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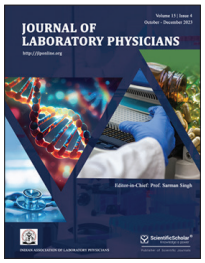

Review Article

Faropenem for the management of infectious diseases – A systematic review of *in vitro* susceptibility tests and clinical studies

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ABSTRACT

This comprehensive review aimed to understand the activity and resistance pattern of faropenem compared to other antimicrobial agents. A literature search was performed using the PubMed database to identify studies published in the English language. The inclusion criteria were clinical studies involving adults and/or children with respiratory or urinary tract infections that evaluated faropenem use and resistance patterns compared to other antibiotics, in inpatient, outpatient, and/or preclinical settings. *In vitro* studies reporting the activity of faropenem against clinical isolates of bacteria were included in the study. Of 327 identified articles, two clinical and 21 *in vitro* studies were considered eligible. The clinical studies, which included adult patients with acute bacterial sinusitis, showed improvement with faropenem compared to cefuroxime. The *in vitro* studies indicated the activity of faropenem against Gram-positive (e.g., *Streptococcus*, *Staphylococcus*, *Clostridium*, and *Enterococcus*) and Gram-negative bacteria (e.g., *Hemophilus influenzae*, *Escherichia coli*, and *Proteus*, *Pseudomonas*, *Citrobacter*, and *Bacteroides* species) compared to amoxicillin-clavulanic acid combination, cefpodoxime, levofloxacin, and azithromycin. Faropenem also showed activity against β-lactamase–producing and penicillin-, ampicillin-, and methicillin-resistant strains. Faropenem exhibited antimicrobial activity against a broad spectrum of bacterial pathogens, including resistant strains. Furthermore, faropenem has the potential to treat community-acquired infections, particularly respiratory tract infections.

Keywords: Aerobes, Anaerobes, Clinical studies, Faropenem, Gram-negative, Gram-positive, *In vitro* studies

INTRODUCTION

Infectious disease is a serious and re-emerging threat to life, causing approximately an estimated 10 million annual deaths.[1] Antimicrobial agents play a crucial role in transforming the therapeutic paradigm and are the second most prescribed drug category.[2] These agents inhibit bacterial growth by disrupting numerous molecular structures within or on the surface of bacteria. However, their increased use and misuse have led to the development of resistance.[1,3] Resistance is most commonly caused by the expression of bacterial β-lactamases, reduced target affinity to the modified penicillin-binding proteins, impaired entry, increased efflux, and a scarcity of effective antimicrobials.[3,4] To overcome these challenges, new targets and antibiotics are needed.[5]

Penems, a class of antimicrobials, are known for their broad antibacterial activity and intrinsic stability against β-lactamases, making them effective against resistant strains.[4] Based on their antibacterial spectra, penems are divided into two subclasses: carbapenem (including doripenem, ertapenem,

imipenem, and meropenem) covers hospital pathogens, and faropenem, a novel oral penem with a low resistance propensity, is effective against community pathogens.[4,6]

Faropenem inhibits penicillin-binding proteins, which is crucial for maintaining cell wall structural integrity during growth and replication.[7] Its bioavailability ranges from 72% to 84% and its plasma protein binding, from 90% to 95%.[6] Faropenem shows bactericidal activity against respiratory pathogens, including methicillin-susceptible staphylococci, penicillin-susceptible/-resistant streptococci, and other aerobic and anaerobic Gram-positive pathogens[4] In India, oral faropenem is approved in 2008 for treating infections such as acute bacterial sinusitis, acute exacerbations of chronic bronchitis, community-acquired pneumonia, and uncomplicated skin and skin-structure infections.[8]

Several *in vitro* studies reported the antimicrobial activity (in terms of minimum inhibitory concentration [MIC]) of faropenem against various Gram-positive and Gram-negative bacterial isolates from children[9-11] and adults.[11,12] The activity of faropenem was also reported against 16 penicillin-susceptible and 26 penicillin-intermediate resistant or resistant strains of *Streptococcus pneumoniae* from both adults and children.[11] Another *in vitro* study showed the activity of faropenem against *Neisseria gonorrhoeae* isolates and also against respiratory pathogens including *S. pneumoniae*, *Moraxella catarrhalis*, and *Hemophilus influenzae*.[13-16] Clinical studies including patients with respiratory tract infections showed the role of faropenem against *S. pneumoniae*, *M. catarrhalis*, and *H. influenzae* associated with community-acquired sinusitis.[17,18] A systematic review including ten clinical studies of oral penems for treating *Enterobacterales* infection, reported resistance emergence following faropenem treatment.[19] In addition, broad-spectrum antibiotics such as azithromycin, second- and third-generation cephalosporins, amoxicillin-clavulanic acid combination (co-amoxiclav), and quinolones were commonly prescribed for infectious disease;[20] however, excess use of broad-spectrum antibiotics can increase the chances of multidrug resistance.[21,22] Hence, there is a need to understand both the broad-spectrum antimicrobial activity and resistance pattern for faropenem compared to other antimicrobial agents.

Hence, this comprehensive systematic review of *in vitro* and comparative clinical studies aimed to understand the activity and resistance pattern of faropenem across a range of microbes and to compare faropenem with antimicrobial agents such as co-amoxiclav, cefpodoxime, levofloxacin, and azithromycin.

MATERIALS AND METHODS

Research questions

We conducted a scoping review of the available literature on faropenem to answer research questions: (1) Is the clinical efficacy of faropenem comparable to other antibiotics in treating infections? (2) Is the *in vitro* activity of faropenem comparable to other antibiotics such as co-amoxiclav, cefpodoxime, levofloxacin, and azithromycin against clinical isolates of bacteria?

We followed the Population, Intervention, Comparison, Outcomes and Study (PICOS) approach to identify eligible publications for review [Table 1]. Briefly, this included studies of patients (adult and/or children) with respiratory or urinary tract infections that evaluated faropenem use and patterns of antibiotic resistance compared to other antibiotics, in inpatient, outpatient and/or preclinical settings. *In vitro* studies were considered for inclusion if they reported the activity of faropenem against clinical isolates of bacterial spectrum [Supplementary Table 1].

Search strategy

The literature search was performed using the PubMed database and keywords: Faropenem, ALP 201, BLA 857, Farom, Faropenem sodium, FRPM, RU 67655, SUN 5555, SY 5555, WY 49605, and YM 044. A random search was performed using Google Scholar.

Table 1: Summary of the PICOS criteria.

Criteria	For clinical studies	For *in vitro* studies
P Population	Patients (adults and/or children) with respiratory or urinary tract infections	Estimated MIC of faropenem against various bacterial isolates
I Intervention	Faropenem monotherapy	Faropenem*
C Comparison	Amoxicillin-clavulanic acid (co-amoxiclav), azithromycin, cefpodoxime (or any cephalosporin group of drugs), and levofloxacin	Amoxicillin-clavulanic acid (co-amoxiclav), azithromycin, cefpodoxime, and levofloxacin*
O Outcomes	Clinical efficacy and safety	MICs (MIC_{50}, MIC_{90}, and MIC range)
S Study	Any clinical study evaluated the efficacy of faropenem in adults or children	Any *in vitro* study estimated the MIC

*As interventional or comparator drug/s. MIC: Minimum inhibitory concentration, PICOS: Population, Intervention, Comparison, Outcomes and Study

The literature search was restricted to English-language articles published until May 18, 2024. Following the database search, the title and abstract of identified articles were screened for eligibility based on the PICOS criteria [Table 1]. Systematic literature reviews, meta-analyses, narrative reviews, non-randomized or observational studies, conference or symposia abstracts or presentations, case series, case trials, editorials, and commentaries were excluded from the study. Further, clinical studies comparing the efficacy of faropenem with other penem drugs were also excluded from this review. The screened articles finally underwent full-text review to determine eligibility for inclusion in the final dataset. Two authors (DP and AP) independently examined the titles and abstracts of the retrieved records and subsequently, the full-text articles, based on the PICOS criteria. Any discrepancies between decisions were discussed with the reviewer (AS) until consensus was reached.

Data extraction

Publications that met the inclusion criteria were classified as clinical studies or *in vitro* studies. From clinical studies, the relevant data on study characteristics, efficacy, and safety were extracted. The data on efficacy were summarized as success rate or cure rate with treatment. The safety endpoint also recorded adverse events (AEs). From *in vitro* studies, the data on study characteristics, clinical isolates/pathogen, and the MIC_{50}, MIC_{90}, and MIC range of faropenem and other antibiotics (co-amoxiclav, cefpodoxime, azithromycin, and levofloxacin) were summarized.

RESULTS

Summary of identified studies

A total of 327 articles were identified in the literature search. Of these, 44 articles were selected for full-text screening, from which two clinical studies and 21 *in vitro* studies were considered eligible and included in the review [Figure 1].

Faropenem in clinical studies

Both clinical studies were multicenter, randomized, and double-blind clinical trials involving adult patients with acute bacterial sinusitis.[17,18] A study by Siegert *et al*., conducted between October 2000 and June 2001, included 561 patients and showed clinical cure rates of 89% for faropenem and 88.4% for cefuroxime at 7–16 days post-therapy.[18] A study by UpChurch *et al*., conducted between October 2000 and November 2001, included 1106 patients and demonstrated clinical cure rates of 80.3% and 81.8% after 7 and 10 days of faropenem treatment, respectively, compared to 74.5% after 10 days of cefuroxime treatment [Table 2].[17]

Faropenem in *in vitro* studies

A total of 21 *in vitro* studies were included in this review.[9-16,23-35] These studies were published between 1995 and 2008, with the majority reporting MIC values (MIC_{50}, MIC_{90}, and MIC range; µg/mL). Among *in vitro* studies, the activity of faropenem was assessed against Gram-positive bacteria in 17 studies, Gram-negative bacteria in 13 studies, and resistant strains such as

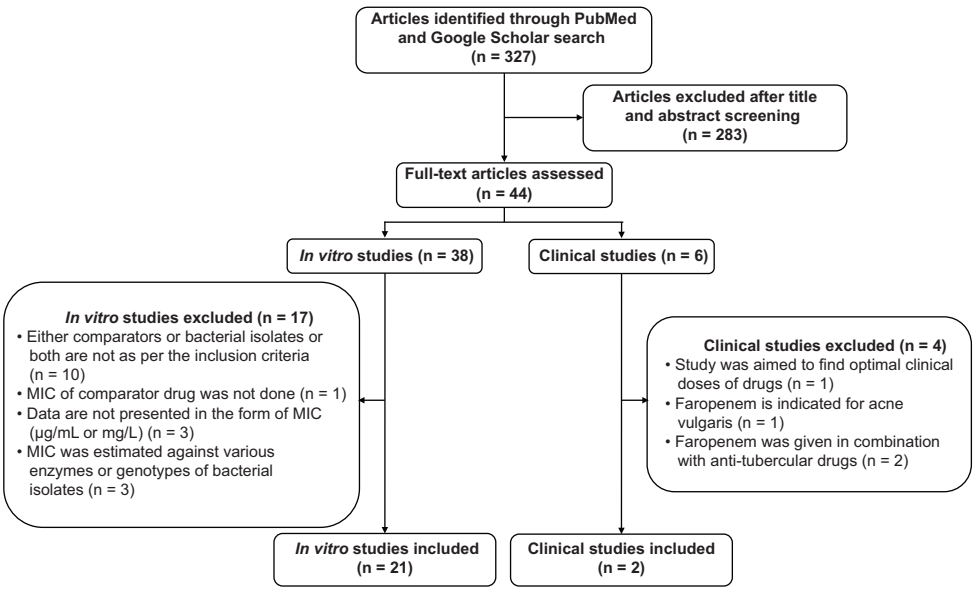

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart. MIC: Minimum inhibitory concentration

Table 2: Characteristics of included clinical studies.

Author-Year	Study design	Country/region	Study duration	Sample size	Indication
Siegert *et al*., 2003[18]	Prospective, multinational, multicenter, double-blind, randomized, comparative study	France, Germany, Greece, Israel, Lithuania, Spain, Sweden	October 2000–June 2001	*n*=561	Acute bacterial maxillary sinusitis
Upchurch *et al*., 2006[17]	Prospective, randomized, double-blind, multicenter, phase III study	USA, Canada	October 2000–November 2001	*n*=1106	Acute bacterial sinusitis
Author-Year	**Intervention**	**Study population**	**Efficacy outcomes**	**Safety outcomes**	
Siegert *et al*., 2003[18]	Faropenem (*n*=228): 300 mg twice daily orally for 7 days Cefuroxime (*n*=224): 250 mg twice daily orally for 7 days	Adults	Clinical cure rates: faropenem 89% and cefuroxime 88.4% Bacteriological success rate at 7–16 days post-therapy: faropenem 91.5% cefuroxime 90.8%	Drug-related AEs: faropenem 9.5% cefuroxime 10.3%	
Upchurch *et al*., 2006[17]	Faropenem (*n*=370): 300 mg twice daily for 7 days Faropenem (*n*=365): 300 mg twice daily for 10 days Cefuroxime (*n*=371) 250 mg twice daily for 10 days	Adults	Clinical cure rates: faropenem (7 days) 80.3% faropenem (10 days) 81.8% cefuroxime 74.5%	Drug-related AEs: faropenem (7 days) 22% faropenem (10 days) 20% cefuroxime 19%	

AEs: Adverse events

penicillin-susceptible/-resistant strains in eight studies, β-lactamase positive/negative strains in eight studies, and methicillin-/oxacillin-resistant strains in six studies [Tables 3 and 4; Supplementary Tables 2–4].

Faropenem activity against Gram-positive bacterial isolates

The most frequently studied bacterial isolates were *S. pneumonia*, followed by *Staphylococcus aureus*, *Enterococcus faecalis*, and *Enterococcus faecium* [Table 3].

The MIC_{90} of faropenem obtained in different studies varied from 0.015 to 1 μg/mL against *Streptococcus* species.[9,10,14,16,23-25,27,31,33,35] However, this was lower than that for comparators: co-amoxiclav, from ≤0.015 to 8 μg/mL;[9,10,14,16,23,24,27,33,35] cefpodoxime, from ≤0.015 to 32 μg/mL;[14,23,25,33] levofloxacin, from 1 to 2 μg/mL;[9,10,16,25,27,31] and azithromycin, from 0.12 to >16 μg/mL.[9,10]

The MIC_{90} of faropenem ranged from 0.06 to >64 μg/mL against *Staphylococcus* species,[14,24,27,33,35] which was lower than that of co-amoxiclav (0.25–64 μg/mL),[14,24,27,33,35] cefpodoxime (8–>32 μg/mL),[14,33] and levofloxacin (0.25–1 μg/mL).[27]

Faropenem showed good activity against *Clostridium* species, with the MIC_{90} ranging from 0.12 to 16 μg/mL,[12,14,28,34] whereas the reported MIC_{90} ranges for co-amoxiclav (0.03–64 μg/mL)[12,14,28,34] and cefpodoxime (8–>128 μg/mL)[14,34] were broader than that for faropenem.

The MIC_{90} against *Enterococcus* species ranged from 1 to >128 μg/mL for faropenem,[14,15,23,24,27,33,35] from >32 to >128 μg/mL for cefpodoxime,[14,15,23,33] and from 0.5 to 64 μg/mL for co-amoxiclav.[14,15,23,24,27,33,35]

Faropenem activity against Gram-negative bacterial isolates

Commonly studied Gram-negative bacterial isolates were *H. influenzae, Escherichia coli,* and *Proteus mirabilis* [Table 4].

In *in vitro* studies, the MIC_{90} of faropenem for *E. coli* ranged from 0.5 to 1 μg/mL[14,15,23,24,33,35] and for *Proteus* species from 2 to 8 μg/mL:[14,15,23,24,33,35] these figures were lower than those for co-amoxiclav (MIC_{90} for *E. coli,* from 8 to 32 μg/mL; for *Proteus* species, from 1 to 32 μg/mL)[14,15,23,24,33,35] and cefpodoxime (MIC_{90} for *E. coli*, from 0.5 to 2 μg/mL and *Proteus* species, from 0.06 to >128 μg/mL.[14,15,23,33]

The MIC_{90} of faropenem ranged from 1 to 4 μg/mL against *Klebsiella* species,[14,15,23,24,35] while the MIC_{90} reported for co-amoxiclav was 8–>32 μg/mL[14,15,23,24,35] and for cefpodoxime 1–32 μg/mL.[14,15,23]

Table 3: Characteristics of *in vitro* studies and minimum inhibitory concentrations of gram-positive bacteria.

Author year (country/ region) comparators	Study organism/pathogen (no. of strains tested)	Faropenem			Comparator 1 (C1)		
		MIC_{50}	MIC_{90}	MIC range	MIC_{50}	MIC_{90}	MIC range
Spangler *et al*., 1994a[34] (USA) C1: Co-amoxiclav C2: Cefpodoxime	*Clostridium perfringens* (21)	0.5	1.0	0.03–4.0	0.25	2.0	0.125–8.0
	Clostridioides difficile (10)	4.0	8.0	2.0–8.0	16.0	64.0	8.0–64.0
	Other *clostridia* (16)[a]	0.25	2.0	0.125–2.0	4.0	8.0	0.25–16.0
	Peptostreptococci (55)[b]	0.125	1.0	0.015–2.0	1.0	4.0	0.125–64.0
Sewell *et al*., 1995[35] (USA) C1: Co-amoxiclav	*Enterococcus faecalis* (185)	1.0	4.0	0.06–>64.0	0.5	1.0	0.06–>64.0
	Enterococcus faecium (11)	>64.0	>64.0	1.0–>64.0	8.0	64.0	0.5–>64.0
	Enterococcus spp. (101)	1.0	>64.0	0.06–>64.0	0.5	8.0	≤0.03–>64.0
	Streptococcus agalactiae (29)	≤0.03	0.06	≤0.03–0.06	0.06	0.06	≤0.03–0.06
	Streptococcus pyogenes (100)	0.06	0.06	≤0.03–0.25	≤0.03	≤0.03	≤0.03–0.5
	Staphylococcus aureus (386)	0.12	0.50	0.03–>64.0	1.0	4.0	0.12–>64.0
	Staphylococcus epidermidis (134)	0.12	2.0	≤0.03–>64.0	1.0	4.0	≤0.03–>64.0
	Staphylococcus hemolyticus (16)	0.12	>64.0	≤0.03–>64.0	0.25	64.0	0.06–64.0
	Staphylococcus saprophyticus (20)	0.5	0.5	0.06–1.0	0.5	1.0	0.25–2.0
	Staphylococci (CN) (264)	0.12	4.0	≤0.03–>64	1.0	8.0	≤0.03–>64.0
Fuchs *et al*., 1995[24] (USA) C1: Co-amoxiclav	*Enterococcus durans* (10)	2.0	16.0	0.06–>16.0	0.25	1.0	≤0.006-2.0
	Enterococcus faecalis (10)	1.0	1.0	1.0	0.5	0.5	0.25–0.5
	Enterococcus faecium (10)	8.0	>16.0	1.0–>16.0	0.5	4.0	0.12–4.0
	Streptococcus pneumoniae (15)[c]	0.06	0.25	≤0.03–0.5	≤0.06	0.5	≤0.06–1.0
	Streptococcus viridans (10)	0.25	0.06	≤0.03–0.5	0.12	1.0	≤0.06–2.0
	Streptococcus agalactiae (15)	0.06	0.06	≤0.03–0.06	≤0.06	≤0.06	≤0.06–0.12
	Groups C and G *Streptococcus* (20)	≤0.03	≤0.03	≤0.03	≤0.06	≤0.06	≤0.06
	Streptococcus spp. (15)	≤0.03	≤0.03	≤0.03	≤0.06	≤0.06	≤0.06
	Staphylococcus epidermidis (12)	0.06	0.25	0.06–>16.0	0.25	2.0	≤0.06–8.0
	Staphylococcus hemolyticus (10)	4.0	>16.0	0.12–>16.0	16.0	>16.0	1.0–>16.0
	Staphylococcus saprophyticus (10)	0.5	0.5	0.25–0.5	0.25	0.25	0.25–0.5
	Staphylococcus spp. (7)[d]	0.12	NA	0.06–0.25	≤0.12	NA	≤0.06–0.25
Eliopoulos *et al*., 1995 (USA)[23] C1: Co-amoxiclav C2: Cefpodoxime	*Enterococcus faecium* (20)	128.0	>128.0	2.0–>128.0	16.0	16.0	0.12–64.0
	Enterococcus avium (10)	2.0	4.0	1.0–4.0	0.50	0.50	0.25–1.0
	Enterococcus raffinosus (11)	128.0	128.0	64.0–>128.0	8.0	16.0	2.0–16.0
	Enterococcus casseliflavus/gallinarum (10)	4.0	8.0	1.0–8.0	1.0	1.0	0.5–1.0
	Enterococcus faecalis (15)	1.0	2.0	0.5–4.0	1.0	1.0	0.5–1.0
	Group A *streptococci* (10)	0.03	0.03	0.016–0.03	0.03	0.03	0.016–0.03
	Group B *streptococci* (10)	0.06	0.06	0.03–0.12	0.12	0.12	0.06–0.12
	Group C and G *streptococci* (9)	NA	NA	0.016–0.03	NA	NA	0.016–0.06
Mortensen *et al*., 1995[15] (USA) C1: Co-amoxiclav C2: Cefpodoxime	*Enterococcus* spp. (20)	2.0	>32.0	1.0–>32.0	1.0	16.0	0.5–>32.0
Ubukata *et al*., 1996[25] (Japan) C1: Cefpodoxime C2: Levofloxacin	*Streptococcus pneumoniae* (1283)	0.031	0.5	0.004–4.0	4.0	32.0	0.063–64.0

(Contd...)

Table 3: *(Continued).*

Author year (country/ region) comparators	Study organism/pathogen (no. of strains tested)	Faropenem			Comparator 1 (C1)		
		MIC_{50}	MIC_{90}	MIC range	MIC_{50}	MIC_{90}	MIC range
Woodcock *et al*., 1997[14] (UK) C1: Co-amoxiclav C2: Cefpodoxime	*Clostridium perfringens* (10)	0.5	1.0	0.25–1.0	0.12	0.25	0.06–0.25
	Clostridioides difficile (10)	4.0	8.0	1.0–8.0	0.5	1.0	0.25–2.0
	Enterococcus faecalis (10)	1.0	2.0	0.25–4.0	0.5	0.5	0.25–0.5
	Enterococcus faecium (10)	64.0	>128.0	8.0–>128.0	16.0	16.0	1.0–16.0
	Group A *streptococci* (19)	0.015	0.015	0.015	0.015	0.015	0.015
	Group B *streptococci* (20)	0.03	0.03	0.03	0.06	0.06	0.06
	Peptostreptococcus spp. (19)	0.06	0.5	0.008–1.0	0.12	0.5	0.06–1.0
	Streptococcus pneumoniae (20)	0.008	0.25	0.004–0.5	0.015	1.0	0.015–2.0
	Streptococcus milleri (28)	0.03	0.06	0.03–0.25	0.12	0.25	0.03–0.5
	Staphylococcus epidermidis (20)	0.06	0.5	0.06–>128.0	0.25	1.0	0.12–>128.0
	Staphylococcus saprophyticus (28)	0.5	0.5	0.12–0.5	0.25	0.5	0.12–0.5
Wexler *et al*., 2002[28] (USA) C1: Co-amoxiclav	*Clostridioides difficile* (11)	8.0	16.0	0.5–32.0	1.0	2.0	0.12–2.0
	Clostridium perfringens (20)	0.5	0.5	0.12–1.0	0.12	0.12	0.12–1.0
	Clostridium ramosum (10)	0.25	1.0	0.12–1.0	0.12	0.25	0.12–1.0
	Clostridium sordellii (10)	0.12	0.12	0.12–5.0	0.12	0.12	0.12–0.25
	Clostridium sporogenes (10)	1.0	1.0	0.5–1.0	0.25	0.50	0.12–0.5
	Clostridium spp. (10)[e]	2.0	8.0	0.5–8.0	0.5	2.00	0.25–8.0
Goldstein *et al*., 2002[27] (USA) C1: Co-amoxiclav C2: Levofloxacin	*Enterococcus* spp. (10)[f]	0.5	1.0	0.03–1.0	0.125	0.5	≤0.015–0.5
	Peptostreptococcus spp. (16)[g]	0.125	1.0	≤0.015–4.0	0.25	2.00	≤0.015–4.0
	Streptococcus spp. (37)[h]	0.06	0.06	0.03–0.25	0.06	0.25	≤0.015–1.0
	Staphylococcus aureus (19)	0.125	0.25	0.06–0.5	0.5	2.00	0.125–4.0
	Staphylococcus epidermidis (12)	0.06	0.5	0.06–1.0	0.125	0.50	0.03–1.0
	Staphylococci (CN) (11)[i]	0.06	0.06	0.03–1.0	0.06	0.25	≤0.015–2.0
Milatovic *et al*., 2002[33] (Netherlands) C1: Co-amoxiclav C2: Cefpodoxime	*Enterococcus faecalis* (291)	1.00	8.00	0.06–>32.0	1.0	1.0	0.03–>32.0
	Enterococcus faecium (220)	>32	>32.0	0.06–>32.0	32.0	>32.0	0.12–>32.0
	Group A *Streptococci streptococci* (186)	0.03	0.03	≤0.015–0.06	≤0.015	≤0.015	≤0.015–0.12
	Group B *Streptococci streptococci* (163)	0.06	0.06	0.03–0.12	0.12	0.12	≤0.015–0.25
	Streptococcus milleri (38)	0.06	0.12	≤0.015–0.12	0.12	0.25	≤0.015–0.25
	Streptococcus viridans (191)	0.12	1.0	≤0.015–8.0	0.12	2.0	≤0.015–>32.0
	Staphylococci (CN) (354)	0.12	4.00	<0.015–>32.0	1.0	8.0	0.03–>32.0
Milazzo *et al*., 2003[30] (Italy) C1: Co-amoxiclav	*Peptostreptococcus* spp. (11)	0.06	0.12	≤0.03–16.0	0.12	0.25	≤0.03–16.0
Decousser *et al*., 2003[31] (France) C1: Levofloxacin	*Streptococcus pneumoniae* (194)[j]	0.032	0.25	0.008–1.0	1.0	1.0	0.25–2.0
	Streptococcus pneumoniae (60)[k]	0.016	0.5	0.008–1.0	1.0	1.0	0.5–2.0
Walsh *et al*., 2003[16] (UK) C1: Co-amoxiclav C2: Levofloxacin	*Streptococcus pneumoniae* (100)	0.008	0.25	0.002–1.0	0.016	0.5	0.004–2.0
Behra-Miellet *et al*., 2005[12] (France) C1: Co-amoxiclav	*Clostridium perfringens* (29)	0.25	0.5	0.03–0.5	0.03	0.03	0.03–0.12
	Clostridioides difficile (26)	1.0	2.0	0.03–2.0	0.5	2.0	0.06–2.0
	Gram-positive anaerobes (197)	0.25	1.0	0.015–2.0	0.12	1.0	0.03–2.0
	Other *clostridium* (22)[l]	0.12	2.0	0.015–2.0	0.25	0.5	0.03–2.0

(Contd...)

Table 3: *(Continued).*

Author year (country/ region) comparators	Study organism/pathogen (no. of strains tested)	Faropenem			Comparator 1 (C1)		
		MIC_{50}	MIC_{90}	MIC range	MIC_{50}	MIC_{90}	MIC range
Stone *et al*., 2007[10] (Israel) C1: Co-amoxiclav C2: Levofloxacin C3: Azithromycin	*Streptococcus pneumoniae* (393)	NA	0.5	≤0.004–1.0	NA	2.0	≤0.015–4.0
Stone *et al*., 2007[10] (Costa Rica) C1: Co-amoxiclav C2: Levofloxacin C3: Azithromycin	*Streptococcus pneumoniae* (168)	NA	0.06	≤0.004–2.0	NA	0.12	≤0.015–16.0
	Streptococcus pyogenes (30)	0.015	0.015	0.008–0.015	≤0.015	≤0.015	≤0.015
Critchley *et al*., 2008[9] (USA) C1: Co-amoxiclav C2: Levofloxacin C3: Azithromycin	*Streptococcus pneumoniae* (393)	NA	1.0	NA	NA	8.0	NA
Author year (country/ region) comparator	**Study organism/pathogen (no. of strains tested)**	**Comparator 2 (C2)**			**Comparator 3 (C3)**		
		MIC_{50}	MIC_{90}	MIC range	MIC_{50}	MIC_{90}	MIC range
Spangler *et al*., 1994a[34] (USA) C1: Co-amoxiclav C2: Cefpodoxime	*Clostridium perfringens* (21)	1.0	8.0	0.06–>32.0	NA	NA	NA
	Clostridioides difficile (10)	>32.0	>32.0	16.0–>32.0	NA	NA	NA
	Other *clostridia* (16)[a]	8.0	>32.0	0.125–>32.0	NA	NA	NA
	Peptostreptococci (55)[b]	0.5	16.0	0.06–32.0	NA	NA	NA
Sewell *et al*., 1995[35] (USA) C1: Co-amoxiclav	*Enterococcus faecalis* (185)	NA	NA	NA	NA	NA	NA
	Enterococcus faecium (11)	NA	NA	NA	NA	NA	NA
	Enterococcus spp. (101)	NA	NA	NA	NA	NA	NA
	Streptococcus agalactiae (29)	NA	NA	NA	NA	NA	NA
	Streptococcus pyogenes (100)	NA	NA	NA	NA	NA	NA
	Staphylococcus aureus (386)	NA	NA	NA	NA	NA	NA
	Staphylococcus epidermidis (134)	NA	NA	NA	NA	NA	NA
	Staphylococcus hemolyticus (16)	NA	NA	NA	NA	NA	NA
	Staphylococcus saprophyticus (20)	NA	NA	NA	NA	NA	NA
	Staphylococci (CN) (264)	NA	NA	NA	NA	NA	NA
Fuchs *et al*., 1995[24] (USA) C1: Co-amoxiclav	*Enterococcus durans* (10)	NA	NA	NA	NA	NA	NA
	Enterococcus faecalis (10)	NA	NA	NA	NA	NA	NA
	Enterococcus faecium (10)	NA	NA	NA	NA	NA	NA
	Streptococcus pneumoniae (15)[c]	NA	NA	NA	NA	NA	NA
	Streptococcus viridans (10)	NA	NA	NA	NA	NA	NA
	Streptococcus agalactiae (15)	NA	NA	NA	NA	NA	NA
	Groups C and G *Streptococcus* (20)	NA	NA	NA	NA	NA	NA
	Streptococcus spp. (15)	NA	NA	NA	NA	NA	NA
	Staphylococcus epidermidis (12)	NA	NA	NA	NA	NA	NA
	Staphylococcus hemolyticus (10)	NA	NA	NA	NA	NA	NA
	Staphylococcus saprophyticus (10)	NA	NA	NA	NA	NA	NA
	Staphylococcus spp. (7)[d]	NA	NA	NA	NA	NA	NA

(Contd...)

Table 3: *(Continued).*

Author year (country/ region) comparators	Study organism/pathogen (no. of strains tested)	Comparator 2 (C2)			Comparator 3 (C3)		
		MIC_{50}	MIC_{90}	MIC range	MIC_{50}	MIC_{90}	MIC range
Eliopoulos *et al*., 1995 (USA)[23] C1: Co-amoxiclav C2: Cefpodoxime	*Enterococcus faecium* (20)	>128.0	>128.0	>128.0	NA	NA	NA
	Enterococcus avium (10)	8.0	64.0	8.0–128.0	NA	NA	NA
	Enterococcus raffinosus (11)	>128.0	>128.0	>128.0	NA	NA	NA
	Enterococcus casseliflavus/ gallinarum (10)	>128.0	>128.0	32.0–>128.0	NA	NA	NA
	Enterococcus faecalis (15)	>128.0	>128.0	>128.0	NA	NA	NA
	Group A *streptococci* (10)	0.016	0.016	0.008–0.016	NA	NA	NA
	Group B *streptococci* (10)	0.06	0.06	0.03–0.25	NA	NA	NA
	Group C and G *streptococci* (9)	NA	NA	0.016–0.03	NA	NA	NA
Mortensen *et al*., 1995[15] (USA) C1: Co-amoxiclav C2: Cefpodoxime	*Enterococcus* spp. (20)	>32.0	>32.0	>32.0	NA	NA	NA
Ubukata *et al*., 1996[25] (Japan) C1: Cefpodoxime C2: Levofloxacin	*Streptococcus pneumoniae* (1283)	1.0	2.0	0.25–64.0	NA	NA	NA
Woodcock *et al*., 1997[14] (UK) C1: Co-amoxiclav C2: Cefpodoxime	*Clostridium perfringens* (10)	8.0	16.0	1.0–16.0	NA	NA	NA
	Clostridioides difficile (10)	128.0	>128.0	128.0–>128.0	NA	NA	NA
	Enterococcus faecalis (10)	8.0	>128.0	2.0–>128.0	NA	NA	NA
	Enterococcus faecium (10)	>128.0	>128.0	128.0–>128.0	NA	NA	NA
	Group A *streptococci* (19)	0.03	0.03	0.03	NA	NA	NA
	Group B *streptococci* (20)	0.03	0.06	0.03–0.06	NA	NA	NA
	Peptostreptococcus spp. (19)	1.0	8.0	0.25–32.0	NA	NA	NA
	Streptococcus pneumoniae (20)	0.03	2.0	0.03–4.0	NA	NA	NA
	Streptococcus milleri (28)	0.25	0.5	0.03–32.0	NA	NA	NA
	Staphylococcus epidermidis (20)	2.0	16.0	0.25–>128.0	NA	NA	NA
	Staphylococcus saprophyticus (28)	4.0	8.0	1.0–8.0	NA	NA	NA
Wexler *et al*., 2002[28] (USA) C1: Co-amoxiclav	*Clostridioides difficile* (11)	NA	NA	NA	NA	NA	NA
	Clostridium perfringens (20)	NA	NA	NA	NA	NA	NA
	Clostridium ramosum (10)	NA	NA	NA	NA	NA	NA
	Clostridium sordellii (10)	NA	NA	NA	NA	NA	NA
	Clostridium sporogenes (10)	NA	NA	NA	NA	NA	NA
	Clostridium spp. (10)[e]	NA	NA	NA	NA	NA	NA
Goldstein *et al*., 2002[27] (USA) C1: Co-amoxiclav C2: Levofloxacin	*Enterococcus* spp. (10)[f]	0.5	1.0	≤0.06–1.0	NA	NA	NA
	Peptostreptococcus spp. (16)[g]	0.5	4.0	≤0.06–8.0	NA	NA	NA
	Streptococcus spp. (37)[h]	1.0	1.0	0.5–2.0	NA	NA	NA
	Staphylococcus aureus (19)	0.125	0.25	≤0.06–0.25	NA	NA	NA
	Staphylococcus epidermidis (12)	0.125	0.25	0.125–8.0	NA	NA	NA
	Staphylococci (CN) (11)[i]	0.125	0.125	0.125–1.0	NA	NA	NA

(Contd...)

Table 3: *(Continued).*

Author year (country/ region) comparators	Study organism/pathogen (no. of strains tested)	Comparator 2 (C2)			Comparator 3 (C3)		
		MIC_{50}	MIC_{90}	MIC range	MIC_{50}	MIC_{90}	MIC range
Milatovic *et al*., 2002[33] (Netherlands) C1: Co-amoxiclav C2: Cefpodoxime	*Enterococcus faecalis* (291)	>32.0	>32.0	0.25–>32.0	NA	NA	NA
	Enterococcus faecium (220)	>32.0	>32.0	0.25–>32.0	NA	NA	NA
	Group A *Streptococci streptococci* (186)	≤0.015	≤0.015	≤0.015–0.12	NA	NA	NA
	Group B *Streptococci streptococci* (163)	0.06	0.06	≤0.015–0.12	NA	NA	NA
	Streptococcus milleri (38)	0.25	0.5	≤0.015–0.5	NA	NA	NA
	Streptococcus viridans (191)	0.25	4.0	≤0.015–>32.0	NA	NA	NA
	Staphylococci (CN) (354)	4.0	>32.0	0.06–>32.0	NA	NA	NA
Milazzo *et al*., 2003[30] (Italy) C1: Co-amoxiclav	*Peptostreptococcus* spp. (11)	NA	NA	NA	NA	NA	NA
Decousser *et al*., 2003[31] (France) C1: Levofloxacin	*Streptococcus pneumoniae* (194)[j]	NA	NA	NA	NA	NA	NA
	Streptococcus pneumoniae (60)[k]	NA	NA	NA	NA	NA	NA
Walsh *et al*., 2003[16] (UK) C1: Co-amoxiclav C2: Levofloxacin	*Streptococcus pneumoniae* (100)	1.0	2.0	0.12–2.0	NA	NA	NA
Behra-Miellet *et al*., 2005[12] (France) C1: Co-amoxiclav	*Clostridium perfringens* (29)	NA	NA	NA	NA	NA	NA
	Clostridioides difficile (26)	NA	NA	NA	NA	NA	NA
	Gram-positive anaerobes (197)	NA	NA	NA	NA	NA	NA
	Other *clostridium* (22)[l]	NA	NA	NA	NA	NA	NA
Stone *et al*., 2007[10] (Israel) C1: Co-amoxiclav C2: Levofloxacin C3: Azithromycin	*Streptococcus pneumoniae* (393)	NA	1.0	0.25–2.0	NA	≥8.0	≤0.03–≥8.0
Stone *et al*., 2007[10] (Costa Rica) C1: Co-amoxiclav C2: Levofloxacin C3: Azithromycin	*Streptococcus pneumoniae* (168)	NA	1	0.5–1.0	NA	4.0	≤0.03–≥8.0
	Streptococcus pyogenes (30)	0.5	1.0	0.25–2.0	0.06	0.12	0.06–0.12
Critchley *et al*., 2008[9] (USA) C1: Co-amoxiclav C2: Levofloxacin C3: Azithromycin	*Streptococcus pneumoniae* (393)	NA	1.0	NA	NA	>16.0	NA

All MICs are presented in µg/mL. The number mentioned in parentheses after each bacterium denotes no. of strains tested. [a]Includes *Clostridium ramosum* (2), *Clostridium tertium* (2), *Clostridium innocuum* (1), *Clostridium sporogenes* (1), *Clostridium butyricum* (2), *Clostridium cadaveris* (2), *Clostridium bifermentans* (2), *Clostridium sordellii* (1), *Clostridium septicum* (1), *Clostridium histolyticum* (1), *Clostridium paraperfringens* (1). [b]Includes *Peptostreptococcus asaccharolyticus* strains (2), *Peptostreptococcus magnus* (14), *Peptostreptococcus prevotii* (1), *Peptostreptococcus micros* (2), *Peptostreptococcus anaerobius* (6), *Peptostreptococcus tetradius* (21), *Peptostreptococcus productus* (3), *Peptostreptococci* spp. (3), *Staphylococcus intermedius* (3). [c]Includes penicillin-intermediate strains (2), penicillin-susceptible strains (13). [d]Includes *Staphylococcus hominis* (2), *Staphylococcus simulans* (3), *Staphylococcus warneri* (2). [e]Includes *Clostridium butyricum* (3), *Clostridium clostridioforme* (4), *Clostridium innocuum* (3). [f]Includes *Enterococcus avium* (1), *Enterococcus durans* (3), *Enterococcus faecalis* (6). [g]Includes *Peptostreptococcus anaerobius* (5), *Peptostreptococcus asaccharolyticus* (1), *Peptostreptococcus ivorii* (1), *Peptostreptococcus magnus* (2), *Peptostreptococcus micros* (4), *Peptostreptococcus prevotii* (2), *Peptostreptococcus tetradius* (1). [h]Includes *Streptococcus anginosus* (7), *Streptococcus constellatus* (6), *Streptococcus intermedius* (7), *Streptococcus mitis* (6), *Streptococcus mutans* (1), *Streptococcus oralis* (3), *Streptococcus salivarius* (2), *Streptococcus sanguis* (2), *Aerococcus viridans* (1), *Stomatococcus mucilaginosus* (2). [i]Includes *Staphylococcus* hyicus (2), *Staphylococcus intermedius* (5), *Kocuria kristinae* (1), *Micrococcus* spp. (2), *Rhodococcus* spp. (1). [j]*Streptococcus pneumoniae* strains isolated from blood cultures of adult patients. [k]*Streptococcus pneumoniae* strains isolated from blood cultures of children. [l]Includes *Clostridium baratii* (1), *Clostridium bifermentans* (1), *Clostridium fallax* (2), *Clostridium histolyticum* (1), *Clostridium ramosum* (3), *Clostridium sphenoides* (2), *Clostridium sporogenes* (2), *Clostridium sordelii* (4), *Clostridium septicum* (1), *Clostridium* spp. (5). Co-amoxiclav: Amoxicillin-clavulanic acid combination, CN: Coagulase negative, MIC: Minimum inhibitory concentration, NA: Not available

Table 4: Characteristics of in vitro studies and minimum inhibitory concentrations of Gram-negative bacteria.

Author year (country/region) comparators	Study organism/ pathogen (no. of strains tested)	Faropenem			Comparator 1 (C1)		
		MIC_{50}	MIC_{90}	MIC range	MIC_{50}	MIC_{90}	MIC range
Spangler *et al*., 1994a[34] (USA) C1: Co-amoxiclav C2: Cefpodoxime	*Bacteroides fragilis* (30)	0.5	2.0	0.06–4.0	1.0	4.0	0.25–4.0
Sewell *et al*., 1995[35] (USA) C1: Co-amoxiclav	*Citrobacter diversus* (8)	0.5	NA	0.25–1.0	2.0	NA	1.0–4.0
	Citrobacter freundii (41)	1.0	2.0	0.25–>64.0	64.0	>64.0	≤0.03–>64.0
	Escherichia coli (817)	0.5	1.0	≤0.03–16.0	4.0	32.0	0.5–>64.0
	Klebsiella oxytoca (45)	0.5	4.0	0.25–64.0	4.0	16.0	0.12–32.0
	Klebsiella pneumoniae (186)	0.5	2.0	0.12–4.0	2.0	8.0	0.25–64.0
	Proteus mirabilis (52)	4.0	8.0	0.25–16.0	1.0	32.0	0.12–>64.0
	Proteus vulgaris (9)	2.0	NA	0.5–16.0	16.0	NA	2.0–64.0
	Pseudomonas spp. (8)	64.0	NA	2.0–>64.0	64.0	NA	1.0–>64.0
	Pseudomonas aeruginosa (246)	>64.0	>64.0	8.0–>64.0	>64.0	>64.0	32.0–>64.0
Fuchs *et al*., 1995[24] (USA) C1: Co-amoxiclav	*Citrobacter diversus* (10)	0.25	0.5	0.25–0.5	2.0	2.0	2.0–8.0
	Citrobacter freundii (21)	2.0	4.0	0.25–4.0	>16.0	>16.0	8.0–>16.0
	Escherichia coli (25)	0.5	0.5	0.25–2.0	2.0	8.0	1.0–16.0
	Klebsiella spp. (25)	0.5	2.0	0.25–4.0	2.0	16.0	1.0–16.0
	Moraxella catarrhalis (15)	0.12	0.5	≤0.03–0.5	≤0.06	0.12	≤0.06–0.25
	Neisseria meningitidis (10)	≤0.03	≤0.03	≤0.03	0.12	0.12	≤0.06–0.12
	Proteus mirabilis (10)	2.0	2.0	1.0–2.0	0.5	1.0	0.25–1.0
	Proteus vulgaris (10)	2.0	2.0	1.0–2.0	4.0	8.0	4.0–16.0
	Pseudomonas aeruginosa (15)	>16.0	>16.0	>16.0	>16.0	>16.0	>16.0
	Pseudomonas spp. (20)[a]	>16.0	>16.0	16.0–>16.0	>16.0	>16.0	1.0–>16.0
	Salmonella spp. (15)[b]	0.5	0.5	0.12–1.0	0.5	>16.0	0.25–>16.0
	Shigella spp. (20)[c]	0.25	0.5	0.12–1.0	2.0	8.0	1.0–16.0
Eliopoulos *et al*., 1995[23] (USA) C1: Co-amoxiclav C2: Cefpodoxime	*Bacteroides fragilis* (30)	0.25	4.0	0.03–8.0	0.5	4.0	0.25–8.0
	Citrobacter freundii (20)	1.0	4.0	0.5–16.0	64.0	64.0	16.0–128.0
	Escherichia coli (30)	0.5	1.0	0.5–4.0	8.0	16.0	4.0–32.0
	Klebsiella pneumoniae (20)	0.5	1.0	0.5–4.0	4.0	16.0	1.0–32.0
	Proteus mirabilis (20)	4.0	4.0	1.0–8.0	2.0	4.0	1.0–16.0
	Proteus vulgaris (10)	8.0	8.0	4.0–8.0	16.0	32.0	8.0–32.0
	Pseudomonas aeruginosa (10)	>128.0	>128.0	32.0–>128.0	>128.0	>128.0	>128.0
	Salmonella spp. (13)	2.0	2.0	0.5–4.0	2.0	2.0	0.5–32.0
Mortensen *et al*., 1995[15] (USA) C1: Co-amoxiclav C2: Cefpodoxime	*Citrobacter freundii* (12)	1.0	8.0	0.06–8.0	>32.0	>32.0	8.0–>32.0
	Escherichia coli (67)	0.5	1.0	0.25–2.0	16.0	32.0	1.0–>32.0
	Klebsiella oxytoca (23)	0.5	1.0	0.25–2.0	16.0	>32.0	8.0–>32.0
	Klebsiella pneumoniae (36)	1.0	2.0	0.25–32.0	8.0	>32.0	1.0–>32.0
	M. catarrkalis (27)	0.5	1.0	0.03–1.0	0.5	1.0	0.25–2.0
	Proteus mirabilis (17)	4.0	8.0	2.0–8.0	1.0	32.0	1.0–32.0
	Salmonella enteritidis (25)	0.5	1.0	0.25–1.0	1.0	32.0	1.0–32.0
	Shigella spp. (11)	0.5	1.0	0.5–1.0	32.0	32.0	32.0–>32.0
Woodcock *et al*., 1997[14] (UK) C1: Co-amoxiclav C2: Cefpodoxime	*Bacteroides fragilis* (24)	1.0	4.0	0.12–32.0	1.0	2.0	0.25–4.0

(Contd...)

Table 4: *(Continued).*

Author year (country/region) comparators	Study organism/ pathogen (no. of strains tested)	Faropenem			Comparator 1 (C1)		
		MIC_{50}	MIC_{90}	MIC range	MIC_{50}	MIC_{90}	MIC range
	Citrobacter spp. (10)[d]	0.5	4.0	0.25–4.0	16.0	64.0	1.0–128.0
	Escherichia coli (71)	0.5	1.0	0.06–8.0	4.0	16.0	0.5–32.0
	Haemophilus influenzae (35)	0.5	1.0	0.25–2.0	0.5	2.0	0.25–4.0
	Klebsiella spp. (47)	0.5	2.0	0.06–8.0	2.0	8.0	0.5–32.0
	Moraxella catarrhalis (35)	0.25	0.5	0.03–1.0	0.12	0.25	0.015–1.0
	Neisseria gonorrhoeae (35)	0.03	0.06	0.008–0.25	0.25	1.0	0.06–2.0
	Neisseria meningitides (10)	0.008	0.008	0.008	0.06	0.06	0.06
	Proteus mirabilis (49)	1.0	2.0	0.25–2.0	0.5	2.0	0.25–16.0
	Proteus vulgaris (20)	1.0	4.0	0.5–4.0	2.0	4.0	1.0–8.0
	Pseudomonas aeruginosa (9)	>128.0	>128.0	8.0–>128.0	64.0	128.0	32.0–>128.0
	Providencia stuartii (20)	1.0	2.0	0.06–4.0	64.0	128.0	2.0–>128.0
	Salmonella spp. (5)	0.5	0.5	0.5	1.0	16.0	0.5–16.0
	Shigella spp. (5)	0.5	0.5	0.25–0.5	4.0	8.0	1.0–8.0
Wexler *et al*., 2002[28] (USA) C1: Co-amoxiclav	*Bacteroides fragilis* (68)	0.25	1.0	0.12–64.0	0.5	8.0	0.25–64.0
Milatovic *et al*., 2002[33] (Netherlands) C1: Co-amoxiclav C2: Cefpodoxime	*Escherichia coli* (323)	0.5	1.0	0.25–32.0	8.0	16.0	2.0–>32.0
	Moraxella catarrhalis (307)	0.12	0.5	≤0.015–1.0	0.06	0.25	≤0.015–0.5
	Proteus mirabilis (282)	4.0	4.0	0.25–16.0	2.0	16.0	0.5–>32.0
	Proteus vulgaris (85)	4.0	8.0	0.5–16.0	4.0	16.0	1.0–>32.0
	Pseudomonas aeruginosa (228)	>32.0	>32.0	2–>32.0	>32.0	>32.0	2.0–>32.0
Walsh *et al*., 2003[16] (UK) C1: Co-amoxiclav C2: Levofloxacin	*Haemophilus influenzae* (100)	0.5	1.0	0.06–4.0	0.25	0.5	0.016–2.0
Jones *et al*. 2005 [13] (USA) C1: Levofloxacin C2: Azithromycin	*Neisseria gonorrhoeae* (265)	0.06	0.25	≤0.008–0.5	0.016	4.0	≤0.008–>4.0
Behra-Miellet *et al*., 2005[12] (France) C1: Levofloxacin C2: Azithromycin	*Bacteroides fragilis* (85)	0.01	0.5	0.015–>128.0	0.25	4.0	0.06–>64.0
	Gram-negative anaerobes (265)	0.12	1.0	0.015–>128.0	0.25	8.0	0.03–>64.0
Stone *et al*., 2007[10] (Israel) C1: Co-amoxiclav C2: Levofloxacin C3: Azithromycin	*Haemophilus influenzae* (367)	NA	0.25	0.015–4.0	NA	1.0	0.12–8.0
Stone *et al*., 2007[10] (Costa Rica) C1: Co-amoxiclav C2: Levofloxacin C3: Azithromycin	*Haemophilus influenzae* (187)	NA	0.5	0.008–4.0	NA	1.0	0.03–2.0
	Moraxella catarrhalis (43)	0.25	0.5	0.008–0.5	0.12	0.25	0.015–0.5

Author year (country/region) comparators	Study organism/ pathogen (no. of strains tested)	Comparator 2 (C2)			Comparator 3 (C3)		
		MIC_{50}	MIC_{90}	MIC range	MIC_{50}	MIC_{90}	MIC range
Spangler *et al*., 1994a[34] (USA) C1: Co-amoxiclav C2: Cefpodoxime	*Bacteroides fragilis* (30)	32.0	>32.0	0.5–>32.0	NA	NA	NA

(Contd...)

Table 4: *(Continued).*

Author year (country/region) comparators	Study organism/ pathogen (no. of strains tested)	Comparator 2 (C2)			Comparator 3 (C3)		
		MIC_{50}	MIC_{90}	MIC range	MIC_{50}	MIC_{90}	MIC range
Sewell *et al*., 1995[35] (USA) C1: Co-amoxiclav	*Citrobacter diversus* (8)	NA	NA	NA	NA	NA	NA
	Citrobacter freundii (41)	NA	NA	NA	NA	NA	NA
	Escherichia coli (817)	NA	NA	NA	NA	NA	NA
	Klebsiella oxytoca (45)	NA	NA	NA	NA	NA	NA
	Klebsiella pneumoniae (186)	NA	NA	NA	NA	NA	NA
	Proteus mirabilis (52)	NA	NA	NA	NA	NA	NA
	Proteus vulgaris (9)	NA	NA	NA	NA	NA	NA
	Pseudomonas spp. (8)	NA	NA	NA	NA	NA	NA
	Pseudomonas aeruginosa (246)	NA	NA	NA	NA	NA	NA
Fuchs *et al*., 1995[24] (USA) C1: Co-amoxiclav	*Citrobacter diversus* (10)	NA	NA	NA	NA	NA	NA
	Citrobacter freundii (21)	NA	NA	NA	NA	NA	NA
	Escherichia coli (25)	NA	NA	NA	NA	NA	NA
	Klebsiella spp. (25)	NA	NA	NA	NA	NA	NA
	Moraxella catarrhalis (15)	NA	NA	NA	NA	NA	NA
	Neisseria meningitidis (10)	NA	NA	NA	NA	NA	NA
	Proteus mirabilis (10)	NA	NA	NA	NA	NA	NA
	Proteus vulgaris (10)	NA	NA	NA	NA	NA	NA
	Pseudomonas aeruginosa (15)	NA	NA	NA	NA	NA	NA
	Pseudomonas spp. (20)[a]	NA	NA	NA	NA	NA	NA
	Salmonella spp. (15)[b]	NA	NA	NA	NA	NA	NA
	Shigella spp. (20)[c]	NA	NA	NA	NA	NA	NA
Eliopoulos *et al*., 1995[23] (USA) C1: Co-amoxiclav C2: Cefpodoxime	*Bacteroides fragilis* (30)	32.0	>128.0	4.0–>128.0	NA	NA	NA
	Citrobacter freundii (20)	4.0	>128.0	2.0–>128.0	NA	NA	NA
	Escherichia coli (30)	0.5	0.5	0.12–2.0	NA	NA	NA
	Klebsiella pneumoniae (20)	0.25	1.0	0.06–>128	NA	NA	NA
	Proteus mirabilis (20)	0.12	0.25	0.06–1.0	NA	NA	NA
	Proteus vulgaris (10)	2.0	>128.0	0.25–>128.0	NA	NA	NA
	Pseudomonas aeruginosa (10)	>128.0	>128.0	>128.0	NA	NA	NA
	Salmonella spp. (13)	2.0	2.0	0.25–2.0	NA	NA	NA
Mortensen *et al*., 1995[15] (USA) C1: Co-amoxiclav C2: Cefpodoxime	*Citrobacter freundii* (12)	8.0	>32.0	0.25–>32.0	NA	NA	NA
	Escherichia coli (67)	0.5	2.0	0.06–32.0	NA	NA	NA
	Klebsiella oxytoca (23)	>16.0	>16.0	>16.0	NA	NA	NA
	Klebsiella pneumoniae (36)	0.25	32.0	0.06–>32.0	NA	NA	NA
	M. catarrkalis (27)	1.0	2.0	0.25–2.0	NA	NA	NA
	Proteus mirabilis (17)	0.06	8.0	0.03–>32.0	NA	NA	NA
	Salmonella enteritidis (25)	0.25	1.0	0.25–1.0	NA	NA	NA
	Shigella spp. (11)	0.5	1.0	0.5–1.0	NA	NA	NA
Woodcock *et al*., 1997[14] (UK) C1: Co-amoxiclav C2: Cefpodoxime	*Bacteroides fragilis* (24)	64.0	>128.0	8.0–>128.0	NA	NA	NA
	Citrobacter spp. (10)[d]	1.0	64.0	0.25–>128.0	NA	NA	NA
	Escherichia coli (71)	0.25	1.0	0.06–>128.0	NA	NA	NA
	Haemophilus influenzae (35)	0.06	0.12	0.06–0.5	NA	NA	NA
	Klebsiella spp. (47)	0.12	4.0	0.015–128.0	NA	NA	NA
	Moraxella catarrhalis (35)	0.5	1.0	0.12–1.0	NA	NA	NA

(Contd...)

Table 4: *(Continued).*

Author year (country/region) comparators	Study organism/ pathogen (no. of strains tested)	Comparator 2 (C2)			Comparator 3 (C3)		
		MIC_{50}	MIC_{90}	MIC range	MIC_{50}	MIC_{90}	MIC range
	Neisseria gonorrhoeae (35)	0.03	0.03	0.002–0.06	NA	NA	NA
	Neisseria meningitides (10)	0.004	0.004	0.002–0.004	NA	NA	NA
	Proteus mirabilis (49)	0.06	0.06	0.03–0.12	NA	NA	NA
	Proteus vulgaris (20)	0.12	0.5	0.06–1.0	NA	NA	NA
	Pseudomonas aeruginosa (9)	>128.0	>128.0	128.0–>128.0	NA	NA	NA
	Providencia stuartii (20)	0.06	2.0	0.015–16.0	NA	NA	NA
	Salmonella spp. (5)	1.0	2.0	0.5–2.0	NA	NA	NA
	Shigella spp. (5)	0.5	0.5	0.25–0.5	NA	NA	NA
Wexler *et al*., 2002[28] (USA) C1: Co-amoxiclav	*Bacteroides fragilis* (68)	NA	NA	NA	NA	NA	NA
Milatovic *et al*., 2002[33] (Netherlands) C1: Co-amoxiclav C2: Cefpodoxime	*Escherichia coli* (323)	0.5	1.0	0.12–>32.0	NA	NA	NA
	Moraxella catarrhalis (307)	0.5	1.0	≤0.015–1.0	NA	NA	NA
	Proteus mirabilis (282)	0.06	8.0	≤0.015–>32.0	NA	NA	NA
	Proteus vulgaris (85)	0.5	16.0	0.06–>32.0	NA	NA	NA
	Pseudomonas aeruginosa (228)	>32.0	>32.0	16.0–>32.0	NA	NA	NA
Walsh *et al*., 2003[16] (UK) C1: Co-amoxiclav C2: Levofloxacin	*Haemophilus influenzae* (100)	0.008	0.016	0.004–1.0	NA	NA	NA
Jones *et al*. 2005[13] (USA) C1: Levofloxacin C2: Azithromycin	*Neisseria gonorrhoeae* (265)	0.25	0.5	0.03–2.0	NA	NA	NA
Behra-Miellet *et al*., 2005[12] (France) C1: Levofloxacin C2: Azithromycin	*Bacteroides fragilis* (85)	NA	NA	NA	NA	NA	NA
	Gram-negative anaerobes (265)	NA	NA	NA	NA	NA	NA
Stone *et al*., 2007[10] (Israel) C1: Co-amoxiclav C2: Levofloxacin C3: Azithromycin	*Haemophilus influenzae* (367)	NA	0.015	≤0.004–0.03	NA	2.0	0.25–4.0
Stone *et al*., 2007[10] (Costa Rica) C1: Co-amoxiclav C2: Levofloxacin C3: Azithromycin	*Haemophilus influenzae* (187)	NA	0.015	≤0.004–1.0	NA	2.0	0.12–4.0
	Moraxella catarrhalis (43)	0.015	0.03	0.004–0.5	0.03	0.03	0.03–0.5

All MICs are presented in μg/mL. The number mentioned in parentheses after each bacterium denotes no. of strains tested. [a]Includes *Pseudomonas cepacia* (5), *Pseudomonas fluorescens* (6), *Pseudomonas putida* (4), *Pseudomonas stutzeri* (5). [b]Includes *Salmonella enteritidis* (10), *Salmonella* typhi (5). [c]Includes *Shigella dysenteriae* (5), *Shigella flexneri* (5), *Shigella boydii* (5), *Shigella sonnei* (5). [d]Includes *Citrobacter freundii* (6), *Citrobacter diversus* (4). Co-amoxiclav: Amoxicillin-clavulanic acid combination, MIC: Minimum inhibitory concentration, NA: Not available

Against *Pseudomonas* species, faropenem had the lowest reported MIC_{90} (0.5 μg/mL)[14,23,24,33,35] compared to co-amoxiclav (16 μg/mL)[14,23,24,33,35] and cefpodoxime (>32 μg/mL).[14,23,33] The maximum reported values for the MIC_{90} of faropenem,[14,23,24,33,35] co-amoxiclav,[14,23,24,33,35] and cefpodoxime[14,23,33] were similar (>128 μg/mL).

Further, faropenem showed good activity against *Citrobacter* species, with the lowest MIC_{90} of 0.5 μg/mL to the highest of 8 μg/mL[14,15,23,24,35] and against *Bacteroides* species, from 0.5 μg/mL to 4 μg/mL,[12,14,23,28,34] compared to co-amoxiclav and cefpodoxime. The reported MIC_{90} of co-amoxiclav against *Citrobacter* species ranged from 2 μg/mL to >64 μg/mL[14,15,23,24,35] and against *Bacteroides* species from 2 μg/mL to 8 μg/mL,[12,14,23,28,34] whereas the MIC_{90} of cefpodoxime against *Citrobacter* species ranged from >32 μg/mL to >128 μg/mL[14,15,23] and against *Bacteroides* species from >32 μg/mL to >128 μg/mL.[14,23,34]

Faropenem activity against resistant species

The MIC_{90} of faropenem against penicillin-susceptible *Streptococcus* species ranged from 0.008 to 0.12 μg/mL[10,11,15,23,29,31,33,35] and was lower than co-amoxiclav (≤0.03–0.5 μg/mL),[10,15,23,29,33,35] cefpodoxime (0.03–0.5 μg/mL),[15,23,33] azithromycin (0.06–>128 μg/mL),[10,11] and levofloxacin (1 μg/mL).[10,11,29,31] Against penicillin-intermediate resistant or resistant strains of *S. pneumoniae*, the lowest reported MIC_{90} (0.25 μg/mL) was similar for faropenem[10,11,15,23,29,31,33,35] and cefpodoxime,[15,23,33] whereas the highest reported MIC_{90} (8 μg/mL) for faropenem[10,11,15,23,29,31,33,35] was similar to co-amoxiclav;[10,15,23,29,33,35] lower than cefpodoxime (16 μg/mL)[15,23,33] and azithromycin (>128 μg/mL);[10,11] and higher than levofloxacin (1 μg/mL) [Supplementary Table 2].[10,11,29,31]

The MIC_{90} of faropenem ranged from 0.25 to 4 μg/mL against β-lactamase negative strains of *H. influenzae*,[10,15,24,26,29,32,33,35] whereas that of co-amoxiclav ranged from 0.5 to 8 μg/mL).[10,15,24,26,29,32,33,35] The MIC_{90} of cefpodoxime was 0.12 μg/mL;[15,26,32,33] levofloxacin, 0.015 μg/mL;[10,29] and azithromycin, 2 μg/mL;[10,26] all were lower compared to faropenem. The reported MIC_{90} of faropenem against β-lactamase positive strains of *H. influenzae* ranged from 0.25 to 64 μg/mL,[10,15,24,26,29,32,33,35] that was broader than that of all comparators: co-amoxiclav (1–2 μg/mL);[10,15,24,26,29,32,33,35] cefpodoxime (0.12–0.25 μg/mL);[15,26,32,33] levofloxacin (0.015 μg/mL);[10,29] and azithromycin (2 μg/mL).[10,26] The MIC_{90} of faropenem ranged from 0.12 to 0.5 μg/mL against β-lactamase–negative and from 0.25 to 1 μg/mL against β-lactamase–positive strains of *M. catarrhalis*;[26,29,35] for co-amoxiclav, the MIC_{90} ranges were 0.03–0.5 μg/mL and 0.25–0.5 μg/mL, respectively [Supplementary Table 3].[26,29,35]

The MIC_{90} of faropenem ranged from 0.1 to 0.25 μg/mL against methicillin- or oxacillin-sensitive *S. aureus*,[14,15,23,24,33,35] which was lower than the MIC_{90} of co-amoxiclav (0.5–4 μg/mL)[14,15,23,24,33,35] and cefpodoxime (4–16 μg/mL).[14,15,23,33] However, against methicillin- or oxacillin-resistant *S. aureus*, the MIC_{90} of faropenem and comparators was similar: faropenem, 2–>128 μg/mL;[14,15,23,24,33,35] co-amoxiclav, 8–64 μg/mL;[14,15,23,24,33,35] and cefpodoxime, >32–>128 μg/mL [Supplementary Table 4].[14,15,23,33]

DISCUSSION

This comprehensive systematic review of 21 *in vitro* studies and two clinical comparative studies demonstrates the antimicrobial activity and resistance pattern of faropenem compared to other antibiotics against a variety of bacterial isolates. Two clinical comparative studies of faropenem versus other antibiotics reported a higher bacteriological success rate with faropenem than cefuroxime in treating respiratory infection (acute bacterial maxillary sinusitis) in adults,[18] and the 7-day and 10-day twice-daily treatment regimen of faropenem (300 mg) was non-inferior to the standard 10-day twice-daily cefuroxime (250 mg) regimen in terms of clinical cure rates and drug-related AEs.[17] Furthermore, *in vitro* studies identified in this review have demonstrated the good activity of faropenem, in terms of MIC, compared to co-amoxiclav, cefpodoxime, levofloxacin, and azithromycin against a wide bacterial spectrum. The findings of this review suggest the potential of faropenem against Gram-positive and Gram-negative aerobes and anaerobes, especially community pathogens causing respiratory tract infections. Bacterial strains producing β-lactamase and other strains resistant to penicillin, methicillin, and oxacillin were also found to be susceptible to faropenem.

A prospective, multinational, multicenter, double-blind, randomized, comparative study by Siegert *et al.*, included 561 adult patients with acute bacterial maxillary sinusitis, with the predominant causative organisms *S. pneumoniae* (47.1%), *H. influenzae* (30.1%), *S. aureus* (14.7%), and *M. catarrhalis* (8.8%). The study demonstrated a higher bacteriological success rate after 7-10 days post-treatment with twice-daily faropenem 300 mg (91.5%) than cefuroxime axetil 250 mg (90.8%), with clinical cure rates of 89% with faropenem and 88.4% with cefuroxime. Drug-related AEs were found to be similar between faropenem (9.5%) and cefuroxime (10.3%).[18] Another prospective, multicenter, double-blind, randomized, phase III study by UpChurch *et al*., including 1106 patients with acute bacterial sinusitis, compared two regimens of faropenem 300 mg twice daily for 7 days and 10 days, with one of cefuroxime 250 mg twice daily for 10 days. This study reported the efficacy as clinical cure rates of faropenem (80.3% for 7 days and 81.8% for 10 days) versus cefuroxime axetil (74.5%), which suggests that both faropenem regimens were non-inferior to the standard 10-day cefuroxime regimen in terms of efficacy and safety.[17] Cefuroxime axetil has low oral bioavailability (about 36–52%), which may affect the clinical efficacy despite its low MIC against the bacterial strains causing the infection,[36,37] whereas faropenem demonstrates high oral bioavailability (70–80%),[19] which could be responsible for higher bacterial and clinical success rate. The study also showed that patients treated with cefuroxime axetil had liver function abnormality, which is a known effect of β-lactams, and the evidence of hepatic enzyme elevation by cefuroxime has been shown by previous evidence.[18,36] Further, there are limited comparative clinical studies of faropenem versus other antibiotics; hence, drawing conclusions on the therapeutic response of faropenem versus other antibiotics is difficult and could point to future avenues of research.

The MIC values serve as the basis for assessing the degree of susceptibility or resistance of pathogens to a specific antibiotic[38] and help to select the most appropriate treatment.[39] A study by Stone *et al.* demonstrated the

activity of faropenem against respiratory pathogens such as *S. pneumoniae* and *H. influenzae*, isolated from middle ear fluid, compared to other antimicrobial agents including co-amoxiclav, azithromycin, and levofloxacin. Faropenem also showed activity against *M. catarrhalis* and *Streptococcus pyogenes.*[10] Further, faropenem showed potent anti-gonococcal activity against *N. gonorrhoeae*, regardless of resistance phenotype.[13] Faropenem had a broad spectrum of antibacterial activity against lower respiratory tract pathogens such as *S. pneumoniae, H. influenzae*, and *M. catarrhalis*,[16,33] with *S. pneumoniae* being the most susceptible. Two *in vitro* studies showed activity of faropenem (MIC_{90} 0.25 and 1 μg/mL) against *S. pneumoniae* strains isolated from adults and children compared to quinolones and cephalosporins.[9,31] The activity of faropenem (MIC_{90} 0.5 and 1 μg/mL) was comparable to co-amoxiclav (MIC_{90} 0.25 and 0.5 μg/mL) against *H. influenzae* and *M. catarrhalis* isolated from the lower respiratory tract.[16] These findings suggest the potential of faropenem against a variety of community pathogens, suggesting its effectiveness in treating community-acquired infections, especially respiratory tract infections.

The irrational use of antibiotics significantly contributes to antimicrobial resistance, the emergence of multidrug-resistant bacteria, delayed antimicrobial response, and even therapeutic failures.[21,22] Faropenem possesses unique characteristics that make it resistant to hydrolysis by nearly all β-lactamases.[40] *In vitro* studies (n=12) identified in this review showed the activity of faropenem with other antimicrobial agents such as β–lactams, quinolones, and cephalosporins against penicillin-resistant, β-lactamase–positive, and amoxicillin- or oxacillin-resistant strains. Critchley *et al.* reported that faropenem is less active against penicillin-intermediate resistant and *S. pneumoniae*-resistant strains compared to susceptible strains.[29] However, it was demonstrated that the activity of faropenem is not compromised against β-lactamase–producing *H. influenzae* and *M. catarrhalis* strains.[10,29] Furthermore, the MIC_{90} of faropenem was 0.015 μg/mL for penicillin-susceptible isolates of *S. pneumoniae,* while it was 1 μg/mL for penicillin-resistant strains, which was generally comparable to that of levofloxacin.[10] Milatovic *et al.* showed that the MICs of faropenem against β-lactamase positive and negative *H. influenzae* and *M. catarrhalis* strains were generally similar. The activity of faropenem against *H. influenzae* was comparable to that of co-amoxiclav, and its activity against *M. catarrhalis was* two- to eight-fold higher than that of cefpodoxime.[33] Furthermore, faropenem was demonstrated to have activity against methicillin- or oxacillin-resistant *S. aureus.*[14,15,33] These findings suggest that faropenem has activity against β-lactamase–producing bacterial isolates as well as penicillin-, methicillin-, and cloxacillin-resistant strains; however, comparative inference with other antibiotics is difficult due to variation in isolated strains, and methodology in studies.

This systematic review has several strengths. It is a comprehensive review of *in vitro* and comparative clinical trials demonstrating the activity of faropenem against a wide range of pathogens, including resistant strains. Furthermore, it compares the activity of faropenem with antibiotics of different classes, highlighting its clinical and microbiological efficacy. Several limitation*s* should also be noted. This review is limited to presenting the full-text articles published in the English language identified, through PubMed and Google Scholar, based on set PICOS inclusion criteria. We intended to understand how the therapeutic response obtained in comparative clinical trials of faropenem correlated with the *in vitro* activity of faropenem versus other antibiotics. However, a paucity of clinical comparative trials and the variation in *in vitro* studies of faropenem versus other antibiotics led to difficulties in making any definite inferences. In addition, we could not present the details of the risk of bias assessment for the clinical studies that were included since only a few studies met the inclusion criteria. There are limited *in vitro* studies reporting the activity of faropenem against azithromycin and levofloxacin.

CONCLUSIONS

This systematic review consolidates *in vitro* as well as clinical evidence of faropenem against a wide microbial spectrum. In *in vitro* studies, faropenem showed better antimicrobial activity compared to other antimicrobial agents such as co-amoxiclav, cefpodoxime, levofloxacin, and azithromycin against a wide spectrum of bacterial pathogens, including Gram-positive and Gram-negative aerobes and anaerobes, β-lactamase producers, and various resistant strains. Clinical studies demonstrated comparable clinical cure rates of faropenem compared to cefuroxime axetil in patients with acute bacterial sinusitis within 7 days of treatment. Furthermore, the findings underscore the potential for faropenem in treating community-acquired infections, particularly respiratory tract infections. However, more comparative clinical research is required for a definitive understanding of the antimicrobial activity and resistance pattern of faropenem compared to other antibiotics.

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