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Impact of whole-cell bacterial immunoprophylaxis in the management of recurrent urinary tract infections in the frail elderly

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ABSTRACT

Purpose: This study aimed to determine the effectiveness of whole-cell bacterial immunotherapy, *i.e.* MV140 and autovaccines, in reducing the number of urinary tract infections (UTIs) in frail elderly patients with recurrent UTI (RUTI).

Method: A prospective cohort observational study was performed including 200 frail elderly subjects suffering RUTI, both females and males, between 2016 and 2018. The effectiveness of autovaccines and the polybacterial formulation MV140 (Uromune®), consisting of whole-cell heat-inactivated Escherichia coli 25%, Klebsiella pneumoniae 25%, Proteus vulgaris 25% and Enterococcus faecalis 25% were evaluated. Subjects initiated a 3-month sublingually daily course with MV140 or autovaccine, either first treatment or a new course if they had been previously vaccinated prior to inclusion in the study. Number of UTIs and quality of life (QoL, SF-36 score) were measured in the different study groups.

Results: The mean age for participants was 82.67 (SD, 7.12) for female and 80.23 (SD, 11.12) for male subjects. In all groups, 12 months following bacterial immunotherapy, the number of UTIs significantly decreased compared to before the treatment with autovaccine or MV140: the rate of reduction ranged between 7- and 40-fold. An increase in QoL scoring was also observed in any study group. When comparing medical interventions, MV140 conferred significantly higher benefit than autovaccines. For previously vaccinated individuals, a new 3-month course with MV140 or autovaccines provided further clinical improvement.

Conclusions: MV140 and autovaccines emerge as valuable immunoprophylaxis for the management of RUTI in the frail elderly, contributing to an improvement in patient's quality of life. Herein, MV140 has shown to confer a higher effectiveness compared to autovaccines, regardless sex or course of treatment.

1. Introduction

The frail elderly is defined as individuals over 65, dependents on others for activities of daily living and often at institutional care [1]. This population has a decrease in physiological reserves and

Abbreviations: GMP, Good Manufacturing Practices; QoL, Quality of life; RUTI, Recurrent UTI; UTIs, Urinary tract infections.

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a greater risk of decline, which places them in a situation of greater vulnerability to external disturbances and results in a greater probability of function loss, disability, dependence or presenting adverse health episodes, such as urinary tract infections (UTIs) [2–4]. Furthermore, age-associated changes in their immune system, together with increased exposure to nosocomial pathogens put the elderly at high risk for developing infections [5].

Recurrent urinary tract infections (RUTI) are defined as 3 or more episodes of UTIs within the last 12 months or 2 or more episodes within 6 months [6]. It has been widely demonstrated for many years that around 30% of women who present their first symptomatic infection suffer recurrences [7]. RUTI in postmenopausal women occurs with a frequency of 15–20%, being higher in institutionalized women [8]. In the male elderly, UTIs are more frequent in those individuals older than 65 years, due to a greater presence of prostatic pathology, urological manipulations, and reduced antibacterial activity of prostate secretions [9]. In addition to the fact that UTIs are the most common bacterial infections in the elderly, frail elderly population group has a high comorbidity, instrumentation and hospitalization rate, making UTIs more frequent [10]. As for the germs, *E. coli* is the most prevalent specie [11].

Non-antibiotic interventions that include bacterial immunoprophylaxis have gained relevance in the last few years for the management of recurrent infections [13]. Polyvalent bacterial preparations are not as pathogen-specific as autovaccines, that are elaborated from microorganisms isolated from urine samples of each patient, but have a broader spectrum of action. The immune system stimulation that is achieved with these polybacterial formulations exceeds the specific response against them, due to their great capacity to activate innate immunity and likely involving trained immunity mechanisms [13–16].

There are multiple studies that have demonstrated the clinical benefit of bacterial vaccines in the prevention of RUTI [17–19]. Particularly the sublingual polybacterial preparation MV140, that contains whole-cell heat-inactivated bacteria including the most common urinary pathogens (*E. coli, K. pneumoniae, E. faecalis, P. vulgaris*), has shown to strongly reduce the incidence as well as prevent the recurrence of UTI for a period of up to 24 months [20–26]. However, to date, there have been barely studies focused on the use of this immunoprophylaxis in frail elderly patients, as well as research evaluating the clinical benefit conferred by autovaccines in the management of RUTI.

In this study, we have evaluated the effectiveness of the polybacterial mixture MV140 and autovaccines, in frail elderly subjects with RUTI, assessing their ability to decrease the number of UTI episodes and to improve quality of life (QoL).

2. Methods

2.1. Study design and participants

An observational quasi-experimental prospective cohort study was carried out including two hundred subjects classified as "frail elderly" that suffered RUTI. The effectiveness of prophylaxis with the polybacterial preparation MV140 and autovaccines were evaluated, by measuring the reduction in the number of UTIs and improvement of quality of life. Subjects were enrolled in the study from March 1st 2016 to January 1st 2018. Both female (n = 160) and male (n = 40) participated in this study. The main inclusion criteria were frail elderly suffering RUTI, aged between 64 and 90 years old and capable of giving their informed consent (otherwise, it was provided by a legal representative). Subjects were excluded if they were allergic to any of the components of the treatment administered, suffered from urinary lithiasis or urinary bladder diverticula, had been subjected to urinary incontinence surgery or presented post-void residual urine greater than 100 mL. Subjects were allocated to treatment groups following pseudo-randomization (assignment based on period of entry to the study) as follows: from March 2016 to June 2017 subjects were included in MV140-receiving groups; from July 2017 to January 2018 subjects were included in autovaccine-administered groups.

Subjects received immunoprophylaxis with either autovaccines or MV140 (Uromune®; both manufactured by Inmunotek S.L., Spain; and distributed by QPharma, Spain). Both are immunotherapy (IT) consisting of whole-cell heat-inactivated microorganisms indicated for sublingual administration by spray. MV140 is a polybacterial preparation containing selected strains of the most common bacteria responsible for UTIs (*Escherichia coli* (25%), *Klebsiella pneumoniae* (25%), *Proteus vulgaris* (25%) and *Enterococcus faecalis* (25%)); whereas autovaccines are individualized treatments prepared from the microorganisms isolated from the urine sample of a patient. As excipients, both formulations contain glycerol, pineapple artificial flavouring, sodium chloride and water. Regarding preparation, microorganisms are grown from stock cultures (MV140) or urine samples (autovaccines), and, subsequently, are further inactivated by heat. Concentrates are resuspended in the described diluent and adjusted to the same final concentration (300 Formazin Turbidity Units -FTU/mL). All the manufacturing process is performed following Good Manufacturing Practices (GMP) procedures. Products are stored at 2–8 °C. The administered dose is 2 puffs of 100 μL each daily, avoiding the concomitant intake of food or beverages. Subjects without previous bacterial immunotherapy initiated a 3-month sublingually daily course with MV140 (n = 60 females and n = 10 males) or autovaccines (n = 20 females and n = 10 males). Additionally, a distinct group of subjects (following the same allocation strategy), that had received bacterial IT one year and a half before, were included in the study and administered a new 3-month daily course or 'boost'. All the individuals were followed up for a total of 12 months since initiation of the treatment.

We visited all enrolled subjects according to the following: first visit for study inclusion, follow-up at 3-, 6- and 12-months following initiation of the treatment.

We analyzed the following variables: age, sex, medical records (secondary diagnoses, concomitant treatments) as well as response to prophylaxis: UTI number and quality of life (QoL, score from SF-36 questionnaire).

Collaborating professionals filled out a data collection notebook per subject. In this notebook, there were no personal data or data that could allow subject's recognition, complying with current legislation on General Data Protection Regulation. All procedures carried out by people who took part in the research comply with the standards and current legislation of good clinical practice [27]. Subsequently, data was organized in an Excel document for independent statistical analysis.

The study was performed according to the Declaration of Helsinki and was approved by the local ethics committee (Ávila Medicines Research Ethics Committee).

2.2. Statistical analysis

Normal distribution was assessed by using Kolmogorov-Smirnov test. As result of non-normal distribution, median and interquartile range were used for statistical analysis of UTI and quality of life variables. Statistical significance for comparison between two treatment groups was determined by using Student's t-, U Mann-Whitney or Chi-square tests. Wilcoxon signed-rank test was used for within group analysis (before and after medical intervention). Kruskal-Wallis and multiple regression analysis were used for several comparison groups. All analysis was performed

using NCSS 2020 Statistical Software (NCSS, LCC) and Prism (GraphPad) software. Differences were considered significant at $p < 0.05$ as indicated.

3. Results

3.1. Clinical profile

The mean age of participants was 82.67 years (SD 7.12) for females and 80.23 years (SD 11.12) for males ($p = 0.220$). Guiding symptoms ordered from highest to lowest frequency during infectious episodes were agitation, dysuria, disorientation, hematuria, foul-smelling urine and general deterioration ($p = 1.000$). The mean number of treatments other than immunoprophylaxis used in the previous year for the management of UTIs was 12 (SD 5.31).

The description for concomitant diseases: depression, cardiorespiratory pathology, metabolic disorders is found in Supplementary table 1.

No differences between groups ($p > 0.05$) nor changes throughout the study in concomitant diseases were found, including concomitant urological pathologies that were tightly monitored. When needed, antibiotics were prescribed on demand for respiratory infections (as well as for acute urinary infection episodes), with no significant differences between groups.

3.2. Safety

None of the subjects reported any side effects, either local at the site of administration or systemic.

3.3. Urinary tract infections

Prior to the initiation of the study, subjects reported a median number of UTIs ranging from 2.0 to 5.0 episodes per month, depending on the study group (Table 1). This number was significantly lower in individuals that had been administered bacterial immunotherapy 1.5 years before and were included for a new 3-month course than in untreated individuals, regardless females ($p < 0.001$) or males ($p < 0.01$). In groups receiving immunotherapy for the first time, females also showed increased number of infections compared to males at the baseline ($p < 0.01$).

Following bacterial immunoprophylaxis, the number of UTIs significantly decreased 12 months following treatment with either autovaccine or MV140, compared to the episodes before IT in all treatment groups, both males and females (Table 1, Fig. 1). The median number of UTIs after prophylaxis ranged from 0.0 to 0.3 episodes per month, depending on the study group. Although individuals that had received bacterial immunotherapy before showed reduced basal number of UTIs, further clinical benefit was achieved in all cases following a new course of any bacterial preparation (Table 1, Fig. 1b). Overall, the rate of reduction ranged from 7-fold for subjects receiving a new course of autovaccine to 40-fold for women on first treatment with MV140. Noteworthy, in all groups, a significant reduction in UTIs was observed in MV140-receiving individuals compared to those that were administered autovaccines (Table 1, Fig. 1). We found a positive correlation between the intervention and the number of UTIs in the linear regression analysis (beta coefficient 2.86, 95% confidence interval 2.47 to 3.25). No differences in UTI number between sex, nor first treatment and boost-receiving groups were found at the end of the study.

Regarding the proportion of UTI-free subjects, up to 60.0% of individuals receiving MV140 remained totally free of urinary infections at the end of the follow-up period, but none from autovaccine groups (Table 2). In this regard, females receiving MV140 for a second time (boost) showed significantly higher UTI-free rates than counterparts receiving autovaccines or being vaccinated for the first time. Moreover, the proportion of individuals reporting<3 episodes per year following immunotherapy, thus not fulfilling RUTI criteria anymore, ranged from 10.0% to 40.0% for autovaccines. This rate extended over 80.0% in the case of MV140 (Table 2). Herein, statistically significant differences were found between the two medical interventions in all study groups except for male on first bacterial IT treatment. For the above-mentioned parameters, no differences between sex were found.

In summary, these data highlight the fact that both prophylaxes significantly decrease UTI in frail population, with MV140 providing a higher clinical benefit than autovaccines. Moreover, results support that administration of a new course of immunoprophylaxis (boost) may be an effective strategy to improve and extent the clinical benefit and protection achieved with bacterial immunotherapy.

3.4. Quality of life

At baseline, following completion of SF-36 questionnaire, subjects reported a QoL score ranging from 50 to 60 points, depending on the study group (Table 3). This basal number was significantly lower in females despite having been administered bacterial immunotherapy before, compared to males ($p < 0.001$) or untreated women ($p < 0.001$).Table 4.

Following bacterial immunoprophylaxis, the QoL score significantly increased 3 months following treatment with either autovaccine or MV140, both in males and females (Table 3, Fig. 2). The median score after immunotherapy ranged from 68 to 92 points, depending on the study group. Individuals that had received bacterial immunotherapy before showed comparable scores to untreated individuals at the baseline, but these were further improved following a new course of any bacterial immunoprophylaxis (Table 3, Fig. 2b). Of note, in all groups, a significantly higher QoL score was observed in MV140-receiving individuals compared to those that were administered autovaccines (Table 3, Fig. 2). Again, no differences between sex, nor 1st treatment and boost-receiving groups were found at the end of the study.

4. Discussion

Urinary tract infections are among the most frequent bacterial infections in elderly population. It is the most frequently diagnosed

Table 1
Distribution of UTI episodes per month in study groups. Results before and 12 months following initiation of bacterial immunoprophylaxis are shown as median (min–max range).

		Female		Male	
		Before	After	Before	After
1st treatment	**MV140**	**5.0** (3.0–7.0)	**0.1** (0.0–0.4)	**4.0** (3.0–4.0)	**0.1** (0.0–0.3)
	Autovaccines	**5.0** (4.0–6.0)	**0.3** (0.2–0.5)	**3.5** (3.0–4.0)	**0.3** (0.1–0.3)
New 3-month course (boost)	**MV140**	**2.0** (2.0–4.0)	**0.0** (0.0–0.3)	**2.0** (2.0–3.0)	**0.1** (0.0–0.2)
	Autovaccines	**2.0** (2.0–3.0)	**0.3** (0.1–0.4)	**2.0** (2.0–3.0)	**0.3** (0.2–0.4)

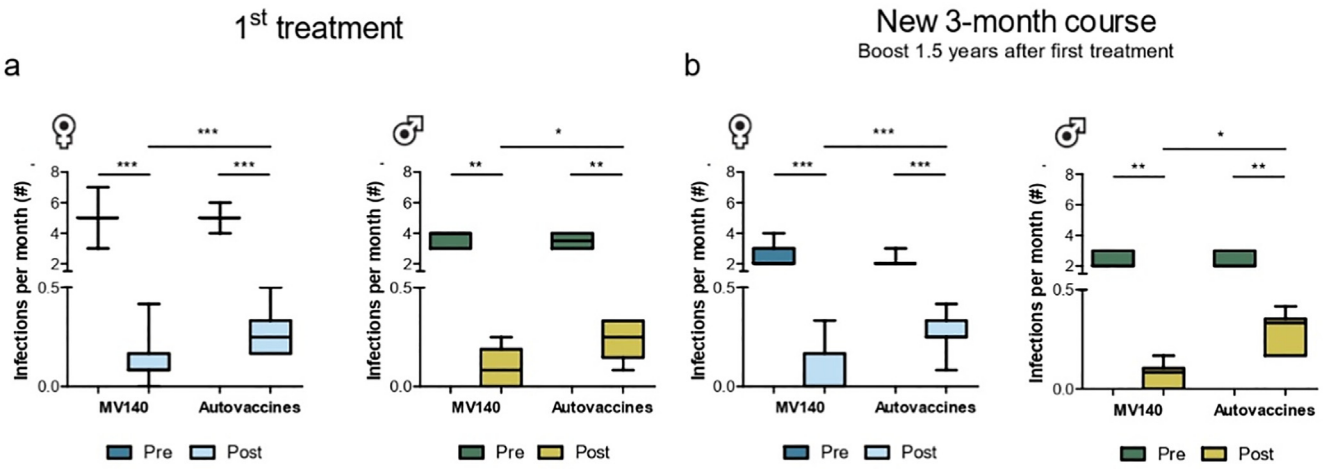

Fig. 1. Incidence of urinary tract infections decreases following bacterial immunotherapy. (a, b) Episodes of UTI per month scored 1 month prior to immunoprophylaxis (pre) and 12 months following initiation of the treatment (post), either groups receiving treatment for the first time (a) or a new 3-month course (b) in both female (left panels, ♀, blue boxplots) and male (right panels, ♂, green boxplots). Median values and min–max ranges are shown. Normal distribution was assessed using Kolmorogov-Smirnov test. Wilcoxon test was used for within group analysis, pre- and post-treatment. U Mann-Whitney test was used for comparison between treatment groups. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Rates of infection-free and non-RUTI subjects in study groups. Results 12 months following initiation of bacterial immunoprophylaxis are shown as percentage of total subjects. *p* values were calculated by using Fisher's exact test. ** $p < 0.01$, *** $p < 0.001$.

		Female				Male			
		UTI free		< 3 UTI/year		UTI free		< 3 UTI/year	
		%	*p*-value	%	*p*-value	%	*p*-value	%	*p*-value
1st treatment	**MV140**	**18.3**	0.057	**81.7**	***	**40.0**	0.087	**80.0**	0.170
	Autovaccines	**0.0**		**35.0**		**0.0**		**40.0**	
New 3-month course (boost)	**MV140**	**60.0**	***	**80.0**	***	**40.0**	0.087	**100**	**
	Autovaccines	**0.0**		**10.0**		**0.0**		**30.0**	

Table 3
Distribution of quality of life scores in study groups. Results before and 12 months following initiation of bacterial immunoprophylaxis are shown as median (min–max range).

		Female		Male	
		Before	After	Before	After
1st treatment	**MV140**	**57** (52–65)	**87** (78–89)	**58** (55–58)	**88** (85–88)
	Autovaccines	**58** (55–65)	**71** (70–79)	**59** (57–59)	**68** (65–68)
New 3-month course (boost)	**MV140**	**56** (52–61)	**92** (85–96)	**60** (60–65)	**89** (85–89)
	Autovaccines	**50** (50–55)	**75** (71–76)	**61** (61–65)	**87** (85–88)

Table 4
The values of the unadjusted and adjusted coefficients of the multiple regression (relationship between prophylaxis and the variables age, number of UTIs and score in the QoL), constant Coefficient B 6.592, Adjusted R Square 2.86, 95% CI 3.848–9.335 (p = 0.0004), we can observe that the correlation between prophylaxis and the number of UTIs at 3 months (p = 0.007), 6 months (p = 0.034) and 12 months (p = 0.043) is negative, with the prophylaxis the number of UTIs decreases and the QoL score increases (p = 0.00016) (Fig. 3).

Variables	Unstandardized Coefficients Beta	Standardized Coefficients Beta	p-value	C.I 95% Lower Bound	C.I 95% Upper Bound
Sex	0.107	0.093	0.097	−0.019	0.233
Age	−0.008	−0.021	0.63	−0.039	0.024
Number UTI pre-treatment year	−0.051	−0.161	0.3	−0.085	−0.018
Number UTI treatment 3 months	−0.08	−0.162	0.007	−0.138	−0.022
Number UTI treatment 6 months	−0.093	−0.105	0.034	−0.073	0.167
Number UTI treatment 12 months	−0.037	−0.151	0.043	−0.091	0.161
QoL pre-treatment year	0.003	0.021	0.627	−0.009	0.015
QoL post treatment	0.054	0.924	0.00016	−0.058	−0.049

infection in long-term care residents, and it also accounts for a third of nursing home-associated infections [5]. Its prevalence increases in the elderly since aging produces an alteration of the defensive mechanisms against infection. Adding to this the fact that this population group has a high comorbidity, instrumentation and hospitalization being frequent, which increases nosocomial infections. Clinical manifestations are often less specific, with more severe presentation and worse prognosis. Its management is more

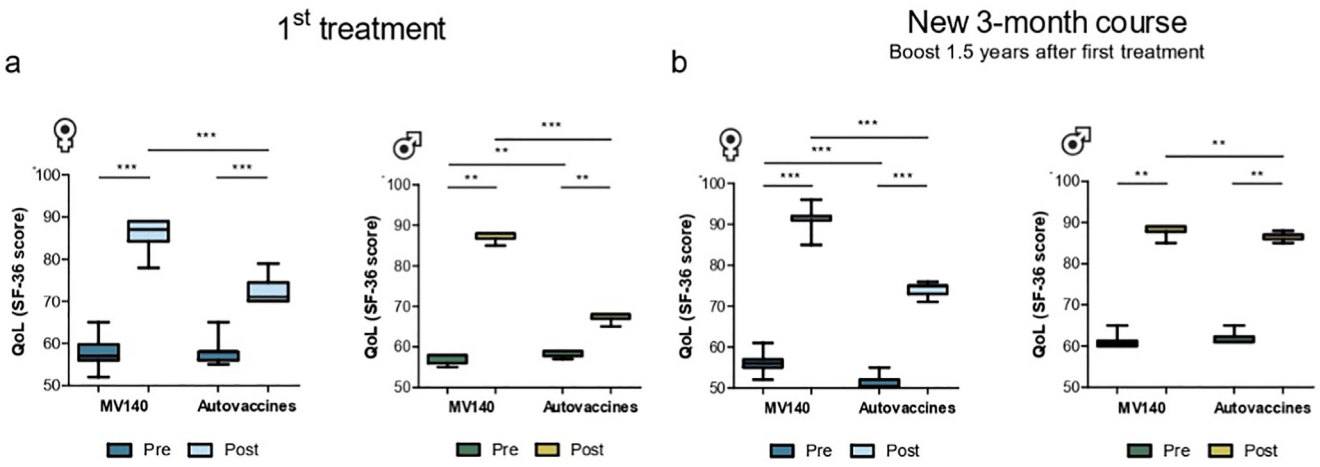

Fig. 2. Quality of life scoring is improved upon bacterial immunoprophylaxis. (a, b) Quality of life score (SF-36 questionnaire) scored 1 month prior to immunoprophylaxis (pre) and 3 months following initiation of the treatment (post), either groups receiving treatment for the first time (a) or a new 3-month course (b) in both female (left panels, ♀, blue boxplots) and male (right panels, ♂, green boxplots). Median values and min–max ranges are shown. Normal distribution was assessed using Kolmorogov-Smirnov test. Wilcoxon test was used for within group analysis, pre- and post-treatment. U Mann-Whitney test was used for comparison between treatment groups. ** $p < 0.01$, *** $p < 0.001$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

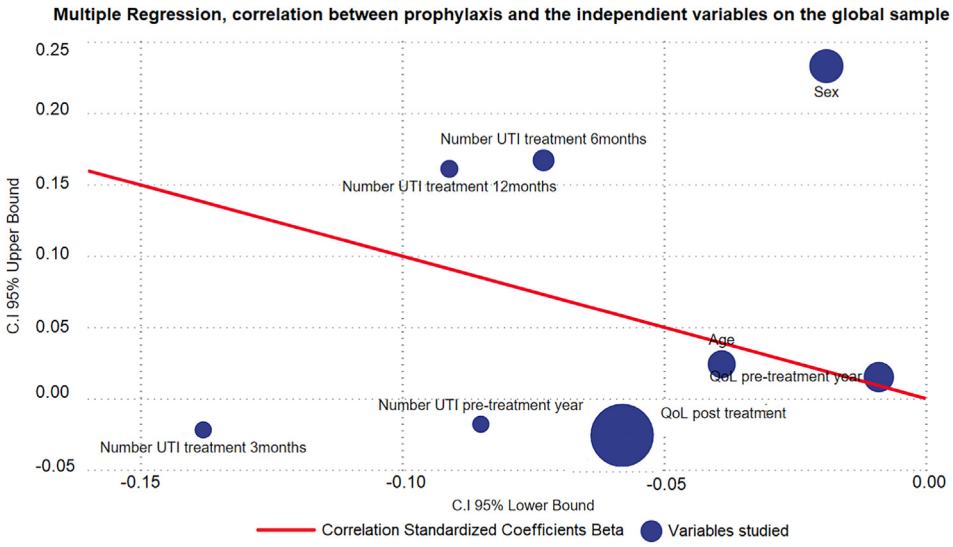

Fig. 3. Multiple regression, relationship between prophylaxis and the variables age, number of UTIs and score in the QoL.

complicated, since aging leads to a decrease in antimicrobial clearance, thus increasing side effects [10]. Taking into account that RUTI are commonly treated with antibiotics and that long-term antibiotic treatment leads to dysbiosis and increase in antimicrobial resistance [10,28], alternative approaches for the prevention and treatment of RUTI are urgently needed, especially in vulnerable populations. In this regard, different potential non-antibiotic strategies have been addressed and developed during the last few years. Currently, immunoprophylaxis, including vaccination with bacterial formulations, are among the most promising strategies, with higher level of scientific and clinical evidence [12,19].

Different studies have demonstrated the effectiveness of bacterial vaccines in RUTI prevention, including MV140 formulation [17–26]. There were also those that evaluated the capacity of this polybacterial preparation in reducing kidney damage, compared to antibiotic therapy [29]. However, to date, to the best of our knowledge, there are no published studies comparing the clinical benefit of different types of bacterial immunoprophylaxis in reducing RUTI, especially focusing on elderly patients. Herein we have addressed the effectiveness of administering MV140 or autovaccines in elderly patients suffering from RUTI. Moreover, whether a new course or boost 1.5 years later provides further clinical benefit has been also evaluated.

It is noted that in all groups UTI number significantly decreased upon a 3-month daily sublingual course of either MV140 or autovaccines (Table 1, Fig. 1). These results support and confirm the usefulness of bacterial formulations in the prevention of RUTIs in previously published studies [22,23,25,26,30]. Of note, although we did not evaluate antibiotic consumption, we may speculate that a decrease in UTI might led to a reduction in antibiotic uptake.

It is noteworthy that the decrease in UTI was significantly greater in groups receiving the polybacterial mixture MV140 than in autovaccine groups (Tables 1-2, Fig. 1), which is a novel finding given that both prophylactic methods had not been compared in previous studies. MV140 has shown a broad spectrum of protection, generating a specific response against vaccine components, but also increasing anti-infective resistance against other microorganisms not contained in its composition [15,25]. No studies have

addressed, so far, if this is the case for autovaccines. In this sense, previous mechanistic studies showed that the immune response in the dendritic cell-T cell axis is superior when cells are stimulated with MV140 rather than with the individual bacteria [31].

In all groups QoL SF-36 score significantly increased at 3 months respect to baseline for any medical intervention (MV140 or autovaccines). Again, this improvement was significantly higher in MV140-receiving individuals compared to autovaccines. Altogether, this variable should be studied over a longer period to confirm or refute the findings of this study.

From the group receiving bacterial IT for a second time (boost), a basal number of UTIs was still observed. This could be explained by waning of part of the protection conferred by the first prophylaxis over time due to a mid-term effect of the immune response generated. Nevertheless, both in terms of urinary infections and quality of life, our data demonstrate that the administration of a new course one year and a half following first treatment provides further clinical benefit. These results could serve as basis for optimizing vaccination schedules and providing high-level protection.

Limitations of the present prospective observational study include the relatively small number of subjects recruited for male study groups and lack of randomization. Despite this, a significant reduction in the rate of UTIs has been demonstrated after MV140 and autovaccine treatments in these settings. Moreover, the particular characteristics of the studied population group (frail elderly), as well as the clinical comparison of two types of bacterial preparation for the first time, emerge as key strengths and novelty of this work.

5. Conclusions

In conclusion, the data from this prospective study suggest that the bacterial immunoprophylaxis Uromune®, MV140 and autovaccines, may emerge as a relevant strategy in the management of frail elderly with RUTIs. Both have demonstrated a significant decrease in UTI episodes and provided an improvement in quality of life in this highly vulnerable population, regardless of sex. When comparing between medical interventions, MV140 is highlighted as a more effective strategy than autovaccines. Administration of a second course of bacterial immunotherapy provided further clinical benefit against RUTI. Further studies are needed to confirm the protection conferred by these bacterial formulations in frail elderly population and to better understand their mechanism of action.

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CRediT authorship contribution statement

María Fernanda Lorenzo-Gómez: Conceptualization, Methodology, Supervision. **Bárbara Padilla-Fernández:** Validation. **Javier Flores-Fraile:** Methodology, Writing – original draft, Writing – review & editing. **Sebastián Valverde-Martínez:** Project administration. **Ignacio González-Casado:** Investigation. **José-María De Dios Hernández:** Investigation. **Alfonso Sánchez-Escudero:** Investigation. **Manuel-José Vicente Arroyo:** Investigation. **Misericordia Martínez-Huélamo:** Investigation. **Filomena Herrera Criado:** Software. **Emilio Blanco-Tarrío:** Software. **Magaly Márquez-Sánchez:** Formal analysis, Data curation. **María-Carmen Flores-Fraile:** Resources, Writing – review & editing, Visualization. **Paula Saz-Leal:** Resources. **José-Antonio Mirón-Canelo:** Supervision. **Herney-Andrés García-Perdomo:** Visualization. **María-Begoña García-Cenador:** Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.08.093.

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