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Vaginal microbiota and urinary tract infections in women: the protective role of vaginal lactobacilli in counteracting urinary tract infections occurrence and recurrence

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SUMMARY

Urinary Tract Infections (UTIs) are common clinical conditions. Women are affected by UTIs more than men and their probability of experiencing such conditions is high (60%). The vagina and its defensive system play a key role in the pathogenesis of UTIs, making the vaginal microbiota (VMB) a target for controlling UTIs and their recurrence (rUTIs). Current therapy consists of low-dose antibiotics for rUTIs prevention. The increasing incidence of antimicrobial resistance documented to date has rendered this strategy less attractive. The initial step of UTIs pathogenesis involves colonization of the vaginal introitus and periurethra by uropathogens. The following steps may include the ascension of uropathogens via the urethra to the bladder and kidneys. Vaginal infections may be caused by uropathogens from the intestinal microbiota, taking advantage of the proximity between the anus and the vagina. Nevertheless, uropathogens may arise from the vagina itself because of alterations in VMB. Changes in VMB lead to Bacterial Vaginosis (BV), which consists of the replacement of healthy lactobacilli with unhealthy Gram-negative bacteria, such as *Escherichia coli*. The documented relationship between BV and UTIs supports the intriguing hypothesis that restoring VMB may represent a new option to control UTIs and rUTIs after short-term antibiotic treatment in a safe and cost-effective manner.

Keywords: UTIs, bacterial vaginosis, vaginal microbiota, lactobacillus therapy.

INTRODUCTION

The genitourinary microbiome plays a pivotal role in maintaining female urological health, particularly in the context of urinary tract infections (UTIs). These interactions are especially relevant in women, who experience UTIs more frequently than men, partly due to anatomical and hormonal factors [1]. The lifetime risk of UTI in women exceeds 50%, with recurrence rates affecting the quality of life [2, 3]. Recurrence is defined as three or more UTI episodes within 1 year, or more than two episodes within 6 months. Approximately 25% of women experiencing a first UTI will develop a second episode, and 25% of them will show a third and further recurrence [4, 5]. Therefore, recurrent UTIs (rUTIs) represent a significant clinical and economic burden, particularly in postmenopausal women, where standard therapies often fail to prevent recurrence [6].

Antibiotic therapy remains the gold standard for the management and prevention of UTIs. Current guidelines recommend appropriate diagnostic

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procedures, including accurate symptom assessment, urine culture when indicated, and antibiotic selection based on local resistance patterns, patient-specific factors and in vitro sensitivity testing [3]. However, the indiscriminate and repeated use of antibiotics contributes to the emergence of antimicrobial resistance, particularly in *Escherichia coli (E. coli)*, which is the most frequent causative pathogen of UTIs. Recent epidemiological data highlight a worrying trend, with increasing resistance rates against commonly prescribed agents such as fluoroquinolones, trimethoprim-sulfamethoxazole, and cephalosporins [7]. In a large cohort of female patients, *E. coli* was confirmed as the predominant uropathogen, with high levels of resistance to ampicillin and amoxicillin, and resistance to cephalosporins and fluoroquinolones [8]. While effective in acute management, limitations of antibiotics are increasingly evident: their prolonged use is associated with the emergence of antimicrobial resistance and disruption of the host microbiota, both of which may further predispose women to recurrent infections [1-3, 9].

In women, the anatomical proximity between the genital and urinary tracts facilitates ascending infections, making the genital tract a key reservoir for uropathogens such as *E. coli*, *Staphylococcus saprophyticus*, and *Streptococcus agalactiae*, which can ascend to the bladder and initiate infections [1, 10]. In addition to these classical uropathogens, several vaginal species, such as *Gardnerella vaginalis*, *Aerococcus*, and *Ureaplasma* are increasingly recognized as contributors to urinary tract pathology, either through direct infection or modulation of host susceptibility [11]. Vaginal microbiota (VMB) composition plays a pivotal role in the process of ascending infections, and recent research has emphasized the role of the urogenital microbiota in modulating host susceptibility to UTIs. A lactobacillus-dominated microbiota is associated with protection, as Lactobacillus species maintain a low vaginal pH, produce antimicrobial compounds such as lactic acid and hydrogen peroxide, and inhibit uropathogen adhesion and growth. Depletion of these *Lactobacillus* species has been linked to increased colonization by E. coli and other pathogens, and this dysbiosis is related to the most prevalent vaginal infection in women: Bacterial Vaginosis (BV) [2, 6]. A dysbiotic state enriched with facultative anaerobic Gram-negative bacteria, such as *Gardnerella vaginalis* and *E. coli*, characterizes BV, and is strongly associated with increased UTI susceptibility and recurrence [9, 12]. BV is characterized by a decrease in *lactobacilli* in the vaginal microbiota rather than by the presence of a single responsible bacterium, indicating the importance of vaginal eubiosis in preventing vaginal infections [13]. Several recent clinical studies have demonstrated that topical *Lactobacillus* therapy as "complementary treatment" after antibiotic therapy, especially with vaginal suppositories, can significantly reduce the frequency of rUTIs, even in postmenopausal women with refractory infections [6, 14-16], highlighting the therapeutic potential of microbiome-targeted strategies. Menopause induces profound hormonal changes that reshape the genitourinary microbiome, leading to increased vaginal pH and a reduction in protective *Lactobacillus* species, thereby promoting dysbiosis, compromising mucosal integrity and immune defense, and increasing the incidence of recurrent cystitis and other lower urinary tract symptoms. These shifts support evidence that dysbiosis – whether induced by antibiotics, hormonal changes, or behavioral factors – can compromise mucosal defenses and promote pathogen colonization [2, 6].

Taken together, current evidence emphasizes the need for microbiota-centered strategies for UTI prevention and management. In this review, we specifically highlight the protective role of *Lactobacillus* spp. as a promising alternative to antibiotic-based strategies to improve long-term outcomes in women with recurrent UTIs.

This manuscript is a narrative review. A non-systematic search of the literature was conducted in PubMed using keywords related to urinary tract infections, vaginal microbiota, *Lactobacillus* spp., bacterial vaginosis, and probiotics. Relevant articles published in English from 1994 to 2025 were considered. Additional references were identified from the bibliographies of selected publications.

The aim of this narrative review is to summarize current evidence on the role of the urogenital (vaginal) microbiota in the pathogenesis of recurrent urinary tract infections in women and to explore the hypothesis that long-term restoration of the vaginal ecosystem through validated topical probiotic approaches may represent an effective complementary strategy to antibiotic therapy for preventing ascending recurrences.

ANTIBIOTIC RESISTANCE IN URINARY TRACT INFECTIONS

Antibiotic resistance in UTIs is increasing owing to two major factors: the worldwide spread of such infections and the widespread use of antibiotics as the gold standard therapy for UTIs [17]. As outlined in the introduction, several causes can significantly contribute to the development and increase of antibiotic resistance, including poor adherence to antibiotics prescribed regimens, self-medication, and hospital-associated infections, where antibiotics use is more intensive and multidrug-resistant bacteria are more common [18, 19]. The resuming scheme is illustrated in (*Figure 1*).

Among the pathogens responsible for UTIs, several microorganisms can resist antibiotic therapies. *E. coli* is the most common being responsible for UTIs in the 85% of community acquired infections and in about 50% of hospital-acquired instances [20, 21]. *E. coli*-resistant strains are becoming increasingly common, especially those producing Extended-Spectrum Beta-Lactamases (ESBLs) [13]. Indeed, *E. coli* strains can be selected and raised during therapy because of their ability to resist several classes of antibiotics becoming a Multi Drug Resistance (MDR) pathogen. These MDR pathogens may inhibit antibiotics targeting protein synthesis, and nucleic acid synthesis; highly affecting the outcome in patients with UTI [21].

In addition to *E. coli*, other microorganisms have been reported to contribute to resistant UTIs: *Klebsiella sp.*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Enterococcus sp.* Their prevalence is much lower than that of *E. Coli*, but their capability for MDR formation is well known, as well as their contribution to increasing the challenges for treatment [18].

Antibiotic resistance in UTIs is a growing public health challenge worldwide. The consequences of this may lead to: I) a higher failure rate of antibiotic therapy, making infections harder to treat and more prolonged; II) more serious complications such as kidney infections (pyelonephritis) or even sepsis, especially in vulnerable populations (elderly, pregnant women, diabetics); III) more frequent medical examinations, prolonged hospital stays, and the use of more expensive second-line antibiotics contributing to increased healthcare costs.

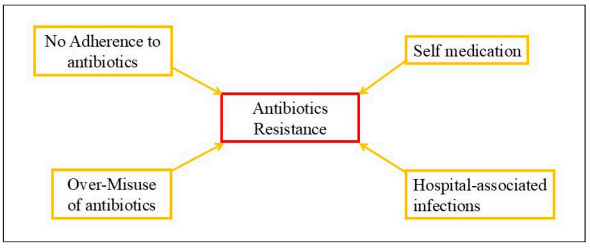

Figure 1 - Antibiotic resistance.

RECURRENCE OF UTIs AND VAGINAL MICROBIOME

Recurrences are more common in women than in men because of risk factors such as sexual intercourse, urogenital aging, pelvic organ prolapse, urethral diverticula, vesicovaginal fistula, urinary incontinence, menopause, and pregnancy [5]. Recurrent UTIs are often caused by the same bacterium that remains hidden in the bladder between an acute cystitis event and a subsequent infection that is undetected by urine culture collected 2 or 3 weeks after a short term antibiotic treatment [22].

To date, the standard therapy for recurrent UTIs is to treat each episode using a short antibiotic treatment cycle. When the interval between infection events is short, prolonged use of prophylactic antibiotics may be administered [22]. Moreover, since pathogen-causing cystitis is often the same, the patient could be prone to self-medication with a prearranged prescription by one's general practitioner. This practice can lead to the selection of antibiotic-resistant pathogens within a couple of years [23].

These findings explain the close association between rUTIs and antibiotic resistance [5]. Increasing the use of antibiotics worldwide, prolonged use of prophylactic antibiotics, or frequent use of several other antibiotics in patients with rUTI does not seem to be a better solution. The burden of bacterial antimicrobial resistance is well known and represented by *E. coli*, the pathogen with the highest MDR-related mortality rate [24].

Recent studies have highlighted the importance of Intracellular Bacterial Communities (IBCs) for bacterial survival, pathogen recognition, and barrier function after antibiotic treatment. IBCs are bacteria contained in the endosomes of urothelial cells protected by the antibiotic effect during therapy [22]. The IBCs may lead to a phenomenon known as Bacterial persistence: an identical path-

ogen remaining dormant between two isolated episodes of UTIs [5, 22]. IBCs have long been reported in the urine of patients with acute cystitis; however, they have not been detected in the urine of patients with acute episodes of rUTIs [25]. Thus, proof of the existence of bacterial persistence and a pathogenetic link between subsequent UTIs is still lacking.

Nevertheless, IBCs could play a critical role in the failure to eradicate pathogens as well as in the increase in antibiotic-resistant bacteria. In both situations, rUTIs are difficult to treat using gold standard therapy. Clinicians cannot cure rUTI effectively and it can cause a significant burden on the healthcare system. Although antibiotics have been used successfully in the treatment, recent increases in the prevalence of antibiotic-resistant uropathogenic strains in the community have caused chronic and recurrent UTIs to become a common threatening disease [5].

rUTIs treatment problems can be solved by understanding the pathophysiology of the infections. Actually, it is known that, during UTIs, the urothelial system is invaded by pathogens, mainly *E. coli*, and a change in the microbial population of vagina and urinary tract is observed.

In addition to the gut, scientists have recently begun to study the vaginal and urinary microbiota. Owing to new laboratory technologies, great progress has been made in the detection and quantification (by qPCR and NGS) [26] of microorganisms living in the vagina and the urinary tract. Five major subcategories of cervicovaginal bacterial species were identified and defined as Community State Types (CSTs). CSTs represent a classification system used to describe groups of bacteria involved in the maintenance of vaginal balance between physiological and pathological flora. Among the four groups, there was a high prevalence of lactobacilli. In particular, *L. crispatus* prevailed in CST I, *L. gasseri* in CST II, *L. iners* in CST III, and *L. jensenii* in CST V. In the remaining Community state type (CST IV) predominate anaerobic bacteria, such *G. vaginalis*, *Atopobium vaginae*, and *Megasphaera* spp., similar to the vaginal microbiota in bacterial vaginosis [27, 28]. Interestingly, a recent meta-analysis reported that *Prevotella bivia*, *G. vaginalis*, *Chlamydia trachomatis*, and human papillomavirus infections are more common in women with lower levels of Lactobacillus in their CST IV cervico-vaginal microbiota than in women with higher levels of Lactobacillus [29]. Several Lactobacillus species, such as *L. crispatus*, *L. jensenii*, *L. gasseri*, and *L. iners*, constitute most of the vaginal microbiota in women of reproductive age [1, 30, 31]. These bacteria produce lactic acid, which helps maintain the acidic pH of the vaginal acidic pH [32, 33]. Vaginal lactobacilli perform a protective function by producing bacteriocins and hydrogen peroxide and inhibiting the colonization of other potential pathogens, particularly *E. coli* [26, 30]. Therefore, lower lactobacilli levels promote bacterial vaginosis or vaginal *E. coli* colonization, which increases the risk of UTI recurrence [1, 14, 34, 35]. The vagina also represents a reservoir for pathogens, and literature indicates that women with a history of UTI exhibit more *E. coli* colonization in the vaginal introitus (>10^5 CFU/mL), highlighting the importance of the vaginal microenvironment in the pathogenesis of rUTIs [36].

Such findings are valuable because they help scientists to better understand the biology of rUTIs and at the same time suggest better treatment strategies for clinicians.

The pathogenesis of rUTIs is significantly influenced by the vaginal microenvironment, in contrast to the widespread assumption that bacteria causing UTIs typically originate from the altered gut microbiota as the only way of infection [37].

Several studies have demonstrated the therapeutic benefits of lactobacilli both in pathophysiology and in the treatment of rUTIs [38].

Among the studies reporting the success of the lattobacilli administration against rUTIs, the use of lactobacillus vaginal suppositories is frequently reported [14, 39, 40]. Sadahira *et al*. showed that the administration of the GAI 98,322 strain of *L. crispatus* significantly reduced recurrent cystitis in 86% of patients. More importantly, the suppressive effect persisted in 77% of the patients for at least a year after the end of therapy, with a significant decrease in the mean number of cystitis episodes both during and after administration [41]. *L. crispatus* appears to be the most used lactobacillus in rUTIs therapy, and its success has been well-documented. However, other lactobacilli have been studied and administered to rUTIs, with similar success rates.

L. rhamnosus has been studied as a *L. crispatus* because of its well-known probiotic characteristics in different parts of the human body. Here, we report an interesting study involving the strain *Lactobacil-*

lus rhamnosus BMX 54 administered as a vaginal drug in a tablet containing lactose as a prebiotic [42]. Approximately 3000 women with bacterial vaginosis (BV) have been enrolled in clinical trials and treated with this symbiotic (probiotic plus prebiotic) biotherapeutic agent, demonstrating that a combination therapy between the Center for Disease Control (CDC) standard of care for BV (metronidazole 500 mg twice daily for 1 week), followed by a long-term course of *Lactobacillus rhamnosus BMX 54* + lactose, leads to a significant reduction in the recurrence rates of BV, not only during treatment but also during the follow-up [43-46].
These important results demonstrate that dysbiotic events such as BV (often a precondition and prelude for UTIs) can be controlled and reverted to physiological eubiosis by multiple therapeutic approaches, including the CDC standard of care, probiotics, and prebiotics.

DISCUSSION

The results obtained using a topical symbiotic approach (*Lactobacillus rhamnosus BMX 54* + lactose) as a complementary treatment to antibiotics for the prevention of BV recurrence rate, encouraging the long-lasting chronic use of this therapy.
During the last 20 years, several clinical trials have been published using this approach [47-65]: following the Friedrich three-step model (*Figure 2*), a specific protocol has been used and validated in more than 3000 women affected by vaginitis [42].
After using a specific antibiotic treatment against the causative agent, the vaginal application of a symbiotic drug (vaginal tabs containing *Lactobacillus rhamnosus BMX 54* as the active principle plus lactose as the selected prebiotic), according to the following protocol, has been clinically validated and used with statistically significant effectiveness in counteracting vaginitis recurrences (*Figure 3*).
Although these studies support the effectiveness of the symbiotic protocol, some heterogeneity in study design, methodology, randomization, number of enrolled patients, treatment schedules, and definitions of recurrence should be acknowledged. More specific double-blind randomized controlled studies are required to confirm the results obtained by this topical symbiotic approach.
Considering that the urinary ecosystem is anatomically related to the genital tract and that both ecosystems have lactobacilli-dominated flora in eubiotic conditions, the hypothesis of using the same protocol to reduce the recurrence rates of UTIs in women has to be considered [6, 33, 67].
The "well-known" activity of lactobacilli in uro-genital tract in women makes this hypothesis suggestive (*Figure 4*).
Therefore, probiotic vaginal application with *lactobacilli* could be considered such as "an effective physiological antibiotic" and may represent a natural complementary therapy after antibiotic treatment. Nevertheless, additional controlled studies are needed to better define the optimal regimen and the duration required to maintain a stable lactobacilli-dominated environment.
The hypothesis of topical vaginal treatment with

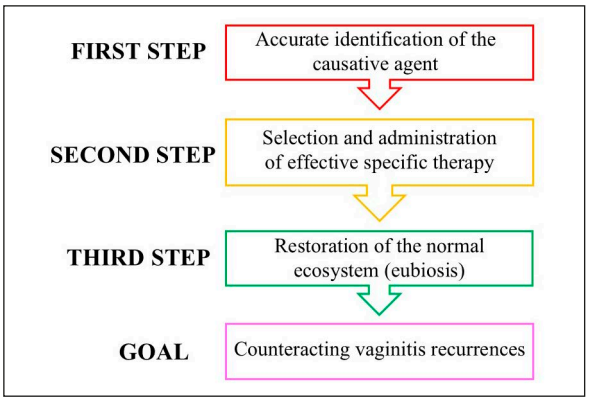

Figure 2 - Diagnosis and Management of the common Vaginitis [66].

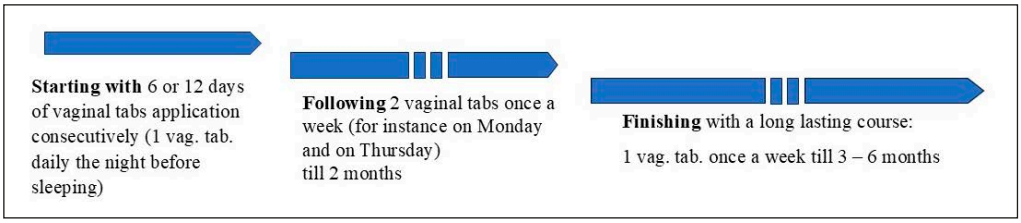

Figure 3 Clinical protocol for vaginitis treatment and prevention [47–65].

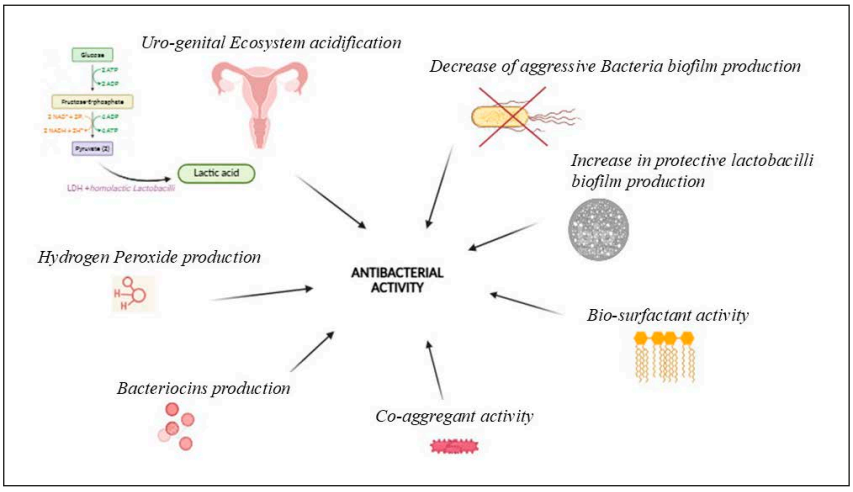

Figure 4
Main activities of lactobacilli.

probiotics to reduce the likelihood of rUTIs in women was recently published by Ebell, in which 174 women affected by rUTIs were enrolled in the trial [16]. Briefly, four different groups were identified based on the therapy protocol: in the first group, oral and vaginal placebo were administered; the second group received oral probiotic and vaginal placebo; the third group was treated with oral placebo and vaginal probiotic; and in the fourth group, a combination of oral and vaginal probiotics was used. The results showed that vaginal probiotics with or without oral probiotics outperformed oral probiotics alone and that vaginal probiotics alone provided a similar benefit to oral plus vaginal probiotics [16] after 4 months and after 12 months. However, the recurrence rates after 4 and 12 months for the placebo and oral probiotic groups did not show a statistically significant difference. The difference was statistically significant when the third group (vaginal probiotics alone) and the fourth group (association between vaginal probiotics and oral probiotics) were compared to the placebo and oral probiotic control groups [16]. Considering that vaginal probiotics alone provide similar benefits to oral plus vaginal probiotics, the author concluded that vaginal probiotic administration seems to be the least invasive and least costly option (Level of Evidence 1b) [16]. It is also interesting to note that at the end of the study, women were asked to rate their improvement, and most in the vaginal and vaginal-plus-oral probiotic groups reported significant improvement with no adverse effects. [16]. Although this clinical trial clearly demonstrated the superiority of vaginally administered probiotics over oral probiotics for the prevention of rUTIs in women, further independent studies with longer follow-up and larger populations would be useful to confirm these findings. Furthermore, similar to previous studies, this study highlights and confirms the pivotal role of *Lactobacillus* restoration in the urogenital ecosystem as an interesting step in reducing/avoiding rUTIs [16]. The inclusion of this clinical approach (level of evidence 1b) in the guidelines of the authors clearly demonstrates the potential of this new approach to prevent UTIs recurrence in women [16].

As mentioned in several studies, the results obtained using "a long-term course" of vaginal lactobacilli application in BV prevention with a vaginal symbiotic also highlight the central role of the combination of probiotics and prebiotic [47–65]. Probiotics can be defined as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" – from the latin term "for life" [68] – while Prebiotics are "a substrate that is selectively utilized by host microorganisms conferring a health benefits" [69]. In a healthy human uro-genital tract the microbiota is a "lactobacilli-dominated" system, making the local application of such lactobacilli selected species: "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" [68]. In the female urogenital tract, there is another relevant factor making the vaginal and urogenital tracts more susceptible to UTI

and UTIs recurrence when compared with men: the "hormonal factor" [70]. Estrogen secretion in women is pivotal to allow lactobacilli to conserve their protective/physiological microenvironment. *Lactobacilli* are directly dependent on glycogen and their optimal metabolic substrates for fermentation [70]. Glycogen production in women is strictly regulated by estrogen secretion; therefore, when estrogen levels are low, no amount of glycogen is produced and lactobacilli are unable to survive (the natural physiological prebiotic decreases) [70]. Lactobacillus metabolism is sugar dependent. They ferment sugar (prebiotic) and create an acidic uro-genital tract ecosystem, "lactobacillocentric" (lactobacilli live in acid microenvironment while pathogen bacteria cannot) and not "pathogenocentric" [70]. Lactobacilli can create local acidification (low pH <4.5) as a physiological defence in the female urogenital tract. Gram-negative bacteria, such as *E. coli*, do not survive or reproduce in acidic microenvironments [70]. Considering that low estrogen production in women is frequent during different phases of their life (for instance, during menopause), it seems reasonable to use a probiotic plus a prebiotic (lactose) to restore the urogenital ecosystem and make it more resistant to pathogenic bacteria such as *E. coli* [70]. In recent years, several authors have reported that the bacteria usually responsible for UTIs are the same as those responsible for BV, which is the most common asymptomatic vaginal infection in women, and the idea of using a symbiotic vaginal approach to prevent UTIs in women seems to be intriguing [6, 70]. Obviously, the selection of the right microorganism for Probiotic administration seems to be pivotal: in the case of *Lactobacillus rhamnosus*, its topical application in the vagina allows this population to restore the vaginal ecosystem during the 7th weeks post application [51, 47-65].

Clinical trials published in recent years have shown that this topical symbiotic approach is effective in decreasing the recurrence rates [47-65]. More recent experience on long-term vaginal probiotic application for rUTI prevention [16] suggests that a symbiotic previously shown to be effective against BV recurrence could also improve outcomes in women with rUTIs. Well-designed, controlled, double-blind clinical trials are needed to confirm this hypothesis, especially given the variability in study design, treatment protocols, and follow up durations in the existing literature. Despite these limitations, the safety, low-cost, and feasibility of long-term topical symbiotics use could represent a potentially valuable option to control UTI recurrence in women. Given that BV recurrence rate has been effectively controlled using this approach [47–65], it appears reasonable to explore its application to rUTIs using the same long-lasting protocol. Considering that the U.S. annual UTI-related costs reach 2$ billion dollars and that recurrent infections represent a significant economic and antimicrobial stewardship burden, the development of non-antimicrobial preventive strategies remains of great public health relevance [71, 72].

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Conflicts of interest
Francesco Moriconi and Margherita Pelagagge are employees of Laboratori Baldacci S.p.A and Marco Bertini is R&D Manager of Laboratori Baldacci S.p.A. The authors had no other conflicts of interest.

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