

The Uromune Vaccine-A New Era in UTI Management: A Review

ABSTRACT

Urinary tract infections (UTIs) are some of the most common bacterial infections. UTIs are categorized into uncomplicated and complicated. UTIs are symptomatic when there are clinical urinary symptoms that indicate infection, such as micturition, dysuria, or pollakiuria. UTIs are recurrent when at least two episodes appear over a 6 months period, or three over a 12 months period. The most prevalent location of UTI is the bladder, where they cause cystitis. Women can be up to 30 times more predisposed than men to suffer from them. The antibiotics usually suggested are sulfamethoxazole (200mg), trimethoprim (40mg), nitrofurantoin (100mg). Prolonged consumption of antibiotics is not free of side effects. They can damage the intestinal microbiota and favor the emergence of bacterial resistance. In view of this situation and as an alternative to the antibiotics for the prevention of uncomplicated recurrent UTI, a simple vaccine has been brought for this urinary tract infection by the researchers at the Royal Berkshire Hospital in England. This vaccine is called 'uromune' should be sprayed under the tongue. From there this vaccine enters other mucosal parts of the body and fight against 88 types of bacteria that cause UTI. Vaccines are usually made with inactivated bacteria. But this vaccine doesn't kill bacteria in the body, it stops the bacteria from moving and keeps the bacterial protein intact. The human body's immune system recognises the protein and kills the non-motile bacteria. This vaccine is been used experimentally for 9 years without any problems.

Keywords: vaccine, uromune, antibiotic resistance, protein, recurrent UTI, bacterial infection

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INTRODUCTION

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Urinary tract infections (UTIs) are considered the most common bacterial infections, especially in women. The bladder is the most prevalent site of infection (cystitis). Some authors stated that women are 30 times more prone to have UTIs than men, while other authors reported 8:1 ratio. Because 50–60 % of women report at least one UTI in their lifetime, UTIs have become a common condition diagnosed and treated by urologists, gynecologists, and other health care providers. At least one fourth of these patients will have a recurrence within a year, and 22 % will have recurrent urinary tract infections (RUTIs). Infections are considered recurrent when patients have three or more culture-documented infections in a year or two or more in 6 months [1]. Additionally, it's estimated that one to three women under the age of 24 have needed antibiotic treatment as a result of a UTI episode. Moreover, up to 60% of women who are sexually active will experience an episode, and 15% of them will have a urinary infection. Depending on whether a urinary tract infection occurs in the upper or lower urinary tract, it can be categorized. They can be initial, persistent, or recurrent; symptomatic or asymptomatic; acute or chronic; complex or uncomplicated. Urinary tract infections classified as

uncomplicated UTIs are those that happen without any functional or anatomical changes to the urinary system. On the other hand, anatomical or functional urinary abnormalities those promotes persistence, recurrence, and are secondary to complex UTI. When there are clinical indications of an infection, such as micturition, dysuria, or pollakiuria, urinary tract infections are considered symptomatic. Additionally, Infections confirmed by urine culture When at least two episodes occur over the course of six months, or three during the course of a year, urinary tract infections are considered recurrent. The bladder is the most common site of UTIs, which can result in cystitis. It has been observed that women are up to 30 times more likely than men to experience them. *Escherichia coli* is the most often isolated pathogen (80%) in UTI patients, followed by *Klebsiella pneumoniae*, *Proteus* species, *Enterococcus* species, and *Staphylococcus saprophyticus*. Sustaining antibiotic treatment is advised for the prevention of recurrent urinary tract infections. Either with 100 mg of nitrofurantoin or 200 mg of sulfamethoxazole/40 mg of trimethoprim (SMX/TMP) taken orally every 24 hours for a period of six months [10–12]. Extended use of antibiotics can have negative side effect impacts. They have the potential to harm the gut flora and encourage the development of bacterial resistance. A bacterial vaccination known as uromune®, produced by Immunotek (Madrid, Spain) and supplied by Q Pharma (Alicante, Spain), was introduced to the Spanish market in October 2010 in response to this circumstance and as an alternative to antibiotics for the prevention of simple recurrent UTIs [2].

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DISCUSSION

Fifty percent of women suffer from urinary tract infections (UTIs), a crippling ailment that result in 20–30% of cases of recurring infections. Positive results have been seen with Uromune®, a once-daily polybacterial sublingual vaccination made of inactivated entire bacteria (*E. coli*, *Klebsiella*, *E. faecalis*, and *Proteus*) [3]. Recently, uromune has been created with encouraging results when taken sublingually. It contains bacterial lysates from different strains of UPEC as well as other uropathogenic bacteria. The polymicrobial combination Solco-Urovac is made of heat-inactivated Uropathogens that are available in a number of European nations. This immunostimulant contains 10 organisms, six of which are *E. coli*. Other strains include *Proteus mirabilis*, *Klebsiella pneumoniae*, *Morganella morganii*, and *Enterococcus faecalis*. In 50% of women, vaccination prevented urinary tract reinfection throughout a 24 weeks and notably prolonged the period before reinfection in contrast to the group receiving a placebo. But some research found negative side effects as discomfort, fever, burns, bleeding, vaginal itching, and nausea, which made the vaccine less widely used. Moreover, it was not feasible to exhibit its effectiveness in combating foreign strains or capacity to elicit a long-lasting immunological reaction. *Proteus vulgaris*, *Enterococcus faecalis*, *Klebsiella pneumoniae*, and *E. coli* bacterial lysates make up uromone. Seventy-eight percent of the women with recurrent UTIs had not had

a recurrence in twelve months following three months of treatment, according to the first study conducted in the United Kingdom employing the bacterial vaccine Uromune [4].

When given sublingually, Uromune® operates on the mucous membranes, stimulating the production of immunoglobulin A, which prevents germs from adhering to the mucous membranes and activates innate immunity through dendritic cells, natural-killer cells, and macrophages. Furthermore, Uromune® promotes humoral immunity by means of certain antibodies as well as B and T cells. Numerous studies conducted over the past ten years have demonstrated the effectiveness and efficiency of Uromune®, together with its high tolerance and low side effect rate. Additionally, published studies on Uromune® have demonstrated a noteworthy clinical improvement in patients receiving immunosuppressive treatment, autoimmune diseases, recurrent genital candidiasis, smokers, pregnant women, individuals with neurogenic bladders, chronic prostatitis, chronic renal disease, renal transplant, and lymphoproliferative disorders, as well as females following trans-obturator tape surgery[5].

C Ramírez Sevilla, E Gómez Lanza...et al in a study named “Active immunoprophylaxis with uromune® decreases the recurrence of urinary tract infections at three and six months after treatment without relevant secondary effects”concluded that at three and six months of follow-up, Uromune® showed a substantial reduction in the frequency of episodes of UTIs. With few side effects, Uromune® decreased the frequency of episodes to 0 or 1 in 71.7 and 64.7% at three and six months. Women who were over 50 had the best results. Based on the sample evaluated, the therapy of choice for the prevention of simple recurring UTIs could be sublingual immunoprophylaxis with uromune®[6].

In a research paper titled “PD63-01 evaluating the safety and effectiveness of uromune ® bacterial vaccine over a 9- year period in the UK: A study on managing recurrent urinary tract infection. In men and women” Sagar Kanabar, Stephen J Foley, Bob Yang et al found that it is the first long-term study on Uromune®, and it shows that there are very few long-term adverse effects and a good safety record. It also highlights the continued effectiveness of Uromune, albeit at a lower rate than the results of earlier one-year trials. In lieu of traditional treatments, Uromune® exhibits considerable promise in avoiding recurring UTIs. Research on its efficacy in treating neurogenic bladders and complicated UTIs is still ongoing. Its safety and effectiveness at larger dosages are also being investigated [7].

In a study titled “PLLBA-02 A novel sublingual vaccine will dramatically alter the clinical management of recurrent urinary tract infections in women” Curtis Nickel, María Fernanda Lorenzo-Gómez, Stephen Foley, Paula Saz-Leal et al came to the conclusion that Clinical research backs up the MV140 vaccine’s theoretical advantages as a secure and reliable method of preventing or lowering the occurrence of rUTI in females. There will soon be an evidence-based substitute for antibiotic treatment available to medical professionals who treat rUTI and women who experience it[8].

In a study titled “Analysis of the Efficacy of a Sublingual Bacterial Vaccine in the Prophylaxis of Recurrent Urinary Tract Infection” Pedro Carrión-López, Jesús Martínez-Ruiz et al came to the conclusion that a sublingual bacterial vaccination is a safe, efficient way to prevent urinary tract infections in women. It reduces symptoms significantly, prolongs the duration of the illness-free time, and lowers the incidence of recurrences. The sublingual vaccination may be helpful in reducing the number of antibiotic prescriptions and so alleviating the issue of antibiotic multiresistance, given the high prevalence of antibiotic resistance among patients with recurrent UTI[9].

Sara Wawrysiuk, Kurt Naber, Tomasz Rechberger, Pawel Miotlaet al according to the study titled “Prevention and treatment of uncomplicated lower urinary tract infections in the era of increasing antimicrobial resistance—non-antibiotic approaches: a systemic review,” this study provides the first active comparator data on Women of all ages frequently experience UTIs. However, UTIs are not just a patient-specific issue; they also contribute to the health care system’s excessive costs. Interest in using various non-antibiotic methods of treating and preventing mild lower urinary tract infections has increased due to the rise in antimicrobial resistance and its costs and health effects. Unfortunately, there hasn’t been any solid proof in the last 20 years of study on non-antibiotic methods for treating UTIs that non-antibiotic alternatives can totally replace the use of antibiotics. Antibiotics are still the gold standard for treating and preventing UTIs as a result. Antimicrobial resistance may be avoided, at least in part, by altering the therapeutic approach and including non-antibiotic strategies in the management of UTI. The European Association of Urology’s 2019 amended guidelines state that the prevention of recurrent urinary tract infections entails non-antimicrobial measures first, counseling on risk factor avoidance second, and antimicrobial prophylaxis third. It is important to emphasize that order when incorporating these interventions. A significant reduction in rUTI could likely be achieved with appropriate identification of UTI risk factors, including gender, history of UTIs, vaginal infection, sexual activity, use of spermicidal agents, trauma/manipulation, diabetes mellitus, obesity, and anatomic abnormalities. Antibiotic prophylaxis would then only be necessary for a small number of patients as a last resort. Even while using various NSAIDs to treat an uncomplicated UTI was often still less effective than using antibiotics, treating the infection similarly to other mostly benign bacterial diseases—that is, by focusing on the host rather than the bacteria—may encourage more research into more effective treatments. It’s important to highlight that the clinical result of treating an uncomplicated UTI with the phytodrug Canephron N was comparable to that of antibiotic therapy in terms of symptom reduction. To better understand the advantages and risks of non-antibiotic alternatives for the prevention and treatment of simple lower urinary tract infections, well-designed, randomized trials are still necessary[10].

Shabaka, Amir¹; de la Manzanara, Virginia López¹ et al according to the study titled “Clinical and Immunological Response to Sublingual Vaccination for the Prevention of Recurrent Urinary Tract Infections in Kidney Transplant Patients” concluded that by eliciting a humoral immune

response, sublingual delivery of the polybacterial vaccine Uromune® can lower the incidence of UTI in kidney transplant recipients with recurrent UTI. No alterations in renal function or the emergence of fresh anti-HLA antibodies were seen in our investigation[11].

These findings imply that using this bacterial mixture as a treatment considerably lowers the incidence of recurrent UTIs, making it a viable tactic to lower the frequency of recurrent UTIs. According to the study by Maria.F Lorenzo – Gomez, Barabara padilla Fernandez et al, titled “Comparison of sublingual therapeutic vaccine with antibiotics for the prophylaxis of recurrent urinary tract infections”, Because antibiotic resistance is on the rise, it lowers antibiotic intake in line with current recommendations. More precisely, randomized, double-blind, placebo-controlled clinical trials are required to determine the clinical effect of this bacterial preparation in recurrent UTI patients[12].

In the study titled “ The burning issue of urinary tract infection” Emma Duffield, Bob Yang, Steve Foley et al came to the conclusion that Urine dipstick tests and clinical characteristics should be used to make the diagnosis, and urine cultures should be used to guide antibiotic therapy. Personalized treatment is the best option, particularly as cystitis symptoms frequently go away on their own. A new global health crisis is emerging as a result of increased pressure on health systems brought on by rising rates of antibiotic resistance around the globe, which are exacerbated and facilitated by antibiotic overuse. There are a number of antibiotic substitutes that are presently being researched[13].

In the study titled “Preventing and Treating UTIs” Leah Bedrosian, Gerda Endeman et al came to a conclusion that clinical trial of the bacterial vaccination Uromune who have recurrent UTIs. The four most prevalent organisms that cause UTIs are found in Uromune in inactive form: Enterococcus faecalis, Proteus vulgaris, E. coli, and Klebsiella pneumoniae. For three months, the individuals will get the vaccine orally as a spray to evaluate if it lowers the incidence of UTIs [14].

In a study titled “Vaccines for the prevention of recurrent urinary tract infections: a systematic review” Nikoo Aziminia, Marios Hadjipavlou, Yiannis Philippou, Shivkumar S Pandian, Sachin Malde, Mohamed Y Hammadeh et al Came to a conclusion that there is some evidence that vaccination reduces the risk of recurrence in patients with recurrent UTIs; however, more RCTs with large sample sizes, uniform definitions, and vaccines both currently under development and evaluated in this review are necessary before any vaccines can be recommended for routine clinical use. Future studies should evaluate the long-term vaccine efficacy with long-term follow-up, since the goal of vaccination is to create immunological memory to guarantee persistent immunity. Although the vaccines that have been tested thus far have demonstrated some effectiveness based on clinical indicators, there is currently insufficient data to explain their immunogenicity. Future studies should take into account either serum or urine antibody titres because antibody induction is essential for adaptive immune responses to uropathogens [15].

In “Urinary tract infection in Parkinson’s disease” Elliot Hogg, Samuel Frank, Jillian Oft, Brian Benway, Mohammad Harun Rashid, Shouri Lahiri et al concluded that At a relative risk OM-89 significantly reduced recurrent UTIs when compared to a placebo group in four randomized, placebo-controlled studies including 891 patients . A sublingual vaccine called MV140 (Uromune) against four common strains of inactivated uropathogens—E. coli, K. pneumoniae, P. vulgaris, and E. faecalis—was shown to significantly lower the mean number of UTIs at three months when compared to standard care with antibiotics in preliminary studies [16].

MV140, also known as Uromune, is a sublingual vaccine composed of a mixture of inactivated Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris and Enterococcus faecalis currently pre-licensed in phase 3 stage. According to the study by Giada Antonelli, Luigia Cappelli et al titled “Strategies to Tackle Antimicrobial Resistance: The Example of Escherichia coli and Pseudomonas aeruginosa” Although randomized placebo-controlled clinical trials are still underway, preliminary data from retrospective and prospective uncontrolled studies reported a significant efficacy of the vaccine to prevent recurrent UTIs in women between 16 and 97 years old [17].

In a research paper titled “Current Stage in the Development of Klebsiella pneumoniae Vaccines”, Raquel Girardello, Thiago Rojas Converso, Michelle Darrieux et al found that In a phase II study, immunization against recurrent UTI in women was achieved using Uromune®, a sublingual spray containing inactivated K. pneumoniae, E. coli, Proteus vulgaris, and Enterococcus faecalis. Only one subject reported experiencing formulation-related adverse responses, although seven participants experienced minor possible adverse reactions. Similar outcomes in terms of a decrease in recurring UTIs were observed in a study conducted in Spain with 784 patients, the majority of whom were women. There were also few reported adverse effects. These investigations did not examine the particular immunological responses elicited by this formulation [18].

David Hernández-Hernández, Bárbara Padilla-Fernández et al according to the study titled “Recurrent Urinary Tract Infections and Asymptomatic Bacteriuria in Adults” concluded that A polyvalent bacterial preparation called MV140, sometimes referred to as Uromune®, has equal parts of Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris, and Enterococcus faecalis. The bacteria are heat-inactivated. Patients treated with MV140 exhibited considerably greater UTI-free rates (35–90%) than subjects treated with six months of antibiotic prophylaxis (0%) throughout a 15-month period after receiving two puffs (each containing 108 germs) sublingually every day for three months [19].

In a study titled “A Combination of Polybacterial MV140 and Candida albicans V132 as a Potential Novel Trained Immunity-Based Vaccine for Genitourinary Tract Infections” L Martin-Cruz, C Sevilla-Ortega et al found that the polyvalent bacterial preparation MV140 (Uromune), which is used to prevent RUTIs, is based on entire heat-inactivated components . The germs responsible for most RUTIs in Europe are included in this sublingual vaccine: 25% are Gram-

positive (*Enterococcus faecalis*) and 75% are Gram-negative (*Escherichia coli*, *Proteus vulgaris*, and 25% *Klebsiella pneumoniae*). Clinical evidence demonstrated that MV140 dramatically lowered the infection rates in RUTI patients [20].

In “Recurrent urinary tract Infection in women” Keren E Wales, Lauren, Thomas Gray et al concluded that Uromune is an immunomodulation treatment that increases the immune response of *E. coli*, *K. pneumoniae*, *P. mirabilis*, and *E. faecalis* to the mucosa. It is used as a sublingual spray with a pineapple flavor. Early findings from research conducted in the UK and Spain are positive. No further UTIs were reported by the patients during the follow-up period. It needs more research to be compared to the finest antimicrobial therapy currently on the market[21].

In research paper titled “MV140 mucosal bacterial vaccine improves uropathogenic *E. coli* clearance in an experimental model of urinary tract infection” Paula Saz-Leal, Marianne M Ligon, et al found that the sublingual vaccination known as MV140, which is made up of specific strains of inactivated whole-cell bacteria (V121 *E. coli*, V113 *K. pneumoniae*, V125 *E. faecalis*, and V127 *P. vulgaris*), has demonstrated long-term efficacy in preventing recurrent UTIs in women for as long as a year of follow-up . According to preclinical research, after sublingual or intranasal vaccination, MV140 triggers humoral and systemic CD4+ T cell responses against MV140-contained microorganisms. Nevertheless, there isn't any concrete proof that MV140 can fend off UTIs in lab settings or that the vaccination response can shield against strains of UPEC that aren't in the MV140 formulation[22].

Néha Sihra ,Sachin Malde, Tamsin Greenwell et al According to the study titled “Management of recurrent urinary tract infections in women” concluded that a more recent sublingual vaccination called Uromune, which contains full inactivated strains of *Enterococcus faecalis*, *Proteus vulgaris*, *Klebsiella pneumoniae*, and *E. coli*, will attract Mucosa-associated lymphoid tissue regions around the body, strengthening the host's defenses against illness. This vaccine has shown efficacy in small cohort studies and can be sprayed on patients with ease[23].

In a study titled “New Strategies for the Prevention of Urinary Tract Infections by Uropathogenic *Escherichia coli*” Juan Xicohtencatl-Cortes, Sara A. Ochoa et al found that a minor reduction in UTI was seen in the preliminary study; which demonstrated the functional immune response for a reduction in bacterial count. Merely 1.7% of minor adverse events were observed with the UROMUNE® (MV140) vaccination, indicating its efficiency and safety. For three months, this vaccination was administered under the tongue once a day using glycerinated solutions of heat-inactivated whole bacteria from four different uropathogens. Despite data suggesting that this vaccine may be useful, reports came to opinion that certain recurrent UTI patients may be able to stop having UTIs[24].

In “ Sublingual vaccination with MV140 prevents recurrent urinary tract infections in women: Preliminary results from a randomized, double-blind, placebo-controlled trial” Miguel Casanovas, Paula Saz-Leal et al concluded that first MV140 RCT's preliminary, late-breaking analysis demonstrates clinical efficacy and safety in lowering UTI incidence and preventing

recurrence. In the treatment of rUTI, women will have an efficient, evidence-based alternative to antibiotics when this innovative sublingual bacterial vaccination prophylactic is used in the clinical setting [25].

CONCLUSION

Urinary tract infections (UTIs) are a frequent infection that has grown to be a significant global public health issue. Both Gram-positive and Gram-negative bacteria as well as certain fungal species can cause them. But the main cause of UTIs is Gram-negative bacteria, namely *Escherichia coli* (UPEC) and *Klebsiella pneumoniae*. Researchers at the Royal Berkshire Hospital in England have developed a straightforward vaccination against this urinary tract infection. The “uromune” vaccination is to be applied beneath the tongue. The vaccination then moves on to other mucosal regions of the body, where it combats 88 different kinds of bacteria that can lead to UTIs. Inactivated microorganisms are typically used to make vaccines. However, this vaccination prevents bacteria from growing and preserves the bacterial protein rather than killing the germs already present in the body. The immune system of the human body recognizes the protein and eliminates the non-motile bacteria. For nine years, this vaccine has been used in trials without any issues. When Uromune® was used for three and six months of follow-up, it significantly decreased the frequency of UTI episodes. Uromune® decreased the quantity of occurrences at three and six months, to zero or one in 71.7 and 64.7% with less side effects. Using uromune® for sublingual immunoprophylaxis could be the first line of treatment for preventing simple recurring UTIs.

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