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Use of *Lactobacillus* spp. to prevent recurrent urinary tract infections in females

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ABSTRACT

Urinary tract infections (UTIs) are the most common bacterial infections seen in the community, especially amongst females. The widespread use of antibiotics has led to the increased occurrence of *E. coli* resistant isolates worldwide. A promising non-antibiotic approach is the use of probiotic lactobacilli strains. This paper hypothesizes that *Lactobacillus* spp. containing products are able to prevent recurrent urinary tract infections in females. Using the keywords [lactobacillus OR lactobacilli OR probiotic] and [urinary tract infection OR UTI OR cystitis], a preliminary search on the PubMed, Ovid, Google Scholar and ClinicalTrials.gov database yielded 1,647 papers published in English between 1-Jan-1960 and 1-May-2017. 9 clinical trials with a total of 726 patients were reviewed. Different lactobacilli strains (in either oral or suppository formulation) were utilized and they demonstrated varying efficacy in the prevention of recurrent UTIs. Using a random-effects model, pooled risk ratio of at least one recurrent UTI episode during the entire study duration was 0.684 (95% CI 0.438 to 0.929, $p < 0.001$), per-protocol analysis. However, key limitations include significant inter-study variability and the limited duration of follow-up of most studies. Our hypothesis on the chemoprophylactic effects of probiotics for UTIs is plausible and supported by current data. *Lactobacillus rhamnosus* GR1 and *Lactobacillus reuteri* RC14 were the most commonly studied lactobacilli strains. Further and more robust randomized controlled trials with standardized lactobacilli strains and formulation are required for confirmation of effects.

Introduction

Urinary tract infections (UTIs) are commonly occurring community-based infections associated with a significant healthcare burden [1–3]. Anatomical and physiological risk factors predispose women to UTIs, with an estimated 1 in 2 women contracting a UTI during her lifetime. 30% of these women experience recurrent infections and go on to contract a minimum of three further symptomatic UTIs per year [2]. Urgency, frequency and dysuria are the three major hallmarks of a UTI and drastically reduce the quality of life of those affected. Treatment is currently centred on the use of antibiotics. However, rising rates of antibiotic resistance coupled with increasing UTI recurrence call for the development of new and effective treatment strategies to combat their prevalence.

Seventy to ninety-five percent of UTIs can be attributed to gram-negative *Escherichia coli* (*E. coli*) originating from intestinal microflora [1–3]. *E. coli* colonize the vaginal and periurethral environments, ascend the urethra to the bladder causing cystitis or even up the ureters into the kidneys leading to pyelonephritis. A short course of antibiotics is the treatment of choice for acute, symptomatic UTIs while post-coital or monthly courses of antibiotics are used as prophylaxis against recurrent UTIs (rUTIs). Antimicrobial selection is based on local patterns of sensitivity, with quinolones being the most popular choice. In recent years, indiscriminate use of antibiotics, especially quinolones, has spearheaded bacterial resistance to antimicrobial treatments. Data from the World Health Organisation (WHO) suggests that more than 50% of uropathogens are resistant to quinolones, with an alarming proportion of *E. coli* strains being multi-drug resistant [4]. Lack of effective antimicrobial treatment can prolong the duration and severity of UTIs and thereby increase the already extensive socioeconomic costs associated with the disease [1].

Current research focuses on using non-antimicrobial treatments for the prevention of recurrent UTIs [5–9]. Vaginal suppositories containing lactobacilli present a promising new avenue of research as

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maintenance of normal vaginal flora (comprising largely of lactobacilli) is associated with reduced rates of UTI recurrence [8,9]. *Lactobacillus* suppositories aim to restore normal vaginal flora and exert a protective effect against UTIs by four main mechanisms: 1) releasing antimicrobial substances such as lactic acid, 2) out-competing pathogenic bacteria like *E. coli*, 3) preventing the adhesion of pathogens to epithelial cells and 4) non-specific activation of the innate immune system [5–9]. In addition to preventing bacterial resistance, *Lactobacillus* suppositories eliminate the side effects of long-term antibiotic use such as yeast vaginitis [9]. The protective barrier they form against uropathogens inherently reduces susceptibility to UTIs and further differentiates *Lactobacillus* suppositories from standard prophylactic antibiotics.

Given the many advantages of probiotic products (either oral or suppository formulation), several clinical trials have tested their efficacy in preventing recurrent UTIs. Results have thus far yielded conflicting results [5–9]. The last meta-analysis, conducted in 2012, analysed data from only five studies and found no statistically significant difference in the risk for rUTI in patients receiving *Lactobacillus* products compared to controls [10]. Through an up-to-date review of available literature, we aimed to re-examine and evaluate our hypothesis that products containing *Lactobacillus* spp. are able to prevent rUTIs in females.

Hypothesis

Products containing *Lactobacillus* spp. are able to prevent recurrent urinary tract infections in females.

Evaluation of hypothesis

Literature search was done in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Using the keywords [lactobacillus OR lactobacilli OR probiotic] and [urinary tract infection OR UTI OR cystitis], a preliminary search on the PubMed, Ovid, Google Scholar and ClinicalTrials.gov database yielded 1647 papers published in English between 1-Jan-1960 and 1-May-2017. Grey literature was not searched. Title/abstract screening were performed independently by the researchers to identify articles of interest. For relevant abstracts, full articles were obtained, reviewed and also checked for references of interest.

Full articles were reviewed by three researchers for inclusion. Any disagreement was resolved by discussion and consensus amongst the three researchers. The inclusion criteria for this review were: (1) published clinical trial, (2) specified dose of probiotic was administered as an active intervention, and (3) female subjects with clearly defined recurrent UTIs. Methodological quality of the eligible clinical trials was appraised using the Cochrane Collaboration's tool for assessing risk of bias [11] of randomized controlled trials.

Data such as study design, study population and demographics and outcome measures were extracted. The primary outcome measures of interest were prophylactic efficacy and safety/incidence of adverse effects. For each eligible study, risk ratio of at least one recurrent UTI episode during the study period was calculated, comparing lactobacilli prophylaxis and placebo/control, per-protocol analysis. All analyses were done using MedCalc Statistical Software version 14.8.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2014).

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

The abstraction process was illustrated in Fig. 1. The key characteristics of each study were extracted and summarized in Table 1. Three studies were excluded from the final meta-analysis as two of them were open, uncontrolled trials with a high risk of bias and one compared lactobacilli prophylaxis to a historic control.

Three of the 9 clinical trials were open trials, one of which was a non-randomized, non-controlled pilot study (Table 2).

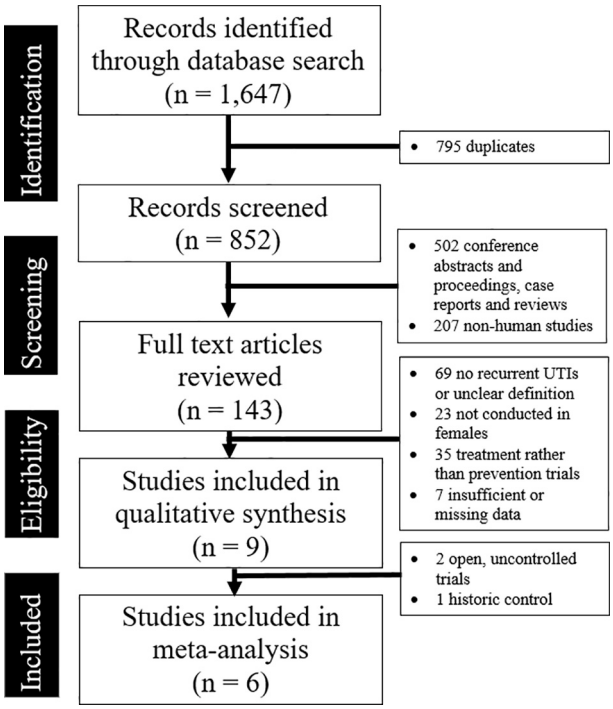


Fig. 1. PRISMA flowchart showing the studies identified during the literature search and abstraction process.

With regard to the possibility of publication bias, visual inspection of the funnel plot revealed a largely symmetrical distribution of studies (Fig. 2) and Egger test was not significant for publication bias (P = 0.9228). One of the studies [13] was excluded from the funnel plot as it was a significant outlier. However, as the number of studies available was small (< 10), assessment of publication bias was less reliable [19]. In view of the small number of studies available, a sensitivity analysis was also not feasible.

The study duration ranged from 4 weeks to 12 months. Six studies randomizing 620 patients to either *Lactobacillus* prophylaxis or placebo/control were included in the meta-analysis. Using a random-effects model (forest plot shown in Fig. 3), pooled risk ratio of at least one recurrent UTI episode during the entire study duration was found to be 0.684 (95% CI 0.438 to 0.929, p < 0.001), supporting a statistically significant and beneficial prophylactic effect of *Lactobacillus* products for recurrent UTI in females.

Discussion

Current clinical trial data has yielded promising results regarding the use of lactobacilli products for prophylaxis against recurrent UTIs (pooled risk ratio = 0.684, 95% CI 0.438 to 0.929, p < 0.001). This differs from the results of the last meta-analysis conducted in 2012 [10], which found no statistically significant difference in the risk of rUTI in patients receiving *Lactobacillus* products when compared to controls, with a pooled risk ratio of 0.85 (95% CI 0.58 to 1.25, p = 0.41). Compared to the last meta-analysis, which analysed data from 294 patients across 5 studies, our study systematically reviewed 9 studies and pooled 6 studies randomizing a total of 620 patients. Our findings significantly strengthen the evidence base for the prophylactic use of *Lactobacillus* products for rUTIs in females. Intravaginal suppositories containing *Lactobacillus crispatus* CTV05, *Lactobacillus rhamnosus* GR1 and *Lactobacillus reuteri* RC14 are particularly effective against uropathogens and show the greatest efficacy for UTI prophylaxis. Notably, probiotic suppositories are well-tolerated with no major side effects and avoid the growing issue of antibiotic resistance. As such, there are significant clinical and public health benefits that favor

Table 1
Characteristics of all studies included in this review (arranged alphabetically by first Author's last name).

Author, year	Country	*Lactobacillus* strain	Study design	Study population	Intervention	Conclusions
Baerheim, 1994 [12]	Norway	*L. casei var. rhamnosus* LCR35	Randomized, placebo-controlled, double-blind trial	N = 47, women aged 18 to 50 with ≥ 3 UTIs in prior 12 months and no UTI at study entry	Vaginal suppository of > 7.5×10^8 CFU/ suppository, twice weekly for 26 weeks	No significant difference in incidence of lower UTI at 6 months follow up between the control and treatment groups.
Beerepoot, 2012 [7]	Netherlands	*Lactobacillus rhamnosus* GR1 and *Lactobacillus reuteri* RC14	Randomized, double-blind, noninferiority trial	N = 252, postmenopausal women (mean age 65.4 ± SD8.3) with at least 3 self-reported symptomatic UTIs in the preceding year	- 12 months' use of trimethoprim-sulfamethoxazole, 480 mg, 1 tablet at night and 1 placebo capsule twice daily - 12 months' use of 1 capsule containing at least 10^9 CFU of *L. rhamnosus GR1* and *L. reuteri RC14* twice daily and 1 placebo tablet at night	No significant difference in the incidence of lower UTI at 12 months follow up between the Trimethoprim and *Lactobacillus* group. Resistance of *E. coli* to Trimethoprim occurred within one month in the Trimethoprim group, which can be prevented by using *Lactobacillus* as prophylaxis instead.
Czaja, 2007 [13]	United States	*L. crispatus* CTV05	Randomized, placebo-controlled, double-blind trial	N = 30, premenopausal women aged 18–35 years with a history of three or more uncomplicated UTIs diagnosed in the past year, or two uncomplicated UTIs diagnosed in the past six months	- Vaginal suppository of L. - crispatus CTV05 at a dose of 5 × 108 CFU - placebo vaginal suppository to be inserted daily for - five days	Usage of vaginal *Lactobacillus* suppositories were effective in preventing lower UTI and well-tolerated with good compliance.
Kontiokari, 2001 [14]	Finland	*L. casei var. rhamnosus* GG	Open, randomized, controlled trial	N = 150, women (mean age 30 ± 11.8) who had a urinary tract infection caused by *Escherichia coli* (≥10^5 colony forming units/ml in clean voided midstream urine) and were not taking antimicrobial prophylaxis.	- 100 mL of > 4 × 1010 CFU L. casei var rhamnosus GG, 5 days per week for twelve months - 50 mL of cranberry-lingonberry juice concentrate daily for six months	At 6 months follow-up, cranberry juice reduced recurrence of lower UTI by 38% compared to only 16% by *Lactobacillus*.
Montorsi, 2016 [15]	Italy	*L. rhamnosus* SGL06	Open, pilot study	N = 42, women (mean age 35.4), with at least 3 episodes of UTIs with documented positive urine culture (≥10^3 colony forming units/ml) in the last 12 months.	- 120 mg cranberry powered extract (minimum proanthocyanidin content: 32 mg) - 1 billion heat-killed L. rhamnosus SGL06, − 750 mg vitamin C orally thrice daily for 20 days.	72% of participants did not have any recurrence of lower UTI at 3 months and 6 months follow-up. *Lactobacillus* treatment was well-tolerated with good compliance.
Reid, 1992 [16]	United States	*L. casei* var. *rhamnosus* GR1 and *L. fermentum* B54	Randomized, placebo-controlled, double-blind trial	N = 41, pre-menopausal adult women pretreated for three days with norfloxacin or trimethoprim/ sulfamethoxazole for an acute, uncomplicated lower UTI	Vaginal suppositories of > 1.6×10^9 CFU/ suppository *L. rhamnosus GR*1 and *L. fermentum B54*, twice weekly for 2 weeks then at the end of each week for the next 2 months	Recurrence rate of lower UTI at 6 months follow-up of only 21% in treatment group as compared to 47% in control group.
Reid, 1995 [17]	United States	*L. casei* var. *rhamnosus* GR1 and *L. fermentum* B54	Randomized, controlled, double-blind, compared to *Lactobacillus* growth factor and historic control	N = 55, premenopausal adult women with ≥4 UTIs in the preceding 12 months, no UTI at study entry	Vaginal suppository of > 1×10^9 CFU/ suppostirory L. *casei var rhamnosus GR1* and *L. fermentum B54*, weekly for 12 months	No significant difference of incidence of lower UTI at 12 months follow-up between the two groups.
Stapleton, 2011 [18]	United States	*L. crispatus* CTV05	Randomized, placebo-controlled, double-blind trial	N = 100, premenopausal adult women with an acute, uncomplicated lower UTI and ≥1 UTI treated within the last 12 months	Vaginal suppository (10^8 CFU *L. crispatus CTV05*, daily for 5 days then once week for 10 weeks.	Recurrence rate of lower UTI at 6 months follow-up of only 15% in treatment group as compared to 27% in control group.
Uehara, 2006 [9]	Japan	*L. crispatus* GAI 98,322	Open-label, compared to historic control	N = 9, adult women (aged 37 to 80 years old) with ≥ 2 episodes of UTI in the preceding 12 months and were suffering from recurrent UTI for at least 2 years	Vaginal suppository of *L. crispatus GAI 98332*, 1.0×10^8 CFU, every 2 days for 1 year before going to bed	Number of recurrent episodes of lower UTI at 12 months follow-up of only 1.3 in treatment group compared to 5.0 in control group.

Abbreviations: CFU, colony forming units; RR, risk ratio; UTI, urinary tract infection; CI, confidence interval.

Table 2
Results of Cochrane Collaboration's tool for assessing risk of bias.

Study (author, year)	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other bias
Baerheim, 1994 [12]	?	?	+	+	+	?
Beerepoot, 2012 [7]	+	+	+	+	+	?
Czaja, 2007 [13]	+	+	+	?	?	?
Kontiokari, 2001 [14]	+	+	–	+	?	?
Montorsi, 2016 [15]	–	–	–	?	?	–
Reid, 1992 [16]	?	?	+	?	+	+
Reid, 1995 [17]	?	?	+	?	+	+
Stapleton, 2011 [18]	+	+	+	?	+	+
Uehara, 2006 [9]	–	–	–	?	?	–

Key: + low risk of bias; - high risk of bias; ? unclear risk of bias.

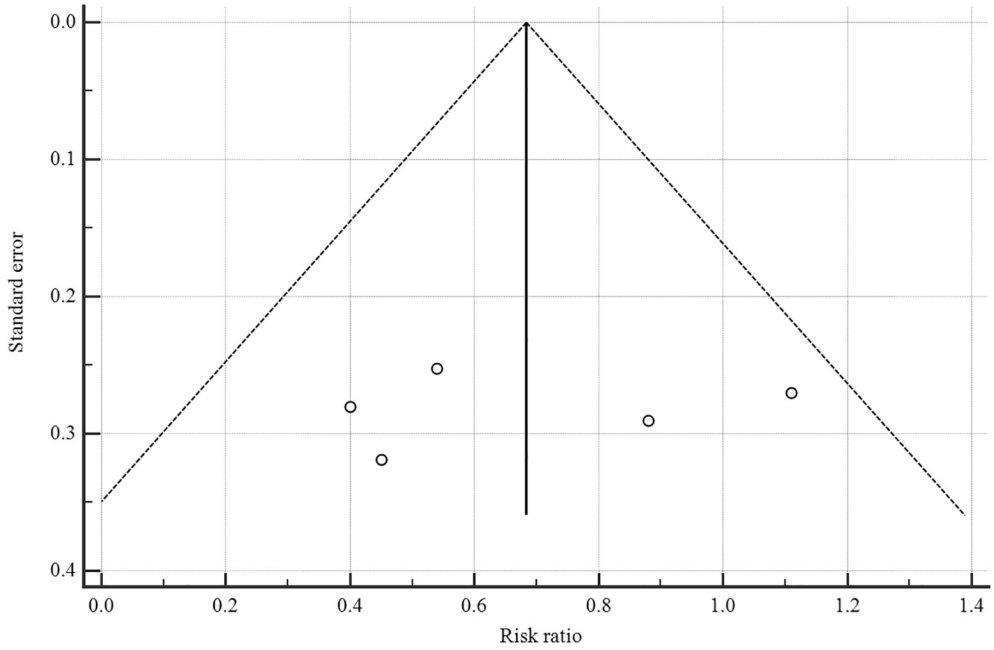
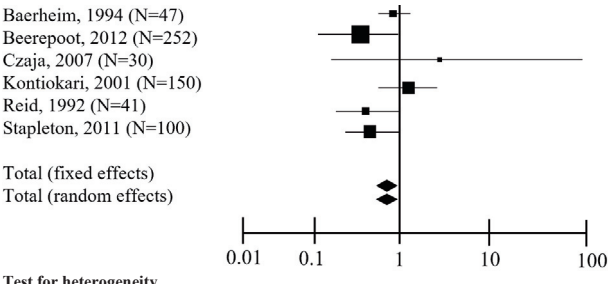


Fig. 2. Funnel plot to assess publication bias; Egger test for publication bias = −2.07, 95% CI −25.34 to 21.20, P = 0.7959.



Test for heterogeneity

Q	4.8551
DF	5
Significance level	P = 0.4338
I^2 (inconsistency)	0.00%
95% CI for I^2	0.00 to 74.62

Fig. 3. Forest plot showing pooled risk ratio analysis of at least one recurrent UTI episode during study duration.

the use of *Lactobacillus* suppositories over long-term antibiotics.

The role of probiotic prophylaxis in chronic infection is centered around restoring and maintaining a healthy host microbiome [20]. In the case of recurrent UTIs (rUTIs), disruption of normal vaginal flora has been shown to predispose patients to chronic intermittent urogenital infections [21]. Introduction of benign, commensal bacteria (such as lactobacilli) decreases the population of pathogenic organisms and re-establishes a healthy bacterial homeostasis [22]. Probiotic suppositories are thought to exert their prophylactic effects through bacteriostatic and bactericidal means.

The bacteriostatic effect of probiotics is primarily achieved through direct competition with uropathogens for a limited nutrient pool and a finite number of attachment sites. Fierce competition within the microbiome diminishes the capacity of pathogenic bacteria to flourish and infect the urinary tract [23]. Furthermore, increasing evidence suggests that byproducts of *Lactobacillus* (such as lactic acid and hydrogen peroxide) downregulate the expression of bacterial genes encoding pathogenic virulence factors. A study by Cadieux et al. [24] found that *Lactobacillus* byproducts inhibit the expression of genes encoding type 1 and p-fimbriae in *E. coli*, impeding their capacity to adhere to epithelial cells and invade the urinary tract. Similarly, decreased expression of the *stx* genes encoding shiga toxin in *E. coli* reduces their pathogenic capacity and puts them at a competitive disadvantage against other bacteria as well as the host immune system [25].

In addition to the bacteriostatic effect of probiotics, various mechanisms exist by which lactobacilli exert a bactericidal effect on uropathogens. Certain strains of *Lactobacillus* produce antimicrobial peptides known as bacteriocins that reduce the population of pathogenic bacteria while being entirely non-toxic to the host [26]. Their antimicrobial activity is, however, limited to bacterial strains closely related to the strain of origin [27], meaning bacteriocins produced by gram-positive lactobacilli are unlikely to affect gram-negative *E. coli*. Various in vitro studies have begun to identify species of *Lactobacillus*

that produce bacteriocins efficacious against *E. coli* [28–30]. Further research in this field can help identify *Lactobacillus* species capable of exerting broad-spectrum antimicrobial effects on multi-drug resistant bacteria. Another means of bactericidal activity is through non-specific modulation of the immune system. At present, little is known regarding the interplay of probiotics with host immunity, however, studies have shown that bacterial strains that secrete bioactive "immunomodulins" and regulatory cytokines such as IL-10 and TNF-β, act synergistically with the host's innate immune system to reduce infection by pathogenic bacteria [31,32]. *Lactobacillus* species could exert anti-inflammatory and immune-regulatory actions [33]. Additional studies are needed to better understand the role of lactobacilli in the microenvironment of the urogenital immune system.

Despite several unanswered questions regarding the mechanism of action of probiotics, their prophylactic potential against a range of chronic infections is well supported by our results. The multiple gaps that exist in the current evidence base necessitate further investigations in the field. In the context of recurrent UTIs, it is unclear whether the efficacy of probiotics would be observed in other vulnerable patient groups such as young children, male patients, patients with a neurogenic bladder or those with a long-term urinary catheter, as the causative uropathogens in these subgroups can differ significantly from those of pre- and post-menopausal women [34]. In the wider context of preventing recurrent infections, little is known regarding the adverse effects of probiotic therapy. This is of substantial concern in prophylactic therapy, where the balance between clinical benefit and treatment risk should be carefully considered prior to commencing treatment. As with the vast majority of trials on probiotic therapy, major inter-study variations with respect to probiotic formulations, treatment dose, dosage routes (oral versus vaginal) and duration of treatment, negatively impact the collective impact of randomized controlled trials (RCTs) and reduce the quality of evidence while increasing the risk of bias. Future studies should, therefore, aim to standardize treatment by identifying the ideal combination of each variable that is most likely to be beneficial for UTI prophylaxis. Additionally, prospective studies would be useful to further establish the preventative efficacy of probiotics as the limited duration of follow-up in the majority of current RCTs is an additional drawback to their statistical and clinical impact.

With the growing evidence base supporting the use of probiotics for UTI prophylaxis, lactobacillus-containing products offer a promising new alternative to currently used antibiotics. Their safety, efficacy and cost-effectiveness make them an ideal candidate for prophylactic use, whilst avoiding the long-term complications of sustained antibiotic treatment. A deeper understanding of the intricate interplay between lactobacilli, uropathogens and the host immune system should be the objective of future research. Larger scale clinical trials with standardized treatment regimens, reliable controls and good reproducibility are necessary for the clinical recommendation of prophylactic lactobacilli for recurrent UTIs. The reassuring results from current trial data do, however, demonstrate the proof of concept of probiotics and the beneficial effects of a healthy host microbiome on chronic, recurrent infections.

Conclusion

Our initial hypothesis that products containing *Lactobacillus* spp. are able to prevent recurrent urinary tract infections in females is highly plausible and supported by current data. Using random-effects meta-analysis, the pooled risk ratio (RR) based on 6 randomized controlled trials with a total of 620 patients was 0.684 (95% CI 0.438 to 0.929, $p < 0.001$), supporting a beneficial prophylactic effect of lactobacilli products for UTI. However, more robust randomized controlled trials with standardized lactobacilli strains and formulation are required to confirm these results. It remains unclear if the same effects will be observed in other patient groups, e.g. young children, male patients or patients with a neurogenic bladder, as current trial data focuses on pre- and post-menopausal women in whom different microbes are implicated. In this era of increasing bacterial resistance to antibiotics, research into alternative, harmless approaches to treating and preventing infections is of vital significance. Research into probiotic use for the prevention of recurrent UTIs should be encouraged.

Contributions

Qin Xiang Ng conceived, designed and carried out the study, and the relevant data analysis and interpretation. Christina Peters and Nandini Venkatanarayanan carried out the study, and the relevant data analysis and interpretation. Yan Yih Goh, Collin Yih Xian Ho and Wee-Song Yeo contributed to the data analysis and interpretation.

All authors discussed the results and contributed to the writing and proofreading of the final manuscript.

Conflict of interest

None.

Acknowledgements

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.mehy.2018.03.001.

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