Review

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Vaccines for the prevention of recurrent urinary tract infections: a systematic review

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Objectives

To systematically review the evidence regarding the efficacy of vaccines or immunostimulants in reducing the recurrence rate of urinary tract infections (UTIs).

Materials and Methods

The Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica dataBASE (EMBASE), PubMed, Cochrane Library, World Health Organization (WHO) International Clinical Trials Registry Platform Search Portal, and conference abstracts were searched up to January 2018 for English-titled citations. Randomised placebo-controlled trials evaluating UTI recurrence rates in adult patients with recurrent UTIs treated with a vaccine were selected by two independent reviewers according to the Population, Interventions, Comparators, and Outcomes (PICO) criteria. Differences in recurrence rates in study populations for individual trials were calculated and pooled, and risk ratios (RRs) using random effects models were calculated. Risk of bias was assessed using the Cochrane Collaboration's tool and heterogeneity was assessed using chi-squared and I^2 testing. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to evaluate the quality of evidence (QOE) and summarise findings.

Results

In all, 599 records were identified, of which 10 studies were included. A total of 1537 patients were recruited and analysed, on whom data were presented. Three candidate vaccines were studied: Uro-Vaxom® (OM Pharma, Myerlin, Switzerland), Urovac® (Solco Basel Ltd, Basel, Switzerland), and ExPEC4V (GlycoVaxyn AG, Schlieren, Switzerland). At trial endpoint, the use of vaccines appeared to reduce UTI recurrence compared to placebo (RR 0.74, 95% confidence interval [CI] 0.67–0.81; low QOE). Uro-Vaxom showed the greatest reduction in UTI recurrence rate; the maximal effect was seen at 3 months compared with 6 months after initial treatment (RR 0.67, 95% CI 0.57–0.78; and RR 0.78, 95% CI 0.69–0.88, respectively; low QOE). Urovac may also reduce risk of UTI recurrence (RR 0.75, 95% CI 0.63–0.89; low QOE). ExPEC4V does not appear to reduce UTI recurrence compared to placebo at study endpoint (RR 0.82, 95% CI 0.62–1.10; low QOE). Substantial heterogeneity was observed across the included studies (chi-squared = 54.58; $P < 0.001$, $I^2 = 84\%$).

Conclusions

While there is evidence for the efficacy of vaccines in patients with recurrent UTIs, significant heterogeneity amongst these studies renders interpretation and recommendation for routine clinical use difficult at present. Further randomised trials using consistent definitions and endpoints are needed to study the long-term efficacy and safety of vaccines for infection prevention in patients with recurrent UTIs.

Keywords

urinary tract infection, vaccine, Uro-Vaxom, Urovac, ExPEC4V, #UroUTI

Introduction

UTIs are amongst the commonest bacterial infections, with a worldwide prevalence of community-associated UTIs of 0.7%. They pose a significant burden of disease globally, accounting for a significant proportion of healthcare-associated infections; almost a quarter of such infections occur in developing countries, with 12.9% and 19.6% occurring in the USA and Europe, respectively [1]. Women are disproportionately affected, with 10% aged >18 years

reporting at least one suspected UTI per year, of whom 20–40% experience recurrent infection [2,3]. The treatment of UTIs has become increasingly hindered by growing antibiotic resistance. Resistance to trimethoprim, the first-line agent for uncomplicated lower UTIs in many parts of the UK, has been reported as >20%. Furthermore, resistance to co-trimoxazole, the most common first-line treatment worldwide, is also widespread, particularly in developing countries, where it has been reported as high as 64%. Isolation of resistant urinary isolates is often associated with previous exposure to antibiotics [4]. In light of the high prevalence and recurrence rates of UTIs and rising antibiotic resistance, a number of different preventative interventions have been investigated in recent years.

Vaccine Strategies

Vaccines for the prevention of recurrent UTIs have been an important focus of study, the main aim of which is, rather than to kill infectious pathogens, to protect the host against infection by priming the immune response to uropathogens. Proof of concept and attempts at developing vaccines preceded an understanding of the exact mechanism of action of such immunostimulants.

Different vaccines strategies have employed the use of extracts derived from a range of uropathogens. OM-89, also known as Uro-Vaxom® (Vifor Pharma Ltd, OM Pharma, Myerlin, Switzerland), was initially registered for the prevention of recurrent cystitis in Germany and Switzerland [5]. This bacterial extract consists of lyophilised bacterial lysates derived from 18 different strains of *Escherichia coli* frequently implicated in the pathogenesis of UTIs. Another vaccine preparation, Urovac® (Solco Basel Ltd, Basel, Switzerland), consists of 10 heat-killed uropathogenic species; this includes six serotypes of *E. coli*, *Proteus vulgaris*, *Klebsiella pneumoniae, Morganella morganii*, and *Enterococcus faecalis*, thereby incorporating a broader range of commonly implicated uropathogens and in theory providing broad protection. Moreover, one of the most recent developments is ExPEC4V (GlycoVaxyn AG, Schlieren, Switzerland), consisting of four bioconjugates containing O-antigens of *E. coli* serotypes O1A, O2, O6A, and O25B, a key immune evasion strategy utilised by the bacterium.

The objective of the present systematic review was to determine the efficacy and safety of immunostimulants in preventing UTI in adult patients with a history of recurrent UTIs.

Materials and Methods

Search Methods

We searched The Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica dataBASE (EMBASE), PubMed, Cochrane Library and the WHO International Clinical Trials Registry Platform Search Portal in January 2018 using search terms listed in Appendix 1. In addition, hand-searching of urology-related journals and proceedings of major urology conferences was undertaken.

Eligibility Criteria

Types of studies, participants, and interventions

All randomised controlled trials (RCTs) assessing the effects of uropathogen-based candidate vaccines in comparison to placebo in human subjects were eligible. Adult (>18 years) male and female participants with a history of recurrent UTIs, as defined by the study authors, were eligible. Studies including the following populations or groups were excluded: indwelling catheter; pregnancy; lactation; complicated neurogenic urogenital disorders; severe cardiovascular disease, renal or hepatic insufficiency; immunosuppressed patients; and uncontrolled diabetes mellitus.

Outcome Measures

The primary outcome measure was the rate of UTI recurrence at trial endpoint. Secondary outcome measures on which data are presented are dysuria and adverse events (AEs).

Data Collection and Analysis

Two reviewers (N.A. and M.H.) screened all abstracts and full-text articles independently. Any disagreement was resolved by discussion. Data were collected on study characteristics (year of study, use of intervention, use of placebo, study setting, inclusion and exclusion criteria, follow-up duration, funding sources), patients' characteristics (gender, age, UTI recurrence), and outcome data. Outcome measures are as aforementioned. References were managed using Mendeley Desktop. The reference lists of other review articles and key studies were also reviewed to ensure that no relevant studies were missed. We used standard methods according to the Preferred Reporting Items for Systematic Reviews (PRISMA) tool. The study protocol is registered on the International prospective register of systematic reviews: PROSPERO (CRD42017070006).

Data Analysis

Data on our outcomes of interest from the included RCTs were combined by meta-analysis to provide pooled effect estimates. We performed the statistical analyses according to the guidelines contained in the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0 [6]. For dichotomous outcomes, we used the Mantel–Haenszel method; for continuous outcomes, we used the inverse

Table 1 Included studies – vaccines, controls, study population, inclusion and exclusion criteria.

Study	Vaccine	Comparator(s)	*N* patients (Group 1)	*N* patients (Group 2)	*N* patients (Control)	Inclusion criteria	Exclusion criteria
Bauer et al. 2005 [13]	Uro-Vaxom	Placebo	231	N/A	222	Ambulatory female patients; age 18–65 years; ≥3 episodes/year; clinical signs persist ≥2 days; bacterial count $\geq 10^3$ in urine	Complicated/neurogenic urogenital disorders; severe fever; severe cardiovascular disease' renal or hepatic insufficiency
Frey et al. 1986 [12]	Uro-Vaxom	Placebo	32	N/A	32	Age 22–84 years; recurrent lower UTI (≥2 symptomatic episodes/year)	None stated.
Hopkins et al. 2007 [11]	Urovac	Urovac + booster vs Urovac vs placebo	26	24	25	Women; ≥3 UTIs previous year	Anatomical abnormalities; neurogenic bladder; interstitial cystitis; renal calculi; indwelling catheter; urinary diversion.
Huttner et al. 2017 [9]	ExPEC4V	ExPEC4V target dose vs EXPEC4V low dose vs placebo	93	6	95	Healthy women; age 18–70 years; clinical history recurrent UTI; ≥1 positive *E. coli* urine culture	Pregnant; lactating; active urinary tract disease/UTI; HIV seropositivity; uncontrolled diabetes mellitus; post-coital antibiotic; previous immune stimulatory therapy
Magasi et al. 1994 [15]	Uro-Vaxom	Placebo	58	N/A	54	Age 16–82 years; recurrent lower UTIs; bacteriuria with $\geq 10^5$ organisms/mL MSU	Pregnant; obstructive uropathy; indwelling catheter; chronic pyelonephritis; VUR; lithiasis.
Schulman et al. 1993 [16]	Uro-Vaxom	Placebo	82	N/A	78	Symptomatic recurring UTI; ≥2 recurrences/year; urine sample $\geq 10^5$ MSU/ $\geq 10^4$ CSU	Pregnant; dysuria without positive bacteriological findings; urinary tract anomalies with retention or lithiasis
Tammen et al. 1990 [14]	Uro-Vaxom	Placebo	61	N/A	59	Acute UTI; $\geq 10^5$ organisms MSU/10^4 organisms CSU; ≥2 recurrences preceding 6 months.	Dysuria without positive bacteriological findings; indwelling catheter; pregnancy; urinary tract anomalies; recurrent post-coital cystitis
Uehling et al. 2003 [10]	Urovac	Urovac + booster vs Urovac vs placebo	43	49	56	Age 18–74 years; ≥3 UTIs in previous year	Anatomical abnormalities of urinary tract as shown on excretory urogram or renal ultrasonography and cystoscopy
Uehling et al. 1997 [8]	Urovac	Urovac high dose vs Urovac low dose vs placebo	31	30	30	Age 18–82 years; ≥3 UTIs in previous year; normal excretory urography and/or renal ultrasonography; cystoscopy normal or with inflammatory changes	Neurogenic bladder; interstitial cystitis; renal calculi; indwelling catheter; urinary diversion; renal transplant recipients.
Wagenlehner et al. 2015 [17]	Uro-Vaxom	Placebo	132	N/A	131	Clinical/microbiological evidence uncomplicated UTI; ≥2 clinical symptoms within 7 days of study entry; negative urine analysis following antimicrobial treatment of acute UTI episode	Antibiotic prophylaxis within 1 month of study entry; immunostimulating therapy within 3 months of enrolment.

CSU, clean catch urine sample.

variance method. We used Review Manager (RevMan), version 5.3, software to perform the analyses.

Assessment of Scientific Quality

We determined the overall quality of evidence (QOE) according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which took into account five criteria not only related to internal validity (risk of bias, inconsistency, imprecision, and publication bias) but also external validity such as directness of the results. Two authors (N.A. and M.H.) independently rated the QOE for each outcome as 'high', 'moderate', 'low' or 'very low'; discrepancies were resolved by consensus or if needed by arbitration with the third author (Y.P.). We presented a summary of the evidence for the main outcomes in a 'summary of findings' table. This was performed using GRADEpro GDT software.

Assessment of Risk of Bias

Risk of bias was assessed according to the Cochrane Collaboration's tool for assessing risk of bias [7]. Studies were assessed according to risk of selection, performance, detection, attrition, and reporting bias, and were graded as 'low', 'high', and 'unclear' risk as defined in the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0.

Assessment of Heterogeneity

Heterogeneity of data was assessed using chi-squared testing and I^2 percentage.

Results

Description of Studies

Results of the Search

The study selection process is outlined in Appendices 2 and 3. We identified 599 records. After abstract and full-text screening, 589 records were excluded as they did not meet the eligibility criteria for this review. Characteristics of included studies are summarised in Table 1 [8–17].

On this basis, 10 RCTs were included, with a total of 1780 participants. Across the trials, data were not presented on a total of 243 patients; this was due to reasons as listed in Table 2 [8–17]. Data were therefore presented on 1537 patients according to the specified outcome measures.

Study Design

The included studies consisted of parallel RCTs using active comparators vs placebo, a non-immunogenic component administered by the same route as in the intervention groups.

Table 2 Number of participants recruited compared with number of participants on which data are presented, with reasons for any discrepancy.

Study	Total recruited	Total data presented	Reasons data not presented
Bauer et al. 2005 [13]	453	453	N/A
Frey et al. 1986 [12]	64	58	Reasons not given
Hopkins et al. 2007 [11]	75	75	N/A
Huttner et al. 2017 [9]	194	169	Violation of inclusion/exclusion criteria, withdrawal of consent, loss to follow-up, withdrawn by investigator, vaccine administration error, lack of efficacy data (reduced dose group), other non-specified reasons
Magasi et al. 1994 [15]	112	112	N/A
Schulman et al. 1993 [16]	166	142	Intolerable AEs, protocol deviation, inefficacy, other unknown reasons
Tammen et al. 1990 [14]	120	120	N/A
Uehling et al. 2003 [10]	54	54	N/A
Uehling et al. 1997 [8]	91	91	N/A
Wagenlehner et al. 2015 [17]	451	263	Dropped out of study, withdrawal of consent, loss to follow-up, AEs, other unknown reasons

With the exception of four studies, all used two groups; candidate vaccine vs placebo/control group. The remaining studies used three groups, so as to measure the effects of different vaccine doses [8,9], and the effects of primary and secondary immunisations [10,11], as shown in Table 3 [8–17]. Of these, for the purposes of comparison with the other studies, the group receiving the longest duration, highest dose, and/or additional booster, were used for greater comparison with placebo. In addition, the studies using three groups were also compared to one another separately, to assess the importance of dose, treatment duration, and secondary immunisation in order to confer the greatest degree of protection against recurrent UTI.

Sample Sizes

All studies took place in the outpatient setting. The smallest study included 64 participants [12] and the largest 453 participants [13]. Six studies recruited >100 participants [9,13–17].

Source of Funding

As shown in Table 4 [8–17], authors of five RCTs disclosed sources of funding for their work [8–11,13]. The authors of

Table 3 Included studies – vaccine and placebo regimens with follow-up. All studies took place in an outpatient setting.

Study	Group 1	Group 2	Control	Follow-up timeframe
Bauer et al. 2005 [13]	One capsule 6 mg lyophilised lysate *E. coli* daily during months 1–3, first 10 days each of months 7–9, no treatment in between and in months 10–12	N/A	One capsule placebo daily during months 1–3, first 10 days each of months 7–9, no treatment in between and in months 10–12	1-year follow-up Enrolment day 0 Control visits days 30, 90, 180, and 270. Final visit day 360. AE information, compliance monitoring, clinical assessment. Urine sample day 30. Blood samples days 90 and 270. Global assessment of efficacy day 360.
Frey et al. 1986 [12]	One capsule OM-8930 daily for first 3 months	N/A	One capsule placebo daily for first 3 months	6-month follow-up Examinations for bacteriuria, dysuria, and leucocyturia at: Study outset 1 week after end of antibiotic/ chemotherapeutic use 3 months after study outset 6 months after study outset At any symptomatic recurrence
Hopkins et al. 2007 [11]	Three 1×10^9 bacteria vaginal vaccine suppositories at weekly intervals followed by three vaccine suppositories at monthly intervals	Three 1×10^9 bacteria vaginal vaccine suppositories at weekly intervals followed by 3 placebo suppositories at monthly intervals	Three vaginal placebo suppositories at weekly intervals followed by three placebo suppositories at monthly intervals	22-week follow-up Collection of urine and vaginal secretion samples at: Before study entry Weeks following first suppository (2, 6, 10, 14, 18, 22) ELISA assay anti-*E. coli* antibodies UTIs and AE reporting
Huttner et al. 2017 [9]	Target-dose ExPEC4V (4 µg each surface polysaccharide)	Reduced-dose ExPEC4V (1 µg each surface polysaccharide)	Placebo	9-month follow-up. Clinical and laboratory assessments at days 1, 7, 30, and 270. Telephone check-up days 2, 90, 150, and 210.
Magasi et al. 1994 [15]	One capsule 6 mg lyophilised lysate *E. coli* daily for 3 months	N/A	One capsule placebo daily for 3 months	6-month follow-up. Examinations for bacteriuria, dysuria, and leucocyturia at: Study outset 1 week, 3 months, and 6 months following end of initial treatment, and at any symptomatic recurrence.
Schulman et al. 1993 [16]	One capsule bacterial extract daily for 3 months	N/A	One capsule placebo daily for 3 months	6-month follow-up. Clinical and laboratory assessments at entry, following first dose, 3 and 6 months. Additional visits at any eventual recurrence.
Tammen et al. 1990 [14]	One capsule 6 mg lyophilised lysate *E. coli* daily for 3 months	N/A	One capsule placebo daily for 3 months	3-month follow-up. Medical examination at 3 and 6 months.

Table 3 (continued)

Study	Group 1	Group 2	Control	Follow-up timeframe
Uehling et al. 2003 [10]	Vaginal vaccine suppository at weeks 0, 1, 2, 6, 10, and 14	Vaginal vaccine suppository at weeks 0, 1, and 2 Vaginal placebo suppository at weeks 6, 10 and 14	Vaginal placebo suppository at weeks 0, 1, 2, 6, 10, 14	6-month follow-up. Speculum examination and vaginal cultures at study outset, and repeated upon abnormal vaginal secretions or patient symptomatic. Collection of serum, urine, and cervical-vaginal secretions at intervals for each patient.
Uehling et al. 1997 [8]	Three 4×10^9 killed organisms (high dose) vaginal vaccine suppositories at weekly intervals	Three 2×10^9 killed organisms (low dose) vaginal vaccine suppositories at weekly intervals	Three vaginal placebo suppositories at weekly intervals	20-week follow-up. 4 weeks following initial treatment then at 4-weekly intervals through to week 20. Serum, urine, and vaginal irrigates.
Wagenlehner et al. 2015 [17]	One capsule of 6 mg OM-89S daily for 90 consecutive days	N/A	One capsule of placebo daily for 90 consecutive days	3-month follow-up following each of treatment Periods 1 and 2.

the remaining five RCTs did not disclose any sources of funding [12,14–16], of which one disclosed information regarding employment involvement of study authors with listed pharmaceutical companies [17].

Outcomes

UTI Recurrence Rate

UTI recurrence rate at trial endpoint was determined for each of the included studies with results pooled and a meta-analysis performed. Subgroup analyses for each vaccine at different time points where applicable were also performed. Overall at trial endpoint, the use of vaccines appears to reduce UTI recurrence compared to placebo (risk ratio [RR] 0.74, 95%CI 0.67–0.81; low QOE) (Fig. 1). Subgroup analysis at 3 and 6 months following Uro-Vaxom suggests that UTI recurrence is reduced compared to placebo with the greatest effect seen at 3 months (RR 0.67, 95%CI 0.57–0.78; low QOE) (Fig. 2) compared to 6 months (RR 0.78, 95%CI 0.69–0.88; low QOE) (Fig. 3).

All three RCTs studying Urovac used three study populations: two used vaccine with booster, without booster, and placebo [10,11]; whereas one used high-dose vaccine, low-dose-vaccine, and placebo [8]. Data on UTI recurrence rate were presented for each group in two studies [10,11] and in one study was presented collectively as vaccine vs placebo [8].

Overall Urovac reduces the risk of UTI recurrence (RR 0.75, 95%CI 0.63–0.89; low QOE). This effect appears more pronounced in patients receiving vaccine with booster compared to those receiving vaccine alone (Fig. 4).

A single RCT investigated ExPEC4V vs placebo on UTI recurrence [9]. The evidence from this trial suggests that ExPEC4V does not reduce UTI recurrence compared to placebo at study endpoint (RR 0.82, 95%CI 0.62–1.10; low QOE).

In accordance with the GRADE approach, the quality of evidence for the use of vaccines in the prevention of UTIs was rated 'low' (Table 5).

In the overall comparison of UTI recurrence rates reported at trial endpoint in each trial, data for 1495 patients are presented, as shown in Fig. 1. This discrepancy is because of the use of three patient groups in the Urovac studies. High-dose and booster-immunisation groups were used in comparison with placebo, when compared overall with the other UTI vaccine RCTs. Of the three Urovac RCTs, one RCT presented efficacy data for treatment groups collectively [8]. The other two Urovac RCTs presented these separately, and so data for the patients receiving Urovac without booster immunisation were not presented in the overall comparison, but has been presented in subgroup analysis (Fig. 4).

Table 4 Included studies – information on source of funding for each RCT.

Study	Source of funding
Bauer et al. 2005 [13]	Study supported by grant from OM Pharma, Meyrin/Geneva, Switzerland. No other financial support of any of the authors or members of Multicenter UTI Study Group.
Frey et al. 1986 [12]	No information on source of funding disclosed.
Hopkins et al. 2007 [11]	Study supported by National Institute of Health Grants DK30808, DK44378, and DK61574.
Huttner et al. 2017 [9]	GlycoVaxyn, Janssen Vaccines. Confirmation that funders of study had no role in data collection, data monitoring, safety monitoring, or data analysis.
Magasi et al. 1994 [15]	No information on source of funding disclosed.
Schulman et al. 1993 [16]	No information on source of funding disclosed.
Tammen et al. 1990 [14]	No information on source of funding disclosed.
Uehling et al. 2003 [10]	Study supported by National Institute of Health Grant DK30808 and Solco Basel Ltd, Basel, Switzerland.
Uehling et al. 1997 [8]	Study supported by Public Health Service Grant DK 30808 and Solco Basel Ltd, Basel, Switzerland.
Wagenlehner et al. 2015 [17]	No information on source of funding disclosed. Disclosure statement regarding employment and involvement of study authors with pharmaceutical companies. No direct involvement of said companies in study stated.

UTI Symptoms

Five studies assessed the role of Uro-Vaxom in reducing UTI symptoms in the form of dysuria vs placebo [12–16]. Overall, Uro-Vaxom appears to result in a large reduction in UTI symptoms in the form of dysuria at 6-months follow-up (RR 0.41, 95%CI 0.27–0.61; low QOE) (Fig. 5). None of the other included RCTs specifically reported on UTI symptom outcomes.

AEs

Five studies reported on the incidence of AEs. Four studies reported on the incidence of AEs in participants receiving Uro-Vaxom vs placebo [13,14,16,17]. These found no difference between Uro-Vaxom and placebo (RR 1.00, 95% CI 0.91–1.10).

A single RCT reported on the incidence of AEs in participants receiving ExPEC4V vs placebo [9]. This showed no significant difference in the incidence of AEs in those receiving ExPEC4V with those receiving placebo (RR 1.22, 95% CI 0.94–1.58).

Overall, no difference was seen in the incidence of AEs between patients receiving vaccine and placebo (RR 1.03, 95% CI 0.95–1.13; low QOE; Fig. 6).

AEs reported in patients receiving Uro-Vaxom included headache, gastro-intestinal (GI) side-effects, vertigo, pruritus, allergic reaction, and subcutaneous nodules. Those experienced in patients receiving ExPEC4V included injection-site affects, headache, and nausea. No AEs experienced with study treatments were reported to have resulted in hospitalisation or death (Table 6 [9,13,14,16,17]).

None of the studies assessing Urovac and the remaining Uro-Vaxom studies presented data on AEs.

Risk of Bias

Quality appraisal of the 10 included RCTs was performed using the Cochrane Collaboration's tool for assessing risk of bias, as shown in Fig. 7 [7]. In summary, methodology pertaining to patient recruitment and randomisation was unclear, suggesting possible risk of selection bias. Blinding of participants and personnel was satisfactory and blinding of outcome assessment was similarly acceptable in all but one case. Outcome measurement and reporting were deemed at high risk of bias where outcome data were not reported fully.

Discussion

In the present systematic review, we evaluated whether existing candidate vaccines were clinically effective in the prevention of recurrent UTIs. The pooled results of the RCTs suggest a possible role for vaccines and immunostimulants in the management of patients with recurrent UTIs, having found a reduced UTI recurrence rate at trial endpoints compared with placebo (Fig. 1). However, these results should be interpreted with caution due to the low quality of the included trials.

At this stage, a firm conclusion over the most effective vaccine for reducing the recurrence rate of UTIs cannot be reached. The heterogeneity of the definitions used for UTI, trial endpoints, eligibility criteria, and study protocols amongst the trials included in the review, together with the low QOE was a major limiting factor for reliable and accurate comparison.

As discussed, 10 RCTs were included that studied three candidate vaccines; six studied Uro-Vaxom; three studied Urovac; and one studied ExPEC4V. One paper, Wagenlehner et al., 2015 [17], studied OM-89S, a vaccine using the same strains of *E. coli* as Uro-Vaxom (OM-89) but manufactured by a different process; a modified lytic procedure was employed with this vaccine. It is unclear whether this manufacturing process has any effect on the overall efficacy of the vaccine, but OM-89S is no longer being produced.

The comparison of the studies was limited by the nature of definition of UTIs, and the duration over which the interventions were assessed against placebo. Schulman et al. [16] defined recurrence of UTI as the presence of bacteriuria with $\geq 10^5$ bacteria/mL; however, in the absence of symptoms,

Fig. 1 UTI recurrence rate across all RCTs, as assessed at the trial endpoints respectively. M-H, Mantel–Haenszel.

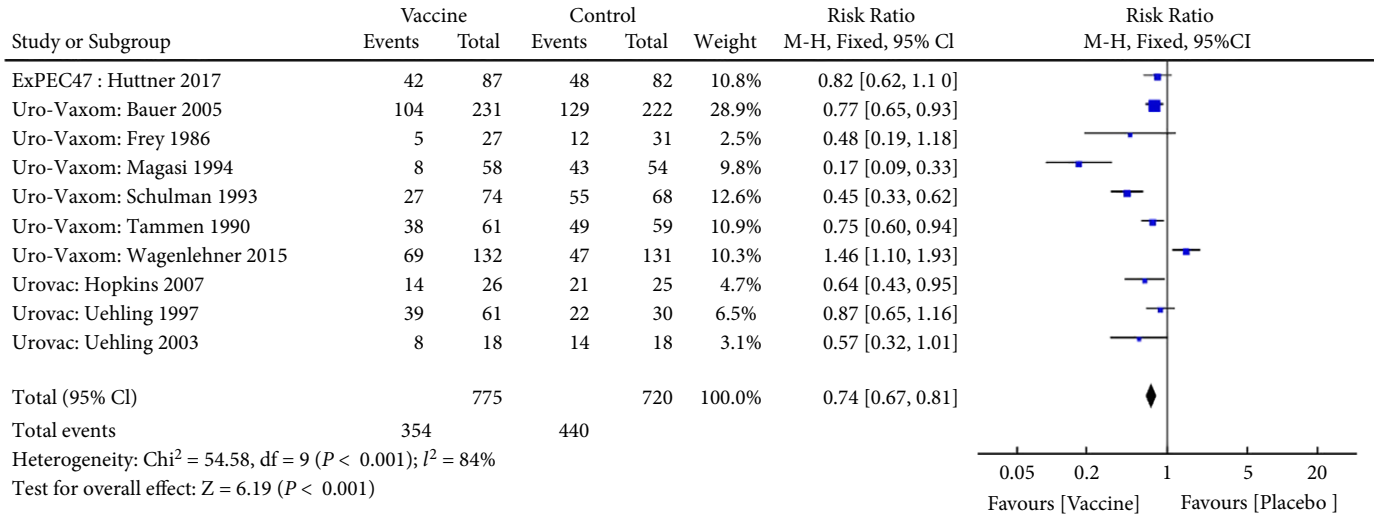


Fig. 2 UTI recurrence rate at 3 months, Uro-Vaxom vs placebo. M-H, Mantel–Haenszel.

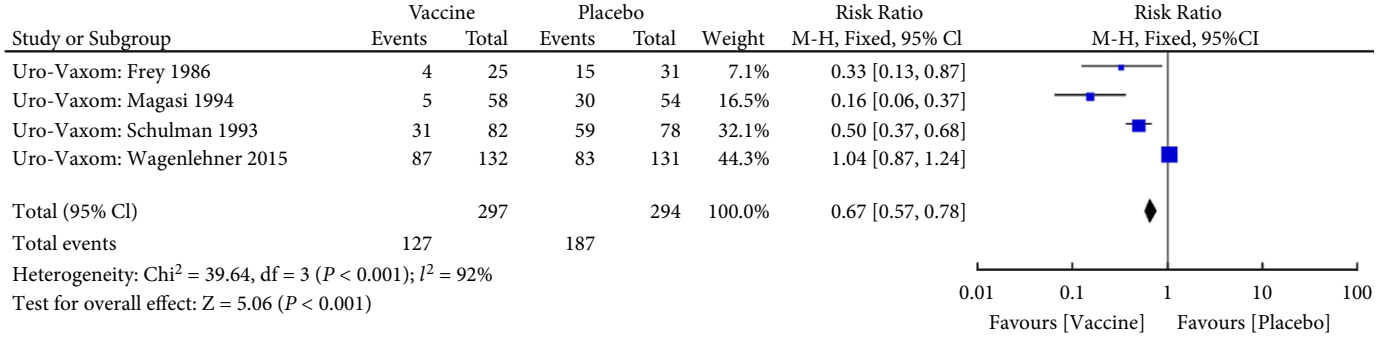
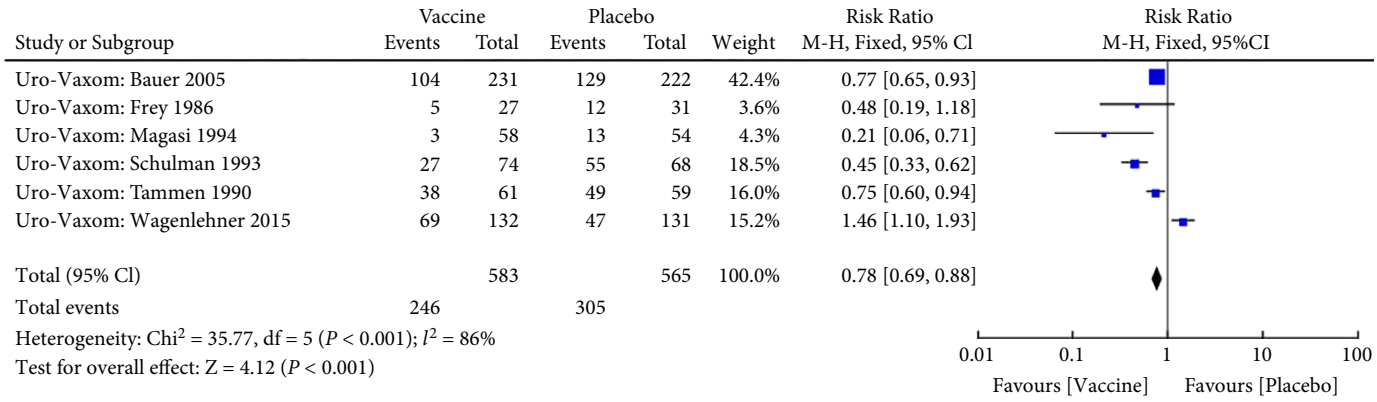


Fig. 3 UTI recurrence rate at 6 months, Uro-Vaxom vs placebo. M-H, Mantel–Haenszel.



this may be classed as asymptomatic bacteriuria as opposed to recurrence of UTI, as defined by Wagenlehner et al. [17], who rather defined UTI as the presence of at least two clinical symptoms accompanied by bacteriuria with $\geq 10^3$ bacteria/mL. Equally, Bauer et al. [13] provided a clear definition of acute UTI as the presence of bacteriuria of $\geq 10^3$ bacteria/mL, with at least two of the three symptoms (dysuria, burning sensation of micturition, and urinary frequency) lasting for ≥2 days. Given the wide discrepancy of definition, it is difficult to comment on whether the data provided by these studies corresponds to the precisely identical clinical phenomenon that is UTI.

Fig. 4 All UTI recurrence rate at 20 weeks, Urovac vs placebo. M-H, Mantel–Haenszel.

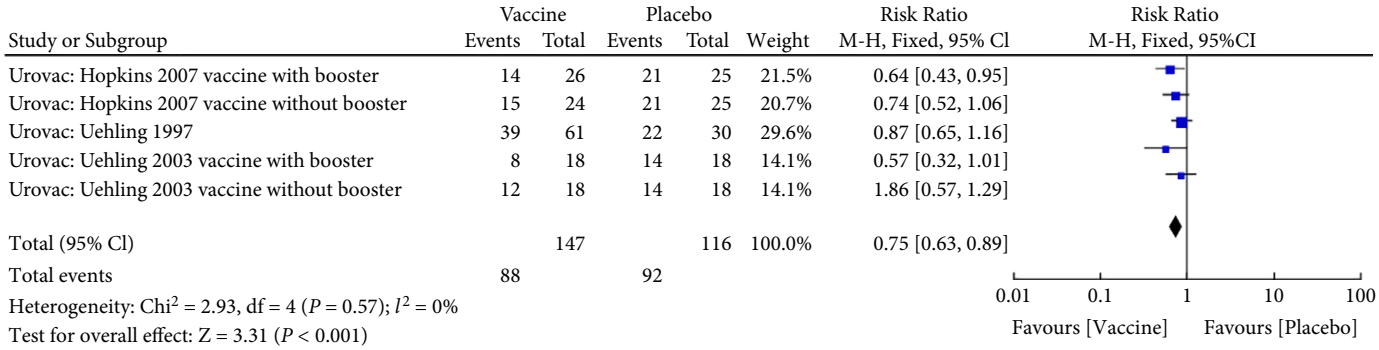
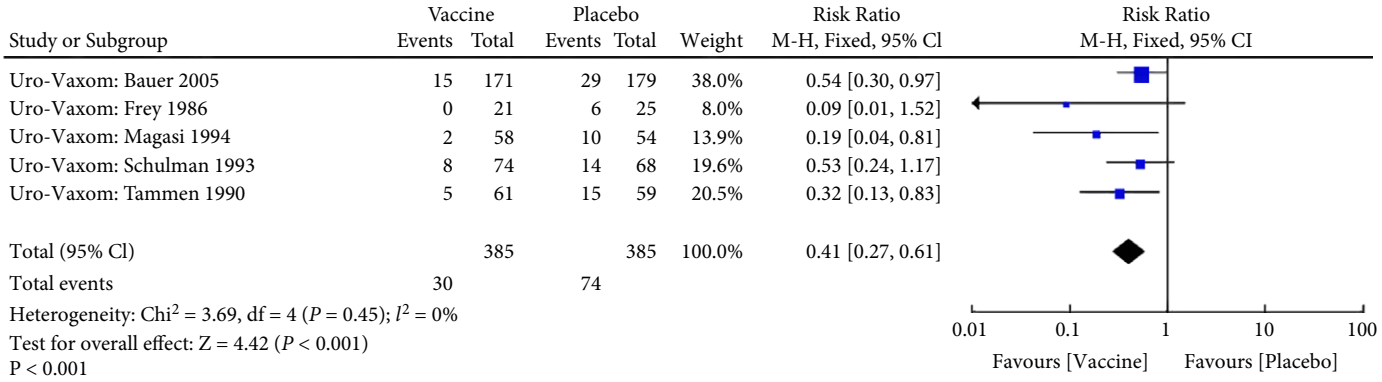


Table 5 Summary of findings and assessment of quality of evidence for outcomes.

Outcomes	No. of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects Risk with placebo	Anticipated absolute effects Risk difference with UTI vaccines
UTI recurrence rate (overall)	1495 (10 RCTs)	⨁⨁◯◯ LOW*,†,‡	RR 0.74 (0.67–0.81)	611 per 1000	159 fewer per 1000 (202 fewer to 116 fewer)
UTI recurrence rate at 20 weeks	263 (5 RCTs)	⨁⨁◯◯ LOW*,†,‡	RR 0.75 (0.63–0.89)	793 per 1000	198 fewer per 1000 (293 fewer to 87 fewer)
UTI recurrence rate at 3 months	591 (4 RCTs)	⨁⨁◯◯ LOW *,†,‡	RR 0.67 (0.57–0.78)	636 per 1000	210 fewer per 1000 (274 fewer to 140 fewer)
UTI recurrence rate at 6 months	1148 (6 RCTs)	⨁⨁◯◯ LOW *,†,‡	RR 0.78 (0.69–0.88)	540 per 1000	119 fewer per 1000 (167 fewer to 65 fewer)
Dysuria at 6 months	770 (5 RCTs)	⨁⨁◯◯ LOW *,†,‡	RR 0.41 (0.27–0.61)	192 per 1000	113 fewer per 1000 (140 fewer to 75 fewer)
AEs	1378 (5 RCTs)	⨁⨁◯◯ LOW *,†,‡	RR 1.03 (0.95–1.13)	469 per 1000	14 more per 1000 (from 23 fewer to 61more)

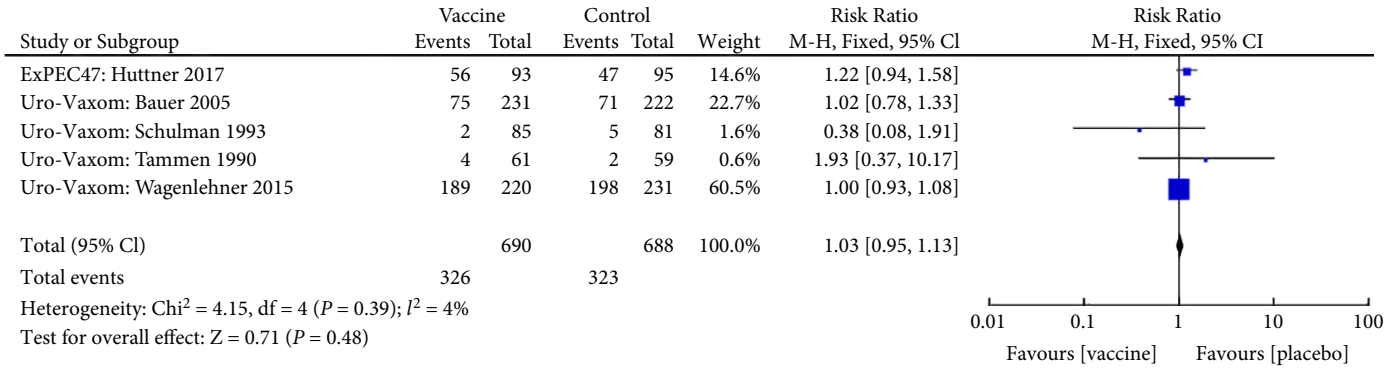
*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). GRADE Working Group grades of evidence. High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. *Reporting bias. †Inconsistent outcome definitions. ‡Variable vaccine and/or dosage protocol.

Fig. 5 Dysuria at 6 months, Uro-Vaxom vs placebo. M-H, Mantel–Haenszel.



This might in part be contributed to by the study populations used, as illustrated by the differences in inclusion and exclusion criteria. On a broader level, adult patients with a history of recurrent UTIs were included in all studies; however, the definition of recurrent UTI was not uniform across all studies. Schulman et al. [16] defined this as ≥2 episodes/year, with Frey et al. [12] going further as to specify these as symptomatic episodes, whereas other studies defined this as ≥3 episodes/year [8,10,11,13]. Huttner et al. [9] provided two possible definitions, with two or more

Fig. 6 Incidence of AEs, vaccine vs placebo. M-H, Mantel–Haenszel.



recurrences over 6 months, as also stated by Tammen et al. [14]; or alternatively three or more over the past year [9,15]. By contrast, Magasi et al. [15] provided no definition at all for what constituted a history of recurrent UTIs.

More contentious was the issue of exclusion criteria. Firstly, Frey et al. [12] did not state any exclusion criteria at all. While Frey et al. [12] stated the inclusion of adult patients with recurrent UTI, defining this as ≥2 episodes/year, and with acute UTI, defined as at least 10^4/mL mid-stream urine (MSU), no other differentiators are stated; therefore, one cannot comment on whether these patients had urogenital tract abnormalities. All other studies specifically excluded patients with urogenital tract abnormalities. Furthermore, Huttner et al. [9] excluded patients with acute urinary tract disease or infection from the comparison of ExPEC4V with placebo.

An additional limitation of the existing RCTs is the lack of subgroup analysis, including no differentiation between male and female participants; whilst some trials specified female participants amongst inclusion criteria [9,11,13], not all clarified this and appeared to include both male and female patients with recurrent UTIs. As the pathogenesis of UTIs affecting some men may be different to those of women, while most of the studies excluded patients with urogenital tract abnormalities [8,10,11,13–16], this limited interpretation of the results. On the same level, the lack of differentiation of specific patient populations, such as those with neurogenic lower urinary tract dysfunction, would also affect interpretation of the results. Further studies specifically within the population of male patients experiencing recurrent UTIs and also with subgroup analyses for specific patient groups experiencing recurrent UTIs are therefore needed to analyse efficacy of vaccines in preventing UTIs in different patient groups.

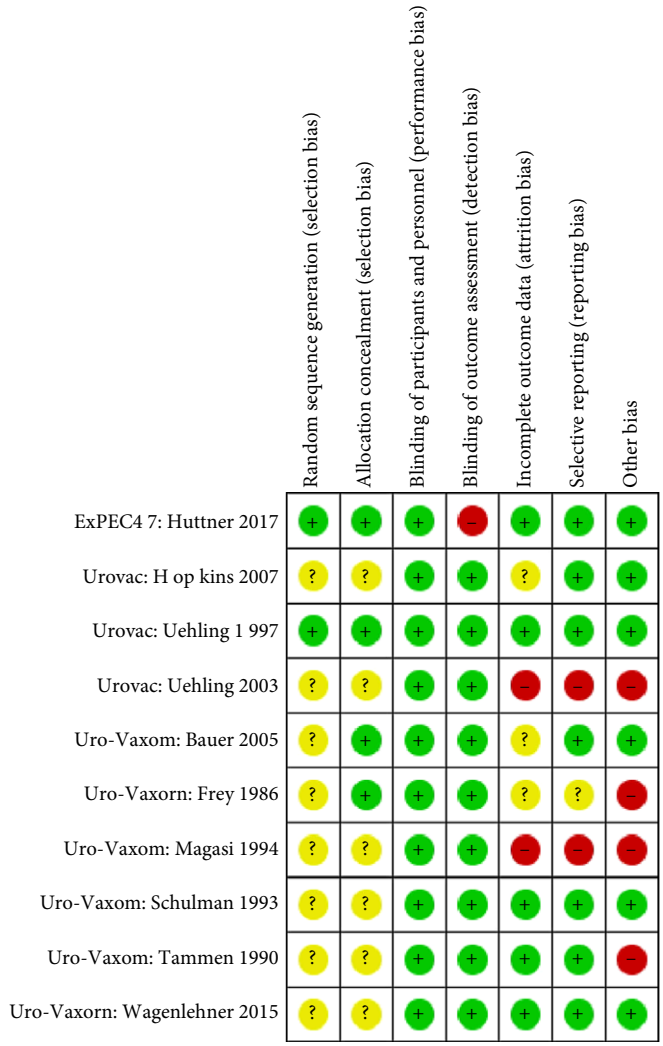
Moreover, one of the most important prerequisites of a successful vaccine in order to prevent future re-infection is the establishment of immune memory, in order for a secondary immune response to be triggered upon confrontation of the immune system with the uropathogens included within the vaccine formulations. None of the Urovac papers were able to illustrate statistically significant differences in anti-*E. coli* antibody concentrations within urine, serum, and vaginal secretions; nevertheless, Hopkins et al. [11] concluded that Urovac has greater potential in the induction of an antibody response within the vagina and bladder mucosa than a parenteral vaccine. Not only did comparison with placebo not yield any results of statistical significance, but no study has compared vaccine efficacy of parenteral vs vaginal vaccines in terms of antibody induction.

With regards to the safety and incidence of AEs in patients receiving vaccine vs placebo, four of six Uro-Vaxom RCTs and the ExPEC4V RCT presented data on AEs. Reassuringly, no AEs resulting in hospitalisation or death were reported. Of the AEs reported by study participants, the tenacity of any causal link with either vaccine remains to be fully elucidated and indeed not all were deemed directly attributable to either treatment. As shown in Table 6, a range of AEs were reported; however, not described in all cases in detail by the study authors. As in the case of Wagenlehner et al. [17], serious AEs were noted; however, with no description provided. Also, the degree of variation of the incidence of AEs as reported by these studies is intriguingly vast, even with the same vaccine preparation; Wagenlehner et al. 2015 reported an incidence of AEs of 85.91% amongst participants receiving Uro-Vaxom, whereas that reported by Schulman et al. 1993 was 2.35% [16,17]. This raises questions regarding the methods by which patients were assessed for AEs by study investigators, and how links were drawn between the symptoms with which the study participants presented and the treatments they received; there is the possibility that studies reporting high AE rates may have erroneously attributed idiosyncratic symptoms to the vaccine and likewise those reporting low AEs failed to attribute reactions to the vaccine. Indeed in some cases, a distinction was made between AEs reported and those deemed attributable to the vaccine by physicians [16,17]; it would be interesting to see how the investigators determined the possibility of direct

Table 6 Description of AEs as reported in the RCTs.

Study	Vaccine	Comparator(s)	Incidence of AEs, % (Vaccine)	Incidence of AEs, % (Control)	Details of AEs
Huttner et al. 2017 [9]	ExPEC4V	Placebo	60.22	49.47	Most common side-effects (ExPEC4V vs placebo): • Injection-site erythema (30% vs 21%) • Injection-site pain (31% vs 21%) • Injection-site swelling (19% vs 13%) • Headache (17% vs 12%) • Nausea (4% vs 3%) Other less frequent AEs experienced with ExPEC4V: dizziness, fever, chills, diarrhoea, dysgeusia, epigastric pain, hyperhidrosis, injection-site warmth, upper abdominal pain.
Bauer et al. 2005 [13]	Uro-Vaxom	Placebo	32.47	31.98	Most common side effects: • Headache (17% both groups) • GI side-effects (15% both groups)* Serious AEs: Uro-Vaxom (n = 11), placebo (n = 4)* No hospitalisations due to study treatments. *Nature not described
Schulman et al. 1993 [16]	Uro-Vaxom	Placebo	2.35	6.17	Uro-Vaxom: • Vertigo with visual disturbance (n = 1) • Subcutaneous nodules (n = 1)* Placebo: • Vertigo (n = 2)^{0} • Vomiting (n = 2)^{0} • Epigastric pain (n = 1)^{0} • Sleep disturbances (n = 1)^{0} • Subcutaneous nodules (n = 1)$^{\sim}$ • Pollakiuria (n = 1)* • Precipitated voiding (n = 1)* ^{0}AEs deemed to have possible relationship to treatment $^{\sim}$AEs deemed to have unlikely relationship to treatment *AEs deemed to have no relationship with treatment
Tammen et al. 1990 [14]	Uro-Vaxom	Placebo	6.56	3.38	Uro-Vaxom: • Pruritus (n = 1) • Allergic reaction leading to withdrawal* (n = 1) • Diarrhoea (n = 1) • Headache with flushing (n = 1) Placebo: • Nausea (n = 1) • Erythema (n = 1) *Nature not described
Wagenlehner et al. 2015 [17]	Uro-Vaxom	Placebo	85.91	85.71	Uro-Vaxom: • 189 patients had AEs. • 13 patients had serious AEs • 7 patients discontinued treatment Placebo: • 198 patients had AEs • 15 patients had serious AEs • 9 patients discontinued treatment No description of any AEs. No AEs leading to death.

Fig. 7 Risk of bias summary.



association of certain AEs with vaccine, with no statistically significant difference in symptoms as experienced between vaccine and placebo groups, and while the exact intended therapeutic effect of such vaccines remains to be fully elucidated.

While RCTs on vaccines for the prevention for recurrent UTIs have only been completed for those discussed, other vaccine strategies are in the process of development and merit mention. MV140 (Uromune®; Immunotek, Madrid, Spain) is a bacterial vaccine consisting of a mixture of selected strains of *E. coli, K. pneumoniae, P. vulgaris*, and *E. faecalis*, incorporated into a sublingual preparation. A retrospective observational study showed reduction in the mean number of infections and in total number of positive urine cultures in patients receiving MV140 compared with those receiving prophylactic antibiotics [18]. Similarly positive effects were observed in a retrospective cohort study, which reported significantly longer UTI-free period [19]. A recent study documented the first experience of MV140 in the UK in the treatment of women with recurrent UTIs, which found 78% of women receiving the vaccine to not experience UTI recurrence in the 12-month follow-up period [20]. At present, a multicentre RCT involving three treatment groups is in the process of recruitment, aiming to study the efficacy and safety of MV140 in women with recurrent UTIs; however, as no RCT has been performed using this vaccine to date, it has not been included in our present analysis and no recommendation can be made regarding its use.

Conclusions

There is some evidence for reduction of recurrence in patients affected by recurrent UTIs receiving vaccination; however, before any vaccines can be recommended for routine clinical use, further RCTs are required, using uniformity of definitions and large sample populations, using the vaccines evaluated in the present review and those currently in development.

As the purpose of vaccination is to induce immune memory to ensure lasting immunity, future trials should aim to also assess long-term vaccine efficacy with long-term follow-up. While the vaccines trialled to date have shown some efficacy according to clinical parameters, there is little evidence to date accounting for their immunogenicity. As antibody induction is key to adaptive immune responses to uropathogens, future trials should consider assessing for serum or urine antibody titres.

Acknowledgements

None.

Conflicts of interest

The authors confirm there are no conflicts of interest and no funding or other support was received for this systematic review.

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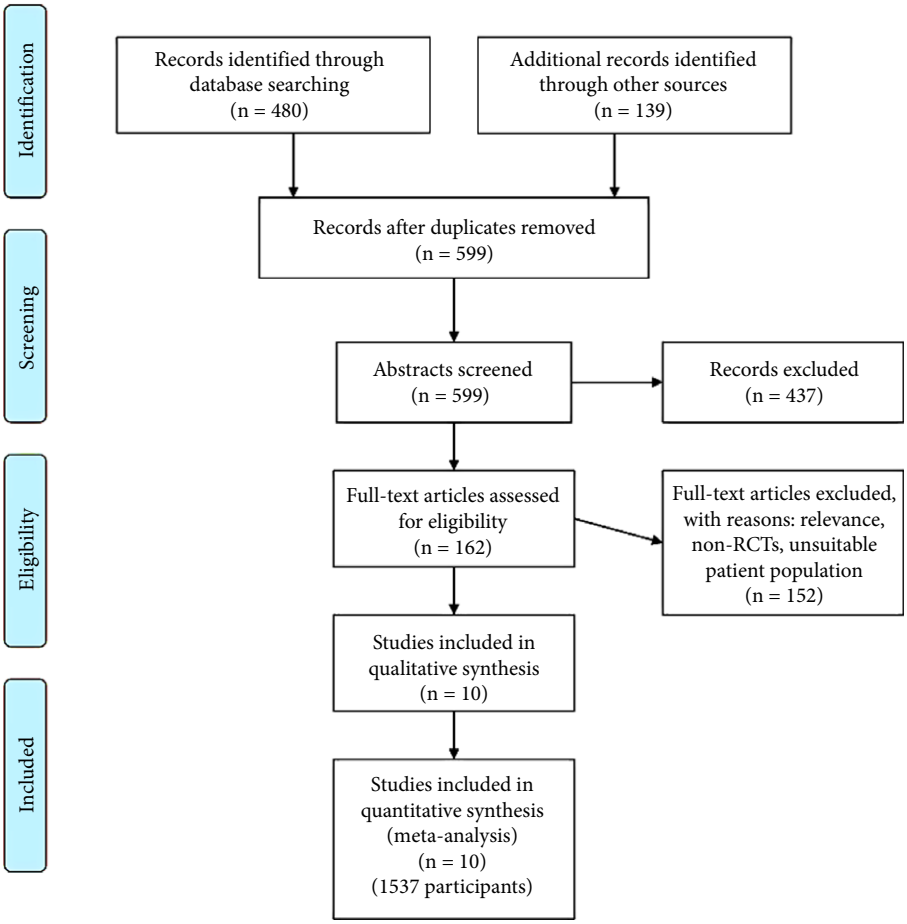
20 **Yang B, Foley S**. First experience in the UK of treating women with recurrent urinary tract infections with the bacterial vaccine Uromune®. *BJU Int* 2018; 121: 289–92

Appendix 1

Literature search terms used in this systematic review.

PUBMED: (((vaccine) OR (vaccines) OR (vaccination) OR (immunisation) OR (immunization)) AND ((urinary tract infection) OR ((urinary tract) AND (infection)) OR (UTI) OR (cystitis)) AND (recurrent)) ((('vaccines'[MeSH Terms] OR 'vaccines'[All Fields] OR 'vaccine'[All Fields]) OR ('vaccines'[MeSH Terms] OR 'vaccines'[All Fields]) OR ('vaccination'[MeSH Terms] OR 'vaccination'[All Fields]) OR ('immunisation'[All Fields] OR 'vaccination'[MeSH Terms] OR 'vaccination'[All Fields] OR 'immunization'[All Fields] OR 'immunization'[MeSH Terms]) OR ('immunisation'[All Fields] OR 'vaccination'[MeSH Terms] OR 'vaccination'[All Fields] OR 'immunization'[All Fields] OR 'immunization'[MeSH Terms])) AND (('urinary tract infections'[MeSH Terms] OR ('urinary'[All Fields] AND 'tract'[All Fields] AND 'infections'[All Fields]) OR 'urinary tract infections'[All Fields] OR ('urinary'[All Fields] AND 'tract'[All Fields] AND 'infection'[All Fields]) OR 'urinary tract infection'[All Fields]) OR (('urinary tract'[MeSH Terms] OR ('urinary'[All Fields] AND 'tract'[All Fields]) OR 'urinary tract'[All Fields]) AND ('infection'[MeSH Terms] OR 'infection'[All Fields])) OR UTI[All Fields] OR ('cystitis'[MeSH Terms] OR 'cystitis'[All Fields])) AND recurrent[All Fields]) AND ('loattrfull text'[sb] AND 'humans'[MeSH Terms])MeSH, Medical Subject Headings.

Appendix 2
PRISMA flowchart of study selection.



Appendix 3
PRISMA 2009 checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6,7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6,7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	16
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6,7,17
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6,7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10-11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Abbreviations: AE, adverse event; GI, gastro-intestinal; GRADE, Grading of Recommendations Assessment, Development and Evaluation (approach); MSU, mid-stream urine; PRISMA, Preferred Reporting Items for Systematic Reviews; QOE, quality of evidence; RCT, randomised controlled trial; RR, risk ratio.