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Outcome of debridement, antibiotics and implant retention for streptococcal hip and knee prosthetic joint infections: A systematic review and meta-analysis

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A B S T R A C T

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Objectives: This systematic review and meta-analysis was conducted to assess the outcome of streptococcal hip and knee prosthetic joint infection (PJI) treated with Debridement, Antibiotics and Implant Retention (DAIR) and to evaluate risk factors associated with failure.

Methods: We conducted a systematic literature search on PubMed, Embase, Web of Science, and Cochrane library from inception until October 2021. Random effects meta-analyses (i.e. relative risk) were used to estimate the success rate at the study level and its association with possible risk factors for failure with a specific focus on the use of rifampicin.

Results: 25 observational studies were included, incorporating 1367 patients with streptococcal PJIs treated with DAIR. An overall pooled success rate of 71% (95% confidence interval (95%CI) 64–77%) was found for streptococcal PJI treated with DAIR. Treatment success was 76% (95%CI 62% to 91%) for knee PJI and 58% (95%CI 52% to 65%) for hip PJI. Treatment success differed for patients receiving rifampicin (84%, 95% CI 78% to 90%) compared to patients not receiving rifampicin (74%, 95% CI 63% to 85%), but this effect was no longer present in subsequent meta-analyses.

Conclusions: The meta-analysis showed no clear benefit for rifampicin administration after DAIR for streptococcal PJI. Better outcome was observed for knee PJI compared to hip PJI.

1. Introduction

A (peri)prosthetic joint infection (PJI) is a severe and devastating complication of total joint arthroplasties, often resulting in surgical procedures, long-term antibiotic treatment, and significant patient morbidity and mortality. Debridement, antibiotics and implant retention (DAIR) is considered the treatment of choice for acute PJI. Compared to revision surgery, with DAIR the implant can be preserved, and morbidity and treatment costs are lower [19]. For chronic PJI, one- or two-stage revision surgery is the preferred strategy. For some patients, long-term suppressive antibiotic treatment is needed. Reported success rates after DAIR range from as low as 11.1% to as high as 93.8% [12]. Factors which may be associated with this success rate are follow-up period, geographic location (i.e. treatment protocols may differ between countries), type of joint, antibiotic treatment strategy, type of infection (early vs late), duration of treatment, need for consecutive DAIR, primary or revisional nature of arthroplasty, causative pathogen (i.e. streptococcal subtypes or polymicrobial PJI) and, the used definition of failure in studies [12,15,20].

Streptococcal PJI has been estimated to account for 10% of PJI [23]. Periprosthetic joint infection (PJI) induced by streptococcal bacteria typically arises from a distant focus through hematogenous dissemination *via* the bloodstream [24]. Data on overall treatment outcome, preferred antimicrobial treatment strategy and other factors influencing outcome after DAIR for streptococcal PJI is limited.

Moreover, the value of rifampicin for streptococcal PJI is unclear. However, rifampicin combination therapy has been adopted as the preferred treatment strategy in many guidelines for streptococcal PJI. A clinical study by Fiaux et al. has suggested beneficial outcome for patients with streptococcal PJI treated with rifampicin combination therapy [7]. The literature on treatment outcome of streptococcal PJI and possible factors associated with outcome after DAIR has not yet been evaluated systematically.

Therefore, this study aimed to perform a meta-analysis and

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systematic review (i) to assess the success rate of DAIR in streptococcal PJI and (ii) to evaluate risk factors associated with success with a specific focus on the use of rifampicin

2. Methods

The reporting of this systematic review and meta-regression was conducted in accordance with the PRISMA statement [16]. In the current systematic review, we used the same methodology as previously used in a systematic review on staphylococcal hip and knee PJI [17]. This review was registered at PROSPERO (ID 367411). The population of interest consisted of patients with streptococcal PJI who were treated with DAIR. The outcome of interest was success rate after a DAIR, which was mostly defined as eradication of infection in terms of absence of recurrence (as defined in each paper), absence of long-term antibiotic suppression and absence of subsequent resection during follow-up [8, 17].

We aimed to evaluate risk factors associated with success, with specific focus on the use of rifampicin. We assessed several study-level and clinical characteristics: continent of study population, proportion of hip and knee PJI in study cohort, duration of follow up, use of rifampicin and methodological quality of the study. All observational studies and randomised controlled trials (RCTs) assessing outcome of streptococcal hip or knee PJI after DAIR were included and subjected to later sensitivity analyses. All studies including PJI of hip and knee implants irrespective follow-up periods were considered. Studies reporting outcome of streptococcal PJI of hemiarthroplasties, unicompartimental knee implants and hip resurfacing procedures were also excluded. We used meta-regression to determine, at a study level, the association between rifampicin use, continent of study population, median of study period, follow-up period, proportion of hip and knee PJI, type of infection (early vs late), primary or revisional nature of arthroplasty, presence of polymicrobial PJI, study quality and success rate. Early postoperative PJI was defined as development of PJI within the first 3 months after implantation of the arthroplasty. Late postoperative PJI was defined as development of PJI after the first 3 months of implantation of the arthroplasty [8,17].

2.1. Data sources and search strategy

The literature search was designed and conducted by the first reviewer (blinded) and an experienced librarian (blinded). The following databases were searched from their inception up to and including October 2021: MEDLINE (PubMed), Embase (OVID), Web of Science and the Cochrane Library. Articles in languages spoken by the study team were considered: English, German, French, Spanish and Dutch. Bibliographies of relevant articles were cross-checked for references missing in the original search. No restrictions regarding patient background and year of publication applied. Further details regarding the search strategy are presented in Appendix A.

2.2. Study selection

Two reviewers (blinded) independently screened the titles and abstracts of studies identified by the search strategy. Both reviewers independently recorded their findings in an electronic database that was designed before the start of the screening. These databases were compared and any disagreement was resolved by consensus or consulting a third member of the study group/team.

Three reviewers (MG, HS & BP) independently evaluated the full-text papers of eligible studies against the inclusion and exclusion criteria. Any disagreement was resolved by consensus or by consulting a third reviewer (MG, HS &BP). We included studies reporting outcome of patients with streptococcal hip or knee PJI after DAIR. We excluded: (i) studies with less than 10 patients; (ii) non-original data publications such as editorials and reviews; (iii) studies not available in full-text (conference proceedings, (iv) non-articulating implants such as intramedullary nails, plates, screws used for osteosynthesis or arthrodesis, (v) studies not written in English, German, French, Spanish and Dutch.

2.3. Data extraction and quality assessment

Three reviewers (MG, HS &BP) independently extracted data and appraised the study quality from included studies regarding the outcome of interest, patient demographics and study characteristics in a predefined electronic datasheet. The most comprehensive publication was included when there were multiple or overlapping publications on the same patient cohort.

Study quality was assessed independently by three authors (MG, HS &BP)using AQUILA the Assessment of Quality In Lower limb Arthroplasty (AQUILA) tool [3]. AQUILA is specifically designed to assess the methodological quality of observational studies on lower limb arthroplasties. In the quality assessment of the included studies, the 'competing risk analysis' section of the AQUILA tool was modified and replaced with 'presence of multivariate risk analyses. This modification was done because failure of PJI often happens relatively early during follow-up. Therefore, the possible influence of death as a competing risk was considered to be small compared to studies for aseptic loosening with e.g. 10 years of follow-up. Studies with an AQUILA score of 0–3 points were considered to be of *low* quality, 4–7 points of *moderate* quality and 8 points or higher of *high* quality [3].

2.4. Data analysis

Random effect models were employed (due to assumed heterogeneity) to pool study-specific measures, proportion and (RR) in order to estimate overall effect and its associated confidence intervals (CIs) [4, 17]. Inverse variance method, which gives more weight to larger studies, was used to pool outcomes for different studies. Overall effects estimated with a random-effects model are reported together in the same forest plots along with their CIs. The sizes of the square boxes on the forest plot are proportional to the total number of patients in the selected trials. Statistical heterogeneity between studies was assessed by calculating I^2 statistics [9,10]. The I^2 statistic estimates the extent to which the total variability in the effect size estimates is due to heterogeneity among the true effects. To estimate the between-study variance as "tau" in the forest plots, DerSimonian-Laird's method was employed [5]. Treatment success, measured as proportion of healed cases in total cases with accompanying 95% CIs, was used as summary outcome measure for each included study. Moreover, a prediction interval was calculated to predict future observations based on the existing model and to identify outliers.

In the presence of heterogeneity, a random-effects meta-regression was performed on the following predefined factors (study-level covariates): rate of rifampicin use, geographical region of study, median of study period, follow-up period, median of study period, proportion of hip and knee PJI in study cohort and study quality items. On patient-level, subgroup analyses were performed on rifampicin administration and patient outcome. To account for geographical differences between study populations (e.g. in treatment protocols, rifampicin use and resistance patterns), subgroup analyses were performed on geographical region.

A funnel plot was constructed for studies reporting the primary outcome to assess publication bias. To assess frequencies of characteristics in the patient population, the Shapiro-Wilk test was employed. Data were analysed using package Metafor in R version 3.6.2 (The R

Foundation for Statistical Computing Platform) and SPSS statistical software version 25.0 (SPSS Inc., Chicago) [21].

3. Results

3.1. Study selection and study characteristics

Our literature search revealed 2425 papers, of which 1438 were unique (no double entries for different databases). After abstract selection, 25 studies encompassing 1367 patients were included (Table 1 and Appendixes A and B).

From the included studies, nine were from the USA, three were from the Netherlands, two from Switzerland, one from the UK, one from Spain, one from Germany, one from France, one from Denmark, one from Sweden, and three from a consortium of European countries and the USA. In one study the geographical location of the patient cohort was not specified. Mean follow-up was 41 months (range 13–100) for all included cohorts. The mean number of patients with streptococcal PJI included from each study was 46 patients (range 10–444).

3.2. Treatment success

Overall pooled success rate of included studies was 71% (95% CI 64%–77%), with substantial heterogeneity (I^2=83%). Therefore, a prediction interval was calculated (95% CI 43%–97%), see Fig. 1.

At patient level, success rates were numerically higher for patients treated with rifampicin (84%, 95% CI 78% to 90%) compared to treatment success for patients treated without rifampicin (74%, 95% CI 63% to 85%), but the confidence intervals overlapped. Outcome at patient level was described for 111 patients receiving rifampicin and 293 patients not receiving rifampicin. At study level, study outcome was similar in studies in which rifampicin was part of the treatment protocol (74% success rate (95% CI, 52%−95%)) compared to studies in which rifampicin was not part of the treatment protocol (74% success rate (95% CI, 58%−90%) or when the use of rifampicin was not reported in the manuscript (69% (95% CI, 60%−79%). The pooled relative risk ratio of success rates after rifampicin administration compared to success rates after no rifampicin administration was 1.15 (95% CI 0.91–1.45) (Fig. 2).

No statistically significant difference in outcome after DAIR for streptococcal PJI was observed when comparing different geographical locations. The success rate in European studies (including UK) was 75% (95% CI 66% to 84%), and for studies in the USA 70% (95% CI 57% to 83%), see Appendix C. In four studies, no specific geographical location was mentioned.

The meta-regression model showed that the success rate after DAIR was 58% for streptococcal hip PJI (95% CI 52% to 65%) and 76% for streptococcal knee PJI (95% CI 62% to 91%). However, both of these estimated success rates are based on a low number of studies and the confidence intervals were wide (Table 2). There was considerable heterogeneity (I^2=80%), therefore a subgroup and meta-regression analysis was performed for the knee PJI studies. In this meta-regression, follow-up duration, presence of polymicrobial PJI, primary or revisional nature of PJI, type of infection (acute vs late) and time of study were not identified as effect modifiers for the success rate of DAIR for streptococcal PJI.

3.3. Study quality

The mean AQUILA methodological quality score was 6 points out of a maximum of 11 points (range 3–11) and was not an effect modifier on the association between rate of component exchange and success rate of DAIR procedure. There were n = 0 studies of low quality, n = 20 studies of moderate quality and n = 5 studies if high quality, see Table 1. The main methodological flaw concerned the item "How was FU performed?": In only one of the studies follow-up was performed on a predefined time schedule, in 22 out of 25 studies the follow-up was performed when patients had complaints or by chart review at a certain point in time (of non-predefined FU). In 2 out of 25 studies it was unclear how the follow-up was performed. Two out of 25 studies did not include a comprehensive primary research question. These retrospective studies evaluated patient characteristics and treatment modalities and analysed associations with treatment outcome. See Appendix D for the methodological score for each item.

The funnel plot appeared asymmetric (Appendix E), suggesting publication bias. A trim-and-fill analysis was performed to explore the magnitude and direction of possible publication bias. This analysis, however, suggested no missing studies, so the influence of possible publication bias on the estimated results was considered to be small.

4. Conclusions

4.1. Main study findings & interpretation

In this systematic review and meta-analysis, we determined the overall success rate of DAIR for streptococcal PJI and we evaluated the association between several study and patient characteristics and success rate of streptococcal PJI after DAIR.

Our results showed an overall success of 70% for streptococcal PJI treated with DAIR. This is similar to the outcome of staphylococcal PJI of 69%, as previously reported by Scheper et al. [18] Regarding streptococcal PJI, the absolute success rate was slightly higher for patients treated with rifampicin compared to patients not treated with rifampicin, but this effect was not statistically significant (RR 1.15, 95% CI 0.91–1.45).. Considering the relatively small effect of rifampicin and the methodological flaws of included studies (all were observational and scored around half of the possible AQUILA quality score), no clear conclusion can be made regarding the use of rifampicin in patient with streptococcal PJI.

4.2. Comparison to current literature

To our knowledge, this meta-analysis is the first to analyse the outcome of streptococcal PJI treated with DAIR. In a meta-analysis by Scheper et al., evaluating only patients with staphylococcal PJI, a small increase in success rate if rifampicin was administered after DAIR was found, but the authors concluded that the quality of this evidence was weak considering bias and confounding in the included studies [17]. They also reported that the ratio of included knee PJI compared to hip PJI per study strongly affected outcome and that the small attributive value of adjunctive rifampicin was mainly restricted to patients with a knee PJI.

Several *in-vitro* studies have demonstrated streptococcal species' capability to form biofilm [11,22]. It has been shown that rifampicin is not able to eradicate bacteria residing in biofilms although several experimental animal models have shown high success rates if foreign body infections were treated with rifampicin combination therapy [1]. Moreover it has been demonstrated that rifampicin does not eradicate the more 'chronic' biofilms, which exist for more than two weeks [13]. Based on the clinical data presented in this meta-analysis, it remains unclear whether rifampicin could be beneficial in reducing recurrence rate for streptococcal PJI. This absence of evidence may relate to the highly bactericidal activity of penicillin against streptococci for which no additional antibiotic is needed to further reduce the bacterial load.

In our study, the outcome after DAIR for streptococcal PJI did not differ between different geographical locations. However, Kunutsor

Table 1
Baseline characteristics of included cohorts (n=25).

Author	Country	Sample size	Inclusion/Exclusion criteria	Antibiotic treatment	outcome	Follow-up (Months)	Quality of evidence
Andronic et al. (2021)	Switzerland	22	Streptococcal PJIs (all joints), undergoing DAIR/ one stage revision/two stage revision/implant removal with minimum FU of 12 months	Median antibiotic treatment 83 days (range 38 −133). Rifampin was used in five cases (23%). And for 2/12 (17%) cases in the DAIR subgroup.	Treatment success in 15/22 cases (68%), treatment success in 6/ 12 patients (50%) in DAIR subgroup.	Median follow-up 15 (range 12–83)	High
Dx Duffy et al. (2018)	UK	59	Knee PJIs treated with DAIR, with minimum FU of 12 months	All patients treated with IV vancomycin and oral rifampicin pending culture results. Antibiotic treatment was adjusted when culture results became available. Standard approach: 5–10 days IV therapy followed by 5–6 months oral	Treatment success in 41/58 (69%), treatment success in 10/13 (23%) of streptococcal PJIs	Mean follow-up 27 months	Moderate
Fehring et al. (2013)	USA	86	PJIs within 3 months of primary arthroplasty treated with DAIR, with a minimum FU of 24 months	No uniform postoperative antibiotic treatment.	Treatment success in 32/86 patients (37%). Of streptococcal PJIs 4/ 10 (40%) treatment success	Mean 46 (range 24–106)	Moderate
Hirsiger et al. (2019)	Switzerland	112	PJIs (all joints) treated with DAIR	Median duration of antibiotic treatment 3 months (range 1.5–6), with a mean of 12 days intravenously. No uniform postoperative treatment	Treatment success in 94/112 patients (84%). Treatment success in streptoccal PJI subgroup 21/22 (95%)	Median follow-up 40 months (range 23 – 92)	Moderate
Katakam et al. (2020)	USA	263	Hip or knee PJI treated with DAIR	No uniform postoperative antibiotic treatment.	Treatment success in 153/263 patients (58%). Treatment success in streptococcal PJI 15/42 (36%)	Mean follow-up 100 months	Moderate
Klare et al. (2018)	USA	99	Knee PJI undergoing DAIR	Antibiotic therapy guided by cultures, no standard antibiotic regimen.	Treatment success in 64/99 patients (65%), 14/19 (74%) of streptococcal PJIs	Median follow-up 31 months (range 38 days – 83 months)	Moderate
Kuo et al. (2019)	Not stated	49	Hip and knee PJI undergoing DAIR, with minimum FU of 12 months	Antibiotic therapy guided by cultures, no standard antibiotic regimen.	Treatment success in 26/49 patients (53%), 11/15 streptoccal PJI (73%)	Minimum FU of 12 months	
Kuiper et al. (2013)	The Netherlands	91	Hip or knee PJI treated with DAIR	Minimum antibiotic treatment for 6 weeks, antibiotic therapy guided by cultures,	Treatment success in 60/91 (66%). Treatment success in 10/11 streptococcal PJIs	Mean follow-up of 35 months (range 0–79 months)	High
Lam et al. (2018)	Sweden	83	Hip and knee streptococcal PJI[a], with minimum FU of 12 months	Median duration of antibiotic treatment treatment 15weeks (rifampicin n=12, non-rifampicin n= 71)	Treatment successs in 74/84 (89%)and 53/64 (83%) in DAIR subgroup, not stratified for rifampicin use	Median follow-up of 29 months (IQR 8 −42)	Moderate
Lora-tamayo et al. (2017)	Spain	444	Streptococcal PJIs managed with DAIR	Antibiotic treatment was primarily using β-lactams, and 37% of patients received rifampin	Treatment success in 257/444 (58%) streptococcal PJIs	Not stated	Moderate
Löwik et al. (2018)	The Netherlands	386	Patients with early acute hip or knee PJI (< 3 months after primary implantation) treated with DAIR	Antibiotic therapy guided by cultures, no standard antibiotic regimen. Rifampin was added for staphyloccal PJIs.	Treatment success in 238/386 (61%), Treatment success in 44/66 streptococcal PJIs (	Not stated	Moderate
Löwik et al. (2020)	Consortium of countries	769	Patients with early acute hip or knee PJI (< 3 months after primary implantation) treated with DAIR, with minimum FU of 1 year	Antibiotic therapy guided by cultures . IV antibiotics for at least 2 weeks, oral antibiotics for 10 weeks. Rifampin was added for staphyloccal PJIs.	Treatment success in 475/769 (62%) PJIs. Streptoccal PJIs 54/85	Mean follow-up 38 (range 12 – 180 months)	Moderate
Mahieu et al. (2019)	France	70	Monomicrobial streptococcal hip or knee PJIs with minimum 24 months of FU	Antibiotic therapy guided by cultures, no standard antibiotic regimen. Most common antimicrobial treatment: amoxicillin (39 patients), rifampicin (31 patients, levofloxacin (24 patients)	Treatment success in 51/70 patients (73%) Treatment success DAIR subgroup 19/39 (50%) successful.	Mean follow-up 32 months (range 25–43 months)	Moderate
Marculescu et al. (2006)	USA	91	Hip or knee PJIs treated with DAIR	Median duration of IV was 28 days. Most common antimicrobial treatments: Oral β-lactam antibiotics were used in 53%. Minocycline was used in 7% of the episodes, trimethoprim-	Treatment success in 46/99 patients (46%) and 11/14 (78.5%) in DAIR subgroup	Median follow-up 23 months (range 0 - 91)	Moderate

(*continued on next page*)

Table 1 (*continued*)

Author	Country	Sample size	Inclusion/Exclusion criteria	Antibiotic treatment	outcome	Follow-up (Months)	Quality of evidence
				sulfamethoxazole in 10%, and quinolones in 8%.			
Meehan et al. (2003)	USA	19	Hip or knee streptoccal PJI, treated with DAIR	Median duration of IV therapy 28 days. Most common antimicrobial treatments: Penicillin/ampicillin in 47.3% of the cases, ceftriaxone in 26.3%, cefazolin in 26.3%.	Treatment success in 17/19 patients (89%)	Mean follow-up 47 months (range 4–260)	Moderate
Odum et al. (2011)	USA	150	Hip or knee PJI treated with DAIR	No standard antibiotic regimen.	Treatment success in 46/150 patients (31%) Treatment success in 11/31 patients with streptococcal PJI (35%)	Not stated	Moderate
Ottesen et al. (2019)	Denmark	58	Acute hip or knee PJI treated with DAIR, with minimum FU of 2 years	IV antibiotic treatment for 2 weeks followed by at least 4 weeks oral antibiotics. Mean duration of AB treatment was 81 days. Rifampicin was added to 38% of the cases of staphylococcal PJI.	Successful outcome in 49/58 patients (84%). Treatment success for streptococcal PJIs 12/16 (75%)	Followed for a minimum of 24 months.	Moderate
Renz et al. (2019)	Germany	69	Streptoccocal PJI (all joints)	Empiric IV antibiotic treatment for 2–4 weeks, then switched to oral antibiotics. 84% received IV penicillin derivative, 9% received IV cephaloporine, 37% received oral treatment with rifampicin.	Succesful outcome in 45/69 patients (65%). Successful outcome in DAIR subgroup in 23/27 patients (85%)	Mean follow-up 13 (range 0.5 −111)	High
Shohat et al. (2020)	Consortium of countries (USA +EU)	1174	Hip or knee PJI treated with DAIR with minimum of 1 year FU	Not stated.	Treatment success in 769/1174 patients (65%). Treatment success for streptoccal PJIs 128/194 (66%)	Minimum of 1 year follow-up	Moderate
Swenson et al. (2018)	USA	72	Hip or knee acute or acute hematogenous PJIs treated with DAIR, with minimum FU of 6 months	No standard antibiotic regimen.	Treatment success in 19/72 patients (26%). Treatment success in 16/18 streptoccal PJIs	Mean follow-up 35 (range 6 – 76 months)	High
Tirumala et al. (2021)	USA	149	Knee or hip PJI treated with DAIR with at least 3 year FU	Patients were treated with organism-specific IV for a minimum of 6 weeks. Oral antibiotics were used for a duration of at least 6 weeks. Antibiotic therapy guided by cultures.	Treatment success in 123/149 patients (83%). Treatment success in 17/22 (77%) streptococcal PJIs.	Median follow-up 73 months (range 47– 126 months)	Moderate
Wouthuyzen et al. (2019)	International consortium of countries	340	Late acute PJI treated with DAIR	Among streptococcal PJI: 58% receiving amoxicillin, 13% receiving clindamycin, 4% receiving linezolid and 23% receiving rifampicin-based regimen	Treatment success in 187/340 patients (55%). Treatment success in 61/97 (63%) streptococcal PJIs	Mean follow-up 25 (IQR 11–31)	High
Wouthuyzen et al. (2020)	Netherlands	455	Acute PJI of hip and knee treated with DAIR, with minimum FU of 1 year	IV antibiotic treatment for 2 weeks followed by at least 4 weeks oral antibiotics. Antibiotic regimen guided by culture results. In case of staphylococcal PJI, rifampicin was added.	Treatment success in 418/455 (92%). Treatment success for streptococcal PJIs 20/25 (80%)	Minimum follow-up of 12 months.	Moderate
Zhu et al. (2021)	New Zealand	230	Knee PJI treated with DAIR.	IV antibiotic treatment for 2 weeks followed by at least 4 weeks oral antibiotics.	Treatment success in 124/230 patients (54%). Treatment success in 25/52 streptococcal PJIs (48%)	Mean follow-up 83 months	Moderate
Zmitowski et al. (2016)	USA	153	Hip or knee PJI treated with DAIR	Not stated	Treatment success in 80/153 patients (52%). Treatment success in 7/11 streptococcal PJIs (64%).	Not stated	Moderate

a= in the entire cohort there was 1 included shoulder prosthesis besides hip and knee arthroplasties.

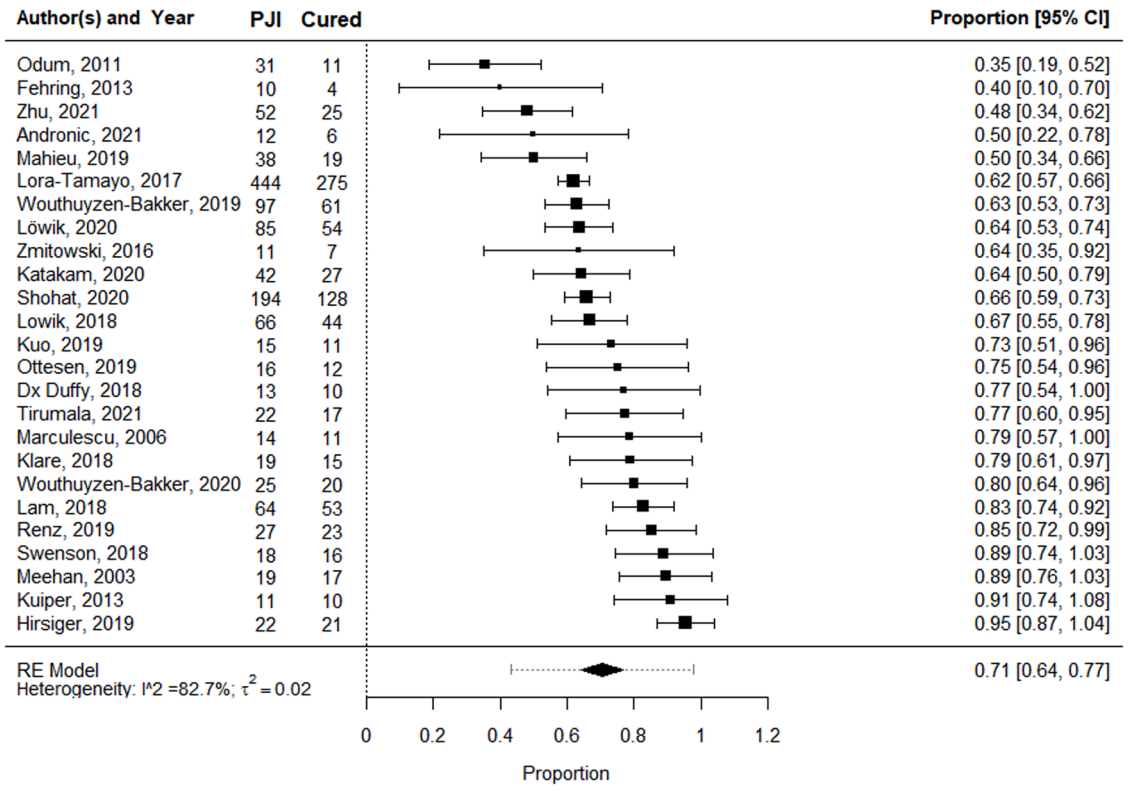

Fig. 1. Treatment success in included studies, including overall success rate with accompanying prediction interval (dotted line segment).

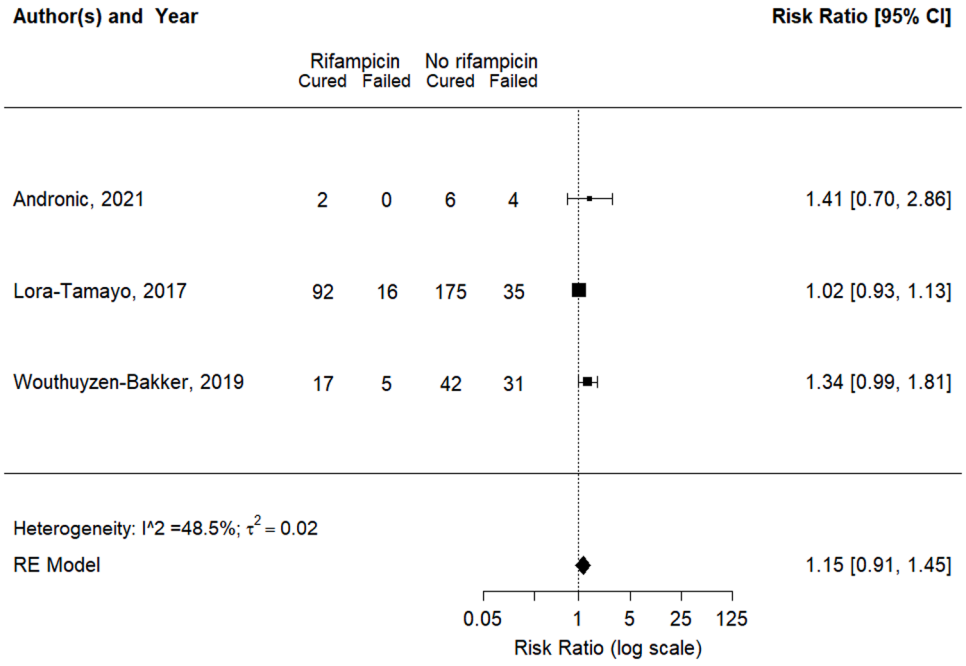

Fig. 2. Relative risk ratio of treatment success comparing patients treated with or without rifampicin combination therapy.

Table 2
Success rate per joint type.

Joint type	Treatment success for streptococcal PJI after DAIR		
	Estimate (SE)	95% C.I.	Number of studies
Knee	76% (8%)	(62% - 91%)	K = 5
Hip	58% (4%)	(52% - 65%)	K= 2
Total	71% (3%)	(64%–77%)	K= 25

et al. showed lower success rates for PJI treated with DAIR in North American and European populations, respectively 52% vs 70%. This may be explained by the fact that we only assessed streptococcal species while the study of Kunutsor et al. included all type of micro-organisms, which may be associated with more heterogeneity in the outcome [12].

4.3. Limitations & strengths

First, all included studies in this review were observational and therefore subject to bias and possible confounding factors. Confounding by indication in the case of rifampicin administration has been described in the literature, where patients who were not treated with rifampicin had diabetes, rheumatoid arthritis, and liver disease more often [2,14]. Second, publication bias may have influenced the observed results. In order to determine the possible influence of publication bias on the results, a trim-and-fill analysis was performed. This analysis showed that the potential influence of publication bias on the results was considered to be small. Third, the definition of treatment failure varied across included studies. Because there is no universally accepted definition for treatment success or failure after PJI, we accepted the different definitions as defined in the included paper Uniform definitions of treatment failure are needed to make comparison between studies more accurate. Fourth, most included PJI studies also included patients with PJI caused by other micro-organisms. Although the presence of polymicrobial PJIs did not seem to affect the primary outcome in our study, the analysis was significantly constrained due to limited data regarding polymicrobial PJI.Therefore, it cannot be excluded from our data that polymicrobial PJI explains the difference in outcome between hip and knee PJI in this study. Furthermore, not all studies specified details regarding the outcome per affected joint (hip or knee) or causative streptococcal species, resulting in low power for subgroup analyses. Based on virulence, two different groups of streptococci species can be distinguished. The 'high virulence' beta-hemolytic streptococci are known to cause acute and severe, invasive infections, whilst the 'low virulence' viridans streptococci often cause more chronic infections [6]. *Streptoccocus agalactiae* (group B streptococci) has been described to be an independent risk factor for treatment failure of PJI in comparison with other causative pathogens [23]. Subgroup analysis of this type of the different types of streptococcal species was not possible due to little specified data in the included studies. Moreover, subgroup analysis on the duration of rifampicin was not possible due to unavailable data.

In this study, a meta-analysis was performed showing a relatively small effect of rifampicin administration on the outcome of streptococcal PJI, and this effect was no longer present in subsequent relative risk analyses. Statistical analyses were limited by the small number of included studies, with little specified data on possible confounding factors.

Our review has the following strengths: to the best of our knowledge, this is the first systematic overview appraising outcome of streptococcal PJI treated with DAIR in combination with correction for important confounders (at a study level). We included a large number of 25 studies, encompassing a total of 1367 patients. All phases of the review were performed by two reviewers and checked with a referee if needed. Furthermore, the small effect of rifampicin decreased after sensitivity analyses.

4.4. Final conclusion & future perspective

The success rate for streptococcal PJI treated with DAIR ranged from 35% to 95% with an overall pooled estimate of 71%. Success rates varied per affected joint type. Overall treatment success for knee PJI was 76% and 58% for hip PJI. There were no clinically relevant differences between geographical locations or administration of rifampicin.

In conclusion, this meta-analysis encompassing 1367 patients found no clear risk factors associated with failure of treatment after DAIR. There seemed to be no benefit of rifampicin administration to improve outcome after DAIR for streptococcal PJI. Considering this absence of evidence, in clinical practice, the possibly limited effect of rifampicin should be weighed against the risks of using rifampicin on an individual patient basis. In light of this clinical equipoise, a well-designed RCT is needed.

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Ethical approval statement

Not applicable.

Registration

This review was registered in PROSPERO (ID: 367411).

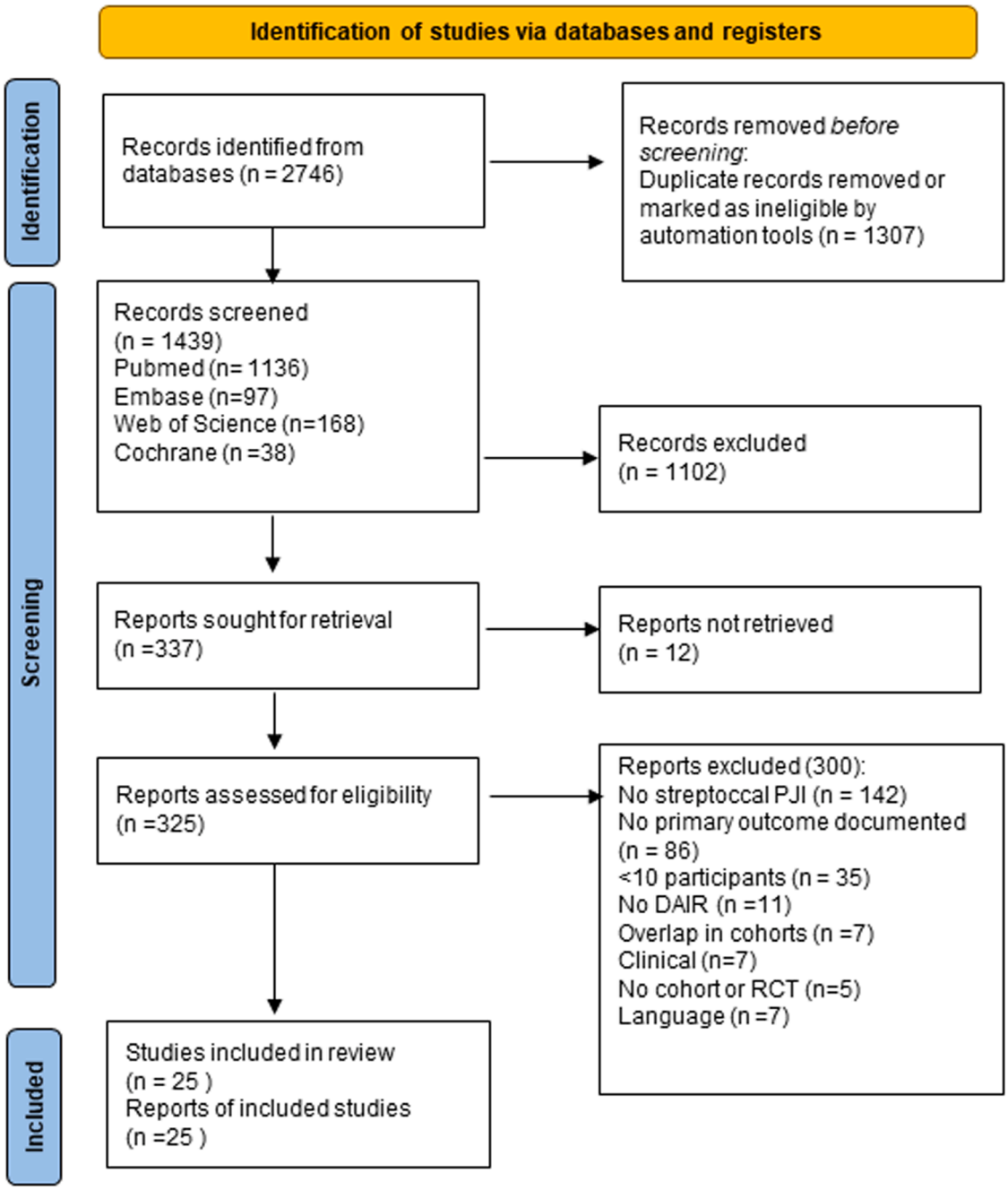
CRediT authorship contribution statement

Laura M. Gerritsen: Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization, Methodology, Formal analysis. **Henk Scheper:** Writing – review & editing, Writing – original draft, Conceptualization, Methodology, Data curation. **Mark G. J. de Boer:** Writing – review & editing, Writing – original draft, Conceptualization, Methodology. **Jan W. Schoones:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization, Methodology. **Rob G.H.H. Nelissen:** Writing – review & editing, Writing – original draft, Conceptualization, Methodology. **Bart G.C. Pijls:** Writing – review & editing, Writing – original draft, Conceptualization, Methodology, Data curation, Formal analysis.

Declaration of Competing Interest

Authors (MG, HS, JS, MB) declare they have no financial or non-financial interests to disclose. Two of the authors (RN and BP) are listed as inventors on a provisional patent application from the Leiden University Medical Center (WO2020/067898) on induction heating of metal implants. Author RN has received research funding (VENI grant). This research has not been funded, and all authors had final responsibility for the decision to submit for publication.

Appendix A. Flowchart of literature selection



Appendix B. Search strategy of included articles

B.1. MEDLINE (PubMed)

(("Debridement"[Mesh] OR "debridement"[tiab] OR debrid*[tiab] OR "DAIR"[tiab] OR "debridement, antibiotics and implant retention"[tiab] OR "debridement, antibiotics and implant retention dair"[tiab] OR "debridement, antibiotics, and implant retention"[tiab] OR "implant retention"[tiab]) AND ("Prosthesis-Related Infections"[mesh] OR "Prosthesis Infection"[tiab] OR "Prosthesis Infections"[tiab] OR "Prosthetic Infection"[tiab] OR "Prosthetic Infections"[tiab] OR "Prosthetic Joint Infection"[tiab] OR "Prosthetic Joint Infections"[tiab] OR "Prosthesis-Related Infections"[tiab] OR "Prosthesis-Related Infection"[tiab] OR "peri prosthetic joint infection"[tiab] OR "peri prosthetic joint infections"[tiab] OR "periprosthetic joint infection"[tiab] OR "periprosthetic joint infections"[tiab] OR (("Joint Prosthesis"[majr] OR "Arthroplasty, Replacement"[majr]) AND ("Infections"[majr] OR infect*[ti] OR "deep infection"[ti] OR "Wound Infection"[majr] OR "Sepsis"[majr] OR "Surgical Wound Infection"[majr])) OR (("Prosthesis"[ti] OR prosthe*[ti]) AND ("Joint"[ti] OR "Joints"[ti] OR "Joints"[majr] OR "knee"[ti] OR "shoulder"[ti] OR "elbow"[ti] OR "hip"[ti] OR "knees"[ti] OR "shoulders"[ti] OR "elbows"[ti] OR "hips"[ti]) AND ("Infections"[majr] OR infect*[ti] OR "deep infection"[ti] OR "Wound

Infection"[majr] OR "Sepsis"[majr] OR "Surgical Wound Infection"[majr])) AND ("success rate"[tiab] OR "success rates"[tiab] OR "success"[tiab] OR succes*[tiab] OR "failure rate"[tiab] OR "failure rates"[tiab] OR "failure"[tiab] OR fail*[tiab] OR "infection control"[tiab] OR "Treatment Outcome"[mesh] OR "Treatment Outcome"[tiab] OR "outcome"[tiab] OR "outcomes"[tiab])) NOT ("Animals"[mesh] NOT "Humans"[mesh]) NOT (("Case Reports"[ptyp] OR "case report"[ti]) NOT ("Review"[ptyp] OR "review"[ti] OR "Clinical Study"[ptyp] OR "trial"[ti] OR "RCT"[ti])).

B.2. Embase (OVID)

((*"Debridement"/ OR "debridement".ti,ab OR debrid*.ti,ab OR "DAIR".ti,ab OR "debridement, antibiotics and implant retention".ti,ab OR "debridement, antibiotics and implant retention dair".ti,ab OR "debridement, antibiotics, and implant retention".ti,ab OR "implant retention".ti,ab) AND ("Prosthesis Infection".ti,ab OR "Prosthesis Infections".ti,ab OR "Prosthetic Infection".ti,ab OR "Prosthetic Infections".ti,ab OR "Prosthetic Joint Infection".ti,ab OR "Prosthetic Joint Infections".ti,ab OR "Prosthesis-Related Infections".ti,ab OR "Prosthesis-Related Infection".ti,ab OR "peri prosthetic joint infection".ti,ab OR "peri prosthetic joint infections".ti,ab OR "periprosthetic joint infection".ti,ab OR "periprosthetic joint infections".ti,ab OR ((exp *"Joint Prosthesis"/ OR "Arthroplasty, Replacement"/) AND (exp *"Infection"/ OR infect*.ti OR "deep infection".ti OR exp *"Wound Infection"/ OR exp *"Sepsis"/ OR exp *"Surgical Wound Infection"/)) OR (("Prosthesis".ti OR prosthe*.ti) AND ("Joint".ti OR "Joints".ti OR "Joints"/ OR "knee".ti OR "shoulder".ti OR "elbow".ti OR "hip".ti OR "knees".ti OR "shoulders".ti OR "elbows".ti OR "hips".ti) AND (exp*"Infection"/ OR infect*.ti OR "deep infection".ti OR exp *"Wound Infection"/ OR exp *"Sepsis"/ OR exp *"Surgical Wound Infection"/))) AND ("success rate".ti,ab OR "success rates".ti,ab OR "success".ti,ab OR succes*.ti,ab OR "failure rate".ti,ab OR "failure rates".ti,ab OR "failure".ti,ab OR fail*.ti,ab OR "infection control".ti,ab OR exp *"Treatment Outcome"/ OR "Treatment Outcome".ti,ab OR "outcome".ti,ab OR "outcomes".ti,ab)) NOT (exp "Animals"/ NOT exp "Humans"/) NOT (("Case Reports"/ OR "case report".ti) NOT ("Review"/ OR "review".ti OR "Clinical Study"/ OR "trial".ti OR "RCT".ti)).

B.3. Web of Science

(ts=("Debridement" OR "debridement" OR debrid* OR "DAIR" OR "debridement, antibiotics and implant retention" OR "debridement, antibiotics and implant retention dair" OR "debridement, antibiotics, and implant retention" OR "implant retention") AND (ts=("Prosthesis Infection" OR "Prosthesis Infections" OR "Prosthetic Infection" OR "Prosthetic Infections" OR "Prosthetic Joint Infection" OR "Prosthetic Joint Infections" OR "Prosthesis-Related Infections" OR "Prosthesis-Related Infection" OR "peri prosthetic joint infection" OR "peri prosthetic joint infections" OR "periprosthetic joint infection" OR "periprosthetic joint infections") OR ti=(("Prosthesis" OR prosthe*) AND ("Joint" OR "Joints" OR "Joints" OR "knee" OR "shoulder" OR "elbow" OR "hip" OR "knees" OR "shoulders" OR "elbows" OR "hips") AND ("Infection" OR infect* OR "deep infection" OR "Wound Infection" OR "Sepsis" OR "Surgical Wound Infection"))) AND ts=("success rate" OR "success rates" OR "success" OR succes* OR "failure rate" OR "failure rates" OR "failure" OR fail* OR "infection control" OR "Treatment Outcome" OR "Treatment Outcome" OR "outcome" OR "outcomes")) NOT ti=("veterinary" OR "rabbit" OR "rabbits" OR "animal" OR "animals" OR "mouse" OR "mice" OR "rodent" OR "rodents" OR "rat" OR "rats" OR "pig" OR "pigs" OR "porcine" OR "horse" OR "horses" OR "equine" OR "cow" OR "cows" OR "bovine" OR "goat" OR "goats" OR "sheep" OR "ovine" OR "canine" OR "dog" OR "dogs" OR "feline" OR "cat" OR "cats") NOT ti=(("Case Reports" OR "case report") NOT ("Review" OR "review" OR "Clinical Study" OR "trial" OR "RCT")).

B.4. Cochrane Library

(("Debridement" OR "debridement" OR debrid* OR "DAIR" OR "debridement, antibiotics and implant retention" OR "debridement, antibiotics and implant retention dair" OR "debridement, antibiotics, and implant retention" OR "implant retention") AND (("Prosthesis Infection" OR "Prosthesis Infections" OR "Prosthetic Infection" OR "Prosthetic Infections" OR "Prosthetic Joint Infection" OR "Prosthetic Joint Infections" OR "Prosthesis-Related Infections" OR "Prosthesis-Related Infection" OR "peri prosthetic joint infection" OR "peri prosthetic joint infections" OR "periprosthetic joint infection" OR "periprosthetic joint infections") OR (("Prosthesis" OR prosthe*) AND ("Joint" OR "Joints" OR "Joints" OR "knee" OR "shoulder" OR "elbow" OR "hip" OR "knees" OR "shoulders" OR "elbows" OR "hips") AND ("Infection" OR infect* OR "deep infection" OR "Wound Infection" OR "Sepsis" OR "Surgical Wound Infection"))) AND ("success rate" OR "success rates" OR "success" OR uccess* OR "failure rate" OR "failure rates" OR "failure" OR fail* OR "infection control" OR "Treatment Outcome" OR "Treatment Outcome" OR "outcome" OR "outcomes")):ti,ab,kw.

Appendix B. Included studies

1. Andronic O, Achermann Y, Jentzsch T, Bearth F, Schweizer A, Wieser K, Fucentese SF, Rahm S, Zinkernagel AS, Zingg PO (2021) Factors affecting outcome in the treatment of streptococcal periprosthetic joint infections: results from a single-centre retrospective cohort study. Int Orthop 45:57–63. doi:10.1007/s00264-020-04722-7.
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4. Hirsiger S, Betz M, Stafylakis D, Götschi T, Lew D, Uçkay I (2019) The Benefice of Mobile Parts' Exchange in the Management of Infected Total Joint Arthroplasties with Prosthesis Retention (DAIR Procedure). J Clin Med 8. doi:10.3390/jcm8020226.
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19. Shohat N, Goswami K, Tan TL, Yayac M, Soriano A, Sousa R, Wouthuyzen-Bakker M, Parvizi J (2020) 2020 Frank Stinchfield Award: Identifying who will fail following irrigation and debridement for prosthetic joint infection. Bone Joint J 102-b:11-19. doi:10.1302/0301-620x.102b7.Bjj-2019-1628.R1.
20. Swenson RD, Butterfield JA, Irwin TJ, Zurlo JJ, Davis CM, 3rd (2018) Preoperative Anemia Is Associated With Failure of Open Debridement Polyethylene Exchange in Acute and Acute Hematogenous Prosthetic Joint Infection. J Arthroplasty 33:1855-1860. doi:10.1016/j.arth.2018.01.042.
21. Tirumala V, Smith E, Box H, van den Kieboom J, Klemt C, Kwon YM (2021) Outcome of Debridement, Antibiotics, and Implant Retention With Modular Component Exchange in Acute Culture-Negative Periprosthetic Joint Infections. J Arthroplasty 36:1087-1093. doi:10.1016/j.arth.2020.08.065.
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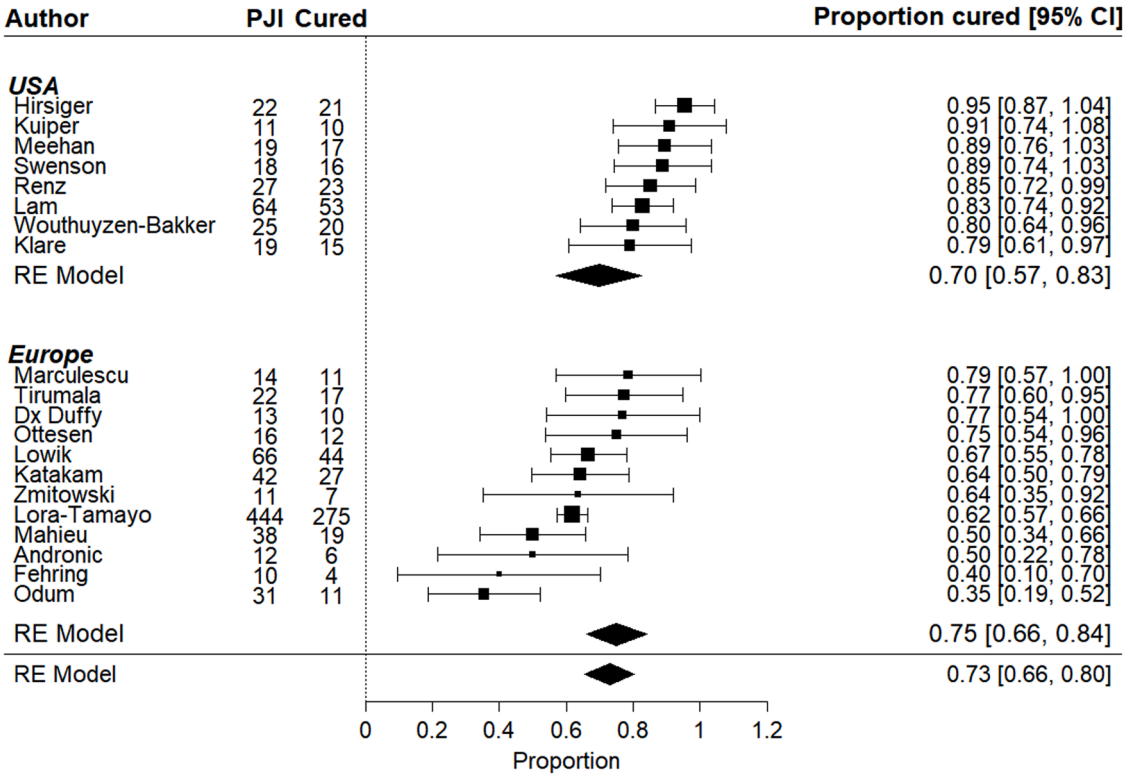
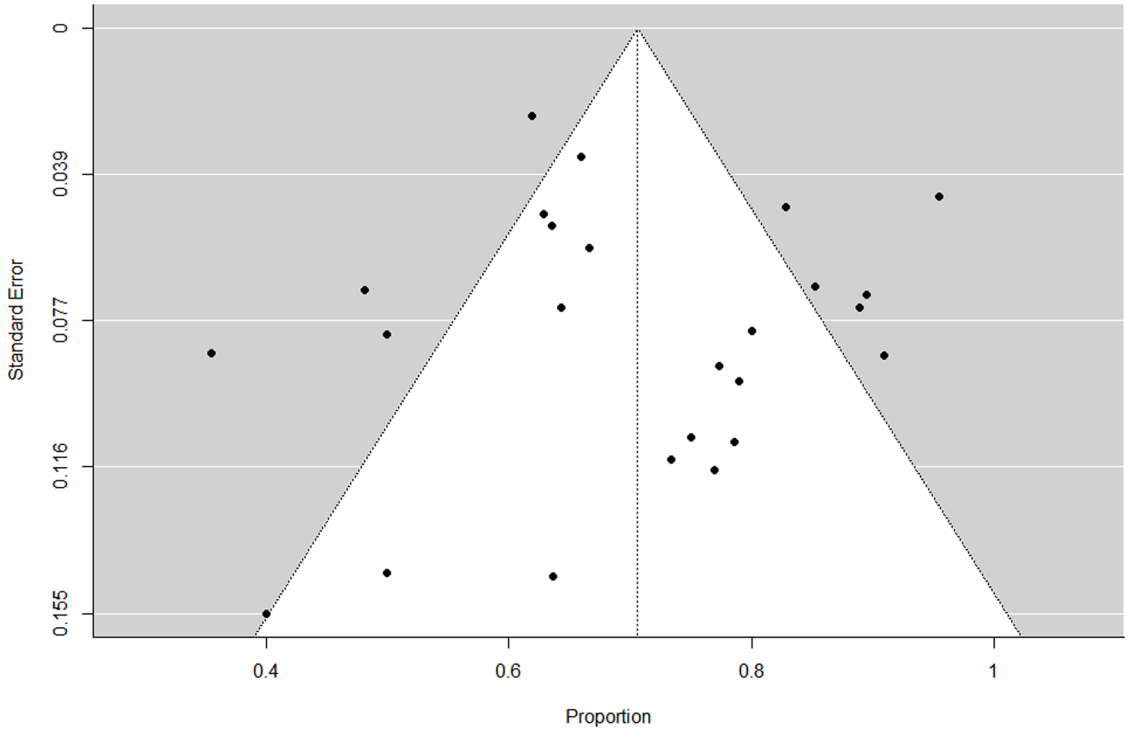
Appendix C. Forest plot for European studies and studies in the USA



Appendix D. AQUILA score for included articles

AQUILA Methodological Quality Items	Number of Studies
1. Is there a clear primary research question/hypothesis?	Yes: 23 of 25
2. How were the cohorts constructed?	
A Consecutively	A: 22 of 25
B Non-consecutively	B: 2 of 25
C Unknown	C: 1 of 25
3 How adequate was the follow-up?	
A Fully completed FU	A: 2 of 25
B $\leq$ 5% lost-to-FU or FU quotient is $\leq$ 1	B: 1 of 25
C $>$ 5% lost-to-FU or FU quotient is $>$ 1	C: 4 of 25
D unknown	D: 18 of 25
4. How was the follow-up performed?	
A Predefined (e.g. yearly)	A: 1 of 25
B When the patient had complaints or FU)	B: 22 of 25
C Unknown	C: 2 of 25
5. How many arthroplasties are at risk at the FU of interest?	
A $\geq$ 20	A: 13 of 25
B $<$ 20	B: 12 of 25
C Unknown	C: 0 of 25
6. Has a multivariate risk analysis for competing factors been performed?	Yes: 7 of 25

Appendix E. Funnel plot of the included studies



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