Managing Common Infections

Recurrent urinary tract infections: antimicrobial prescribing

08/05/2017 – 05/06/2018

ID	ORGANISATION NAME	DOCUMENT	PAGE NO.	LINE NO.	COMMENTS Please insert each new comment in a new row	DEVELOPER'S RESPONSE Please respond to each comment
1	British Infection Association	Guideline	General	General	There is no definition of what constitutes "recurrent UTI". The number of episodes over what duration is not defined, We are unclear from the draft what a recurrent UTI which warrants treatment is in this context.	Thank you for your comment. A definition of recurrent UTI is provided in the 'terms used in the guideline' section of the guideline. We have used the definition in the European Association of Urology guidelines on urological infections (2017).
2	British Infection Association	Guideline	General	General	There is no mention of asymptomatic bacteriuria and its distinction from recurrent UTI.	Thank you for your comment. Recurrent UTI is defined in adults as repeated UTI with a frequency of 2 or more UTIs in the last 6 months or 3 or more UTIs in the last 12 months. Recurrent UTI is diagnosed in children and young people under 16 years if they have: • 2 or more episodes of UTI with acute pyelonephritis/upper UTI, or • 1 episode of UTI with acute pyelonephritis plus 1 or more episode of UTI with cystitis/lower UTI, or • 3 or more episodes of UTI with cystitis/lower UTI. See the NICE guideline on urinary tract infection in under 16s. UTI is a separate diagnosis from asymptomatic bacteriuria and therefore is not covered by this guideline.
3	British Infection Association	Guideline	General	General	There is no mention in the document of the use of stand-by courses of antibiotics rather than long term prophylaxis. The section on self care and the rest of the guidelines completely ignore what is thought to be by many an important strategy to control recurrent UTIs in women: "self-start antibiotic therapy" also known as "patient-initiated treatment" or "patient-administered treatment". This strategy plays a central role in the recommendation for recurrent UTIS by the Canadian Urology Association (Dason S, et al. Guidelines for the diagnosis and management of recurrent urinary tract infection in women. Can Urol Assoc J 2011;5(5):316-22; DOI:10.5489/cuaj.11214) as shown in figure 2 of their article This approach is mostly based on common sense. For instance, Arnold JJ et al favour this approach (Common Questions About Recurrent Urinary Tract Infections in Women. American Family Physician. 93(7):560-9, 2016 Apr 01.) stating that: Patient-initiated treatment lowers the cost of diagnosis, number of physician visits, and number of symptomatic days compared with physician-initiated treatment. It also reduces antibiotic exposure compared with antibiotic	Thank you for your comment. Stand-by antibiotics were named in the NICE search strategy, however we did not identify any evidence on this intervention. While the committee recognised that they may have a role in some specialist cases, stand-by antibiotics could potentially lead to inappropriate antibiotic use, which would not reflect the principles of antimicrobial stewardship (as described in the committee discussion on antibiotic dosing and course length). Based on this, and as no evidence was identified to show the effectiveness or safety of stand-by antibiotics, the committee were not able to make a recommendation on their use. In relation to the submitted articles:

					prophylaxis. Antibiotic prophylaxis effectively limits UTI recurrence but increases the risk of antibiotic resistance and adverse effects. The NICE draft guideline completely ignores this approach. A number of observational studies have reported that intermittent self-start therapy is effective, safe and economical in women with the ability to recognize the typical and familiar UTI symptoms. Suggested references include: Schaeffer AJ, Stuppy BA. Efficacy and safety of self-start therapy in women with recurrent urinary tract infections. J Urol 1999;161:207-11. Gupta K, Hooton TM, Roberts PL, et al. Patient-initiated treatment of uncomplicated recurrent urinary tract infections in young women. Ann Intern Med 2001;135:9-16. Wong ES, McKevitt M, Running K, et al. Management of recurrent urinary tract infections with patient-administered single-dose therapy. Ann Intern Med 1985;102:302-7.	• Dason (2011) did not meet the criteria for inclusion based on publication type (other guidance) • Arnold (2016) did not meet the criteria for inclusion based on study type (narrative review) • Schaeffer (1999) did not meet the criteria for inclusion based on date and study type (observational) • Gupta (2001) did not meet the criteria for inclusion based on date and study type (observational) • Wong (1985) did not meet the criteria for inclusion based on date
4	British Infection Association	Guideline	Section 1.1.3 and associated sections	General	Surely all patients with genuine recurrent UTI should be referred for specialist assessment and investigation not just men, children, pregnant women and those with recurrent upper UTI. Such an opinion should certainly be sought prior to contemplating antibiotic prophylaxis.	Thank you for your comment. This was discussed further by the committee and a recommendation has been included to seek specialist advice for women aged 16 years and over with recurrent lower UTI if the underlying cause is unknown or requires further investigation. The committee was unable to make a recommendation for referral for specialist assessment for all people with recurrent UTI due to resource implications, and agreed upon specific populations who require specialist assessment, based on possible anatomical abnormalities or high risk of complications.
5	British Infection Association	Guideline	4	Antibiotic Prophylaxis section	This needs to include information on when to discontinue prophylaxis e.g. if patient has a urinary tract infection with an organism resistant to the agent being used as prophylaxis or the prophylaxis is ineffective.	Thank you for your comment. This was discussed by the committee and they agreed to amend the recommendation on reviewing treatment success to include more details, including discussing continuing, stopping or changing antibiotic prophylaxis as appropriate.
6	British Infection Association	Guideline	4	Section 1.1.10 and 1.1.12	‘Returning for review after 3 months, or other agreed time’: this statement needs to be more explicit i.e. suggest remove ‘or other time’ as the latter is more likely to lead to the prophylaxis not being reviewed in a timely manner.	Thank you for your comment. This was discussed by the committee and the recommendation on reviewing treatment success has been amended to be more specific, suggesting a review within 6 months.
7	British Infection Association	Guideline	5	Section 1.1.12	This section needs to give more explicit advice on the maximum duration of prophylaxis e.g. maximum of 6 months. Indefinite continuation of prophylaxis particularly in primary care is a significant problem sometimes even despite the patient having UTIs with organisms resistant to the antibiotic being given as prophylaxis.	Thank you for your comment. This was discussed by the committee and the recommendation on reviewing treatment success has been amended to include more details, including discussing continuing, stopping or changing antibiotic prophylaxis as appropriate. A specific review date of within 6 months has also been specified.
8	British Infection Association	Guideline	8	Table 1	The inclusion of pivmecillinam as prophylaxis is a concern – this is one of the few useful oral agents against multi-resistant Gram negative pathogens and UTI such as extended spectrum beta lactamase and AmpC producers hence	Thank you for your comment. The committee discussed pivmecillinam and agreed that it should be removed from the antibiotic

					use as prophylaxis is likely to make it much less useful for treatment of infection. This should be reserved for treatment only.	recommendations table, based on reserving pivmecillinam use for treatment and safety concerns including carnitine deficiency with long term use.
9	British Infection Association	Guidelines	General	General	One responder stated as follows: There should be some mention of the problem of distinguishing UTI requiring antibiotics from the bladder pain syndrome (otherwise known as the urethral syndrome or the frequency dysuria syndrome or interstitial cystitis). If standard microbiological culture is negative in otherwise well women, symptoms may be due to this condition, whose aetiology is not fully understood. It is suggested that it is caused by antibiotics interfering with the normal flora of the urethra, so that more fastidious organisms are selected – these organisms are not detected by the routine microbiological culture methods used in most laboratories (See Maskell RM The natural history of urinary tract infection in women. Medical Hypotheses 74 2010 802-806). For such women, antibiotics can be causing the problem and more antibiotics may make it worse. Urological and GP clinics have regular numbers of such women who have had repeated antibiotics in the past. This treatment doesn't stop the symptoms but does increase the risk of antibiotic resistance. In the guidance, there was no mention of simple medications for culture negative, otherwise well patients, such as alkalising the urine with medications such as sodium bicarbonate or citrate, available in high street chemists. Also need to consider other causes for symptoms such as Chlamydia, Mycoplasma etc which can respond to a single dose of azithromycin (as do some of the fastidious organisms mentioned above).	Thank you for your comment. The remit of the guideline does not cover the diagnosis of recurrent UTI. Only people with recurrent UTI are considered as part of this guidance. In relation to the submitted article: • Maskell (2010) did not meet the inclusion criteria based on study type (narrative review)
10	British Infection Association	Guidelines	P15-17		Some responders were concerned that the document in its current form is overly negative with respect to the use of vaginal oestrogen quoting the BNF re: risks of oestrogen & cardiovascular disease & DVT etc –as the risks for topical oestrogen are not the same as oral & supposedly a year's supply of topical oestrogen is equivalent to having one tablet of standard HR. Ref: Santen R J : vaginal administration of estradiol: effects of dose, preparation & timing on plasma estradiol levels. Climacteric 2015 Apr18 (2):121-34).	Thank you for your comment. Evidence was identified that vaginal oestrogen is associated with more adverse events than placebo or oral antibiotics. There is also consideration made to topical vaginal oestrogens in BNF which states that endometrial safety of long-term or repeated use is uncertain (BNF, June 2018). The committee agreed that it would be unethical practice not to warn women of possible adverse effects, which comes from the BNF and summary of product characteristics on hormone replacement therapy in oral or topical forms. In relation to the submitted article: • Santen (2015) did not meet the inclusion criteria, based on population (not UTI)
11	British Infection Association	Guideline	General	1.1.6 & pages 11-12	Consider D-mannose1 as a self-care treatment for women with recurrent UTI. Support for D-mannose was expressed however this recommendation seemed to be based on a single randomised trial which also had a number of exclusion criteria. There is another more recently published study which appears to support the use of D Mannose (Domenici L. et al. D-mannose: a promising support for acute urinary tract infections in women. A pilot study. European Review for Medical and Pharmacological Sciences 2016; 20: 2920-2925). One difficulty is that these 2 studies have used different D-mannose preparations, and there are many more D-mannose preparations on the market. The experience with cranberry products is that not all cranberry products are equivalent: some cranberry preparations might be "stronger" and	Thank you for your comment. The committee has discussed the evidence on D-mannose and the recommendations have been amended and moved to self-care, to reflect the strength of the limited evidence. However, the committee agreed that there is evidence of some benefit and a recommendation has been made that some women may wish to try D-mannose. The committee were not able to make a specific recommendation for the preparation of D-mannose to use based on the limited evidence available.

					more effective, and this –perhaps – could be the case for D-mannose (D-mannose, like cranberry, is not a standardised medicinal product).	In relation to the submitted article: • Domenici (2016) - this study uses uncontrolled observational methods to evaluate D-mannose for treatment of acute UTI, therefore is not included in the related lower UTI guideline (as it is not a relevant study type). This study was not identified in the NICE search as it is not described as a randomised control trial. However, it is noted that there is limited randomised controlled data on prophylaxis for recurrent UTI included within the results; however, this has not been added to the recurrent UTI evidence review as the conclusion that D-mannose is effective for the prophylaxis of recurrent UTI would not impact the recommendations.
12	British Infection Association	Guideline	General		Methenamine hippurate needs further study though is used by some of our members. However are we clear on the possible long-term risks of conversion to formaldehyde in situ?	Thank you for your comment. Methenamine hippurate was specifically included by name in the NICE search strategy. However the search was not designed to identify evidence on long term risks. Safety data on methenamine hippurate would be available from sources such as the BNF and SPC but has not been included as this antibiotic has not been recommended. Methenamine hippurate was less effective than antibiotic prophylaxis with nitrofurantoin, and the committee was also aware that methenamine hippurate is a medicine that is considered less suitable for prescribing (BNF, August 2018).
13	British Infection Association	Guideline	P26		Pulmonary fibrosis is mentioned as a complication of the use of long-term nitrofurantoin for UTI prophylaxis. Anecdotally, many of us have come across the odd case. A literature review to quantify this risk would have been helpful (if possible) as it might be an important consideration, when choosing between different options (e.g. self-start antibiotics or intra-vaginal oestrogen or long-term nitrofurantoin prophylaxis).	Thank you for your comment. The NICE search strategy was not developed to identify evidence on complications with long-term use. Safety information is available in sources such as the BNF, the SPC, and from Drug Safety update, which has been considered. Information from the BNF included in the 'safety of antibiotic prophylaxis' section of the guideline states that people given nitrofurantoin should be monitored for pulmonary symptoms.
14	British Infection Association	Guideline	P5 (1.1.13)		Antibiotic prophylaxis is recommended for men with recurrent UTIs who have had no improvement after behavioural and personal hygiene measures. The NICE guidelines completely ignore a significant part of the literature that suggests that, in men, recurrent UTIs can be a manifestation of chronic prostatitis that would require a single course of 4-6 weeks of appropriate antibiotics with good prostatic penetration, rather than long-term low-dose prophylaxis. Some of the articles supporting this viewpoint are: i. Recurrent urinary tract infections in men. Characteristics and response to therapy. Smith JW; Jones SR; Reed WP; Tice AD; Deupree RH; Kaijser B. Annals of Internal Medicine. 91(4):544-8, 1979 Oct.	Thank you for your comment. The recommendations suggests that men with recurrent urinary tract infection should be sent for specialist assessment and investigations. Recommendations also suggest that when antibiotic prophylaxis is given, further investigations which may be needed to identify an underlying cause should be taken into account. This guideline only considers people with recurrent urinary tract infection

					ii. Norfloxacin versus co-trimoxazole in the treatment of recurring urinary tract infections in men. Sabbaj J; Hoagland VL; Cook T. Scandinavian Journal of Infectious Diseases Supplement. 48:48-53, 1986. iii. Urinary tract infections in men. Epidemiology, pathophysiology, diagnosis, and treatment. [Review] [107 refs] Lipsky BA. Annals of Internal Medicine. 110(2):138-50, 1989 Jan 15. iv. Prostatitis and urinary tract infection in men: what's new; what's true?. [Review] [76 refs] Lipsky BA. American Journal of Medicine. 106(3):327-34, 1999 Mar. v. Fluoroquinolone antimicrobial agents in the treatment of prostatitis and recurrent urinary tract infections in men. [Review] [68 refs] Wagenlehner FM; Naber KG. Current Urology Reports. 5(4):309-16, 2004 Aug. vi. Urinary tract infections and bacterial prostatitis in men. [Review] Wagenlehner FM; Weidner W; Pilatz A; Naber KG. Current Opinion in Infectious Diseases. 27(1):97-101, 2014 Feb.	and therefore treatment for chronic prostatitis is not considered. In relation to the submitted articles: • Smith (1979) did not meet the inclusion criteria based on date • Sabbaj (1986) did not meet the inclusion criteria based on date • Lipsky (1989) did not meet the inclusion criteria based on date • Lipsky (1999) did not meet the inclusion criteria based on date • Wagenlehner (2004) did not meet the inclusion criteria based on date • Wagenlehner (2014) did not meet the inclusion criteria based on study type (narrative review)
15	British Infection Association	Guideline	P26		Cefalexin is mentioned as a second-line option for prophylaxis, on the basis of the experience of the authors of the NICE guidelines. One of our member's experience is different: when they check urine culture reports, if they see in the clinical details that the patient is on antibiotic prophylaxis, invariably the break-through UTI is caused by a bacterium resistant to that antibiotics. Coliforms resistant to cephalexin often produce ESBL or AmpC beta-lactamases with few or no other oral treatment options. It seems to them that cephalexin is an antibiotic to be kept in reserve for treatment, not wasted on prophylaxis. The NICE guidelines do not include a review of the frequency of selection of resistance with antibiotic prophylaxis: unfortunately there is a limited amount of data as the published studies were usually over limited periods of 6-12 months (in practice prophylaxis is often given for longer) and not many of the study authors have bothered to look for and report resistance (in stool specimens or in the urines from break-through UTIs). However, there are some studies, like the one from Brumfitt et al. (A clinical comparison between macrodantin and trimethoprim for prophylaxis in women with recurrent urinary infection. J Antimicrob Chemother 1985;16:111-120) that have monitored the acquisition of antibiotic resistance and showed that with trimethoprim the acquisition of resistance by faecal coliforms occurred at a rate of about 5% per month.	Thank you for your comment. The committee discussed cefalexin however, based on evidence of efficacy, experience and resistance data, they agreed to include cefalexin as a second choice antibiotic. In relation to the submitted article: • Brumfitt (1985) did not meet the inclusion criteria based on date
16	Scottish Antimicrobial Prescribing Group	Visual summary	General	General	Sentence about cranberry and probiotics would be better in Self-care info box Also maybe a better definition of what 'recurrent' means in terms of frequency as defining it in terms of reinfection and relapse I find a bit misleading as to how a clinician differentiates this from persistent infection. The 3 in 12 months criteria was always useful as a benchmark, although we have always qualified that locally by stating that it is 3 confirmed episodes of UTI as otherwise there is a risk that symptomatic but non-bacterial presentations such as urethritis as counted and patients escalate to easily to antibiotics. In general it would be useful to have hyperlinks across the UTI guidelines to any relevant patient information to support clinician access and utilisation of these (e.g. TARGET leaflets). Refer to guideline for CaUTI	Thank you for your comment. The visual summary has been amended to include a self-care box, including recommendations on probiotics, cranberries and D-mannose. Recurrent urinary tract infection is defined in 'terms used in the guideline' in terms of frequency. However, the information regarding relapse and reinfection has not been amended in the visual summary, as this is background to the different types of recurrent UTI.

					Give the fact that D-Mannose only has evidence from 1 RCT and women were also on ciprofloxacin is this valid enough to put as a recommendation? If so then there are other preps like methenamine that would hold similar weighting (which is also mentioned in PHE guidance). I am not sure if there is robust enough evidence to add these though particularly when a cost-effective analysis has not been undertaken. Self-care should also include bowel management as bowel and bladder health should be promoted jointly. Consider including referral for KUB scan as incomplete bladder emptying may predispose to recurrent UTI. Consider when women should be referred for cystoscopy to exclude serious pathology – this is not included at any point in the visual guideline. Returning for review in 3 months or other agreed time is inappropriate. They must be reviewed at 3 months with max 6 months prophylaxis. The term 'continuous' antibiotics may be misleading in this respect and means it is not considered as a fixed term course with review which is appropriate at the outset for managing patient expectations. Not enough information about when to stop prophylaxis – this is essential! Should we include anything about what to do when a patient is on prophylaxis and develops an acute infection? MSSU should be used in recurrent UTI to ensure no multi-resistant UTI e.g. ESBL have been excluded. Antibiotics should be based on sensitivities which should be available. The evidence for prophylaxis in pregnancy and men is extremely poor and so should be discouraged. Recurrent UTI in men especially does not usually happen without cause and until this is resolved antibiotics are unhelpful. Also see SAPG recommendation. I am not sure 'consider oestrogen' should be a statement like this in the treatment box, and it should be more about consider differential diagnosis and then expanding on this in the supplementary info box as to what could be a differential diagnosis and how this should be treated. I didn't think the evidence base was that strong for this and could generate unnecessary treatment as it currently reads just to save an antibiotic prescription. Where patients don't need an antibiotic we don't necessarily want prescribers to give them something else just to give them something.	Any tools and resources that have been endorsed by NICE will be included in this tab of the webpage. The related antimicrobial prescribing guidelines on urinary tract infections (UTI), including catheter associated UTI will be linked to on the guideline webpage. The committee discussed the evidence on D-mannose and the recommendations have been amended, to reflect the strength of the evidence. However, the committee agreed that there is evidence of some benefit and a recommendation has been made that some women may wish to try D-mannose. Methenamine hippurate was specifically included by name in the NICE search strategy. We identified evidence on methenamine hippurate compared with nitrofurantoin, which showed effectiveness of nitrofurantoin over methenamine hippurate. No further evidence which met the inclusion criteria was identified on this intervention. The committee was also aware that methenamine hippurate is a medicine that is considered less suitable for prescribing (BNF, August 2018). Therefore, they were not able to make a recommendation on its use. Bowel management is outside of the scope for this guideline, which only considers the management of recurrent urinary tract infections. The committee considered including referral for underlying causes of UTI, including incomplete bladder emptying and serious pathologies requiring cystoscopy. As there are a number of possible causes of recurrent UTI, the committee agreed to make a recommendation to Seek specialist advice for women aged 16 years and over with recurrent lower UTI if the underlying cause is unknown or requires further investigation. They also made a recommendation to refer adults, young people and children with suspected cancer for specialist assessment and investigations, in line with the NICE guideline on suspected cancer: recognition and referral. A summary of the referral recommendations is given in the visual summary. The committee have considered the review period for antibiotic prophylaxis and amended the recommendation to state that review

						takes place within 6 months. The committee agreed that a period of 6 months was appropriate for enabling clinicians to determine if the treatment has been successful. The term ‘continuous’ has been amended to the term ‘daily’. The recommendation on reviewing treatment success has been amended to include more details, including discussing continuing, stopping or changing antibiotic prophylaxis as appropriate. The treatment of acute UTI is outside the scope of this guideline, including for people on antibiotic prophylaxis. The remit of the guideline does not cover the diagnosis of recurrent UTI, therefore the use of midstream urine analysis is outside the scope. However, the committee were able to make a recommendation included in the antibiotic prescribing tables (table 1 and 2) that antibiotics should be chosen according to recent culture and susceptibility results where possible. The committee recognised the limitations of the evidence on antibiotic prophylaxis in pregnant women and men. Therefore, the committee agreed that is was appropriate to refer all pregnant women to an obstetrician if recurrent UTI is diagnosed during pregnancy. They also agreed that most men with recurrent UTI should be referred for further specialist investigation and management, and that any decision to prescribe antibiotic prophylaxis should be under specialist advice. The committee considered the evidence on oestrogen and based on evidence of effectiveness made a recommendation on its use in postmenopausal women who have had no improvement after behavioural and personal hygiene measures. The committee agreed that this population require treatment, and that consideration should be given to using vaginal oestrogens before antibiotic prophylaxis. This has therefore been included in the visual summary as a treatment option. Diagnosis is outside the scope of this guideline, and therefore information on considering differential diagnosis will not be added.

17	Scottish Antimicrobial Prescribing Group	Guideline	General	General	Is D-mannose readily available? There is fairly limited evidence to support it being a recommendation. This will be a new approach to most HC practitioners. Was methenamine hippurate considered for short term prophylaxis? Potential risks of developing multi-resistant infection e.g. ESBL e.coli with long term prophylaxis, especially with beta-lactams. Current lack of availability of trimethoprim liquid.	Thank you for your comment. The committee discussed the evidence on D-mannose and recognised its limitations. The recommendation has been amended and moved to the self-care section, to reflect the strength of the limited evidence. However, the committee agreed that there is evidence of some benefit and a recommendation has been made that some women may wish to try D-mannose. The committee were aware that D-mannose is a nutritional supplement (not a medicine) and is available as a self-care treatment, and agreed there was sufficient evidence to make a recommendation. Methenamine hippurate was specifically included by name in the NICE search strategy. We identified evidence on methenamine hippurate compared with nitrofurantoin, showing evidence of effect for nitrofurantoin, however no further evidence on this intervention was identified. The committee was also aware that methenamine hippurate is a medicine that is considered less suitable for prescribing (BNF, August 2018). Therefore, they were not able to make a recommendation on its use. The committee were aware of the risks of antimicrobial resistance with antibiotic prophylaxis, therefore recommended that it is considered only when other management options have not been successful. The committee also considered the increased risks of antimicrobial resistance with broader spectrum antibiotics, and therefore included amoxicillin and cefalexin as second choice antibiotics, suggesting trimethoprim and nitrofurantoin as first choice. The committee agreed that based on evidence of no major differences in clinical effectiveness between classes of antibiotics, the choice of antibiotic prophylaxis should largely be driven by minimising the risk of resistance, but have agreed multiple choices of antibiotics in the case that trimethoprim is not available in an appropriate formulation.
18	Scottish Antimicrobial Prescribing Group	Guideline	5		Guideline inclusive of all populations. Evidence for prophylaxis in men poor.	Thank you for your comment. The committee considered the evidence for antibiotic prophylaxis in men, and were aware of its limitations. Therefore, the committee agreed that most men with recurrent UTI should be

						referred for further specialist investigation and management, and any decision to prescribe antibiotic prophylaxis should be under specialist advice.
19	Scottish Antimicrobial Prescribing Group	Guideline	8		Second choice abx – “WATCH” promoted over “ACCESS”.	Thank you for your comment. The committee discussed the comment and made no changes as no ‘WATCH’ antibiotics are recommended for recurrent UTI. However, the committee agreed that for some serious UTIs, such as acute pyelonephritis or acute prostatitis, ‘WATCH’ antibiotics such as third generation cephalosporins or quinolones, which are at relatively high risk of selection of bacterial resistance, may be required because these infections can have serious complications, such as sepsis. The committee agreed that having several antibiotics available enables antibiotics to be selected based on the severity of illness, antibiotic susceptibilities from culture results when available, local resistance patterns, risk of resistant bacteria, the setting, and known patient factors (such as whether the person has a higher risk urinary tract infection). In line with antimicrobial stewardship, narrower spectrum antibiotics should always be used first wherever possible.
20	Scottish Antimicrobial Prescribing Group	Guideline	14		D Mannose may be easier to use than cranberry (there is no evidence for this) Should it be clarified that topical oestrogens may be helpful if post-menopausal atrophy is thought to be a contributing factor to recurrent UTI? The draft only seems to specify ‘post-menopausal women’ – and it may be helpful to further quantify this?	Thank you for your comment. The statement regarding D-mannose which may be easier to use than cranberry was based on committee experience. This statement has been removed from the guideline. The evidence identified on topical oestrogens was in a population of post-menopausal women, which did not specify a sub-population of women with post-menopausal atrophy. Therefore, the committee were not able to make a specific recommendation regarding atrophy.
21	Scottish Antimicrobial Prescribing Group	Guideline	18		The reference to the nitrofurantoin study by Muller is potentially unhelpful as it is such a heterogeneous group.	Thank you for your comment. The committee were aware of the heterogeneous population of the Muller systematic review, however, they agreed that it could be used to inform recommendations on antibiotic prophylaxis in pregnant women and men, considering that this should be given under specialist advice.
22	Scottish Antimicrobial Prescribing Group	Guideline	19		Pulmonary reactions secondary to nitrofurantoin increase in likelihood with duration of therapy, but can happen at any time during treatment.	Thank you for your comment. The safety information regarding nitrofurantoin and pulmonary reactions is taken from the BNF.
23	Scottish Antimicrobial Prescribing Group	Guideline	25		What is the evidence for antibiotic cycling? Why is rotational use of antibiotics needed, based on local policies? NICE should be looking for evidence as to whether rotational antibiotics are beneficial or harmful. They should not include rotational treatment just because that’s what local policies say – the guidance should be directed the other way.	Thank you for your comment. The NICE search strategy included terms for prescribing strategies, however, did not specifically include terms on rotational use or cycling. No evidence on rotational use was found.

					“For infections that are not life threatening, broad spectrum antibiotics should be reserved for second choice”. There may be an argument that if the infection is not life threatening, then broad spectrum prophylaxis potentially should not be used as the risk/benefit ratio is poorer.	However, the footnote included in the antibiotic choice table on rotational use, is based on the committee’s experience and resistance data. The committee considered that effective treatment options are necessary for recurrent urinary tract infection, and therefore the recommendation of broader spectrum antibiotics as second choice, when narrow spectrum antibiotics are ineffective is appropriate, despite antibiotic resistance risk.
24	British Association of Urological Surgeons (BAUS)	Guideline	General	General	There is no mention of the use of methenamine hipprex in recurrent UTIs. Cochrane review to support its use RR=0.24 compared with RR of 0.21 with antibiotic prophylaxis – “Lee BSB, Bhuta T, Simpson JM, Craig JC. Methenamine hippurate for preventing urinary tract infections. Cochrane Database Syst Rev 2012;359:CD003265.pmid:23076896”.	Thank you for your comment. Methenamine hippurate was specifically included by name in the NICE search strategy. We identified evidence on methenamine hippurate compared with nitrofurantoin, which showed effectiveness of nitrofurantoin over methenamine hippurate. No further evidence which met the inclusion criteria was identified on this intervention. The committee was also aware that methenamine hippurate is a medicine that is considered less suitable for prescribing (BNF, August 2018). Therefore, they were not able to make a recommendation on its use. In relation to the submitted article: • Lee (2012) did not meet the inclusion criteria based on population (majority of participants were ‘high risk for UTI’ rather than people who had a previous diagnosis of UTI)
25	British Association of Urological Surgeons (BAUS)	Guideline	General	General	There is no mention of vaccines in the prevent of recurrent UTIs. EAU recommended – “Naber KG, Cho YH, Matsumoto T, Schaeffer AJ. Immunoactive prophylaxis of recurrent urinary tract infections: a meta-analysis. Int J Antimicrob Agents 2009;359:111-9. doi:10. 1016/j.ijantimicag.2008.08.011 pmid:18963856	Thank you for your comment. Making recommendations on vaccination is not within the remit of NICE guidance. In relation to the submitted article: • Naber (2009) did not meet the inclusion criteria based on intervention
26	British Association of Urological Surgeons (BAUS)	Guideline	General	General	No mention has been made of the role of Intravesical GAG replacements. A meta-analysis that supports it use – “De Vita D, Antell H, Giordano S. Effectiveness of intravesical hyaluronic acid with or without chondroitin sulfate for recurrent bacterial cystitis in adult women: a meta-analysis. Int Urogynecol J 2013;359:545-52. doi:10.1007/s00192-012-1957-y pmid:23129247”	Thank you for your comment. The committee prioritised non-antimicrobial interventions to be included in the evidence review for this guideline, based on the interventions which are in common use in UK practice. Intravescial glycoaminoglycogen replacement was not included as a prioritised intervention as this is not in common use and therefore has not been considered in the guideline. In relation to the submitted article:

						• De Vita (2013) did not meet inclusion criteria based on intervention
27	British Association of Urological Surgeons (BAUS)	Evidence review	General	General	There is no comment relating to cranberry juice recent meta analysis J Nutr. 2017 Dec;147(12):2282-2288. doi: 10.3945/jn.117.254961. Epub 2017 Oct 18.Cranberry Reduces the Risk of Urinary Tract Infection Recurrence in Otherwise Healthy Women: A Systematic Review and Meta-Analysis.Fu Z1, Liska D2, Talan D3, Chung M4.	Thank you for your comment. The literature search was conducted before the publication of this systematic review. This systematic review has now been included. The evidence has been considered by the committee alongside the evidence on cranberry products that was already included, and changes have been made to the recommendations. The committee agreed that there is uncertain evidence of benefit for cranberry products, but some women who are not pregnant may wish to try them.
28	British Association of Urological Surgeons (BAUS)	Guideline	7	Table 1	Second line agents for prophylaxis include amoxicillin which have a high resistance rates so this should be reconsidered or according to local policy	Thank you for your comment. The committee considered that effective treatment options are necessary for recurrent urinary tract infection, and therefore the recommendation of amoxicillin as a second choice, when narrower spectrum antibiotics are ineffective is appropriate, despite the risk of antibiotic resistance. The recommendation to follow the antibiotic choices in tables 1 and 2 has been amended to include taking account of local antimicrobial resistance data.
29	British Association of Urological Surgeons (BAUS)	Guideline	General	General	Does not mention use of self-start antibiotic courses	Thank you for your comment. Stand-by (self-start) antibiotics were named in the NICE search strategy, however we did not identify any evidence on this intervention. Therefore, while the committee recognised that they may have a role in some specialist cases, they were not able to make a recommendation on their use (as described in the committee discussion on antibiotic dosing and course length).
30	British Association of Urological Surgeons (BAUS)	Guideline		1.3.2	6 months review may be an appropriate review of the success of the prophylaxis but the current wording is acceptable	Thank you for your comment. The recommendation has been amended to state that a review should be held within 6 months.
31	Chronic Urinary Tract Infection Campaign	Evidence review	Page 7	Line 20-23	“Lower UTI (cystitis) recurs within a year in 25 to 50% of women, usually as reinfections (rather than relapses)”. This assumption is not certain, current research suggest that recurrence may be reactivation of the same infection living inside biofilms and intracellular reservoirs. Ikaheimo R, Siitonen A, Heiskanen T, Karkkainen U, Kuosmanen P, Lipponen P, et al. Recurrence of urinary tract infection in a primary care setting: analysis of a 1-year follow-up of 179 women. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 1996; 22(1):91-9. Epub 1996/01/01. PubMed PMID: 8824972. Jacobson SH, Kuhn I, Brauner A. Biochemical fingerprinting of urinary Escherichia coli causing recurrent infections in women with pyelonephritic	Thank you for your comment. The statement regarding reinfections comes from the NICE clinical knowledge summary of lower urinary tract infections. The cause of recurrence is not within the scope of this guideline and this information is only included as background information. In relation to the submitted articles: • Ikaheimo (1996) did not meet the inclusion criteria based on date • Jacobson (1992) did not meet the inclusion criteria based on date

					renal scarring. Scandinavian journal of urology and nephrology.1992;26(4):373-7. Epub 1992/01/01. PubMed PMID: 1292076. Kerrn MB, Struve C, Blom J, Frimodt-Moller N, Krogfelt KA. Intracellular persistence of Escherichia coli in urinary bladders from mecillinam-treated mice. The Journal of antimicrobial chemotherapy. 2005;55(3):383-6. Epub 2005/02/01. doi: 10.1093/jac/dki002. PubMed PMID: 15681580. Cheng Y, Chen Z, Gawthorne JA, Mukerjee C, Varettas K, Mansfield KJ, et al. Detection of intracellular bacteria in exfoliated urothelial cells from women with urge incontinence. Pathogens and disease. 2016;74(7). Epub 2016/07/13. doi: 10.1093/femspd/ftw067. PubMed PMID: 27402784. Tajbakhsh E, Ahmadi P, Abedpour-Dehkordi E, Arbab-Soleimani N, Khamesipour F. Biofilm formation, antimicrobial susceptibility, serogroups and virulence genes of uropathogenic E. coli isolated from clinical samples in Iran. Antimicrobial resistance and infection control. 2016;5:11. Epub 2016/04/05. doi: 10.1186/s13756-016-0109-4. PubMed PMID: 27042294; PubMed Central PMCID: PMCPMC4818419.	• Kerrn (2005) did not meet the inclusion criteria based on date • Cheng (2016) did not meet the inclusion criteria based on study type • Tajbakhsh (2016) did not meet the inclusion criteria based on study type (non-intervention, in vitro study of bacteria properties and antibiotic resistance)
32	Chronic Urinary Tract Infection Campaign	Evidence review	General		Pleasing to see the evidence on probiotics, D-mannose and Cranberry, HRT, vaginal oestrogen has been included in the evaluation.	Thank you for your comment.
33	Chronic Urinary Tract Infection Campaign	Evidence review	Page 13-17	Studies included in the review	We are concerned with the duration and follow up time of included studies, given the present risk of antimicrobial resistance. Studies lasted from 28 days follow up, 6 months, 12 months, others not reported, with only one study lasting 4 years. Most of these studies do not allow enough time to access long term rates of resistance especially as resistance rates often build up gradually over time. More longitudinal studies are needed to evaluate the risk. Additionally with prophylaxis there is a risk of under-dosing and giving sub-lethal doses of antibiotic leading to anti-microbial resistance.	Thank you for your comment. We searched for and reported evidence from systematic reviews and RCTs which provided antibiotic resistance data, however only limited evidence was identified. The dosages for single dose trigger related antibiotic prophylaxis were discussed by the committee and amended where necessary to recommend a single treatment dose. The dosages stated for daily antibiotic prophylaxis in the guideline are taken from the BNF (except amoxicillin which is not licensed specifically for preventing UTIs; the dose is half a single treatment dose and was agreed by committee consensus).
34	Chronic Urinary Tract Infection Campaign	Evidence review	Page 13-17	Studies included in the review	Given the recent discovery that biofilm infections cause UTIs, the property and nature of these types of infections suggest that there will an antibiotic penetration problem. It is now known that uropathogens utilise biofilms (microbial communities protected by an extra-cellular matrix) and undergo morphological changes increasing resistance to both the immune response and to antibiotics, and that prophylaxis may lead to long term failure and possible antibiotic resistance due to sub lethal dosage. This recent research appears not to have been considered with-in the guidelines, but needs to be urgently addressed by NICE and the Committee. 1. Tenke P, Koves B, Nagy K, Hultgren SJ, Mendling W, Wullt B, et al. Update on biofilm infections in the urinary tract. World JUrol. 2011. 2. Blango MG, Mulvey MA. Persistence of uropathogenic Escherichia coli in the face of multiple antibiotics. AntimicrobAgents Chemother. 2010;54(5):1855-63.	Thank you for your comment. The committee considered antibiotic efficacy evidence as well as evidence regarding antibiotic resistance when making the recommendations in the guideline. However, the microbiological mechanism underlying antimicrobial resistance is outside the scope for this guideline. In relation to the submitted articles: • Tenke (2011) did not meet the inclusion criteria based on study type (non-intervention, in vitro study of bacteria properties) • Blango (2010) did not meet the inclusion criteria based on being an animal study

					3. Hoiby N, Bjarnsholt T, Givskov M, Molin S, Ciofu O. Antibiotic resistance of bacterial biofilms. Int J Antimicrob Agents. 2010;35(4):322-32. doi: 10.1016/j.ijantimicag.2009.12.011. PubMed PMID: 20149602. 4. Anderson GG, Dodson KW, Hooton TM, Hultgren SJ. Intracellular bacterial communities of uropathogenic Escherichia coli in urinary tract pathogenesis. Trends Microbiol. 2004;12(9):424-30. 5. Anderson GG, Palermo JJ, Schilling JD, Roth R, Heuser J, Hultgren SJ. Intracellular bacterial biofilm-like pods in urinary tract infections. Science. 2003;301(5629):105-7. Epub 2003/07/05. doi: 10.1126/science.1084550. PubMed PMID: 12843396. 6. Reid G. Biofilms in infectious disease and on medical devices. IntJAntimicrobAgents. 1999;11(3-4):223-6. 7. Costerton JW, Cheng KJ, Geesey GG, Ladd TI, Nickel JC, Dasgupta M, et al. Bacterial biofilms in nature and disease. AnnuRevMicrobiol. 1987;41:435-64. 8. Soto. Importance of Biofilms in Urinary Tract Infections: New Therapeutic Approaches. Advances in Biology 2014. Article ID 543974 9. Flores-Mireles et al. Urinary Tract Infections: Epidemiology, mechanisms	• Hoiby (2010) did not meet the inclusion criteria based on study type (narrative review) • Anderson (2004) did not meet the inclusion criteria based on date • Anderson (2003) did not meet the inclusion criteria based on date • Reid (1999) did not meet the inclusion criteria based on date • Costerton (1987) did not meet the inclusion criteria based on date • Soto (2014) did not meet the inclusion criteria based on study type (narrative review) • Flores-Mireles (2015) did not meet the inclusion criteria based on study type (narrative review)
35	Chronic Urinary Tract Infection Campaign	Draft guideline	Page 2	1.1.2 Line 4-8	This guideline mentions the possibility of relapse with the same strain but fails to clearly link that to a failure for previous treatment to successfully eradicate the original infection. This is clinically very important and is likely to become a lot more common with the increased use of shorter courses of antibiotics for standard treatment. Any patient with a history of recurrence of a UTI should receive a longer course of antibiotic treatment until symptoms completely resolve. Failure to completely eradicate infection increases the risk of complex or resistant bacterial infection developing.	Thank you for your comment. The treatment of acute UTIs is not covered by this guideline. However, from the evidence base for treating lower UTI (see antimicrobial prescribing guideline on lower UTI), it was not possible to analyse a population with recurrent UTI only. Some studies excluded people with recurrent UTI and others did not, and no sub-group analyses of people with recurrent UTI were presented.
36	Chronic Urinary Tract Infection Campaign	Draft Guideline	Page 2	1.1.3, 1.1.4 and 1.1.5 Line 10- 23	These guidelines recommend referral to specialist assessment and investigation. However there is only one clinic currently treating recurrent and chronic UTI and at present referral cannot come direct from the GP. This needs urgent resolution. In particular for pregnant women and paediatric patients, referral to consultants without adequate specialism in recurrent/chronic UTI is inadequate. These infections need expert and experienced treatment.	Thank you for your comment. This was discussed further by the committee and the recommendation has been amended to be clearer that referral for specialist assessment and investigations should be made to a urology specialist. The recommendations on referral for pregnant women and women aged under 16 years have not been amended, as the committee agreed that specialist assessment should be provided by obstetricians and paediatricians, respectively.
37	Chronic Urinary Tract Infection Campaign	Draft guideline	Page 2	1.1.3 Line 10-16	A concern is the referral of patients with only upper urinary tract recurrent infections. Analysis of the whole urinary tract should be investigated not just those with Upper UTI infections. Patients should be sent for pelvic floor and urogenital imaging particularly if known history of genito-urinary co-morbidities.	Thank you for your comment. This was discussed further by the committee and a recommendation has been added to cover seeking specialist advice for women aged 16 years and over with recurrent lower urinary tract infection if the underlying cause of recurrence is unknown or requires further investigation.

38	Chronic Urinary Tract Infection Campaign	Guideline	Page 3	1.1.6 Line 2-8	Recommendation of D Mannose. The following points should be noted: In the RCT by Kranjcec et al 2014, participants were diagnosed with acute cystitis not ongoing, recurrence of symptoms. There is a critical difference. Additionally, d- mannose may not be effective against certain strains of UPEC (uro-pathogenic e-coli) or other uro-pathogenic bacteria that do not express type 1 pili and FimH. Any clinician guidance must take this into account. References: Pathogens. 2016 Mar; 5(1): 30. Published online 2016 Mar 15. doi: 10.3390/pathogens5010030 PMCID: PMC4810151 PMID: 26999218 Infect Immun. 1980 Jul; 29(1): 226–233. PMCID: PMC551100 PMID: 6105132 Kranjcec et al excluded diabetic patients from the study. The use of D-mannose in diabetic mellitus (DM) patients needs to be further evaluated. Kranjcec et al treated the acute cystitis prior to administration of the therapy allowing the study to focus on the prophylactic nature of D- mannose. Future longitudinal studies do need to be completed. The dosing of D-mannose is not fully established. No dosing details are provided for GP guidance to pass for patient. Only note on bottom of Page 3 is D Mannose used in study is 1% solution. That does not provide any guidance for patient or GP as to how to administer dosage to manage infection. D Mannose is available in powder and tablet format.	Thank you for your comment. The RCT by Kranjcec et al. 2014 met the inclusion criteria for this review, as participants were women who had acute cystitis and a history of recurrent cystitis, and recurrence of urinary tract infection was a reported outcome. The committee has discussed the evidence on D-mannose and the recommendations have been amended, to reflect the strength of the evidence. However, the committee agreed that there is evidence of some benefit and a recommendation has been made that some women may wish to try D-mannose. Acknowledgement of the sugar content of D-mannose has also been included in the recommendation, and a recommended dosage. In relation to the submitted articles: • Spaulding (2016) did not meet the inclusion criteria based on study type (narrative review) • Van Den Bosch (1980) did not meet the inclusion criteria based on date
39	Chronic Urinary Tract Infection Campaign	Draft guideline	Page 4	1.1.9 Line 6-16	We welcome that patients should be advised of triggers and education provided by GP of management of triggers to avoid further infection. However, in the case of recurrent UTI, we note caution in the usage of single dose antibiotics. A recent study has shown antibiotic failure of low single dose antibiotics against that of a 5-day course of Nitrofurantoin. Further, a randomised placebo controlled trial by Rudenko et al. demonstrated that 10 x daily 3 g Fosfomycin prophylaxis is effective at reducing the rate and recurrence of urinary tract infections. Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women A Randomized Clinical Trial Angela Huttner, MD et al JAMA. doi:10.1001/jama.2018.3627 Published online April 22, 2018. Rudenko N, Dorofeyev A. Prevention of recurrent lower urinary tract infections by long-term administration of fosfomycin trometamol. Double blind, randomized, parallel group, placebo controlled study. Arzneimittelforschung. Germany; 2005;55(7):420–7.	Thank you for your comment. The committee discussed the concerns on single dose antibiotic prophylaxis, however the recommendation has not been amended. This recommendation is based on evidence identified showing no difference in efficacy of single dose antibiotics taken when exposed to triggers, compared with a 12 month course of continuous antibiotics. The committee agreed that single-dose prophylaxis was as effective as continuous prophylaxis, with fewer adverse effects in non-pregnant women with an identifiable trigger, and should be considered as the first option for antibiotic prophylaxis in this group of women. In relation to the submitted articles: • Huttner (2018) did not meet the inclusion criteria based on intervention (not recurrent UTI prevention, but acute UTI treatment)

						• Rudenko (2005) did not meet the inclusion criteria based on date
40	Chronic Urinary Tract Infection Campaign	Draft guideline	Page 4	1.1.9 Line 6-16	We have concerns regarding the use of prophylactic antibiotic when they are at sub-clinical dose as these can increase the risk of resistant bacterial infection developing if used when a pre-existing infection has not been fully eradicated. They may keep such an infection at bay but once prophylaxis stops it is likely to recur and may have developed resistance/become much more difficult to treat.	Thank you for your comment. The committee discussed single dose antibiotic prophylaxis, including dosages. The committee agreed that a single treatment dose is appropriate for single dose prophylaxis when exposed to a trigger, and doses have been amended where necessary to reflect this. The dosages stated for daily antibiotic prophylaxis in the guideline are taken from the BNF (except amoxicillin which is not licensed specifically for preventing UTIs; the dose is half a single treatment dose and was agreed by committee consensus).
41	Chronic Urinary Tract Infection Campaign	Draft guideline	Page 4	1.1.10 Line 17-23	This point advises patents to return if there are symptoms of acute UTI - but no advice on how to distinguish these from ongoing symptoms which may not have resolved. Prophylactic treatment is not appropriate for those who still have unresolved symptoms and infection from an inadequately treated UTI.	Thank you for your comment. The treatment of acute urinary tract infection (UTI) is not covered in this guideline. This is covered by 4 other NICE Antimicrobial Prescribing Guidelines, which include recommendations on treating unresolved symptoms of an acute UTI.
42	Chronic Urinary Tract Infection Campaign	Draft guideline	Page 4 Page 5	1.1.11 Line 26-28 Line 1-10	We have particular concern in the systematic and meta-analyses RCT study provided Muller et al 2017 for recommendation of Nitrofurantoin. This study was based on meta-analyses of short term defined as between 3-14 day courses of antibiotics rather than “at least 3 months” as noted in your guidelines. Additionally, it is noted in Muller’s review that “this review's primary outcome of interest is nitrofurantoin's clinical efficacy, as defined in the respective studies, for therapy of acute UTI at short-term follow-up”. Evidence is therefore guided in this systematic review by acute UTI symptoms rather than recurrence of symptoms which may be defined as ongoing and unresolved rather than reinfection. We also note from the study provided Muller et al 2017 that they state: “Overall, the use of the comparator was more likely to result in microbiological cure than nitrofurantoin (RR 0.93, 95% CI 0.89–0.97), with little heterogeneity (I2=16%). When only double-blind randomized controlled trials were included (results not shown), the comparator still emerged with a more favourable outcome, although the difference was not significant. A further analysis including only studies deemed ‘fair’ in the risk-of-bias and overall quality assessments yielded the same results, but with no statistical significance. The comparator in this instance is stated as “nitrofurantoin at a different dose, frequency or duration”.	Thank you for your comment. We have amended the guideline to reflect the correct follow up period in the evidence from Muller et al., 2017. This was corrected to ‘5 weeks to 24 months’, which was the follow up in the subgroup analysis included in the evidence review. The committee were aware of the limitations of the evidence however, they agreed that a recommendation could be made for antibiotic prophylaxis based on the evidence available.
43	Chronic Urinary Tract Infection Campaign	Draft guideline	Page 5	1.1.12 Line 11-16	We have concerns that there is an assumption of antibiotic resistance to higher dose antibiotics over prophylaxis. Recent published clinical patient research from this year notes that longer term antibiotic treatment is appropriate for patients who report failure on initial antibiotic treatment.	Thank you for your comment. The committee discussed evidence of antibiotic resistance occurring during antibiotic prophylaxis (as detailed in the evidence review). Therefore, the committee agreed it was appropriate to include advice about the risk of resistance with long-term antibiotics and no amendments will be made to the recommendation.

					This clinical research noted disease regression was achieved with a low frequency of AE and no increase in the proportion of resistant bacterial isolates. Clinical research period was 10 years involving a patient cohort of 654 women. Swamy S, Barcella W, De Iorio M, Gill K, Kupelian A, Khasriya R, et al. Recalcitrant chronic bladder pain and recurrent cystitis but negative urinalysis – What should we do? International urogynecology journal. 2018	In relation to the submitted article: • Swamy (2018) did not meet the inclusion criteria based on study type (observational study – case series)
44	Chronic Urinary Tract Infection Campaign	Draft guideline	Page 7	1.3 Line 11-16	Choice of Antibiotic prophylaxis A Cochrane review of 2004 concluded that antibiotic prophylaxis with multiple low-dose antibiotics was effective at reducing the rate of recurrent UTI during prophylaxis when compared to placebo. The review of 19 randomized controlled trials looked at 1120 healthy women in 2004. However, notably, the same review demonstrated that recurrent UTI in the treated group of patients relapsed to match the placebo group when treatments were ceased. A low-dose long-term regime is not sufficient to eradicate the causative agent to prevent further relapse. Inadequate treatment of UTI may actually promote the establishment chronic subclinical-grade infection and increase antimicrobial resistance in the remaining, partially treated infection. Albert X, Huertas I, Pereiro II, Sanfelix J, Gosalbes V, Perrota C. Antibiotics for preventing recurrent urinary tract infection in non-pregnant women. Cochrane database Syst Rev. England; 2004;(3):CD001209.	Thank you for your comment. The highlighted systematic review has been identified and is included in the evidence review (Albert et al. 2004). The committee discussed the evidence on long-term prophylaxis and were aware of the evidence suggesting prophylaxis is only effective whilst treatment is ongoing. However, the committee agreed that antibiotic prophylaxis should be recommended considering the evidence of effectiveness. The committee agreed to amend the recommendation on reviewing treatment success to include more details, including discussing continuing, stopping or changing antibiotic prophylaxis as appropriate.
45	Chronic Urinary Tract Infection Campaign	Draft guideline	Page 9	Line 9-10	“The diagnosis of recurrent UTI should be confirmed by Urine culture” Given the current evidence has found that dipsticks and cultures miss up to 50% of infection how should clinicians manage patients with recurrent UTI, but negative test results? Advice is needed so that this patient group does not suffer unnecessarily because of the failure of the tests. 1. Gill K, Kang R, Sathiananthamoorthy S, Khasriya R, Malone-Lee J. A blinded observational cohort study of the microbiological ecology associated with pyuria and overactive bladder symptoms. Int Urogynecol J. 2018. Epub 2018/02/20. doi: 10.1007/s00192-018-3558-x. PubMed PMID: 29455238. 2. Price et al. The Clinical Urine Culture: Enhanced Techniques Improve Detection of Clinically Relevant Microorganisms. Journal of Clinical Microbiology. May 2016 (54) 5 3. Khasriya and Malone-Lee. The Inadequacy of Urinary Dipstick and Microscopy as Surrogate Markers of Urinary Tract Infection in Urological Outpatients with Lower Urinary Tract Symptoms Without Acute Frequency and Dysuria. Journal of Urololgy. 2010 183(5): 1843–1847 4. Heytens et al. Women With Symptoms of a Urinary Tract Infection but a Negative Urine Culture: PCR-based quantification of Escherichia coli suggests infection in most cases. Clinical Microbiology and Infection. 2017 5. Swerkersson et al. Urinary Tract Infection in Infants: The significance of low bacterial count. Paediatric Nephrology 2016. 31:239–245 6.. Stamm et al. Diagnosis of Coliform Infection in Acutely Dysuric Women. New England Journal of Medicine. 1982 307(8): 463-468	Thank you for your comment. The remit of the guideline does not cover the diagnosis of recurrent UTI. The definition of recurrent urinary tract infection has been amended, by removing the statement “The diagnosis of recurrent UTI should be confirmed by urine culture”. In relation to the submitted articles: • Gill (2018) did not meet the inclusion criteria based on study type (observational study – cohort) • Price (2016) did not meet the inclusion criteria based on intervention type • Khasriya (2010) did not meet the inclusion criteria based on intervention • Heytens (2017) did not meet the inclusion criteria based on intervention • Swerkersson (2016) did not meet the inclusion criteria based on intervention • Stamm (1982) did not meet the inclusion criteria based on date

46	Chronic Urinary Tract Infection Campaign	Draft guideline	Page 9	Terms used in Guideline Line 6-11	We have particular concern regarding the statement that recurrent UTI should be confirmed by urine culture. In all patients with acute symptoms, current medical practice involves initial urinary dipstick testing for leucocyte esterase and nitrites. If acute symptoms are typical, a mid-stream, clean catch urine sample may be sent for culture, despite negative dipstick results. If the symptoms are equivocal (commonly occurring in chronic, non-dysuric LUTS patients) and the initial urinary dipstick is negative, the sample may not be sent for culture at all. Urine culture also has substantial limitations. For largely historical reasons, the gold standard has long been defined as bacterial growth of a single organism at more than 105 CFU/ml, with epithelial cells indicating contamination from the perineum. The 105 CFU/ml threshold was set out by Kass in 1957, and is widely criticized, as his patients' urine samples were collected from only 74 women with acute kidney infections, with bacteria thriving in their urine. Since the late 1950s there have been reports that such a threshold is not sufficiently sensitive to pick up all urinary infections, but the concerns of numerous scholars have been largely ignored by the medical community. In early reports, Stamm and colleagues have demonstrated that the threshold set out by Kass can only pick up 50% of urinary tract infections. They proposed a more sensitive diagnostic criterion of 102 CFU/ml, which has been supported by many others, recent studies. It should also be noted that "mixed growth" culture with evidence of epithelial shedding, in the context of symptomatic, pyuric patients, point to a very significant pathological state, and should not be dismissed as "contaminated samples". Early observations that identical bacterial strains were isolated in every episode of recurrent UTI suggest that there might be a latent, chronic infection periodically flaring up, undetectable by routine microbiological techniques. However, we note that it is felt that with recurrent UTIs occurrence is due to re-infection rather than continuance of the same pathogen (s) not resolved through antibiotic treatment. We must also draw the committee's attention to the following noted in the European Association of Urology Guidelines on Urological Infections 2017 from which some of this guidance is drawn: In patients presenting with typical symptoms of uncomplicated cystitis, urine analysis (i.e. urine culture, dip stick testing, etc.) leads only to a minimal increase in diagnostic accuracy. However, if the diagnosis is unclear dipstick analysis can increase the likelihood of a uncomplicated cystitis diagnosis if leukocytes and nitrite are positive, only nitrite or nitrite and blood are positive or leukocytes and blood are positive. Taking a urine culture is recommended in patients with atypical symptoms, as well as those who fail to respond to appropriate antimicrobial therapy. In patients presenting with symptoms of uncomplicated cystitis a colony count of 103 cfu/mL of uropathogens confirms microbiologically the diagnosis. Based on these notes and our previous comments, we would draw the committee's attention to the fact that most GPs would not have the knowledge to request a lower CFU count for a patient, particularly if the initial dipstick or urine analysis was unclear or negative. If these recommendations are being made by the EAU then it should be reflected in these guidelines.	Thank you for your comment. The remit of the guideline does not cover the diagnosis of recurrent UTI. The definition of recurrent urinary tract infection has been amended, by removing the statement "The diagnosis of recurrent UTI should be confirmed by urine culture". In relation to the submitted articles: • Heytens (2017) did not meet the inclusion criteria based on intervention • Drake (2017) did not meet the inclusion criteria based on study type (narrative review) • Hilt (2014) did not meet the inclusion criteria based on intervention • Price (2016) did not meet the inclusion criteria based on intervention • Khasriya (2010) did not meet the inclusion criteria based on intervention • Deville (2004) did not meet the inclusion criteria based on intervention • Hurlbut (1991) did not meet the inclusion criteria based on date • Gorelick (1999) did not meet the inclusion criteria based on date • Stamm (1982) did not meet the inclusion criteria based on date

					There are serious shortcomings affecting the routine diagnostic tests health practitioners rely on to diagnose UTIs, with many health practitioners unaware of their frequent failures to detect or correctly identify pathogenic bacteria. Heytens et al. Women with Symptoms of a Urinary Tract Infection but a Negative Urine Culture: PCR-based quantification of Escherichia coli suggests infection in most cases. Clinical Microbiology and Infection. 2017 Drake et al. The Urinary Microbiome and Its Contribution to Lower Urinary Tract Symptoms. Neurology and Urodynamics. 2017 36:850–853 22. Hilt et al. Urine Is Not Sterile: Use of enhanced urine culture techniques to detect resident bacterial flora in the adult female bladder. Journal of Clinical Microbiology. 2014 52(3):871-6 Price et al. The Clinical Urine Culture: Enhanced Techniques Improve Detection of Clinically Relevant Microorganisms. Journal of Clinical Microbiology. May 2016 (54) 5 Khasriya and Malone-Lee. The Inadequacy of Urinary Dipstick and Microscopy as Surrogate Markers of Urinary Tract Infection in Urological Outpatients with Lower Urinary Tract Symptoms Without Acute Frequency and Dysuria. Journal of Urololgy. 2010 183(5): 1843–1847 Deville WL, Yzermans JC, van Duijn NP et al: The urine dipstick test useful to rule out infections. A meta-analysis of the accuracy. BMC Urol 2004; 4: 4. Hurlbut TA 3rd and Littenberg B: The diagnostic accuracy of rapid dipstick tests to predict urinary tract infection. Am J Clin Pathol 1991; 96: 582. Gorelick MH and Shaw KN: Screening tests for urinary tract infection in children: a meta-analysis. Pediatrics 1999; 104: e54. Stamm et al. Diagnosis of Coliform Infection in Acutely Dysuric Women. New England Journal of Medicine. 1982 307(8): 463-468	
47	Chronic Urinary Tract Infection Campaign	Draft guideline	Page 9	Terms used in the guideline Line 6-11	This fails to clarify the difference between recurring and recurrent UTI - i.e. UTI where initial infection has not been adequately treated and recurs or repeated new infections in a 12 month period. This difference is clinically vital.	Thank you for your comment. The remit of the guideline does not cover the diagnosis of recurrent UTI. This includes diagnosing the presence of either a relapse (inadequate treatment of initial infection) or a reinfection (repeated new infections). Details on the distinction between relapse and reinfection are included in the background section of the evidence review.
48	Chronic Urinary Tract Infection Campaign	Draft guideline	Page 9	Terms used in the guideline Line 6-11	This point also says that the diagnosis of recurrent UTI should be confirmed by urine culture - but cultures are unreliable and have a high false negative rate. There is no advice regarding the appropriate collection of urine samples (eg not too dilute, what to do if frequency is high) and how to manage a situation where repeated samples are negative/show mixed growth/come back as possibly contaminated. Advice must be given to treat according to symptoms and clinical judgement.	Thank you for your comment. The definition of recurrent urinary tract infection has been amended, by removing the statement “The diagnosis of recurrent UTI should be confirmed by urine culture”.

49	Chronic Urinary Tract Infection Campaign	Draft guideline	Page 18	Line 1-9 Line 27-33	Note that prophylaxis reduces the risk of recurrence of infection whilst ongoing: however once prophylaxis stops the rate of recurrent infections is no different. This suggests that in many cases an original infection is not being adequately eradicated and instead lies dormant until prophylaxis finishes. If this is the case then prophylaxis may increase the risk of antibiotic resistant infection and may be clinically very unwise for this group of patients who instead need extended and adequate treatment for their initial infection. We note also that antibiotic prophylaxis does not reduce the risk of infection recurrence or relapse in under 18s. This is a serious issue and appropriate treatment of this vulnerable patient group is essential.	Thank you for your comment. The committee discussed the evidence on long-term prophylaxis and were aware of the evidence suggesting prophylaxis is only effective whilst treatment is ongoing. However, the committee agreed that antibiotic prophylaxis should be recommended considering the evidence of effectiveness, and amended the recommendation on reviewing treatment success to include more details, including discussing continuing, stopping or changing antibiotic prophylaxis as appropriate. The committee considered the evidence on antibiotic prophylaxis in children, concluding that there was considerable uncertainty in the evidence (all very low quality), as noted in the committee discussion on antibiotic prophylaxis. Therefore, the committee agreed that antibiotic prophylaxis could be considered in children and young people under 16 years, only under specialist advice and when other management options has been unsuccessful.
50	Chronic Urinary Tract Infection Campaign	Draft guideline	Page 26	Antibiotic Dosing and Course length Line 22-27	Concern is raised in light of the poor quality evidence provided. The study is based on one RCT of post-menopausal women. The vaginal and bladder microbiome of post-menopausal women is significantly different to that of pre and peri-menopausal women and an unfair bias has been applied. It has been shown that between 25–35 percent of patients treated according to current guidelines fail treatment (whether prescribed antibiotics for 3 or 14 days). These guidelines offer no GP guidance on how to treat the subgroup who fail to respond. Price TK, Dune T, Hilt EE, Thomas-White KJ, Kliethermes S, Brincat C, et al. The clinical urine culture: enhanced techniques improve detection of clinically relevant microorganisms. J Clin Microbiol. 2016;54(5):1216–22 Wolfe AJ, Toh E, Shibata N, Rong R, Kenton K, Fitzgerald M, et al. Evidence of uncultivated bacteria in the adult female bladder. J Clin Microbiol. 2012;50(4):1376–83	Thank you for your comment. The evidence for antibiotic prophylaxis compared with single dose antibiotics comes from 1 randomised controlled trial (RCT) (Zhong et al. 2011) in post- menopausal women and 1 RCT within a systematic review (Albert et al. 2004) in pre-menopausal women. Therefore, the committee agreed that evidence was available to make a recommendation on antibiotic prophylaxis for women. The committee agreed to amend the recommendation on reviewing treatment success to include more details, including discussing continuing, stopping or changing antibiotic prophylaxis as appropriate. In relation to the submitted articles: • Price (2016) did not meet the inclusion criteria based on intervention type • Wolfe (2012) did not meet the inclusion criteria based on population (women without UTI)
51	Chronic Urinary Tract Infection Campaign	Draft guideline	General		We are surprised not to see any mention of Hipprex (Methenamine) in the long term management of recurrent UTI as there is significant research suggesting it is an effective therapeutic option and an alternative to or addition to antibiotic use in this patient group.	Thank you for your comment. Methenamine hippurate was specifically included by name in the NICE search strategy. We identified evidence on methenamine hippurate compared with nitrofurantoin, which showed effectiveness of nitrofurantoin over methenamine hippurate. No further evidence

						which met the inclusion criteria was identified on this intervention. The committee was also aware that methenamine hippurate is a medicine that is considered less suitable for prescribing (BNF, August 2018). Therefore, they were not able to make a recommendation on its use.
52	National Minor Illness Centre	Visual summary Guideline	1 7	Second purple box 7	The recommendation to “Explain inconclusive evidence that cranberry products and probiotics reduce risk” is ambiguous. How will the patient take this advice? The fact that the clinician has mentioned cranberry products suggests that they might have some value. The word ‘inconclusive’ suggests that there is evidence for but some against and we are still weighing up the need for these products. It would be clearer to say that there is NO evidence that these products help. As a GP I would ask the patient if they are taking anything over the counter and only discuss the issue if they were taking a cranberry product, advising that as we have no evidence to recommend these, they may be wasting their money. If some people do get benefit from cranberry, it may be because it contains D-mannose, in which case they would be better investing in that OTC.	Thank you for your comment. This was discussed by the committee and an amendment has been made to the recommendations on probiotics and cranberry products, which have been separated. This has also been reflected in the visual summary.
53	National Minor Illness Centre	Visual summary Guideline	1 13	Second purple box 12	The case for or against the use of probiotics is more complex as these may help the gut flora recover after an antibiotic treatment as there being “some evidence to support the use of ‘effective strains’” for prevention. As most lower UTIs come from gut bacteria, there is a background rationale for suspecting that probiotics may have a role. Taking these points into consideration, it seems inappropriate to lump together probiotics with cranberry products.	Thank you for your comment. The committee discussed the evidence on probiotics (as described in the committee discussion on self-care) and agreed that evidence was inconclusive. Therefore the committee was unable to make a recommendation on its use, but agreed to provide an explanatory recommendation highlighting the inconclusive evidence. An amendment has been made to the recommendations on probiotics and cranberry products, which have been separated. This has also been reflected in the visual summary.
54	National Minor Illness Centre	Visual summary Guideline	1 14	Dark grey box 13	Self-care will not be implemented unless the clinician knows a dose. This may be sought in the guideline, but even there it is not clear what NICE is recommending. As the recommendation is based on a specific RCT, it would seem reasonable to quite that dose (2g daily with water).	Thank you for your comment. This was discussed by the committee and an amendment has been made to the recommendation on D-mannose to include a footnote describing that a dose of 2g daily with water was used in the study. However, this level of detail has not been reflected in the visual summary.
55	National Minor Illness Centre	Visual summary Guideline	1 9, 13	Light grey box 21, 6	Unless there is any evidence to support the recommendation for adequate fluid intake, the fact that it has been suggested by clinicians in the past is not sufficient reason for continuing what might be a myth. The other suggestions at least have a logical reason behind them. Rather than including “Triggers include sexual intercourse” as a bland statement (leaving it like that implies abstinence as an option to avoid recurrent UTIs), it would be more helpful to replace “adequate fluid intake” with a recommendation to pass urine after sexual intercourse, which at least has a rationale to it.	Thank you for your comment. The committee discussed the comment and amended the recommendation to: advise people with lower UTI about drinking enough fluids to avoid dehydration. The committee discussed fluid intake for prevention of urinary tract infection (UTI), and acknowledged the lack of evidence in this area. However, based on their experience, the committee agreed that water intake is likely to be important for UTI prevention due to the location of potential

						infection. This level of detail has not been included in the visual summary.
56	National Minor Illness Centre	Visual summary	2	Right box	The age range for the dose of trimethoprim, nitrofurantoin and amoxicillin go up to 17 but the table only applies to people under the age of 16.	Thank you for your comment. This has been amended in both the visual summary and guideline.
57	National Minor Illness Centre	Visual summary Guideline	2 8	Right box Table 2	There is no link to a footnote warning not to use nitrofurantoin at term in pregnancy in women under the age of 16, but in other NICE UTI guidelines the box about treating pregnant women goes down to age 12.	Thank you for your comment. This has been amended in both the visual summary and guideline.
58	National Minor Illness Centre	Guideline	29	6	There is a generic manufacturer of pivmecillinam: Aurobindo Pharma - Milpharm Ltd. https://www.medicines.org.uk/emc/product/4982/smpc	Thank you for your comment. The committee discussed pivmecillinam and agreed that it should be removed from the antibiotic recommendations table, based on reserving pivmecillinam use for treatment and safety concerns including carnitine deficiency with long term use.
59	NHS Bath and North East Somerset CCG	Guideline	2	1.1.3	• This should link to the NICE NG12 Bladder cancer guidance which includes referral for people with rUTI	Thank you for your comment. This was considered by the committee and a recommendation has been added to refer adults, young people and children with suspected cancer for specialist assessment and investigations, in line with the NICE guideline on suspected cancer: recognition and referral.
60	NHS Bath and North East Somerset CCG	Guideline	3	1.1.6	• 'Consider D-mannose' guideline advice is based on 1 published trial of 308 women. This does not seem an adequate level of evidence to justify inclusion in this guideline	Thank you for your comment. The committee discussed the evidence on D-mannose and the recommendations have been amended and moved to self-care, to reflect the strength of the limited evidence. However, the committee agreed that there is evidence of some benefit and a recommendation has been made that some women may wish to try D-mannose.
61	NHS Bath and North East Somerset CCG	Evidence	19	21	• Consider D-mannose guideline advice is based on 1 published trial of 308 women. This does not seem an adequate level of evidence to justify inclusion in this guideline	Thank you for your comment. The committee discussed the evidence on D-mannose and the recommendations have been amended, to reflect the strength of the evidence. However, the committee agreed that there is evidence of some benefit and a recommendation has been made that some women may wish to try D-mannose.
62	NHS Bath and North East Somerset CCG	Guideline	13		• Welcome guidance on the use of cranberry products which have to date caused debate at local guideline level	Thank you for your comment.
63	NHS Bath and North East Somerset CCG	Guideline	4	1.1.11	• Advice to use continuous antibiotic prophylaxis vs repeated acute treatment courses: why is the latter approach not included when many microbiologists now have moved to this approach to reduce the risk of/rate of resistance? Zhong et al. (2011) (n=83) is one very small study that does not find a statistical difference between the two groups. Given that continuous prophylaxis has the greatest risk for AMR – should we even be advocating this approach if the former one has failed. The evidence base quoted here is poor.	Thank you for your comment. The committee considered the evidence on single dose compared with long-term prophylaxis and were aware of the quality of the evidence. The committee considered the risk of antimicrobial resistance with long-term antibiotic use, however acknowledged that people in who single dose prophylaxis had

						been unsuccessful required further treatment. Therefore, the committee agreed that daily antibiotic prophylaxis should be given only to women who have had no improvement with single-dose antibiotic prophylaxis or have no identifiable triggers and only to men, pregnant women and children and young people under 16 years with specialist advice when behavioural and personal hygiene measures have been unsuccessful.
64	NHS Bath and North East Somerset CCG	Guideline	8		• What evidence supports the advice to use pivmecillinam for continuous prophylaxis without harm? Clinicians have some concerns about long-term use causing carnitine deficiency and oesophageal erosions and would not choose to include as an option in these guidelines until further evidence of safety is available	Thank you for your comment. The committee discussed pivmecillinam and agreed that there are possible safety issues, including carnitine deficiency. They also discussed reserving pivmecillinam use for treatment rather than prophylaxis. Therefore, pivmecillinam has been removed as an antibiotic choice.
65	Whittington Health NHS Trust	Guideline	9	General	MSU culture and urinary dipsticks miss a significant proportion of urine infections. There is no good means of detecting infection using dipstick and urine culture. These tests are specific because they become positive only in the late stage of the disease. Kass' criteria are affected by spectrum bias and the dichotomous threshold is arbitrary . This diagnostic method has been consistently refuted in literature. This should be acknowledged in the guideline as many patients are not treated due to negative or inconclusive dipstick or culture data. Many peer-reviewed papers highlight the unreliability of the tests Brubaker L, Wolfe AJ. The Female Urinary Microbiota/Microbiome: Clinical and Research Implications. RambamMaimonides medical journal. 2017;8(2).5. Price TK, Dune T, Hilt EE, Thomas-White KJ, Kliethermes S,Brincat C, et al. The clinical urine culture: enhanced techniquesimprove detection of clinically relevant microorganisms. J ClinMicrobiol. 2016;54(5):1216–22. Swamy S, Barcella W, De Iorio M, Gill K, Khasriya R, , Kupelian A, Rohn J, Malone-Lee J. Int Urogynecol J. 2018 Mar 20 Recalcitrant chronic bladder pain and recurrent cystitis but negative urinalysis: What should we do? Kass EH. Bacteriuria and the diagnosis of infection in the urinary tract. ArchInternMed. 1957;100:709-714. Gill K, Kang R, Sathiananthamoorthy S, Khasriya R, Malone-Lee J. A blinded observational cohort study of the microbiological ecology associated with pyuria and overactive bladder symptoms. Int Urogynecol J. 2018. Stamm WE, Counts GW, Running KR, Fihn S, Turck M, Holmes KK. Diagnosis of coliform infection in acutely dysuric women. NEnglJMed. 1982;307(8):463-468. Bartlett RC, Treiber N. Clinical significance of mixed bacterial cultures of urine. American journal of clinical pathology. 1984;82(3):319-322 Latham RH, Wong ES, Larson A, Coyle M, Stamm WE. Laboratory diagnosis of urinary tract infection in ambulatory women. Jama. 1985;254(23):3333-3336. Hooton TM. Practice guidelines for urinary tract infection in the era of managed care. IntJAntimicrobAgents. 1999;11(3-4):241-245 Naber KG, Bergman B, Bishop MC, et al. EAU guidelines for the management of urinary and male genital tract infections. Urinary Tract Infection (UTI)	Thank you for your comment. The remit of the guideline does not cover the diagnosis of recurrent UTI. In relation to the submitted articles: • Brubaker (2017) did not meet the inclusion criteria based on study type (narrative review) • Price (2016) did not meet the inclusion criteria based on intervention (diagnosis) • Swamy (2018) did not meet the inclusion criteria based on study type (observational study – case series) • Kass (1957) did not meet the inclusion criteria based on date • Gill (2018) did not meet the inclusion criteria based on study type (observational study – cohort) • Stamm (1982) did not meet the inclusion criteria based on date • Bartlett (1984) did not meet the inclusion criteria based on date • Latham (1985) did not meet the inclusion criteria based on date • Hooton (1999) did not meet the inclusion criteria based on date • Naber (2001) did not meet the inclusion criteria based on date

					Working Group of the Health Care Office (HCO) of the European Association of Urology (EAU). Eur Urol. 2001;40(5):576-588.	
66	Whittington Health NHS Trust	Guideline	9	General	In the absence of good diagnostic tests, patient history should be considered a strong indicator for infection. Khasriya R, Barcella W, De Iorio M, Swamy S, Gill K, Kupelian A, Malone-Lee J. Lower urinary tract symptoms that predict microscopic pyuria. Int Urogynecol J. 2017 Oct 2. There are important implications in not treating a patient before the MSU test results become available. Diabetics, neurological disorder patients, elderly patients, LUTS and recurrent UTI patients, pregnant population and children can deteriorate significantly and may develop severe pyelonephritis within 48 hours while awaiting results of the cultures. This contributes to a significant proportion of the population so the above statement provided by NICE is indefensible.	Thank you for your comment. This guideline does not cover diagnosis or the treatment of an acute urinary tract infection. In relation to the submitted article: • Khasriya (2017) did not meet the inclusion criteria based on intervention (diagnosis)
67	Whittington Health NHS Trust	Guideline	3	General	It should be made clear that these adjunctive therapies should not be used D mannose is an expensive treatment. and the consumption of such a high concentration of sugars may have other consequences to patients. The data from RCT studies with D mannose are flawed in terms of methodology with no long term data, so the data needs to be interpreted with caution. PHE and HEE leaflets on prevention of UTI are considering removing Cranberry and D mannose. With-holding of antibiotics for such patients will risk prolonging debilitating symptoms and increase the likelihood of sepsis and pyelonephritis. How long will you let such patients 'self care' and 'self-manage?' The section on self-care sends out the wrong message and will endorse practitioner's with-holding treatment. Cochrane Database Syst Rev. 2004;(3):CD001209.Antibiotics for preventing recurrent urinary tract infection in non-pre Cochrane Database Syst Rev. 2004;(3):CD001209.	Thank you for your comment. The committee discussed self-care, including D-mannose and cranberry products and recognised the quality of the evidence. The recommendations on D-mannose have been amended and moved to self-care, to reflect the strength of the limited evidence. However, the committee agreed that there is evidence of some benefit and a recommendation has been made that some women may wish to try D-mannose. The recommendations in this guideline (including self-care) are for the prevention of recurrent urinary tract infection (UTI), not the treatment of acute UTI. Further recommendations indicate that when there has been no improvement with self-care, antibiotic prophylaxis should be considered, and treatment success should be reviewed within 6 months. In relation to the submitted article: • Albert (2004) has been included in the evidence review
68	Whittington Health NHS Trust	Evidence	17		Antibiotic resistance involves complex microbial and environmental factors which should be acknowledged. The consumption of antibiotics is not the only driver of antibiotic resistance. This document does not recognise that **inadequate and sub-therapeutic** doses of antibiotics such as low dose prophylaxis have been linked to multi-drug resistance in diseases such as Tuberculosis (Gumbo T, Louie A, Deziel MR, Liu W, Parsons LM, Salfinger M, et al. Concentration-dependent Mycobacterium tuberculosis killing and prevention of resistance by rifampin. Antimicrobial agents and chemotherapy. 2007;51(11):3781–8. Elliott AM, Berning SE, Iseman MD, Peloquin CA. Failure of drug penetration and acquisition of drug resistance in chronic tuberculous empyema. Tuber Lung Dis. 1995;76(5):463–7). Inadequately treating a UTI may also cause drug resistance. Stopping treatment before the patients symptoms settle is known to be responsible for recurrence of UTI and this may also be contributing to the emerging resistance. A Cochrane review	Thank you for your comment. The dosages for daily and single dose antibiotic prophylaxis have been discussed by the committee. The committee agreed that a single treatment dose is appropriate for single dose prophylaxis when exposed to a trigger, and doses have been amended where necessary to reflect this. The treatment of acute urinary tract infections (UTI) is not covered by this guideline. However, from the evidence base for treating lower UTI (see antimicrobial prescribing guideline on lower UTI), it was not possible to analyse a population with recurrent UTI only. Some studies excluded people with recurrent

					reported symptomatic and microbiological failure rates of 37 and 28% 4–10 weeks after treatment 12. Amongst healthy young women with their first UTI, the risk of recurrence within 6 months is 24%. If they have a history of one or more UTIs, the risk of recurrence rises to 70% in that same year [13]. In a Canadian surveillance study, 14% of 30,851 residents with UTI experienced more than one episode during the 2-year study period, and 2% had six or more episodes [14] Milo G, Katchman EA, Paul M, Christiaens T, Baerheim A, Leibovici L. Duration of antibacterial treatment for uncomplicated urinary tract infection in women. Cochrane Database Syst Rev. 2005;2:CD004682.Google Scholar Foxman B. The epidemiology of urinary tract infection. Nat Rev Urol. 2010;7Google Scholar Laupland KB, Ross T, Pitout JD, Church DL, Gregson DB. Community-onset urinary tract infections: a population-based assessment. Infection. 2007;35(3):150–3. In addition, not treating an infection will cause morbidity for the patient including debilitating urinary symptoms, pain, impact on sleep, work and relationships, as well as increase the risk of pyelonephritis or sepsis.	UTI and others did not, and no sub-group analyses of people with recurrent UTI were presented. In relation to the submitted articles: • Gumbo (2007) did not meet inclusion criteria based on study type (non-intervention, in vitro study) • Elliott (1995) did not meet inclusion criteria based on date • Milo (2005) did not meet inclusion criteria based on population • Foxman (2010) did not meet inclusion criteria based on study type (narrative review) • Laupland (2007) did not meet inclusion criteria based on non-UK based resistance data
69	Whittington Health NHS Trust	Evidence	17	Antibiotic prophylaxis	Long term prophylaxis It should be recognised that there are a cohort of patients (30%) who will not respond to 3-6 months of prophylactic antibiotics and patients who will have recurrence of symptoms after stopping prophylaxis. While there is evidence that self-start antibiotics may be beneficial in treating infection right at the onset, there is no robust data on prophylaxis and emergence of multi drug resistance in patients who have been treated with prophylactic cycling with 3 antibiotics and prophylactic monotherapy. Recalcitrant chronic bladder pain and recurrent cystitis but negative urinalysis: What should we do? Swamy S, Barcella W, De Iorio M, Gill K, Khasriya R, Kupelian AS, Rohn JL, Malone-Lee J. Int Urogynecol J. 2018 Mar 20.; Rambam Maimonides Med J. 2017 Apr 28;8(2). The Female Urinary Microbiota/Microbiome: Clinical and Research Implications. Brubaker L, Wolfe AJ.	Thank you for your comment. The committee were aware of evidence that showed antibiotic prophylaxis is effective at preventing recurrent urinary tract infections, and further evidence that recurrence may return to pre-prophylaxis rates when stopped. The committee agreed to amend the recommendation on reviewing treatment success to include more details, including discussing continuing, stopping or changing antibiotic prophylaxis as appropriate. The committee were aware of the risk of antibiotic resistance with long term prophylaxis, therefore only made recommendations for this intervention when other treatment options had been considered. Stand-by (self-start) antibiotics were named in the NICE search strategy, however we did not identify any evidence on this intervention. Therefore, while the committee recognised that they may have a role in some specialist cases, they were not able to make a recommendation on their use (as described in the committee discussion on antibiotic dosing and course length). In relation to the submitted articles:

						• Swamy (2018) did not meet the inclusion criteria based on study type (observational study – case series) • Brubaker (2017) did not meet the inclusion criteria based on study type (narrative review)
70	Royal College of General Practitioners		3	1.1.6	D-Mannose is never used at present in general practice. There are possibilities of confusing this with mannitol. There are complete de novo training requirements for all GPs and their HCPs if using this effectively as a new evidence based guideline for GPs As this medication is new, there needs to be an explanation of its mechanism of action to explain to clinicians and patients and recommended dosage. There needs to be explanation about its effects on the body and whether it could cause obesity or it's potential effects on people with diabetes. This may be additional paper to support its use in acute urinary tract infections https://www.europeanreview.org/wp/wp-content/uploads/2920-2925-D-mannose-a-promising-support-for-acute-urinary-tract-infections-in-women.-A-pilot-study.pdf	Thank you for your comment. The committee were aware that D-mannose is a nutritional supplement (not a medicine) and is available as a self-care treatment (not for GP prescribing). The recommendations on D-mannose have been amended and moved to self-care, and a footnote has been included in the guideline to state that D-mannose is a sugar that is available to buy and not a medicine. In relation to the submitted article: • Domenici (2016) did not meet the inclusion criteria based on intervention (treatment of acute UTI)
71	Royal College of General Practitioners		8		GPs are likely to be unfamiliar with Pivmecillinam so if this is going to be introduced to the GP formulary and skills via this guideline then pharmacists need to stock it in advance of publication and GPs and their HCPs need full coverage of training in the product: any interactions, contraindications etc for safety reasons cross the UK	Thank you for your comment. The committee discussed pivmecillinam and agreed that it should be removed from the antibiotic recommendations table, based on reserving pivmecillinam use for treatment rather than prophylaxis and safety concerns including carnitine deficiency with long term use.
72	Royal College of General Practitioners		10		States no significant benefit to lactobacillus in recurrent UTI but then says NNT 7 which is reasonable.	Thank you for your comment. With regard to the section on lactobacillus versus placebo, the evidence shows that when analysis of the included studies in the meta-analysis is restricted to 'effective strains' of lactobacillus (as defined by study authors), results were statistically significantly different (RR 0.51, 95% CI 0.26 to 0.99; NNT 7 [95% CI 4 to 64]). However no significant difference was found in risk of recurrent UTI between lactobacillus and placebo in the overall meta-analysis. The review did not provide any information on different strains of lactobacillus.
73	Royal College of General Practitioners				Comment of vaginal pessaries of oestrogen and pessaries in general. In postmenopausal women the vaginal microbiome is different and the mucus etc and the ability of the postmenopausal woman to dissolve pessaries is reduced and creams are potentially better	Thank you for your comment. The recommendation on considering vaginal oestrogen is specifically made for postmenopausal women, as evidence was only identified on this intervention for this specific population. Evidence was identified in postmenopausal women which indicated that both vaginal pessaries of oestrogen and oestrogen creams were effective compared with placebo. Therefore, the committee made a recommendation acknowledging a choice of effective treatment options, which should be discussed with the woman.

74	Royal College of General Practitioners		15		Typo: vagainal oestrogen	Thank you for your comment. This error has been corrected.
75	Royal College of General Practitioners				Did the guidance committee consider special groups such as breast cancer survivors who frequently experience recurrent bacterial cystitis due to oestrogen deficicency. There is a study to evaluate the effectiveness of N-acetylcysteine, D-mannose and Morinda citrifolia fruit extract (NDM), when associated to antibiotic therapy, in reducing the persistence of recurrent cystitis in this risk population. The study shows the combination of NDM and antibiotic therapy showed a greater efficacy in reducing urinary tract infections and urinary discomfort with respect to antibiotic use only. http://iv.iiarjournals.org/content/31/5/931.full	Thank you for your comment. No evidence was identified specifically on treatment of recurrent urinary tract infection in breast cancer survivors, or any other specific groups. Evidence in specific populations would have been included in the evidence review and considered by the committee if identified. In relation to the submitted article: • Marchiori (2017) did not meet the inclusion criteria based on study type (observational – cohort study)
76	UK Clinical Pharmacy Association	Visual summary	General	General	Background should come before treatment advice	Thank you for your comment. The visual summary has been amended to bring background information before treatment advice.
77	UK Clinical Pharmacy Association	Visual summary	General	General	It would be worth mentioning about stand by antibiotic courses or post-coital antibiotics as an option	Thank you for your comment. Stand-by antibiotics were named in the NICE search strategy, however we did not identify any evidence on this intervention. Therefore, while the committee recognised that they may have a role in some specialist cases, they were not able to make a recommendation on their use (as described in the committee discussion on antibiotic dosing and course length). Recommendations on single-dose prophylaxis refer to taking single dose antibiotics upon exposure to triggers, such as sexual intercourse. As there a number of possible identifiable triggers, these have not all been listed in the visual summary.
78	UK Clinical Pharmacy Association	Visual summary	2	Table 2	Where has the dosing for prophylactic amoxicillin in children come from – not listed in BNF-C	Amoxicillin is licensed for treating UTIs, but does not have a specific license for preventing UTIs. This has been added as a footnote to the table. The dose was agreed by committee consensus – in children, the daily prophylaxis dose is half of a single treatment dose. The BNF-C update their content to reflect recommendations from NICE guidelines.
79	UK Clinical Pharmacy Association	Draft Guideline	8	Table	Where has the dosing for prophylactic amoxicillin in children come from – not listed in BNF-C	Amoxicillin is licensed for treating UTIs, but does not have a specific license for preventing UTIs. This has been added as a footnote to the table. The dose was agreed by committee consensus – in children, the daily prophylaxis dose is half of a single treatment dose. The BNF-C update their content to reflect recommendations from NICE guidelines.

80	UK Clinical Pharmacy Association	General	General	General	Nitrofurantoin suspension is ~ £450 per bottle. In secondary care we tend to reserve this as a second line option for prophylaxis in children. Although we want to encourage the use of narrow spectrum agents such as trimethoprim / nitrofurantoin in reality cefalexin may be prescribed in preference to nitrofurantoin if the child cannot swallow tablets / capsules due to cost pressure. However appreciate that cephalosporins now classed as Watch antibacterials whereas nitrofurantoin classed as Access.	Thank you for your comment. The committee considered the cost of nitrofurantoin, however agreed that it should be recommended as first choice antibiotic prophylaxis, alongside trimethoprim. This was based on committee experience and evidence of effectiveness. The committee were also aware that nitrofurantoin and trimethoprim have less effect on the normal intestinal microflora in the gastrointestinal tract compared with other antibiotics.
81	UK Clinical Pharmacy Association	General	General	General	Since antimicrobials listed have wide therapeutic ranges in practice it is preferable to use the dose banding rather than the ml/kg dosing in most cases even if children are considered small for their age, this allows for ease of administration and improves adherence. We need to try to avoid unnecessarily complex dosing such as 2.6ml.	Thank you for your comment. The committee discussed the comment and made no changes. Doses for children are given as in the BNF for Children, where doses based on both age bands and mg/kg are given for some medicines.
82	Royal College of Pathologists	Guideline	General	General	All five guidelines have insufficient discussion on the diagnosis of urinary tract infections. All five guidelines start with an assumption that a correct clinical diagnosis of UTI has been made. In practice, this aspect of UTI management is probably the most problematic.	Thank you for your comment. The remit of this guidance is the management of common infections not diagnosis.
83	Royal College of Pathologists	Guideline	2	1.1.2	Recommend include interstitial cystitis (bladder pain syndrome) as a differential diagnosis of recurrent UTI	Thank you for your comment. The remit of this guidance is the management of common infections not diagnosis.
84	Royal College of Pathologists	Guideline	5	1.1.11, 1.1.13	In section on any further investigations (for example, ultrasound), can you provide more guidance on what these further investigations might be?	Thank you for your comment. This recommendation has not been amended as the committee agreed that a number of further investigations may be needed depending on the individual, and these should be chosen by the clinician.
85	Royal College of Pathologists	Guideline	7	1.2.1	Is there any evidence that verbal and written advice about behavioural and personal hygiene measures is an effective intervention? Are symptoms and trigger diaries useful?	Thank you for your comment. The committee made this recommendation by consensus based on their clinical experience, as this may help to reduce the risk of UTI. The committee was not able to make more specific recommendations, for example about symptom and trigger diaries.
86	Royal College of Pathologists	Guideline	7	1.3.2	Recommend remove “ or other agreed time”. This could drift into never review.	Thank you for your comment. The committee discussed the review period for antibiotic prophylaxis and agreed a specific time frame was appropriate for review. The recommendation has been amended to remove ‘or other agreed time’.
87	Royal College of Pathologists	Guideline	General	General	The evidence review provides very little support for the effectiveness of antibiotic prophylaxis, and it is disappointing to see such a strong support for prophylaxis in the guideline. There appears to have been insufficient consideration of the public health consequences of antibiotic resistance in the support for prophylaxis.	Thank you for your comment. The committee considered the evidence on antibiotic prophylaxis, which showed antibiotic prophylaxis was effective for preventing urinary tract infection, and were aware of the quality of the evidence. The committee considered the risk of antimicrobial resistance with antibiotic use, and therefore agreed that antibiotic prophylaxis should only be considered when other management options had not been successful. Therefore, the

						recommendations on antibiotic prophylaxis have not been amended.
88	Royal College of Pathologists	Guideline	10	Cranberry products	The possibility of harm (impairment of diabetes control, dental caries) from the high sugar content of cranberry product should be included in this section	Thank you for your comment. The committee considered the high sugar content of cranberry products and agreed to include a statement that people choosing to take cranberry products should consider them as part of their daily sugar intake.
89	Royal College of Pathologists	Guideline	11	D-mannose	There are reports of impairment of blood sugar control in diabetes taking D-mannose	Thank you for your comment. The committee considered the high sugar content of D-mannose and agreed to include a statement that people choosing to take D-mannose should consider this as part of their daily sugar intake.
90	British Society for Antimicrobial Chemotherapy	Guideline	General	General	No definition of what constitutes recurrent UTIs warranting treatment	Thank you for your comment. This guideline provides recommendations on the treatment of recurrent urinary tract infection as defined in the 'terms used in this guideline' section.
91	British Society for Antimicrobial Chemotherapy	Guideline	General	General	Need red flags for further investigation/ urology referral	Thank you for your comment. The focus of the guideline is managing recurrent UTI, however the committee agreed to include a recommendation to seek specialist advice for women aged 16 years and over with recurrent lower UTI if the underlying cause is unknown or requires further investigation.
92	British Society for Antimicrobial Chemotherapy	Guideline	General	General	Over negative re the use of vaginal oestrogen quoting the BNF re: risks of oestrogen & cardiovascular disease & DVT etc – but the risks for topical oestrogen are not the same as oral & supposedly a year's supply of topical oestrogen is equivalent to having one tablet of standard HRT.(Santen R J : vaginal administration of estradiol: effects of dose, preparation & timing on plasma estradiol levels. Climacteric 2015 Apr18 (2):121-34)	Thank you for your comment. Evidence was identified that vaginal oestrogen is associated with more adverse events than placebo or oral antibiotics. There is also consideration made to topical vaginal oestrogens in BNF which states that endometrial safety of long-term or repeated use is uncertain (BNF, June 2018). The committee agreed that it would be unethical practice not to warn women of possible adverse effects, which comes from the BNF and summary of product characteristics on hormone replacement therapy in oral or topical forms. In relation to the submitted article: • Santen (2015) did not meet the inclusion criteria based on population
93	British Society for Antimicrobial Chemotherapy	Guideline	General	General	The choice should be identical to that suggested in the PHE Primary Care Guidelines.	Thank you for your comment. NICE are aware of the important role played by Public Health England guidance on the treatment of UTI. We have worked closely with Public Health England to produce this guideline and the NICE antimicrobial prescribing guidelines will replace the PHE guidance as they are published.
94	Aspire Pharma	Draft Guideline	General	N/A	iAluRil (sodium hyaluronate 1.6%/ sodium chondroitin 2%) has not been included as a treatment option prior to prophylactic antibiotics despite evidence that it is an effective treatment for the prevention of rUTIs (recurrent	Thank you for your comment. The committee prioritised non-antimicrobial interventions to be included in the evidence review for this guideline, based on the interventions which

					urinary tract infections) and is superior to placebo and non-inferior to prophylactic antibiotics. The quality of the evidence is discussed in relation to each of the papers excluded from the search criteria. In 2013/14 the NHS spent £434 million on treating 184,000 hospital admissions for UTI. (1) Antibiotic resistance rates are increasing and are a public health concern (2). iAluRil offers a real non-antimicrobial alternative to prophylactic antibiotics to treat rUTIs and should be considered in this guideline despite the 'interventional' nature of GAG (glucosaminoglycan) therapy. Considering the widespread and long-term impact of antibiotic resistance, it is important that clinicians should be recommended to consider all valid therapy options (interventional or not) and that antibiotic prophylaxis should be considered a last resort treatment. In 2018, an iAluadaptor will be included within the iAluRil package, which will allow for direct insertion into the urethra, avoiding the need for catheterisation. The adaptor is inserted into the external urethral orifice and the sealing collar allows for instillation without leaks. (3) The iAluRil pre-filled syringe, is attached to the adaptor and is administered, coating the urethra and bladder with iAluRil. This will minimise the 'interventional' nature of the product and will allow for self-administration by patients. A change to the leaflet to update to allow patients to self-administer is also pending with the Notified Body. Considering the above, we consider that iAluRil should be recommended to patients, who have had a history of rUTI (three episodes within the last 12 months or 2 within the last 6 months). Patients should be prescribed iAluRil to prevent recurrence of UTI after their last UTI bout has been cleared with antibiotics. As mentioned previously, this course of treatment should be considered prior to prescribing antibiotic prophylaxis. References: 1. MTG Press release Nov 2015 (http://www.mtg.org.uk/wp-content/uploads/2016/07/Admissions-of-Failure-report-release-FINAL-131115-1.pdf) 2. PHE Published Dec 2015 (https://www.gov.uk/government/publications/health-matters-antimicrobial-resistance/health-matters-antimicrobial-resistance) 3.ialuadaptor patent (https://patents.google.com/patent/WO2017046621A4/en)	are in common use in UK practice. iAluRil was not included as a prioritised intervention as it is not in common use and therefore has not been considered in the guideline. In relation to the submitted articles: • MTG Press release Nov 2015 did not meet the inclusion criteria based on study type • PHE (2015) did not meet the inclusion criteria based on study type • ialuadaptor patent did not meet the inclusion criteria based on study type
95	Aspire Pharma	Evidence review Appendix J: Excluded studies	92	Study reference Damiano et al (2011) Prevention of recurrent UTIs by intravesical administration…	Exclusion based on 'poor relevance against search terms (intervention)'. The study by Damiano et al is a placebo controlled randomised study comparing instillation of iAluRil against instillation of a placebo (Sodium chloride). Results after 12 months, showed that mean time to UTI was reduced by 86.6% in patients given iAluRil versus 9.6% in patients administered placebo. This equated to a mean time to UTI of 185.2 days (~6 months) for iAluRil and 52.7 days for placebo. This was a statistically significant reduction in the number of recurrent UTIs in patients over a year. One hundred percent of patients, who received placebo experienced at least one UTI within the study period.	Thank you for your comment. The committee prioritised non-antimicrobial interventions to be included in the evidence review for this guideline based on the interventions which are in common use in UK practice. iAluRil was not included as a prioritised intervention as it is not in common use and therefore has not been considered in the guideline. In response to concerns regarding the prioritised non-antimicrobial interventions, the committee has discussed the evidence on

					The placebo within this study was saline solution, which was considered as part of this guidance as a treatment option. Only minor adverse events were seen in this study for three patients treated with iAluRil. Comparing this with the reduction seen for D-Mannose, a recommended nutritional treatment, in which there is no defined pharmacokinetic data or dose. Patients were removed from the study, once a UTI was diagnosed, therefore, no mean UTIs per year can be provided. Over the 6-month period, 15/100 patients experienced UTI episodes versus 62/100 patients for no treatment. Of those that did experience a UTI on prophylaxis treatment, the median time to onset of symptoms was 30 days. 38 patients, in whom no treatment was provided, did not experience a UTI in 6 months. (1) Use of vaginal oestrogen administration has also been recommended, despite its use being off-label. Recommended vaginal application methods include, cream (two RCTs (randomised controlled trials), first reduced the risk of rUTI by 75% against placebo and the second looked at only 3 months treatment but was shown to be superior to prophylactic antibiotics), vaginal ring (reduced risk of rUTI by 36% compared with placebo) and pessaries (which increased the risk of recurrence compared with prophylactic antibiotics). Despite strong evidence for the use of vaginal oestrogen creams, more adverse events were experienced compared with treatment of oral antibiotics. There is also an increased risk of venous thromboembolism, stroke, endometrial cancer etc (as quoted in page 15 of the draft consultation) when using oestrogen. The paper by Damiano et al does not include results of UTI frequency at 6 months, however, during the 6-month instillation period, 63 UTI episodes were experienced in the control group, whereas only 6 UTI episodes were recorded in the treatment group. Additionally, considering that very few adverse events are experienced by patients on iAluRil the recommendation of a medical device prior to an uncontrolled nutritional or off-label medication with safety concerns should be preferred. References: Kranjcec et al (2014) https://link.springer.com/article/10.1007/s00345-013-1091-6	D-mannose and the recommendations have been amended, to reflect the strength of the evidence. However, the committee agreed that there is evidence of some benefit and a recommendation has been made that some women may wish to try D-mannose. The committee discussed the safety data for vaginal oestrogens and agreed that based on evidence of effectiveness, a recommendation could be made on its use, only after no improvement after taking behavioural and personal hygiene measures and taking into account all the safety concerns on an individual patient basis. In relation to the submitted article: • Kranjcec (2014) is included in the evidence review
96	Aspire Pharma	Evidence review Appendix J: Excluded studies	92	Study reference De Vita et al (2012) Effectiveness of intravesical hyaluronic acid… a randomised study	Exclusion based on ‘poor relevance against search terms (intervention)’. This study shows that after 12 months treatment, UTI recurrence reduced to 1/ year (6.3 pre-trial) versus 2.3/ year on prophylactic antibiotics (5.9/ year pre-trial). This equates to an 84% reduction in rUTI when patients were treated with iAluRil. From discussions with the author, the two patients lost to follow-up were not for reasons of adverse events or lack of efficacy. A follow-up study has just been published which presents the results three years post-treatment (1). This shows that the benefits experienced after 12 months, are maintained 3 years later, with a mean frequency of 0.9 UTIs/year. No adverse events were recorded for iAluRil in this study. A metanalysis of 7 trials, showed that the risk of rUTI was reduced by 85% with prophylaxis antibiotics (0-0.9 recurrences/year). (2) After discontinuing prophylaxis, women were found to revert to their previous frequency, (3) and	Thank you for your comment. The committee prioritised non-antimicrobial interventions to be included in the evidence review for this guideline based on the interventions which are in common use in UK practice. iAluRil was not included as a prioritised intervention as it is not in common use and therefore has not been considered in the guideline. The committee discussed the evidence on long-term prophylaxis and were aware of the evidence suggesting prophylaxis is only effective whilst treatment is ongoing. However, considering the evidence of effectiveness, the committee agreed that antibiotic prophylaxis should be recommended. The committee agreed to amend the recommendation on reviewing

					years of daily use of nitrofurantoin can cause pulmonary toxicity even at low doses (common side effects include nausea and candidiasis). (4) Nitrofurantoin has been recommended as first line therapy alongside trimethoprim in this guideline, due to increasing resistance to trimethoprim. Prophylactic therapy with Trimethoprim showed resistant organisms after two weeks of treatment in 95% of healthy volunteers (5) Resistant strains to nitrofurantoin have been detected in the Northwest of England (6), therefore, further widespread use as prophylaxis is likely to spread these resistant strains, despite the low propensity for Nitrofurantoin to develop resistance. Considering that recurrence of UTI was found to revert to its previous frequency post-treatment for antibiotic prophylaxis, this demonstrates that prophylactic antibiotics are not a long-term solution for rUTIs. Considering, that within this small placebo-controlled trial, long-term effects of iAluRil have been shown, this further supports our position that iAluRil should be used prior to administration of prophylactic antibiotics. References: De vita et al Long-term efficacy of intravesical instillation of hyaluronic acid/chondroitin sulfate in recurrent bacterial cystitis: 36 months' follow-up Clin Exp Obstet Gynecol (2018) (doi: 10.12891/ceog4571.2018) Albert X et al Antibiotics for preventing recurrent urinary tract infection in non-pregnant women. Cochrane Database syst rev 2004 (3) Dason et al Guidelines for the diagnosis and management of recurrent urinary tract infection in women Can Urol Assoc J 2011 5(5): 316-322 Gupta & Trautner, Diagnosis and management of recurrent urinary tract infections in non-pregnant women 2013 346:f3140 Murray, B.E. et al. Emergence of high-level trimethoprim resistance in fecal Escherichia coli during oral administration of trimethoprim or trimethoprim—Sulfamethoxazole. N. Engl.J. Med. 1982, 306, 130–135. Gibreel et al Population structure, virulence potential and antibiotic susceptibility of uropathogenic Escherichia coli from Northwest England J Antimicrob chemother 2012 67(2): 346-356	treatment success to include more details, including discussing continuing, stopping or changing antibiotic prophylaxis as appropriate. The committee discussed the risks of antimicrobial resistance with antibiotic prophylaxis using nitrofurantoin and trimethoprim. However based on the evidence of efficacy, their experience and resistance data, the committee agreed that nitrofurantoin and trimethoprim were appropriate as first choice antibiotics. The recommendation has been amended to include taking account of local resistance data to help mitigate the spread of antibiotic resistance. In relation to the submitted articles: • De Vita (2018) did not meet the inclusion criteria based on intervention • Albert (2004) is included in the evidence review • Dason (2011) did not meet the inclusion criteria based on study type (other guidance) • Gupta and Trautner (2013) did not meet the inclusion criteria based on study type (narrative review) • Murray (1982) did not meet the inclusion criteria based on date • Gibreel (2011) did not meet the inclusion criteria based on outcomes reported
97	Aspire Pharma	Evidence review Appendix J: Excluded studies	92	De vita et al (2012) Effectiveness of intravesical hyaluronic acid… a metanalysis	Exclusion based on 'poor relevance against search terms (intervention)'. Four studies were identified in this meta-analysis and the results as presented were shown not have been impacted by publication bias. A significant decrease in UTI rate per person year was shown with a mean of -3.41/year (CI: -4.33 to -2.49) compared with pre-treatment. A significant increase in the time to UTI was also found (compared with pre-treatment values) 187.35 days (CI 94.33 – 280.37 days). Therefore, we consider the results of this study should have been included to support the use of GAG therapy, and in particular, iAluRil for the treatment of rUTIs.	Thank you for your comment. The committee prioritised non-antimicrobial interventions to be included in the evidence review for this guideline, based on the interventions which are in common use in UK practice. iAluRil was not included as a prioritised intervention as it is not in common use and therefore has not been considered in the guideline.
98	Aspire Pharma	Evidence review	General	N/A	The following studies have not been identified as part of the search even though they fulfil the following criteria: 'Urinary tract infections' AND 'Bladder instillation' AND 'observational studies'. Summarised in the section below are the following papers:	Thank you for your comment. Observational studies were included in the search strategy, however as sufficient evidence was identified in each area of interest from systematic reviews and RCTs, we did not include observational studies in the evidence review. The committee prioritised non-antimicrobial

					Cicione et al Intravesical treatment with highly concentration hyaluronic acid and chondroitin sulphare in patients with recurrent urinary tract infections: results from a multicentre study Can Urol Assoc J 2014 8(9-10):e721-7 Gugliotta et al Is intravesical instillation of hyaluronic acid and chondroitin sulfate useful in preventing recurrent bacterial cystistis? A multicentre case control analysis Taiwan J Obsete Gynecol 2015 54(5):537-540 Torella et al Intravesical therapy in recurrent cystitis: a multi-center experience J infect Chemother 2013 19(5):920-5 In a retrospective cohort study, 157 patients treated with iAluRil were followed for 12 months. After 12 months therapy, the mean time to rUTI had increased to 178.4 days compared with 94.8 days pre-treatment. The rUTI rate had also decreased to 0.44 UTIs/ year compared with 4.13 UTIs/year pre-study. (1) In a retrospective study by Gugliotta et al, at the 12-month follow-up after treatment with iAluRil or sulfamethoxazole/trimethoprim, 36.7% and 21.0% of patients were UTI free respectively. (2) No serious adverse events were reported during this trial. Finally, Torella et al, was a retrospective-prospective analysis comparing instillation of sodium hyaluronate plus chondroitin sulfate (iAluRil) versus prophylactic Fosfomycin treatment or combined treatment with both iAluRil and Fosfomycin. Using iAluRil increased the number of patients who were UTI free to 72.7% for iAluRil alone, 75% for combined treatment versus 30.4% for Fosfomycin only. (3) No adverse events were recorded for patients of iAluRil during this trial. Considering the depth of literature supporting the use of GAG therapy, in particular iAluRil, we consider that this should be considered as a treatment for rUTIs prior to antibiotic prophylaxis to minimise resistance to antibiotics.	interventions to be included in the evidence review for this guideline. iAluRil was not included as a prioritised intervention and therefore has not been considered in the guideline. In relation to the submitted articles: • Cicione (2014) did not meet the inclusion criteria based on study type (observational – cohort study) • Gugliotta (2015) did not meet the inclusion criteria based on study type (observational – cohort study) • Torella (2013) did not meet the inclusion criteria based on intervention
99	Healthcare Infection Society	Guideline	General	General	The guideline needs a clear definition of recurrent UTI at the start (not hidden in definitions near the end).	Thank you for your comment. The list of terms used in the guideline will be clear in the final published online version of the guideline. A hyperlink is also used to take users directly to the definition.
100	Healthcare Infection Society	Guideline	General	General	For lower-tract infection, it needs to include symptomatic infections (with LUTS, i.e. not non-specific symptoms) and culture confirmation (i.e. not positive dipstick), and make it explicit that ASB is excluded.	Thank you for your comment. This guideline does not consider the treatment of symptomatic infections, or diagnosis. Recurrent UTI is defined in adults as repeated UTI with a frequency of 2 or more UTIs in the last 6 months or 3 or more UTIs in the last 12 months. Recurrent UTI is diagnosed in children and young people under 16 years if they have: • 2 or more episodes of UTI with acute pyelonephritis/upper UTI, or • 1 episode of UTI with acute pyelonephritis plus 1 or more episode of UTI with cystitis/lower UTI, or • 3 or more episodes of UTI with cystitis/lower UTI. See the NICE guideline on urinary tract infection in under 16s.

						UTI is a separate diagnosis from asymptomatic bacteriuria and therefore is not covered by this guideline.
101	NNEdPro Global Centre for Nutrition and Health				The recommendation on cranberry acknowledges the widespread use of cranberry and the potential benefit on reducing antibiotic resistance. The guidance states that the evidence is inconclusive about whether cranberry products reduce the risk of UTI in people with recurrent UTI, based on the single systematic review and meta-analysis of randomised controlled trials by Jepson et al. (2012) where cranberry products were compared with placebo, no treatment or antibiotics. The main issue with this source of evidence is that the studies that met the inclusion criteria were classified by GRADE as low quality and the observed effects were weak. Furthermore, there was a marked heterogeneity in the populations in these studies (pregnant women, elderly individuals) and in the design of RCTs thus limiting the interpretation of the pooled findings. As there is the potential for cranberry to be a widely acceptable (with patients/public), scalable and low cost intervention that could be recommended at a public health/population level, if the evidence becomes available to support this, we believe this is an area for health professionals/NICE to keep under active review as further data becomes available. Support should therefore be expressed to encourage the undertaking of well-designed studies into the effects of cranberry, the mechanistic role of cranberry components and impact on recurrent UTIs in different populations in appropriately powered and scaled studies, so as to account for inter-individual variation. Additional research that we believe meets the inclusion criteria and therefore can already be considered includes: Fu Z et al. Cranberry Reduces the Risk of Urinary Tract Infection Recurrence in Otherwise Healthy Women: A Systematic Review and Meta-Analysis. Journal of Nutrition. 2017;147(12):2282-2288. Luís, Ângelo et al. Can Cranberries Contribute to Reduce the Incidence of Urinary Tract Infections? A Systematic Review with Meta-Analysis and Trial Sequential Analysis of Clinical Trials. The Journal of Urology. Sept 2017;198(3):614–621. Roshdibonab F, Mohammadbager FazlJoo S, Torbati M, Mohammadi Gh, Asadloo M, Noshad H. The Role of Cranberry in Preventing Urinary Tract Infection in Children; a Systematic Review and Meta-Analysis. Int J Pediatr 2017; 5(12): 6457-68. DOI: 10.22038/ijp.2017.27041.2327.	Thank you for your comment. The literature search was conducted before the publication of the systematic reviews by Fu et al. (2017) and Roshdibonab et al. (2017). Following consideration, these systematic reviews have been included and the evidence has been considered by the committee alongside the evidence on cranberry products that was already included, and changes have been made to the recommendations. The committee agreed that there is uncertain evidence of benefit for cranberry products, but some women who are not pregnant may wish to try them. In relation to the other submitted article: • Luis A (2017) meets the inclusion criteria but has been deprioritised as a higher quality systematic review covering the same intervention has been prioritised (Fu 2017)
102	NNEdPro Global Centre for Nutrition and Health				The recommendation on cranberry acknowledges the widespread use of cranberry and the potential benefit on reducing antibiotic resistance. The guidance states that the evidence is inconclusive about whether cranberry products reduce the risk of UTI in people with recurrent UTI, based on the single systematic review and meta-analysis of randomised controlled trials by Jepson et al. (2012) where cranberry products were compared with placebo, no treatment or antibiotics. The main issue with this source of evidence is that the studies that met the inclusion criteria were classified by GRADE as low quality and the observed effects were weak. Furthermore, there was a marked heterogeneity in the populations in these studies (pregnant women, elderly individuals) and in the design of RCTs thus limiting the interpretation of the pooled findings.	Thank you for your comment. The literature search was conducted before the publication of the systematic reviews by Fu et al. (2017) and Roshdibonab et al. (2017). Following consideration, these systematic reviews have been included and the evidence has been considered by the committee alongside the evidence on cranberry products that was already included, and changes have been made to the recommendations. The committee agreed that there is uncertain evidence of benefit for cranberry products, but

					As there is the potential for cranberry to be a widely acceptable (with patients/public), scalable and low cost intervention that could be recommended at a public health/population level, if the evidence becomes available to support this, we believe this is an area for health professionals/NICE to keep under active review as further data becomes available. Support should therefore be expressed to encourage the undertaking of well-designed studies into the effects of cranberry, the mechanistic role of cranberry components and impact on recurrent UTIs in different populations in appropriately powered and scaled studies, so as to account for inter-individual variation. Additional research that we believe meets the inclusion criteria and therefore can already be considered includes: Fu Z et al. Cranberry Reduces the Risk of Urinary Tract Infection Recurrence in Otherwise Healthy Women: A Systematic Review and Meta-Analysis. Journal of Nutrition. 2017;147(12):2282-2288. Luís, Ângelo et al. Can Cranberries Contribute to Reduce the Incidence of Urinary Tract Infections? A Systematic Review with Meta-Analysis and Trial Sequential Analysis of Clinical Trials. The Journal of Urology. Sept 2017;198(3):614–621. Roshdibonab F, Mohammadbager FazlJoo S, Torbati M, Mohammadi Gh, Asadloo M, Noshad H. The Role of Cranberry in Preventing Urinary Tract Infection in Children; a Systematic Review and Meta-Analysis. Int J Pediatr 2017; 5(12): 6457-68. DOI: 10.22038/ijp.2017.27041.2327.	some women who are not pregnant may wish to try them. In relation to the other submitted article: • Luis A (2017) meets the inclusion criteria but has been deprioritised as a higher quality systematic review covering the same intervention has been prioritised (Fu et al. 2017)