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REVIEW

Comparison of fosfomycin against fluoroquinolones for transrectal prostate biopsy prophylaxis: an individual patient-data meta-analysis

Matthew J. Roberts[1,2,3] · Susan Scott[2,4] · Patrick N. Harris[2,5] · Kurt Naber[6] · Florian M. E. Wagenlehner[7] · Suhail A. R. Doi[8]

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Abstract

Purpose To systematically review and meta-analyse available evidence comparing fosfomycin trometamol (FT) to fluoroquinolone (FQ) prophylaxis to prevent transrectal ultrasound-guided prostate biopsy (TRUSPB) related infectious complications.

Methods Electronic databases were queried for studies comparing FT to FQ-based TRUSPB prophylaxis. Studies were assessed for comparable outcomes and methodological quality (ROBINS-I modification). The primary outcome measure was the relative odds of overall infectious complications following TRUSPB according to FT/FQ treatment, which was evaluated with meta-analysis. Safety and tolerability were also assessed. The relative odds of infections of different severity [Grade 1, bacteriuria and afebrile urinary tract infection (UTI); Grade 2, bacteraemia, febrile UTI, and urosepsis] according to FT/FQ treatment were also estimated.

Results Five studies, being three prospective randomised trials and two retrospective cohort studies, representing 3112 patients, were included. The relative odds of an infectious complication (OR 0.22, 95% CI 0.09–0.54) or of a more severe (Grade 2) infection (OR 0.13, 95% CI 0.07–0.26) were significantly lower in those receiving FT compared to FQ prophylaxis. A low incidence of medication-related side effects was observed. There were less observed infections due to FQ-resistant pathogens in those receiving FT prophylaxis.

Conclusions Patients who received FT prophylaxis were less likely than those who received FQ prophylaxis to develop infections overall, as well as severe and resistant infections after TRUSPB. Assessing the performance of FT in other geographic locations or in comparison to targeted prophylaxis based on risk assessment or rectal cultures is desired.

Keywords Prostate · Biopsy · Complications · Fluoroquinolone resistance · Sepsis

Background

More than 1 million transrectal ultrasound-guided prostate biopsies (TRUSPB) are performed each year for prostate cancer diagnosis or monitoring [1]. Antimicrobial prophylaxis reduces TRUSPB-related infectious complications

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✉ Matthew J. Roberts
m.roberts2@uq.edu.au

1 Centre for Clinical Research, The University of Queensland, Brisbane, Australia

2 Faculty of Medicine, The University of Queensland, Brisbane, Australia

3 Department of Urology, Royal Brisbane and Women's Hospital, Brisbane, QLD 4006, Australia

4 Department of Urology, Sunshine Coast University Hospital, Birtinya, Australia

5 Department of Microbiology, Central Laboratory, Pathology Queensland, Royal Brisbane and Women's Hospital, Brisbane, Australia

6 Department of Urology, Technical University of Munich, Munich, Germany

7 Clinic for Urology, Pediatric Urology and Andrology, Justus Liebig University Giessen, Giessen, Germany

8 Department of Population Medicine, College of Medicine, Qatar University, Doha, Qatar

[2], with fluoroquinolone (FQ) antimicrobials most commonly used and recommended by North American and other international urology associations [3]. Despite prophylaxis, TRUSPB-related infectious complications have increased worldwide in this millennium [4, 5], presumably related to increasing antimicrobial resistance [6]. This trend has prompted recommendations for urology–microbiology collaboration and review of local antibiograms [7–9].

FQ resistance in the rectal flora of patients undergoing TRUSPB has been established to be a significant risk factor of subsequent infectious complications [10, 11], and this has been reported to be more important than virulence genotype [12]. While reported prevalence of FQ resistance is less than 20% [10, 11], altered prophylaxis regimes using risk assessment or rectal cultures are being commonly used to reduce infectious complications [13, 14], with an unclear cost–benefit or burden. Recent reports of successful use of fosfomycin trometamol (FT) for complicated lower urinary tract infections [15, 16] have prompted investigation of FT as prophylaxis for TRUSPB. FT is bactericidal with broad Gram-positive and Gram-negative coverage, including *E. coli, Citrobacter, Enterobacter, Klebsiella,* and *Enterococcus* spp., but is less effective against *Pseudomonas* and *Acinetobacter* spp. [17]. FT is safe, can be administered orally, is rapidly distributed, and has an acceptable prostatic penetration, following a single 3-g oral dose [18, 19]. Thus, it represents a favourable alternative for TRUSPB prophylaxis [18, 20]. There is, however, a paucity of conclusive data on the overall performance of FT in this setting.

The aims of this study were, therefore, to (1) critically appraise the available literature on FT for TRUSPB prophylaxis, (2) describe efficacy of FT-based prophylaxis using meta-analysis, and (3) compare randomised data to retrospective cohort studies.

Methods

A systematic review was performed according to the Cochrane Collaboration guidelines and PRISMA statement [21, 22]. This review was registered in the PROSPERO database (registration number CRD42017057632).

Data sources

An electronic search for manuscripts published in English was performed during March 2017 using literature databases including Cochrane Library, EMBASE, and Web of Science (all databases, including MEDLINE). Studies were retrieved from the database search (strategy listed in Supplementary Table 1) and reference lists of related manuscripts into EndNote X7 (Thomson Reuters, USA), and duplicates were removed (Fig. 1).

Eligibility criteria

Studies were included if the manuscript reported males undergoing TRUSPB with comparison of FT and FQ antimicrobial prophylaxis. No specific exclusion criteria were applied, other than those factors limiting the complete assessment of studies (including published abstract and duplicate publication). Two authors (MR, SS) independently reviewed the search strategy, screened database entries based on title and abstract, and retrieved full manuscripts to assess suitability and quality.

Quality assessment and data extraction

Quality assessment of included studies was performed by two reviewers (MR, SS) using a modified tool that combined aspects of the ROBINS-I and Risk of Bias 2.0 tools published by the Cochrane Collaboration [23, 24], as shown in Supplementary Table 2. This was done to enable the risk of bias assessment to be made across experimental and observational study designs using a common tool. Extracted study data included study characteristics, interventions, and outcomes as outlined in Table 1 and Supplementary Tables 3 and 4.

Statistical methods

The primary outcome measure was the relative odds of overall infectious complications following TRUSPB. This was evaluated via meta-analysis comparing FT treated to FQ treated patients using the inverse variance heterogeneity (IVhet) model [25] and conducted using MetaXL 5.3 (http://www.epigear.com) [26]. The safety and tolerability of FT treatment when compared to FQ treatment in this setting was also described. Effect size heterogeneity was assessed using the Q statistic ($p < 0.1$) or $\tau^2 > 0$ [27]. A sensitivity analysis was performed using the quality effects model [28] to see if heterogeneity in quality had an impact. Publication bias was assessed through a *Doi* plot [29, 30] given the small number of studies as funnel plots require a minimum of 10 studies [31].

A secondary outcome was the relative odds of infectious complications (FT treated versus FQ treated) by severity: Grade 1, bacteriuria and afebrile urinary tract infection (UTI); Grade 2, bacteraemia febrile UTI and urosepsis. Individual participant data meta-analysis was undertaken for this purpose using a generalised linear model (GLM; binary or multinomial logistic regression) with cluster robust error variances (by study) and adjusted

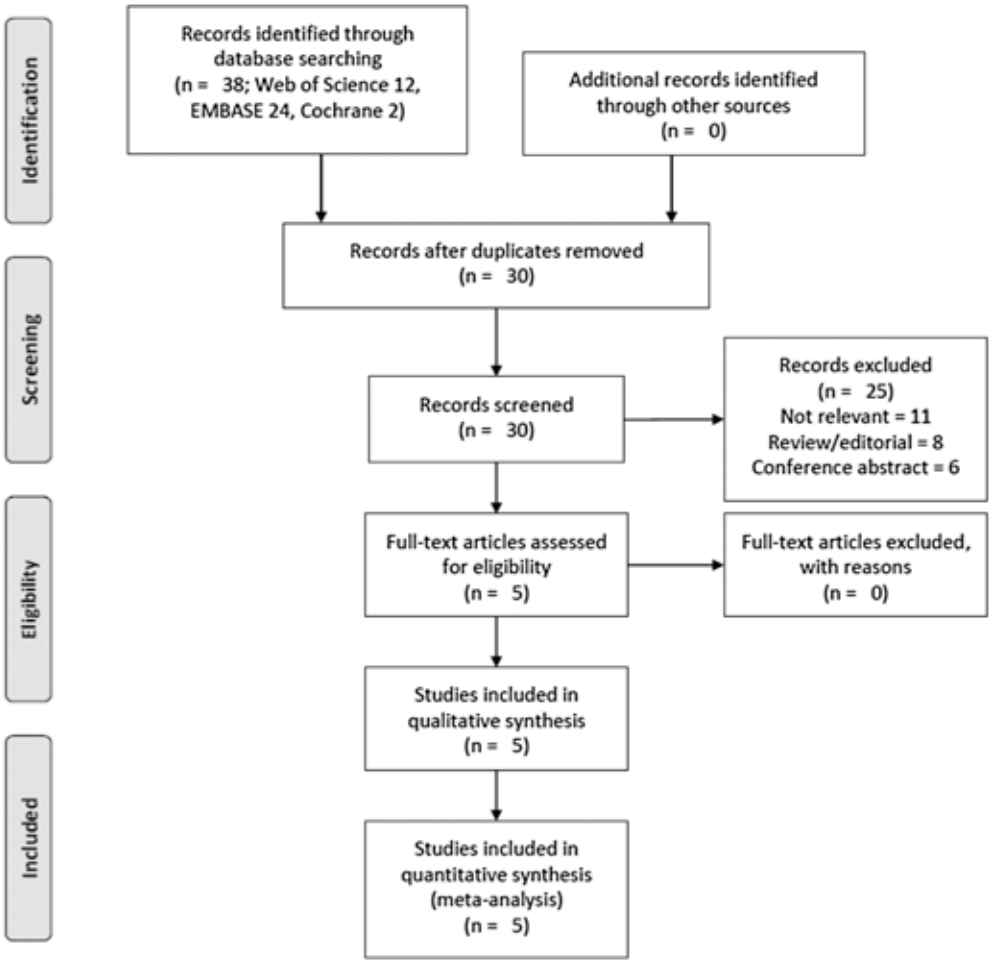

Fig. 1 Flow diagram of study selection according to the preferred reporting items for systematic reviews and meta-analyses' (PRISMA) statement

by an indicator variable for the study [32] conducted using Stata version 13 (StataCorp. College Station, Texas USA).

Results

Characteristics of included studies and descriptive outcomes

The database search identified 36 entries that were screened for suitability, resulting in 5 manuscripts that were suitable for inclusion in the final analysis (Fig. 1). Three studies were randomised controlled trials comparing FT to FQ (ciprofloxacin 500 mg orally for varied durations) [33–35], while the other two studies were retrospective consecutive cohort series comparing FT to FQ (ciprofloxacin 500 mg or levofloxacin 500 mg orally for varied durations) [36, 37]. The overall risk of bias across the randomised and retrospective studies was low and high, respectively. Details of the risk of bias assessments are provided in Supplementary Table 2 and consisted of 29 safeguards against which studies were assessed. The RCTs ranked much higher than both observational studies in terms of risk of bias (Supplementary Table 2).

Studies were located in Turkey (2), Egypt (1), Spain (1), and Italy (1), and performed between 2009 and 2015 (Supplementary Table 3). Randomisation techniques were largely adequate and exclusion criteria were appropriate. Outcome measure definitions and use of FQ (ciprofloxacin or levofloxacin) were mostly consistent, while variation existed in timing of antimicrobial administration, biopsy technique, and follow-up. Within each study, no significant differences existed between treatment groups. Between studies, populations were of similar ages, while differences in serum PSA, prostate volume, and proportion of patients undergoing repeat biopsy are presented in Supplementary Table 4. Biopsy particulars, non-infectious complications, and drug tolerance data are presented in Table 1. A low incidence of side effects to the study medications was reported across four studies. No side effects were reported for two studies, while similar proportions of minor side effects (digestive intolerance or diarrhoea) were reported in two studies. Two patients suffered serious side effects (anaphylaxis, hives), both in the FT group (0.15%).

Table 1 Population characteristics' summary

Study name Study design	Prospective randomised studies						Retrospective consecutive cohort studies				
	Fahmy		Lista		Sen		Cai		Ongün		
Prophylactic agent	FT: 3 g orally, 1–2 h before biopsy (single dose) CIP: 500 mg and metronidazole 500 mg orally > 1 h before biopsy; twice daily for 3 days		FT: 3 g orally 24 h before, 24 h after biopsy CIP: 500 mg bd for 5 days		FT: 3 g orally, night before biopsy (single dose) CIP: 500 mg orally, 60 min before biopsy		FT: 3 g orally, 3 h before biopsy then 3 g 24 h after first dose CIP: 500 mg orally, twice daily starting 1 day before biopsy for total 5 days		FT: 3 g orally, night before biopsy (single dose) CIP: 500 mg orally, twice daily starting 1 day before biopsy for total 5 days Levo: 500 mg orally, 1 h pre-biopsy		
Total patients	FT	CIP	FT	CIP	FT	CIP	FT	CIP	FT	CIP	Levo
	202	210	359	312	150	150	632	477	104	406	110
Demographics											
Age ± SD (years)	68.8 ± 4.2	62.5 ± 2.8	66.5 ± 6.6 ($p > 0.05$)		63.5 ± 7.5	62.9 ± 7.6	65.9 ± 8.3	66.9 ± 8.9	61.5 ± 6.6	63.9 ± 7.3	63.23 ± 7.8
PSA total ± SD (ng/ml)	23.9 ± 5.8	17.8 ± 3.2			12.9 ± 1.8	12.0 ± 1.2	7.1 ± 4.3	7.7 ± 5.1			
Prostate volume ± SD (cm^3)	67.3 ± 31.2	59.8 ± 28.5			53.1 ± 22.5	51.3 ± 24.6			46.1 ± 22.6	48.9 ± 24.2	46.7 ± 25.3
Repeat biopsy (*n*)	13	5					90	63	17	37	19
Diabetes mellitus (*n*)							62	40	16	46	7
Biopsy particulars											
Number of biopsy cores ± SD (*n*)			11.3 ± 3.25 ($p > 0.05$)						10.3 ± 0.8	10.2 ± 0.6	10.3 ± 0.7
Histology											
PCa (*n*)			236 ($p > 0.05$)		36	39	285	210			
BPH (*n*)					45	36	332	251			
Non-infectious complications											
Macrohaematuria (*n*)	25	21	43	38			442	338			
Hematospermia (*n*)			16	31			34	22			
Acute urinary retention (*n*)			9	7			41	36			
Hematochezia (*n*)			4	3			17	5			
Drug tolerance											
Total adverse drug reaction (*n*)	0	0	10	10	0	0	4	2			
Digestive intolerance/diarrhoea (*n*)	0	0	9	10	0	0	3	2			
Anaphylaxis (*n*)	0	0	1	0	0	0	0	0			
Hives (*n*)	0	0	0	0	0	0	1	0			

FT fosfomycin trometamol, *CIP* ciprofloxacin, *Levo* levofloxacin, *SD* standard deviation, *PCa* prostate cancer, *BPH* benign prostatic hyperplasia

Post-biopsy infectious complications—grouped meta-analysis

Grouped, or conventional, meta-analysis of all studies demonstrated that the odds of FT treated patients having an infectious complication (overall) was reduced (OR 0.25, 95% CI 0.11–0.58; Fig. 2) as compared to FQ-based prophylaxis, despite significant heterogeneity in the pooled estimate (Q 13.93; $p = 0.01$) presumably due to study design and a heterogenous population across studies.

When the effect sizes were grouped according to study design, the effect was exaggerated in retrospective cohort (OR 0.16, 95% CI 0.05–0.52; Fig. 2) versus randomised (OR 0.43, 95% CI 0.17–1.12; Fig. 2) studies, with more (Q 3.94; $p = 0.05$) and less (Q 4.48; $p = 0.11$) heterogeneous estimates, respectively. In both subgroups, however, τ^2 was greater than zero. A sensitivity analysis using the QE model resulted in similar results (OR 0.30, 95% CI 0.13–0.67; Figure S1). Given the small number of studies, a funnel plot was not feasible, but a *Doi* plot revealed no evidence of asymmetry that would suggest publication bias (Figure S2).

Post-biopsy infectious complications—individual participant data meta-analysis

When overall infectious complications were considered using individual participant data (3112 patients), a similar estimated odds reduction for FT treated patients was seen (OR 0.22, 95% CI 0.09–0.54; Table 2) as reported above from the grouped data. When this was broken down by complication severity grade, a greater infection odds reduction was seen across all grades for FT treated patients (Table 2) but more so for the higher grade infectious complications [Grade 2 (OR 0.13, 95% CI 0.07–0.26)] than for Grade 1 infectious complications (OR 0.30, 95% CI 0.13–0.69).

Using data available from three studies [33, 35, 37], we looked at infectious complications according FQ resistance (FQR) and FQ sensitive (FQS) status of the causative pathogen. Reduced odds of infection due to both FQR (OR 0.14, 95% CI 0.05–0.42), and FQS pathogens (OR 0.61, 95% CI 0.18–1.98) was observed in FT treated patients. The odds reduction lacked precision for FQS infections, presumably because FT confers less benefit as prophylaxis for FQS

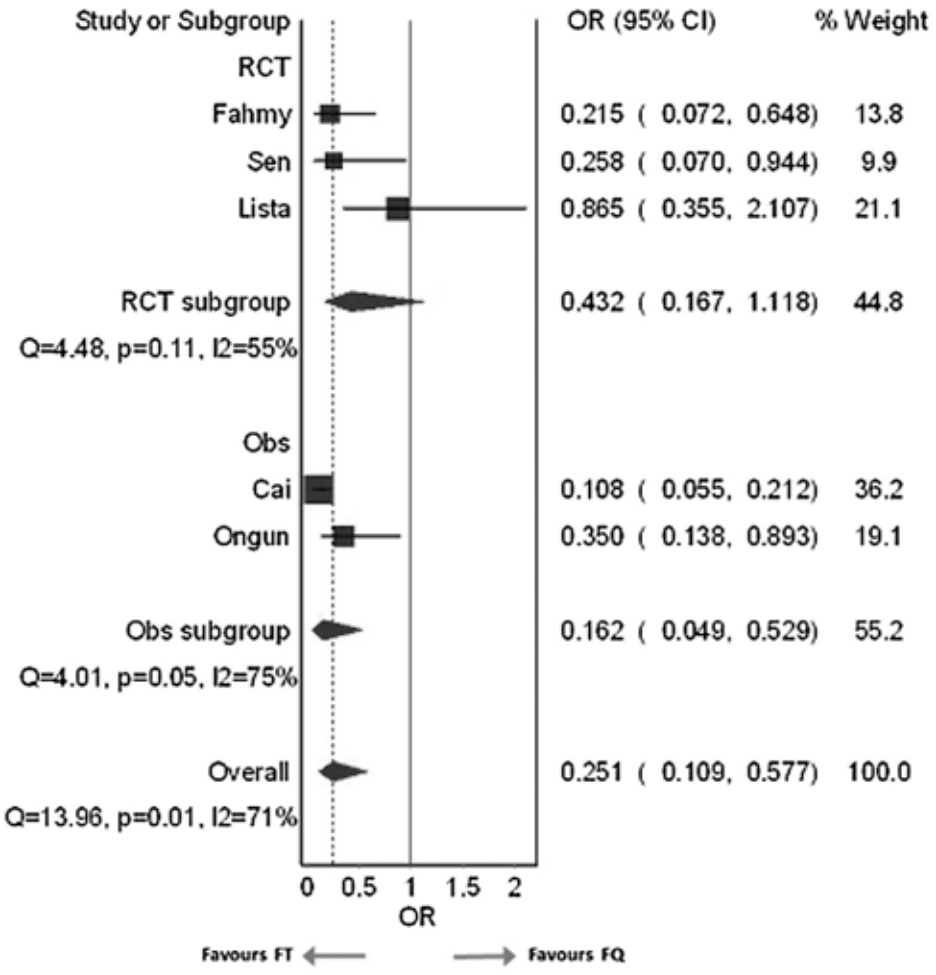

Fig. 2 Forest plot of overall complications comparing FT to FQ across all studies, stratified according to study design. *RCT* randomised controlled trial, *Obs* observational study, *OR* odds ratio, *CI* confidence interval

Table 2 Adjusted relative odds of infection according to antibiotic treatment status (individual patient-data meta-analysis)

	Odds ratio	95% Conf. interval		$p > \|z\|$
A. Overall infection; $N = 3112$; 5 studies				
FQ	1			
FT	0.22	0.09	0.54	0.001
B. *Grade of infection; $N = 3112$; 5 studies				
No infection (base outcome)				
Grade 1: Bacteriuria and afebrile urinary tract infection (UTI)				
FQ	1			
FT	0.30	0.13	0.69	0.005
Grade 2: Bacteraemia, febrile UTI or urosepsis				
FQ	1			
FT	0.13	0.07	0.26	< 0.001
C. *Resistance status; $N = 1332$; 3 studies				
No infection (base outcome)				
Sensitive infection				
FQ	1			
FT	0.61	0.18	1.98	0.406
Resistant infection (FQR)				
FQ	1			
FT	0.14	0.05	0.42	< 0.001

GLM (binary or *multinomial logistic regression) with cluster robust standard errors (clusters are the studies) adjusted by an indicator variable for study of origin of the patient

FQ fluoroquinolone, *FT* fosfomycin, *FQR* fluoroquinolone resistance

pathogens; however, this effect magnitude remains clinically significant.

Discussion

In this meta-analysis, we systematically appraised available evidence to determine that FT treated patients had reduced infectious complications post TRUSPB when this was used as prophylaxis in comparison to fluoroquinolones. The benefits were seen overall as well as at an individual patient level through different complication grades. This benefit was preserved when considering mechanisms of antimicrobial resistance (FQR, ESBL) in causative pathogens. Our findings present FT as an appropriate and superior alternative to FQ-based TRUSPB prophylaxis.

FT also has properties that are suitable for TRUSPB prophylaxis. The oral sachet formulation and pharmacokinetics resulting in favourable bioavailability, both in serum and in prostatic tissue, within 1–4 h of administration allows for convenient administration prior to biopsy [20]. Patient compliance and counselling would be similar to using an oral fluoroquinolone, as is already commonly practiced. Despite different FT dosing regimens being implemented across included studies, we have shown that FT outperforms fluoroquinolones in reducing overall complications, with incremental benefit observed for severity grades. While use of FT for TRUSPB prophylaxis would be "off-label", and thus restricted in some jurisdictions, these findings are consistent with those observed for complicated and uncomplicated ESBL *E. coli* UTIs as well as in multi-drug-resistant Enterobacteriaceae [17]. Evidence for use of FT in men with complicated UTIs is limited and further research is warranted [38].

Antimicrobial resistance is a significant factor that has plagued TRUSPB pathways and prostate cancer diagnosis overall. An increasing incidence in infectious complications following TRUSPB has mandated the review and implementation of various strategies to combat this problem [39], including the American Urological Association White Paper on the Prevention and Treatment of Common Complications Related to Prostate Biopsy [9]. Fluoroquinolone-based prophylaxis regimes may be implemented more cautiously, or less commonly, following a recent Federal Drug Administration warning regarding serious side effects [39]. Targeted prophylaxis as directed by pre-biopsy rectal cultures may also serve to reduce infectious complications [13, 14], similar to the use of FT prophylaxis; however, the associated logistic or cost burden of these methods is yet to be prospectively assessed [39]. For these reasons, some clinicians have abandoned TRUSPB in favour of the transperineal, transcutaneous approach [39]. While the transperineal approach produces a similar risk of hospitalisation due to non-infectious complications, such as acute urinary retention [30], the requirement for general anaesthesia and brachytherapy grid or other equipment probably renders it unfeasible for a large proportion of urologists worldwide [39].

Until improvements are made in the accuracy and accessibility of biomarkers and imaging for prostate cancer, TRUSPB will continue to be commonly used by urologists. As FT-based TRUSPB prophylaxis results in less infections due to pathogens displaying FQ resistance and ESBL production, this approach may serve to reduce TRUSPB-associated morbidity and mortality. In addition, FT exerts a lower collateral damage on the microbiome than other broad spectrum antimicrobial agents, such as FQs, cephalosporins, or carbapenems, and such support antimicrobial stewardship, where the urological contribution has been shown to be an important factor [40]. As FT is an important agent used in other scenarios, such as ESBL *E. coli* multi-drug resistant Enterobacteriaceae infections [17], judicious use is recommended to reduce the development of resistance observed for FQs. Similar growth in resistance to FT with increased use may be observed, thus local microbiological surveillance protocols and resistance patterns should be considered by treating clinicians.

Our study has several limitations. Most notably, we have combined data from prospective randomised trials with

retrospective cohort studies. These studies have undergone quality assessment according to Cochrane guidelines and differences in study quality have been adjusted for in the pooled estimates. Despite observing mostly consistent effect sizes, combining data with heterogeneous follow-up methodology, such as asymptomatic bacteriuria assessed in all patients [34], and study group size asymmetry [37], may have affected the FQ sensitive pooled estimates. Furthermore, the indications for FT prophylaxis in the non-randomised studies were unclear. Study locations were mostly centred around the Mediterranean Sea, an area known to display high endemic fluoroquinolone resistance [7], and thus, the effects of FT may be over-estimated in comparison to other populations.

Conclusions

In summary, our study has shown that FT is more effective as TRUSPB prophylaxis in comparison to FQs, present through various analyses and antimicrobial resistance considerations. While TRUSPB remains a mainstay of prostate cancer diagnosis until wider uptake of multiparametric magnetic resonance imaging and fusion biopsy strategies or improved biomarkers, improved TRUSPB prophylaxis will serve to reduce morbidity outcomes for patients. Future research to assess the performance of FT in various geographic locations or in comparison to targeted prophylaxis based on risk assessment or rectal cultures is desired. FT appears a potential substitute to FQs for TRUSPB prophylaxis and implementation in clinical practice should be considered.

Author contributions MJR: project development, data collection, and manuscript writing. SES: data collection, manuscript editing. PNH: manuscript editing, critical revisions, and guidance. KN: manuscript editing, critical revisions, and guidance. FMEW: manuscript editing, critical revisions, and guidance. SARD: statistical and epidemiological guidance, analysis and manuscript editing.

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Compliance with ethical standards

Conflict of interest K.N. is a paid consultant to Bionorica, DaiichiSankyo, Enteris Biopharma, Leo Pharma, MerLion, OM Pharma, Paratek, Rosen Pharma, and Zambon. F.W. is a paid consultant to Achaogen, Act elion, AstraZeneca, Bionorica, GSK, MSD, Janssen, and Pfizer. All other authors: none to declare.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants within the included manuscripts included in this study.

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