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Clinical outcomes of rifampicin combination therapy in implant-associated infections due to staphylococci and streptococci: A systematic review and meta-analysis

Erlangga Yusuf[a], Wichor Bramer[b], Adam A. Anas[a,c,*]

[a] Department of Medical Microbiology and Infectious Diseases, Erasmus University Medical Center, Rotterdam, the Netherlands
[b] Medical Library, Erasmus University Medical Center, Rotterdam, the Netherlands
[c] Department of Internal Medicine, Section of Infectious Diseases, Erasmus University Medical Center, Rotterdam, the Netherlands

A R T I C L E   I N F O

A B S T R A C T

Objectives: Adjunctive rifampicin for implant-associated infections is controversial. This study investigated the clinical outcomes of rifampicin combination therapy compared with monotherapy in treating prosthetic joint infection (PJI) or prosthetic valve endocarditis (PVE) due to staphylococci and streptococci.
Methods: A systematic search was performed from inception to 13 June 2022 in Embase, MEDLINE, Cochrane and Web of Science to investigate the clinical outcomes of rifampicin combination therapy compared with monotherapy in treating staphylococcal and streptococcal PJI or PVE. Randomised controlled trials (RCTs) and observational studies were included in the systematic review and meta-analysis.
Results: Fourteen studies were included. A moderate quality of evidence was found in favour of rifampicin in patients with staphylococcal PJI who underwent a debridement, antibiotics and implant retention (DAIR) procedure [odds ratio = 2.49, 95% confidence interval (CI) 1.93–3.23]. Including the two RCTs only, adding rifampicin to the antibiotic regimen after DAIR was also in favour of rifampicin, but this was not statistically significant (risk ratio = 1.27, 95% CI 0.79–2.04; $n = 126$). Pooling data for patients with staphylococcal PJI who underwent a two-stage procedure showed that adding rifampicin was not associated with therapeutic success. Limited evidence was found for the use of rifampicin for PVE caused by staphylococci.
Conclusions: Adding rifampicin in the treatment of staphylococcal PJI treated by DAIR clearly increased the likelihood for therapeutic success. The clinical benefit of adjunctive rifampicin in the treatment of other staphylococci and streptococci implant-associated infections is still unclear.

1. Introduction

Prosthetic joint infection (PJI) and prosthetic valve endocarditis (PVE) are significant complications of prosthetic joint and heart valve surgeries. The cumulative risk for developing these infections following arthroplasty and cardiac valve surgery at 10 years has been estimated at 1.4% and 4.5%, respectively [1,2]. *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS) and viridans group streptococci (VGS) are prevalent causes of PJI and PVE [3,4]. Infections of foreign body materials caused by these micro-organisms are characterised by biofilm formation, which requires adjustment of antibiotic treatment.

Rifampicin is a broad-spectrum bactericidal antibiotic that achieves high intracellular levels and is considered a biofilm-active antibiotic [5,6]. Due to the rapid development of resistance, rifampicin cannot be used as monotherapy. Combination antimicrobial therapy with rifampicin has been included in several guidelines on staphylococcal PJI [7] and staphylococcal PVE [8]. Concomitant use of rifampicin has been assessed in several systematic reviews previously, but almost all of these reviews have been published more than 10 years ago or did not focus on foreign body infections [9,10]. Conducting a systematic review on this topic may pose a challenge since the main analysis in potentially relevant studies does not directly compare rifampicin combination therapy with monotherapy, requiring more in-depth analysis of the results.

The aim of this systematic review and meta-analysis was to investigate the outcomes of rifampicin combination therapy compared with monotherapy to treat foreign body material infection due to *S. aureus*, CoNS and VGS.

* Corresponding author. Mailing address: Department of Medical Microbiology and Infectious Diseases, Department of Internal Medicine, Erasmus University Medical Center, Dr. Molewaterplein 40, 3015 GD Rotterdam, the Netherlands.
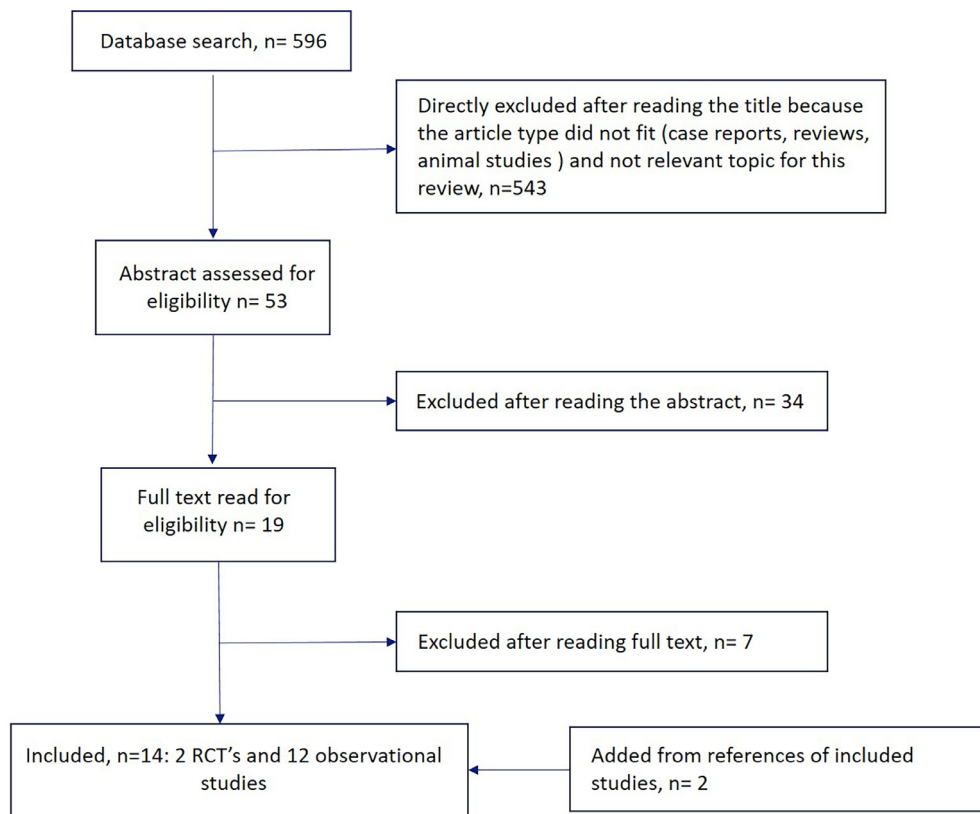*E-mail address:* a.anas@erasmusmc.nl (A.A. Anas).

Fig. 1. Flow chart of study selection.

2. Materials and methods

2.1. Literature search

This systematic review and meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [11]. Together with a medical librarian (W.B.), two reviewers (E.Y., a clinical microbiologist and clinical epidemiologist with 10 years' experience; and A.A.A., an internal medicine–infectiologist with 8 years' experience) conducted a comprehensive search of the medical databases Embase, MEDLINE ALL via Ovid, Web of Science Core Collection and Cochrane Central Register of Controlled Trials from inception to 13 June 2022 for studies with data regarding rifampicin use as combination therapy in foreign body material infection due to *S. aureus*, CoNS and VGS. The search terms can be found in Supplementary Table S1. Only studies in English were retrieved. Additional articles were searched in the reference lists of identified articles and in Google Scholar. No language restriction was applied for these additional articles.

2.2. Eligibility criteria and quality assessment

Two reviewers (E.Y. and A.A.A.) independently read the abstracts of all retrieved studies for obvious exclusions and subsequently read the full-text of remaining studies.

Randomised controlled trials (RCTs) and observational studies that fulfilled the following criteria were included: (i) studied population consisted of patients aged >16 years with foreign body-associated infection (i.e. PJI and PVE) due to *S. aureus*, CoNS or streptococci; (ii) study contained data allowing creation of a contingency table that compared the outcomes of patients receiving monotherapy and combination therapy with rifampicin; and (iii)

the clinical outcome was clearly mentioned. Excluded were animal or in vitro studies, studies on other uses of rifampicin (e.g. prophylaxis, rifampicin-impregnated devices), studies that did not contain original research (reviews, abstracts, letters to the editor, case reports and case series) and studies that included <25 patients. Differences between the two reviewers were solved by re-reading the articles and by consensus.

The quality of the included papers was assessed independently by E.Y. and A.A.A. using the Jadad scale (possible scores 0–5) [12] for RCTs and using the Newcastle–Ottawa scale (possible scores 0 to 9) [13] for observational studies. Any difference was solved by re-reading the specific item on the manuscript and by consensus.

2.3. Data extraction

The following data were extracted: (i) study characteristics; (ii) definition of infections and involved micro-organism; (iii) surgical treatment (in case of PJI); (iv) demographic data of both groups (combination and monotherapy) as well as the dose and duration of rifampicin and other antibiotics; and (v) clinical outcomes. Both reviewers extracted the data independently and differences were resolved by consensus.

2.4. Statistical analysis

Meta-analysis software Review Manager (RevMan) (Computer program) version 5.4 (The Cochrane Collaboration, 2020) was used to perform data analysis. Using this software, the odds ratio (OR) and corresponding 95% confidence interval (CI) was calculated using data obtained from observational studies and RCTs. Since ORs may overestimate the risk ratio (RR) in RCTs [11], the RR was also calculated to check whether the OR as calculated for the RCT did

Table 1

Data extracted from studies investigating prosthetic joint infection (PJI) and spinal implant infection due to staphylococci and streptococci.

Reference	Study characteristic and micro-organism involved	Definition of infection[a]	Type of surgery	Rifampicin group Demographic [*n*, % male, mean or median age (SD or range) years] Type of foreign body Antibiotics (dose, combination and duration)	Comparator Demographic [*n*, % male, mean or median age (SD or range) years] Type of foreign body Antibiotics (dose, and duration)	Outcome definition and outcome in rifampicin combination therapy vs. monotherapy, effect size (when available)
Staphylococcus **Prosthetic joint** Randomised control trials with combination therapy vs. monotherapy as main research question						
Karlsen, [21] [b]	Multicentre, Norway, 2006–2012 *S. aureus* (MSSA and MRSA) or CoNS	- Pain, redness or wound discharge - 2 of 8 tissues grew the same micro-organism - Symptoms <30 days after prosthetic surgery (acute) or <3 weeks (haematogenous)	DAIR	*n* = 33 allocated (23 included) 65%, 70 (37–92) 20 hip, 3 knee Rifampicin (300 mg td po, 6 weeks) + Cloxacillin (1000 mg qid po, 4 weeks) after: flucloxacillin (1 g qid iv, 2 weeks), *n* = 16 or vancomycin (1 g bd iv, 6 weeks), *n* = 7	*n* = 33 allocated (25 included) 68%, 66 (39–84) 19 hip, 6 knee Cloxacillin (1000 mg qid po, 4 weeks) after flucloxacillin (1 g qid iv, 2 weeks), *n* = 19 or vancomycin (1 g bd iv, 6 weeks), *n* = 6	Cure: lack of clinical signs and symptoms of PJI, CRP < 10 mg/dL, ESR prior to index operation, no radiological signs of loosening at 2-year follow-up 17/23 (74%) vs. 18/25 (72%) OR = 1.1 (95% CI 0.3–4.0), RR = 1.0 (95% CI 0.7–1.4)
Zimmerli [20] [b]	Single centre, Switzerland, 1992–1997 *S. aureus* (MSSA and MRSA) or CoNS	- Diagnosis of orthopaedic device-related infection (not further specified) and stable implant - Symptoms <1 year at randomisation	DAIR	*n* = 18 (12 full follow-up) 50%, 66 (15) 5 hip, 3 knee, 10 OSM Rifampicin (450 mg bd po) + ciprofloxacin (750 mg bd po) after: flucloxacillin (2 g qid iv, 2 weeks), *n* = 13 or vancomycin (1 g bd iv, 2 weeks), *n* = 5	*n* = 15 (12 full follow-up) 33%, 67 (15) 3 hip, 4 knee, 8 OSM Ciprofloxacin (750 mg bd po) after flucloxacillin (2 g qd iv), *n* = 13, or vancomycin (1 g bd iv), *n* = 2	Cure: lack of clinical signs, CRP < 5 mg/dL, absence of loosening at 2-year follow-up. Follow-up time varied between groups 12/12 (100%) vs. 7/12 (58%) OR [c], RR = 1.7 (95% CI 1.1–2.8)
Observational study, rifampicin is named in the title						
Becker, [28]	Multicentre, France, 2011–2016	IDSA guideline	DAIR	*n* = 58 No demographic information can be derived for rifampicin group only Rifampicin (median 15.3 mg/kg, median duration 75 days) + fluoroquinolone (*n* = 36), after broad-spectrum β-lactam agent and second antimicrobial agent with activity against methicillin-resistant staphylococci	*n* = 21 No demographic information can be derived for monotherapy group only	Failure: prosthesis removal, additional debridement, additional antibiotic, persistent signs of infection and microbiology after 2 years, death due to infection Success [d]: 41/58 (71%) vs. 13/21 (62%) OR = 1.5 (95% CI 0.5–4.2)
Beldman, [18] [b]	Multicentre, Spain, Portugal and Netherlands *S. aureus* (no information on MSSA and MRSA)	International Consensus Meeting criteria	DAIR (including modular component exchange)	*n* = 407 43.5%, 23.4% older than 80 years Knee and hip (unknown number) Rifampicin (450 mg bd po or 600 mg od) with levofloxacin (47.1%), ciprofloxacin (29.3%) and moxifloxacin (20.4%), after 2 weeks of iv antibiotic	*n* = 262 43.9%, 18.3% older than 80 years Knee and hip (unknown number) No information on comparison antibiotic	Failure: need for further surgery related to infection, PJI-related death, need for suppressive long therapy ≥1 year after DAIR 131/407 vs. 142/262 No failure [d]: 276/407 (68%) vs. 120/262 (46%) OR = 2.5 (95% CI 1.8–3.4)

(continued on next page)

Table 1 (*continued*)

Reference	Study characteristic and micro-organism involved	Definition of infection[a]	Type of surgery	Rifampicin group Demographic [n, % male, mean or median age (SD or range) years] Type of foreign body Antibiotics (dose, combination and duration)	Comparator Demographic [n, % male, mean or median age (SD or range) years] Type of foreign body Antibiotics (dose, and duration)	Outcome definition and outcome in rifampicin combination therapy vs. monotherapy, effect size (when available)
El Helou, [29]	Single centre, USA, 2000–2006	- >2 cultures from joint aspirates or intra-operative tissue or - 1 specimen with purulence + pu- rulence or infection histopathological tissue, or sinus tract	DAIR	n = 45 (retrospective and prospective cohorts) 53%, 68 (18–95) Prospective cohort: Rifampicin (450 mg bd) + levofloxacin (750 mg od po) median length 148 days and 112 days, respectively Retrospective: Rifampicin po (+ other po antibiotic) after cefazolin or vancomycin iv 39 *S. aureus*, 6 CoNS	n = 56 48%, 75 (26–94) 35 hip, 21 knee Any po antibiotic after cefazolin or vancomycin iv 30 *S. aureus*, 26 CoNS	Treatment failure: recurrence, death related to PJI or clinical failure during 1-year follow-up No failure [d]: 34/45 (76%) vs. 35/56 (63%) OR = 1.9 (95% CI 0.8–4.4)
Observational study, rifampicin is not named in the title but data on rifampicin could be derived						
Ascione, [19]	Single centre, Italy, 2009–2013	>3 of: - clinical signs and symptoms with presence of a sinus tract - 2 positive identical intra-operative culture or joint aspirates, or removed implant sonication - acute inflammation on histopathology - ≥1700/mm³ (knee) or ≥4000/mm³ (hip) or >65% neutrophils in synovial fluid - elevated ESR or CRP Or MSIS criteria	Two-stage	n = 44 No demographic information can be derived for rifampicin group only 10–12 weeks, no further information about dose	n = 41 No demographic information can be derived for monotherapy group only No further information about dose and duration of other antibiotics	Cure assessed during 96-week follow-up period. Disappearance of all clinical and radiological evidence of PJI and normalisation of CRP during 96-week follow-up after discontinuation of antibiotic treatment Two-stage: 41/44 (93%) vs. 39/41 (95%)
Holmberg, [27] [b]	Register study, Sweden, 2000–2008 *S. aureus* (MSSA and MRSA) n = 53, or CoNS n = 33 (studies included other micro-organisms, but rifampicin only given for PJI due to staphylococci)	- Sinus tract, pathogen or pus - >1 tissues or synovial fluid with the same micro-organism	DAIR	n = 69 No demographic information can be derived for rifampicin group only All knee No further information about dose and duration of rifampicin and combination antibiotic	n = 17 No demographic information can be derived for monotherapy group only All knee No further information about dose and duration of other antibiotics	Healed. Failure to heal defined as: died, revision of prosthetic, suppression therapy, chronic infection. Follow-up was not standardised. Information on date of death was gathered from the Swedish Cause of Death Register 56/69 (81%) vs. 8/17 (47%) OR = 4.9 (95% CI 1.6–15.0)

Table 1 (*continued*)

Reference	Study characteristic and micro-organism involved	Definition of infection[a]	Type of surgery	Rifampicin group Demographic [*n*, % male, mean or median age (SD or range) years] Type of foreign body Antibiotics (dose, combination and duration)	Comparator Demographic [*n*, % male, mean or median age (SD or range) years] Type of foreign body Antibiotics (dose, and duration)	Outcome definition and outcome in rifampicin combination therapy vs. monotherapy, effect size (when available)
Muñoz-Gallego, [26] [b]	Multicentre, Spain, 2016–2017 *S. aureus* (MSSA and MRSA)	- Compatible clinical presentation - ≥1 surgical, joint aspirate or blood culture with the same micro-organism - Symptoms <3 months after prosthetic surgery, or >3 months and haematogenous	DAIR, prosthesis removal (but no analysis regarding rifampicin)	*n* = 37 No demographic information can be derived for rifampicin group only Knee and hip (unknown number) Rifampicin (600 mg od) + other antibiotics, i.e. levofloxacin, oxacillin, daptomycin (no further information about dose and duration)	*n* = 18 No demographic information can be derived for monotherapy group only Knee and hip (unknown number) Levofloxacin, oxacillin, daptomycin (no further information about dose and duration)	Cure: no failure (death from any cause within 90 days of surgery, persisting or relapsing signs of infection and need for salvage therapy) Follow-up until death, failure or loss to follow-up, at least 1 year DAIR: 25/37 (68%) vs. 4/18 (22%) OR = 7.3 (95% CI 2.0–26.7)
Senneville, [25] [b]	Multicentre, France, 2000–2006 *S. aureus* (MSSA and MRSA)	- No information on clinical signs and symptoms - ≥1 intra-operative specimen with the same micro-organism	DAIR, prosthesis removal	*n* = 63 68.8 (13.9), no further demographic information can be derived Knee and hip (unknown number) Rifampicin (20 mg/kg po, 3–6 months) + fluoroquinolone, *n* = 39 or other antibiotics, *n* = 29 (no further information about dose and duration, except mention of 10 patients with MRSA)	*n* = 18# 64.5 (14.4) years, no further demographic information can be derived Knee and hip (unknown number) Linezolid, *n* = 11, others, *n* = 19 (no further information about dose and duration, except mention of 7 patients with MRSA)	Remission: absence of local or systemic sign and no need for re-surgery or antibiotic. Follow-up duration at minimum 2 years DAIR 25/31 (81%) vs. 7/10 (70%) OR = 2.8 (95% CI 0.6–13.1) One-stage: 11/11 (100%) vs. 3/3 (100%) OR na [c] Two-stage: 18/21 (86%) vs. 4/5 (80%) OR = 1.5 (95% CI 0.1–18.4) Resection arthroplasty: 1/1 (100%) vs. 3/8 (38%) Total: 54/63 (86%) vs. 13/18 (72.2%) OR = 2.3 (95% CI 0.7–8.1)
Vilchez, [24]	Single centre, Spain, 2000–2007 *S. aureus* (MSSA and MRSA)	Early PJI: presence of local inflammation (<15 days of symptoms) <2 months after arthroplasty	DAIR	*n* = 43 No demographic information can be derived for rifampicin group only Rifampicin (600 mg od, 90 days) + levofloxacin (500 mg od, po), *n* = 33 or clindamycin (300 mg td po), *n* = 4, linezolid (600 mg bd), *n* = 3, amoxiclav (875/125 mg q8h), *n* = 2 and co-trimoxazole 800 mg q12h), *n* = 1 after ceftazidime and vancomycin or cloxacillin for 10 days	*n* = 10 No demographic information can be derived for monotherapy group only	Remission: no symptom of infection, no prosthesis removal, CRP < 1 mg/dL No failure [d]: 37/43 (86%) vs. 3/4 (75%) OR = 14.4 (95% CI 2.9–71.6)

Table 1 (*continued*)

Reference	Study characteristic and micro-organism involved	Definition of infection[a]	Type of surgery	Rifampicin group Demographic [*n*, % male, mean or median age (SD or range) years] Type of foreign body Antibiotics (dose, combination and duration)	Comparator Demographic [*n*, % male, mean or median age (SD or range) years] Type of foreign body Antibiotics (dose, and duration)	Outcome definition and outcome in rifampicin combination therapy vs. monotherapy, effect size (when available)
Spinal implant						
Observational study, rifampicin is not named in the title but data on rifampicin could be derived						
Cho, [23] [b]	Multicentre, South Korea, 2006–2014 *S. aureus* (MSSA and MRSA)	- signs or symptoms of spinal infection (fever, increasing pain, wound drainage and wound erythema) <30 days (early) and >30 days after surgery (late)	DAIR, prosthesis removal	*n* = 30 No demographic information can be derived for rifampicin group only Rifampicin (600 mg od, no information about duration) + fluoro-quinolone or cefuroxime or trimetho-prim/sulfamethoxazole after cefazolin or nafcillin (*n* = 3, MSSA), or vancomycin or teicoplanin (*n* = 27, MRSA)	*n* = 72 No demographic information can be derived for monotherapy group only Fluoroquinolone cefuroxime or trimetho-prim/sulfamethoxazole after Cefazolin or nafcillin (*n* = 23 MSSA), or vancomycin and teicoplanin (*n* = 49 MRSA)	Treatment failure: infection-related death, primary failure, recurrence or a new infection. Follow-up was not standardised DAIR: No failure [d]: 22/25 (88%) vs. 31/56 (55%) OR = 5.9 (95% CI 1.6–22.1) Prosthesis removal: No failure [d]: 5/5 (100%) vs. 12/14 (86%) OR na [c] Total: No failure [d]: 27/30 (90%) vs. 43/70 (61%) OR = 5.7 (95% CI 1.6–20.5)
Streptococcus **Prosthetic joint**						
Fiaux, [16] [b]	Multicentre, France, 2001–2009	IDSA guideline definition ≥2 surgical, joint aspirates or blood cultures with same micro-organism	DAIR and prosthesis removal	*n* = 52 Rifampicin 10 mg/kg bd + levofloxacin (*n* = 28) or other antibiotics (*n* = 24) after β-lactam agent	*n* = 43 Amoxicillin, ceftriaxone, teicoplanin	Remission: absence of local or systemic signs, absence of new surgery or antibiotic therapy. No specific follow-up mentioned, median was 895 days (IQR 395–1649) DAIR: 23/30 (76.7%) vs. 9/25 (36.0%) OR = 5.8 (95% CI 1.8–19.3) One-stage: 7/8 (87.5%) vs. 3/5 (60.0%) OR = 4.7 (95% CI 0.3–73.4) Two-stage: 10/10 (100%) vs. 8/9 (88.9%) OR [c] Resection: 4/4 (100%) vs. 3/4 (75.0%) OR [c] Total: 44/52 (84.6%) vs. 23/43 (53.5%) OR = 4.8 (95% CI 1.8–12.5)

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Table 1 (*continued*)

Reference	Study characteristic and micro-organism involved	Definition of infection[a]	Type of surgery	Rifampicin group Demographic [n, % male, mean or median age (SD or range) years] Type of foreign body Antibiotics (dose, combination and duration)	Comparator Demographic [n, % male, mean or median age (SD or range) years] Type of foreign body Antibiotics (dose, and duration)	Outcome definition and outcome in rifampicin combination therapy vs. monotherapy, effect size (when available)
Mahieu, 2019 [17] [b]	Multicentre, France, 2010–2012	IDSA guideline definition	DAIR (n = 70), prosthesis removal	n = 31 No demographic information can be derived for rifampicin group only No further information about dose and duration of rifampicin and combination antibiotic	n = 39 No demographic information can be derived for monotherapy group only No further information about dose and duration of other antibiotics	Remission: disappearance of local sings of infection, improvement of functional activity, normalisation of CRP (relapse: new sample with same *Streptococcus* sp.). At least 2 years of follow-up DAIR and prosthesis removal: 23/31 (74%) vs. 28/39 (72%) OR = 1.1 (95% CI 0.4–3.3)

bd, twice daily; CI, confidence interval; CoNS, coagulase-negative staphylococci; CRP, C-reactive protein; DAIR, debridement, antibiotics and implant retention; ESR, erythrocyte sedimentation rate; IDSA, Infectious Diseases Society of America; MSIS, Musculoskeletal Infection Society; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; na, not applicable; od, once daily; OR, odds ratio; OSM, osteosynthesis material; po, orally; q8h, every 8 h; q12, every 12 h; qid, four times a day; RR, risk ratio; td, three times a day.

[a] Standardised criteria. IDSA, International Consensus Meeting or MSIS are mentioned when explicitly mentioned by the authors. Otherwise, criteria were described.
[b] Papers identified by both reviewers.
[c] Cannot be calculated as there is a cell with 0 value.
[d] For analysis, positive outcomes were used (i.e. remission instead of failure), unlike in the original calculation in the papers.

not deviate from the RR. RevMan software was also used to calculate the I^2 statistic to asses any possible heterogeneity among studies [14].

Cure or remission as mentioned by the authors was used as the study outcome of interest, and for the purpose of this paper this outcome will be referred to as 'therapeutic success'. When failure was mentioned by the authors, the complementary number was calculated as therapeutic success. The pooled effect sizes were pooled and stratified by type of surgery [debridement, antibiotics and implant retention (DAIR) or removal of prosthesis] in the case of PJIs and by micro-organisms (*S. aureus* and *Streptococcus*).

To determine the level of evidence, five levels of evidence were used (strong, moderate, limited, conflicting and no evidence) as used by the Cochrane Collaboration Back Review Group [15].

Possible publication bias was assessed by generating a funnel plot, where the OR on the horizontal axis was plotted against the standard error of the OR using RevMan software.

3. Results

3.1. Study selection and characteristics of included studies

The flow of studies in the systematic review is presented in Fig. 1. A total of 14 papers were included, of which 12 [16–27] fulfilled the inclusion and exclusion criteria and an additional 2 [28,29] were identified through reference searching of the included studies (Tables 1 and 2). Of these 14 included studies, 2 were RCTs [20,21] and the remainder were observational studies. Of the 14 studies, 12 included patients infected with staphylococci (10 on PJI [18–21,24–29], 1 on spinal implant infection [23] and 1 on patients with PVE due to *S. aureus* [22]) and 2 studies included patients with streptococcal PJI [16,17].

In only 6 of the 14 publications was the main research question the comparison monotherapy versus combination therapy with rifampicin.

Patients included in nine of the ten studies on staphylococcal PJI underwent DAIR [18,20,21,24–29]. Two other studies included patients with staphylococcal PJI who underwent two-stage revision only [19] or a combination of surgical procedures (DAIR, one-stage, two-stage and resection arthroplasty) [25].

The quality assessment of included studies can be found in Supplementary Table S2. One of the two included RCTs had a considerable risk of bias [21]. None of the observational studies were deemed of high quality (score >7). The observational studies often did not mention the frequency of follow-up or who performed the clinical follow-up.

3.2. Effect size

Data for 1150 patients with staphylococcal PJI who underwent DAIR were pooled. In this population, rifampicin combination therapy was associated with a 2.5 × higher odds of therapeutic success (95% CI 1.93–3.23; $P < 0.05$) in comparison with monotherapy (Table 3; Fig. 2). Including the two RCTs only, adding rifampicin to the antibiotic regimen after DAIR was more likely to lead to therapeutic success in comparison with monotherapy, but effect sizes were not statistically significant (OR = 3.2 (95% CI 0.2–50.7); RR = 1.27 (95% CI 0.79–2.04); n = 126). The I^2 statistic was low (8%) indicating no heterogeneity, and hence nothing to be explored in a subgroup or moderator analysis [14].

Pooling data for patients with staphylococcal PJI who underwent a two-stage procedure showed that adding rifampicin was not associated with therapeutic success. However, therapeutic success in both groups was already high (>90%). Only one paper was

Table 2

Data extracted from studies investigating *Staphylococcus aureus* prosthetic valve endocarditis (PVE).

Reference	Study characteristics and micro-organism involved	Definition of infection	Type of surgery Rifampicin group Demographics: [n, % female, mean or median age (SD or range) years] Involved valves (%) Antibiotics (dose and combination)	Comparator group (n, antibiotic dose, and duration)	Outcome definition and outcome in rifampicin combination therapy vs. monotherapy, effect size (when available)
Observational study, efficacy of rifampicin combination therapy is main aim					
Le Bot, [22] [a]	Multicentre, France, 2000–2018 *Staphyloccosu aureus* (MSSA and MRSA) and CoNS	Modified Duke criteria Early: <2 months after implantation	n = 101 73.3%, 69 (12.8) 77.2% aortic, 13.9% mitral, 1.7% tricuspid, 1.0% pulmonary, 5.9% multiple Rifampicin (median dose 1200 mg/day, median duration 33 days)	n = 79 73.4%, 72 (11.6) 75.9% aortic, 13.9% mitral, 1.3% tricuspid, 8.9% multiple Cloxacillin or oxacillin + Gentamicin for MSSA or Vancomycin or dapto-mycin + gentam-icin for MRSA	Death due to any cause during 1-year follow-up: Survival [b] 63/101 (62.4%) vs. 54/79 (68.4%) OR = 0.8 (95% CI 0.4–1.4) Relapse (new diagnosis with same micro-organism) 95/101 (94.1%) vs. 72/79 (91.1%) OR = 1.5 (95% CI 0.5–4.8)

CI, confidence interval; CoNS, coagulase-negative staphylococci; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; OR, odds ratio; SD, standard deviation.

[a] Paper identified by both reviewers.

[b] For analysis, positive outcomes were used (i.e. survival instead of death, or no relapse instead of relapse), unlike in the original calculation in the papers).

Table 3

Effect size of adding rifampicin versus no rifampicin in various types of implant-associated infection.

Infection, surgical procedure	n	No. and type of studies	OR (95% CI)	P-value
PJI due to staphylococci, DAIR	1150	9 (2 RCTs, 7 observational)	2.49 (1.93–3.23)	<0.000
PJI due to staphylococci, removal	76	2 observational	0.89 (0.20–3.88)	0.88
Spinal implant infection due to staphylococci, debridement and removal	102	1 observational	5.40 (1.49–19.51)	0.01
PJI due to streptococci, DAIR and removal	283	2 observational	2.37 (0.58–9.74)	0.23
PVE due to staphylococci	180	1 observational	0.80 (0.40–1.41)	0.46

CI, confidence interval; DAIR, debridement, antibiotics and implant retention; OR, odds ratio; PJI, prosthetic joint infection; PVE prosthetic valve endocarditis; RCT, randomised controlled trial.
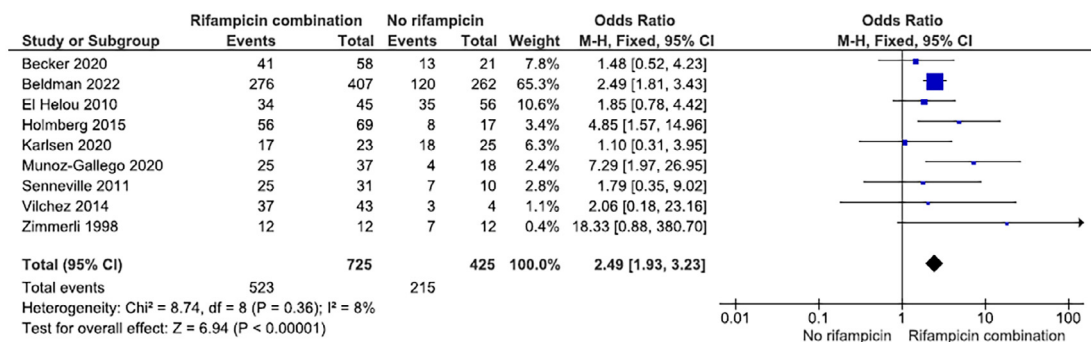

Fig. 2. Forest plot on the effect of adjunctive rifampicin versus no rifampicin in patients who underwent a debridement, antibiotics and implant retention (DAIR) procedure. CI, confidence interval.

found on the use of rifampicin combination therapy in patients with PVE caused by staphylococci. Addition of rifampicin to the antibiotic treatment of patients with streptococcal implant-associated infections was assessed in a limited number studies (Table 3).

3.3. Level of evidence

The level of evidence for adding rifampicin in patients with staphylococcal PJI who underwent DAIR was moderate (i.e. consistent findings among multiple low-quality RCTs and observational studies). The evidence for rifampicin treatment in patients with PJI caused by staphylococci and treated with a two-stage procedure is limited and based on only two studies. The level of evidence was limited (one low-quality observational study) for patients with *S. aureus* PJI who underwent removal and those with *S. aureus* spinal implant infection. For PJI due to streptococci, the level of evidence of adding rifampicin was conflicting. For PVE due *S. aureus*, the level of evidence was no evidence (no RCT or observational study showing the benefit).

3.4. Publication bias

Visual analysis of the funnel plot (Supplementary Figure S1) did not show a high risk of publication bias.

4. Discussion

To the best of our knowledge, this is the first meta-analysis conducted to evaluate the efficacy of rifampicin in implant-associated infections caused by staphylococci and streptococci, despite the fact that rifampicin has been used in combination therapy for nearly three decades [5]. The most important finding of this review is that adding rifampicin was associated with a higher likelihood for therapeutic success than monotherapy in patients with staphylococcal PJI who underwent DAIR (moderate level of evidence).

Implant-associated infections are characterised by biofilm formation [30]. Biofilm is composed of a matrix of extracellular polymeric substances that are produced by bacteria and in which a microbial community is embedded. Due to extracellular matrix formation and because biofilm-producing bacteria are generally in a dormant state, implant-associated infections may be difficult to treat. One of the few antibiotics that can penetrate biofilms and kill micro-organisms in the sessile phase of growth is rifampicin. It has broad-spectrum activity and results in antimicrobial activity by inhibiting DNA-dependent RNA polymerase [30]. In a tissue cage infection guinea pig model, combination therapy with rifampicin has been shown to eradicate biofilm in staphylococci [methicillin-resistant *S. aureus* (MRSA), methicillin-susceptible *S. aureus* (MSSA) and CoNS] [5,31–33]. Data on the effect of rifampicin on streptococci implant-associated infection in animal models are scarce. The limited animal data on streptococcal implant-associated infections are reflected in the limited number of clinical trials.

In this meta-analysis, we were able to pool data for more than 1000 patients with staphylococci PJI who underwent DAIR. Despite the fact that the data originated from studies of limited quality, this systematic review has enough power to conclude the discussion on the need for adding rifampicin in this type of patient [34]. Nonetheless, in this review we were not able to determine the best timing to start rifampicin following a DAIR procedure. In one of the original animal studies, rifampicin was shown to be able to prevent implant-associated infections caused by staphylococci, implying that it should be given early during the infection course [35]. However, this view has been shifted to administering rifampicin only after the bacterial load has been reduced in order to prevent the development of resistance during treatment. These concerns for the development of rifampicin resistance are merely based on the observation that 21.4% of patients with *S. aureus* native valve endocarditis developed rifampicin resistance before the clearance of bacteraemia [36]. This resistance development is perhaps due to the high load of *S. aureus* during bacteraemia, but might not be so relevant in patients with PJI due to *S. aureus* who undergo a DAIR procedure that leads to a reduction in bacterial load. In the present review, most of the included papers were published after the publication of the paper on rifampicin resistance development during bacteraemia [36], and most of the studies included patients with rifampicin added not immediately after DAIR but later (up to 2 weeks). One might thus argue that this timing is indeed the best time to add rifampicin after DAIR in staphylococcal PJIs. However, additional reasons for delaying treatment with rifampicin to minimise resistance development is to wait until the wound is dry after surgery and to remove any drains, as well as to minimise the risk of oral intolerance of rifampicin and wait until the patient is fully recovered, as most of the adverse effects are gastrointestinal.

It is important to realise that even with the addition of rifampicin, therapeutic failure after DAIR in staphylococcal PJI as found in this meta-analysis is still around 30%, leaving room for optimisation of treatment to further increase successful outcomes.

Another finding of this review is the limited number of studies investigating rifampicin combination therapy for other types of surgery (i.e. one- or two-stage prosthesis removal) for PJI and for PVE. Interestingly, from the two studies where the clinical outcome

data of adding rifampicin to patients with staphylococcal PJI after prosthesis removal were available, we noticed that the therapeutic success rate was already high (>90%) in the group without rifampicin. A large number of patients would be needed to demonstrate a positive effect of adding rifampicin, and therefore it questionable whether such a trial would be feasible. This high rate of therapeutic success will perhaps limit the detection of a therapeutic effect of adding rifampicin, if there is any. In contrast, treatment with rifampicin in patients with streptococcal PJI might be useful to investigate owing to the low therapeutic success rate [16,17].

It is worth noting regarding combination therapy with rifampicin in PJI that other systematic reviews have been published [37,38]. However, they focused on DAIR only [37] or pooled data for all surgical treatment options for PJI [38]. This will limit the comparison of the effectiveness of adding rifampicin among the surgical options.

The main strength of this study is that the data were also extracted from studies that did not investigate the clinical outcome of rifampicin combination therapy as the main objective. This endeavour to find 'hidden' data may reduce the risk of publication bias and is further supported by the funnel plot. However, the drawback is that we cannot select other variables that may influence the effect size and, consequently, we cannot correct for any other possible confounders. Another limitation of this study is that the study search was limited to English language studies only. The literature list of included studies was screened to identify studies published in languages other than English, but none were found.

In conclusion, this meta-analysis including data for more than 1000 patients showed that adding rifampicin in staphylococcal PJI treated by DAIR was clearly associated with a higher likelihood of therapeutic success. This finding might end the discussion on the use of rifampicin in DAIR. However, due to the lack of clinical studies, the clinical benefit of adding rifampicin to antibiotic treatment of other staphylococci and streptococci implant-associated infections is still unclear.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2023.107015.

References

[1] Tsaras G, Osmon DR, Mabry T, Lahr B, St Sauveur J, Yawn B, et al. Incidence, secular trends, and outcomes of prosthetic joint infection: a population-based study, Olmsted County, Minnesota, 1969–2007. Infect Control Hosp Epidemiol 2012;33:1207–12.

[2] Østergaard L, Valeur N, Ihlemann N, Bundgaard H, Gislason G, Torp-Pedersen C, et al. Incidence of infective endocarditis among patients considered at high risk. Eur Heart J 2018;39:623–9.

[3] Benito N, Mur I, Ribera A, Soriano A, Rodríguez-Pardo D, Sorlí L, et al. The different microbial etiology of prosthetic joint infections according to route of acquisition and time after prosthesis implantation, including the role of multidrug-resistant organisms. J Clin Med 2019;8:673.

[4] Oberbach A, Schlichting N, Hagl C, Lehmann S, Kullnick Y, Friedrich M, et al. Four decades of experience of prosthetic valve endocarditis reflect a high variety of diverse pathogens. Cardiovasc Res 2023;119:410–28.

[5] Zimmerli W, Sendi P. Role of rifampin against staphylococcal biofilm infections in vitro, in animal models, and in orthopedic-device-related infections. Antimicrob Agents Chemother 2019;63:e01746 -18.

[6] Jacqueline C, Caillon J. Impact of bacterial biofilm on the treatment of prosthetic joint infections. J Antimicrob Chemother 2014;69(Suppl 1):i37–40.

[7] Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2013;56:e1–25.

[8] Baddour LM, Wilson WR, Bayer AS, Fowler VG, Tleyjeh IM, Rybak MJ, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications. Circulation 2015;132:1435–86.

[9] Stengel D, Bauwens K, Sehouli J, Ekkernkamp A, Porzsolt F. Systematic review and meta-analysis of antibiotic therapy for bone and joint infections. Lancet Infect Dis 2001;1:175–88.

[10] Perlroth J, Kuo M, Tan J, Bayer AS, Miller LG. Adjunctive use of rifampin for the treatment of *Staphylococcus aureus* infections: a systematic review of the literature. Arch Intern Med 2008;168:805–19.

[11] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.

[12] . Appendix: Jadad scale for reporting randomized controlled trials. In: Halpern SH, Douglas MJ, editors. Evidence-based Obstetric Anesthesia. Blackwell Publishing Ltd.; 2005. p. 237–8.

[13] Appendix E. Decision rules for application of the Newcastle–Ottawa scale-Validity and Inter-Rater Reliability Testing of Quality Assessment Instruments. Hartling L, Hamm M, Milne A, et al., editors. Rockville, MD: Agency for Healthcare Research; 2012.

[14] Hak T, van Rhee H, Suurmond R. How to interpret results of meta-analysis. https://www.erim.eur.nl/fileadmin/erim_content/images/meta-essentials/How_to_interpret_results_of_meta-analysis_1.4.pdf [accessed 19 November 2022].

[15] van Tulder M, Furlan A, Bombardier C, Bouter L. Updated method guidelines for systematic reviews in the Cochrane Collaboration Back Review Group. Spine (Phila Pa 1976) 2003;28:1290–9.

[16] Fiaux E, Titecat M, Robineau O, Lora-Tamayo J, El Samad Y, Etienne M, et al. Outcome of patients with streptococcal prosthetic joint infections with special reference to rifampicin combinations. BMC Infect Dis 2016;16:568.

[17] Mahieu R, Dubée V, Seegers V, Lemarié C, Ansart S, Bernard L, et al. The prognosis of streptococcal prosthetic bone and joint infections depends on surgical management—a multicenter retrospective study. Int J Infect Dis 2019;85:175–81.

[18] Beldman M, Löwik C, Soriano A, Albiach L, Zijlstra WP, Knobben BAS, et al. If, when, and how to use rifampin in acute staphylococcal periprosthetic joint infections, a multicentre observational study. Clin Infect Dis 2021;73:1634–41 Erratum in: Clin Infect Dis 2022;74:1890.

[19] Ascione T, Pagliano P, Mariconda M, Rotondo R, Balato G, Toro A, et al. Factors related to outcome of early and delayed prosthetic joint infections. J Infect 2015;70:30–6.

[20] Zimmerli W, Widmer AF, Blatter M, Frei R, Ochsner PE. Role of rifampin for treatment of orthopedic implant-related staphylococcal infections: a randomized controlled trial. JAMA 1998;279:1537–41.

[21] Karlsen ØE, Borgen P, Bragnes B, Figved W, Grøgaard B, Rydinge J, et al. Rifampin combination therapy in staphylococcal prosthetic joint infections: a randomized controlled trial. J Orthop Surg Res 2020;15:365.

[22] Le Bot A, Lecomte R, Gazeau P, Benezit F, Arvieux C, Ansart S, et al. Is rifampin use associated with better outcome in staphylococcal prosthetic valve endocarditis? A multicenter retrospective study. Clin Infect Dis 2021;72:E249–55.

[23] Cho OH, Bae IG, Moon SM, Park SY, Kwak YG, Kim BN, et al. Therapeutic outcome of spinal implant infections caused by *Staphylococcus aureus*: a retrospective observational study. Medicine (Baltimore) 2018;97:e12629.

[24] Vilchez F, Martínez-Pastor JC, García-Ramiro S, Bori G, Maculé F, Sierra J, et al. Outcome and predictors of treatment failure in early post-surgical prosthetic joint infections due to *Staphylococcus aureus* treated with debridement. Clin Microbiol Infect 2011;17:439–44.

[25] Senneville E, Joulie D, Legout L, Valette M, Dezèque H, Beltrand E, et al. Outcome and predictors of treatment failure in total hip/knee prosthetic joint infections due to *Staphylococcus aureus*. Clin Infect Dis 2011;53:334–40.

[26] Muñoz-Gallego I, Viedma E, Esteban J, Mancheño-Losa M, García-Cañete J, Blanco-García A, et al. Genotypic and phenotypic characteristics of *Staphylococcus aureus* prosthetic joint infections: insight on the pathogenesis and prognosis of a multicenter prospective cohort. Open Forum Infect Dis 2020;7:ofaa344.

[27] Holmberg A, Thórhallsdóttir VG, Robertsson O, W-Dahl A, Stefánsdóttir A. 75% success rate after open debridement, exchange of tibial insert, and antibiotics in knee prosthetic joint infections: report on 145 cases from the Swedish Knee Arthroplasty Register. Acta Orthop 2015;86:457–62.

[28] Becker A, Kreitmann L, Triffaut-Fillit C, Valour F, Mabrut E, Forestier E, et al. Duration of rifampin therapy is a key determinant of improved outcomes in early-onset acute prosthetic joint infection due to *Staphylococcus* treated with a debridement, antibiotics and implant retention (DAIR): a retrospective multicenter study in France. J Bone Jt Infect 2020;5:28–34.

[29] El Helou OC, Berbari EF, Lahr BD, Eckel-Passow JE, Razonable RR, Sia IG, et al. Efficacy and safety of rifampin containing regimen for staphylococcal prosthetic joint infections treated with debridement and retention. Eur J Clin Microbiol Infect Dis 2010;29:961–7.

[30] Costerton JW, Khoury AE, Ward KH, Anwar H. Practical measures to control device-related bacterial infections. Int J Artif Organs 1993;16:765–70.

[31] Bahl D, Miller DA, Leviton I, Gialanella P, Wolin MJ, Liu W, et al. In vitro activities of ciprofloxacin and rifampin alone and in combination against growing and nongrowing strains of methicillin-susceptible and methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother 1997;41:1293–7.

[32] Peck KR, Kim SW, Jung S-I, Kim Y-S, Oh WS, Lee JY, et al. Antimicrobials as potential adjunctive agents in the treatment of biofilm infection with *Staphylococcus epidermidis*. Chemotherapy 2003;49:189–93.

[33] Zheng Z, Stewart PS. Penetration of rifampin through *Staphylococcus epidermidis* biofilms. Antimicrob Agents Chemother 2002;46:900–3.

[34] Renz N, Trampuz A, Zimmerli W. Controversy about the role of rifampin in biofilm infections: is it justified? Antibiotics (Basel) 2021;10:165.

[35] Tshefu K, Zimmerli W, Waldvogel FA. Short-term administration of rifampin in the prevention or eradication of infection due to foreign bodies. Rev Infect Dis 1983;5(Suppl 3):S474–80.

[36] Riedel DJ, Weekes E, Forrest GN. Addition of rifampin to standard therapy for treatment of native valve infective endocarditis caused by *Staphylococcus aureus*. Antimicrob Agents Chemother 2008;52:2463–7.

[37] Scheper H, Gerritsen LM, Pijls BG, Van Asten SA, Visser LG, De Boer MGJ. Outcome of debridement, antibiotics, and implant retention for staphylococcal hip and knee prosthetic joint infections, focused on rifampicin use: a systematic review and meta-analysis. Open Forum Infect Dis 2021;8:ofab298.

[38] Kruse CC, Ekhtiari S, Oral I, Selznick A, Mundi R, Chaudhry H, et al. The use of rifampin in total joint arthroplasty: a systematic review and meta-analysis of comparative studies. J Arthroplasty 2022;37:1650–7.