Could sublingual vaccination be a viable option for the prevention of recurrent urinary tract infection in Canada? A systematic review of the current literature and plans for the future

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J. Curtis Nickel, MD, FRCSC[1], Paula Saz-Leal, PhD[2], R. Christopher Doiron, MD[1]

[1]Department of Urology, Queen's University, Kingston, ON, Canada; [2]Inmunotek S.L., Alcalá de Henares, Madrid, Spain

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Abstract

Introduction: We conducted a systematic review to examine the role of a novel sublingual vaccine – Uromune – for prevention of recurrent urinary tract infection (rUTI) to understand its potential role for Canadian women suffering from rUTI.

Methods: Databases were searched for studies published from 2010–2020 that investigated use of Uromune in the management of rUTI. Only original clinical studies that included use of Uromune as prophylaxis for uncomplicated rUTI in women that included UTI-free rate following initiation of vaccine as an outcome were included.

Results: Of 73 publications related to Uromune and UTIs, 19 unique clinical studies were identified evaluating Uromune for prevention of rUTI. Five studies met our inclusion criteria for primary review. These included 1408 women treated with Uromune. In two retrospective comparative studies, subjects treated with Uromune daily for three months (519 women in total) had significantly higher UTI-free rates (35–90%) than subjects treated with six months of antibiotic prophylaxis (0% in 499 women in total) over 15 months ($p<0.001$ for both studies). In three prospective, uncontrolled studies, UTI-free rates for subjects treated with Uromune ranged from 33–78% over 9–24 months. No major safety issues were identified in these trials. Additional unique studies evaluating Uromune for rUTI that did not meet our criteria added consistent confirmation of the potential effectiveness and safety of Uromune to prevent rUTI.

Conclusions: Although these findings require confirmation in currently active, prospective clinical studies, including a randomized placebo-controlled trial, Uromune may be an alternative to antibiotics to prevent rUTI in Canadian women.

Introduction

The management, both treatment and prevention, of recurrent urinary tract infection (rUTI) in women involves the use of antibiotics. Antibiotics are typically prescribed for 3–7 days for each acute episode and six weeks to six months for prophylaxis. They are also prescribed for self-start treatment and post-coital dosing in sexually active females.[1] Approximately 50–60% of women experience a UTI in their lifetime,[2] with >25% developing rUTI, requiring multiple short- and long-term dosing of antibiotics.[3] In Canada, this represents an exorbitant amount of antibiotics — a significant cost and burden to both society and patients.[4]

rUTI is defined as ≥3 episodes of UTI within the last 12 months or ≥2 episodes within six months.[1] The primary therapy for these patients comes with a price. Typical side effects with first-line antibiotics include gastric upset, rash, and other allergic reactions or intolerances with sulfamethoxazole-trimethoprim (TMP-SMX), fluoroquinolones, and nitrofurantoin. Furthermore, more serious and even life-threatening consequences, such as toxic epidermal necrolysis and Stevens-Johnson Syndrome with TMP-SMX; potential neurotoxicity and liver/lung autoimmune disease with nitrofurantoin; and *C. difficile* infection, the musculoskeletal/neurological/psychiatric triad, and aorta rupture/tearing with fluoroquinolones should make practitioners think twice about prolonged antibiotic treatments for rUTI.[5,6]

The Public Health Agency of Canada provides surveillance reports for attributable costs and mortality associated with UTIs and the figures are staggering.[7] The rapidly rising antibiotic resistance rates for uropathogens, attributed mostly to the widespread use of antibiotics to treat and manage UTI, is exacerbating this problem. The Canadian Council of Academies has estimated that in 2018,[8] approximately 23.9% of UTIs in Canada were resistant to drugs generally used to treat them, costing the Canadian healthcare system approximately 350 million dollars with 6700 deaths and 3000 years of lost employment.

UTI represents one of the most common causes of infection requiring antibiotics (second only to skin and soft tissue infection) and, therefore, one of the most common causes of increasing bacterial resistance in our communities. Antibiotic stewardship is a worthy goal but the non-antibiotic alternatives (cranberry extract, D-Mannose, probiotics, etc.) appear to provide only marginal benefit in preventing rUTI.[1,3,9] The stated priority of Health Canada[10] is to incentiv-

ize innovation for human antimicrobial products, including the advancement and development of antibiotic candidates, non-traditional therapeutics, and/or biologics/vaccines. A recent systematic review on the role of vaccines for rUTI[11] concluded that vaccines seem to have an increasing role in the prevention of rUTI with tolerable side effects, however, more work needs to be done, including inclusion of other high-risk patient groups.

Uromune (Red Leaf Medical, Canada/Inmunotek S.L., Spain), a bacterial mucosal rUTI vaccine in the form of a sublingual spray, is currently pre-licensed in phase 3 development stage, available under the named patient programs (e.g., compassionate use) in 26 countries worldwide (such as the U.K., New Zealand, Netherlands, Germany, Spain, and many other Western European countries). Efforts are underway to make Uromune available to Canadian patients (at present time, Canadian women cannot access this product).

The vaccine is a glycerinated suspension of whole-cell, heat-inactivated bacteria, including equal amounts of four common UTI-causing pathogens: *Escherichia coli; Klebsiella pneumoniae; Proteus vulgaris;* and *Enterococcus faecalis* (MV140 formulation). There are several European studies examining the impact of Uromune on rUTI in various populations of patients. Most are uncontrolled and retrospective studies, but there are enough evaluation studies, some with an antibiotic prophylaxis comparator, to examine the potential benefits of Uromune with respect to reducing the risk of rUTI in women.

We systemically reviewed the role of Uromune in the prevention of rUTI in an attempt to understand its potential role for Canadian women suffering from this condition.

Methods

Search strategy

The search strategy for this systematic review was conducted to find all abstracts and publications relevant to the specific vaccine (Uromune or MV140) and rUTI. Search terms included: "urinary tract infection" or "recurrent urinary tract infection" or "UTI" and "Uromune" or "sublingual vaccine" or "sublingual vaccination" or "mucosal stimulation" or "mucosal vaccination" or "MV140".

Databases EMBASE and MEDLINE were searched for publications published January 1, 2010 to March 31, 2020. Authors JCN and RCD cross-checked selected studies. References from identified studies were also screened for additional relevant publications. The published proceedings of international urology, urogynecology, microbiology and infectious diseases meetings held between 2010 and 2020 that included any reference to Uromune were further reviewed via Inmunotek's prospectively maintained database of meeting presentations.

Inclusion and exclusion criteria

Only original clinical studies that included the use of Uromune as treatment for uncomplicated rUTI in women were included. Female subjects must have met the definition of rUTI and trials must have reported UTI-free rate following initiation of the vaccine as an outcome. Non-original articles, case reports, reviews, and non-clinical articles were excluded, while studies that examined men only, included only complicated UTI, or included pediatric subjects were also excluded from the review.

Data extraction

Data extraction from articles/abstracts identified for the primary analysis was carried out by two authors (JCN and RCD) and checked by the third author (PSL); the final report represented mutual consensus. Studies written in Spanish were translated by one of the authors (PSL). Data collected included type and date of study publication/presentation, subject population demographics (including age and gender), adherence to rUTI definition, duration of vaccine administration, duration of followup, and rUTI outcomes. The primary outcome for this evaluation was the reported UTI-free rate after administration of the vaccine. Secondary outcomes included safety, change in frequency of UTI, time to first UTI, and comparator

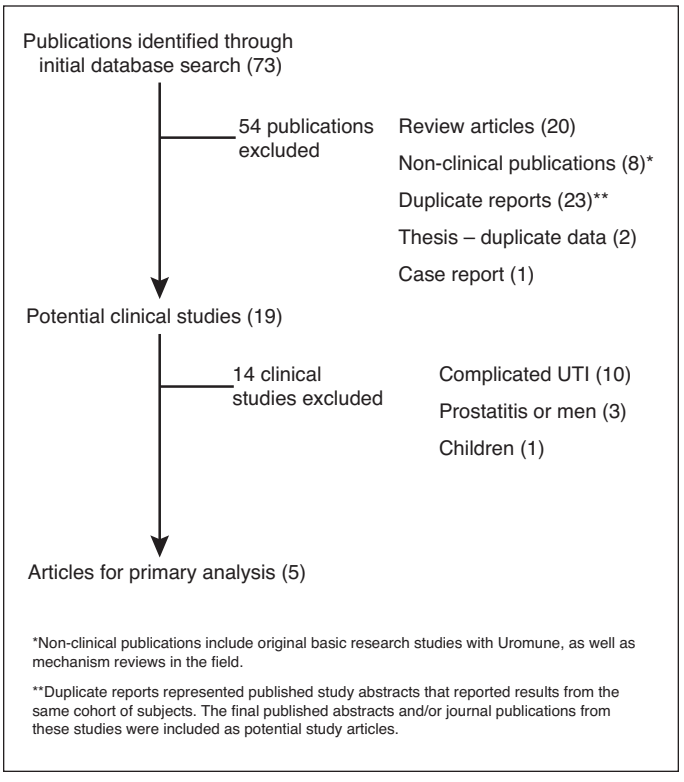

Fig. 1. Flow chart of literature search and included studies.

analyses. A quality analysis of included articles was carried out using the Newcastle-Ottawa Scale.[12]

Results

Identification of studies

A total of 73 articles and/or presentation abstracts related to the use of Uromune for UTI were found. After excluding duplicate studies and those that were not related to the clinical evaluation of Uromune, 19 studies evaluating Uromune for the prevention of rUTI remained (Fig. 1). Five studies that met our inclusion criteria were included in the primary review. Fourteen studies that examined the impact of Uromune in subjects with rUTI but did not fully comply with our inclusion criteria (e.g., complicated rUTI, male population, etc.) were further evaluated in a secondary review (one study in the primary analysis included men and women with rUTI with separate gender-specific analyses available).

Prevention of uncomplicated rUTI in women

In review of the five studies that met inclusion criteria, a total of 1408 female subjects with rUTI were treated with Uromune and 499 with antibiotic prophylaxis as a control group (Table 1). Included in the five studies were two retrospective[13,14] and three prospective cohort studies.[15-17] None of the studies were randomized or placebo-controlled and the heterogeneous design of the five included studies precluded a formal meta-analysis. In all five studies, female subjects with rUTI received sublingual Uromune vaccination daily for three months. Two of the studies[13,14] included a comparator group treated with six months of antibiotic prophylaxis. One study[16] enrolled both women and men with rUTI (women with rUTI analyzed separately), while another included women with uncomplicated and complicated rUTI.[17] Whole study periods ranged from nine months[16] to 24 months,[17] while the average age enrolled ranged from 47.7 years[15] to 73.5 years.[16] (Table 1).

The study by Lorenzo-Gómez et al[13] was a retrospective, observational evaluation of 159 women with rUTI treated with three months of Uromune compared to 160 similar women who were managed with six months of SMX-TMP prophylaxis. At all time points, the UTI-free rate in the Uromune group was significantly higher than in the antibiotic group; at the end of the study period (15 months), 34.6% (n=55) of the women who had received Uromune were UTI-free compared to 0 women who had antibiotic prophylaxis ($p<0.001$). In a further retrospective comparative cohort study,[14] 90.3% (n=325) of 360 women with rUTI treated with Uromune were UTI-free at the end of the 12-month followup period. This was in contrast to the 339 women managed with either six months of SMX/TMP or nitrofurantoin prophylaxis, of whom 0 were reported to be UTI-free at 12-months of followup ($p<0.001$). Yang et al[15] prospectively followed 75 women out of 77 who started Uromune therapy for rUTI and observed a 78.7% (n=59) UTI-free rate at 12 months from initiation of the treatment. A study reported by Ramírez-Sevilla et al,[16] which evaluated rUTI in male and female

Table 1. Summary data from selected Uromune clinical studies evaluating women with rUTI

Study	Date	Treatment (duration)	Eligible subjects (n)	Age years (range)	Study period (months)*	UTI-free rate % (n) at indicated timepoints
Lorenzo-Gómez et al[13]	2013	Uromune (3 months)	159	47.7 (16–85)	3 9 15	63.5 (101)*** 56.6 (90)*** 34.6 (55)***
		SMX/TMP (6 months)	160	48.1 (16–87)	3 9 15	5.6 (9) 2.5 (4) 0 (0)
Lorenzo-Gómez et al[14]	2015	Uromune (3 months)	360	60 (44–70)	12**	90.3 (325)***
		SMX/TMP or nitrofurantoin (6 months)	339	59 (49–59)	12**	0 (0)
Yang et al[15]	2018	Uromune (3 months)	75	56 (18–87)	12	78.7 (59)
Ramírez-Sevilla et al[16]	2019	Uromune (3 months)	648	73.5 (19–97)	3** 6**	45.4 (294) 32.7 (212)
Carrión-López et al[17]	2020	Uromune (3 months)	166	62.3 (19–89)	3 6 12 24	74.4 (124) 68.1(113) 52.4 (87) 44.5 (43/96)

All subjects were treated for 3 months with Uromune (and in 2 studies 6 months of antibiotic prophylaxis) with a total study period from initiation of treatment ranging from 9–24 months. *Unless otherwise specified, timepoint since initiation of the treatment. **Followup period that begins after completion of vaccination. ***$p<0.0001$ comparing Uromune group to group receiving prophylactic antibiotics. rUTI: recurrent urinary tract infection; SXM/TMP: trimethoprim/sulfamethoxazole.

subjects treated with Uromune, included 648 females (84% of the study population). They reported a UTI-free rate in the female subjects of 45.4% (n=294) at three-month followup, which dropped to 32.7% (n=212) at six months. A study by Carrión-Lopez et al[17] included 166 female subjects, 53.6% categorized as uncomplicated UTI. The rest of the cohort had associated risk factors. The UTI-free rate for the entire group was 74.4% (n=124) at three months after initiating vaccination, 68.1% (n=113) at six months, and 52.4% (n=87) at 12 months. Of the 96 subjects followed for 24 months, the UTI-free rate was 44.5% (n=43). They reported that the mean time to first UTI in uncomplicated rUTI subjects was longer if the patients had no UTI risk factors compared to those with identified risk factors (13.9 months vs. 11.2 months; p=0.048). Those with uncomplicated UTIs had fewer rUTI after vaccination compared to those with complicated UTIs (coefficient β 0.40; -0.8 to -0.14; p=0.015). The reliability for reporting secondary effectiveness outcomes — UTI rate in previous year, time to first UTI, and UTI frequency during and after Uromune treatment — was so inconsistent that these variables could not be accurately compared between the five studies.

Safety assessment in women with uncomplicated UTI

The overall safety data from these five studies did not indicate any major safety concerns. There were no adverse events reported for the two major comparative studies,[13,14] one serious adverse event (allergic reaction) and seven minor adverse events (post-nasal drip, stinging around mouth, pruritus over old BCG scar, pruritus over abdomen, intermittent abdominal pain, mild nausea, and exacerbation of underlying asthma) in the U.K. prospective study.[15] Only minor side effects were reported in the two remaining studies. These minor side effects included in one study[16] were dry mouth in eight subjects, gastritis in four, and general illness in four. Other minor side effects included were two reports of mild glossitis and one flareup of rheumatoid arthritis, which was not believed to be associated with treatment.[17]

Assessment of study quality

Results from the assessment of study quality using the Newcastle-Ottawa Scale [12] are shown in Table 2. All studies were open-label and non-blinded. Three of the five studies were prospective in nature and did not include a comparator group, while two were retrospective comparator studies that included a control group treated with prophylactic antibiotics. Recruitment into most of the studies was unclear, while followup was at least 12 months in 4/5 studies, and six months in one study. The studies selected for review appeared to enroll females with an accepted diagnosis of rUTI and all had at least one major common reported outcome — UTI-free rate — during the followup period. The definition of UTI-free status (symptoms, culture, or both) was, however, unclear. Overall, the five studies would be considered level III evidence, with significant potential for reporting bias.

Prevention of rUTI in other populations

A number of studies evaluated the impact of Uromune on rUTI in populations that did not include (or differentially analyzed) women with uncomplicated rUTI but rather included studies that enrolled men, children, the frail elderly, or subjects with complicated UTI. Of the 784 subjects enrolled by Ramírez-Sevilla et al,[16] 136 were men who experienced a 38% and 30% UTI-free rate at three- and six-month followup, respectively. Yang et al[18] described 14 men with rUTI treated with three months of Uromune followed for a total of 12 months and reported a UTI-free rate of 71% (10/14). Arce et al[19] presented a study of 58 men and women (unknown ratio) with rUTI treated with Uromune for three months and followed for a total of nine months and observed an overall UTI-free rate of 50% at three months, 44.8% at six months, and 37.9% at nine months following initiation of the treatment.

Other studies evaluating subjects (men and/or women) with complicated UTI, including men with prostatitis,[20] neurogenic bladder,[21] autoimmune disease and treatment-mediated immunosuppressed patients,[22] chronic renal disease and kidney transplant,[23-26] lymphoproliferative disorders,[27] frail elderly,[28,29] children,[30] and post-surgery,[31] consistently reported favorable UTI-free rates ranging from 30–50%, significant UTI reduction rates after Uromune treatment, and/or improved quality of life (Table 3). Moreover, one study addressed that re-vaccination a year-and-a-half later, as well as being safe, may confer further benefit to individuals with rUTI.[29] The studies either did not report adverse events and/or observed no safety issues in respect to Uromune therapy.

Table 2. Results of quality assessment using the Newcastle-Ottawa Scale[12] for assessment of cohort studies

Study	Selection	Comparability	Outcome	Total
Lorenzo-Gómez et al (2013)[13]	4/4	0/2	3/3	7/9
Lorenzo-Gómez et al (2015)[14]	4/4	0/2	3/3	7/9
Yang et al (2018)[15]	3/4	N/A	3/3	6/9
Ramírez-Sevilla et al (2019)[16]	3/4	N/A	2/3	5/9
Carrión-López et al (2020)[17]	3/4	N/A	3/3	6/9

Table 3. Clinical studies evaluating Uromune for rUTI in populations not included in primary analysis

Study	Date	Subject population (n)	Study period (months)*	Pertinent observations/findings at indicated time points
Ramírez-Sevilla et al[16]	2019	Men (136)	6**	3-mo followup: 38.2% UTI-free rate (men) 6-mo followup: 30.1% UTI-free rate (men)
Yang et al[18]	2017	Men (14)	12	71% (10/14) UTI-free rate
Arce et al[19]	2013	Men and women (58)	9	3-mo: 50% UTI-free rate (all) 6-mo: 44.8% UTI-free rate (all) 9-mo: 37.9% UTI-free rate (all)
Lorenzo-Gómez et al[20]	2018	Men with prostatitis (100:50 in each group)	15	Uromune + bromazepam + *Serenoa repens* vs. Bromazepam + *Serenoa repens* Improved quality of life compared to control group at 3, 9, and 15 months (p<0.0001)
Ordaz-Jurado et al[21]	2014	Neurogenic bladder (14 men; 3 women)	12	Decrease in UTI rate Median 4 (range 1–12)/yr previous to 0 (range 0–3)/yr after vaccination (p=0.9)
Sánchez-Ramón et al[22]	2020	Autoimmune disease and immunosuppression treatment (38)	12	Significant decrease in UTI rate from 5.57±8.41/yr before to 1.0±1.28/yr after vaccination (p<0.05)
García-Agudo et al[23]	2015	Chronic renal disease (21 women; 5 men)	6	19.2% UTI-free rate Significant decrease in UTI from 3.62±1.77/6 mo previous to 1.69±1.62/6 mo after vaccination
García-Ledesma et al[24]	2016	Chronic renal disease including 23% transplant (12 women; 1 man)	12	Significant decrease in UTI Mean from 5.8±2.4/yr prior to 1.7±2.6/yr after vaccination
Castro-Alonso et al[25]	2016	Chronic renal disease (25 women; 7 men)	6	43.8% UTI-free rate Significant decrease in UTI from 2.63±5.54/6 mo previous to 0.9± 0.8/6 mo after vaccination (p<0.001)
Shabaka et al[26]	2018	Renal transplant (43)	12 (6-month Uromune vaccination)	16.3% UTI-free UTI rate (mean) from 4.2/yr previous to 2.7/yr after vaccination (40% reduction; p<0.001)
Ochoa-Grullón et al[27]	2017	Lympho-proliferative disorder (14 women; 4 men)	12	Significant decrease in UTI rate from 4.6±1.8/yr before to 1.22±0.44/yr after vaccination (p<0.0001)
Lorenzo-Gómez et al[28]	2018	Frail elderly (50: 28 women; 22 men in each group)	Unclear	Uromune vs. antibiotic prophylaxis Reduced UTI average/mo (0.212±0.14) compared to antibiotic group (0.66±0.31 (p<0.0213)
Padilla-Fernández et al[29]	2019	Frail elderly (60 women; 10 men)	1st vaccination: 6 mo	women 1st (n=60), 17.3-fold reduction of UTI rate men 1st (n=10), 12.27-fold reduction of UTI rate
			Boost (new 3-mo course 1.5 yr later): 6 mo	women boost (n=60), 12.42-fold decreased UTI rate men boost (n=10), 14.6-fold decreased UTI rate
Martínez-Camacho et al[30]	2015	Children with urological/renal complications (3 female)	12–18	Reduced UTI rate (one UTI-free; one asymptomatic bacteriuria; one *E. coli*-causing UTI)
Lorenzo-Gómez et al[31]	2015	Females after transobturator tape surgery (420; 60 with rUTI)	12	82% overall UTI-free rate No clarity on Uromune impact (no analysis of rUTI subjects)

*Unless otherwise specified, timepoint since initiation of the treatment, including three-month vaccination with Uromune and followup period. **Followup period, just after completing vaccination. rUTI: recurrent urinary tract infection.

Discussion

The prevention of rUTI in women remains a significant healthcare issue despite seemingly effective antibiotic therapy.[2,4] Infection recurs after antibiotic treatment, even long-term antibiotic prophylaxis.[1,3] Continued use of antibiotics for this condition causes side effects in treated women and measurable costs to society,[2,4] while contributing to the frightening scenario of increasing antibiotic resistance.[7,8] Most of the non-antibiotic options available have not proven effective.[9] A recent evaluation of the role of vaccines for rUTI included Uromune (sublingual spray), OM-89/UroVaxom (oral tablet), Solco-Urovac (vaginal suppository/intramuscular injection), and ExPEC4V (intramuscular injection).[11] The assessment concluded that overall vaccine therapy seemed to be efficacious at six months (odds ratio [OR] 0.17; 95% confidence interval [CI] 0.006–0.50) compared to comparator or placebo, with Uromune demonstrating superior

outcomes. The overall efficacy remained significant at 12 months (OR 0.20; 95% CI 0.07–0.59). However, if Uromune was removed from the analysis, efficacy was no longer significant (OR 0.66; 95% CI 0.35–1.26).

Our comprehensive, systematic review of the world literature indicates that Uromune may benefit women suffering from uncomplicated rUTI by increasing the probability of UTI-free status and/or reducing the frequency of UTI. Studies showing this possibility included retrospective[13,14] and prospective studies,[15-17] but they were not controlled and did not compare the UTI-free rate of patients treated with Uromune with a placebo. However, all five studies[13-17] selected reported the UTI-free rate after initiation of Uromune in women with rUTI, a clinically valid outcome. The impact of Uromune compared to antibiotic prophylaxis was evaluated in two large studies[13,14] and both showed a clear superiority of Uromune compared to long-term antibiotics. But again, even the design of these studies with a comparator group was not prospective or randomized.

Despite the limitations of these studies, the evidence does suggest that Uromune appears to be effective, even more so than antibiotic prophylaxis, in achieving UTI-free status in women suffering from rUTI. In this population of women with uncomplicated rUTI, there was an excellent safety profile with Uromune therapy. Compilation of safety issues in the five included studies bring up mostly mild adverse reactions in 1.7% of total subjects. Moreover, only two of 1407 women treated with Uromune in these selected studies decided to discontinue the treatment. The overall safety of Uromune is confirmed with safety reports from over 20 500 subjects receiving Uromune in the 2014–2020 period in compassionate or named patient programs (ClinicalTrial.Gov: NCT 04173013). Only eight reports of adverse reactions have been filed for over 1.5 million doses (data on file, Pharmacovigilance Department, Inmunotek, Spain).

While only five studies met our criteria of including uncomplicated rUTI in women, we noted 14 unique studies evaluating Uromune in other populations of patients suffering from rUTI. In men, elderly, children, and those with complicated UTIs (neurogenic bladders, immunological disorders, renal disease [including those with kidney transplant], immunological disease, and post-surgery), Uromune seems to provide a safe alternative to antibiotics to reduce risk of UTI among populations other than women with uncomplicated rUTI. These studies, which did not meet our inclusion criteria, while poorly designed and reported, add further confirmation of the potential safety and clinical benefits of Uromune. Moreover, re-vaccination may confer further clinical benefit and it is anticipated that future studies will evaluate the safety and efficacy of repeated doses of the vaccine if it appears the beneficial impact decreases over time.

Uromune is a sublingual spray that consists of a suspension of whole-cell, heat-inactivated bacteria: *Escherichia coli; Klebsiella pneumoniae; Proteus vulgaris*; and *Enterococcus faecalis* (MV140 formulation). The sublingual route of immunization is gaining interest compared to other mucosal routes, as it has been shown to avoid degradation by gastric fluids and gastrointestinal enzymes and has the potential to induce mucosal immune responses in a broad range of tissues, including the genitourinary tract.[32,33] Dissemination of immunity to the effector site, the bladder mucosa, is possible via the migration of lymphocytes and other immune cells from the inductor site, the sublingual mucosa, via the mucosal associated lymphoid tissue.[34] In this regard, studies have shown[35,36] that stimulation of the sublingual mucosa with Uromune induces immune responses both systemically and at the level of the genitourinary tract. This response comprises the induction of a T-cell-specific adaptive immune response, as well as of the innate immune system. This is the mechanism of action postulated for this sublingual vaccination strategy.

Although the evidence evaluated in this report may not be sufficient for the product to obtain Health Canada regulatory approval for an indication to manage uncomplicated rUTI in women, it does suggest that it might be appropriate for it to be available on a compassionate, patient-by-patient basis with stringent followup reporting. A prospective Health Canada and Queen's University IRB-approved early clinical practice experience study is presently underway (unfortunately impacted by the 2020 COVID-19 pandemic) in Kingston, Ontario, Canada to assess the benefits and safety of Uromune in real-world Canadian practice (ClinicalTrial.gov: NCT04096820).

Furthermore, the ultimate assessment of efficacy and safety will come from a European randomized placebo-controlled trial (ClinicalTrial.gov: NCT02543827) that is presently nearing completion. If this trial confirms the findings and conclusion of our systematic review, then women with rUTI should be hopeful that a vaccine may be available in Canada in the near future. Such a strategy will be good for Canadian women suffering from rUTI and will result in better antibiotic stewardship for Canada.

Conclusions

The novel sublingual spray vaccine, Uromune, appears to be a safe and effective alternative to repeated or long-term dosing of antibiotics to prevent rUTI in Canadian women.

Competing interests: Dr. Nickel has been a consultant for Alivio, Farr Labs, Inmunotek, Kanglaite, MicroGenDx, Redleaf Medical, Seikagaku Corp, TEVA, Urogen Pharma, and Valensa Int; has participated in scientific studies/trials supported by CIHR, Inmunotek, MicroGenDx, NIH, and Redleaf Medical; and is the Editor of AUA Update Series. Dr. Saz-Leal is an employee of Inmunotek. Dr. Doiron reports no competing personal or financial interests related to this work.

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Correspondence: Dr. J. Curtis Nickel, Department of Urology, Queen's University, Kingston, ON, Canada; jcn@queensu.ca

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