinical and cost-effectiveness of methenamine hippurate when compared to antibiotics in the prevention of recurrent UTIs for adults and children?

1.1.1 Introduction

Widespread use of antimicrobials has been linked to microbes such as bacteria and viruses changing and becoming resistant to treatment. It is therefore important to reduce the use of antimicrobials, particularly antibiotics, to protect our health and the health of future generations. Methenamine hippurate is a urinary antiseptic drug used for the prevention of recurrent UTIs, but there is limited evidence on its effectiveness.

The aim of this review is to assess whether methenamine hippurate is a clinical and cost-effective option for people with recurrent UTIs as an alternative option to daily prophylactic antibiotics.

1.1.2 Summary of the protocol

Table 1 PICO inclusion criteria

Population	Adults and children (aged 72 hours and older) with recurrent UTIs* of any severity *See full protocol in Appendix A for minimum threshold for classifying as recurrent UTI
Interventions	Methenamine hippurate prophylaxis
Comparator	Antibiotic prophylaxis
Outcomes	Primary outcomes • Recurrence of UTI (as defined by study authors) • Serious adverse events (as defined by study authors) • Antibiotic resistance (as defined by study authors)

	• Patient satisfaction Secondary outcomes • Antibiotic use (other than the prescribed intervention) • Gastrointestinal issues • Generic health- and social care-related or disease-specific quality of life measured using a validated instrument
Study type	• Systematic reviews of RCTs • RCTs

Abbreviations: RCT: randomised controlled trial; UTI: urinary tract infection

For the full protocol see appendix A.

1.1.3 Methods and process

Methods specific to this review question are described in the review protocol in appendix A and the methods section in appendix J.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

This review included 2 studies which were both randomised controlled trials. One study (Botros 2022) was conducted in the USA, while the other (Harding 2022) was conducted in the UK. One study compared methenamine hippurate to trimethoprim (Botros 2022), and 1 study compared methenamine hippurate to different antibiotics (Harding 2022). The Botros (2022) trial reported recurrence of UTI and gastrointestinal issues, while Harding (2022) reported recurrence of UTI, serious adverse events, antibiotic resistance, patient satisfaction, antibiotic use (other than the prescribed intervention), and gastrointestinal issues. Both studies included a population of women aged 18 years and older with recurrent UTI.

The effectiveness evidence study selection is presented as a PRISMA diagram in appendix C.

See section 1.1.12 for the full references of the included studies.

1.1.4.2 Excluded studies

Details of studies excluded at full text, along with reasons for exclusion, are given in appendix I.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2 Intervention evidence

Study details	Location	Population	Intervention	Comparison	Outcomes	Risk of Bias
Botros 2022 N=92 Study type: RCT Follow-up time: 12 months	USA	Women aged 18 years and older with recurrent UTI (at least two in the past 6 months or 3 in the past year that were symptomatic and had positive urine culture) **Age in years (Mean±SD):** 71.9±13 **Postmenopausal (n):** 86 (93%) **UTI prior to enrolment (Mean±SD):** 3.9±1.8	Methenamine hippurate: 1g twice daily	Trimethoprim: 100mg once nightly	• Recurrence of UTI • Gastrointestinal issues (diarrhoea)	High risk of bias due to missing outcome data
Harding 2022 N=240	UK	Women aged 18 years and older with recurrent UTI (at least two in the past 6 months	Methenamine hippurate: twice daily, 12h apart	Antibiotics: Once daily as a single dose at bedtime (either 50mg or 100mg of	• Recurrence of UTI • Serious adverse events	High risk of bias due to missing outcome data

Study details	Location	Population	Intervention	Comparison	Outcomes	Risk of Bias
Study type: RCT Follow-up time: 18 months		or 3 in the past year that were symptomatic or a single severe infection requiring hospitalisation) **Age in years (Mean±SD):** 50.1± 18.6 **Postmenopausal (n):** 141 (59%) **Self-reported UTI episodes in the last 12 months (Mean±SD):** 6.9±3.6		nitrofurantoin, 100mg of trimethoprim, or 250mg of cefalexin)	• Antibiotic resistance • Patient satisfaction • Antibiotic use (other than prescribed intervention) • Gastrointestinal issues (diarrhoea)	

Abbreviations: RCT: randomised controlled trial; UTI: urinary tract infection

See appendix D for full evidence tables and appendix E for forest plots.

1.1.6 Summary of the effectiveness evidence

All studies compared the effectiveness of methenamine hippurate (MH) prophylaxis to daily antibiotic prophylaxis; evidence was judged to be of very low certainty. Evidence was downgraded for imprecision, inconsistency, and risk of bias.

Evidence from 1 study found evidence of higher total numbers of UTI episodes in people taking MH compared with antibiotics during prophylactic treatment (IRR: 1.52, CI: 1.16 to 1.99; very low certainty) and during the follow-up period (IRR: 1.45, CI: 1.16 to 1.81; very low certainty).

Evidence from 1 study for the outcome of antibiotic resistance in E. coli found fewer antimicrobial categories (MD -0.4, -0.74 to -0.06; very low certainty) and fewer antibiotics (MD: -0.6, -1.07 to -0.13; very low certainty) to which E. coli from perineal swabs was resistant for people taking MH compared with antibiotics during prophylactic treatment. In contrast, at the end of the follow-up period evidence from 1 study found a higher number of antibiotics to which E. coli from perineal swabs was resistant (MD: 0.4, 0.01 to 0.79; very low certainty) for people taking MH compared with antibiotics.

Evidence from 1 study also showed a higher rate of antibiotics used for other reasons during the follow-up period (RR: 1.87, CI: 1.05 to 3.31; very low certainty) and antibiotics used for UTI (other than the prescribed intervention) during the prophylactic treatment (RR: 1.31, CI: 1.01 to 1.71; very low certainty) for people taking MH compared with antibiotics.

No evidence of difference between MH and antibiotic prophylaxis were found for the following outcomes: recurrent UTI during prophylactic treatment and during follow-up; time to subsequent infection during prophylactic treatment; mean number of episodes of symptomatic UTI during prophylactic treatment and during follow-up; serious adverse events during prophylactic treatment; antibiotic resistance when measured as number of antimicrobial categories resistance to E. coli from perineal swab at the end of the follow-up period, at least one E. coli isolate from perineal swab demonstrating resistance to at least one antibiotic during prophylactic treatment and at the end of the follow-

up, at least one E. coli isolate from perineal swab demonstrating MDR during prophylactic treatment and at the end of follow-up, at least one E. coli isolate from urine sample demonstrating resistance to at least one antibiotic during prophylactic treatment and during follow-up, at least one E. coli isolate from urine sample demonstrating MDR during prophylactic treatment and during follow-up, and any resistance in any significant isolate from symptomatic urine samples during prophylactic treatment and during follow-up; patient satisfaction during prophylactic treatment and during follow-up; antibiotic use when measured as therapeutic antibiotics for other reasons during prophylactic treatment or therapeutic antibiotics for UTI during follow-up; and lastly for rate of diarrhoea events during prophylactic treatment.

There was no evidence identified for the outcome of generic health- and social care-related or disease specific quality of life measured using a validated instrument.

See appendix F for full GRADE tables.

1.1.7 Economic evidence

A systematic literature search was undertaken to identify published health economic evidence relevant to the review question. Studies were identified by searching databases such as MEDLINE, Embase and Health Technology Assessment. The searches were conducted in April 2024; the study selection is shown in appendix G. A total of 28 records were retrieved. After title and abstract screening against the review protocol, one study was screened by its full text and included in this review. Based on one of the analyses performed in the included HTA report by Harding et al. (2022), a spin-off paper by King et al. (2024) was also published outside our search dates. However, the results of the spin-off paper were identical to that of one of the economic analyses reported in the HTA, and hence not included in our review. Full economic evidence tables along with the checklists for study applicability and study limitations are shown in appendix H.

1.1.7.1 Included studies

One study (Harding et al., 2022) was included in the review. The study included two health economic analyses, a trial-based analysis for a time horizon of 18 months and a model-based analysis for a time horizon of 50 years. Both analyses are summarised separately below (**Error! Reference source not found.**).

Table 3 Summary of economic evidence

Methods, applicability, and limitations	Base-case results						Uncertainty
	Intervention	Absolute		Incremental			
		Cost (£)	QALYs	Cost (£) 95% CI	QALYs 95% CI	ICER	
Harding et al. (2022): Trial-based analysis							
A trial-based analysis (ALTAR trial), with total costs collected on all participants (205 participants) until 18 months post randomisation. **Time horizon:** 18 months QoL data were collected at baseline, 3-, 6-, 9-, 12-, 15- and 18-months post randomisation via EQ-5D-5L questionnaires. Costs were based on the intervention medications, the use of healthcare services, medications used to manage UTIs and concomitant medications. Medication costs were obtained from the BNF, management costs from NHS reference costs 2020-21, and relevant unit costs from PSSRU 2019. Healthcare service use was calculated via questionnaires given to patients at follow-up points. The study included an adjusted analysis where costs and QALYs were estimated	Antibiotic prophylaxis	£931 (Unadjusted analysis)	1.182 (Unadjusted analysis)	-	-	-	Using the bootstrapped results, methenamine hippurate had a 51% probability of being cost effective at a threshold per QALY of £0 but rising to 65% at a threshold per QALY of £20,000. A sensitivity analysis was performed incorporating the cost of antimicrobial resistance. In this scenario, methenamine hippurate remained dominant based on the results from the adjusted analysis; methenamine hippurate had a 69% probability of being
	Methenamine hippurate	£1,013 (Unadjusted analysis)	1.133 (Unadjusted analysis)	-£40 (-£684 to £603) (Adjusted analysis)	0.014 (-0.05 to 0.07) (Adjusted analysis)	**Adjusted analysis:** methenamine hippurate was dominant. **Unadjusted analysis:** methenamine hippurate was dominated.	

Methods, applicability, and limitations	Base-case results						Uncertainty
	Intervention	Absolute		Incremental			
		Cost (£)	QALYs	Cost (£) 95% CI	QALYs 95% CI	ICER	
simultaneously in which 5 patients in antibiotic arm and 21 patients in methenamine hippurate arm were censored. **Directly applicable with minor limitations (Table 6 and Table 7)**							cost effective at a threshold per QALY of £0 (rising to 76% at a £20,000 per QALY threshold).
Harding et al. (2022): Model-based analysis							
A Markov state transition model, including Mild (1 UTI episode), Moderate (2 or more UTI episode), Death, and Asymptomatic health states, to extrapolate the results of the ALTAR trial beyond 18 months. The model had 6-monthly cycles. All patients began in the moderate health state. **Time horizon:** Lifetime QoL data were based on the utility values estimated from the ALTAR trial using EQ-5D-5L. An OLS regression was used to estimate potential differences in utilities between health states. Costs considered were those associated with the intervention medications for the first two cycles only, health-care resource use (through UK specific costs) and concomitant	Antibiotic prophylaxis	£7,231	15.24	-	-	-	In probabilistic sensitivity analysis, antibiotic prophylaxis had a 60% probability of being cost-effective at a £20,000 per QALY gained threshold.
	Methenamine hippurate	£7,876	14.96	£645 (£359 to £931)	-0.283 (-0.35 to -0.22)	Dominated	

Methods, applicability, and limitations	Base-case results						Uncertainty
	Intervention	Absolute		Incremental			
		Cost (£)	QALYs	Cost (£) 95% CI	QALYs 95% CI	ICER	
medications reported by those receiving each intervention medication during their time in the trial, and additional antibiotics received to treat UTIs. **Directly applicable with minor limitations (Table 6 and Table 7)**							

Abbreviations: BNF: British National Formulary; ICER: incremental cost-effectiveness ratio; NHS: National Health Service; OLS: ordinary least squares; QoL: quality of life; QALYs: quality-adjusted life years; UTI: urinary tract infection

1.1.7.2 Excluded studies

No studies were excluded at full text review.

1.1.8 Summary of included economic evidence

The HTA study by Harding et al. (2022) conducted two health economic analyses: a trial-based analysis for a time horizon of 18 months and a model-based analysis for a time horizon of 50 years, to assess the clinical effectiveness and cost-effectiveness of methenamine hippurate compared with antibiotic prophylaxis for recurrent urinary tract infection prevention in women aged ≥18 years.

Using QALYs gained as the outcome measure, the trial-based analysis (18 months) found that methenamine hippurate dominated antibiotic prophylaxis in the adjusted analysis, while antibiotic prophylaxis dominated methenamine hippurate in the unadjusted analysis. The adjusted analysis used seemingly unrelated regressions, where the costs and QALYs were estimated simultaneously, to account for any possible correlations between the two dependent variables. These results were subject to uncertainty as, in both circumstances, the 95% confidence intervals around the difference in costs and QALYs were wide. Based on the adjusted analysis, the bootstrapped results showed methenamine hippurate to have a 65% probability of being cost effective at a £20,000 per QALY threshold. When the benefits of reduced antibiotic use were included in the analysis, methenamine hippurate had a 76% probability of being cost effective.

The model-based analysis, where the trial-based analysis was extrapolated for 50 years using a Markov state transition model, found that antibiotic prophylaxis dominated methenamine hippurate. In probabilistic sensitivity analysis, antibiotic prophylaxis had a 60% probability of being cost effective at a £20,000 per QALY threshold.

1.1.9 Economic model

No de novo economic modelling was undertaken for this review question.

1.1.10 Committee discussion and interpretation of the evidence

1.1.10.1 Key outcomes

When choosing which outcomes to prioritise, the committee considered the outcomes used in the previous NICE guideline on this topic (NICE 2018), a core outcome set (COS) for treatment of UTIs (Beecher 2022; in the absence of a COS for prophylaxis for recurrent UTIs), and their knowledge and experience. As the aim of prophylactic treatment is to prevent future occurrences, the committee agreed to select the recurrence of UTI as a primary outcome. Furthermore, the committee agreed to include serious adverse events, antibiotic resistance, and patient satisfaction as primary outcomes. Adverse events were included as an outcome in the COS. The committee discussed that serious adverse events are rare with antibiotics and methenamine hippurate but were aware that they can occur (for example risk of anaphylaxis with antibiotics) and agreed that capturing this would be more useful than including a composite measure of all adverse events. They also discussed the importance of capturing more common adverse events that can impact quality of life and agreed that gastrointestinal issues were the most likely given the medications in question, so they included this as a secondary outcome. The committee agreed that other less serious adverse events would be captured as part of patient satisfaction, which was also included in the COS. Antibiotic resistance was chosen as a primary outcome due to concerns about widespread use of antimicrobials, particularly antibiotics, contributing to bacteria becoming resistant to treatment, which may have serious consequences in terms of the future effectiveness of antibiotics. Therefore, if use of methenamine hippurate reduces antibiotic resistance, this would contribute to antimicrobial stewardship aims.

The committee agreed that antibiotic use (other than the prescribed intervention) and generic health- and social care-related or disease-specific quality of life should also be included as secondary outcomes. Antibiotic use was included as an outcome for the same reason as antibiotic resistance but was considered less critical as it does not provide direct evidence regarding the impact on resistance. Quality of life was included as a secondary outcome

as an overall measure of the impact of prophylactic treatment with methenamine hippurate or antibiotics on people's wellbeing.

1.1.10.2 Quality of the evidence

The quality of the evidence for quantitative outcomes was assessed using GRADE methodology and the overall certainty in the findings was rated as very low. Findings were downgraded in 3 areas. The most common reason for downgrading was risk of bias due to missing outcome data, imprecision due to small sample sizes (for continuous outcomes) and low event rates (for dichotomous outcomes). The outcome of rate of diarrhoea events was downgraded for risk of bias due to this being a patient-reported outcome (and patients being aware of treatment assignment). The outcome of episodes of symptomatic UTI during prophylactic treatment was downgraded for inconsistency as there was significant heterogeneity across groups and sub-group analysis to explain this heterogeneity was not possible.

There was no evidence identified for the outcome of generic health- and social care-related or disease specific quality of life measured using a validated instrument.

1.1.10.3 Benefits and harms

The committee discussed that the aim of this review was to determine if methenamine hippurate is a suitable alternative option to daily prophylactic antibiotics, due to antimicrobial stewardship aims. Therefore, the focus was to determine if methenamine hippurate was non-inferior to antibiotics, rather than determining which is most effective. Results showed no evidence of difference for most outcomes. However, there was evidence of higher incidence rates for total numbers of UTI during prophylactic treatment and during follow-up in people who received methenamine hippurate prophylaxis compared to antibiotics. The absolute difference in number of UTI episodes was approximately 0.5 episodes more per person per year in the methenamine hippurate group. The committee discussed whether this difference would constitute a clinically meaningful difference and were aware that the ALTAR trial (Harding 2022) specified one UTI per 12 months as their non-inferiority

margin, based on semi-structured interviews with women. The committee agreed that a reduction of 1 episode per person per year would be considered as a clinically important difference based on their experience and awareness of similar patient consultations. Therefore, the difference in incidence rates between groups observed in the evidence would not be considered clinically meaningful. However, the committee acknowledged that any significant improvement, in terms of fewer or less severe episodes, would be positive and may be important to individuals.

The committee also discussed the results for antibiotic resistance in E. coli (number of antimicrobial categories and number of antibiotics from perineal swab) where there was evidence of less resistance during the prophylactic treatment in those who had methenamine hippurate prophylaxis compared to those who had antibiotics; however, this finding was not maintained at the end of the follow-up, where there was some evidence of higher numbers of antibiotics being resistant to E. coli in people who received methenamine hippurate. Results for antibiotic use (other than the prescribed intervention) showed a higher rate of antibiotic use for methenamine hippurate compared to antibiotics during the follow-up period (therapeutic antibiotics for other reasons) and during prophylactic treatment (therapeutic antibiotics for UTI). The committee noted that antibiotic use other than the prescribed intervention was considered a less critical outcome than antibiotic resistance. The committee also discussed that the higher use of antibiotics other than the prescribed intervention could potentially confound the results for antibiotic resistance, as participants who needed additional antibiotics may be more likely to develop antibiotic resistance. Although this cannot be confirmed as the results did not report such detail. Furthermore, the committee acknowledged that the treatment time for the study included in this outcome was 12 months, while in reality actual prophylactic treatment lasts longer than 12 months. Prophylactic treatment may last for many years as underlying factors increasing the risk of UTIs are likely to persist; therefore, stopping treatment would likely cause an increase in UTI symptoms or episodes. As a result, the lack of benefit and potential harm seen at the end of the follow-up period could be a result of the rebound effect of needing to start antibiotics

again following the end of prophylactic treatment in the study. The committee also noted that there was no evidence of difference for serious adverse events for methenamine hippurate compared to daily antibiotics, which was further confirmed by the lack of differences for patient satisfaction between methenamine hippurate and antibiotics.

The committee discussed that although results only derived from 2 individual studies and the overall certainty of results was very low, generally non-inferiority of methenamine hippurate compared to antibiotics was evident and that methenamine hippurate should be considered as an alternative treatment to antibiotics for women with recurrent UTI. The committee discussed that methenamine hippurate should be considered as a second line treatment when single-dose antibiotic prophylaxis, behavioural and personal hygiene measures and vaginal oestrogen are not effective or appropriate.

The committee discussed that the evidence only included women aged 18 years over in their population and caution should be taken not to extrapolate to other populations. The committee agreed based on their knowledge and experience that there is no clinical reason to expect any differences in effectiveness of methenamine hippurate in a 16- or 17-year-old person compared to 18-year-old people; therefore, they agreed the recommendation should also cover 16- and 17-year-olds, to align with recommendations in the existing UTI guideline. The committee also agreed that the recommendations should apply to trans men and non-binary people with female urinary systems. In the committee's knowledge and experience methenamine hippurate may be effective in men, trans women and non-binary people with male genitourinary systems, and children with recurrent UTIs, however there is no clinical effectiveness evidence for these populations. There was also no evidence of effectiveness during pregnancy and the committee were aware that the BNF (Joint Formulary Committee 2024) states it is preferable to avoid methenamine hippurate during pregnancy as there is inadequate evidence of safety. Furthermore, there was no evidence on the effectiveness of methenamine hippurate for people with upper UTI or complicated lower UTI. Therefore, the committee agreed to add a recommendation to seek specialist

advice if considering methenamine hippurate prophylaxis for recurrent UTI in such populations, as they did not want to preclude the use of methenamine hippurate in these groups but could not provide recommendations on when or for whom it may be beneficial.

The committee discussed the importance of shared decision making with patients and highlighted that methenamine hippurate will be a new drug to many GP practices and patients. The committee therefore agreed to add a recommendation on important factors to discuss about using methenamine hippurate for preventing recurrent UTIs. In the committee's knowledge and experience it is common for people who experience recurrent UTIs to take alkalinising agents, which are available over the counter, in order to reduce and manage symptoms experienced with recurrent UTIs. However, the committee discussed that alkalinising agents make urine more alkaline and can therefore make methenamine hippurate less effective. They agreed that people should not use alkalinising agents while taking methenamine hippurate.

The committee discussed that methenamine hippurate is licensed for long term use but agreed that effectiveness of and patient satisfaction with the treatment should be reviewed to ensure that people are using the treatment that works best for them. They agreed that an initial review within 6 months of starting the treatment followed by annual reviews or earlier if agreed with the person would be sufficient. This is less frequent than existing recommendations about monitoring for daily antibiotic prophylaxis because the committee agreed there would be fewer concerns about antibiotic resistance or side effects for methenamine hippurate.

The committee highlighted the gap in the evidence for the effectiveness of methenamine compared to antibiotics in populations other than women aged 18 years and over and therefore made a recommendation for further research. The committee also discussed that any evidence on the effectiveness of methenamine hippurate prophylaxis where the comparison was not limited to antibiotics (for example, comparison with placebo or no treatment) would provide important information about its effectiveness; however, it was not

within the scope of this guideline to broaden the comparator of this research recommendation, as the evidence review was limited to comparison with antibiotics.

1.1.10.4 Cost effectiveness and resource use

The committee considered the economic evidence presented, centred around two analyses by Harding et al. (2022). The model-based analysis showed that over a lifetime horizon, antibiotic prophylaxis dominating methenamine hippurate with having a 60% probability of being cost effective at a £20,000 per QALY threshold. On the other hand, the trial-based analysis showed mixed results over a time horizon of 18 months, with methenamine hippurate dominating antibiotic prophylaxis in the adjusted analysis (where 26 patients were censored) accounting for any possible correlations between the two dependent variables, while antibiotic prophylaxis dominating methenamine hippurate in the unadjusted analysis. The committee also discussed the benefits of reduced antibiotic use, whereby methenamine hippurate remained cost effective in the adjusted analysis.

The committee considered both the model-based and trial-based analyses as equally important in the decision making. Although the model-based analysis showed antibiotic prophylaxis to be more cost effective, it did not include the consequences of additional monitoring required for antibiotic prophylaxis that is not required for methenamine hippurate. However, with methenamine hippurate only cost effective under a specific analysis in the trial-based analysis, the committee agreed to make a recommendation to consider methenamine hippurate in specific conditions (patients who are not pregnant and have recurrent UTI that has not been adequately improved by behavioural and personal hygiene measures, vaginal oestrogen or single dose antibiotic prophylaxis) and recommended it as an alternative to antibiotic prophylaxis for other people after referral, specialist advice and further investigation.

Methenamine hippurate is already being used variably in the NHS as an alternative to antibiotic prophylaxis for people with recurrent UTI. The use of methenamine hippurate has increased across all regions in England since

2019 and a consider recommendation may further increase its use. It is more expensive than antibiotic prophylaxis, and so there would be additional drug costs to the NHS if it is prescribed as an alternative to antibiotic prophylaxis, but additional costs would vary and depend on local prescribing strategies. However, the use of methenamine hippurate prophylaxis may reduce the use of antibiotics and consequences such as adverse events and antibiotic resistance giving some drug cost and capacity savings.

1.1.10.5 Other considerations

The committee discussed their concerns with referring to behavioural and personal hygiene measures in the recommendations. In the committee's knowledge and experience, asking people about their personal hygiene can seem insulting and discourage people from seeking further treatment. The committee highlighted that issues with personal hygiene are not common with people who present with recurrent UTIs and where they do occur it is usually in combination with other issues such as incontinence or limited cognitive ability. The committee discussed that it should be at the practitioner's discretion whether personal hygiene may be an issue and, therefore, whether to discuss this with the person in question. However, it was not within the scope of this guideline update to remove mention of this from the guideline as a whole. As a result, they included behavioural and personal hygiene measures in the recommendations as an example of treatments that may be tried before methenamine hippurate prophylaxis for consistency with the existing guideline recommendations.

The committee were aware that methenamine hippurate requires acidic urine for its antimicrobial activity and discussed the testing of urine pH in people where methenamine hippurate does not appear to be effective. However, the committee did not make recommendations about testing urine pH as the evidence reviewed did not look at the effectiveness of these tests.

1.1.11 Recommendations supported by this evidence review

This evidence review supports recommendations 1.2.8 to 1.2.11, and the research recommendation on clinical and cost-effectiveness of methenamine hippurate in other populations.

1.1.12 References

1.1.12.1 Effectiveness evidence

Botros 2022

Botros C, Lozo S, Iyer S et al. (2022) Methenamine hippurate compared with trimethoprim for the prevention of recurrent urinary tract infections: a randomized clinical trial. International Urogynecology Journal 33(3): 571-580

Harding 2022

Harding C, Chadwick T, Homer T et al. (2022) Methenamine hippurate compared with antibiotic prophylaxis to prevent recurrent urinary tract infections in women: the ALTAR non-inferiority RCT. Health Technology Assessment (Winchester, England) 26(23): 1-172

1.1.12.2 Economic evidence

Harding C, Chadwick T, Homer T et al. (2022) Methenamine hippurate compared with antibiotic prophylaxis to prevent recurrent urinary tract infections in women: the ALTAR non-inferiority RCT. Health Technology Assessment (Winchester, England) 26(23): 1-172.

1.1.13 Miscellaneous

Beecher 2022

Beecher C, Duane S, Vellinga A et al. (2022) COSUTI: A Core Outcome Set (COS) for interventions for the treatment of uncomplicated urinary tract Infection (UTI) in Adults. Antibiotics 11(12): 1846

Joint Formulary Committee 2024

Joint Formulary Committee, British National Formulary (online). London: BMJ Group and Pharmaceutical Press. Available at: http://www.medicinescomplete.com [Accessed 23/07/2024]

NICE 2018

Urinary tract infection (recurrent): antimicrobial prescribing (2018) NICE guideline NG112

Appendices

Appendix A Review protocols

Review protocol for Effectiveness of methenamine hippurate in the prevention of recurrent urinary tract infections (UTIs)

ID	Field	Content	Developer comments *(delete before publication)*	QA comments *(delete before publication)*
0.	PROSPERO registration number	CRD42024544581		
1.	Review title	Effectiveness of methenamine hippurate in the prevention of recurrent urinary tract infections (UTIs)	Original question: What pharmacological (antimicrobial and non-antimicrobial) and non-pharmacological interventions are effective in managing recurrent urinary tract infections? Scope question: What is the clinical and cost-effectiveness of methenamine hippurate when compared to antibiotics in the prevention of recurrent UTIs for adults and children?	
2.	Review question	What is the clinical and cost-effectiveness of methenamine hippurate when		

		compared to antibiotics in the prevention of recurrent UTIs for adults and children?		
3.	Objective	To assess whether methenamine hippurate is a clinical and cost-effective option for people with recurrent UTIs as an alternative option to prophylactic antibiotics.		

4.	Searches	The following databases will be searched:
		
		• Clinical searches –
		  ○ Cochrane Central Register of Controlled Trials (CENTRAL)
		  ○ Cochrane Database of Systematic Reviews (CDSR)
		  ○ Embase
		  ○ MEDLINE
		  ○ Epistemonikos
		
		• Economic searches –
		  ○ MEDLINE
		  ○ Embase
		  ○ CRD HTA (last updated 31st March 2018)
		  ○ INAHTA International HTA Database		

		Database functionality will be used, where available, to exclude: • Animal studies • Editorials, letters, news items and commentaries • Conference abstracts and posters • Registry entries for ongoing clinical trials or those that contain no results • Theses and dissertations • Papers not published in the English language. Date limits: 2006 - current Search filters and classifiers: The following standard NICE filters will be used to limit results by study type: systematic reviews / randomised controlled trials/ economics / modelling and quality of life. The information services team at NICE will quality assure the principal search strategy. Any revisions or additional steps will be agreed by the review team before being implemented.		

		The full search strategies for all databases will be published in the final review.		
5.	Condition or domain being studied	Recurrent UTIs		

6.	Population	Inclusion: Adults and children (aged 72 hours and older) with recurrent UTIs* of any severity.
		
		* Minimum thresholds for classifying as recurrent UTI:
		• In adults:
		  ○ 2 or more UTIs in 6 months, or
		  ○ 3 or more UTIs in 12 months (EAU 2017)
		• In children:
		  ○ 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
			Info/context for the technical team:
			• The definition of 'recurrence' of UTI varies. Agreed that we will not include studies where the definition is more lenient than that from the terms used in the previous guideline (minimum thresholds included in the population), but we will include studies with a more permissive definition. In the absence of a definition, we will include studies and downgrade for an indirect population.
			• More info available here: ..\10. Background reading\rUTI definitions info.docx
			
			Note. To include link to NG113 re: catheter.	

		Exclusions: • Adults and children with a catheter • People receiving treatment for active UTI only	Re. 'people receiving active treatment for UTI only', we would not include studies where people are prescribed MH to deal with active symptoms, but we wouldn't exclude: • People receiving 'rescue treatment' for recurrent episodes occurring during the study period, or • People being prescribed MH/Abx prophylaxis at the same time as treatment who are told to start the prophylaxis once initial symptoms have subsided (committee raised this is common in practice), or • People starting MH/Abx prophylaxis immediately after treatment for active episode (i.e., no washout period)	
7.	Intervention	Methenamine hippurate prophylaxis		
8.	Comparator	Antibiotic prophylaxis		
9.	Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs • RCTs Exclude: • Conference abstracts		

10.	Other exclusion criteria	Studies conducted prior to 2006 for consistency with the cut-off used in NG112. Studies published not in English-language		
11.	Context	This review is a partial update of the following: Urinary tract infection (recurrent): antimicrobial prescribing (NG112). The above guideline makes no recommendations about methenamine hippurate so recommendations would either be new or change existing recommendations about the use of antibiotic prophylaxis.		
12.	Primary outcomes (critical outcomes)	• Recurrence of UTI (as defined by study authors; e.g., incidence, presence of recurrence, number of episodes) • Serious adverse events (as defined by study authors) • Antibiotic resistance (as defined by study authors) • Patient satisfaction	Info/context for the technical team: • One accepted definition of SAEs is: Serious intervention-related adverse effects leading to death, disability or prolonged hospitalisation or that are life threatening or otherwise considered medically significant. Not limiting based on this but provided for info about how it may be reported. • Antibiotic resistance likely to be reported in terms of resistant	

			bacteria identified in samples/swabs (e.g., urine sample, perineal swab).	
13.	Secondary outcomes (important outcomes)	• Antibiotic use (other than the prescribed intervention) • Gastrointestinal issues • Generic health- and social care-related or disease-specific quality of life measured using a validated instrument		
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study		

		excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.		
15.	Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklist: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.		
16.	Strategy for data synthesis	Quantitative findings will be formally summarised in the review. Where multiple studies report on the same outcome for the same comparison, meta-analyses will be conducted using		

		Cochrane Review Manager software. A fixed effect meta-analysis will be conducted, and data will be presented as risk ratios if possible or odds ratios when required (for example if only available in this form in included studies) for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed by visual inspection of the forest plots and consideration of the I^2 statistic. I^2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis, then a random effects model will be used for meta-analysis, or the data will not be pooled. The confidence in the findings 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/
		Where published, validated minimally important differences (MIDs) are available, importance and imprecision will be assessed against these. In the absence of published MIDs, effect sizes and confidence intervals will be considered qualitatively by the guideline committee and their discussion will be captured in the committee discussion of the evidence section. Imprecision will be judged based on number of events for dichotomous outcomes and sample size for continuous outcomes, as follows:
		• Dichotomous outcomes:
		  ○ <150 events: very serious imprecision
		  ○ 150 – 299 events: serious imprecision
		• Continuous outcomes:
		  ○ Sample size <200: very serious imprecision
		  ○ Sample Size 200-399: serious imprecision		

17.	Analysis of sub-groups	Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes: • Age:		

		○ Women ≥16 years of age (non-pregnant) ○ Women ≥16 years of age (pregnant) ○ Men ≥16 years of age ○ Children (72 hours to 15 years of age) • Older people (frailty, care home resident, dementia) • Mixed population (women, men and children) • People with 'complicated'[1] lower UTI or upper UTI. • Antibiotic used. • Definition of recurrence used in studies. Where evidence is stratified or subgrouped, the committee will consider on a case-by-case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions		

		will have similar effects in that group compared with others.				
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)				
19.	Language	English				
20.	Country	England				
21.	Anticipated or actual start date	15/04/2024				
22.	Anticipated completion date	13/11/2024				
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**		
		Preliminary searches	☐	☐		
		Piloting of the study selection process	☐	☐		
		Formal screening of	☐	☐		

		search results against eligibility criteria				
		Data extraction	☐	☐		
		Risk of bias (quality) assessment	☐	☐		
		Data analysis	☐	☐		
24.	Named contact	**5a. Named contact** Guideline development team NGA **5b Named contact e-mail** UTIrecurrent@nice.org.uk **5e Organisational affiliation of the review** Guideline Development Team NGA, Centre for Guidelines, National Institute for Health and Care Excellence (NICE)				
25.	Review team members	• Senior Technical Analyst: Guideline Development Team NGA, Centre for Guidelines, National Institute for Health and Care Excellence (NICE) • Technical Analyst: Guideline Development Team NGA, Centre for				

		Guidelines, National Institute for Health and Care Excellence (NICE)		
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Development Team NGA, Centre for Guidelines, which receives funding from the National Institute for Health and Care Excellence (NICE).		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		

28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: Project information | Urinary Tract Infection (recurrent): antimicrobial prescribing | Guidance | NICE		
29.	Other registration details	None		
30.	Reference/URL for published protocol	TBC		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.		

32.	Keywords	Recurrent urinary tract infection, UTI, methenamine hippurate, antibiotic, prophylaxis		
33.	Details of existing review of same topic by same authors	None		
34.	Current review status	☐ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued		
35..	Additional information	None		
36.	Details of final publication	www.nice.org.uk		

Abbreviations: NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trials; RoB: risk of bias; ROBIS: risk of bias in systematic reviews; UTI: urinary tract infection

[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)

Appendix B Literature search strategies

What is the clinical and cost-effectiveness of methenamine hippurate when compared to antibiotics in the prevention of recurrent UTIs for adults and children?

Background and development

Search design and peer review

A NICE Senior Information Specialist (SIS) conducted the literature searches for the evidence review. The searches were run between 29-30 April 2024.

This search report is compliant with the requirements of the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (for further details see: Rethlefsen M et al. PRISMA-S. *Systematic Reviews*, 10(1), 39).

The MEDLINE strategies below were quality assured (QA) by a trained NICE SIS. All translated search strategies were peer reviewed by another SIS to ensure their accuracy. Both procedures were adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. *Journal of Clinical Epidemiology*, 75, 40-46).

The principal search strategies were developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess "low-probability" matches. All decisions made for the review can be accessed via the deduplication history.

Prior work

The search strategy was based on the terms used for the NG112 NICE guideline. Modifications were made to the original search strategy for the specifications in the review protocol.

Search limits and other restrictions

Formats

Limits were applied in adherence to standard NICE practice and the review protocol to exclude:

- Animal studies
- Editorials, letters, news items and commentaries
- Conference abstracts and posters
- Registry entries for ongoing clinical trials or those that contain no results
- Theses and dissertations
- Papers not published in the English language.

The National Guideline Alliance (NGA) Medline and Embase Exclusion filters were used in the search strategies for Ovid Medline and Ovid Embase databases.

Date limits

A date limit of 01/01/2006 to 30/04/2024 was applied, as stated in the review protocol, for consistency with the cut-off used in the NG112 guideline.

Search filters and classifiers

Effectiveness searches

The NGA Medline and Embase RCT Sensitive filter, and the NGA Medline and Embase Systematic Review filters were used in the search strategies for Ovid Medline and Ovid Embase databases. The effectiveness filters are adaptations of Cochrane filters.

Cost effectiveness searches

The NGA Medline and Embase Economics Sensitive filter, and the NGA Medline and Embase Modelling filters were used in the search strategies for Ovid Medline and Ovid Embase databases. The cost effectiveness filters are adaptations of SHARR filters.

Key decisions

The search strategy was developed to find evidence on for the specified population and intervention in the review protocol.

The search strategy translation was modified for the Epistemonikos database to the intervention terms only.

Clinical searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Medline-ALL	29th April 2024	Ovid	Ovid MEDLINE(R) ALL <1946 to April 26, 2024>	79
Embase	29th April 2024	Ovid	Embase <1974 to 2024 April 26>	69
Cochrane Database of Systematic Reviews (CDSR)	29th April 2024	Wiley	Cochrane Database of Systematic Reviews Issue 4 of 12, April 2024	2
Cochrane Central Register of Controlled Trials (CENTRAL)	29th April 2024	Wiley	Cochrane Central Register of Controlled Trials Issue 3 of 12, March 2024	31
Epistemonikos	29th April 2024	Epistemonikos Foundation	April 2024	17

Search strategy history

Database name: MEDLINE

Searches		
1	exp Urinary Tract/	476139
2	exp Urinary Tract Infections/	51643
3	exp Cystitis/	10777
4	Vesico-Ureteral Reflux/	8852
5	exp Pyelitis/	15679
6	exp Urinary Calculi/	39476

Searches
7 Urethritis/ 4760
8 (UTI or UTIs or RUTI or cystitis* or bacteriuria* or pyelitis or pyelonephriti* or pyelonephrites or pyonephros* or pyelocystitis or cystopyelitis or pyuria or VUR or urosep* or urethriti*).tw. 54225
9 ((urin* or renal* or kidney*) adj1 (system* or tract* or calculus or calculi* or stone* or sepsis*)).tw. 120017
10 ((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 inflamm*)).tw. 113242
11 ((upper or lower) adj3 urin*).tw. 31513
12 (schistosom* adj3 (h?ematobi* or urin* or urogenit* or infect*)).tw. 10826
13 ((vesicoureteral or vesicoureteric or vesicorenal or vesico ureteral or vesico renal or vesico ureteric or bladder* or cystoureteral or cysto ureteral or ureter* or urether* or nephropathy*) adj3 (backflow* or reflux* or (flow* adj2 (backward* or back or abnormal* or retrograde)))).tw. 9451
14 or/1-13 680245
15 Methenamine/ 1111
16 (methenamine* or aminoform* or hexamethylen* or hexamine* or hippurate* or hiprex* or haiprex* or urotropin* or "hip rex*" or hipeksal* or hippramine* or urex* or urotractan* or ammoform* or antihydral* or cystamin* or formamine* or "formin (heterocycle)" or hexaloid* or metramine* or mictasol* or naphthamine* or uralysol* or uraseptine* or urisol* or uritone* or urogenine* or utropine* or vesalvine*).tw,kf. 8288
17 or/15-16 8785
18 14 and 17 967
19 letter/ 1250357
20 editorial/ 688771
21 news/ 224420
22 exp historical article/ 410451
23 Anecdotes as topic/ 4747
24 comment/ 1034831
25 case reports/ 2398881
26 (letter or comment*).ti. 199022
27 or/19-26 5073307
28 randomized controlled trial/ or random*.ti,ab. 1641339
29 27 not 28 5039541
30 animals/ not humans/ 5181854
31 exp Animals, Laboratory/ 958445
32 exp Animal Experimentation/ 10473
33 exp Models, Animal/ 648984
34 exp Rodentia/ 3603529
35 (rat or rats or rodent* or mouse or mice).ti. 1493450
36 or/29-35 11153869

Searches		
37	18 not 36	566
38	limit 37 to English language	472
39	randomized controlled trial.pt.	611821
40	controlled clinical trial.pt.	95537
41	pragmatic clinical trial.pt.	2309
42	randomi#ed.ab.	768070
43	placebo.ab.	247793
44	drug therapy.fs.	2688423
45	randomly.ab.	432314
46	trial.ab.	695425
47	groups.ab.	2670182
48	or/39-47	5964911
49	meta-analysis/	199568
50	meta-analysis as topic/	23969
51	(meta analy* or metanaly* or metaanaly*).ti,ab.	303373
52	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.	382739
53	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.	57262
54	(search strategy or search criteria or systematic search or study selection or data extraction).ab.	90799
55	(search* adj4 literature).ab.	107294
56	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.	401691
57	cochrane.jw.	16697
58	or/49-57	735544
59	38 and (48 or 58)	220
60	limit 59 to ed=20060101-20240430	71
61	limit 59 to dt=20060101-20240430	76
62	60 or 61	76

Database name: Embase

Searches		
1	exp urinary tract/	598421
2	urinary tract infection/ or schistosomiasis haematobia/ or urosepsis/	138260
3	kidney infection/ or kidney abscess/ or pyonephrosis/	4991
4	bacteriuria/	8034
5	pyuria/ or urogenital tract infection/	8576
6	exp cystitis/	29790

Searches
7 urethritis/ or nonspecific urethritis/ 6624
8 vesicoureteral reflux/ 14772
9 exp pyelonephritis/ 25446
10 exp urolithiasis/ 76389
11 (UTI or UTIs or RUTI or cystitis* or bacteriuria* or pyelitis or pyelonephriti* or pyelonephrites or pyonephros* or pyelocystitis or cystopyelitis or pyuria or VUR or urosep* or urethriti*).tw. 79298
12 ((urin* or renal* or kidney*) adj1 (system* or tract* or calculus or calculi* or stone* or sepsis*)).tw. 177310
13 ((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 inflamm*)).tw. 167007
14 ((upper or lower) adj3 urin*).tw. 47327
15 (schistosom* adj3 (h?ematobi* or urin* or urogenit* or infect*)).tw. 11611
16 ((vesicoureteral or vesicoureteric or vesicorenal or vesico ureteral or vesico renal or vesico ureteric or bladder* or cystoureteral or cysto ureteral or ureter* or urether* or nephropathy*) adj3 (backflow* or reflux* or (flow* adj2 (backward* or back or abnormal* or retrograde)))).tw. 12278
17 or/1-16 936832
18 methenamine/ or methenamine hippurate/ or methenamine mandelate/ 3808
19 (methenamine* or aminoform* or hexamethylen* or hexamine* or hippurate* or hiprex* or haiprex* or urotropin* or "hip rex*" or hipeksal* or hippramine* or urex* or urotractan* or ammoform* or antihydral* or cystamin* or formamine* or "formin (heterocycle)" or hexaloid* or metramine* or mictasol* or naphthamine* or uralysol* or uraseptine* or urisol* or uritone* or urogenine* or utropine* or vesalvine*).tw,kf. 8809
20 or/18-19 11173
21 17 and 20 1439
22 letter.pt. or letter/ 1326409
23 note.pt. 982802
24 editorial.pt. 804449
25 case report/ or case study/ 3069199
26 (letter or comment*).ti. 244400
27 or/22-26 5910393
28 randomized controlled trial/ or random*.ti,ab. 2178884
29 27 not 28 5849102
30 animal/ not human/ 1216320
31 nonhuman/ 7704667
32 exp Animal Experiment/ 3176637
33 exp Experimental Animal/ 848803
34 animal model/ 1785717
35 exp Rodent/ 4136216
36 (rat or rats or rodent* or mouse or mice).ti. 1671908

Searches	
37	or/29-36 15379737
38	21 not 37 861
39	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. 5903186
40	38 not 39 761
41	limit 40 to English language 608
42	random*.ti,ab. 2060861
43	factorial*.ti,ab. 49231
44	(crossover* or cross over*).ti,ab. 129939
45	((doubl* or singl*) adj blind*).ti,ab. 282310
46	(assign* or allocat* or volunteer* or placebo*).ti,ab. 1309841
47	crossover procedure/ 77825
48	single blind procedure/ 54482
49	randomized controlled trial/ 818823
50	double blind procedure/ 218348
51	or/42-50 3035203
52	systematic review/ 463522
53	meta-analysis/313666
54	(meta analy* or metanaly* or metaanaly*).ti,ab. 383792
55	((systematic or evidence) adj2 (review* or overview*)).ti,ab.447418
56	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. 70339
57	(search strategy or search criteria or systematic search or study selection or data extraction).ab. 108449
58	(search* adj4 literature).ab. 134159
59	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab. 486963
60	((pool* or combined) adj2 (data or trials or studies or results)).ab. 96778
61	cochrane.jw. 25061
62	or/52-61 1030114
63	41 and (51 or 62) 111
64	limit 63 to dc=20060101-20240430 69

Database name: Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials

Searches	
#1	MeSH descriptor: [Urinary Tract] explode all trees 7706
#2	MeSH descriptor: [Urinary Tract Infections] explode all trees 3295

Searches
#3 MeSH descriptor: [Cystitis] explode all trees 618
#4 MeSH descriptor: [Vesico-Ureteral Reflux] this term only 197
#5 MeSH descriptor: [Pyelitis] explode all trees 319
#6 MeSH descriptor: [Urinary Calculi] explode all trees 1880
#7 MeSH descriptor: [Urethritis] this term only 220
#8 (UTI or UTIs or RUTI or cystitis* or bacteriuria* or pyelitis or pyelonephriti* or pyelonephrites or pyonephros* or pyelocystitis or cystopyelitis or pyuria or VUR or urosep* or urethriti*):ti,ab 5794
#9 ((urin* or renal* or kidney*) NEAR/1 (system* or tract* or calculus or calculi* or stone* or sepsis*)):ti,ab 13919
#10 ((bladder* or genitourin* or genito NEXT urin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) NEAR/3 (infect* or bacteria* or microbial* or block* or obstruct* or inflamm*)):ti,ab 11371
#11 ((upper or lower) NEAR/3 urin*):ti,ab 4410
#12 (schistosom* NEAR/3 (hematobi* or haematobi* or urin* or urogenit* or infect*)):ti,ab 364
#13 ((vesicoureteral or vesicoureteric or vesicorenal or "vesico ureteral" or "vesico renal" or "vesico ureteric" or bladder* or cystoureteral or "cysto ureteral" or ureter* or urether* or nephropathy*) NEAR/3 (backflow* or reflux* or (flow* NEAR/2 (backward* or back or abnormal* or retrograde)))):ti,ab 406
#14 {OR #1-#13} 29212
#15 MeSH descriptor: [Methenamine] this term only 71
#16 (methenamine* or aminoform* or hexamethylen* or hexamine* or hippurate* or hiprex* or haiprex* or urotropin* or hip NEXT rex* or hipeksal* or hippramine* or urex* or urotractan* or ammoform* or antihydral* or cystamin* or formamine* or "formin (heterocycle)" or hexaloid* or metramine* or mictasol* or naphthamine* or uralysol* or uraseptine* or urisol* or uritone* or urogenine* or utropine* or vesalvine*):ti,ab 191
#17 {OR #15-#16} 210
#18 #14 AND #17 107
#19 conference:pt or (clinicaltrials or trialsearch):so 741160
#20 #18 NOT #19 with Cochrane Library publication date Between Jan 2006 and Apr 2024 33 (2 – CDSR, 31 – Central)

Database name: Epistemonikos

Searches
(advanced_title_en:((methenamine* OR aminoform* OR hexamethylenetetramine* OR hexamine* OR hippurate* OR hiprex* OR urotropin*)) OR advanced_abstract_en:((methenamine* OR aminoform* OR hexamethylenetetramine* OR hexamine* OR hippurate* OR hiprex* OR urotropin*))) [Filters: classification=systematic-review, cochrane=missing, protocol=no, min_year=2006, max_year=2024]

Cost-effectiveness searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Medline-ALL	30 April 2024	Ovid	Ovid MEDLINE(R) ALL <1946 to April 29, 2024>	8
Embase	30 April 2024	Ovid	Embase <1974 to 2024 April 29>	23
INAHTA	30 April 2024			1
HTA	30 April 2024	CRD	Up to 2018	1

Search strategy history

Database name: MEDLINE

Searches
1 exp Urinary Tract/ 476215
2 exp Urinary Tract Infections/ 51650
3 exp Cystitis/ 10780
4 Vesico-Ureteral Reflux/ 8852
5 exp Pyelitis/ 15680
6 exp Urinary Calculi/ 39478
7 Urethritis/ 4761
8 (UTI or UTIs or RUTI or cystitis* or bacteriuria* or pyelitis or pyelonephriti* or pyelonephrites or pyonephros* or pyelocystitis or cystopyelitis or pyuria or VUR or urosep* or urethriti*).tw. 54253
9 ((urin* or renal* or kidney*) adj1 (system* or tract* or calculus or calculi* or stone* or sepsis*)).tw. 120079
10 ((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 inflamm*)).tw. 113305
11 ((upper or lower) adj3 urin*).tw. 31530
12 (schistosom* adj3 (h?ematobi* or urin* or urogenit* or infect*)).tw. 10827
13 ((vesicoureteral or vesicoureteric or vesicorenal or vesico ureteral or vesico renal or vesico ureteric or bladder* or cystoureteral or cysto ureteral or ureter* or

Searches
urether* or nephropathy*) adj3 (backflow* or reflux* or (flow* adj2 (backward* or back or abnormal* or retrograde)))).tw. 9451
14 or/1-13 680418
15 Methenamine/ 1111
16 (methenamine* or aminoform* or hexamethylen* or hexamine* or hippurate* or hiprex* or haiprex* or urotropin* or "hip rex*" or hipeksal* or hippramine* or urex* or urotractan* or ammoform* or antihydral* or cystamin* or formamine* or "formin (heterocycle)" or hexaloid* or metramine* or mictasol* or naphthamine* or uralysol* or uraseptine* or urisol* or uritone* or urogenine* or utropine* or vesalvine*).tw,kf. 8291
17 or/15-16 8788
18 14 and 17 967
19 letter/ 1250743
20 editorial/ 689141
21 news/ 224494
22 exp historical article/ 410524
23 Anecdotes as topic/ 4747
24 comment/ 1034877
25 case reports/ 2399765
26 (letter or comment*).ti. 199095
27 or/19-26 5074976
28 randomized controlled trial/ or random*.ti,ab. 1642403
29 27 not 28 5041191
30 animals/ not humans/ 5182870
31 exp Animals, Laboratory/ 958784
32 exp Animal Experimentation/ 10474
33 exp Models, Animal/ 649302
34 exp Rodentia/ 3604503
35 (rat or rats or rodent* or mouse or mice).ti. 1493852
36 or/29-35 11156989
37 18 not 36 566
38 limit 37 to English language 472
39 Economics/ 27531
40 Value of life/ 5825
41 exp "Costs and Cost Analysis"/ 270180
42 exp Economics, Hospital/ 25824
43 exp Economics, Medical/ 14433
44 exp Resource Allocation/ 19043
45 Economics, Nursing/ 4013
46 Economics, Pharmaceutical/ 3132
47 exp "Fees and Charges"/ 31438
48 exp Budgets/ 14209

Searches	
49	budget*.ti,ab. 37319
50	cost*.ti,ab. 826304
51	(economic* or pharmaco?economic*).ti,ab. 392268
52	(price* or pricing*).ti,ab. 56086
53	(financ* or fee or fees or expenditure* or saving*).ti,ab. 312863
54	(value adj2 (money or monetary)).ti,ab. 3187
55	resourc* allocat*.ti,ab. 14363
56	(fund or funds or funding* or funded).ti,ab. 139843
57	(ration or rations or rationing* or rationed).ti,ab. 16759
58	ec.fs. 443383
59	or/39-58 1787517
60	exp models, economic/ 16293
61	*Models, Theoretical/ 64968
62	*Models, Organizational/ 6500
63	markov chains/ 16122
64	monte carlo method/ 32813
65	exp Decision Theory/ 13624
66	(markov* or monte carlo).ti,ab. 88408
67	econom* model*.ti,ab. 5641
68	(decision* adj2 (tree* or analy* or model*)).ti,ab. 41559
69	or/60-68 231076
70	38 and (59 or 69) 10
71	limit 70 to ed=20060101-20240430 7
72	limit 70 to dt=20060101-20240430 7
73	71 or 72 8

Database name: EMBASE

Searches	
1	exp urinary tract/ 598445
2	urinary tract infection/ or schistosomiasis haematobia/ or urosepsis/ 138267
3	kidney infection/ or kidney abscess/ or pyonephrosis/ 4991
4	bacteriuria/ 8034
5	pyuria/ or urogenital tract infection/ 8577
6	exp cystitis/ 29793
7	urethritis/ or nonspecific urethritis/ 6624
8	vesicoureteral reflux/ 14773
9	exp pyelonephritis/ 25447
10	exp urolithiasis/ 76396

Searches
11 (UTI or UTIs or RUTI or cystitis* or bacteriuria* or pyelitis or pyelonephriti* or pyelonephrites or pyonephros* or pyelocystitis or cystopyelitis or pyuria or VUR or urosep* or urethriti*).tw. 79304
12 ((urin* or renal* or kidney*) adj1 (system* or tract* or calculus or calculi* or stone* or sepsis*)).tw. 177322
13 ((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 inflamm*)).tw. 167023
14 ((upper or lower) adj3 urin*).tw. 47330
15 (schistosom* adj3 (h?ematobi* or urin* or urogenit* or infect*)).tw. 11611
16 ((vesicoureteral or vesicoureteric or vesicorenal or vesico ureteral or vesico renal or vesico ureteric or bladder* or cystoureteral or cysto ureteral or ureter* or urether* or nephropathy*) adj3 (backflow* or reflux* or (flow* adj2 (backward* or back or abnormal* or retrograde)))).tw. 12279
17 or/1-16 936884
18 methenamine/ or methenamine hippurate/ or methenamine mandelate/ 3808
19 (methenamine* or aminoform* or hexamethylen* or hexamine* or hippurate* or hiprex* or haiprex* or urotropin* or "hip rex*" or hipeksal* or hippramine* or urex* or urotractan* or ammoform* or antihydral* or cystamin* or formamine* or "formin (heterocycle)" or hexaloid* or metramine* or mictasol* or naphthamine* or uralysol* or uraseptine* or urisol* or uritone* or urogenine* or utropine* or vesalvine*).tw,kf. 8810
20 or/18-19 11174
21 17 and 20 1439
22 letter.pt. or letter/ 1326571
23 note.pt. 982897
24 editorial.pt. 804545
25 case report/ or case study/ 3069506
26 (letter or comment*).ti. 244432
27 or/22-26 5911029
28 randomized controlled trial/ or random*.ti,ab. 2179192
29 27 not 28 5849732
30 animal/ not human/ 1216321
31 nonhuman/ 7705657
32 exp Animal Experiment/ 3177042
33 exp Experimental Animal/ 848938
34 animal model/ 1786021
35 exp Rodent/ 4136626
36 (rat or rats or rodent* or mouse or mice).ti. 1672028
37 or/29-36 15381356
38 21 not 37 861
39 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. 5904020

Searches		
40	38 not 39	761
41	limit 40 to English language	608
42	health economics/	36456
43	exp economic evaluation/	367098
44	exp health care cost/	351875
45	exp fee/	44952
46	budget/	34561
47	funding/	81689
48	resource allocation/	25743
49	budget*.ti,ab.	49128
50	cost*.ti,ab.	1096011
51	(economic* or pharmaco?economic*).ti,ab.	481090
52	(price* or pricing*).ti,ab.	76364
53	(financ* or fee or fees or expenditure* or saving*).ti,ab.	438743
54	(value adj2 (money or monetary)).ti,ab.	4266
55	resourc* allocat*.ti,ab.	17587
56	(fund or funds or funding* or funded).ti,ab.	227655
57	(ration or rations or rationing* or rationed).ti,ab.	19837
58	or/42-57	2250664
59	statistical model/	177102
60	exp economic aspect/	2594289
61	59 and 60	28402
62	*theoretical model/	31706
63	*nonbiological model/	5188
64	stochastic model/	22792
65	decision theory/	1868
66	decision tree/	24196
67	monte carlo method/	53374
68	(markov* or monte carlo).ti,ab.	98767
69	econom* model*.ti,ab.	8271
70	(decision* adj2 (tree* or analy* or model*)).ti,ab.	55457
71	or/61-70	257685
72	41 and (58 or 71)	34
73	limit 72 to dc=20060101-20240430	23

Database name: HTA (CRD databases)

Searches		
1	MeSH DESCRIPTOR Urinary Tract EXPLODE ALL TREES	307

Searches	
2	MeSH DESCRIPTOR Urinary Tract Infections EXPLODE ALL TREES 225
3	MeSH DESCRIPTOR Cystitis EXPLODE ALL TREES 24
4	MeSH DESCRIPTOR Vesico-Ureteral Reflux 19
5	MeSH DESCRIPTOR Pyelitis EXPLODE ALL TREES 14
6	MeSH DESCRIPTOR Urinary Calculi EXPLODE ALL TREES 125
7	MeSH DESCRIPTOR Urethritis 4
8	((UTI or UTIs or RUTI or cystitis* or bacteriuria* or pyelitis or pyelonephriti* or pyelonephrites or pyonephros* or pyelocystitis or cystopyelitis or pyuria or VUR or urosep* or urethriti*)) 257
9	(((urin* or renal* or kidney*) adj1 (system* or tract* or calculus or calculi* or stone* or sepsis*))) 755
10	(((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 inflamm*))) 634
11	(((upper or lower) adj3 urin*)) 147
12	((schistosom* adj3 (hematobi* or haematobi* or urin* or urogenit* or infect*))) 18
13	(((vesicoureteral or vesicoureteric or vesicorenal or vesico ureteral or vesico renal or vesico ureteric or bladder* or cystoureteral or cysto ureteral or ureter* or urether* or nephropathy*) adj3 (backflow* or reflux*))) 28
14	(((vesicoureteral or vesicoureteric or vesicorenal or vesico ureteral or vesico renal or vesico ureteric or bladder* or cystoureteral or cysto ureteral or ureter* or urether* or nephropathy*) adj3 (flow* adj2 (backward* or back or abnormal* or retrograde)))) 0
15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 1295
16	MeSH DESCRIPTOR Methenamine 1
17	((methenamine* OR aminoform* OR hexamethylenetetramine* OR hexamine* OR hippurate* OR hiprex* OR urotropin*)) 11
18	#16 OR #17 11
19	#15 AND #18 8
20	(#15 AND #18) IN HTA date limit 2006-current 1

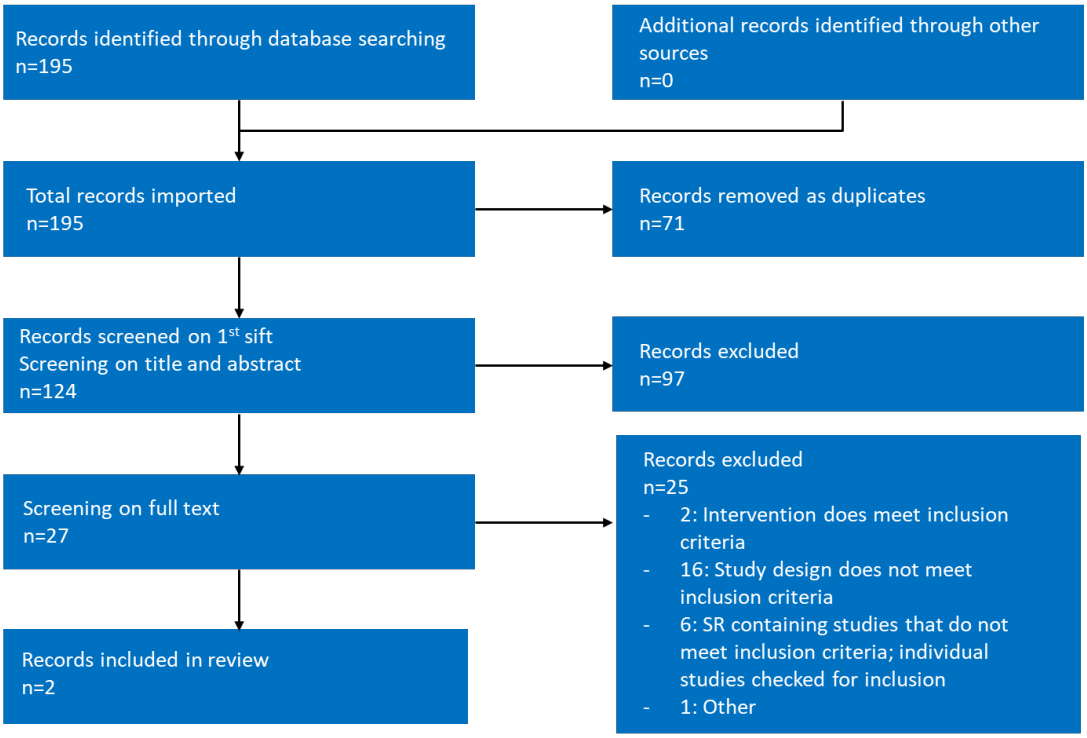
Database name: INAHTA International HTA Database

Searches	
1	"Urinary Tract"[mhe] 210
2	"Urinary Tract Infections"[mhe] 48
3	"Cystitis"[mhe] 10
4	"Vesico-Ureteral Reflux"[mh] 1
5	"Pyelitis"[mhe] 5
6	"Urinary Calculi"[mhe] 13

Searches	
7	"Urethritis"[mh] 2
8	((UTI or UTIs or RUTI or cystitis* or bacteriuria* or pyelitis or pyelonephriti* or pyelonephrites or pyonephros* or pyelocystitis or cystopyelitis or pyuria or VUR or urosep* or urethriti*)) 40
9	(((urin* or renal* or kidney*) AND (system* or tract* or calculus or calculi* or stone* or sepsis*))) 386
10	(((bladder* or genitourin* or genito urin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) AND (infect* or bacteria* or microbial* or block* or obstruct* or inflamm*))) 213
11	(((upper or lower) AND urin*)) 64
12	((schistosom* AND (hematobi* or haematobi* or urin* or urogenit* or infect*))) 0
13	(((vesicoureteral or vesicoureteric or vesicorenal or vesico ureteral or vesico renal or vesico ureteric or bladder* or cystoureteral or cysto ureteral or ureter* or urether* or nephropathy*) AND (backflow* or reflux*))) 2
14	(((vesicoureteral or vesicoureteric or vesicorenal or vesico ureteral or vesico renal or vesico ureteric or bladder* or cystoureteral or cysto ureteral or ureter* or urether* or nephropathy*) AND (flow* AND (backward* or back or abnormal* or retrograde)))) 4
15	#14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 601
16	"Methenamine"[mh] 1
17	((methenamine* or aminoform* or hexamethylen* or hexamine* or hippurate* or hiprex* or haiprex* or urotropin* or "hip rex" or hipeksal* or hippramine* or urex* or urotractan* or ammoform* or antihydral* or cystamin* or formamine* or "formin (heterocycle)" or hexaloid* or metramine* or mictasol* or naphthamine* or uralysol* or uraseptine* or urisol* or uritone* or urogenine* or utropine* or vesalvine*)) 2
18	#17 OR #16 2
19	#18 AND #15 2
20	Year limit 2006 - 20241

Appendix C Effectiveness evidence study selection

Figure 1 Effectiveness evidence



Appendix D Effectiveness evidence

Botros, 2022

Bibliographic Reference	Botros, Carolyn; Lozo, Svjetlana; Iyer, Shilpa; Warren, Alexandra; Goldberg, Roger; Tomezsko, Janet; Sasso, Karen; Sand, Peter; Gafni-Kane, Adam; Biener, Adam; Botros-Brey, Sylvia; Methenamine hippurate compared with trimethoprim for the prevention of recurrent urinary tract infections: a randomized clinical trial.; International urogynecology journal; 2022; vol. 33 (no. 3); 571-580

Study details

Country/ies where study was carried out	USA
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	• English-speaking women aged 18 to 99 • Diagnosis of recurrent UTI (at least two UTIs in the past 6 months or 3 in the past year that were proven culture-positive of a minimum of 10,000 colony forming units per millilitre (CFU/ml)) • Showing symptoms, with any UTI episodes, including acute dysuria, suprapubic pain, fever, worsening urinary urgency, frequency, and urinary incontinence
Exclusion criteria	• Any urinary tract abnormalities • Acute pyelonephritis • Renal insufficiency or failure • Known allergy to medications • Already on prophylaxis for post-coital recurrent UTI
Patient characteristics	**MH** **Age in years (Mean±SD):** 73.2±10.5 **BMI (Mean±SD):** 29.6±7.6 kg/m2 **Postmenopausal (n):** 43 (95.6%) **UTI prior to enrolment, number per year (Mean±SD):** 3.7±1.4 **Prior prophylaxis**: Not reported **Antibiotic resistance:** Not reported **Antibiotics** **Age in years (Mean±SD):** 70.6±15 **BMI (Mean±SD):** 29.3±6.2kg/m2

	Postmenopausal (n): 43 (91.5%) **UTI prior to enrolment, number per year (Mean±SD):** 4.0±2.1 **Prior prophylaxis**: Not reported **Antibiotic resistance:** Not reported
Intervention(s)/control	**Intervention** Methenamine hippurate prescribed as 1g twice daily **Control** Trimethoprim prescribed as 100mg once nightly Patients were advised to start prophylaxis the day of meeting the physician, with the only exception being patients who experienced acute UTI symptoms upon enrolment. In those cases, urine samples were conducted, and a full course of antibiotics provided. Prophylaxis started after the acute UTI treatment. Patients were advised to continue prophylaxis for 6 months after initiation and asked to discontinue treatment if no recurrent UTI developed.
Duration of follow-up	1 year
Sources of funding	No source of financial support
Sample size	N=92

Abbreviations: UTI: urinary tract infection; SD: standard deviation

Study arms

Methenamine hippurate (N = 45)

Trimethoprim (N = 47)

Outcomes

Study timepoints

- 1 year

Outcomes at 12 months

Outcome	Methenamine hippurate, 1 year, N = 43	Trimethoprim, 1 year, N = 43
Recurrent UTI at 1 year **No of events**	n=28 ; %=65.1	n=28 ; %=65.1
Time to subsequent infection (days) **Mean (SD)**	119.3 (94.1)	100.7 (84.4)
Episodes of symptomatic UTI at 1 year **Mean (SD)**	1.6 (1.9)	1.8 (2.1)

Diarrhoea **No of events**	n=2 ; %=4.4	n=1 ; %=2.1

Abbreviations: UTI: urinary tract infection; SD: standard deviation

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Block randomisation via computer generated sequence was used. Randomisation process was concealed and no significant baseline differences between intervention groups revealed.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Trial was non-blinded. However, no deviations arose and intention to treat analysis used.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(Data available only available for 93% of participants and no evidence of results not biased by missing outcome data. Missingness could depend on the true value.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Low risk of bias for all outcomes except diarrhoea as participants were aware of the assignment but outcomes were objectively rated; some concerns for diarrhoea as this was self-reported.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Results reported and data analysed according to registered trial protocol.*
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias due to missing outcome data. Intervention was non-blinded; however appropriate analysis used.)*
Overall bias and Directness	Overall Directness	Directly applicable

Harding, 2022

Bibliographic Reference	Harding, Chris; Chadwick, Thomas; Homer, Tara; Lecouturier, Jan; Mossop, Helen; Carnell, Sonya; King, Will; Abouhajar, Alaa; Vale, Luke; Watson, Gillian; Forbes, Rebecca; Currer, Stephanie; Pickard, Robert; Eardley, Ian; Pearce, Ian; Thiruchelvam, Nikesh; Guerrero, Karen; Walton, Katherine; Hussain, Zahid; Lazarowicz, Henry; Ali, Ased; Methenamine hippurate compared with antibiotic prophylaxis to prevent recurrent urinary tract infections in women: the ALTAR non-inferiority RCT.; Health technology assessment (Winchester, England); 2022; vol. 26 (no. 23); 1-172

Study details

Country/ies where study was carried out	UK
Study dates	June 2016 - January 2020
Inclusion criteria	• Women aged ≥18 years • Recurrent UTI (experienced at least three episodes of symptomatic UTI within the preceding 12 months or two episodes in the last 6 months or a single severe infection requiring hospitalisation*) • Able to take a once-daily oral dose of at least one of nitrofurantoin or trimethoprim or cefalexin • Able to take methenamine hippurate • Able to give informed consent • Able and willing to adhere to an 18-month trial protocol *Although a single severe infection requiring hospitalisation is not consistent with the definition of recurrent UTI specified in the protocol, the study was not downgraded as 88% of participants had at least 4 episodes in the previous 12 months, which is consistent with the protocol definition (number included based on a single severe episode not reported)
Exclusion criteria	• Unable to take methenamine hippurate (e.g., because of known allergy to methenamine hippurate, severe hepatic impairment (Child–Pugh class C, score of ≥10), gout, estimated glomerular filtration rate (eGFR) of <10 ml/minute/1.73m2 and Proteus spp. • Unable to take any of the trial antibiotics • Correctable urinary tract abnormalities that were considered to be contributory to the occurrence of recurrent UTI • Presence of symptomatic UTI

	• Pregnancy or intended pregnancy in the next 12 months • Currently breastfeeding • Already taking methenamine hippurate or antibiotic prophylaxis and declined a 3-month washout period
Patient characteristics	**<u>MH</u>** **Age in years (Mean±SD):** 49.9±19.1 **Weight (Mean±SD):** 75.1±18.5 **Postmenopausal, n (%):** 70(58) **UTI history** **Self-reported UTI episodes in the last 12 months (Mean±SD):** 7.0±3.4 **Positive urine culture reports in last 12 months (Mean±SD):** 3.6±3.0 **Central laboratory urine culture at baseline, n (%):** **- No growth:** 98(82) **- Growth of one or 2 isolates:** 13(11) **Prior prophylaxis** **Previous use of antibiotic prophylaxis, n (%):** 27(23) **Months of antibiotic prophylaxis in last 12 months (Mean±SD):** 1.5±2.7 **Taking any antibiotic prophylaxis in last 6 months, n (%):** 19(16) **3-month washout period required prior to randomisation, n (%):** 16(13) **Previously taken methenamine hippurate, n (%):** 4(3) **Antibiotic resistance in E. coli (taken from urine sample) at baseline (n):** 15/111 **<u>Antibiotics</u>** **Age in years (Mean±SD):** 50.3±18.1 **Weight (Mean±SD):** 70.1±15.3 **Postmenopausal, n (%):** 71(59) **UTI history** **Self-reported UTI episodes in the last 12 months (Mean±SD):** 6.8±3.8 **Positive urine culture reports in last 12 months (Mean±SD):** 2.6±2.6 **Central laboratory urine culture at baseline, n (%):** **- No growth:** 93(78)

	-Growth of one or 2 isolates: 18(15) **Prior prophylaxis** **Previous use of antibiotic prophylaxis, n (%):** 28(23) **Months of antibiotic prophylaxis in last 12 months (Mean±SD):** 1.6±2.8 **Taking any antibiotic prophylaxis in last 6 months, n (%):** 17(4) **3-month washout period required prior to randomisation, n (%):** 16(13) **Previously taken methenamine hippurate, n (%):** 2(2) **Antibiotic resistance in E. coli (taken from urine sample) at baseline (n):** 7/111
Intervention(s)/control	**Intervention** Participants took 1g of methenamine hippurate twice daily 12h apart. **Control** Participants took antibiotic prophylaxis once daily as a single dose at bedtime. In case of severe adverse effects (e.g. nausea with nitrofurantoin or candidiasis with cefalexin), participants were advised to switch to an alternative antibiotic in consultation with the relevant clinician and reasons for the change were recorded. Participants received either 50mg or 100mg of nitrofurantoin (n=66, 55%), 100mg of trimethoprim (n=30, 25%), or 250mg of cefalexin (n=24, 20%). All participants were prescribed the relevant medication for 12 months. Standard care for both arms during the trial was continued. Participants who took part in the trial but were already taking methenamine hippurate or antibiotic prophylaxis underwent a washout period (preventative therapy was stopped for a 3-month washout period).
Duration of follow-up	18 months
Sources of funding	NHS
Sample size	N=240

Abbreviations: E. coli: Escherichia coli; NHS: National Health Service; SD: standard deviation; UTI: urinary tract infection

Study arms

Methenamine hippurate (N = 120)

Antibiotic prophylaxis (N = 120)

Outcomes

Study timepoints

- 12 month (prophylactic treatment period)
- 18 month (prophylactic treatment and follow-up period)
- 6 months follow-up period (follow-up only)

Outcomes with all randomised participants

Outcome	MH, 12 month, N = 120	MH, 18 month, N = 120	MH, 6 months follow-up period, N = 98	Abx, 12 month, N = 120	Abx, 18 month, N = 120	Abx, 6 months follow-up period, N = 97
Episodes of symptomatic UTI **Mean (SD)**	1.37 (1.67)	NR (NR)	0.86 (1.1)	0.88 (1.2)	NR (NR)	0.59 (0.81)
Antibiotic resistance in E. coli (number of antibiotics from perineal swab) **Mean (SD)**	1.1 (1.6)	1.2 (1.8)	NR (NR)	1.7 (1.8)	0.8 (1.2)	NR (NR)
Antibiotic resistance in E. coli (number of antimicrobial categories from perineal swab) **Mean (SD)**	1 (1.2)	1 (1.5)	NR (NR)	1.4 (1.3)	0.7 (1)	NR (NR)
Patient satisfaction (TSQM - Global satisfaction) **Mean (SD)**	77.3 (23.9)	74.4 (27.1)	NR (NR)	80.6 (22.4)	75.8 (25.5)	NR (NR)
Serious adverse events **No of events**	n = 15	n = NR	NR (NR)	n = 23	n = NR	NR (NR)
Diarrhoea **No of events**	n = 4	n = NR	NR (NR)	n = 8	n = NR	NR (NR)
Antibiotic use (therapeutic antibiotics for other reasons) **No of events**	n=38 ; %=32	n=NR ; %=NR	n=28 ; %=29	n=32 ; %=27	n=NR ; %=NR	n=15 ; %=15

Antibiotic use (therapeutic antibiotics for UTI) **No of events**	n=67 ; %=56	n=NR ; %=NR	n=5 ; %=4	n=51 ; %=43	n=NR ; %=NR	n=8 ; %=6

Abbreviation: Abx: antibiotic prophylaxis; MH: Methenamine hippurate; NR: not reported; SD: standard deviation; UTI: urinary tract infection

Incidence rates

Outcome	Methenamine hippurate vs Methenamine hippurate, 12 month, N2 = 103, N1 = 102	Methenamine hippurate vs Methenamine hippurate, 18 month, N2 = , N1 =	Methenamine hippurate vs Methenamine hippurate, 6 months follow-up period, N2 = 98, N1 = 97
Incidence rate for total number of UTI episodes **Incidence Rate Ratio**	1.52 (1.16 to 1.98)	NR	1.45 (1.16-1.81)

Abbreviation: UTI: urinary tract infection

Antimicrobial resistance from perineal swab

Outcome	MH, 12 month, N = 70	MH, 18 month, N = 45	MH, 6 months follow-up period, N = NR	Abx, 12 month, N = 64	Abx, 18 month, N = 39	Abx, 6 months follow-up period, N = NR
Antimicrobial resistance (at least one E. coli isolate from perineal swab demonstrating resistance to at least one antibiotic) **No of events**	n=39	n=19	n=NR	n=46	n=15	n=NR
Antimicrobial resistance (at least one E. coli isolate from perineal swab demonstrating MDR)	n=11	n=9	n=NR	n=12	n=2	n=NR

No of events						

Abbreviation: Abx: antibiotic prophylaxis; MDR: Multiple drug resistance; MH: Methenamine hippurate; NR: not reported; SD: standard deviation; UTI: urinary tract infection

Episodes of symptomatic UTI

Outcome	MH, 12 month, N = 103	MH, 18 month, N = NR	MH, 6 months follow-up period, N = 98	Abx, 12 month, N = 102	Abx, 18 month, N = NR	Antibiotic prophylaxis, 6 months follow-up period, N = 97
Recurrent UTI **No of events**	n=59 ; %=57	n=NR	n=49 ; %=50	n=47 ; %=46	n=NR	n=42 ; %=43

Abbreviation: Abx: antibiotic prophylaxis; MH: Methenamine hippurate; NR: not reported; SD: standard deviation; UTI: urinary tract infection

Antibiotic resistance from urine sample

Outcome	MH, 12 month, N = 21	MH, 18 month, N = NR	MH, 6 months follow-up period, N = 13	Abx, 12 month, N = 20	Abx, 18 month, N = NR	Antibiotic prophylaxis, 6 months follow-up period, N = 8
Antimicrobial resistance (at least one E. coli isolate from urine sample demonstrating resistance to at least one antibiotic) at 12 months (end of treatment) **No of events**	n=12	n=NR	n=8	n=13	n=NR	n=6
Antimicrobial resistance (at least one E. coli isolate from urine sample demonstrating MDR) **No of events**	n=6	n=NR	n=1	n=4	n=NR	n=0

Abbreviation: Abx: antibiotic prophylaxis; MH: Methenamine hippurate; NR: not reported; SD: standard deviation; UTI: urinary tract infection

Any antibiotic resistance (per participant) in any significant isolate from symptomatic urine samples

Outcome	MH, 12 month, N = 27	MH, 18 month, N = NR	MH, 6 months follow-up period, N = 14	Abx, 12 month, N = 25	Abx, 18 month, N = NR	Abx, 6 months follow-up period, N = 18
Any resistance (per participant) in any significant isolate from symptomatic urine samples **No of events**	n=18	n=NR	n=12	n=18	n=NR	n=6

Abbreviation: Abx: antibiotic prophylaxis; MH: Methenamine hippurate; NR: not reported; SD: standard deviation

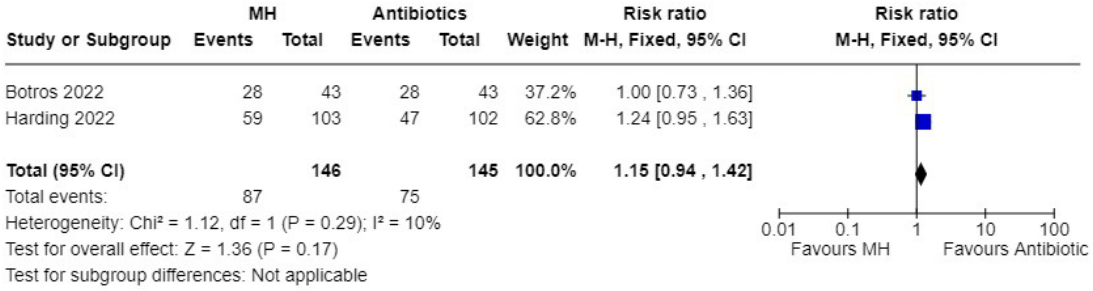
Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Randomisation concealed and no significant baseline differences.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Open label trial; however, no deviations arose and appropriate analysis was performed.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(At 12 months follow-up data available for 72% participants and no evidence of results not biased by missing outcome data. Missingness could depend on the true value.*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Low risk of bias for all outcomes except diarrhoea as participants were aware of the assignment but outcomes were objectively rated; some concerns for diarrhoea as this was self-reported.).)*

Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Results reported and data analysed according to registered trial protocol. Changes to the protocol were defined.)*
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias due to missing outcome data. Intervention was non-blinded; however appropriate analysis used.)*
Overall bias and Directness	Overall Directness	Directly applicable

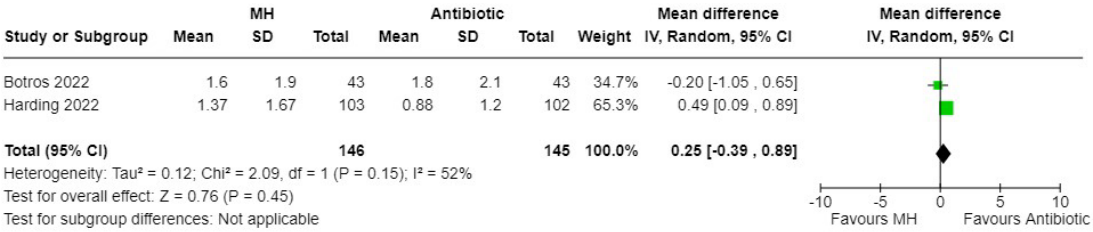
Appendix E Forest plots

Figure 2 Recurrent UTI during prophylactic treatment (12 months)



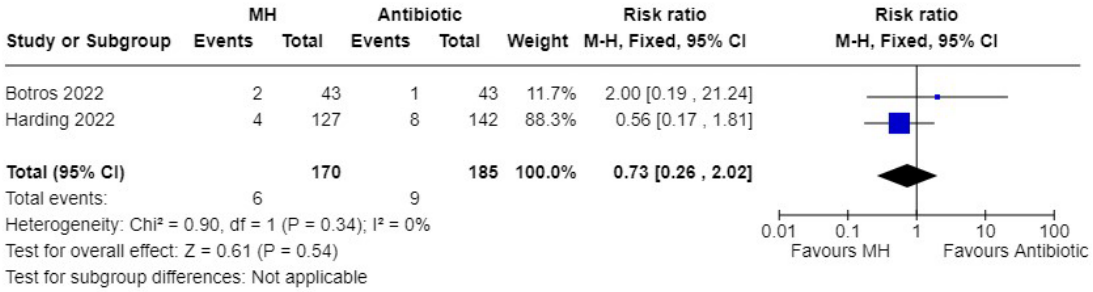
Abbreviations used: CI: confidence interval; M-H: Mantel-Haenszel; MH: Methenamine hippurate; UTI: urinary tract infection

Figure 3 Episodes of symptomatic UTI during prophylactic treatment (12 months)



Abbreviations used: CI: confidence interval; M-H: Mantel-Haenszel; MH: Methenamine hippurate; UTI: urinary tract infection

Figure 4 Diarrhoea during prophylactic treatment (12 months)



Abbreviations used: CI: confidence interval; M-H: Mantel-Haenszel; MH: Methenamine hippurate

Appendix F GRADE tables

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MH	Antibiotics	Relative (95% CI)	Absolute (95% CI)		
Recurrent UTI during prophylactic treatment (12 months)												
2	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	87/146 (59.6%)	75/145 (51.7%)	**RR 1.15** (0.94 to 1.42)	**78 more per 1,000** (from 31 fewer to 217 more)	Very low	CRITICAL NO EV. OF DIFF.
Recurrent UTI during follow-up period (6 months post treatment)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[c]	none	49/98 (50.0%)	42/97 (43.3%)	**RR 1.15** (0.85 to 1.56)	**65 more per 1,000** (from 65 fewer to 242 more)	Very low	CRITICAL NO EV. OF DIFF.
Incidence rate for total numbers of UTI episodes during prophylactic treatment (12 months)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	141/102.03[j]	90/101.32[j]	**Rate ratio 1.52** (1.16 to 1.99)	**490 more per 1000 patient(s) per years** (from 150 more to 840 more)[d]	Very low	CRITICAL POSSIBLE HARM
Incidence rate for total numbers of UTI episodes during follow-up period (6 months post treatment)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[c]	none	84/48.71[l]	57/47.8[l]	**Rate ratio 1.45** (1.16 to 1.81)	**530 more per 1000 patient(s) per years** (from 30 fewer to 1,090 more)[e]	Very low	CRITICAL POSSIBLE HARM
Time to subsequent infection (days) during prophylactic treatment (12 months)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[f]	none	43	43	-	MD **18.6 higher** (19.18 lower to 56.38 higher)	Very low	CRITICAL NO EV. OF DIFF.
Episodes of symptomatic UTI during prophylactic treatment (12 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MH	Antibiotics	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	very serious[a]	serious[g]	not serious	serious[h]	none	146	145	-	MD **0.25 higher** (0.39 lower to 0.89 higher)	Very low	CRITICAL NO EV. OF DIFF.
Episodes of symptomatic UTI during follow-up period (6 months post treatment)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[f]	none	98	97	-	MD **0.27 higher** (0 to 0.54 higher)	Very low	CRITICAL NO EV. OF DIFF.
Serious adverse events during prophylactic treatment (12 months)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[c]	none	15/103 (14.6%)	23/102 (22.5%)	**RR 0.65** (0.36 to 1.17)	**79 fewer per 1,000** (from 144 fewer to 38 more)	Very low	CRITICAL NO EV. OF DIFF.
Antibiotic resistance in E. coli (number of antimicrobial categories from perineal swab) at 6 or 12 months (during prophylactic treatment)												
1	randomised trials	very serious[a]	not serious	not serious	serious[h]	none	103	102	-	MD **0.4 lower** (0.74 lower to 0.06 lower)	Very low	CRITICAL POSSIBLE BENEFIT
Antibiotic resistance in E. coli (number of antimicrobial categories from perineal swab) at 18 months (end of follow-up)												
1	randomised trials	very serious[a]	not serious	not serious	serious[h]	none	120	120	-	MD **0.3 higher** (0.02 lower to 0.62 higher)	Very low	CRITICAL NO EV. OF DIFF.
Antibiotic resistance in E. coli (number of antibiotics from perineal swab) at 6 or 12 months (during prophylactic treatment)												
1	randomised trials	very serious[a]	not serious	not serious	serious[h]	none	103	102	-	MD **0.6 lower** (1.07 lower to 0.13 lower)	Very low	CRITICAL POSSIBLE BENEFIT
Antibiotic resistance in E. coli (number of antibiotics from perineal swab) at 18 months (end of follow-up)												
1	randomised trials	very serious[a]	not serious	not serious	serious[h]	none	120	120	-	MD **0.4 higher** (0.01 higher to 0.79 higher)	Very low	CRITICAL POSSISBLE HARM
Antimicrobial resistance (at least one E. coli isolate from perineal swab demonstrating resistance to at least one antibiotic) at 6 or 12 months (during prophylactic treatment)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MH	Antibiotics	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious[a]	not serious	not serious	very serious[c]	none	39/70 (55.7%)	46/64 (71.9%)	**RR 0.78** (0.60 to 1.00)	**158 fewer per 1,000** (from 288 fewer to 0 fewer)	Very low	CRITICAL NO EV. OF DIFF.
Antimicrobial resistance (at least one E. coli isolate from perineal swab demonstrating resistance to at least one antibiotic) at 18 months (end of follow-up)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[c]	none	19/45 (42.2%)	15/39 (38.5%)	**RR 1.10** (0.65 to 1.85)	**38 more per 1,000** (from 135 fewer to 327 more)	Very low	CRITICAL NO EV. OF DIFF.
Antimicrobial resistance (at least one E. coli isolate from perineal swab demonstrating MDR) at 6 or 12 months (during prophylactic treatment)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[c]	none	11/70 (15.7%)	12/64 (18.8%)	**RR 0.84** (0.40 to 1.76)	**30 fewer per 1,000** (from 112 fewer to 143 more)	Very low	CRITICAL NO EV. OF DIFF.
Antimicrobial resistance (at least one E. coli isolate from perineal swab demonstrating MDR) at 18 months (end of follow-up)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[c]	none	9/45 (20.0%)	2/39 (5.1%)	**RR 3.90** (0.90 to 16.98)	**149 more per 1,000** (from 5 fewer to 819 more)	Very low	CRITICAL NO EV. OF DIFF.
Antimicrobial resistance (at least one E. coli isolate from urine sample demonstrating resistance to at least one antibiotic) at 6 or 12 months (during prophylactic treatment)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[c]	none	12/21 (57.1%)	13/20 (65.0%)	**RR 0.88** (0.54 to 1.44)	**78 fewer per 1,000** (from 299 fewer to 286 more)	Very low	CRITICAL NO EV. OF DIFF.
Antimicrobial resistance (at least one E. coli isolate from urine sample demonstrating resistance to at least one antibiotic) during follow-up period (6 months post treatment)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[c]	none	8/13 (61.5%)	6/8 (75.0%)	**RR 0.82** (0.46 to 1.48)	**135 fewer per 1,000** (from 405 fewer to 360 more)	Very low	CRITICAL NO EV. OF DIFF.
Antimicrobial resistance (at least one E. coli isolate from urine sample demonstrating MDR) at 6 or 12 months (during prophylactic treatment)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MH	Antibiotics	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious[a]	not serious	not serious	very serious[c]	none	6/21 (28.6%)	4/20 (20.0%)	**RR 1.43** (0.47 to 4.32)	**86 more per 1,000** (from 106 fewer to 664 more)	Very low	CRITICAL NO EV. OF DIFF.
Antimicrobial resistance (at least one E. coli isolate from urine sample demonstrating MDR) during follow-up period (6 months post treatment)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[c]	none	1/13 (7.7%)	0/8 (0.0%)	**RR 1.93** (0.09 to 42.35)	**8 more per 1,000** (from 140 fewer to 300 morer)[k]	Very low	CRITICAL NO EV. OF DIFF.
Any resistance (per participant) in any significant isolate from symptomatic urine samples at 6 or 12 months (during prophylactic treatment)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[c]	none	18/27 (66.7%)	18/25 (72.0%)	**RR 0.93** (0.64 to 1.33)	**50 fewer per 1,000** (from 259 fewer to 238 more)	Very low	CRITICAL NO EV. OF DIFF.
Any resistance (per participant) in any significant isolate from symptomatic urine samples during follow-up period (6 months post treatment)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[c]	none	12/14 (85.7%)	18/27 (66.7%)	**RR 1.29** (0.91 to 1.81)	**193 more per 1,000** (from 60 fewer to 540 more)	Very low	CRITICAL NO EV. OF DIFF.
Patient satisfaction (TSQM - Global satisfaction) at 12 months (end of treatment)												
1	randomised trials	very serious[a]	not serious	not serious	serious[h]	none	103	102	-	MD **3.3 lower** (9.64 lower to 3.04 higher)	Very low	CRITICAL NO EV. OF DIFF.
Patient satisfaction (TSQM - Global satisfaction) at 18 months (end of follow-up)												
1	randomised trials	very serious[a]	not serious	not serious	serious[h]	none	120	120	-	MD **1.4 lower** (8.06 lower to 5.26 higher)	Very low	CRITICAL NO EV. OF DIFF.
Antibiotic use (therapeutic antibiotics for other reasons) during prophylactic treatment (12 months)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[c]	none	38/120 (31.7%)	32/120 (26.7%)	**RR 1.19** (0.80 to 1.77)	**51 more per 1,000** (from 53 fewer to 205 more)	Very low	IMPORTANT NO EV. OF DIFF.
Antibiotic use (therapeutic antibiotics for other reasons) during follow-up period (6 months post treatment)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MH	Antibiotics	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious[a]	not serious	not serious	very serious[c]	none	28/120 (23.3%)	15/120 (12.5%)	**RR 1.87** (1.05 to 3.31)	**109 more per 1,000** (from 6 more to 289 more)	Very low	IMPORTANT **POSSIBLE HARM**
Antibiotic use (therapeutic antibiotics for UTI) during prophylactic treatment (12 months)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[c]	none	67/120 (55.8%)	51/120 (42.5%)	**RR 1.31** (1.01 to 1.71)	**132 more per 1,000** (from 4 more to 302 more)	Very low	IMPORTANT **POSSIBLE HARM**
Antibiotic use (therapeutic antibiotics for UTI) during follow-up period (6 months post treatment)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[c]	none	5/98 (5.1%)	8/97 (8.2%)	**RR 0.62** (0.21 to 1.82)	**31 fewer per 1,000** (from 65 fewer to 68 more)	Very low	IMPORTANT NO EV. OF DIFF.
Rate of diarrhoea events during prophylactic treatment (12 months)												
2	randomised trials	very serious[i]	not serious	not serious	very serious[c]	none	6/170 (3.5%)	9/185 (4.9%)	**RR 0.73** (0.26 to 2.02)	**13 fewer per 1,000** (from 36 fewer to 50 more)	Very low	IMPORTANT NO EV. OF DIFF.

Abbreviations: CI: confidence interval; E. coli: Escherichia coli; MD: mean difference; MDR: multidrug resistance; RoB: risk of bias; RR: risk ratio; TSQM: Treatment Satisfaction Questionnaire for Medication; UTI: urinary tract infection

Explanations

a. Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2 (missing outcome data).

b. Serious imprecision as event rate is <300 for dichotomous outcome.

c. Very serious imprecision as event is <150 for dichotomous outcome.

d. Absolute difference calculated based on difference in number of episodes per person-year (and 90% confidence interval) reported in the paper.

e. Absolute difference calculated based on difference in number of episodes per person-year (and 95% confidence interval) reported in the paper.

f. Very serious imprecision as sample size is <200 for continuous outcome.

g. Unexplained serious heterogeneity (No subgroup analysis was performed. The only difference between the 2 studies based on the pre-defined subgroups is the Antibiotics used, however no subgroup analysis was possible as multiple antibiotics were used in 1 paper (Harding 2022)).

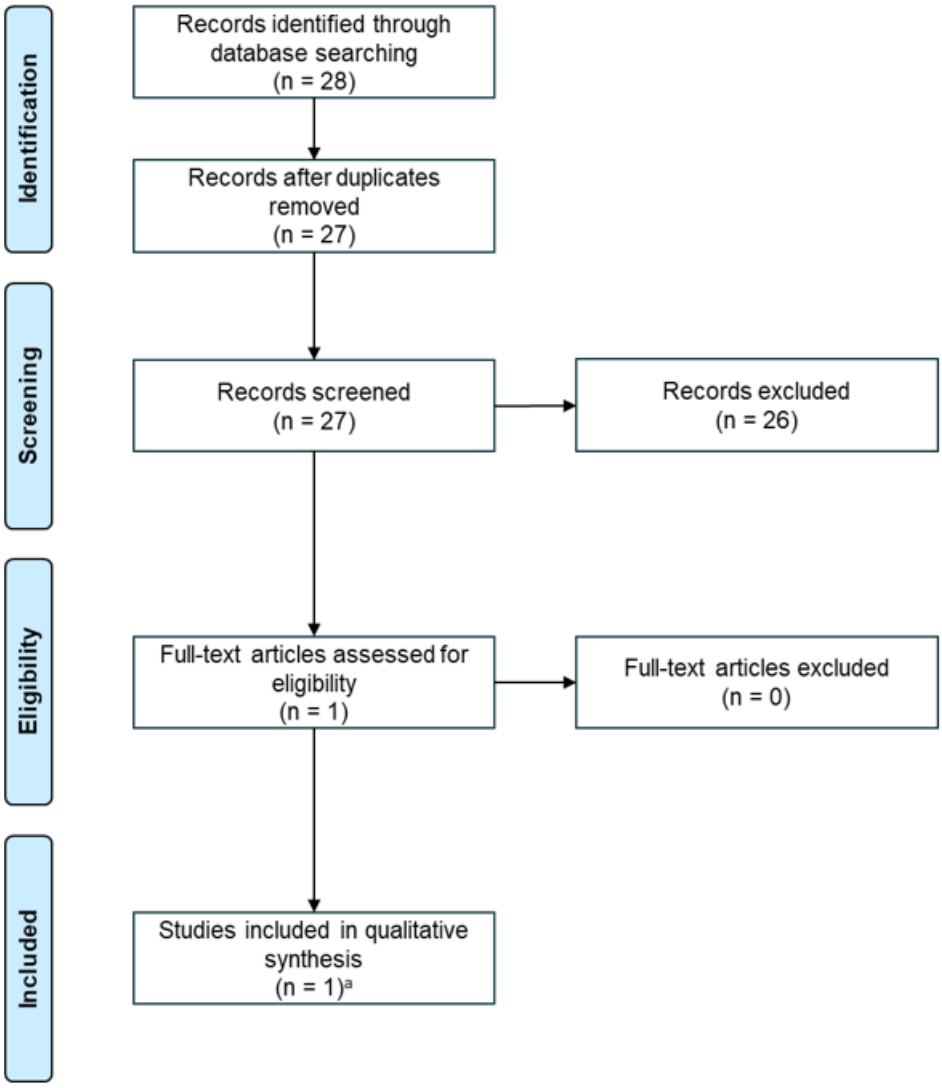
h. Serious imprecision as sample size is <400 for continuous outcome.

i. Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2 (missing outcome data and lack of blinding)

j. Total number of UTI episodes/total follow-up time (patient-years)

k. Absolute effects manually calculated using risk differences as 0 events in the control arm.

Appendix G Economic evidence study selection



[a] Based on one of the analyses performed in the included HTA report by Harding et al. (2022), a spin-off paper was published by King et al. (2024) outside our search dates. Results of the spin-off paper was identical to that of the HTA.

Appendix H Economic evidence tables

Table 4 Harding et al. (2022); Trial based analysis

<table>
<tr><th colspan="6">Harding et al. (2022). Methenamine hippurate compared with antibiotic prophylaxis to prevent recurrent urinary tract infections in women: the ALTAR non-inferiority RCT</th></tr>
<tr><td>Study details</td><td colspan="5">Analysis: Cost utility analysis
Approach to analysis: A trial-based analysis, with total costs collected on all participants until 18 months post randomisation. QoL data were collected at baseline, 3-, 6-, 9-, 12-, 15- and 18-months post randomisation using EQ-5D-5L. Incremental results were calculated at 18 months from the ALTAR trial (205 participants). An adjusted analysis in which costs and QALYs were estimated simultaneously was also conducted.
Time horizon: 18 months
Discounting: 3.5% for costs and outcomes
Setting: UK</td></tr>
<tr><td>Interventions</td><td colspan="5">Intervention 1: Antibiotic prophylaxis for 12 months
Intervention 2: Methenamine hippurate for 12 months</td></tr>
<tr><td>Population</td><td colspan="5">Population: Women aged ≥18 years with recurrent UTI requiring prophylactic treatment</td></tr>
<tr><td>Data sources</td><td colspan="5">Baseline/natural history: ALTAR trial
Incidence of long-term conditions: ALTAR trial
Effectiveness: QoL data were collected at baseline, 3-, 6-, 9-, 12-, 15- and 18-months post randomisation via EQ-5D-5L questionnaires.
Resource use & Costs: Costs were based on the intervention medications, the use of healthcare services, medications used to manage UTIs and concomitant medications. Medication costs were obtained from the BNF, management costs from NHS reference costs 2020-21, and relevant unit costs from PSSRU 2019. Healthcare service use was calculated via questionnaires given to patients at follow-up points.</td></tr>
<tr><td>Base-case results</td><td colspan="5">
<table>
<tr><th rowspan="2">Intervention</th><th colspan="2">Absolute</th><th colspan="3">Incremental</th></tr>
<tr><th>Cost (£)</th><th>QALYs</th><th>Cost (£)</th><th>QALYs</th><th>ICER (£)</th></tr>
<tr><td>Antibiotic prophylaxis</td><td>£931 (Unadjusted analysis)</td><td>1.182 (Unadjusted analysis)</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Methenamine hippurate</td><td>£1,013 (Unadjusted analysis)</td><td>1.133 (Unadjusted analysis)</td><td>-£40 (Adjusted analysis)</td><td>0.014 (Adjusted analysis)</td><td>Adjusted analysis: methenamine hippurate was dominant.

Unadjusted analysis: methenamine hippurate was dominated.</td></tr>
</table>
</td></tr>
<tr><td>Sensitivity analysis</td><td colspan="5">Based on the adjusted analysis, the bootstrapped results found that methenamine hippurate had a 51% probability of being cost effective at a threshold per QALY of £0 but rising to 65% at threshold per QALY of £20,000. A sensitivity analysis was performed incorporating the cost of antimicrobial resistance. In this scenario, methenamine hippurate remained dominant based on the results from the adjusted analysis; methenamine hippurate had a 69% probability of being cost effective at threshold per QALY of £0 (rising to 76% at threshold per QALY of £20,000).</td></tr>
<tr><td>Comments</td><td colspan="5">Source of funding: National Institute for Health Research (NIHR)
Limitations: Minor limitations (Table 7)</td></tr>
</table>

Abbreviations: BNF: British National Formulary; EQ-5D: Euro-qol five dimensions; ICER: incremental cost-effectiveness ratio; NHS: National Health Service; PSSRU:

Personal Social Services Research Unit; QALYs: quality-adjusted life years; QoL: quality of life; UTI: urinary tract infection,

Table 5 Harding et al. (2022), Model-based analysis

<table>
<tr><th colspan="2">Harding et al. (2022). Methenamine hippurate compared with antibiotic prophylaxis to prevent recurrent urinary tract infections in women: the ALTAR non-inferiority RCT</th></tr>
<tr><td>Study details</td><td>Analysis: Cost utility analysis
Approach to analysis: A Markov state transition model, including Mild (1 UTI episode), Moderate (2 or more UTI episodes), Death, and Asymptomatic health states, to extrapolate the results of the ALTAR trial (205 participants) beyond 18 months. The model had 6-monthly cycles. All patients began in the moderate health state.
Time horizon: 50 years
Discounting: 3.5% for costs and outcomes
Setting: UK</td></tr>
<tr><td>Interventions</td><td>Intervention 1: Antibiotic prophylaxis for 12 months
Intervention 2: Methenamine hippurate for 12 months</td></tr>
<tr><td>Population</td><td>Population: Women aged ≥18 years (mean age of 50 years) with recurrent UTI requiring prophylactic treatment</td></tr>
<tr><td>Data sources</td><td>Baseline/natural history: ALTAR trial
Incidence of long-term conditions: Death from UK all-cause mortality rates. UTI episodes incurred beyond 18-month trial period were assumed to be the same as those in the last 6 months of the trial.
Effectiveness: QoL data were based on the utility values estimated from the ALTAR trial using EQ-5D-5L. An OLS regression was used to estimate potential differences in utilities between health states.
Resource use & Costs: Costs considered were those associated with the intervention medications for the first two cycles only, health-care resource use (through UK specific costs) and concomitant medications reported by those receiving each intervention medication during their time in the trial, and additional antibiotics received to treat UTIs.</td></tr>
<tr><td>Base-case results</td><td>
<table>
<tr><th rowspan="2">Intervention</th><th colspan="2">Absolute</th><th colspan="3">Incremental</th></tr>
<tr><th>Cost (£)</th><th>QALYs</th><th>Cost (£)</th><th>QALYs</th><th>ICER (£)</th></tr>
<tr><td>Antibiotic prophylaxis</td><td>£7,231</td><td>15.24</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Methenamine hippurate</td><td>£7,876</td><td>14.96</td><td>£645</td><td>-0.283</td><td>Dominated</td></tr>
</table>
</td></tr>
<tr><td>Sensitivity analysis</td><td>In probability sensitivity analysis, antibiotic prophylaxis had a 60% probability of being considered cost effective at a threshold per QALY of £20,000.</td></tr>
<tr><td>Comments</td><td>Source of funding: National Institute for Health Research (NIHR)
Limitations: Minor limitations (Table 7)</td></tr>
</table>

Abbreviations: BNF: British National Formulary; EQ-5D: Euro-qol five dimensions; ICER: incremental cost-effectiveness ratio; NHS: National Health Service; PSSRU: Personal Social Services Research Unit; QALYs: quality-adjusted life years; QoL: quality of life; UTI: urinary tract infection,

Table 6 Applicability checklist

Study	1.1 Is the study population appropriate for the review question?	1.2 Are the interventions appropriate for the review question?	1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	1.4 Is the perspective for costs appropriate for the review question?	1.5 Is the perspective for outcomes appropriate for the review question?	1.6 Are all future costs and outcomes discounted appropriately?	1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome?	1.8 Overall judgement
Harding et al. (2022): Trial-based analysis	Yes	Yes	Yes (UK based study with an NHS perspective)	Yes (UK based study with an NHS perspective)	Yes (UK based study with an NHS perspective)	Yes (discounted at 3.5% but only limited to 18 months follow-up)	Yes (EQ-5D based utility scores were used)	Directly applicable
Harding et al. (2022): Model-based analysis	Yes	Yes	Yes (UK based study with an NHS perspective)	Yes (UK based study with an NHS perspective)	Yes (UK based study with an NHS perspective)	Yes	Yes (EQ-5D based utility scores were used)	Directly applicable

Abbreviations: EQ-5D: Euro-qol five dimensions; NHS: National Health Service; QALY: quality-adjusted life year

Table 7 Limitations checklist

Study	2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	2.3 Are all important and relevant outcomes included?	2.4 Are the estimates of baseline outcomes from the best available source?	2.5 Are the estimates of relative intervention effects from the best available source?	2.6 Are all important and relevant costs included?	2.7 Are the estimates of resource use from the best available source?	2.8 Are the unit costs of resources from the best available source?	2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	2.11 Has no potential financial conflict of interest been declared?	2.12 Overall assessment
Harding et al. (2022): Trial-based analysis	Yes	Partly (18-month follow-up)	Yes (all outcomes within the follow-up	Partly (based on one RCT)	Partly (from one RCT and not identified via a	Yes (AMR included in sensitivity analysis)	Yes (UK specific sources have been used)	Yes (UK specific sources have been used)	Yes	Yes (appropriate sensitivity analyses	No (authors had industry funded contributions)	Minor limitations

Study	2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	2.3 Are all important and relevant outcomes included?	2.4 Are the estimates of baseline outcomes from the best available source?	2.5 Are the estimates of relative intervention effects from the best available source?	2.6 Are all important and relevant costs included?	2.7 Are the estimates of resource use from the best available source?	2.8 Are the unit costs of resources from the best available source?	2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	2.11 Has no potential financial conflict of interest been declared?	2.12 Overall assessment
			period captured)		systematic review)					were performed)		
Harding et al. (2022): Model-based analysis	Yes	Yes (50 years)	Yes (all outcomes within the follow-up period captured)	Partly (based on one RCT)	Partly (from one RCT and not identified via a systematic review)	Yes (AMR included in sensitivity analysis)	Yes (UK specific sources have been used)	Yes (UK specific sources have been used)	Yes	Yes (probabilistic sensitivity analysis was performed)	No (authors had industry funded contributions)	Minor limitations

Abbreviations: AMR: anti-microbial resistance; RCT: randomised controlled trial

Appendix I Excluded studies

Study	Code [Reason]
Bakhit, Mina, Krzyzaniak, Natalia, Hilder, Joanne et al. (2021) Use of methenamine hippurate to prevent urinary tract infections in community adult women: a systematic review and meta-analysis. The British journal of general practice : the journal of the Royal College of General Practitioners 71(708): e528-e537	- SR containing studies that do not meet inclusion criteria; individual studies checked for eligibility *Individual studies did not meet inclusion criteria for the following reasons: Conducted prior 2006 (5), already included (1)*
Burrows, L.L. (2024) It's uncomplicated: Prevention of urinary tract infections in an era of increasing antibiotic resistance. PLoS Pathogens 20(2): e1011930	- Study design does not meet inclusion criteria *Not a SR or RCT*
Chwa, Amy, Kavanagh, Kevin, Linnebur, Sunny Anne et al. (2019) Evaluation of methenamine for urinary tract infection prevention in older adults: a review of the evidence. Therapeutic advances in drug safety 10: 2042098619876749	- SR containing studies that do not meet inclusion criteria; individual studies checked for eligibility *Individual studies did not meet inclusion criteria for the following reasons: Conducted prior 2006 (4), not a RCT (1)*
Clarke, C. and Harding, C. (2022) Methenamine as prophylaxis for recurrent urinary tract infections: an overview of the ALTAR trial. Obstetrics, Gynaecology and Reproductive Medicine 32(12): 289-290	- Study design does not meet inclusion criteria *Not a SR or RCT*
Costantini, E.; Giannitsas, K.; Illiano, E. (2017) The role of nonantibiotic treatment of community-acquired urinary tract infections. Current Opinion in Urology 27(2): 120-126	- Study design does not meet inclusion criteria *Not a SR or RCT.*
Cox, L. and Cameron, A.P. (2014) Prevention of Urinary Tract Infection for Patients with Neurogenic Bladder. Current Bladder Dysfunction Reports 9(4): 282-288	- Study design does not meet inclusion criteria *Comment paper*

Study	Code [Reason]
Davidson, Spencer M, Brown, Jamie N, Nance, Clayton B et al. (2024) Use of Methenamine for Urinary Tract Infection Prophylaxis: Systematic Review of Recent Evidence. International urogynecology journal 35(3): 483-489	- SR containing studies that do not meet inclusion criteria; individual studies checked for eligibility *Individual studies did not meet inclusion criteria for the following reasons: Comparator (5), already included (2)*
El Sakka, Noha and Gould, Ian M (2016) Role of old antimicrobial agents in the management of urinary tract infection. Expert review of clinical pharmacology 9(8): 1047-56	- Study design does not meet inclusion criteria *Not a SR or RCT*
Gill, Christian M; Hughes, Maria-Stephanie A; LaPlante, Kerry L (2020) A Review of Nonantibiotic Agents to Prevent Urinary Tract Infections in Older Women. Journal of the American Medical Directors Association 21(1): 46-54	- Study design does not meet inclusion criteria *Not a SR or RCT*
Gu, Cindy and Ackerman, A Lenore (2023) An oldie but a goodie: Methenamine as a nonantibiotic solution to the prevention of recurrent urinary tract infections. PLoS pathogens 19(6): e1011405	- Study design does not meet inclusion criteria *Not a SR or RCT*
Harding, Chris, Mossop, Helen, Homer, Tara et al. (2022) Alternative to prophylactic antibiotics for the treatment of recurrent urinary tract infections in women: multicentre, open label, randomised, non-inferiority trial. BMJ (Clinical research ed.) 376: e068229	- Other *Reports on the same participants and outcomes as Harding 2022 (ALTAR trial); no additional outcomes reported*
Kale, Saurabh and Somani, Bhaskar K (2023) The resurgence of methenamine hippurate in the prevention of recurrent UTIs in women- a systematic review. Current opinion in urology 33(6): 488-496	- SR containing studies that do not meet inclusion criteria; individual studies checked for eligibility *Individual studies did not meet inclusion criteria for the following reasons: Conducted prior 2006 (4), already included (2).*
Kwok, Michael, McGeorge, Stephen, Mayer-Coverdale, Johanna et al. (2022) Guideline of guidelines: management of recurrent urinary tract infections in	- Study design does not meet inclusion criteria *Not a SR or RCT*

Study	Code [Reason]
women. BJU international 130suppl3: 11-22	
Lee, Bon San B, Bhuta, Tushar, Simpson, Judy M et al. (2012) Methenamine hippurate for preventing urinary tract infections. The Cochrane database of systematic reviews 10: cd003265	- SR containing studies that do not meet inclusion criteria; individual studies checked for eligibility *Studies included in this review included comparators that do not meet inclusion criteria (no treatment or placebo)*
Li, Jian Mei, Cosler, Leon E, Harausz, Elizabeth P et al. (2024) Methenamine for urinary tract infection prophylaxis: A systematic review. Pharmacotherapy 44(2): 197-206	- SR containing studies that do not meet inclusion criteria; individual studies checked for eligibility *Individual studies did not meet inclusion criteria for the following reasons: Not a RCT (2), Study is ongoing (1), Intervention not relevant (2), Review paper (2), already included (2).*
Muller, A E, Verhaegh, E M, Harbarth, S et al. (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 23(6): 355-362	- Intervention does not meet inclusion criteria
Pat, J.J., Witte, L.P.W., Steffens, M.G. et al. (2022) Quality appraisal of clinical guidelines for recurrent urinary tract infections using AGREE II: a systematic review. International Urogynecology Journal 33(5): 1059-1070	- Study design does not meet inclusion criteria *Quality appraisal of guidelines. Not a SR or RCT*
Peck, J. and Shepherd, J.P. (2021) Recurrent Urinary Tract Infections: Diagnosis, Treatment, and Prevention. Obstetrics and Gynecology Clinics of North America 48(3): 501-513	- Study design does not meet inclusion criteria *Not a SR or RCT*
Pergialiotis, Vassilis, Arnos, Pantelis, Mavros, Michael N et al. (2012) Urinary tract analgesics for the treatment of patients with acute cystitis: where is the	- Study design does not meet inclusion criteria *Not a RCT or SR*

Study	Code [Reason]
clinical evidence?. Expert review of anti-infective therapy 10(8): 875-9	
Price, Jameca Renee, Guran, Larissa A, Gregory, W Thomas et al. (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	- Intervention does not meet inclusion criteria *Review checked for individual studies. Only 2 included studies compared methenamine to nitrofurantoin but were conducted prior 2006.*
Regal, R.E.; Pham, C.Q.D.; Bostwick, T.R. (2006) Urinary tract infections in extended care facilities: Preventive management strategies. Consultant Pharmacist 21(5): 400-409	- Study design does not meet inclusion criteria *Not a SR or RCT*
Saul, Helen, Deeney, Brendan, Cassidy, Samantha et al. (2023) Methenamine is as effective as antibiotics at preventing urinary tract infections. BMJ (Clinical research ed.) 380: 72	- Study design does not meet inclusion criteria *Summary paper*
Sihra, Neha, Goodman, Anna, Zakri, Rhana et al. (2018) Nonantibiotic prevention and management of recurrent urinary tract infection. Nature reviews. Urology 15(12): 750-776	- Study design does not meet inclusion criteria *Not a SR or RCT*
Smith, Ariana L, Brown, Jason, Wyman, Jean F et al. (2018) Treatment and Prevention of Recurrent Lower Urinary Tract Infections in Women: A Rapid Review with Practice Recommendations. The Journal of urology 200(6): 1174-1191	- Study design does not meet inclusion criteria *Not a SR or RCT*
Stair, Sabrina L; Palmer, Cristina J; Lee, Una J (2023) Evidence-based review of nonantibiotic urinary tract infection prevention strategies for women: a patient-centered approach. Current opinion in urology 33(3): 187-192	- Study design does not meet inclusion criteria *Not a SR or RCT*

Abbreviations: ALTAR: ALternatives To prophylactic Antibiotics for the treatment of Recurrent urinary tract infection in women; RCT: randomised controlled trial; SR: systematic review

Appendix J Methods

This guideline was developed using the methods described in the 2018 NICE guidelines manual.

Declarations of interest were recorded according to the NICE conflicts of interest policy (NICE 2022).

Developing the review questions and outcomes

A single review question was developed for this guideline based on the key area identified: What is the clinical and cost-effectiveness of methenamine hippurate when compared to antibiotics in the prevention of recurrent UTIs for adults and children? This was drafted by the NICE development technical team, and refined and validated by the guideline committee.

The review question was based on the population, intervention, comparator and outcome (PICO) framework and a full literature search, critical appraisal and evidence review was completed.

The COMET database was searched for core outcome sets (COS) relevant to this guideline. A COS was identified for treatment of UTIs (Beecher 2022) and this was considered by the committee, but no COS was identified for prophylaxis for recurrent UTIs and, therefore, the outcomes were chosen based on committee discussions.

Searching for evidence

The searches for the effectiveness evidence were run on 29 04 2024. The following databases were searched: Medline ALL (Ovid), Embase (Ovid), Cochrane Database of Systematic Reviews (Wiley), Cochrane Central Register of Controlled Trials (Wiley) and Epistemonikos. Full search strategies for each database are provided in appendix B.

The searches for the cost effectiveness evidence were run on 30 04 2024. The following databases were searched: Medline ALL (Ovid), Embase (Ovid), HTA (CRD) and INAHTA International HTA Database. Full search strategies for each database are provided in appendix B.

A NICE senior information specialist (SIS) conducted the searches. The MEDLINE strategy was quality assured by another NICE SIS. All translated search strategies were peer reviewed to ensure their accuracy. The QA procedures were adapted from the 2015 PRESS Guideline Statement.

Reviewing research evidence

Systematic review process

The evidence was reviewed in accordance with the following approach:

- Potentially relevant articles were identified from the search results by screening titles and abstracts. Full-text copies of the articles were then obtained.
- Full-text articles were reviewed against pre-specified inclusion and exclusion criteria in the review protocol (see appendix A).
- Key information was extracted from each article on study methods and results, in accordance with factors specified in the review protocol. The information was presented in a summary table in the evidence review and in a more detailed evidence table (see appendix D).
- Included studies were critically appraised using an appropriate checklist as specified in Developing NICE guidelines: the manual. Further detail on appraisal of the evidence is provided below.
- A summary of effectiveness evidence by outcome was presented and discussed by the committee.

Dual screening of titles and abstracts was undertaken on a 50% random sample of articles. Any discrepancies were resolved by discussion between reviewers. The draft evidence review was quality assured by the senior reviewer.

Type of studies and inclusion/exclusion criteria

Inclusion and exclusion of studies was based on criteria specified in the review protocol.

Systematic reviews with meta-analyses or meta-syntheses were considered to be the highest quality evidence that could be selected for inclusion. Randomised controlled trials (RCTs) were also prioritised for inclusion because they are considered to be the most robust type of study design that could produce an unbiased estimate of intervention effects. The committee was consulted about any uncertainty regarding inclusion or exclusion of studies. A list of excluded studies, including reasons for exclusion is presented in appendix I.

Narrative reviews, posters, letters, editorials, comment articles, unpublished studies and studies published in languages other than English were excluded. Conference abstracts were not considered for inclusion because conference abstracts typically do not have sufficient information to allow for full critical appraisal.

Methods of combining evidence

Meta-analysis to pool results from comparative intervention studies was conducted where possible using Cochrane RevMan Web.

For dichotomous outcomes, such as recurrent UTI during prophylactic treatment, the Mantel–Haenszel method with a fixed effect model was used to calculate risk ratios (RRs).

For continuous outcomes, measures of central tendency (mean) and variation (standard deviation; SD) are required for meta-analysis. Data for continuous outcomes, such as patient satisfaction, were meta-analysed using an inverse-variance method for pooling weighted mean differences (WMDs).

If a study reported only the summary statistic and 95% CI, the generic-inverse variance method was used to enter data into RevMan Web. If the control event rate was reported this was used to generate the absolute risk difference in GRADEpro.

Potential subgroups to separate evidence into if heterogeneity was encountered, were pre-defined at the protocol stage (see the protocol in appendix A for further detail). However, no subgrouping occurred due to a

lack of variation between studies in the pre-defined subgroups and lack of evidence from some subgroups of interest. Where there was a lack of evidence in one group, the committee considered, based on their experience, whether it was reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.

When meta-analysis was undertaken, the results were presented visually using forest plots generated using RevMan Web (see appendix E).

Appraising the quality of evidence

The evidence for outcomes from included RCTs was evaluated and presented using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology developed by the international GRADE working group.

When GRADE was applied, software developed by the GRADE working group (GRADEpro) was used to assess the quality of each outcome, taking account of individual study quality factors and any meta-analysis results. Results were presented in GRADE profiles (GRADE tables).

The evidence for each outcome was examined separately for the quality elements summarised in Table 8. Criteria considered in the rating of these elements are discussed below. Each element was graded using the quality ratings summarised in Table 9. Footnotes to GRADE tables were used to record reasons for grading a particular quality element as having a ‘serious’ or ‘very serious’ quality issue. The ratings for each component were combined to obtain an overall assessment of quality for each outcome as described in Table 10.

The initial quality rating was based on the study design: RCTs start as ‘high’ quality evidence and the rating was then modified according to the assessment of each quality element (Table 8). Each quality element considered to have a ‘serious’ or ‘very serious’ quality issue was downgraded by 1 or 2 levels respectively (for example, evidence starting as ‘high’ quality was downgraded to ‘moderate’ or ‘low’ quality).

Table 8 Summary of quality elements in GRADE for intervention reviews

Quality element	Description
Risk of bias (study limitations)	This refers to limitations in study design or implementation that reduce the internal validity of the evidence
Inconsistency	This refers to unexplained heterogeneity in the results
Indirectness	This refers to differences in study populations, interventions, comparators or outcomes between the available evidence and inclusion criteria specified in the review protocol
Imprecision	This occurs when a study has few participants or few events of interest
Publication bias	This refers to systematic under- or over-estimation of the underlying benefit or harm resulting from selective publication of study results

Table 9 GRADE quality ratings (by quality element)

Quality issues	Description
None or not serious	No serious issues with the evidence for the quality element under consideration
Serious	Issues with the evidence sufficient to downgrade by 1 level for the quality element under consideration
Very serious	Issues with the evidence sufficient to downgrade by 2 levels for the quality element under consideration

Table 10 Overall quality of the evidence in GRADE (by outcome)

Overall quality grading	Description
High	Further research is very unlikely to change the level of certainty in the estimate of effect
Moderate	Further research is likely to have an important impact on the level of certainty in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on the level of certainty in the estimate of effect and is likely to change the estimate
Very low	The estimate of effect is very uncertain

Assessing risk of bias in intervention reviews

Bias is a systematic error, or consistent deviation from the truth in results obtained. When a risk of bias is present the true effect can be either under- or over-estimated.

Risk of bias in RCTs was assessed using the Cochrane risk of bias 2.0 tool (see Appendix H in Developing NICE guidelines: the manual).

The Cochrane risk of bias tool assesses the following possible sources of bias:

- randomisation process
- deviations from the intended interventions
- missing outcome data
- measurement of the outcome
- selection of the reported result.

A study with a poor methodological design does not automatically imply high risk of bias; the bias is considered individually for each outcome and it is assessed whether the chosen design and methodology will impact on the estimation of the intervention effect.

More details about the Cochrane risk of bias tool can be found in Section 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2020).

Assessing inconsistency in intervention reviews

Inconsistency refers to unexplained heterogeneity in results of meta-analysis. When estimates of treatment effect vary widely across studies (that is, there is heterogeneity or variability in results), this suggests true differences in underlying effects. Inconsistency is, thus, only truly applicable when statistical meta-analysis is conducted (that is, results from different studies are pooled). When outcomes were derived from a single study the rating ‘no serious inconsistency’ was used when assessing this domain, as per GRADE methodology (Santesso 2016).

Inconsistency was assessed visually by inspecting forest plots and observing whether there was considerable heterogeneity in the results of the meta-analysis (for example if the point estimates of the individual studies consistently showed benefits or harms). This was supported by calculating the I-squared statistic for the meta-analysis with an I-squared value of more than 50% indicating serious heterogeneity, and more than 80% indicating very serious heterogeneity. When serious or very serious heterogeneity was observed, possible reasons were explored and subgroup analyses were performed as pre-specified in the review protocol where possible. When no plausible explanation for serious or very serious heterogeneity could be found, the certainty of the evidence was downgraded in GRADE for inconsistency and the meta-analysis was re-run using the Der-Simonian and Laird method with a random effects model and this was used for the final analysis.

Assessing indirectness in intervention reviews

Directness refers to the extent to which populations, interventions, comparisons and outcomes reported in the evidence are similar to those defined in the inclusion criteria for the review and was assessed by comparing the PICO elements in the studies to the PICO defined in the review protocol. Indirectness is important when such differences are expected to contribute to a difference in effect size, or may affect the balance of benefits and harms considered for an intervention.

Assessing imprecision and importance in intervention reviews

Imprecision in GRADE methodology refers to uncertainty around the effect estimate and whether or not there is an important difference between interventions (that is, whether the evidence clearly supports a particular recommendation or appears to be consistent with several candidate recommendations). Therefore, imprecision differs from other aspects of evidence quality because it is not concerned with whether the point estimate is accurate or correct (has internal or external validity). Instead, it is concerned with uncertainty about what the point estimate actually represents. This uncertainty is reflected in the width of the CI.

The 95% CI is defined as the range of values within which the population value will fall on 95% of repeated samples, were the procedure to be repeated. The larger the study, the smaller the 95% CI will be and the more certain the effect estimate.

Imprecision can be assessed by considering whether the 95% CI cross into different decision-making zones, bounded by the thresholds for minimal importance (minimally important differences; MIDs) for benefit and harm. However, the committee were not aware of any recognised or acceptable MIDs in the published literature and community relevant to the review questions under consideration. Therefore, imprecision was assessed according to commonly used optimal information size thresholds. For continuous outcomes, evidence was considered very seriously imprecise for sample sizes less than 200 and seriously imprecise for sample sizes between 200 and 399. For dichotomous outcomes, evidence was considered seriously imprecise if there were less than 300 events, based on the rule-of-thumb specified in version 3.2 of the GRADE handbook (Schünemann 2009), and very seriously imprecise if there were less than 150 events. The threshold for very serious imprecision was a pragmatic decision, in the absence of a rule-of-thumb being available, based on the fact that this is half the number required for serious imprecision, which would be consistent with approach suggested for continuous outcomes.

Assessing publication bias in intervention reviews

The committee subjectively assessed the likelihood of publication bias based on factors such as the proportion of trials funded by industry and the propensity for publication bias in the topic area.

Reviewing economic evidence

Titles and abstracts of articles identified through the economic literature searches were independently assessed for inclusion using the predefined eligibility criteria listed in Table 11.

Table 11 Inclusion and exclusion criteria for the systematic review foreconomic evaluations

Inclusion criteria
Intervention or comparators in accordance with the guideline scope
Study population in accordance with the guideline scope
Full economic evaluations (cost-utility and cost effectiveness) assessing both costs and outcomes associated with interventions of interest
Exclusion criteria
Not a cost-effectiveness or cost utility analysis
Irrelevant population
Irrelevant intervention
Conference abstracts/ editorials/ commentary

Once the screening of titles and abstracts was completed, full-text copies of potentially relevant articles were requested for detailed assessment. Inclusion and exclusion criteria were applied to articles obtained as full-text copies.

Details of economic evidence study selection, lists of excluded studies, economic evidence tables, the results of quality assessment of economic evidence (see below) and health economic evidence profiles are presented in the evidence review.

Appraising the quality of economic evidence

The quality of economic evidence was assessed using the economic evaluations checklist specified in Developing NICE guidelines: the manual.

Cost effectiveness criteria

In general, an intervention was considered to be cost effective if any of the following criteria applied (provided that the estimate was considered plausible):

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more effective compared with all the other relevant alternative strategies)
- the intervention cost less than £20,000 per QALY gained compared with the next best strategy
- the intervention provided important benefits at an acceptable additional cost when compared with the next best strategy.

The committee's considerations of cost effectiveness are discussed explicitly in section 1.1.10.4 'Cost effectiveness and resource use'.

Developing recommendations

Guideline recommendations

Recommendations were drafted on the basis of the committee's interpretation of the available evidence, taking account of the balance of benefits, harms and costs between different courses of action. When effectiveness and economic evidence was of poor quality, conflicting or absent, the committee drafted recommendations based on their expert opinion. The considerations for making consensus-based recommendations include the balance between potential benefits and harms, the economic costs or implications compared with the economic benefits, current practices, recommendations made in other relevant guidelines, person's preferences and equality issues.

The main considerations specific to each recommendation are outlined in section 1.1.10 'Committee discussion and interpretation of the evidence'.

For further details refer to Developing NICE guidelines: the manual.

Research recommendations

When areas were identified for which evidence was lacking, the committee considered making recommendations for future research. For further details refer to Developing NICE guidelines: the manual and NICE's Research recommendations process and methods guide.

Validation process

This guideline was subject to a 2-week public consultation and feedback process. All comments received from registered stakeholders were responded to in writing and posted on the NICE website at publication. For further details refer to Developing NICE guidelines: the manual.

Updating the guideline

Following publication, NICE will undertake a surveillance review to determine whether the evidence base has progressed sufficiently to consider altering the guideline recommendations and warrant an update. For further details refer to Developing NICE guidelines: the manual.

References

Beecher 2022

Beecher C, Duane S, Vellinga A et al. (2022) COSUTI: A Core Outcome Set (COS) for interventions for the treatment of uncomplicated urinary tract Infection (UTI) in Adults. Antibiotics 11(12): 1846

Higgins 2020

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors) (2023) Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 [updated August 2023] The Cochrane Collaboration. Available from www.training.cochrane.org/handbook (accessed 23 July 2024)

McGowan 2016

McGowan J, Sampson M, Salzwedel DM et al. (2016) PRESS Peer Review of Electronic Search Strategies: 2015 guideline statement. Journal of Clinical Epidemiology 75: 40–6

NICE 2022

National Institute for Health and Care Excellence (NICE) (2014) NICE Policy on conflicts of interest (updated 2022). Available from

https://www.nice.org.uk/about/who-we-are/policies-and-procedures (accessed 27 July 2024)

Santesso 2016

Santesso N, Carrasco-Labra A, Langendam M et al. (2016) Improving GRADE evidence tables part 3: detailed guidance for explanatory footnotes supports creating and understanding GRADE certainty in the evidence judgments. Journal of clinical epidemiology 74, 28-39

Schünemann 2009

Schünemann H, Brożek J, Oxman A, (editors) (2009) GRADE handbook for grading quality of evidence and strength of recommendation. Version 3.2 [updated March 2009]

Appendix K Research recommendations

Review question

Effectiveness of methenamine hippurate in the prevention of recurrent urinary tract infections (UTIs).

Research recommendation

What is the clinical and cost-effectiveness of methenamine hippurate when compared to antibiotics in the prevention of recurrent UTIs for men, pregnant women, children and young people, older people and people with upper UTI or complicated lower UTI?

Why this is important

Low-dose antibiotic prophylaxis is the current standard prevention for recurrent UTIs. Widespread use of antimicrobials has been linked to microbes such as bacteria and viruses changing and becoming resistant to treatment. It is therefore important to reduce the use of antimicrobials, particularly antibiotics, to protect our health and the health of future generations. Methenamine hippurate is a urinary antiseptic drug used for the prevention of recurrent UTIs, but there is limited evidence on its effectiveness, and no evidence for populations other than non-pregnant adult women. If widely used it would act as an alternative to low-dose prophylactic antibiotics for recurrent UTIs and may contribute to the aims of antimicrobial stewardship.

Rationale for research recommendation

Importance to the population

If methenamine hippurate can be recommended as an alternative to antibiotic prophylaxis in populations other than non-pregnant adult women, this will provide additional treatment options for such populations. This may also help to reduce health inequalities as certain groups, such as pregnant women, are more at risk from recurrent UTI, both in terms of the likelihood of it recurring and risk from side effects.

Relevance to NICE guidance

Further evidence on the effectiveness of methenamine hippurate in populations other than non-pregnant adult women would potentially allow for stronger recommendations to be made about its use in other populations, which would be essential to inform future updates of this guidance.

Relevance to the NHS

Wider spread use of methenamine hippurate may contribute to the aims of antimicrobial stewardship and therefore have the potential to reduce the likelihood of downstream consequences in response to antibiotic resistance (for example, antibiotics being ineffective or needing to use more costly, resource intensive antibiotics, such as intravenous antibiotics, in the future.

National priorities

The NHS Long Term Plan covers optimising use of, and reducing the need for exposure to, antibiotics as part of tackling antimicrobial resistance.

Current evidence base

There is some evidence that methenamine hippurate prophylaxis is non-inferior to antibiotic prophylaxis in non-pregnant women aged 18 years and older with recurrent UTIs, but there is no evidence for its effectiveness in other populations.

Equality considerations

Low socioeconomic status may be a risk factor for antibiotic resistant UTI. Therefore, people from lower socioeconomic groups may particularly benefit from interventions which reduce the use of antibiotics. The effectiveness of methenamine hippurate for trans people, especially people who have had surgical procedures which have resulted in structural alterations to their genitourinary tract, is currently unclear.

Table 12 Research recommendation PICO

Population	Adults and children (aged 72 hours and older) with recurrent UTIs of any severity, with a focus on: • Men ≥16 years of age

	• Pregnant women ≥16 years of age • Children and young people (72 hours to 15 years of age) • Older people (frailty, care home resident, dementia) • People with upper UTI or 'complicated'[1] lower UTI.
Interventions	Methenamine hippurate prophylaxis
Comparator	Antibiotic prophylaxis
Outcomes	• Recurrence of UTI (as defined by study authors; e.g., incidence, presence of recurrence, number of episodes) • Serious adverse events (as defined by study authors) • Antibiotic resistance (as defined by study authors) • Patient satisfaction • Antibiotic use (other than the prescribed intervention) • Gastrointestinal issues • Generic health- and social care-related or disease-specific quality of life measured using a validated instrument • Cost-effectiveness or resource use
Study type	Randomised controlled trial (non-inferiority)
Timeframe	The research should take place in time to inform future updates of this NICE guideline.

[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)