#### **ORIGINAL ARTICLE**



# Infection risk reduction with povidone-iodine rectal disinfection prior to transrectal prostate biopsy: an updated systematic review and meta-analysis

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#### Abstract

**Background** To prevent infectious complications after transrectal ultrasound-guided prostate biopsy (TRUS-PB), some studies have investigated the efficacy of rectal disinfection using povidone-iodine (PI) and antibiotic prophylaxis (AP). **Objective** To summarize available data and compare the efficacy of rectal disinfection using PI with non-PI methods prior to TRUS-PB.

**Evidence acquisition** Three databases were queried through November 2023 for randomized controlled trials (RCTs) analyzing patients who underwent TRUS-PB. We compared the effectiveness of rectal disinfection between PI groups and non-PI groups with or without AP. The primary outcomes of interest were the rates of overall infectious complications, fever, and sepsis. Subgroups analyses were conducted to assess the differential outcomes in patients using fluoroquinolone groups compared to those using other antibiotics groups.

**Evidence synthesis** We included ten RCTs in the meta-analyses. The overall rates of infectious complications were significantly lower when rectal disinfection with PI was performed (RR 0.56, 95% CI 0.42–0.74, p < 0.001). Compared to AP monotherapy, the combination of AP and PI was associated with significantly lower risk of infectious complications (RR 0.54, 95% CI 0.40–0.73, p < 0.001) and fever (RR 0.47, 95% CI 0.30–0.75, p = 0.001), but not with sepsis (RR 0.49, 95% CI 0.23–1.04, p = 0.06). The use of fluoroquinolone antibiotics was associated with a lower risk of infectious complications and fever compared to non-FQ antibiotics.

**Conclusion** Rectal disinfection with PI significantly reduces the rates of infectious complications and fever in patients undergoing TRUS-PB. However, this approach does not show a significant impact on reducing the rate of sepsis following the procedure.

Keywords Antibiotic prophylaxis · Povidone-iodine · Transrectal ultrasound-guided prostate biopsy

## Introduction

Transrectal ultrasound-guided prostate biopsy (TRUS-PB) and transperineal ultrasound-guided prostate biopsy (TPUS-PB) have been the main procedures to diagnose prostate cancer [1]. Despite the recommendations of the European Association of Urology (EAU) guidelines favoring TPUS-PB over TRUS-Bx, the transrectal approach is still widely utilized worldwide, mainly due to the elaborate technical requirements of TPUS-Bx. However, TRUS-Bx leads to higher incidence of infectious complications based on the translocation of rectal bacteria during the procedure. The estimated incidence rate of infectious complications by TRUS-PB, such as acute bacterial prostatitis, fever, and sepsis, is reported to be as high as 6.3% [2, 3].

Several studies, including randomized controlled trials (RCT), have been conducted to assess the efficacy of PI disinfection of the rectum in reducing infectious complications after TRUS-PB [2, 4–9]. These studies have indicated that PI disinfection can reduce infectious complications, leading to the EAU guidelines to recommend rectal disinfection with PI prior to TRUS-PB [10]. Although previous systematic reviews and meta-analyses compared the efficacy of PI to

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reduce infection between the PI group and non-PI group and between the PI plus AP group and AP monotherapy group, the efficacy of using PI in reducing sepsis remains uncertain when comparing PI plus AP and AP monotherapy [4, 9].

Therefore, the aim of this systematic review and metaanalysis was to evaluate the efficacy of pre-TRUS-PB disinfection with PI plus AP compared to AP monotherapy. We aimed to reassess the role of PI in mitigating infectious complications. Furthermore, we make efforts to clarify and verify the effectiveness of PI in reducing the incidence of sepsis.

## **Evidence** acquisition

We registered the study with the International Prospective Register of Systematic Reviews (PROSPERO: registration number: CRD42023476473). This systematic review and meta-analysis was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (PRISMA 2020 checklist, Supplementary Table 1).

## Search strategy

On November 1st, 2023, the PubMed, Scopus, and Web of Science databases were searched to identify studies investigating the effectiveness of disinfection with PI before TRUS-PB. The search terms included: "prostate biopsy", "povidone iodine". The detailed search strategy is shown in Supplementary Appendix 1. Two investigators independently performed an initial screening based on the titles and abstracts and noted the cause of exclusion of ineligible reports. Full texts were retrieved and evaluated for eligibility. In addition, hand searches of reference lists were performed to identify additional studies of interest. In the case of discrepancies, the disagreements were solved by consensus among the authors.

### Inclusion and exclusion criteria

We included studies that analyzed patients, who underwent TRUS-PB with rectal disinfection using PI with or without AP and compared them with patients who underwent TRUS-PB without PI disinfection, to assess the incidence of pooled infectious complications, including fever, sepsis, symptomatic urinary tract infection (UTI) only in RCTs. Analyses of different subgroups were performed to evaluate the varying results among patients treated with fluoroquinolones vs. those treated with other types of antibiotics. Reviews, meta-analyses, letters, editorials, meeting abstracts, authors' replies, case reports, and non-English articles were excluded. In the case of duplicate publications, either the higher quality or the most recent publication was selected. We scanned references of included manuscripts for additional studies of interest.

#### **Data extraction**

Two reviewers separately extracted data on baseline study and patient's characteristics. The first author's name, published year, inclusion criteria, exclusion criteria, type of prophylactic antibiotic, duration of prophylactic antibiotic, age, previous biopsy, the number of biopsy cores, number of patients, number of infectious complications, including fever and sepsis, were extracted. Subsequently, the risk ratio (RR) and 95% confidence intervals (CI) for infectious complications were retrieved. All discrepancies were resolved by consensus with coauthors.

#### Quality assessment and risk of bias

Study quality and risk of bias were evaluated using the Riskof-Bias version 2 (ROB) tool as outlined in the Cochrane Handbook for Systematic Reviews of Interventions [11]. The RoB assessment of each study was performed by two authors independently. We also performed the funnel plots.

### **Statistical analysis**

All statistical analyses were performed using R Version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria, 2023; meta). Statistical significance was set at p < 0.05. Forest plots with RR and 95% CI were calculated and depicted to assess the efficacy of PI disinfection before TRUS-PB. For further detailed investigation of infection complications, including fever and sepsis, subgroup analyses were conducted. Furthermore, we conducted subgroup analyses to clarify the comparative efficacy of PI with AP vs. AP alone. Cochrane's Q tests and the *I*-square test were used to evaluate the heterogeneity. Significant heterogeneity was indicated by a p value < 0.05 in the Cochrane's Q tests and  $I^2$  greater than 50%. When significant heterogeneity was observed, we attempted to investigate the causes of heterogeneity [12].

## **Evidence synthesis**

### Study selection and characteristics

Our initial search identified 127 records of which 94 were screened for title and abstract after removing duplicates. Overall 27 articles were retrieved and 10 RCTs with 3,297 met our inclusion criteria (Fig. 1) [2, 5–8, 13–17]. All studies were prospective RCTs. The patient characteristics are summarized

#### Fig. 1 PRISMA flowchart



in Table 1. Of ten RCTs, nine studies used the AP. The types of APs included β-lactamase, fluoroquinolones, such as ciprofloxacin, levofloxacin, ofloxacin, and gentamicin. The detailed information on the usage and duration of these APs can be found in Table 1. Only one study, reported by Sharpe et al., did not use any AP before TRUS-PB [14]. All RCTs used fever as the primary outcome, and the recent six RCTs also used sepsis as a primary outcome [2, 5-8, 17]. Fever was defined differently across the RCTs, but it was characterized as body temperature higher than 37.8 °C, 38 °C or 38.5 °C. Sepsis was also defined differently across the studies. Some studies defined sepsis according to the Third International Consensus Definitions for Sepsis and Septic Shock [2, 18]. Other studies used the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference, which defined sepsis as having a positive urine or blood test along with at least two of the listed symptoms within a week of a biopsy. These symptoms include a temperature above 38.0 °C or below 36.0 °C, a heart rate exceeding 90 bpm, breathing faster than 20 times a minute, a white blood cell count above 12.0 or below  $4.0 \times 10^{9}$ /L, or the presence of more than 10% immature forms [8, 19].

#### **Risk of bias assessment**

Authors' judgments about each domain for each included study are graphed in Supplementary Fig. 1. Although some RCTs presented concerns in certain domains, two studies demonstrated low risk across all domains. Despite some observational studies showing low risk in specific categories, the majority of these studies displayed either moderate or serious overall risk of bias. Funnel plots of each analysis are depicted in Supplementary Fig. 1.

#### **Meta-analysis**

#### Infectious complications (PI vs. non-PI)

Ten studies have reported infectious complication in 3297 patients [2, 5–8, 13–17]. There were 1660 patients in the

Tab	ble	1	Characteristics	of	incluc	led	studies
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Author	Published year	Nation	Design	No. of patients	Intervention	Control	AP	Primary outcome
Pontes-Junior	2022	Brazil	RCT	621	PI+AP	AP	Ciprofloxacin 500 mg PO/3 days	Fever, UTI, sepsis
Ergani	2019	Turkey	RCT	50	PI+AP	AP	Ciprofloxacin 500 mg PO + ami- kacin 1 g IM /3 days	UTI, sepsis
Ryu	2019	Korea	RCT	120	PI+AP	AP	Ceftriaxone 2 g IV	Fever, UTI, sepsis
Cadilhe	2017	Portugal	RCT	47	PI+AP	AP	Levofloxacin 500 mg PO/7 days	Fever, UTI, sepsis
Abughosh	2013	Canada	RCT	421	PI+AP	AP	Ciprofloxacin 1000 mg/3 days	Fever, UTI, sepsis
Ghafoori	2012	Iran	RCT	140	PI+AP	AP	Ofloxacin 300 mg/12 h + metro- nidazole 250/8 h/5 day	Fever, sepsis
Huang	2006	Taiwan	RCT	157	PI+AP	AP	Fluoroquinolone 1000 mg/ day + ST were given twice daily for 3 days after the pros- tate biopsy	Fever
Melekos	1990	Greece	RCT	43	$PI(+AP)^*$	(AP)*	Piperacillin 2 g IV	Fever
Sharpe	1982	USA	RCT	40	PI	N/A	N/A	Fever
Brown	1981	USA	RCT	21	PI(+AP)*	(AP)*	Gentamicin 80 mg IM	Fever

AP antibiotic prophylaxis, PI povidone-iodine, RCT randomized controlled trial, ST sulfamethoxazole plus trimethoprim UTI

\*In these studies, not all patients used the antibiotic prophylaxis

PI intervention group and 1637 patients in the non-PI control group. Eighty-seven patients (5.2%) in the intervention group and one hundred seventy-one patients (10.2%) in the control group experienced infectious complications. Nine studies reported infectious complications of fever, six studies reported sepsis, and five studies reported UTI. There was no heterogeneity. Infectious complication rates were significantly lower when the disinfection of rectal disinfection using PI was performed (RR 0.56, 95% CI 0.42–0.74; Fig. 2A).

**Infectious complications (PI plus AP vs. AP monotherapy)** We conducted an analysis to further explore the efficacy of PI before TRUS-PB in an AP setting. Nine studies, comprising 3,163 patients, were analyzed for comparison overall infectious urinary complication rate between the PI plus AP group and AP monotherapy group [2, 5–8, 13, 15–17]. There were 1,592 patients in the PI plus AP group and 1572 patients in the AP monotherapy group. Sixty-nine patients (4.3%) in the intervention group and one hundred forty-six patients (9.3%) in the controlled group experienced infectious complications. The overall infectious complication rate was significantly lower in the PI plus AP group compared to the AP monotherapy group as well as PI compared to the non-PI (RR 0.54, 95% CI 0.40–0.73; Fig. 2B).

**Fever (PI plus AP vs. AP monotherapy)** Then 8 studies, comprising 2941 patients, were analyzed for comparison between the PI plus AP group and the AP monotherapy group in terms of fever rate [2, 5–8, 13, 15, 17]. There were 1434 patients in the PI plus AP group and 1507 patients in the AP monotherapy group. Twenty-seven patients (1.8%)

were in the intervention group and seventy-three patients (4.8%) in the controlled group experienced fever. The fever rates were significantly lower in the PI plus AP group compared to the AP monotherapy group (RR 0.47, 95% CI 0.30–0.74; Fig. 2C).

Sepsis (PI plus AP vs. AP monotherapy) Six studies, comprising 2874 patients, were analyzed for comparison of sepsis rate between PI plus AP group and AP monotherapy group [2, 5–8, 17]. Five RCTs used ciprofloxacin, levofloxacin, or ofloxacin as AP [2, 5, 7, 8, 17]. Only one study, conducted by Rye et al., used ceftriaxone administered intravenously at a single dose of 2 g [6]. There were 1399 patients in the PI plus AP group and 1475 patients in the AP monotherapy group. Nine patients (0.64%) in the PI plus AP group and twenty-five patients (1.7%) in the controlled group experienced sepsis. There was no statistically significant difference between the PI plus AP and AP monotherapy group (RR 0.49, 95% CI 0.23–1.04; Fig. 2D).

#### Discussion

We present the systematic review and meta-analyses that analyzed the effectiveness of rectal disinfection using PI prior to TRUS-PB. There are several key findings of our study. First, PI disinfection reduced the incidence rate of infectious complications in comparison to non-PI disinfection. Second, PI plus AP disinfection reduced the incidence rate of infectious complications in comparison to AP monotherapy. Third, we could not reveal the significant difference

Fig. 2 A Effect of povidoneiodine on infectious complications prior to transrectal ultrasound-guided prostate biopsy. **B** Effect of povidone-iodine and antibiotic prophylaxis on infectious complications prior to transrectal ultrasound-guided prostate biopsy. C Effect of povidone-iodine on fever prior to transrectal ultrasound-guided prostate biopsy. D Effect of povidone-iodine on sepsis prior to transrectal ultrasound-guided prostate biopsy. AP antibiotic prophylaxis, PI povidone-iodine

(A) Overall infec	tious c	ompl	icatio	ons (Pl	vs Non-PI)			
Study	T_eve	ent T	C_ev	ent C	Risk Ratio	RR	95%-CI	Weight
•								
Pontes-Junior 2022	24	621	39	613		0.61	[0.36; 1.02]	29%
Ergani 2019	6	50	15	101		0.81	[0.30; 2.21]	8%
Ryu 2019	0	120	0	130	<	→ 1.08 [0	0.02; 55.03]	1%
Cadilhe 2017	0	47	6	47	<	0.08	[0.00; 1.53]	1%
Abughosh 2013	11	421	20	444		0.58	[0.27; 1.23]	14%
Ghafoori 2012	27	140	51	140		0.53	[0.31; 0.89]	29%
Huang 2006	0	157	6	65	· · · · · ·	0.03	[0.00; 0.63]	1%
Melekos 1990	2	43	7	38	<	0.25	[0.05; 1.29]	3%
Sharpe 1982	16	40	19	40		0.84	[0.38; 1.87]	13%
Brown 1981	1	21	8	19	*	0.11	[0.01; 0.99]	2%
O						0.50		4000/
Common effect mod	el 2 . 0.00	2	0.07/-	0.050		0.56 [	0.42; 0.74]	100%
Heterogeneity: / = 10%	, τ <sup>-</sup> < 0.00	$101, \chi_9 =$	9.97 (p	= 0.353)	01 05 1 2	F		
lest for overall effect. 2 :	= -4.03 (p	< 0.001	)			Non Bll		
						.Non-Fij		
(B) Overall infe	ctious	comp	licatio	ons (P	+ AP vs AP)			
Study	T_event	тс	_event	с	Risk Ratio	RR	95%-CI	Weight
AP - Eluoroquinolono					1			
Pontes- Junior 2022	24	621	30	613		0.61	[0 36· 1 02]	34%
Fraani 2019	6	50	15	101		- 0.81	[0.30; 1.02]	9%
Cadilhe 2017	0	47	6	47	-	0.08	[0.00; 1.53]	1%
Abughosh 2013	11	421	20	444		0.58	[0.27; 1.23]	17%
Ghafoori 2012	27	140	51	140		0.53	[0.31: 0.89]	34%
Huang 2006	0	157	6	65		0.03	[0.00; 0.63]	1%
Common effect model	Ĭ		•		-	0.56	[0.41; 0.76]	97%
Heterogeneity: $I^2 = 15\%$ ,	$\tau^2 = < 0.000$	01, $\chi_5^2 = 1$	5.85 (p =	: 0.321)		0.00	"and anol	-1 10
AP = others								
Ryu 2019	0	120	0	130	· · ·	→ 1.08	[0.02; 55.03]	1%
Melekos 1990	1	25	4	22	· · · ·	- 0.22	[0.02; 2.12]	2%
Brown 1981	0	10	5	10	*	- 0.10	[0.00; 2.08]	1%
Common effect model	2 0 2	0.00 (-	0.0445	-		0.23	[0.04; 1.20]	3%
Heterogeneity: $T = 0\%$ , $\tau$	$= 0, \chi_2 = 0$	0.69 (p =	0.641)					
Test for overall effect: $z =$ Test for subgroup difference	$-3.94 (p < cos: x^2 - 1)$	0.001)			0.1 0.5 1 2	2 3		
(C) Four (DL ) A	Date $\Delta D$	.06, ui =	1 (p = 0.	302)	Favours [PI+AP] Favou	irs [AP]		
(C) Fever (PI + A	P vs AP	) 7)	1 (p = 0.	302)	Favours [PI+AP] Favou	irs [AP]	0.5% 01.1	
(C) Fever (PI + A Study	P vs AP T_feve	2) er T	1 (p = 0. C_fev	302) er C	Favours [PI+AP] Favou Risk Ratio	rs [AP] RR	95%-CI \	Weight
(C) Fever (PI + A Study AP = Fluoroquinolon	P vs AP T_feve	2) er T	C_fev	302) er C	Favours [PI+AP] Favou Risk Ratio	rs [AP] RR	95%-CI \	Weight
(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junior 2022	P vs AP T_feve	621	C_fev	302) er C 613	Favours [PI+AP] Favou	RR 0.72 [(	<b>95%-CI \</b> 0.29; 1.80]	Veight 25%
(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junior 2022 Ergani 2019	P vs AF T_feve 1es 1	er T 621 50	C_fev 11 11 12	er C 613 101	Favours [PI+AP] Favou	RR 0.72 [( 0.17 [0	<b>95%-CI \</b> 0.29; 1.80] 0.02; 1.33]	<b>Veight</b> 25% 5%
(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junior 2022 Ergani 2019 Abughosh 2013	P vs AP T_feve 105 8 1 7	er T 621 50 421	C_fev 11 12 11	er C 613 101 444	Risk Ratio	RR 0.72 [( 0.17 [0 0.67 [0	<b>95%-CI (</b> 0.29; 1.80] 0.02; 1.33] 0.26; 1.75]	<b>Veight</b> 25% 5% 23%
(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junior 2022 Ergani 2019 Abughosh 2013 Ghafoori 2012	P vs AF T_feve 105 8 1 7 11	621 621 50 421 140	C_fev 11 12 11 12 11 27	er C 613 101 444 140	Favours [PI+AP] Favou	RR 0.72 [( 0.17 [0 0.67 [0 0.41 [0	<b>95%-CI N</b> 0.29; 1.80] 0.02; 1.33] 0.26; 1.75] 0.19; 0.85]	Veight 25% 5% 23% 39%
(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junior 2022 Ergani 2019 Abughosh 2013 Ghafoori 2012 Cadilhe 2017	P vs AF T_feve 105 8 1 7 11 0	er T 621 50 421 140 47	C_fev 11 12 11 27 5	er C 613 101 444 140 47	Risk Ratio	RR 0.72 [0 0.17 [0 0.67 [0 0.41 [0 0.10 [0	<b>95%-Cl X</b> 0.29; 1.80] 0.02; 1.33] 0.26; 1.75] 0.19; 0.85] 0.01; 1.88]	<b>Neight</b> 25% 5% 23% 39% 2%
(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junior 2022 Ergani 2019 Abughosh 2013 Ghafoori 2012 Cadilhe 2017 Common effect mod	P vs AP T_feve 10 11 0 11 0	er T 621 50 421 140 47	C_fev 11 12 11 27 5	er C 613 101 444 140 47	Risk Ratio	RR 0.72 [0 0.17 [0 0.67 [0 0.41 [0 0.40 [0	95%-Cl X 0.29; 1.80] 0.02; 1.33] 0.26; 1.75] 0.19; 0.85] 0.01; 1.88] 0.01; 1.88]	Veight 25% 5% 23% 39% 2% 94%
(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junior 2022 Ergani 2019 Abughosh 2013 Ghafoori 2012 Cadilhe 2017 Common effect mod Heterogeneity: I <sup>2</sup> = 0%,	P vs AF T_feven res 8 1 7 11 0 el $\tau^2 = 0, \chi_4^2 : $	er T 621 50 421 140 47 = 3.47 (p	C_fev 11 12 11 12 11 27 5 0 = 0.48	er C 613 101 444 140 47	Risk Ratio	RR 0.72 [0 0.17 [0 0.67 [0 0.41 [0 0.40 [0	95%-Cl V 0.29; 1.80] 0.02; 1.33] 0.26; 1.75] 0.19; 0.85] 0.01; 1.88] 0.31; 0.79]	Veight 25% 23% 39% 2% 94%
(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junior 2022 Ergani 2019 Abughosh 2013 Ghafoori 2012 Cadilhe 2017 Cadilhe 2017 Cadilhe 2017 Heterogeneity: I <sup>2</sup> = 0%,	P vs AF T_feven res. 8 1 7 11 0 el $\tau^2 = 0, \chi_4^2$	er T 621 50 421 140 47 = 3.47 (p	<b>C_fev</b> 11 12 11 27 5 0 = 0.48	er C 613 101 444 140 47	Risk Ratio	RR 0.72 [0 0.17 [0 0.67 [0 0.41 [0 0.49 [0	95%-CI \ 0.29; 1.80] 0.02; 1.33] 0.26; 1.75] 0.19; 0.85] 0.01; 1.88] 0.31; 0.79]	<b>Veight</b> 25% 5% 23% 39% 2% 94%
(C) Fever (PI + A Study AP = Flororoquinolon Pontes-Junior 2022 Ergani 2019 Abughosh 2013 Ghafoori 2012 Common effect mod Heterogeneity: I <sup>2</sup> = 0%, AP = others Bw: 2010	P vs AF T_feven res 8 1 7 11 0 el $\tau^2 = 0, \chi_4^2$	er T 621 50 421 140 47 = 3.47 (p	C_fev 11 12 11 27 5 0 = 0.48	er C 613 101 444 140 47 2)	Risk Ratio	RR 0.72 [0 0.17 [0 0.41 [0 0.41 [0 0.49 [0	<b>95%-CI N</b> 0.29; 1.80] 0.02; 1.33] 0.26; 1.75] 0.19; 0.85] 0.01; 1.88] 0.31; 0.79]	Neight 25% 5% 23% 39% 2% 94%
(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junior 2020 Ergani 2019 Abughosh 2013 Ghafoori 2012 Common effect mod Heterogeneity: I <sup>2</sup> = 0%, AP = others Ryu 2019 Naches 1000	P vs AF T_feven tes: 8 1 7 11 0 el $\tau^2 = 0, \chi^2_4$	er T 621 50 421 140 47 = 3.47 (p	C_fev 11 12 11 27 5 0 = 0.48 0 2	er C 613 101 444 140 47 22)	Risk Ratio	RR 0.72 [0 0.17 [0 0.67 [1 0.41 [0 0.41 [0 0.49 [0 → 1.08 [0	<b>95%-CI 1</b> 0.29; 1.80] 0.02; 1.33] 0.26; 1.75] 0.19; 0.85] 0.01; 1.88] 0.31; 0.79]	Weight 25% 23% 39% 2% 94%
(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junior 2022 Ergani 2019 Abughosh 2013 Ghafoori 2012 Cadilhe 2017 Common effect mod Heterogeneity: / <sup>2</sup> = 0%, AP = others Ryu 2019 Melekos 1990 Berum 1091	P vs AF T_feven tes. 8 1 7 11 0 el $\tau^2 = 0, \chi^2_4$	er T 621 50 421 140 47 = 3.47 (p 120 43 21	C_fev 11 12 11 12 11 27 5 0 = 0.48 0 2 5	er C 613 101 444 140 47 22)	Risk Ratio	RR 0.72 [( 0.17 [( 0.67 [( 0.41 [( 0.49 [( 0.	95%-Cl V 0.29; 1.80] 0.02; 1.33] 0.26; 1.75] 0.19; 0.85] 0.01; 1.88] 0.01; 1.80] 0.01; 5.03] 0.01; 5.05] 0.01; 1.05]	Weight 25% 23% 39% 2% 94%
(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junior 2022 Ergani 2019 Abughosh 2013 Ghafoori 2012 Cadilhe 2017 Common effect mod Heterogeneity: I <sup>2</sup> = 0%, AP = others Ryu 2019 Melekos 1990 Brown 1981 Common effect mod	P vs AF T_fevent res 8 17 11 0 el $\tau^2 = 0, \chi_4^2$	er T 621 50 421 140 47 = 3.47 (p 43 21	C_fev 11 12 11 27 5 0 = 0.48 0 2 5	er C 613 101 444 140 47 2) 130 38 19	Risk Ratio	RR 0.72 [( 0.77 [( 0.67 [( 0.47 [( 0.41 [( 0.44 [( 0.49 [( 0.49 [( 0.99 [( 0.99 [(	95%-Cl \ 0.29; 1.80] 0.02; 1.33] 0.26; 1.75] 0.19; 0.85] 0.01; 1.88] 0.31; 0.79] 0.02; 55.03] 0.01; 5.05] 0.00; 1.77] 0.02; 4.67]	Weight 25% 5% 23% 39% 2% 94% 1% 2% 2%
(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junio 2022 Ergani 2019 Abughosh 2013 Ghafoori 2012 Cadilhe 2017 Common effect mod Heterogeneity: I <sup>2</sup> = 0%, AP = others Ryu 2019 Melekos 1990 Brown 1981 Common effect mod	P vs AF T_feven tes. 8 1 7 11 0 el $\tau^2 = 0, \chi_1^2$	621 50 421 140 47 = 3.47 (p 43 21	C_fev 11 12 11 27 5 0 = 0.48 0 2 5 0 = 0.61	er C 613 101 444 140 47 2) 130 38 19	Risk Ratio	RR 0.72 [( 0.17 [( 0.41 [( 0.41 [( 0.49 [( → 1.08 [0]) → 1.08 [0]) → 1.08 [0] → 0.22 [(	95%-Cl V 0.29; 1.80] 0.02; 1.33] 0.26; 1.75] 0.19; 0.85] 0.01; 1.88] 0.01; 5.05] 0.01; 5.05] 0.00; 1.77] 0.03; 1.47]	Weight 25% 5% 23% 39% 2% 94% 1% 2% 6%
(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junior 2020 Ergani 2019 Abughosh 2013 Ghafoori 2012 Cadilhe 2017 Common effect mod Heterogeneity: I <sup>2</sup> = 0%, AP = others Ryu 2019 Melekos 1990 Brown 1981 Common effect mod Heterogeneity: I <sup>2</sup> = 0%,	P vs AF T_feven tes 8 1 7 11 0 el $\tau^2 = 0, \chi_2^2$	er T 621 50 421 140 47 = 3.47 (p 43 21 = 0.98 (p	$\begin{array}{c} \mathbf{C}_{-} \mathbf{fev} \\ 11 \\ 12 \\ 11 \\ 27 \\ 5 \\ 0 = 0.48 \\ 0 \\ 2 \\ 5 \\ 0 = 0.61 \end{array}$	er C 613 101 444 47 2) 130 38 19 4)	Risk Ratio	rrs [AP] RR 0.72 [[ 0.17 [[ 0.47 [[ 0.49 [[ → 1.08 [0] → 0.22 [[ 0.22 [[	95%-Cl V 0.29; 1.80] 0.02; 1.33] 0.26; 1.75] 0.19; 0.85] 0.01; 1.88] 0.31; 0.79] 0.02; 55.03] 0.01; 5.05] 0.00; 1.77] 0.03; 1.47]	<b>Veight</b> 25% 23% 39% 94% 1% 2% 2% 6%
(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junior 2022 Ergani 2019 Abughosh 2013 Ghafoori 2012 Cadilhe 2017 Common effect mod Heterogeneity: I <sup>2</sup> = 0%, AP = others Ryu 2019 Melekos 1990 Brown 1981 Common effect mod Heterogeneity: I <sup>2</sup> = 0%, Common effect mod	P vs AP T_feven tes. 8 1 7 11 0 0 0 0 0 0 0 0 0 0 0 0 0	621 50 421 140 47 = 3.47 (p 43 21 = 0.98 (p	$\begin{array}{c} \mathbf{C}_{\mathbf{fev}} = 0.\\ \mathbf{C}_{\mathbf{fev}} \\ 11\\ 12\\ 11\\ 27\\ 5\\ 0 = 0.48\\ 0\\ 2\\ 5\\ 0 = 0.61 \end{array}$	er C 613 101 444 140 47 2) 130 38 19 4)	Risk Ratio	rrs [AP] RR 0.72 [( 0.17 [( 0.67 [( 0.41 [( 0.49 [( 0.49 [( 0.49 [( 0.22 [( 0.22 [( 0.47 [	95%-Cl \ 0.29; 1.80] 0.02; 1.33] 0.02; 1.33] 0.01; 1.88] 0.01; 1.88] 0.01; 5.05] 0.00; 1.77] 0.03; 1.47] 0.03; 0.74]	Veight 25% 5% 23% 2% 94% 1% 2% 2% 6% 100%
(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junio 2022 Ergani 2019 Abughosh 2013 Ghafoori 2012 Coddilhe 2017 Common effect mod Heterogeneity: I <sup>2</sup> = 0%, AP = others Ryu 2019 Melekos 1990 Brown 1981 Common effect mod Heterogeneity: I <sup>2</sup> = 0%,	P vs AP T_feve es 8 1 11 0 el $t^2 = 0, \chi_2^2$ el $t^2 = 0, \chi_2^2$	621 50 421 140 47 = 3.47 ( <i>y</i> 120 43 21 = 0.98 ( <i>y</i>	$C_{fev} = 0.$ $C_{fev}$ $11$ $12$ $11$ $27$ $5$ $0$ $2$ $5$ $0$ $2$ $5$ $0$ $0$ $2$ $5$ $0$ $0$ $2$ $5$ $0$ $0$ $2$ $5$ $0$ $0$ $2$ $5$ $0$ $0$ $0$ $2$ $5$ $0$ $0$ $0$ $0$ $0$ $0$ $0$ $0$ $0$ $0$	er C 613 101 444 140 47 (2) 130 38 19 4) 9)	Risk Ratio	rrs [AP] RR 0.72 [( 0.17 [( 0.47 [( 0.41 [( 0.49 [( 0.49 [( 0.49 [( 0.22 [( 0.22 [( 0.47 [(	95%-Cl N 0.29; 1.80] 0.02; 1.33] 0.26; 1.75] 0.19; 0.65] 0.01; 1.88] 0.01; 1.88] 0.01; 5.03] 0.01; 5.05] 0.00; 1.77] 0.03; 1.47]	Weight 25% 23% 39% 2% 94% 1% 2% 2% 6% 100%
(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junio 2020 Ergani 2019 Abughosh 2013 Ghafoori 2012 Codilhe 2017 Common effect mod Heterogeneity: I <sup>2</sup> = 0%, AP = others Ryu 2019 Melekos 1990 Brown 1981 Common effect mod Heterogeneity: I <sup>2</sup> = 0%, Common effect mod Heterogeneity: I <sup>2</sup> = 0%, Test for overall effect z	$\begin{array}{c} \cos x_{1} = 1, \\ \mbox{P vs AP} \\ \mbox{T_feve} \\ \mbox{res} \\ \mbox{s} \\ \mbox{r} \ \mbox{r} \\ \mbox{r} \ \mbox{r} \\ \mbox{r} \ \mbox{r} $	<pre>content = content = c</pre>	$C_{fev} = 0.$ $C_{fev}$ $11 \\ 12 \\ 11 \\ 27 \\ 5 \\ 0 = 0.48 \\ 0 \\ 2 \\ 5 \\ 0 = 0.64 \\ 0 \\ 0 \\ 0 = 0.64 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0$	er C 613 101 444 140 47 (2) 130 38 19 4) 9)	Risk Ratio	RR 0.72 [( 0.17 [( 0.47 [( 0.41 [( 0.49 [( 0.49 [( 0.49 [( 0.49 [( 0.22 [( 0.49 [( 0.22 [( 0.47 [(	95%-Cl V 0.29; 1.80] 0.02; 1.33] 0.26; 1.75] 0.19; 0.85] 0.01; 1.88] 0.01; 1.605] 0.00; 1.77] 0.03; 1.47] 0.30; 0.74]	Weight 25% 5% 23% 39% 2% 94% 1% 2% 6% 100%
(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junior 2022 Ergani 2019 Abughosh 2013 Ghafoori 2012 Cadilhe 2017 Common effect modi Heterogeneity: $l^2 = 0\%$ , AP = others Ryu 2019 Melekos 1990 Brown 1981 Common effect modi Heterogeneity: $l^2 = 0\%$ , Common effect modi Heterogeneity: $l^2 = 0\%$ , Test for overall effect: z Test for subgroup differe	P vs AF T_feven tess 8 1 7 11 0 el $\tau^2 = 0, \chi_2^2$ el el $\tau^2 = 0, \chi_2^2$ el el $\tau^2 = 0, \chi_2^2$	<pre>content = content = c</pre>	$C_{fev} = 0.48$ $C_{fev} = 0.64$ $C_{fev} = 0.64$ $C_{fev} = 0.64$ $C_{fev} = 0.64$	er C 613 101 444 140 47 2) 130 38 19 4) 9) = 0.424)	Risk Ratio	RR 0.72 [( 0.77 [( 0.67 [( 0.41 [( 0.41 [( 0.49 [( 0.49 [( 0.22 [( 0.22 [( 0.22 [( 0.22 [( 0.22 [( 0.27 [(	95%-Cl N 0.29; 1.80] 0.02; 1.33] 0.26; 1.75] 0.19; 0.85] 0.01; 1.88] 0.31; 0.79] 0.02; 55.03] 0.00; 1.77] 0.00; 1.77] 0.03; 1.47]	Veight 25% 5% 23% 39% 2% 94% 1% 2% 6% 5%
(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junior 2022 Ergani 2019 Abughosh 2013 Ghafoori 2012 Cadilihe 2017 Common effect modi Heterogeneity: I <sup>2</sup> = 0%, AP = others Ryu 2019 Melekos 1990 Brown 1981 Common effect modi Heterogeneity: I <sup>2</sup> = 0%, <b>Common effect modi</b> Heterogeneity: I <sup>2</sup> = 0%, Test for overall effect: z Test for subgroup diffect	P vs AP T_feve res. 8 1 7 11 0 el $\tau^2 = 0, \chi_2^2 + \frac{1}{2}$ el $\tau^2 = 0, \chi_2^2 + \frac{1}{2}$ el (0) (0) (0) (0) (0) (0) (0) (0)	621 50 421 140 47 = 3.47 ( <i>j</i> 43 21 = 0.98 ( <i>j</i> = 5.09 ( <i>j</i> 0.64, d	$C_{fev} = 0.48$ $C_{fev} = 0.64$ $C_{fev} = 0.64$ $C_{fev} = 0.64$ $C_{fev} = 0.64$	er C 613 101 444 140 47 (2) 130 38 19 4) 9) = 0.424)	Risk Ratio	rrs [AP] RR 0.72 [( 0.17 [( 0.67 [( 0.41 [( 0.49 [( 0.49 [( 0.49 [( 0.22 [( 0.41 [( 0.41 [( 0.41 [( 0.42 [( 0.42 [( 0.42 [( 0.41 [( 0.41 [( 0.41 [( 0.42 [( 0.42 [( 0.42 [( 0.41 [( 0.41 [( 0.41 [( 0.42 [( 0.42 [( 0.42 [( 0.41 [( 0.42 [( 0.42 [( 0.42 [( 0.41 [( 0.42 [	95%-Cl 1 0.29; 1.80] 0.02; 1.33] 0.02; 1.33] 0.01; 0.26; 1.75] 0.01; 1.88] 0.01; 5.05] 0.00; 1.77] 0.03; 1.47] 0.03; 0.74]	Veight 25% 5% 23% 23% 2% 2% 2% 2% 6% 6% 100%
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(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junio 2022 Ergani 2019 Abughosh 2013 Ghafoori 2012 Coddilhe 2017 Common effect mod Heterogeneity: $I^2 = 0\%$ , AP = others Ryu 2019 Melekos 1990 Brown 1981 Common effect mod Heterogeneity: $I^2 = 0\%$ , Common effect mod Heterogeneity: $I^2 = 0\%$ , Test for overall effect: z Test for subgroup differe (D) Sepsis (PI + J Study	P vs AF T_fev nes 8 1 7 11 0 0 0 0 0 0 el $t^2 = 0, \chi_1^2 + \frac{1}{2}$ $t^2 = 0, \chi_2^2 + \frac{1}{2}$ el $t^2 = 0, \chi_2^2 + \frac{1}{2}$ el $t^2 = 0, \chi_2^2 + \frac{1}{2}$ H r AP vs AF T_sepsis	621 50 421 140 47 = 3.47 (r 43 21 = 5.09 (r = 0.001 e 0.64, d P)	$C_{fev} = 0.$ $C_{fev}$ $11$ $12$ $11$ $27$ $5$ $0$ $2$ $5$ $0$ $0$ $2$ $5$ $0$ $0$ $1$ $1$ $0$ $1$ $5$ $0$ $1$ $1$ $1$ $2$ $5$ $0$ $1$ $1$ $2$ $5$ $0$ $1$ $1$ $2$ $2$ $3$ $2$ $3$ $3$ $3$ $3$ $3$ $4$ $3$ $3$ $4$ $3$ $3$ $4$ $3$ $3$ $4$ $3$ $3$ $4$ $3$ $3$ $4$ $3$ $3$ $4$ $3$ $3$ $4$ $3$ $3$ $4$ $3$ $3$ $4$ $3$ $3$ $4$ $3$ $3$ $4$ $3$ $3$ $4$ $3$ $3$ $4$ $3$ $3$ $4$ $3$ $4$ $3$ $4$ $3$ $4$ $3$ $4$ $4$ $4$ $4$ $4$ $4$ $4$ $4$ $4$ $4$	er C 613 101 444 140 47 22) 130 38 19 9) = 0.424) s C	Risk Ratio	RR 0.72 [( 0.72 [( 0.77 [( 0.41 [( 0.41 [( 0.49 [( 0.49 [( 0.22 [( 0.22 [( 0.22 [( 0.27 [(	95%-Cl 1 0.29: 1.80] 0.02: 1.33] 0.26: 1.75] 0.19: 0.85] 0.01: 1.88] 0.01: 5.03] 0.02: 55.03] 0.01: 5.05] 0.00: 1.77] 0.03: 1.47] 0.03: 0.74]	Weight           25%           5%           23%           34%           1%           2%           1%           2%           1%           2%           1%           2%           100%           Weight
(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junior 2022 Ergani 2019 Abughosh 2013 Ghafoori 2012 Cadilhe 2017 Common effect mod Heterogeneity: $l^2$ = 0%, AP = others Ryu 2019 Melekos 1990 Brown 1981 Common effect mod Heterogeneity: $l^2$ = 0%, Common effect mod Heterogeneity: $l^2$ = 0%, Common effect mod Heterogeneity: $l^2$ = 0%, Test for overall effect. z Test for subgroup differe (D) Sepsis (PI + /	P vs AF T_fev rs 8 1 7 11 0 el $\tau^2 = 0, \chi^2_{2}$ el $\tau^2 = 0, \chi^2_{2}$ el $\tau^2 = 0, \chi^2_{2}$ el <b>el</b> $\tau^2 = 0, \chi^2_{2}$ el <b>el</b> <b>el</b> $\tau^2 = 0, \chi^2_{2}$ el <b>el</b> <b>el</b> $\tau^2 = 0, \chi^2_{2}$ el <b>el</b> <b>el</b> <b>el</b> <b>el</b> $\tau^2 = 0, \chi^2_{2}$ el <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>el</b> <b>e</b> <b>e</b> <b>e</b> <b>e</b> <b>e</b> <b>e</b> <b>e</b> <b>e</b>	621 50 421 140 47 = 3.47 ( <i>j</i> 43 21 = 5.09 ( <i>j</i> = 5.09 ( <i>j</i> = 0.001 = 0.64, d	$C_{fev} = 0.$ $C_{fev} = 0.$ $11 \\ 12 \\ 11 \\ 27 \\ 5 \\ 0 = 0.48$ $0 \\ 2 \\ 5 \\ 0 = 0.64$ $0 \\ 2 \\ 5 \\ 0 = 0.64$ $0 \\ 1 \\ 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ $	613         101           101         444           140         47           22)         1300           38         19           44)         99)           = 0.424)         5	Risk Ratio	rrs [AP] RR 0.72 [( 0.77 [( 0.67 [( 0.41 [( 0.49 [( 0.49 [( 0.49 [( 0.22 [( 0.22 [( 0.22 [( 0.22 [( 0.27 [	95%-Cl \ 0.29; 1.80] 0.02; 1.33] 0.26; 1.75] 0.19; 0.85] 0.01; 1.88] 0.01; 5.05] 0.00; 1.77] 0.03; 1.47] 0.30; 0.74]	Neight 25% 5% 23% 94% 94% 1% 2% 6% 100% Weight
(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junior 2022 Ergani 2019 Abughosh 2013 Ghafoori 2012 Cadilhe 2017 Common effect modi Heterogeneity: $I^2 = 0\%$ , AP = others Ryu 2019 Melekos 1990 Brown 1981 Common effect modi Heterogeneity: $I^2 = 0\%$ , Test for overall effect: z Test for subgroup differe (D) Sepsis (PI + A Study AP = Fluoroquinolone:	P vs AF T_fev Ness 8 1 7 11 0 0 0 0 0 el $t^2 = 0, \chi^2_2$ el $t^2 = 0, \chi^2_2$ el $t^2 = 0, \chi^2_2$ el $t^2 = 0, \chi^2_2$ for the second se	621 50 421 140 47 120 43 21 = 0.98 (; = 5.09 (; = 0.001 = 0.001 = 0.64, d	$C_{fev} = 0.48$ $C_{fev} = 0.64$ $C_{fev} = 0.64$ $C_{fev} = 0.64$	er C 613 101 444 140 47 2) 130 38 19 9) = 0.424) s C 612	Risk Ratio	rrs [AP] RR 0.72 [( 0.77 [( 0.67 [( 0.41 ([ 0.40 [( 0.49 [( 0.49 [( 0.49 [( 0.22 [( 0.47 [	95%-Cl \ 0.29; 1.80] 0.02; 1.33] 0.02; 1.33] 0.01; 0.26; 1.75] 0.01; 1.88] 0.01; 5.05] 0.00; 1.77] 0.03; 1.47] 0.33; 0.74] 95%-Cl	Neight 25% 5% 23% 23% 2% 2% 2% 6% 100%
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(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junior 2022 Ergani 2019 Abughosh 2013 Ghafoori 2012 Cadilhe 2017 Common effect modi Heterogeneity: $l^2 = 0\%$ , AP = others Ryu 2019 Melekos 1990 Brown 1981 Common effect modi Heterogeneity: $l^2 = 0\%$ , Common effect modi Heterogeneity: $l^2 = 0\%$ , Test for overall effect: z Test for overall effect: z Test for overall effect: z Test for overall effect: z Study AP = Fluoroquinoloner Pontes-Junior 2022 Ergani 2019	P vs AF T_feve res 8 17 11 0 ei $\tau^2 = 0, \chi^2_{2} + \frac{1}{2}$ 0 0 0 0 0 0 0 0 0 0 0 0 0	621 50 621 50 621 50 621 50 621 50 621 50 621 50 621 50 621 50 621 50 621	$\begin{array}{c} \mathbf{C}_{-} \mathbf{fev} \\ 11 \\ 12 \\ 11 \\ 12 \\ 7 \\ 5 \\ 0 = 0.48 \\ 0 \\ 2 \\ 5 \\ 0 = 0.64 \\ 0 \\ 1 \\ \mathbf{f} = 1 \left( p \\ \mathbf{c}_{-} \mathbf{sepsia} \right) \\ \mathbf{f} = 1 \left( p \\ \mathbf{c}_{-} \mathbf{sepsia} \right) \\ \mathbf{f} = 1 \left( p \\ \mathbf{c}_{-} \mathbf{sepsia} \right) \\ \mathbf{f} = 1 \left( p \\ \mathbf{c}_{-} \mathbf{sepsia} \right) \\ \mathbf{f} = 1 \\ \mathbf{f} \\ $	er C 613 101 444 140 47 2) 130 38 19 9) = 0.424) s C 613 101 47 47	Risk Ratio	rrs [AP] RR 0.72 [f 0.77 [f 0.67 [f 0.41 [f 0.40 [f 0.49 [f 0.49 [f 0.22 [f] 0.22 [f 0.22 [f] 0.22 [f 0.22 [f 0.22 [f] 0.22 [f]	95%-Cl N 0.29; 1.80] 0.02; 1.33] 0.26; 1.75] 0.19; 0.85] 0.01; 1.88] 0.01; 5.05] 0.00; 1.77] 0.00; 1.77] 0.00; 1.77] 0.33; 1.47] 0.33; 0.74] 95%-Cl [0.11; 3.95] [0.02; 2.27] [0.02; 2.27]	Veight 25% 5% 23% 23% 2% 2% 2% 2% 6% 6% 100%
(C) Fever (PI + A Study $AP = Fluoroquinolon Pontes-Junior 2022 Ergani 2019 Abughosh 2013 Ghafoori 2012 Cadilhe 2017 Common effect modd Haterogeneity: I^2 = 0\%_e.AP = othersRyu 2019Melekos 1909Brown 1981Common effect moddHaterogeneity: I^2 = 0\%_e.Common effect modd$	P vs AF T_fev Ness 8 1 7 11 0 0 0 0 el $t^2 = 0, \chi_2^2$ el $t^2 = 0, \chi_2^2$ el $t^2 = 0, \chi_2^2$ el $t^2 = 0, \chi_2^2$ el transformation tr	621 50 621 50 421 140 427 120 43 21 = 3.47 ( <i>y</i> = 0.98 ( <i>y</i> = 0.001 = 0.001 = 0.64, d P) 50 621 50 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7	$C_{fev} = 0.48$ $0$ $2$ $5$ $0 = 0.64$ $0$ $2$ $5$ $0 = 0.64$ $0$ $2$ $3$ $8$ $1$ $7$	302)           er         C           613         101           444         140           47         22)           130         38           19         9)           = 0.424)         5           613         101           47         444	Risk Ratio	rrs [AP] RR 0.72 [[ 0.67 [[ 0.67 [[ 0.41 [[ 0.49 [[ 0.49 [[ 0.49 [[ 0.49 [[ 0.49 [[ 0.49 [[ 0.47 [[ 0.22 [[ 0.47 [[ 0.22 [] 0.47 [] 0.22 [] 0.47 [] 0.22 [] 0.47 [] 0.22 [] 0.47 [] 0.22 [] 0.47 [] 0.49 [] 0.22 [] 0.47 [] 0.49 [] 0.49 [] 0.22 [] 0.47 [] 0.49 [	95%-Cl 1 0.29; 1.80] 0.02; 1.33] 0.02; 1.75] 0.19; 0.85] 0.01; 1.88] 0.01; 5.05] 0.01; 5.05] 0.01; 5.05] 0.00; 1.77] 0.03; 1.47] 95%-Cl [0.11; 3.95] [0.03; 2.07] [0.02; 15.27] [0.12; 5.27]	Neight 25% 5% 23% 23% 24% 94% 94% 6% 2% 2% 2% 6% 100% <b>Weight</b> 18% 5% 39%
(C) Fever (PI + A Study $AP = Fluoroquinolon Pontes-Junio 2022 Ergani 2019 Abughosh 2013 Ghafoori 2012 Cadilhe 2017 Common effect mod Heterogeneity: I^2 = 0\%,AP = othersRyu 2019Melekos 1990Brown 1981Common effect modHeterogeneity: I^2 = 0\%,Test for overall effect: zTest for subgroup differe(D) Sepsis (PI + AStudyAP = Fluoroquinoloner Pontes-Junior 2022 Ergani 2019 Cadilhe 2017 Abughosh 2013$	P vs AF T_fev 11 0 11 0 0 0 0 0 0 0 0 0 0 0 0 0	621 50 421 140 47 = 3.47 ( <i>j</i> 43 21 = 0.98 ( <i>j</i> = 0.001 = 0.64, d P) 50 57 77 421 140	$\begin{array}{c} \mathbf{C}_{-\mathbf{fev}}\\ 11\\ 12\\ 12\\ 12\\ 12\\ 5\\ 5\\ 5\\ 0 = 0.48\\ 0\\ 2\\ 5\\ 5\\ 0 = 0.64\\ 0\\ 1\\ 5\\ 5\\ 0 = 0.64\\ 1\\ 1\\ 7\\ 6\\ 1\\ 7\\ 6\\ 6\\ 1\\ 7\\ 6\\ 6\\ 1\\ 7\\ 6\\ 1\\ 7\\ 6\\ 1\\ 7\\ 6\\ 1\\ 7\\ 6\\ 1\\ 7\\ 6\\ 1\\ 7\\ 6\\ 1\\ 7\\ 6\\ 1\\ 7\\ 6\\ 1\\ 7\\ 7\\ 6\\ 1\\ 7\\ $	613         101           444         140           47         22           130         38           19         9)           = 0.424)         9           s         C           613         101           47         444	Risk Ratio	RR 0.72 [( 0.77 [( 0.77 [( 0.41 [( 0.41 [( 0.44] [( 0.49 [( 0.49 [( 0.22 [( 0.22 [( 0.22 [( 0.27 [	95%-Cl 1 0.29; 1.80] 0.02; 1.33] 0.26; 1.75] 0.19; 0.85] 0.01; 1.88] 0.01; 5.05] 0.00; 1.77] 0.03; 1.47] 95%-Cl [0.11; 3.95] [0.03; 5.27] [0.03; 12.07] [0.16]; 2.07] [0.07; 152] [0.17]; 2.07] [0.07] 5.207 [0.07] 5.207 [0.0	Weight           25%           5%           23%           23%           24%           1%           2%           94%           1%           2%           94%           1%           2%           94%           1%           2%           94%           1%           2%           5%           100%           Weight           18%           13%           5%           38%           2%           5%           38%
(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junior 2022 Ergani 2019 Abughosh 2013 Ghafoori 2012 Cadilhe 2017 Common effect modi Heterogeneity: $l^2 = 0\%$ , AP = others Ryu 2019 Melekos 1990 Brown 1981 Common effect modi Heterogeneity: $l^2 = 0\%$ , Common effect modi Heterogeneity: $l^2 = 0\%$ , Test for overall effect: z Test for overall effect: z Study AP = Fluoroquinoloner Pontes-Junior 2022 Ergani 2019 Cadilhe 2017 Abughosh 2013 Ghalori 2012	P vs AF T_fev rs 8 1 7 11 0 ei $\tau^2 = 0, \chi^2_{2}$ ei $\tau^2 = 0, \chi^2_{2}$ ei $\tau^2 = 0, \chi^2_{2}$ ei ei $\tau^2 = 0, \chi^2_{2}$ ei ei $\tau^2 = 0, \chi^2_{2}$ ei ei $\tau^2 = 0, \chi^2_{2}$ ei ei ei $\tau^2 = 0, \chi^2_{2}$ ei ei ei ei ei ei ei ei ei ei	621         50           421         50           421         140           47         21           120         43           21         50.09 (g           = 0.98 (g         0.001           = 0.64, d         0.001           = 0.64, d         0.001           = 0.64, d         0.001           = 0.75, 0.001         0.64, d           P)         0.001           50         T           621         50           47         421           140         140	$C_{fev} = 0.$ $C_{fev} = 0.$ $11$ $12$ $11$ $27$ $5$ $0$ $2$ $5$ $0$ $2$ $5$ $0$ $2$ $5$ $5$ $0$ $1$ $1$ $2$ $5$ $5$ $5$ $5$ $5$ $5$ $5$ $5$ $5$ $5$	er C 613 101 444 140 47 2) 130 38 19 4) 9) = 0.424) s C 613 101 47 444 140 47 19	Risk Ratio	rrs [AP] RR 0.72 [f 0.77 [f 0.67 [f 0.41 [f 0.41 [f 0.49 [f → 1.08 [0] → 0.22 [f 0.22 [f 0.22 [f 0.22 [f 0.22 [f 0.23 [f 0.47 [c] RR → 0.66 - 0.55 → 0.55 - 0.60 0.33 0.47	95%-Cl N 0.29; 1.80] 0.02; 1.33] 0.26; 1.75] 0.19; 0.85] 0.01; 1.88] 0.01; 5.05] 0.00; 1.77] 0.03; 1.47] 0.33; 0.74] 95%-Cl [0.11; 3.95] [0.02; 15.27] [0.02; 15.27] [0.02; 15.27] [0.02; 1.68] [0.022; 1.27]	Veight 25% 5% 23% 23% 2% 2% 6% 6% 100% <b>Weight</b> 18% 13% 5% 38% 22%
(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junior 2022 Ergani 2019 Abughosh 2013 Ghafoori 2012 Cadilhe 2017 Common effect modi Heterogeneity: $I^2 = 0\%$ , AP = others Ryu 2019 Melekos 1990 Brown 1981 Common effect modi Heterogeneity: $I^2 = 0\%$ , Common effect modi Heterogeneity: $I^2 = 0\%$ , Test for overall effect: z Test for subgroup differe (D) Sepsis (PI + A Study AP = Fluoroquinoloner Pontes-Junior 2022 Ergani 2019 Cadilhe 2017 Abughosh 2013 Ghadori 2012 Common effect model Heterogeneity: $I^2 = 0\%$ , $\tau^2$	P vs AF T_fev nes 8 1 7 11 0 0 0 0 el $\tau^2 = 0, \chi_2^2 + \frac{1}{2}$ el $\tau^2 = 0, \chi^2 = 0$ el $\tau^2 = 0, \chi^2 = 0$	621 50 421 140 47 = 3.47 ( <i>y</i> 120 43 21 = 0.98 ( <i>y</i> = 0.001 = 0.64, d P) 621 50 421 140 8, ( <i>p</i> = 0.	$C_{fev} = 0.$ $C_{fev} = 0.$ $11$ $12$ $11$ $27$ $5$ $0$ $2$ $5$ $0$ $2$ $5$ $0$ $2$ $5$ $0$ $2$ $5$ $5$ $0$ $2$ $5$ $5$ $5$ $5$ $5$ $5$ $5$ $5$ $5$ $5$	er C 613 101 444 140 47 2) 130 38 19 (1) 19) 9) 9) 9) 9) 613 101 44 140 47 19 19 10 10 10 10 10 10 10 10 10 10	Risk Ratio	rrs [AP] RR 0.72 [f 0.77 [f 0.67 [f 0.41 [f 0.40 [f 0.49 [f 0.49 [f 0.49 [f 0.22 [f 0.22 [f 0.22 [f 0.22 [f 0.22 [f 0.23 [f 0.24 ] 0.25 → 0.66 - 0.65 0.50 - 0.66 0.33 0.47	95%-Cl N 0.29; 1.80] 0.02; 1.33] 0.26; 1.75] 0.19; 0.85] 0.01; 1.88] 0.31; 0.79] 0.02; 55.03] 0.00; 1.77] 0.00; 1.77] 0.03; 1.47] 0.33; 0.74] 95%-Cl [0.11; 3.95] [0.03; 2.07] [0.02; 15.27] [0.02; 15.27] [0.02; 15.27] [0.02; 1.62]	Veight 25% 5% 23% 23% 2% 2% 6% 6% <b>100%</b> <b>Weight</b> 18% 5% 5%
(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junic 2022 Ergani 2019 Abughosh 2013 Ghafoori 2012 Cadilhe 2017 Common effect model Haterogeneity: $I^2 = 0\%$ , AP = others Ryu 2019 Melekos 1990 Brown 1981 Common effect model Haterogeneity: $I^2 = 0\%$ , Common effect model Haterogeneity: $I^2 = 0\%$ , Test for overall effect z Test for subgroup differe (D) Sepsis (PI + A Study AP = Fluoroquinolone: Pontes-Junic 2022 Ergani 2019 Cadilhe 2017 Abughosh 2013 Ghafoori 2012 Common effect model Haterogeneity: $I^2 = 0\%$ , $T^2$	P vs AF T_fev Ness 8 1 7 11 0 0 0 0 el $t^2 = 0, \chi_2^2 + 0$ el $t^2 = 0, \chi_2^2 + 0$ el $t^2 = 0, \chi_2^2 + 0$ AP vs A T_sepsie s 2 1 0 0 0 0 0 0 0 0 0 0 0 0 0	621         50           421         50           421         140           47         120           43         21           = 0.98 (j)         621           = 0.98 (j)         0.04, d           = 0.081 (j)         621           50         421           140         43           21         120           621         50           50         47           421         140           8 (p = 0.000)         8 (p = 0.000)	$\begin{array}{c} 1 \ (p = 0. \\ 11 \\ 11 \\ 11 \\ 27 \\ 5 \\ 0 = 0.48 \\ 0 \\ 2 \\ 5 \\ 0 = 0.64 \\ 0 \\ 1 \\ 1 \\ 1 \\ 0 \\ 1 \\ 1 \\ 1 \\ 0 \\ 1 \\ 1$	302)           er         C           613         101           444         140           47         2)           130         38           19         9)           =         0.424)           s         C           613         101           47         444           140         47	Risk Ratio	rrs [AP] RR 0.72 [( 0.67 [( 0.67 [( 0.41 [( 0.49 [( 0.49 [( 0.49 [( 0.49 [( 0.49 [( 0.49 [( 0.49 [( 0.22 [( 0.67 [( 0.66 [	95%-Cl \ 0.29; 1.80] 0.02; 1.33] 0.26; 1.75] 0.19; 0.85] 0.01; 1.88] 0.01; 5.05] 0.01; 5.05] 0.02; 5.27] 0.02; 15.27] 0.02; 15.27] 0.02; 15.27] 0.02; 15.27] 0.02; 15.27] 0.02; 15.27] 0.02; 15.27] 0.02; 15.27]	Veight 25% 5% 23% 23% 24% 94% 5% 5% 100% Weight 18% 5% 38% 5% 38% 95%
(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junio 2022 Pontes-Junio 2022 Egani 2019 Abughosh 2013 Ghafoori 2012 Codilhe 2017 Common effect model Heterogeneity: $I^2 = 0\%$ , AP = others Ryu 2019 Melekos 1990 Brown 1981 Common effect model Heterogeneity: $I^2 = 0\%$ , Test for overall effect: z Test for subgroup differe (D) Sepsis (PI + J) Study AP = Fluoroquinoloner Pontes-Junior 2022 Ergani 2019 Cadilhe 2017 Abughosh 2013 Common effect model Heterogeneity: $I^2 = 0\%$ , $\tau^2$ AP = Fluoroquinoloner Pontes-Junior 2022 Ergani 2019 Cadilhe 2017 Abughosh 2013 Common effect model Heterogeneity: $I^2 = 0\%$ , $\tau^2$	P vs AF T_fev T_fev Nes 8 1 7 11 0 0 0 0 0 11 $\tau^2 = 0, \chi_4^2 + 0$ $\tau^2 = 0, \chi_7^2 + 0$ AP vs A T_sepsis s 2 1 0 0 0 0 0 0 0 0 0 0 0 0 0	621         50           421         140           47         50           421         140           47         50           43         21           = 0.98 (p         0.001           = 5.09 (p         0.004           50         47           421         140           50         47           421         140           140         8.8 (p = 0.           120         120	$C_{fev} = 0.$ $C_{fev} = 0.$ $111$ $112$ $112$ $27$ $5$ $0$ $2$ $5$ $0$ $2$ $5$ $0$ $0$ $2$ $5$ $0$ $0$ $2$ $3$ $8$ $1$ $7$ $6$ $9380$ $0$ $0$	302)           er         C           613         101           444         140           47         22)           130         38           19         9)           =         0.424)           s         C           613         101           47         444           140         47           130         38	Risk Ratio	RR 0.72 [( 0.77 [( 0.67 [( 0.41 [( 0.41 [( 0.49 [( 0.49 [( 0.49 [( 0.22 [( 0.47 [( 0.22 [( 0.47 [( 0.24 [( 0.24 [( 0.25 [( 0.25 (0.25	95%-Cl V 0.29; 1.80] 0.02; 1.33] 0.26; 1.75] 0.19; 0.85] 0.01; 1.88] 0.02; 55.03] 0.02; 55.03] 0.02; 55.03] 0.02; 55.03] 0.03; 1.47] 95%-Cl [0.11; 3.95] [0.02; 52.07] [0.13; 2.07] [0.02; 1.02] [0.02; 1.02] [0.02; 55.03]	Weight           25%           5%           23%           39%           2%           94%           1%           2%           6%           100%           Weight           18%           38%           26%           96%
(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junior 2022 Ergani 2019 Abughosh 2013 Ghafoori 2012 Cadilhe 2017 Common effect modi Heterogeneity: $I^2 = 0\%$ , AP = others Ryu 2019 Melekos 1990 Brown 1981 Common effect modi Heterogeneity: $I^2 = 0\%$ , Common effect modi Heterogeneity: $I^2 = 0\%$ , Test for overall effect: 2 Test for overall effect: 2 Study AP = Fluoroquinoloner Pontes-Junior 2022 Ergani 2019 Cadilhe 2017 Abughosh 2013 Ghadori 2012 Common effect model Heterogeneity: $I^2 = 0\%$ , $\tau^2$ AP = others Ryu 2019	P vs AF T_fev T_fev Res 8 1 7 11 0 0 0 0 el $\tau^2 = 0, \chi_2^2 + \frac{1}{2}$ el $\tau^2 = 0, \chi_1^2 + \frac{1}{2}$ el $\tau^2$	621 50 421 140 47 = 3.47 ( <i>j</i> 120 43 21 = 0.98 ( <i>j</i> = 0.001 = 0.64, d P) 621 50 421 140 8 ( <i>p</i> = 0. 120	$C_{fev} = 0.$ $C_{fev}$ $11$ $12$ $11$ $27$ $5$ $0$ $2$ $5$ $0$ $2$ $5$ $0$ $2$ $5$ $5$ $5$ $5$ $5$ $5$ $5$ $5$ $5$ $5$	er C 613 101 444 140 47 2) 130 38 19 4) 9) = 0.424) s C 613 101 444 140 130	Risk Ratio	rrs [AP] RR 0.72 [f 0.77 [f 0.67 [f 0.41 [f 0.41 [f 0.49 [f → 1.08 [0] → 0.22 [f 0.22 [f 0.22 [f 0.22 [f 0.22 [f 0.22 [f 0.22 [f 0.23 ] RR → 0.66 - 0.55 - 0.55 - 0.65 - 0.65 - 0.55 - 0.66 0.33 0.47	95%-Cl N 0.29; 1.80] 0.02; 1.33] 0.26; 1.75] 0.19; 0.85] 0.01; 1.88] 0.01; 1.88] 0.02; 55.03] 0.00; 1.77] 0.00; 1.77] 0.00; 1.77] 0.00; 1.77] 0.00; 1.77] 0.00; 1.73] 95%-Cl 0.00; 1.73] 0.00; 1.74] 95%-Cl 0.02; 15.27] 0.02; 15.27]	Weight           25%           5%           23%           23%           23%           24%           1%           2%           94%           1%           2%           6%           100%           Weight           13%           5%           38%           22%           96%           4%
(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junic 2022 Ergani 2019 Abughosh 2013 Ghafoori 2012 Cadilhe 2017 Common effect model Haterogeneity: $I^2 = 0%$ , AP = others Ryu 2019 Melekos 1990 Brown 1981 Common effect model Haterogeneity: $I^2 = 0%$ , Common effect model Haterogeneity: $I^2 = 0%$ , $I^2$ Abughosh 2013 Common effect model Haterogeneity: $I^2 = 0%$ , $I^2$ AP = others Ryu 2019 Common effect model	P vs AF T_fev nes 8 1 7 11 0 0 0 0 el $t^2 = 0, \chi_2^2 + 0$ el $t^2 = 0, \chi_2^2 + 0$ el $t^2 = 0, \chi_2^2 + 0$ AP vs A T_sepsit s 2 1 0 0 0 0 0 0 0 0 0 0 0 0 0	621         50           421         50           421         140           47         21           120         43           21         50           621         50           50         40           60.084         621           50         47           421         140           43         21           5         7           6         621           50         47           120         8           120         120	$\begin{array}{c} \mathbf{C}_{-} \mathbf{fev} \\ 11\\ 12\\ 11\\ 27\\ 5\\ 0 = 0.48\\ 0\\ 2\\ 5\\ 0 = 0.64\\ 0\\ 1\\ \mathbf{f} = 1 \ (p \\ \mathbf{c}_{-} \mathbf{sepsia} \\ \mathbf{sepsia} \\ 1\\ 7\\ 6\\ \mathbf{s} \\ \mathbf{sepsia} \\ 0\\ 0\\ 0\\ 0\\ \end{array}$	613         101           444         140           47         22           130         38           19         9)           4)         9)           5         C           613         101           47         444           140         38           19         9)           4)         101           41         140           130         130	Risk Ratio	rrs [AP] RR 0.72 [( 0.67 [( 0.67 [( 0.41 [( 0.49 [( 0.49 [( 0.49 [( 0.49 [( 0.49 [( 0.22 [( 0.22 [( 0.22 [( 0.27 [( 0.47 [( 0.49 [( 0.49 [( 0.49 [( 0.49 [( 0.49 [( 0.27 [( 0.27 [( 0.27 [( 0.41 [( 0.49 [( 0.49 [( 0.49 [( 0.49 [( 0.49 [( 0.27 [( 0.27 [( 0.27 [( 0.27 [( 0.27 [( 0.49 [( 0.49 [( 0.49 [( 0.49 [( 0.27 [( 0.27 [( 0.27 [( 0.27 [( 0.27 [( 0.49 [( 0.49 [( 0.49 [( 0.27 [	95%-Cl 1 0.29; 1.80] 0.02; 1.33] 0.26; 1.75] 0.19; 0.85] 0.01; 0.85] 0.01; 5.03] 0.02; 55.03] 0.01; 5.05] 0.00; 1.77] 0.03; 1.47] 95%-Cl [0.11; 3.95] [0.03; 2.07] [0.02; 15.27] [0.02; 15	Neight 25% 5% 23% 23% 24% 94% 1% 6% 6% 100%
(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junior 2022 Ergani 2019 Abughosh 2013 Ghafoori 2012 Cadilhe 2017 Common effect modi Heterogeneity: $l^2 = 0\%$ , AP = others Ryu 2019 Melekos 1990 Brown 1981 Common effect modi Heterogeneity: $l^2 = 0\%$ , Common effect modi Heterogeneity: $l^2 = 0\%$ , Common effect modi Heterogeneity: $l^2 = 0\%$ , Study AP = Fluoroquinoloner Pontes-Junior 2022 Ergani 2019 Cadilhe 2017 Abughosh 2013 Chatoori 2012 Common effect model Heterogeneity: $l^2 = 0\%$ , $t^2$ AP = others Ryu 2019 Common effect model Heterogeneity: $l^2 = 0\%$ , $t^2$	P vs AF T_fev Ness 1 7 11 0 0 0 1 7 11 0 0 0 0 1 7 11 0 0 0 0 0 0 0 0 0 0 0 0 0	(a)         (a)           (a)         (a)           (b)         (a)           (c)         (a)           (c)         (a)           (c)         (c)	C_fev 111 121 127 5 0 0 2 5 0 0 0 1 1 2 5 0 0 2 5 0 0 0 2 5 0 0 0 2 5 0 0 0 2 5 0 0 0 0 2 5 0 0 0 0 2 5 0 0 0 0 0 0 0 0 0 0 0 0 0	302)           er         C           613         101           101         444           140         47           22)         130           38         19           4)         9)           =         0.424)           s         C           613         101           47         444           140         1300	Risk Ratio	rrs [AP] RR 0.72 [( 0.77 [( 0.67 [( 0.41 [( 0.41 [( 0.49 [( → 1.08 [0] → 0.22 [( 0.49 [( 0.49 [( 0.49 [( 0.22 [( 0.47 [( 0	95%-Cl \ 0.29; 1.80] 0.02; 1.33] 0.22; 1.33] 0.26; 1.75] 0.19; 0.85] 0.01; 1.88] 0.01; 5.05] 0.02; 55.03] 0.02; 55.03] 0.03; 1.47] 0.03; 1.47] 0.03; 0.74] 95%-Cl [0.11; 3.95] [0.02; 55.7] [0.18; 2.07] [0.07; 1.68] [0.22; 1.02] [0.02; 55.03] [0.22; 1.02]	Weight           25%           5%           23%           39%           2%           94%           1%           2%           94%           1%           2%           94%           1%           2%           5%           100%
(C) Fever (PI + A Study AP = Fluoroquinolon Pontes-Junior 2022 Ergani 2019 Abughosh 2013 Ghafoori 2012 Cadilhe 2017 Common effect model Heterogeneity: $l^2 = 0\%$ , AP = others Ryu 2019 Melekos 1990 Brown 1981 Common effect model Heterogeneity: $l^2 = 0\%$ , Common effect model Heterogeneity: $l^2 = 0\%$ , Test for overall effect: z Test for subgroup differe (D) Sepsis (PI + J Study AP = Fluoroquinolonem Pontes-Junior 2022 Ergani 2019 Cadilhe 2017 Abughosh 2013 Ghafori 2012 Common effect model Heterogeneity: $l^2 = 0\%$ , $t^2$ AP = others Ryu 2019	P vs AF T_fev T_fev Res 8 1 7 11 0 0 0 0 el $\tau^2 = 0, \chi_2^2 + 0$ $\tau^2 = 0, \chi_2^2 + 0$ el $\tau^2 = 0, \chi_2^2 + 0$ AP vs A T_sepsie 8 2 1 0 0 0 0 0 0 0 0 0 0 0 0 0	$\begin{array}{c} \text{621} \\ \text{50} \\ \text{621} \\ \text{50} \\ \text{621} \\ \text{50} \\ \text{621} \\ \text{622} \\ \text{622} \\ \text{623} \\ \text{623} \\ \text{633} \\ \text{64} \\ \text{64} \\ \text{64} \\ \text{65} \\ \text{65} \\ \text{66} \\ 6$	$C_{fev} = 0.$ $C_{fev} = 0.$ $11$ $12$ $11$ $27$ $5$ $0$ $2$ $5$ $0$ $2$ $5$ $0$ $1 + 1 (p - 0)$ $2 + 1 (p - 0)$ $2 + 1 (p - 0)$ $1 + 1 (p -$	er C 613 101 444 140 47 2) 130 38 19 4) 9) = 0.424) s C 613 101 47 444 140 130	Risk Ratio	rrs [AP] RR 0.72 [f 0.77 [f 0.67 [f 0.41 [f 0.49 [f → 0.22 [f 0.22 [f 0.22 [f 0.22 [f 0.22 [f 0.23 [c:pATB] RR → 0.66 - 0.25 - 0.65 0.45 0.45 0.45 0.47 [f 0.47 [f] 0.47 [f 0.47 [f] 0.47 [f 0.47 [f] 0.47 [	95%-Cl \ 0.29; 1.80] 0.02; 1.33] 0.26; 1.75] 0.19; 0.85] 0.01; 1.88] 0.01; 1.88] 0.02; 55.03] 0.00; 1.77] 0.00; 1.77] 0.00; 1.77] 0.00; 1.77] 0.00; 1.73] 95%-Cl 0.03; 2.07] 0.02; 15.27] [0.02; 15.29] [0.02; 15.29]	Veight 25% 5% 23% 23% 2% 94% 1% 2% 6% 100% Weight 18% 13% 5% 38% 22% 96% 4% 100%

in sepsis rate between the PI plus AP group and the AP monotherapy group.

According to our analyses, PI plus AP was a significant reduction in the rate of fever (RR 0.47, 95% CI 0.30-0.74) and total infectious complications (RR 0.54, 95% CI 0.40–0.73) compared to AP monotherapy. This is in line with a previous study by Pu et al. [4] analyzing three RCTs and reporting the effectiveness of PI plus AP in reducing fever (RR 0.11, 95% CI 0.02-0.85), and total infectious complications (RR 0.23, 95% CI 0.10-0.54) compared to AP monotherapy. Based on the findings of previous studies and results of our present study, we confirmed the effectiveness of PI disinfection as prevention of infectious complications after TRUS-PB. Rectal cleansing with povidone-iodine has been shown to be safe and effective in reducing rectal flora counts [20]. Moreover, TRUS-PB transfer colonic bacteria into the prostate, risking infections like sepsis; hence, reducing bacterial translocation is crucial [21].

Our study indicated that disinfection using PI prior to TRUS-PB could not reduce the incidence rate of sepsis. However, these results should be interpreted with caution as the sepsis rate after TRUS-PB is generally very low; therefore, it is difficult to investigate whether there is a statistically significant effect of PI on reducing sepsis. We believe the incidence rate of sepsis (PI plus AP vs. AP: 0.6 and 1.6%) in our study should not be regarded as significant for both patients and urologists. Notably, among included studies, six RCTs [2, 5-8] did not reveal the efficacy of PI in reducing sepsis. Further studies are needed to clarify the efficacy of PI for preventing sepsis. However, it is clear that it is not possible to reduce the incidence rate of sepsis to zero with only PI disinfection. Thus, we believe the selection of an appropriate AP may be important. As previous guidelines traditionally recommended the use of fluoroquinolone, most of these RCTs used fluoroquinolone for AP. Recently, EAU guidelines have recommended against the use of fluoroquinolone for AP [10]. The European Commission has established rigorous regulatory requirements for fluoroquinolones use, leading to the withdrawal of recommendations for their use as peri-operative AP in procedures such as prostate biopsy [10, 22]. Our analysis also show no difference in overall infectious complications between the quinolone subgroup and other antibiotics, supporting this recommendation (p=0.3). Instead of habitual fluoroquinolone usage, it is suggested that conducting rectal swab cultures prior to TRUS-PB may lead to a reduction in sepsis by allowing for the use of selective targeted AP [10].

Although we showed that intervention of PI plus AP before TRUS-PB could reduce infectious complications to 4.33%, we believe this percentage should not be considered negligible for either patients or urologists. Jim et al. revealed there was no infectious complication in TPUS-PB without AP group [23]. A comprehensive analysis of 165 studies

encompassing 162,577 patients reported that the incidence of sepsis was 0.1% in cases of TPUS-PB and 0.8% in TRUS-PB [24]. Further studies are needed to investigate the best protocol to prevent infectious complication after TRUS-PB.

#### Limitations

There are some limitations of our study. First, the duration and types of AP vary across ten included RCTs. No single study employed identical AP protocols. Moreover, the methods of iodine disinfection varied, including techniques such as rubbing with iodine-soaked gauze and rectal administration via syringe. In addition, the time before TRUS-PB and the waiting period after disinfection differed for each study. Second, there were some differences in the quality of bias among the RCTs. Thus, the results of our analysis have some limitations. Third, due to the low incidence of sepsis, there may not have been sufficient analysis. Finally, the patient-specific risk of infection, including diabetes, degree of urinary dysfunction, residual urine volume, and estimated prostate size, was unclear.

## Conclusion

Our analyses demonstrated that prophylaxis with PI prior to TRUS-PB reduced the risk of infectious complications compared with non-PI disinfection. We yield to detect a benefit to prophylaxis with PI prior to TRUS-PB in reducing the risk of sepsis compared with AP monotherapy. Although we did not detect a statistically significant difference in the rate of sepsis, the findings indicated a possible downward trend in its occurrence. Further research is needed to help develop a strategy to minimize the risk of infectious complications with prostate biopsy.

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Author contributions IT and AM contributed to protocol/project development, data collection and management, data analysis, and manuscript writing/editing. MP, JK, SM, SC, TF, EL, TK, SK, TI, KB, KW contributed to manuscript writing/editing. MA and SFS contributed to supervision and manuscript editing.

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Data availability Data can be provided upon inquiry.

#### Declarations

**Conflict of interest** None of the authors have conflicts of interest to disclose.

#### Ethical approval None.

**Research involving human participants and/or animals** This review does not involve human participants and/or animals.

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