CMI COMMUNICATIONS 2 (2025) 105103

Contents lists available at ScienceDirect

CMI Communications

journal homepage: www.elsevier.com/locate/cmicom

Systematic Review

To heal or harm: A systematic review of the role of fluoroquinolones in periprosthetic joint infections

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ARTICLE INFO

Handling Editor: Dr. Joshua S. Davis

Keywords:
Fluoroquinolones
Periprosthetic joint infections
Efficacy
Toxicity
Systematic review

ABSTRACT

Background: Fluoroquinolones (FQs) are currently recommended for the treatment of periprosthetic joint infections (PJIs) caused by staphylococci and Gram-negative bacteria (GNB) in patients undergoing debridement, antibiotics and implant retention (DAIR). In recent decades, reports of serious adverse events associated with FQ use have led to official regulatory recommendations for their restricted use. This review aims to describe the evidence for, and discuss the risks and benefits of, FQ use for PJI.

Methods: A comprehensive search of MEDLINE and EMBASE up to October 2024 was conducted using predefined criteria to identify studies addressing (i) the efficacy of FQs in treating staphylococcal and GNB-PJI, and (ii) serious adverse events associated with FQs. A narrative synthesis of the results was performed.

Results: No randomized controlled trials were identified. A total of 19 retrospective studies were reviewed to assess the efficacy of FQs in treating staphylococcal and GNB-PJI, though the sample sizes in these studies were relatively small. Fifty-seven studies, mostly large retrospective epidemiological cohorts, were found evaluating adverse events associated with FQ treatment.

Conclusions: There is evidence supporting the use of FQ monotherapy for GNB-PJI and FQ combined with rifampin for staphylococcal PJIs following DAIR over other antimicrobial regimens. There is evidence that FQs are associated with an increased risk of tendinopathy, prolonged QTc interval, peripheral neuropathy and dysglycaemia, however the absolute risk is low. When FQs are used in the treatment of PJIs, an individualized risk assessment and close monitoring during treatment are recommended.

Introduction

Fluoroquinolones (FQs) were first introduced in the 1960s [1] and are widely used to treat a variety of infections. They are often considered to be important in the management of periprosthetic joint infection (PJI), particularly when PJI is treated with debridement, antibiotics and implant retention (DAIR) or single-stage exchange [2]. Due to their activity against biofilms produced by Gram-negative pathogens, FQs are recommended for the oral treatment phase of Gram-negative PJI (GNB-PJI) [3–5]. For staphylococcal PJI, a FQ/rifampin combination has been proposed as first-line oral treatment due to the biofilm activity of rifampin against staphylococci and the ability of FQ as a companion antimicrobial to prevent the development of rifampin resistance. Alternative oral antibiotics include fusidic acid, trimethoprim-sulfamethoxazole, minocycline, linezolid, or clindamycin [3–7]. However, significant drug-drug interactions leading to low serum

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https://doi.org/10.1016/j.cmicom.2025.105103
Received 5 May 2025; Received in revised form 2 June 2025; Accepted 8 June 2025
Available online 9 June 2025

concentrations have been reported for some of these antibiotics [8,9]. Thus, even though the clinical significance remains uncertain, there are indications that the choice of a companion drug to rifampin may influence the outcome in the treatment of PJI [10,11].

Warnings about tendinopathy as an adverse drug reaction from FQ were first released by the US Food and Drug Administration (FDA) in 2008, and followed by additional statements on neuropathy, dysglycaemia, and aortic aneurysm [1], with the most recent updates in 2018. In response to these potentially disabling and irreversible side effects, several official regulatory recommendations have been published during the last decade recommending restricting the use of FQs [12–15]. PJIs are not explicitly included in these restrictions. FQ use for PJI is often prolonged and many patients with PJI have specific characteristics, such as older age, the presence of comorbidities and polypharmacy, that may put them at increased risk of adverse events.

The aim of this review is to provide a broad overview of the known risks and benefits associated with the use of FQs in PJI treatment.

Methods

Data sources and searches

Two separate literature searches were conducted by librarians at Central Hospital, Karlstad, Sweden on October 18th, 2024. The first focused on the efficacy of FQs in PJIs treated with implant retention, while the second focused on adverse events due to FQ use. These searches were performed in MEDLINE and EMBASE (See Supplementary Material). This project was an expansion of a brief review [16] initiated as part of the 3rd International Consensus Meeting on Orthopaedic Infections (ICM) 2025 (www.icmortho.org).

Study selection

The inclusion criteria for the study question regarding the efficacy of FQ for PJI were (i) studies assessing the efficacy of FQs in staphylococcal and Gram-negative PJIs (ii) treated with DAIR or single-stage exchange and (iii) using a comparator group. Studies involving other pathogens or non-PJI were excluded.

For the study question regarding adverse events from FQ use, studies examining all treatment indications were included and were not limited to those describing FQ use for PJI. Inclusion criteria for this question encompassed (i) treatment durations of up to 12 weeks in line with general PJI treatment recommendations [5] and (ii) adverse events including tendinopathy, central and peripheral neuropathy, retinal detachment, arrythmia, aortic aneurysm/dissection and dysglycaemia. Pathogens requiring a longer treatment, e.g., mycobacteria, were excluded.

As both questions focused on the most commonly recommended FQs in clinical guidelines [5], studies predominantly focusing on other FQs than ciprofloxacin, levofloxacin and moxifloxacin were excluded. Additionally, reviews, pharmacovigilance studies, case reports, animal studies and conference abstracts were not considered. The selection process was performed as single-reviewer screening (S.T.) using Covidence.

Data extraction

Full-text articles of the included studies were retrieved for data extraction. For the first question regarding FQ efficacy, data extracted included pathogen type, surgical intervention, number of patients and outcome (FQ group vs. comparator). When stratified data were available, these were extracted and pooled for analysis. For the second question regarding FQ adverse effects, the extracted data included study design, study setting, number of patients, type of adverse event, stratification by FQ, comparator, significant covariates and outcome measure. All authors participated in the data extraction process.

Data synthesis and analysis

All authors reviewed the extracted data and, if necessary, re-examined the original studies during the analysis process. A narrative synthesis of the results was performed. Although no formal risk-of-bias assessment was conducted using standardized tools, potential sources of bias were considered in the narrative synthesis, including study design, population characteristics, and reporting limitations. Additionally, published systematic reviews and other relevant papers identified during the screening process but excluded based on pre-defined criteria, were reviewed to inform the discussion.

Ethics

No ethical approval was required for this review.

Results

The PRISMA flowcharts for identifying and screening studies from the database searches are shown in Figs. 1 and 2. The first search (FQs and efficacy) identified a total of 1942 studies. Of these, 1923 were excluded, whereof 587 were duplicates. After abstract and full-text screening, 19 studies were included. The second search (adverse events in FQ treatment) identified 2443 studies, whereof 822 were duplicates. After screening abstracts and full-texts, 57 studies were included.

Fluoroquinolones in Gram-negative periprosthetic joint infection

No prospective randomized controlled trials have directly compared FQ treatment to other antibiotic strategies. However, seven studies [17–23] compared FQs to other regimen(s) in GNB-PJI, with four reporting superior outcomes with FQs use [17,18,20,21]. Pooled data from six studies [17–21,23] demonstrated a significant increase in treatment success with FQs (83% vs. 57%, $p = 0.0001$), although the total cohort included only 326 patients (Table 1). In contrast, a recent prospective cohort [22] found no significant advantage in using FQs in GNB-PJIs ($n = 100$). Notably, the impact of FQs may depend on the comparator antibiotic, with one retrospective cohort finding no difference in failure rates when comparing FQs to intravenously administered beta-lactam antibiotics for the entire treatment duration [23].

Fluoroquinolones in staphylococcal periprosthetic joint infection

As the landmark trial by Zimmerli et al. [24] included a mix of patients with PJI and infected osteosynthesis, no RCTs have directly compared FQ/rifampin combinations to other regimens in PJIs. Additionally, there was insufficient data to draw any conclusions regarding treatment outcomes after single-stage exchange.

Twelve studies [17,25–35] have compared FQ-containing regimens to other treatments in staphylococcal PJIs managed with DAIR. While most studies found no significant differences, pooled data of 778 patients from eight studies [17,25–31], suggested evidence of increased treatment success with a FQ-based regimen (87% vs. 75%, $p < 0,0001$) (Table 2). However, these results must be interpreted cautiously given study heterogeneity and the relatively small size of individual cohorts. Several studies [30,31,35] observed a positive effect of FQs with univariate analysis, but this was not confirmed with multivariable analysis.

Conversely, Shabana et al. [34], identified FQ resistance as an independent risk factor for clinical failure in their multivariable analysis (OR 5.45, 95 % CI 1.67–17.83), while Senneville et al. [27] found that an ASA score ≤ 2 and FQ/rifampin therapy were independent factors for remission. One previous meta-analysis of 6 studies [11] found that FQ/rifampin combinations were more effective than other antibiotic strategies, including alternative rifampin-based regimens in the treatment of staphylococcal PJIs managed with DAIR.

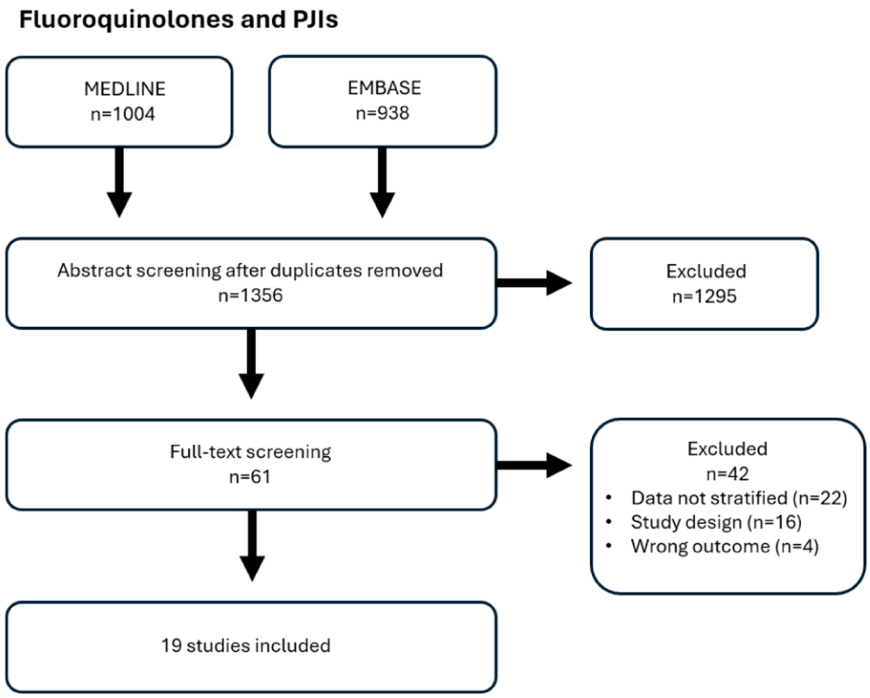

Fig. 1. PRISMA flowchart [1].

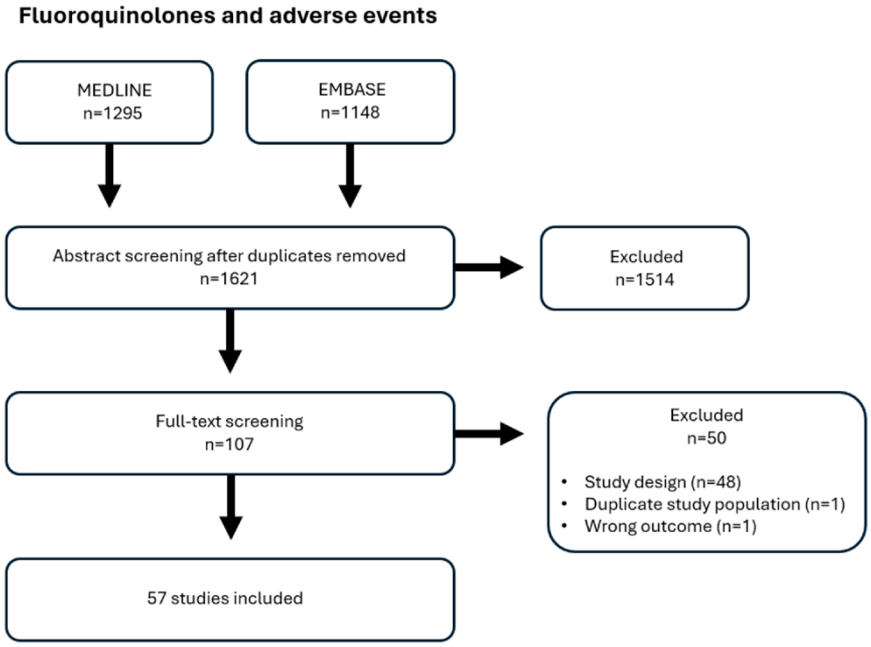

Fig. 2. PRISMA flowchart [2].

Tendinopathy (Table 3)

Animal models have demonstrated tendon lesions (oedema with mononuclear cell infiltration) induced by FQ administration, as well as a reduction in the synthesis of collagen type I, elastin, fibronectin and proteoglycan [36].

Fourteen studies have evaluated the impact of ciprofloxacin, levofloxacin or moxifloxacin in tendon injury and/or rupture [37–50]. In one population-based cohort study from Taiwan, the incidence of tendinitis was higher in FQ-treated patients (6.61 per 10^5 person-years) compared to controls (3.64 per 10^5 person-years) [45]. In another medical-insurance based cohort comprising patients treated for community-acquired pneumonia, the odds ratio (OR) for tendinitis was elevated at one month (OR 1.42; 95 % CI 1.19–1.70) but not at six months (OR 1.07; 95 % CI 0.98–1.17), indicating a short-term risk for tendon injury [42]. A study showed that the hazard ratio (HR) for Achilles tendon rupture was significantly higher for levofloxacin (HR 2.20; 95 % CI 1.50–3.24) but not for ciprofloxacin or moxifloxacin. Interestingly, cephalexin was also found to associated with an elevated HR for tendon rupture (HR 1.93; 95 % CI 1.35–2.75), suggesting potential confounding by indication [47]. Other studies have reported a higher tendinopathy risk for levofloxacin compared to ciprofloxacin or

Table 1
Pooled data on efficacy of FQs in GNB-PJI treated with DAIR.

Author	Antibiotic	Remission (n)	Failure (n)	p value
Martinez-Pastor, 2009 [21]	FQ	26	2	*0.0013*
	other	9	10	
Rodriguez-Pardo, 2014 [18]	FQ	98	26	*0.0026*
	other	6	9	
Tornero, 2014 [20]	FQ	18	1	*0.0143*
	other	0	2	
Mancheno-Losa, 2021 [17]	FQ	14	1	0.1279
	other	7	4	
Aboltins, 2011 [19]	FQ	13	1	0.3309
	other	2	1	
Grossi, 2016 [23]	FQ	45	13	0.7480
	other	15	3	
Pooled data	all	253	73	
	FQ	214	44	*0.0001*
	other	39	29	

Table 2
Pooled data on efficacy of FQs in staphylococcal PJI treated with DAIR.

Author	Antibiotic	Remission (n)	Failure (n)	p value
Tornero, 2012 [25]	levo/rif	44	6	0.3781
	other	30	8	
Soriano, 2006 [26]	levo/rif	10	1	0.3271
	other	9	4	
Senneville, 2011 [27]	FQ/rif	15	1	0.0829
	other	10	5	
Lourtet-Hascoet, 2016 [28]	FQ	14	1	1
	other	2	0	
Mancheno-Losa, 2021 [17]	FQ	54	1	*0.0487*
	other	72	9	
Espindola, 2022 [29]	FQ	44	16	0.269
	other	24	15	
Beldman, 2021 [30]	FQ	137	22	0.0716
	other	113	32	
Becker, 2020 [31]	FQ	31	5	0.0031
	other	23	20	
Pooled data	all	632	146	
	FQ	349	53	*0.0001*
	other	283	93	

Abbreviations: levo; levofloxacin, rif; rifampin.

moxifloxacin [37,39,47,49,51], though a systematic review found no difference between levofloxacin and ciprofloxacin [52].

Patients receiving ciprofloxacin or levofloxacin within three months after Achilles tendon or rotator cuff surgery were more likely to require revision surgery within two years compared to controls. Specifically, 5.0 % of Achilles tendon and 7.5 % of rotator cuff surgeries required revision in the FQ-group, compared to 1.8 % and 4.1 % in the control group, respectively [37].

Additional risk factors for tendinopathy in patients taking FQ include corticosteroid use, advanced age ≥60 years), chronic kidney disease, diabetes, obesity, and smoking [38,40,41,45,46,50,51].

Arrhythmia (Table 4)

Fluoroquinolones (FQs) can inhibit cardiac potassium channels, leading to delayed repolarization and prolonged QT interval [53,54]. In a randomized study on healthy volunteers, Chen et al. [55] observed an 8.35 ms increase in QTc interval at 4 h after receiving a single 400 mg dose of moxifloxacin. Additionally, moxifloxacin caused a maximum heart rate increase of 2.4 beats per minute (bpm) (95 % CI 1.6–3.3) two hours post administration, with individual increases of up to 36 bpm [56]. A prospective randomized study comparing levofloxacin to ciprofloxacin showed that levofloxacin was associated with a higher risk for QTc prolongation in both diabetic and non-diabetic patients [57].

Reported incidence of cardiac events after moxifloxacin exposure varies from 1.2 % to 8.3 %, depending on the definition, monitoring methods, and population studied [58,59]. In a retrospective cohort of patients with prolonged QTc at admission who received levofloxacin, 0.2 % (95 % CI, 0.0–0.7) experienced ventricular tachycardia, though the small number of events and the lack of control group limit the interpretation of these findings [60].

Eight epidemiological studies assessed the risk of arrhythmia associated with ciprofloxacin, levofloxacin or moxifloxacin, using beta-lactam antibiotics as comparators. Four studies investigated any FQ [53,61] or ciprofloxacin [62,63] and found no significant differences in arrhythmia risk. Four studies [57,62–65] focused on levofloxacin; two found no difference, one suggest a protective effect (HR 0.40; 95 %CI 0.18–0.87), while the last one reported an elevated risk (HR 2.43; 95 % CI 1.56–3.79). Two studies assessed moxifloxacin [62,63], both indicating an increased risk for serious arrhythmia (OR 1.87; 95 %CI 1.15–3.11 and aOR 3.30; 95 % CI, 2.07–5.25, respectively). Polgreen et al. [66] found that the increased risk for ventricular arrhythmia associated with levofloxacin and moxifloxacin was no longer statistically significant when controlling for multiple covariates. Furthermore, a Danish population-based study found no difference in out-of-hospital cardiac arrests when comparing previous use of FQs (mainly ciprofloxacin and moxifloxacin) to amoxicillin (OR 0.91; 95 % CI 0.71–1.16) [67].

A 2017 systematic review [68] concluded that while treatment with FQs was associated with an increased relative risk of serious arrythmia (2.29; 95 % CI: 1.20–4.36) and cardiovascular death (1.60; 95 % CI:1.17–2.20), there was no associated increase in all-cause mortality (1.02; 95 % CI: 0.76–1.37).

Aortic aneurysm (AA) or aortic dissection (AD) (Table 5)

The baseline annual incidence of AA in population-based studies ranges from 3 to 13.7/100,000 persons, while AD occurs at a rate of 3 to 20/100,000. Established risk factors for AA/AD include advanced age, male sex, family history, hypertension, chronic inflammation and smoking [69]. FQs may contribute to an increased risk of AA/AD by upregulating matrix metalloproteinases, leading to collagen degradation and vascular wall damage [70].

Eighteen studies explored the relationship between FQ use and AA/AD [43,49,61,71–85]. Since only two studies [49,76] provided stratified data on the different FQs, other studies were included for analysis regardless of this limitation.

The results of epidemiological studies were mixed. Eight studies suggested a potential association between FQ use and an increased risk of AA/AD [43,49,61,76–80], while six others did not [71,74,75,81–83]. Gopalakrishnan et al. [81] found a significant association between FQs and AA/AD compared to amoxicillin (HR, 1.54; 95 %CI, 1.33–1.79). However, when excluding patients without baseline imaging, the association was no longer statistically significant (HR, 1.13; 95 %CI, 0.96–1.33). Most studies excluded patients with pre-existing AA/AD, however Chen et al. [72] described a higher risk of AA/AD-related death (aHR: 1.80; 95 % CI 1.50–2.15) and subsequent aortic surgery (1.49; 95 %CI 1.24–2.06) in patients with pre-existing AA/AD exposed to FQs.

Table 3
Summary of included studies on tendinopathy.

Author, year	Country	Study Type	Sample size	Study drug	Comparator drug	Outcome	Outcome measure	Result (95 %CI)
Corrao, 2006 [50]	Italy	case/control	22,194	FQ	n/a	tendon disorder	OR	1.7 (1.4–2.0)
				FQ	n/a	tendon rupture (achilles)	OR	4.1 (1.8–9.6)
			n/a	FQ+CS	n/a	tendon rupture (achilles)	OR	43.2 (5.5–341.1)
Daneman, 2015 [43]	Canada	cohort	657,950	FQ	n/a	tendon rupture (any)	aHR	2.4 (2.24–2.57)
Nyyssönen, 2017 [39]	Finland	case/control	1118	FQ	n/a	achilles rupture	OR	2.20 (1.28–3.76)
			n/a	ciprofloxacin	n/a	achilles rupture	OR	1.22 ($p = 0.59$)
			n/a	levofloxacin	n/a	achilles rupture	OR	3.00 ($p = 1.00$)
Jupiter, 2018 [41]	USA	cohort	645,034	FQ	other antibiotics	achilles tendinitis	OR	1.24 (1.17–1.31)
			716,522	FQ	no antibiotics	achilles tendinitis	OR	1.54 (1.44–1.64)
Morales, 2019 [40]	UK	nested case/ control	4836	FQ	n/a	tendon rupture (any)	aIRR	1.61 (1.25–2.09)
			1577	FQ	n/a	achilles rupture	aIRR	3.14 (2.11–4.65)
			1557	FQ+CS	n/a	achilles rupture	aIRR	19.36 (7.78–48.19)
Persson, 2019 [38]	UK	nested case/ control	3957	FQ	n/a	tendon rupture (any)	aOR	1.30 (0.93–1.81)
				FQ		achilles rupture	aOR	2.08 (1.22–3.53)
				FQ		bicep rupture	aOR	1.08 (0.49–2.36)
Baik, 2020 [47]	USA	cohort	328,654	FQ	amoxicillin	achilles rupture	HR	1.49 (0.69–3.19)
			234,994	ciprofloxacin	no ciprofloxacin	achilles rupture	HR	1.06 (0.70–1.60)
			155,991	levofloxacin	no levofloxacin	achilles rupture	HR	2.20 (1.50–3.24)
			14,728	moxifloxacin	no moxifloxacin	achilles rupture	HR	0.97 (0.15–6.24)
Chang, 2022 [45]	Taiwan	cohort	383,279	FQ	no FQ	tendon disorder	aHR	1.42 (1.02–1.87)
Waters, 2023 [37]	USA	cohort	448	FQ	no FQ	revision after distal biceps repair	OR	2.13 (1.09–4.04)
			2538	FQ	no FQ	revision after rotator cuff repair	OR	1.77 (1.48–2.15)
			996	FQ	no FQ	revision after achilles tendon repair	OR	2.15 (1.40–3.27)
Patel, 2024 [49]	USA	cohort (CAP)	1071	levofloxacin	no levofloxacin	adverse tendon event	OR	3.05 (1.22–8.67)
Fleming, 2024 [42]	USA	cohort (CAP)	136,515	FQ	other antibiotics	tendon injury (1 month)	OR	1.42 (1.19–1.70)
			82,984	FQ	other antibiotics	tendon injury (6 months)	OR	1.07 (0.98–1.17)

Abbreviations: FQ; fluoroquinolones, CS; corticosteroid, OR; odds ratio, aOR; adjusted odds ratio, HR; hazard ratio, aHR; adjusted hazard ratio, aIRR; adjusted incidence rate ratio, CAP; community acquired pneumonia. Sample size denotes either number of patients exposed to study drug or number of cases, depending on study design.

Several systematic reviews also reported an elevated risk of AA following FQ use compared to other antibiotics or no antibiotic treatment [86–90]. However, two of these found no association between FQs and AD [88,89], and one reported no increased risk for AA/AD when patients treated with broad-spectrum antibiotics were used as the comparator [89].

Retinal detachment (RD) (Table 6)

Collagen degeneration/degradation associated with FQ use may contribute to retinal detachment (RD), as collagen is a key retinal component. Twelve studies investigating this hypothesis were reviewed [43,91–101].

In a case-control study of 4384 patients with retinal detachment, Etminan et al. [91] reported a significant association between current FQ use and RD, with an adjusted rate ratio of 4.50 (95 %CI 3.56–5.70), though no link was observed with recent or past use. In a similar, larger study, Fife et al. [94] were unable to replicate these findings. More recent studies also reported an association between FQ treatment and RD [96–99] with levofloxacin [97] and ciprofloxacin [96] being linked to the highest risk in two of these. Interestingly, Shin et al. [99] found a significantly increased IRR not only when FQs were administered 1–30 and 31–60 days before RD diagnosis, but also when the RD was diagnosed 1–30 and 31–60 days prior to FQ treatment, indicating that this association might not be a causal relationship. Two studies [98,99] also found an association between RD and other antibiotics such as cephalosporins, extended- spectrum penicillins and macrolides. Two subsequent systematic reviews did not support a link between FQ use and RD [102,103].

Central or peripheral neuropathy (Table 7)

The proposed mechanism by which FQ may cause peripheral neuropathy involves mitochondrial toxicity, likely due to FQs interfering with mammalian mitochondrial topoisomerase II [104]. CNS neurotoxicity or encephalopathy (headache, lower seizure threshold, psychotic symptoms) may be caused trough GABA receptor inhibition [105,106].

Three case-cohort studies were reviewed [107–109], two of which did not stratify by FQ type. All reported an increased risk of peripheral neuropathy during or after FQ use compared to controls. Etminan et al. [110] reported a rate ratio of 1.83 (95 % CI 1.49–2.27), with similar risks observed for ciprofloxacin, levofloxacin and moxifloxacin. Ellis et al. [111] reported a HR of 1.09 (95 % CI 1.07–1.11), while Morales et al. [112] noted an aIRR of 1.47 (95 % CI 1.13–1.92), with an increased risk for peripheral neuropathy persisting up to 180 days after FQ exposure. The most common signs of peripheral neuropathy described in association with FQ treatment were hypo/hyperaesthesia and muscle weakness, typically appearing within the first week of treatment. Most cases recovered within two weeks, although some persisted or became chronic [105,113,114]. Exacerbation of myasthenia gravis has also been described [104].

Only one study investigated CNS toxicity, [111], reporting an association with an HR of 1.08 (95 %CI 1.05–1.11).

Glucose metabolism (Table 8)

FQs have the potential to inhibit potassium channels expressed in pancreatic α- and β-cells, intestinal l-cells, and skeletal muscle cells

Table 4
Summary of included studies on arrythmia.

Author, year	Country	Study type	Sample size	Study drug	Comparator drug	Outcome	Outcome measure	Result (95 %CI)
Morganroth, 2005 [58]	USA	RCT	394	moxifloxacin	levofloxacin	ventricular arrhythmia	rate	8.3 % vs. 5.1 % (p = 0.29)
Rao, 2014 [65]	USA	cohort	201,798	levofloxacin	amoxicillin	serious cardiac arrhythmia (day 1–5)	HR	2.43 (1.56–3.79)
						serious cardiac arrhythmia (day 6–10)	HR	1.75 (1.09–2.82)
Chou, 2015 [63]	Taiwan	cohort	38,833	moxifloxacin	amoxicillin/clavunate	ventricular arrythmia	aOR	3.30 (2.07–5.25)
			117,352	levofloxacin	amoxicillin/clavunate	ventricular arrythmia	aOR	1.41 (0.91–2.18)
			205,205	ciprofloxacin	amoxicillin/clavunate	ventricular arrythmia	aOR	1.07 (0.69–1.66)
			38,833	moxifloxacin	amoxicillin/clavunate	cardiovascular death	aOR	2.31 (1.39–3.84)
			117,352	levofloxacin	amoxicillin/clavunate	cardiovascular death	aOR	1.77 (1.22–2.59)
			205,205	ciprofloxacin	amoxicillin/clavunate	cardiovascular death	aOR	0.70 (0.44–1.12)
Inghammar 2016 [53]	Denmark/ Sweden	cohort	909,656	FQs	penicillin V	serious arrhythmia	RR	0.85 (0.61–1.18)
Cho, 2018 [62]	Korea	cohort	1466,133	ciprofloxacin	cefixime	serious ventricular arrhythmia	OR	0.72 (0.49–1.06)
			1141,961	levofloxacin	cefixime	serious ventricular arrhythmia	OR	0.92 (0.66–1.29)
			47,080	moxifloxacin	cefixime	serious ventricular arrhythmia	OR	1.87 (1.15–3.11)
Polgreen, 2018 [66]	USA	cohort	9934	moxifloxacin	no antibiotic	ventricular arrythmia	aOR	0.82 (0.56–1.22)
			54,620	levofloxacin	no antibiotic	ventricular arrythmia	aOR	0.98 (0.84–1.16)
Postma, 2019 [64]	Netherlands	post-hoc analysis of CAP RCT	194	levofloxacin	beta-lactam	arrythmia	aHR	0.70 (0.21–2.35)
			566	moxifloxacin	beta-lactam	arrythmia	aHR	0.71 (0.33–1.51)
Aspinall, 2020 [61]	USA	self-controlled case series	3154	FQ	amoxicillin	ventricular arrythmia	aIRR	1.19 (0.91–1.54)
Ellenardóttir, 2024 [67]	Denmark	nested case/ control	276	FQ	amoxicillin	cardiac arrest	OR	0.91 (0.71–1.16)

Abbreviations: FQ; fluoroquinolones, OR; odds ratio, aOR; adjusted odds ratio, HR; hazard ratio, aHR; adjusted hazard ratio, RR; rate ratio, aIRR; adjusted incidence rate ratio, CAP; community acquired pneumonia. Sample size denotes either number of patients exposed to study drug or number of cases, depending on study design.

which are involved in glucose regulation [115]. In a small randomized controlled study on healthy volunteers, moxifloxacin resulted in decreased plasma glucose levels, increased insulin sensitivity, and a higher frequency and severity of hypoglycaemia-related symptoms compared to placebo [115].

Seven cohort studies have explored the association between FQs and dysglycaemia [116–122]. In a nested case/control study, Liao et al. found that all studied antibiotic treatments, including but not limited to FQs, were associated with an increased risk for hypoglycaemia leading to an emergency visit within one week from prescription. However, when comparing FQs to cephalosporins, only levofloxacin (but not ciprofloxacin or moxifloxacin) retained a significant association (aOR 5.13; 95 %CI 2.28–11.52), further increasing when combined with insulin or a sulfonylurea [121]. Similarly, Ellis *et al.* found that only levofloxacin was associated with hypoglycaemia in diabetic patients (OR 1.54; 95 %CI: 1.16–2.05), whereas no association to any FQ was found in patients without diabetes [120].

In a propensity-matched cohort of patients using second-generation sulphonylureas, FQs (primarily ciprofloxacin; 90 %) were not associated with an increased risk of severe hypoglycaemia (HR, 1.17; 95 %CI 0.91–1.50) [122]. In contrast, Cho et al. observed a significant increase in the risk of both hyperglycaemia and hypoglycaemia for all three FQs, with moxifloxacin exhibiting the strongest association, when compared to macrolide antibiotics [119]. A systematic review ultimately concluded that caution is warranted when prescribing FQs to diabetic patients and suggested that ciprofloxacin is likely the least dysglycaemia-inducing among them [123].

Discussion

This review provides a broad overview of the potential benefits and harms of FQs in the treatment of staphylococcal and GNB-PJIs treated with DAIR. Given that FQs appear to be the superior oral antibiotic in GNB-PJI as well as in combination with rifampin in staphylococcal PJI, and the absolute risk for serious adverse events is low, it is reasonable to conclude that FQs still have a role after DAIR in the treatment of PJIs. However, uncertainties still remain, especially as the doses recommended in PJIs are higher and treatment duration longer compared to most data evaluating the safety of FQs. Vollmer et al. [124] evaluated a retrospective cohort of staphylococcal PJIs for safety and tolerability. In the studied population, unplanned drug discontinuation occurred in 35.6 % of patients treated with FQs (mostly levofloxacin), compared with 3 % in the group comprised of other antibiotics (mostly tetracyclines, oral cephalosporins and trimethoprim-sulfamethoxazole). Notably, even though the FQ group comprised of only 90 patients, 9 episodes of tendinopathy and 3 aortic aneurysms were found. These results emphasize the importance of ensuring adequate risk stratification and monitoring when initiating prolonged treatment with FQs in high dose.

Even though available evidence supports FQ treatment in GNB-PJI, the observational nature of these studies, heterogeneity in study designs, resistance pattens and included species of Gram-negative pathogens amounts to an uncertainty in the interpretation of existing data. Furthermore, the rising FQ resistance rates may limit their utility in GNB-PJIs. It also remains unclear whether this benefit is limited to comparisons between FQs and other oral antibiotic options, as similar

Table 5
Summary of included studies on aortic aneurysm/dissection.

Author, year	Country	Study type	Sample size	Study drug	Comparator drug	Outcome	Outcome measure	Result (95 %CI)
Daneman, 2015 [43]	Canada	cohort	657,950	FQs	n/a	aortic aneurysm	aHR	2.24 (2.02–2.49)
Lee, 2015 [77]	Taiwan	nested case/control	1477	FQ	n/a	aortic aneurysm and/or dissection	RR	2.43 (1.83–3.22)
Pasternak, 2018 [79]	Sweden	cohort	360,088	FQ	amoxicillin	aortic aneurysm	HR	1.90 (1.22–2.96)
						aortic dissection	HR	0.93 (0.38–2.29)
Dong, 2020 [75]	Taiwan	nested case/control	29,948	FQ	amoxicillin-clavulanate or ampicillin-sulbactam	aortic aneurysm and/or dissection	OR	1.01 (0.82–1.24)
				FQ	extended-spectrum cephalosporins	aortic aneurysm and/or dissection	OR	0.88 (0.70–1.11)
Aspinall, 2020 [61]	USA	self-controlled case series	2027	FQ	amoxicillin	aortic aneurysm and/or dissection	aIRR	1.50 (1.01–2.25)
			2027	FQ	trimethoprim/sulfamethoxazole	aortic aneurysm and/or dissection	aIRR	0.81 (0.53–1.25)
Gopalakrishnan, 2020 [81]	USA	cohort (PNE)	139,772	FQ	azithromycin	aortic aneurysm and/or dissection	HR	2.57 (1.36–4.86)
		cohort (UTI)	474,182	FQ	trimethoprim/sulfamethoxazole	aortic aneurysm and/or dissection	HR	0.99 (0.62–1.57)
		cohort	3976,162	FQ	amoxicillin	aortic aneurysm and/or dissection	HR	1.54 (1.33–1.79)
		cohort (BI)	542 649	FQ	amoxicillin	aortic aneurysm and/or dissection	HR	1.13 (0.96–1.33)
Lawaetz Kristensen, 2020 [84]	Denmark	case/crossover	58	FQ (28 days)	n/a	ruptured aortic aneurysm	aOR	1.35 (0.98–1.85)
			160	FQ (90 days)	n/a	ruptured aortic aneurysm	aOR	2.21 (1.78–2.75)
Maumus-Robert, 2020 [85]	France	case-time-control	7443	FQ	n/a	ruptured intracranial aneurysm/dissection	aOR	1.26 (0.65–2.41)
Chen, 2021 [72]	Taiwan	cohort (AA/AD)	31,570	FQ	self-control	aortic death	aHR	1.80 (1.50–2.15)
				FQ	self-control	aortic surgery	aHR	1.49 (1.24–2.06)
				FQ	amoxicillin	aortic death	aHR	1.99 (1.44–2.75)
				FQ	amoxicillin	aortic surgery	aHR	1.34 (1.03–1.75)
Newton, 2021 [78]	USA	cohort	9053,961	FQ	other antibiotics	aortic aneurysm	aHR	1.20 (1.17–1.24)
Lundström, 2021 [83]	Sweden	cohort (UP)	192,024	ciprofloxacin	no antibiotic	aortic aneurysm	aHR	1.13 (0.91–1.39)
Chen, 2022 [74]	Taiwan	cohort (UTI)	28,568	FQ	1st/2nd gen cephalosporin	aortic aneurysm and/or dissection	aHR	0.86 (0.59–1.27)
Son, 2022 [80]	Korea	nested case/control	29,638	FQ	n/a	aortic aneurysm and/or dissection	aHR	1.10 (1.07–1.14)
Chen, 2023 [73]	Taiwan	case/crossover (CM)	550	FQ	n/a	aortic aneurysm and/or dissection	OR	1.00 (0.32–3.10)
Huh, 2023 [82]	Korea	self-controlled case series	777,109	FQ	n/a	aortic aneurysm and/or dissection	IRR	2.00 (0.97–4.12)
Brown, 2023 [71]	UK	cohort	1237,947	FQ	cephalosporin	hospitalization with aortic aneurysm and/or dissection	aHR	1.03 (0.91–1.17)
		case/crossover	95,198	FQ	cephalosporin	hospitalization with aortic aneurysm and/or dissection	OR	1.05 (0.87–1.27)
Garg, 2023 [76]	USA	cohort	1587,310	FQ	macrolide	hospitalization with aortic aneurysm and/or dissection	aHR	1.34 (1.17–1.54)

Abbreviations: FQ; fluoroquinolones, aHR; adjusted hazard ratio, RR; rate ratio, IRR; incidence rate ratio, aIRR; adjusted incidence rate ratio, PNE; pneumonia, UTI; urinary tract infection, BI; baseline radiological imaging required, AA/AD; preexisting aortic aneurysm/dissection, UP; urologic prophylaxis, CM; congenital aortic disease and marfan syndrome. Sample size denotes either number of patients exposed to study drug or number of cases, depending on study design.

outcomes have been presented when comparing FQs to intravenous beta-lactam antibiotics [23].

For staphylococcal PJIs treated with DAIR, there is no data supporting monotherapy with FQs. The improved outcomes observed likely reflects the co-administration of rifampin, rather than an independent benefit from FQs. However, in recent years the benefit of using rifampin in these infections has been debated [125–128], despite its theoretical advantage in biofilm-associated infection [7]. Based on a recent meta-analysis [11], FQs together with rifampin seem to provide an advantage over other rifampin combinations after DAIR in staphylococcal PJIs. Nevertheless, considering possible harms of both FQs and rifampin and the lack of high-quality prospective data, there is still a high level of uncertainty on when and how FQs should be used in this setting.

Regarding the serious adverse events reported for FQs, there is a short-term increased risk for tendinopathy, especially rupture of the

Table 6
Summary of included studies on retinal detachment.

Author, year	Country	Study type	Sample size	Study drug	Comparator drug	Outcome	Outcome measure	Result
Etminan 2012 [91]	Canada	nested case/ control	4384	FQ (current use)	n/a	retinal detachment	aRR	4.50 (3.56–5.70)
				FQ (recent use)	n/a	retinal detachment	aRR	0.92 (0.45–1.87)
Pasternak, 2013 [92]	Denmark	cohort	748,792	FQ (current use)	no antibiotic	retinal detachment	aRR	1.29 (0.53–3.13)
				FQ (recent use)	no antibiotic	retinal detachment	aRR	0.97 (0.46–2.05)
Eftekhari, 2014 [93]	UK	cohort	290,393	FQ	betalactam	retinal tear or detachment	HR	1.25 (0.51–3.08)
Fife, 2014 [94]	USA	case-control	7844	FQ	n/a	retinal detachment	aOR	1.17 (1.09–1.26)
		self-controlled case-series	19,191	FQ	n/a	retinal detachment	RR	1.13 (0.99–1.29)
		case-control	3059	FQ	n/a	retinal detachment	aOR	1.22 (1.09–1.38)
		self-controlled case-series	6896	FQ	n/a	retinal detachment	RR	0.85 (0.66–1.09)
Kapoor, 2014 [95]	USA	cohort	38,046	FQ	betalactam or macrolide	retinal detachment repair	rate	0.008 % vs. 0.004 % vs 0.007 % ($p = 0.75$)
Kuo, 2014 [96]	Taiwan	cohort	178,179	FQ	amoxicillin	retinal detachment	aHR	2.07 (1.45–2.96)
				ciprofloxacin	amoxicillin	retinal detachment	aHR	10.68 (3.28–34.82)
				levofloxacin	amoxicillin	retinal detachment	aHR	2.41 (0.76–7.68)
Daneman, 2015 [43]	Canada	cohort	657,950	FQ	n/a	retinal detachment	aHR	1.47 (1.08–2.00)
Raguideau, 2016 [97]	France	case/crossover	27,540	FQ (current use)	n/a	retinal detachment	aOR	1.46 (1.15–1.87).
				FQ (recent use)	n/a	retinal detachment	aOR	0.94 (0.78–1.14)
Baek, 2018 [98]	South Korea	sequence symmetry analysis	5234	FQ	other antibiotics	retinal detachment	aSR	1.70 (1.61–1.80)
Shin, 2018 [99]	South Korea	self-controlled case-series	15,134	FQ (1–30 days prior to event)	n/a	retinal detachment	IRR	1.85 (1.71–1.95)
				FQ (1–30 days after event)	n/a	retinal detachment	IRR	1.58 (1.49–1.68)
Taher, 2022 [100]	USA	nested case/ control	772	ciprofloxacin	n/a	retinal detachment	aOR	0.87 (0.39–1.97)
				levofloxacin	n/a	retinal detachment	aOR	0.61 (0.29–1.30)
				moxifloxacin	n/a	retinal detachment	aOR	1.07 (0.10–11.08)
Brown, 2024 [101]	UK	cohort	1181,195	FQ	cephalosporin	retinal detachment	aHR	1.37 (0.80–2.36)
		self-controlled case series	26,156	FQ	no antibiotic	retinal detachment	aRR	1.15 (0.86–1.54)

Abbreviations: FQ; fluoroquinolones, aHR; adjusted hazard ratio, RR; rate ratio, aRR; adjusted rate ratio, aOR; adjusted odds ratio, aSR; adjusted sequence ratio, IRR; incidence rate ratio. Sample size denotes either number of patients exposed to study drug or number of cases, depending on study design.

Table 7
Summary of included studies on neuropathy.

Author, year	Country	Study Type	Sample size	Study drug	Comparator drug	Outcome	Outcome measure	Result (95 %CI)
Etminan, 2014 [110]	USA	case/control	6226	FQ	n/a	peripheral neuropathy	RR	1.83 (1.49–2.27)
Morales, 2019 [112]	UK	nested case/ control	5357	FQ	n/a	peripheral neuropathy	aIRR	1.47 (1.13–1.92)
						peripheral neuropathy	AR	2.4 (1.8–3.1) per 10 000 patients/year
Ellis, 2021 [111]	USA	cohort	976,568	FQ	other antibiotics	CNS dysfunction	HR	1.08 (1.05–1.11)
						PNS symptoms	HR	1.09 (1.07–1.11)

Abbreviations: FQ; fluoroquinolones, RR; Rate ratio, aIRR; adjusted incidence rate ratio, AR = absolute risk; HR; hazard ratio, CNS; central nervous system, PNS; peripheral nervous system. Sample size denotes either number of patients exposed to study drug or number of cases, depending on study design.

Table 8
Summary of included studies on dysglycaemia.

Author, year	Country	Study type	Sample size	Study drug	Comparator drug	Outcome	Outcome measure	Result
Mohr, 2005 [116]	USA	cohort	17,108	levofloxacin	ceftriaxone	glucose abnormalities	RR	1.55 (1.29–1.88)
LaPlante 2008 [117]	USA	cohort	1573	levofloxacin	azithromycin	dysglycaemia	aOR	0.4 (0.1–1.4)
Aspinall 2009 [118]	USA	cohort	457,994	levofloxacin	azithromycin	hyperglycemia (hospitalization)	OR (diabetes)	1.8 (1.2–2.7)
							OR (non-diabetes)	0.7 (0.3–1.7)
						hypoglycemia (hospitalization)	OR (diabetes)	2.1 (1.4–3.3)
							OR (non-diabetes)	1.6 (0.4–6.6)
			197,940	ciprofloxacin	azithromycin	hyperglycemia (hospitalization)	OR (diabetes)	1.0 (0.6–1.8)
							OR (non-diabetes)	0.9 (0.3–2.6)
						hypoglycemia (hospitalization)	OR (diabetes)	1.1 (0.6–2.0)
							OR (non-diabetes)	0.7 (0.1–6.9)
Chou, 2013 [119]	Taiwan	cohort (diabetes)	11,766	levofloxacin	macrolide	hyperglycemia (hospital contact)	aOR	1.75 (1.12–2.73)
						hypoglycemia (hospital contact)	aOR	1.79 (1.33–2.42),
			12,564	ciprofloxacin	macrolide	hyperglycemia (hospital contact)	aOR	1.87 (1.20–2.93)
						hypoglycemia (hospital contact	aOR	1.46 (1.07–2.00)
			4221	moxifloxacin	macrolide	hyperglycemia (hospital contact)	aOR	2.48 (1.50–4.12)
						hypoglycemia (hospital contact)	aOR	2.13 (1.44–3.14)
Liao, 2022 [121]	Taiwan	nested case/control	26,695	FQ	no antibiotic	hypoglycemic emergency	aOR	12.05 (10.66–13.61)
			n/a	levofloxacin	cephalosporin	hypoglycemic emergency	aOR	5.13 (2.28–11.52)
Ellis, 2022 [120]	USA	cohort (diabetes)	119,112	FQ	other antibiotics	serious hypoglycemia	OR	1.30 (1.05–1.62)
			35,699	ciprofloxacin	other antibiotics	serious hypoglycemia	OR	1.10 (0.76–1.58)
			66,257	levofloxacin	other antibiotics	serious hypoglycemia	OR	1.54 (1.16–2–05)
			15,891	moxifloxacin	other antibiotics	serious hypoglycemia	OR	1.01 (0.55–1.87)
		cohort (non-diabetes)	917,867	FQ	other antibiotics	serious hypoglycemia	OR	1.06 (0.53–2.13)
Dimakos, 2024 [122]	UK	cohort (sulphonylureas)	13,123	FQ	amoxicillin	severe hypoglycaemia	HR	1.17 (0.91–1.50)

Abbreviations: FQ; fluoroquinolones, RR; relative risk, OR; odds ratio, aOR; adjusted odds ratio, HR; hazard ratio.

Achilles tendon, associated with FQ treatment. There is insufficient evidence regarding differential risk among different FQs. Even though the absolute risk is low, indication and risk factors (primarily advanced age, concomitant corticosteroid use and predisposing tendon disorders) should be carefully evaluated prior to prescribing FQs.

There are conflicting results in the currently available literature regarding the risk of clinically significant cardiac arrythmia associated with FQ, that may be explained by differences in controlling for comorbidities and patient demographics. Moreover, there appears to be a differential arrhythmia risk within this antibiotic class, with moxifloxacin being the FQ with the strongest association. ECG for evaluation of QTc and evaluation of potential drug-drug interactions and should be considered before starting treatment in at-risk populations

A higher risk of aortic death and later aortic surgery has been reported in patients with pre-existing AA/AD exposed to FQs [72,86], while data is conflicting in other populations. Several mechanisms for these inconsistent results have been proposed. Bias may arise from baseline differences in patient populations and underlying conditions, such as more frequent infectious conditions in patients with AA/AD. For example, Dong et al. [75] demonstrated that some infectious conditions *per se* were seen more often in patients with AA/AD. Additionally, comparing FQs to antibiotics used for other indications (e.g. amoxicillin) may introduce bias through the likelihood that radiological imaging, which incidentally identifies an asymptomatic AA, is performed. In most studies, differences are driven by AA rather than AD which may support this hypothesis. Still, caution should be taken in the prescription of FQs, especially in patient populations with elevated baseline risk for AA/AD.

Similarly, the association between FQs and RD remains unclear. The potential risk, particularly in patients without pre-existing ocular conditions or other risk factors for retinal detachment, appears too low to influence antibiotic selection in PJIs.

There are limited data on neurological adverse events in association with FQ treatment. As the risk for peripheral neuropathy may increase incrementally with each day of exposure and remain for at least 180 days following FQ exposure, monitoring of patients with pre-existing neuropathy may be considered while on a treatment course with a FQ. Further studies on FQ-associated neuropathy are warranted.

Finally, there is a differential risk for dysglycaemia in diabetic patients for different FQs, with a higher association for moxifloxacin and levofloxacin compared to ciprofloxacin. Chronic kidney disease and concomitant use of insulin or sulphonylureas has been implied to enhance the risk for dysglycaemia during FQ treatment. This should be taken into consideration when deciding on treatment strategies, and the patient should be informed that these adverse events can occur.

Conclusion

Given the low absolute risk of serious adverse events and the existing data on the efficacy of FQs in managing Gram-negative and staphylococcal PJIs treated with DAIR, these antibiotics are still considered a valuable option in this setting. However, as the risk for some of the serious adverse events varies among different FQs, careful selection of the specific agent is crucial for at-risk populations. Additionally, pre-treatment assessments, medication review to mitigate drug-drug interactions, thorough patient education, and close monitoring during treatment should be considered to minimize the risk of potential FQ-related adverse events.

Funding

S.T. is supported by the Research committee of Region Värmland (LIVFOU) and by grants from the Swedish state under the ALF agreement between the Swedish government and the county councils (Region Örebro County, Sweden OLL-967677). B.Y. is supported by the National institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC).

Transparency declaration

All authors declare no conflicts of interest related to the present work.

CRediT authorship contribution statement

Staffan Tevell: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Craig Aboltins:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Angela Hewlett:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Dolors Rodriguez-Pardo:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Bernadette Young:** Writing – review & editing, Validation, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Bernadette Young reports financial support was provided by National institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC). Dolors Rodriguez Pardo reports a relationship with Astellas, MSD, Tillotts, Menarini, Pfizer, MBA, and Angelini that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to thank Marika Svalstedt and Ann Hagberg at the hospital library at the Central Hospital in Karlstad, Sweden, for their assistance in developing the search strategy.

The authors would also like to acknowledge that the initiative for this review was conceived in preparation for the 2025 International Consensus Meeting for Infection (ICM), to which a substantially reduced draft [16], available on the website www.icmortho.org, was submitted. Further thanks go to the Executive committee of the ICM for their contributions in summarizing current evidence on orthopaedic infections.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cmicom.2025.105103.

Data availability

The data that support the findings of this review are available from the corresponding author, S.T., upon reasonable request.

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