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Role of Vaccines for Recurrent Urinary Tract Infections: A Systematic Review

S. Prattley, R. Geraghty, M. Moore, B.K. Somani

In this study, we look at the role of vaccines for recurrent urinary tract infections (UTIs). We found that they seem to have a short-term role in the prevention of recurrent UTIs and might play an increasing role in the future.

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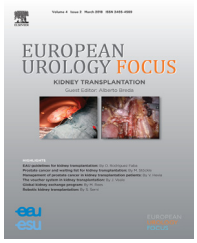

Role of Vaccines for Recurrent Urinary Tract Infections: A Systematic Review

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Abstract

Context: Recurrent urinary tract infections (rUTIs) can be a difficult condition to treat, and the role of vaccines is unclear.
Objective: To systematically review the role of vaccines in the treatment of rUTIs, looking at efficacy, adverse events, and discontinuation from treatment.
Evidence acquisition: We systematically reviewed the role of vaccines for rUTIs using the Cochrane and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) methodologies for all English-language articles from inception of databases to July 2018. Data were collected for different vaccine types, short- (≤6 mo) and long-term (>6 mo) efficacy, and adverse effects with risk of bias assessment of included studies.
Evidence synthesis: After initial identification of 1680 articles, 36 abstracts were screened, 25 full-text articles were assessed, and 17 (including 3228 patients; 1970 in the vaccine group and 1258 in the comparison group) were included. There were three studies in Uromune, nine in OM-89/UroVaxom, four in Solco-Urovac, and one in ExPEC4 V groups. Uromune, UroVaxom, and Solco-Urovac reported on the short-term follow-up, and the overall efficacy for vaccination demonstrated a significant odds ratio (OR) of 0.17 (95% confidence interval [CI] 0.06–0.50). Uromune, UroVaxom, and ExPEC4 V reported on the long-term follow-up, and the overall efficacy for vaccination demonstrated a significant OR of 0.20 (95% CI 0.07–0.59). The reported side effects were mild and varied from 0% to 13% across studies, and treatment withdrawal or exclusion due to adverse events was reported in 11 patients.
Conclusions: Vaccines seem to have a short-term role in the prevention of recurrent urinary tract infections with tolerable side effects. However, due to lack of uniformity of definitions and long-term follow-up, more work needs to be done with inclusion of other high-risk patient groups.
Patient summary: In this study, we look at the role of vaccines for recurrent urinary tract infections. We found that they seem to have a short-term role in the prevention of recurrent urinary tract infections and might play an increasing role in the future.

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1. Introduction

Urinary tract infections (UTIs) are the leading cause of bacterial infection, with approximately 50–60% of women experiencing a UTI during their life time [1] and 20–30% of women affected going on to develop recurrent urinary tract infections (rUTIs) [2]. The socioeconomic impact of UTIs is extensive, not just to the individual, but with an impact on a global scale. It is estimated that annual societal costs for UTIs in the USA is over $2 billion/yr, with sepsis accruing an

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additional $20 billion [3]. It is associated with 7 million office visits, 1 million emergency department visits, and 100 000 hospitalisations each year in the USA alone [1]. On average, each UTI in premenopausal women are associated with 6.1 d of disability and 2.5 d of missing school or work [1].

Current definition for an rUTI according to the European Association of Urology (EAU) is three or more episodes of UTIs within the last 12 mo or two or more episodes within 6 mo [4]. Management sequentially involves counselling and behavioural modifications, with identification and avoidance of risk factors, nonantibacterial measures, and antibiotic treatment or prophylaxis [4].

Prophylactic antibiotic therapy can be difficult, especially with an increase in the antibiotic resistance not only from the causative organism but also in commensal flora, with a recent rise of multiresistant *Escherichia coli* [5]. Disadvantages to antibiotic therapy lie not only with increasing antibiotic resistance, but also in the adverse effect on patients, leading to a reduction in its compliance. It also leads to a destruction of healthy commensal microbiota from the gastrointestinal (GI) and genital tracts, which can lead to reinfection following cessation of treatment [6]. The World Health Organization global action plan was developed in 2015 in response to the growing global antibiotic resistance, with an urgent need to develop new and alternative methods to combat bacterial infection [7]. Since UTIs account for a significant proportion of infections that need antibiotic treatment, it is essential to explore alternative therapies to it. Although there are many reported nonantibiotic therapies, those demonstrating proven efficacy are few [4]. Vaccination against common uropathogens offers an alternative to antibiotic prophylaxis. Current EAU recommendations are limited to OM-89 (UroVaxom) with its proven efficacy and safety profile in uncomplicated rUTIs [8,9]. However, wider application in other patient groups remains to be established [4].

Two aetiological mechanisms exist for the current pathophysiology of rUTIs, being either frequent repeat ascending infection or persistent infection. *E. coli* strains are attributable to 52–77% of rUTIs, with causative pathogens being identical at the primary point of infection and on subsequent recurrences [10,11]. Specific serogroups of *E. coli* have been attributed to rUTIs, with O4, O6, and O75 accounting for nearly 50% cases. Virulence factor genes have also been independently associated with an increased risk of persistence or relapse, postulating that specific patients may be infected with a special type of *E. coli* [11]. The second mechanism is through survival of bacteria within the bladder; as *E. coli* can replicate intracellularly, it can develop intracellular bacterial communities (IBCs), which can be difficult to detect. IBCs can remain quiescent through antibiotic therapy, with discontinuation resulting in recurrence [12].

Vaccines aim to protect us against rUTIs by priming our immune response to pathogens. The aim of our systematic review was to collate available evidence on the use of vaccines for rUTIs and to give an overview of the available literature to date.

2. Evidence acquisition

The inclusion criteria were as follows:

1. All English-language articles of all age groups including paediatric patients
2. Use of vaccination in rUTIs

The exclusion criteria were as follows:

1. Case reports, review articles, and animal and laboratory studies
2. Pregnancy, and immunosuppressed and uncontrolled diabetes mellitus

2.1. Search strategy and study selection

The systematic review was performed according to the Cochrane review and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standards [13]. The search strategy was conducted to find all relevant abstracts and publications about vaccination therapy for rUTIs. The databases searched included EMBASE, CINAHL, MEDLINE, Scopus, Biomed Central, and Web of Science, with references cross checked and individual urology journals hand searched. The search strategy was conducted to find all relevant abstracts regarding "recurrent urinary tract infection", "urinary tract infection", "UTI", "vacc*", "immuno*", "uromune", "urovaxom", "urovac", "solco-urovac", and "ExPEC4V". Boolean operators (AND, OR) were employed to augment the search.

The search was limited to English-language articles from the inception of databases to July 2018. The list of studies generated by the search was screened to identify eligible studies. Data extraction was carried out by two authors (S.P. and B.S.), and any discrepancy was resolved with mutual consensus (Fig. 1). In case of any missing or incomplete data, the authors were contacted directly. Data were collected on patient demographics, vaccine type, method of administration, bacterial content of vaccine, type of study, year of publication, definition of rUTIs, and period of follow-up.

2.2. Outcome measures

Primary outcomes of interest were UTI- and/or bacteriuria-free rates at follow-up. Owing to the level of heterogeneity in the timing of outcome reporting, we have reported outcomes for short (≤6 mo) and long-term (>6 mo) follow-up. Secondary outcome measures include adverse events and discontinuation from treatment. Data were collected using Microsoft Excel. The level of evidence was assessed, and study bias was analysed using the RevMan 5.3 [14] and Newcastle-Ottawa bias assessment tool [15].

2.3. Statistical methods

Risk is presented with a 95% confidence interval (CI) as odds ratio (OR) for both cohort studies and randomised

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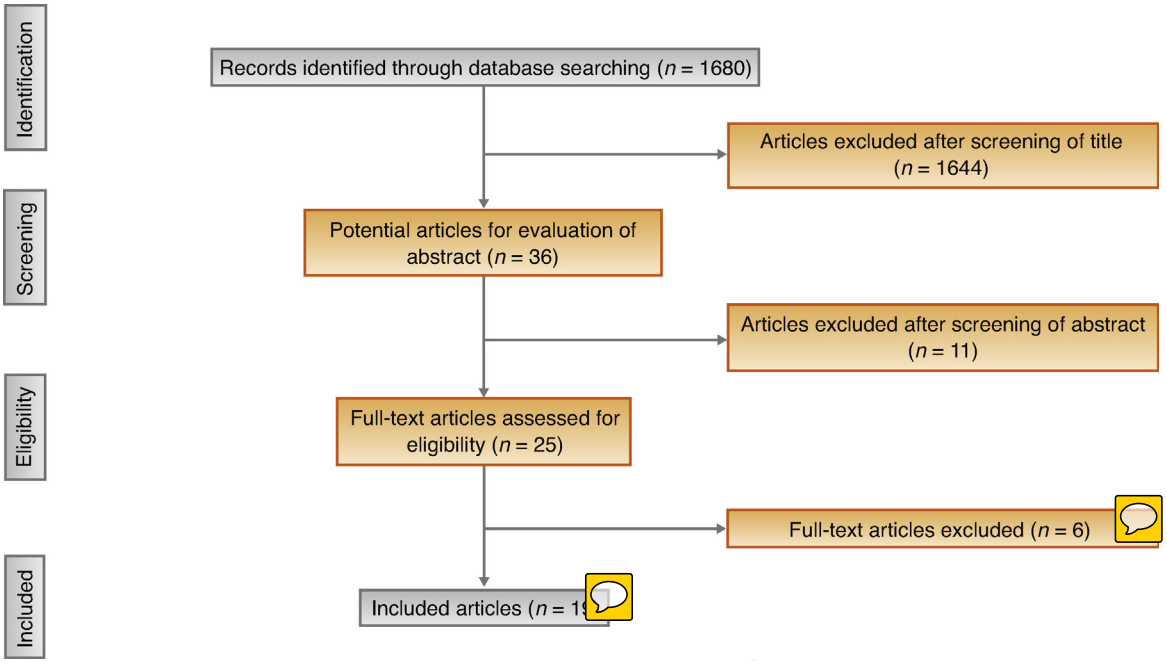

Fig. 1 – PRISMA flowchart of included studies. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses.

controlled trials (RCTs). Statistical heterogeneity was tested for using I^2, tau-square, and chi-square. All $p < 0.05$ were considered statistically significant; I^2 values were interpreted according to chapter 9.5.2 of the Cochrane handbook. Statistical analyses and figures were generated in RevMan 5.3 [14].

3. Evidence synthesis

3.1. Results

After initial identification of 1680 articles, 36 abstracts were screened, 25 full-text articles were assessed, and 17 were included for final review (Fig. 1). Table 1 depicts the current available vaccines (Uromune, OM-89/UroVaxom, Solco-Urovac, and ExPEC4 V) for use against rUTIs.

A total of 3228 patients were included, with 1970 in the vaccine group and 1258 in the comparison group. There were three studies in Uromune (vaccine $n = 594$, comparison $n = 499$) [16–18], nine in OM-89/UroVaxom (vaccine $n = 1205$, placebo $n = 581$) [19–27], four in Solco-Urovac (vaccine $n = 157$, placebo $n = 83$) [28–31], and one in ExPEC4 V (vaccine $n = 93$, placebo $n = 95$) groups [32]. The follow-up outcomes were recorded variably across studies, with seven reporting outcomes to a minimum of 9–12 mo [16–18,22,25,27,31], and the remaining 10 studies reporting outcomes between 5 and 6 mo [19–21,23,24,26,28–30]. We have therefore reviewed vaccine efficacy as short- and long-term outcomes given these time frames.

3.2. Demographics of included studies

3.2.1. Uromune

Three studies reviewed the use of Uromune: a prospective cohort, a retrospective cohort, and a retrospective observational study conducted in the UK and Spain [16–18]. Two studies by Lorenzo-Gomez et al (in 2013 and 2015) [17,18] had control comparator groups that received antibiotics

Table 1 – Available vaccines, administration methods, and vaccine content

Vaccine	Method of administration	Bacterial content
UroVaxom (OM-89)	One oral tablet to be taken once a day for 3 mo ± booster tablet for the first 10 d of months 6–9	6 mg of lyophilised bacterial lysates derived from 18 *E. coli* strains
Uromune	Two doses of 100 μl each (10^8 bacteria/puff) daily sublingually, for a duration of 3 mo	*E. coli, Klebsiella pneumoniae, Proteus vulgaris, Enterococcus faecalis*
Solco-Urovac	Vaginal suppository given weekly for the first 3 wk, then a booster monthly for 3 mo Intramuscular injection, initially weekly for 3 wk, with a booster at 6 mo	10 Uropathogenic strains of bacteria including 6 *E. coli* strains, *K. pneumoniae*, *Proteus mirabilis*, *Proteus morganii*, and *E. faecalis*
ExPEC4V	Single intramuscular injection of 0.5 ml	Genetically detoxified form of exotoxin A from *Pseudomonas aeruginosa* linked to four serotype surface polysaccharide antigens of *E. coli* (O1A, O2, O6A, O25B)

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Table 2 – Study profiles and patient demographics

Author (year)	Study type	*N* = final (initial)		Vaccine	Mean age (range)		Male:female		rUTI definition	Review period
		Vaccine	Comparison group		Vaccine	Comparison group	Vaccine	Comparison group		
Yang (2018) [16]	Prospective cohort	75 (77)		Uromune	56 (18–87)		0:75		≥3 UTIs in 12 mo or ≥2 UTIs within 6 mo	12 mo
Lorenzo-Gomez (2015) [17]	Retrospective cohort	360	339 (Abx)	Uromune	60 (44–70)	59 (49–69)	0:360	0:339	≥3 UTIs in 12 mo or ≥2 UTIs within 6 mo	12 mo
Lorenzo-Gomez (2013) [18]	Retrospective observational	159	160 (Abx)	Uromune	47.7 (16–85)	48.1 (16–87)	0:319		≥3 UTIs in 12 mo or ≥2 UTIs within 6 mo	15 mo
Wagenlehner (2015) [27]	RCT	132 (220)	131 (231; C)	UroVaxom	44.41 (18–75)	43.3 (18–80)	0:220	0:231	≥3 UTIs in 12 mo or ≥2 UTIs within 6 mo	12 mo
Tammen (1988) [19]	Prospective cohort study	451 (521)		UroVaxom	51.8		86:365		Bacteriuria present	6 mo
Tammen (1990) [20]	RCT	61 (76)	59 (74; P)	UroVaxom	51.2	50.4	17:133	No definition	6 mo	
Magasi (1994) [21]	RCT	58 (63)	54 (59; P)	UroVaxom	(16–82)	10:48	7:47	Bacteriuria $>10^5$	6 mo	
Bauer (2005) [22]	RCT	231	222 (P)	UroVaxom	41.7	39.8	0:231	0:222	3 UTIs within previous year + bacteriuria $>10^5$	12 mo
Hachen (1990) [23]	Crossover trial	67 (70)		UroVaxom	37.3	36.7	45:22	Catheter sample urine $>10^4$ on one occasion	6 mo	
Schulman (1993) [24]	RCT	74 (85)	68 (81; P)	UroVaxom	45.3	45	26:140	No definition	6 mo	
Frey (1986) [26]	RCT	32	32 (P)	UroVaxom	(22–84)	Not specified	2 Symptomatic episodes in 1 yr	6 mo		
Lettgen (1996) [25]	RCT	20 (22)	15 (18; P)	UroVaxom	6.9	6.4	0:22	0:18	≥3 UTIs in 12 mo and $>10^{3-5}$ CFU	12 mo
Uehling (1997) [28]	RCT	30 (V) 31 (VB)	30 (P)	Solco-Urovac	49 (V) 45 (VB)	45	30 (V) 31 (VB)	0:30	≥3 UTIs within 12 mo	20 wk
Uehling (2003) [29]	RCT	18 (V) 18 (VB)	18 (P)	Solco-Urovac	47 (V) 43 (VB)	56	0:18 (V) 0:18 (VB)	0:18	≥3 UTIs within 12 mo	6 mo
Hopkins (2007) [30]	RCT	24 (V) 26 (VB)	25 (P)	Solco-Urovac	45 (V) 45.2 (VB)	54.3	0:24 (V) 0:26 (VB)	0:25	≥3 UTIs within 12 mo	6 mo
Nayir (1995) [31]	RCT	10	10 (O)	Solco-Urovac (IM)	9.1 (5–12)	0:10	0:10	≥2 symptomatic UTIs within 12 mo + $>10^5$ CFU	12 mo	
Huttner (2017) [32]	RCT	93 of which 6 low dose	95 (P)	ExPEC4V	41.7 (19–71)	41.6 (18–70)	0:93	0:95	≥3 UTIs within 12 mo, or ≥2 UTIs within 6 mo + one positive urine culture with *E. coli* in last 5 yr	9 mo

Abx = antibiotic group; C = control; CFU = colony-forming unit; IM = intramuscular injection; O = observational Group; P = placebo; RCT = randomised controlled trial; rUTI = recurrence UTI; UTI = urinary tract infection; V = vaccine; VB = vaccine with booster.

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instead of vaccination. All patients reviewed were females, with the average age being 47.7–60 yr (range 16–87 yr). All patients received Uromune sublingually for 3 mo, either with no concomitant food or fasting 2 h prior to taking the vaccine (Table 2).

3.2.2. UroVaxom

A total of nine studies examined the use of UroVaxom, including eight RCTs, two retrospective cohort studies, and a cross over trial [19–27]. Eight studies included a comparator group that was either control or placebo. The method of administration was using oral tablets for the first 3 mo, with two studies by Wagenlehner et al. [27] and Bauer et al. [22] giving a booster between 6 and 9 mo for the first 10 d of each month. The male to female ratio across studies was 195:1586, with the average age ranging from 37.3 to 51.8 yr, excluding the study by Lettgen [25] who reviewed the use of vaccination in children with an average age of 6.9 yr (Table 2).

3.2.3. Solco-Urovac

Four RCTs reviewed the use of Solco-Urovac, three American studies [28–30] examining vaginal suppository vaccine and one Turkish study by Nayir et al. [31] reviewing the use of intramuscular (IM) injection in female children (vaccine $n = 157$, placebo/observational group $n = 83$). Of the vaginal suppository vaccinations, Uehling et al. [28] examined the outcomes between high dose, low dose, and placebo, and Uehling et al. [29] and Hopkins et al. [30] compared vaccine and vaccine with booster at monthly intervals for 3 mo with a placebo. All patients were female, with the mean age ranging from 43 to 49 yr for vaginal suppository vaccination [28–30] and 9.1 yr for IM injection [31] (Table 2).

3.2.4. ExPEC4 V

Huttner et al. [32] have completed the only phase II study for ExPEC4 V to date (vaccine $n = 93$, placebo $n = 95$). All participants were female, with the average age within the vaccine group being 41.7 yr and the placebo group being 41.6 yr (range 18–71 yr). All patients received a single IM injection of the placebo, low-dose vaccine, or full-dose vaccine (Table 2).

3.3. Short-term efficacy (≤6 mo)

Overall efficacy for vaccination across all studies and vaccines demonstrated a significant OR 0.17 (95% CI 0.06–0.50; Fig. 2 and Table 3) [17,18,20,21,24–31]. Uromune demonstrated the most significant outcome at 6 mo; however, both studies were retrospective in nature, and neither were placebo controlled [17,18]. UTI-free rate for vaccine was 63.5–81% in comparison with 3–5.6% for the antibiotic therapy group, overall OR 0.02 (95% CI 0.00–0.07). Efficacy remained statistically significant in favour of vaccine therapy even when the retrospective studies were removed from analysis, with OR 0.30 (95% CI 0.14–0.63) [20,21,24–31].

UroVaxom showed UTI-free rates varying between 52.6% and 87.5% compared with 50% of the placebo group and 71.4–78.6% for the prophylactic antibiotic therapy group. Bacteriuria was absent in 81.3–96.3% of patients at 6 mo for UroVaxom, in comparison with placebo 61.3–88.6%. Overall, UroVaxom showed a significantly improved OR in the short term, being 0.29 (95% CI 0.10–0.87) [20,21,24–27].

Solco-Urovac suppository has only published data to 6-mo efficacy, and while Solco-Urovac with booster has demonstrated significant OR 0.23 (95% CI 0.11–0.48) in

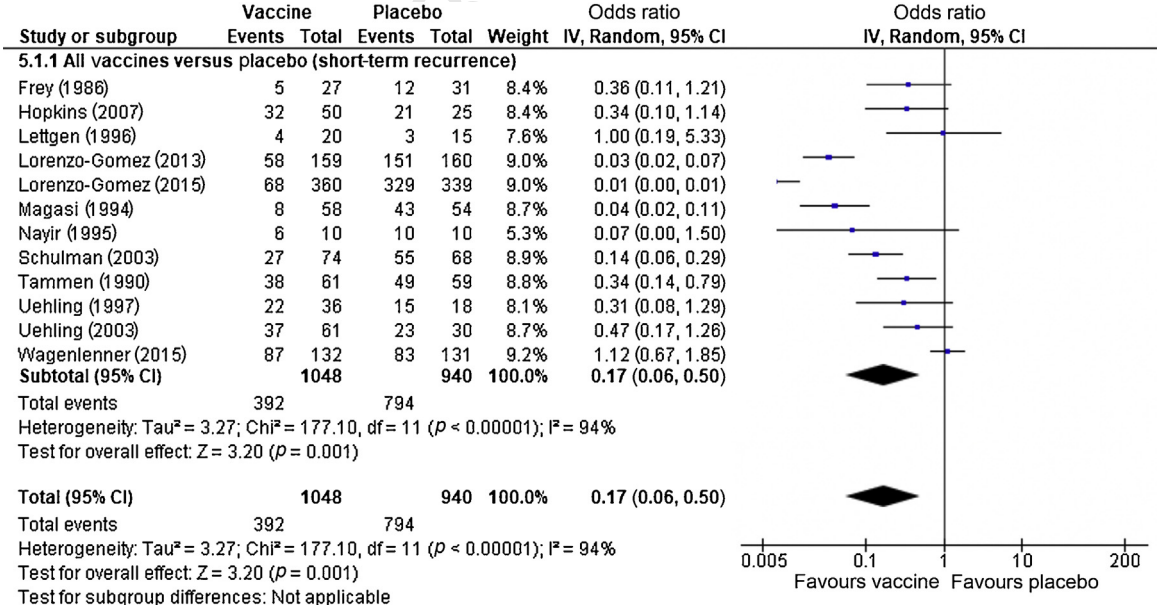

Fig. 2 – Efficacy for vaccination across all studies. CI = confidence interval; IV = inverse variance.

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Table 3 – Outcomes of vaccine for rUTI

Author (year)	Vaccine	3-mo Outcome		6-mo Outcome		9-mo Outcome		12-mo Outcome		Adverse events
		Vaccine	Comparison group	Vaccine	Comparison group	Vaccine	Comparison group	Vaccine	Comparison group	
Yang (2018) [16]	Uromune							78% UTI free		1 Rash 7 Minor potential AE—postnasal drip, stinging, pruritis over BCG scar, pruritis over abdomen, intermittent abdominal pain, mild nausea
Lorenzo-Gomez (2015) [17]	Uromune	81% UTI free	3% UTI free					90.3% UTI free	0% UTI free	Nil reported locally or systemically
Lorenzo-Gomez (2013) [18]	Uromune	63.5% UTI free	5.6% UTI free					56.6% UTI free	3.8% UTI free	Nil reported locally or systemically
Wagenlehner (2015) [27]	UroVaxom							47.8% UTI free	64.1% UTI free	No severe adverse events for vaccine 48 AEs in vaccine group, most mild to moderate 7 AEs in vaccine group leading to permanent exclusion, 9 in placebo group 1 SAE of eczema in placebo group
Tammen (1988) [19]	UroVaxom			52.6% UTI free						4.4% had SE, treatment was discontinued in 2 patients (0.4%), GI upset in 15 cases (1 withdrawal), headache/vertigo in 3, nausea and erythema in 1 with withdrawal, stop of hair growth in 1
Tammen (1990) [20]	UroVaxom			91.8% free of bacteriuria	76.3% free of bacteriuria					4 Possible cases of SE in the vaccine group
Magasi (1994) [21]	UroVaxom	86.2% free of bacteriuria	20.4% free of bacteriuria							Nil reported locally or systemically
Bauer (2005) [22]	UroVaxom							UTI free 55%	UTI free 4 1.9%	13% of 161 AEs in 75 patients considered treatment related, most common headache and GI upset
Hachen (1990) [23]	UroVaxom	Bacteriuria baseline to 3 mo 5.24–2.7	Bacteriuria baseline to 3 mo 5.38–4.15	Vaccine to placebo: 2.7–1.7	Placebo to vaccine: 4.15–1.82					6 Cases of minor and transient AEs, fever, GI upset, bad taste, decreased appetite, diarrhoea, and nausea
Schulman (1993) [24]	UroVaxom	74.3% free of bacteriuria	61.5% free of bacteriuria	81.3% free of bacteriuria	70.6% free of bacteriuria					No side effects noted
Frey (1986) [26]	UroVaxom	84% free of bacteriuria	28.6% free of bacteriuria	81.5% free of bacteriuria 87.5% UTI free	50% UTI free 61.3% free of bacteriuria					One case of allergic exanthema to neck
Lettgen (1996) [25]	UroVaxom			81% UTI free	78.6% UTI free			85% UTI free	69.2% UTI free	Not commented upon
Pisani (1992)	UroVaxom			96.3% free of bacteriuria	88.6% free of bacteriuria					Not commented upon
Uehling (1997) [28]	Solco-Urovac			25% UTI free (V) 50% UTI free (VB)	17% UTI free					No discontinuation for AE, 1 light headedness, 3 minor vaginal irritation
Uehling (2003) [29]	Solco-Urovac			22.2% UTI free (V) 55.6% UTI free (VB)	22.2% UTI free					No SAE Brief vaginal irritation (5), transient diarrhoea

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Table 3 (*Continued*)

Author (year)	Vaccine	3-mo Outcome		6-mo Outcome		9-mo Outcome		12-mo Outcome		Adverse events
		Vaccine	Comparison group	Vaccine	Comparison group	Vaccine	Comparison group	Vaccine	Comparison group	
Hopkins (2007) [30]	Solco-Urovac			25% UTI free (V) 46% UTI free (VB)	16.7% UTI free					No SAE Burning sensation (6), low-grade fever (4), nausea, vaginal bleeding, vaginal rash No SD between V and P
Nayir (1995) [31]	Solco-Urovac (IM)			40% UTI free	0% UTI free			20% UTI free	0% UTI free	Did not comment
Huttner (2017) [32]	ExPEC4V					52% UTI free	41% UTI free			No SAE AE of any severity 60% in vaccine, 49% in placebo, included pain at injection site, swelling at injection site, headache, nausea, fever, dizziness, chills, diarrhoea, dysgeusia, extremity pain, hyperhidrosis, upper abdominal pain, injection site warmth No SD between solicited events or biochemical parameters at 7 or 30 d

AE = adverse event; GI = gastrointestinal; IM = intramuscular injection; rUTI = recurrence UTI; SAE = significant adverse event; SD = stable disease; SE = side effects; UTI = urinary tract infection; V = vaccine; VB = vaccine with booster.

comparison with placebo (Fig. 3), Solco-Urovac without booster did not (Fig. 4; OR 0.71, 95% CI 0.32–1.58) [28–30]. UTI-free rates for vaccine alone ranged from 22.2% to 25% at 6 mo, for vaccine with booster from 46% to 55.6%, and for placebo from 16.7% to 22.2%.

Solco-Urovac for IM injection at 6 mo demonstrated a UTI-free rate of 40% in the vaccine group, in comparison with 0% in the placebo group [31].

3.4. *Long-term efficacy (>6 mo)*

Overall efficacy across all vaccines at 12 mo showed an OR of 0.20 (95% CI 0.07–0.59; Fig. 5 and Table 3) [17,18,20,22,25,27,31,32]. However, if Uromune is removed from analysis, efficacy is no longer significant (OR 0.66, 95% CI 0.35–1.26) [20,22,25,27,31,32].

Uromune demonstrated the most significant OR as 0.00 (95% CI 0.00,–0.43); however, this is again limited by the retrospective nature of the studies and lack of trial design [17,18]. The long-term UTI-free rate for Uromune was between 56.6% and 90.3%, with the longest reported outcomes being 56.6% at 15 mo [18]. This was compared with antibiotic prophylaxis of either sulphamethoxazole/trimethroprim or nitrofurantoin once daily, whereby almost all patients at 12 and 15 mo had experienced at least one UTI. The median time to recurrence was 180 d for Uromune and 19 d for prophylactic antibiotics [16–18].

The only available long-term data for analysis for Solco-Urovac are for IM injection and are limited in its study population to 20 participants. OR was 0.16 (95% CI 0.01–3.85), with all patients in the observation group and 80% in the vaccine group having one or more UTIs by 12 mo [31].

A single study has reviewed the use of ExPEC4 V with a follow-up period of 9 mo. At this stage, UTI-free rate for the vaccine was 52% in comparison with the placebo group of 41% (OR 0.65 [95% CI 0.37–1.16]) [32].

Outcomes for UroVaxom at 12 mo gave an OR of 0.69 (95% CI 0.28–1.66) for the risk of recurrence for the active compared with the placebo group [20,22,25,27] (Fig. 6). However, heterogeneity within studies has been noted. Subgroup analysis of UroVaxom with booster did not show a significant OR at 12 mo, being 1.06 (95% CI 0.33–3.44) [22,27]. The apparent lack of improvement may be explained by an overall low rate of UTIs, high protocol violation, and change in the manufacturing of OM-89S [27].

3.5. *Heterogeneity and sensitivity analysis*

There was marked statistically significant heterogeneity between all studies at both short- and long-term outcomes (unadjusted risk, tau-square = 3.27, chi-square = 177.10, $p < 0.00001$, $I^2 = 94\%$, and tau-square = 2.03, chi-square = 102.99, $p < 0.00001$, $I^2 = 93\%$, respectively). In a subanalysis for individual vaccines, heterogeneity remained statistically significant for both UroVaxom (tau-square = 1.33, chi-square = 66.70, $p < 0.00001$, $I^2 = 91\%$) and Uromune (tau-square = 12.54, chi-square = 12.23, $p = 0.0005$, $I^2 = 92\%$) at 12 mo. Solco-Urovac was the only vaccine to demonstrate a lack of heterogeneity for both with

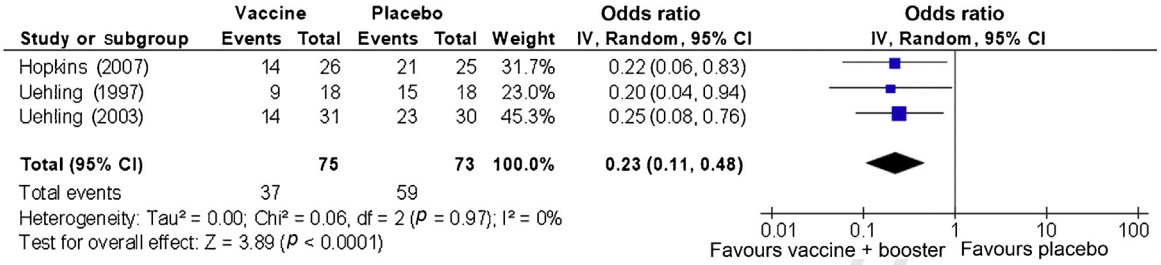

Fig. 3 – Efficacy of Solco-Urovac with booster. CI = confidence interval; IV = inverse variance.

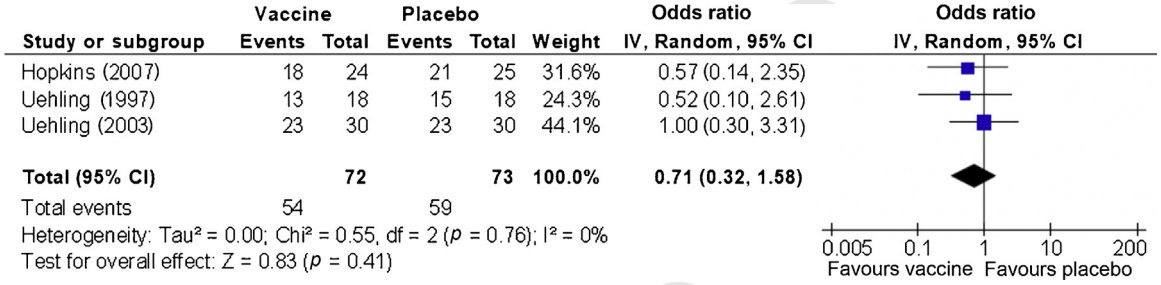

Fig. 4 – Efficacy of Solco-Urovac without booster. CI = confidence interval; IV = inverse variance.

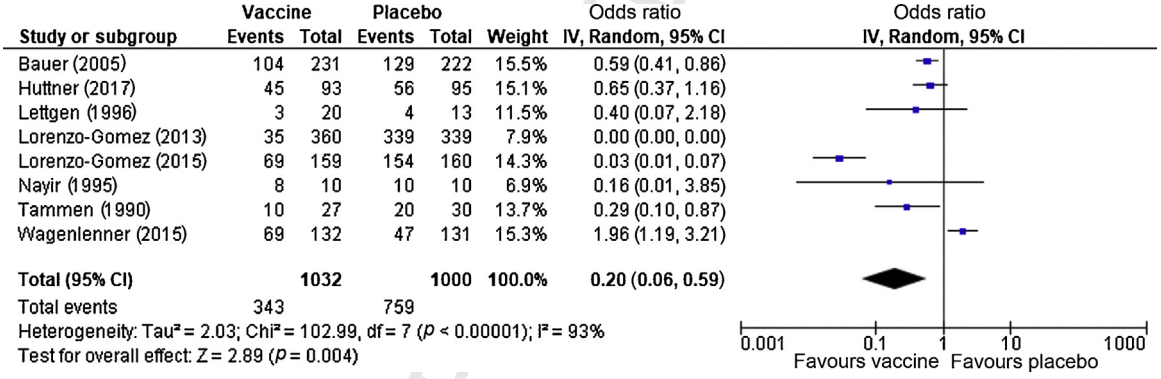

Fig. 5 – Long-term efficacy of vaccines. CI = confidence interval; IV = inverse variance.

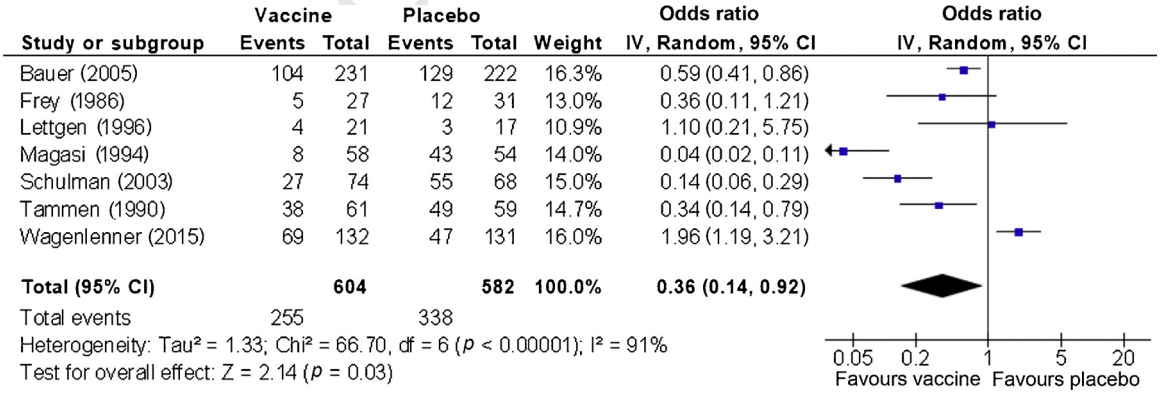

Fig. 6 – Efficacy of UroVaxom vaccine. CI = confidence interval; IV = inverse variance.

booster (tau-square = 0.00, chi-square = 1.34, $p = 0.72$, $I^2 = 0\%$) and without booster (tau-square = 0.00, chi-square = 0.06, $p = 0.97$, $I^2 = 0\%$) at 6 mo.

3.6. Vaccine adverse effects

Table 4 demonstrates the overall safety profile for all vaccination therapy; the adverse effect profile for each individual vaccine is reportedly good with no severe adverse events being recorded for any vaccine. Treatment withdrawal or exclusion due to adverse events was reported in 11 cases of vaccination across all studies (Uromune $n = 2$, UroVaxom $n = 9$) [16,19,27]; in seven of which the cause was not commented upon [27], the remaining being due to rash, incompatibility with lifestyle, GI upset, and nausea and erythema [16,19].

Reported side effects were dependent on the vaccine used, and frequency ranged from 0% to 13% across all studies. The most frequently reported adverse events included GI upset, headache, pain at injection site, and vaginal irritation; other less common adverse events noted included postnasal drip, pruritis, intermittent abdominal pain, nausea, urethral symptoms, light headedness, low grade fever, vaginal bleeding, headache, erythema, and decreased appetite.

Overall, all vaccines demonstrate an acceptable safety profile with minimal adverse events, with all being Clavien-Dindo grade I–II [33].

3.7. Risk of bias

In total, 12 studies (Fig. 7) underwent quality appraisal using the Cochrane Collaboration's tool for assessing the risk of bias [10], and a further four cohort studies (Table 5) were assessed using the Newcastle-Ottawa assessment tool [15].

Blinding for all RCTs was deemed appropriate for both assessors and participants in the majority of cases. One study was single blinded, one study was open label, and a further study did not specify the degree of blinding. Recruitment of participants and randomisation were unclear in the majority of cases, which may lead to a degree of selection bias. In select studies, there was a large proportion of attrition of participants due to major protocol violations, which may result in a reporting bias.

In the quality assessment of cohort studies, selection and outcome reporting were deemed satisfactory; however, comparability was poor, as no study controlled for any potential causative factor.

4. Discussion

4.1.1. Current evidence for vaccines used for rUTIs

The use of vaccine immunotherapy has some promising results and appears to substantially reduce the risk of recurrence for up to 12 mo. However, the evidence is

Table 4 – Exclusion criteria for all studies

Study (year)	Exclusion criteria
Yang (2018) [16]	All patients had undergone renal US or CT and cystoscopy to exclude tumour, lithiasis, or urogenital abnormality
Lorenzo-Gomez (2015) [17]	Chronic kidney insufficiency and immunosuppressive therapy
Lorenzo-Gomez (2013) [18]	Not specified
Wagenlehner (2015) [27]	On-going acute, persistent, or complicated UTI Immunostimulating or suppressive therapy within 3 mo
Brodie (2017)	
Tammen (1988) [19]	Dysuria without positive bacteriological result Confirmed urinary tract anomalies with stasis or lithiasis
Tammen (1990) [20]	Negative bacteriological finding Indwelling urinary catheter, pregnancy, recurrent postcoital cystitis Urinary tract anomalies
Magasi (1994) [21]	Obstructive uropathy, indwelling catheter, chronic pyelonephritis, vesicoureteric reflux, lithiasis
Bauer (2005) [22]	Complicated neurogenic or urogenital disorders, severe fever, CVS, renal or hepatic insufficiency, long-term antibiotic therapy, concomitant immunostimulating therapy
Hachen (1990) [23]	Obstructive uropathy, chronic pyelonephritis, vesicoureteric reflux, lithiasis
Schulman (1993) [24]	Urogenital anomalies, retention, lithiasis, negative bacteriological findings
Frey (1986) [26]	No comment
Lettgen (1996) [25]	Obstructive uropathy, chronic pyelonephritis, vesicoureteric reflux, lithiasis
Pisani (1992)	
Uehling (1997) [28]	Neurogenic bladder, indwelling catheter, kidney stone disease, interstitial cystitis, urinary diversion
Uehling (2003) [29]	Anatomical abnormalities Ceased antibiotic prophylaxis 1 wk prior to commencement
Hopkins (2007) [30]	Urogenital anatomical abnormalities, neurogenic bladder, interstitial cystitis, kidney stone disease, indwelling catheter, or urinary diversion
Nayir (1995) [31]	No anatomical malformation or micturition disorders
Huttner (2017) [32]	Pregnant, lactating, active urinary tract disease/UTI, HIV seropositivity, uncontrolled diabetes mellitus, postcoital antibiotic, previous immune stimulatory therapy

CT = computed tomography; HIV = human immunodeficiency virus; US = ultrasound; UTI = urinary tract infection.

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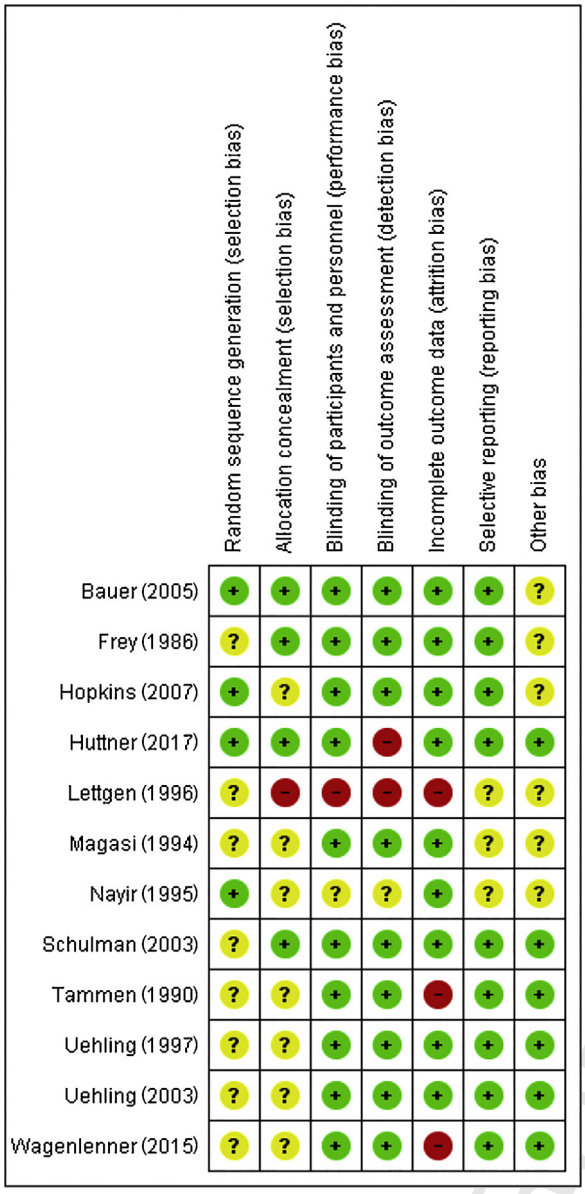

Fig. 7 – Risk of bias assessment.

currently limited by the number, quality, and duration of follow-up reported so far, with some products lacking RCT evidence of efficacy.

To date, the study population focuses on the analysis of female adult patients without urogenital abnormalities. Application of its use has been attempted to be reviewed in a small subset of patients outside of the uncomplicated rUTIs, such as patients with spinal cord injury and female paediatric patients [23,31]. However, analysis in these cohorts is limited to small numbers with poor quality of evidence. Subgroup analysis within studies is lacking; while a proportion of patients are men, there is no study specifically reviewing or comparing these outcomes. Although women are significantly more likely to develop rUTIs than men, a review of outcomes for men in comparison with women is also required.

4.1.2. Long-term role for vaccines in rUTIs

Long-term efficacy (>12 mo) of any available vaccine cannot be commented upon and is a significant limitation to all studies currently available. Uromune provides the longest follow-up data at 15 mo, but this remains in a retrospective cohort study. Overall, seven studies provided data up to 12 mo, with the remaining providing between 5 and 9 mo. There is evidence that UTI recurrence rate increases from 6 to 12 mo (relative risk 0.65 at 6 mo and 0.85 at 12 mo); therefore, duration of efficacy needs to be investigated further along with the role and timing of booster vaccination.

4.1.3. Standardisation of inclusion and exclusion criteria of patients in studies

Inclusion criteria were variable between studies, with a consensus on the definition of an rUTI lacking. In more recent studies, this has moved towards the EAU definition for an rUTI [4], with five studies adhering to this [16–18,27,32], although historically there was a significant variation. Tammen [20] and Magasi et al. [21] defined a UTI as the presence of bacteriuria only, with no specification to symptoms, and two further studies provided no definition. This may account for discrepancies in the number of rUTIs reported between studies. The level of bacteriuria also ranges between 10^3 and 10^5 CFU/ml on urine microscopy. In order for future studies to directly compare the results, a consensus must be reached on the reported definition of rUTIs, further infection, and bacteriuria.

Exclusion criteria, likewise, varied significantly between studies (Table 4); a high proportion excluded patients with urinary tract abnormalities, neurogenic bladder, indwelling catheters or urinary diversion, pre-existing urolithiasis, reflux, or chronic renal insufficiency. However, those that

Table 5 – Newcastle-Ottawa Quality Assessment Scale for cohort studies

Cohort study	Newcastle-Ottawa Quality Assessment Scale			
	Selection (4 stars total)	Comparability (2 stars total)	Outcome (3 stars total)	Total (out of 9)
Yang (2018) [16] (Uromune)	**	–	**	4
Lorenzo-Gomez (2015) [17] (Uromune)	***	–	***	6
Lorenzo-Gomez (2013) [18] (Uromune)	***	–	***	6
Tammen (1988) [19] (UroVaxom)	**	–	**	4

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included patients with these prerequisites did not complete subgroup analysis, nor was it clear whether these conditions were recorded or controlled for.

Many studies reported were of poor quality, with confounding prophylactic antibiotic therapy stopped 2 wk into the study or 1 wk prior to the commencement of the study [28,29]. Several studies also admitted patients in the trial at the time of a UTI, providing them with a treatment course of antibiotics at this stage [19,21,26]. These confounding factors were not adjusted for or commented upon. The majority of exclusions were due to major protocol breaches, which included missed follow-up appointments, poor compliance, and withdrawal of consent. This led to a high level of attrition in certain cases and missing data, leading to a reporting bias.

4.1.4. Patient compliance and satisfaction with the vaccines used

Patient compliance and satisfaction with treatment protocol is essential to assess treatment efficacy. Satisfaction rates of patients using Uromune was high, being straightforward and pain free in its administration [16]. One patient discontinued therapy due to inability to remain fasted 2 h prior to administration. Poor compliance appeared to contribute to 3.5% of dropouts for UroVaxom, and while Solco-Urovac reported no dropouts secondary to compliance, leakage of the vaccine vaginally was noted, and patients were required to remain supine for 15 min [28]. Ease of administration and monitoring must be considered in the on-going evaluation of immunotherapy.

4.1.5. Safety of currently used vaccines

The safety of vaccination for UroVaxom, Uromune, Solco-Urovac vaginal suppository, and ExPEC4 V has been demonstrated in all studies published to date, with minimal adverse events leading to treatment withdrawal, and no adverse event leading to hospitalisation or death. Depending on the vaccine, the most common side effects are GI upset, headache, and vaginal irritation. Importantly, Solco-Urovac IM injection cannot be commented upon, as the single study in this patient cohort did not report a safety profile.

4.1.6. Areas of research and future use of vaccines

While UroVaxom shows efficacy in the short term, all vaccination therapies remain under-reviewed, with a small number of patients contributing to RCTs or larger cohorts retrospectively reviewed. Although the safety profile for vaccination appears to be acceptable, further large-scale, placebo- or antibiotic-controlled trials are required to review the efficacy of Uromune, Solco-Urovac, and ExPEC4 V.

According to the EAU guidelines, UroVaxom (OM-89) has a good safety profile with a proven efficacy and could be recommended for females with rUTIs [34]. Similarly, there seems to be a place for D-mannose and intravesical antibiotics for some patients, but these cannot be recommended routinely [34,35]. Currently, trials are underway for both Uromune and D-mannose, which should report on the findings in the next 2 yr [36,37]. Vaccines are also being trailed for urological malignancies, and new agents and novel combinations will help potentially tailor immunotherapy strategies against malignancies [38].

5. Conclusions

Vaccines seem to have a short-term role in the prevention of rUTIs, with tolerable side effects. However, due to a lack of uniformity of definitions and long-term follow-up, more trials are needed. Similarly, the vaccination schedule and the role of boosters need to be established thorough high-quality large RCTs.

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Study concept and design: Somani.
Acquisition of data: Prattley, Somani.
Analysis and interpretation of data: Geraghty.
Drafting of the manuscript: Prattley.
Critical revision of the manuscript for important intellectual content: Prattley, Moore, Somani.
Statistical analysis: Geraghty.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Somani.
Other: None.

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