Kunutsor, S. K., Barrett, M. C., Whitehouse, M. R., Craig, R. S., Lenguerrand, E., Beswick, A. D., & Blom, A. W. (2020). Incidence, temporal trends and potential risk factors for prosthetic joint infection after primary total shoulder and elbow replacement: Systematic review and meta-analysis. *Journal of Infection*, 80(4), 426-436.
<https://doi.org/10.1016/j.jinf.2020.01.008>

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[10.1016/j.jinf.2020.01.008](https://doi.org/10.1016/j.jinf.2020.01.008)

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Incidence, temporal trends and potential risk factors for prosthetic joint infection after primary total shoulder and elbow replacement: systematic review and meta-analysis

Running Title: PJI following total shoulder and elbow replacement

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Summary

Objectives: We conducted a systematic meta-analysis to evaluate the incidence, temporal trends and potential risk factors for prosthetic joint infection (PJI) following primary total shoulder replacement (TSR) and elbow replacement (TER).

Methods: Longitudinal studies reporting infection outcomes following primary TSR or TER were sought from MEDLINE, Embase and Cochrane Library up to June 2019. Incidence rates and relative risks (with 95% CIs) were calculated.

Results: The search identified 105 eligible articles (108 non-overlapping studies). There were 631,854 TSRs (1,751 PJIs) and 17,485 TERs (525 PJIs). The pooled PJI incidence following TSR was 0.61% (0.34-0.93) over a follow-up period of 1.1 years. The corresponding incidence following TER was 2.53% (1.99-3.12) over a follow-up period of 3.3 years. Shoulder and elbow PJI incidence declined from the 1990s to 2010 and beyond. Males, younger age (<75 years), previous shoulder surgery, reverse TSR, rotator cuff arthropathy and inpatient TSR increased shoulder PJI risk. For TER, high body mass index, psychiatric illness, and previous elbow surgery increased PJI risk.

Conclusions: Shoulder and elbow PJI may be on a temporal decline. Caution should be taken for patients at high PJI risk following primary TSR such as younger males and patients with a previous shoulder surgery.

Systematic review registration: PROSPERO 2019: CRD42019139100

Key words: incidence; temporal trends; risk factor; prosthetic joint infection; total shoulder replacement; total elbow replacement; meta-analysis

Introduction

Prosthetic joint infection (PJI) is a potentially devastating, albeit uncommon complication of total joint replacement (TJR) which often results in the need for implant revision.(1, 2) Prosthetic joint infection carries a substantial public health burden; being an important cause of reduced quality of life in affected patients,(3-5) high healthcare costs(6) and even death if left untreated.(7) Though PJI can occur in any joint following TJR, much of the literature on the incidence, risk factors, diagnosis, prevention, and treatment of PJI following TJR is based on lower extremity joints (hip and knee joints). This is because hip and knee replacement are more common than shoulder and elbow replacements. In England and Wales in 2017, approximately 100,000 joint replacements were performed each in knees and hips; whereas only approximately 7,000 shoulder and 600 elbow replacements were performed, as recorded in the largest mandated national arthroplasty registry – the National Joint Registry for England, Wales and Northern Ireland and the Isle of Man.(8) Though it has been reported that PJI of the shoulder is less frequent compared to PJI of the knee and hip(9) and affects about 1% of patients,(10) treatment of shoulder PJI is more challenging(11, 12) and associated with higher morbidity and costs compared with PJIs of other joints.(13, 14) Compared with hip or knee replacement, there is a higher incidence of PJI following total elbow replacement (TER) which has been reported to range between 1-19%.(15-18)

Given that only relatively few shoulders and elbows are replaced each year, the literature is sparse on incidence rates for PJI and potential factors that influence the risk of PJI for these joints. The reported incidence rates in the literature have been based on small case series and are highly variable. Though there is established evidence that several patient-, surgery-, and hospital-related factors are associated with the risk of PJI following total hip and knee replacement,(19-21) it is uncertain if these potential risk factors also influence PJI risk following total shoulder and elbow replacement in a similar way. Furthermore, different risk factors may be related to different bacterial profiles for PJI in different joints. For example, though the most commonly identified microorganisms in PJI of the shoulder are *Cutibacterium acnes*, *Staphylococcus aureus*, and coagulase-negative *Staphylococcus aureus*, indolent bacteria such as *Cutibacterium acnes* are predominant in shoulder PJIs and are hardly seen in PJIs of the hips and knees.(22) Amongst all orthopaedic joint replacements, the numbers of shoulder and elbow joint replacements are increasing most rapidly; in the United States, the number of shoulder replacements increased from 28,000 per year between 2000 and 2008 to about 100,000 in 2015.(23) It is expected there will be a seven-fold increase in demand of shoulder replacements over the next 15 years.(24) Given recent innovations in total joint replacement or adoption of strategies to mitigate the risk

of PJI, temporal changes in the incidence of PJI are expected. Hence, there is a need for robust aggregation of data on PJI incidence and its temporal trends as well as identification of potential risk factors for the development of PJI following upper extremity joint replacement. This data will be of great value for policy makers, healthcare systems and clinicians to aid in planning and implementing more efficacious preventative strategies. In this context, using a systematic review and meta-analysis, we aimed to (i) pool incidence of PJI following primary total shoulder replacement (TSR) and TER and characterise their temporal trends; (ii) quantify the nature and magnitude of associations of potential patient-, surgery-, and hospital-related factors with the risk of PJI following primary TSR and TER; and (iii) to identify potential gaps in the existing literature.

Methods

Data sources and search strategy

This review conducted according to a pre-defined protocol and PRISMA and MOOSE guidelines(25, 26) (**Supplementary Materials 1-2**) was registered with the prospective register of systematic reviews, PROSPERO (CRD42019139100). An electronic search of MEDLINE, Embase and Cochrane databases was performed from inception to 20 June 2019 for studies reporting on PJI outcomes following TSR or TER. The computer-based searches used free and MeSH search terms and combination of key words related to the population (e.g., “total shoulder replacement”, “total elbow replacement”) and outcome (e.g., “prosthetic joint infection”, “deep infection”) with no language restrictions (**Supplementary Material 3**). Following retrieval of potential studies, the titles and abstracts were initially screened to assess their suitability for inclusion, after which full texts of potentially relevant studies were acquired for more detailed evaluation. The evaluation was conducted independently by two experienced reviewers (SKK and MCB) and where there were disagreements regarding eligibility of an article, this was discussed with a third reviewer (MRW) to reach consensus. Reference lists of relevant studies and reviews were reviewed manually to check for potential eligible studies missed by the search strategy.

Eligibility criteria

All longitudinal studies (prospective or retrospective cohorts, nested case-controls, case-cohorts, case series, or clinical trials) were included in the review if they recruited patients who had undergone elective primary TSR (anatomic TSR or reverse TSR) or TER, reported on outcomes of PJI following the surgery and/or reported on the associations of PJI with any patient-related factors (e.g., sociodemographic characteristics, anthropometric measures,

or past medical and/or surgical history), surgery-related factors (e.g., procedure type or use of bone cement), or hospital-related factors (such as hospital volume or surgeon experience). Studies that included both elective and trauma indications for surgery or included both total and partial (e.g. hemiarthroplasty) joint replacements were considered and included if they contained large mixed samples. The primary outcome was PJI (which included deep infection, deep surgical site infection, or deep prosthetic infection), with superficial wound infection being a secondary outcome. The following studies were excluded: (i) comprising revision total shoulder or elbow joint replacements or a mixture of primary and revision joint replacements from which data could not be extracted on primary joint replacements; (ii) comprising of selected populations or patients with prevalent conditions (e.g. diabetes, haemophilia, etc.) or selected populations with no comparison or control groups; (iii) assessed exposures (conditions) that developed after the joint replacement; and (iv) that exclusively focused on any other surgical approach apart from total elbow or shoulder replacement such as in the setting of trauma, non-union, fracture, bilateral arthroplasty, arthroscopy or hemiarthroplasty.

Data extraction and quality assessment

Data was initially extracted by one experienced reviewer (SKK) using a standardized data collection form which has been pre-tested and employed in several previous reviews of a similar nature.(19, 27) The second reviewer (MCB) independently checked the extracted data with that in original articles and any disagreements were discussed with the third reviewer (MRW) to reach a consensus. Data was extracted on study level characteristics, type of joint, sample size, type of and counts for outcomes, risk estimates for outcomes (relative risks (RRs), hazard ratios (HRs), or odds ratios (ORs)) and degree of adjustment for potential confounders (univariable or multivariable). When there were multiple publications involving the same study or cohort, we extracted the most comprehensive up-to-date single set of results to avoid double counting in our analyses. We contacted study investigators to provide additional data where necessary. The methodological quality of each study was assessed using the nine-star Newcastle-Ottawa Scale (NOS) validated for assessing the quality of non-randomised studies(28) and uses three pre-defined domains including: (i) selection of participants; (ii) comparability; and (iii) ascertainment of outcomes of interest. Nine points on the NOS reflects the highest study quality.

Data synthesis and analyses

In pooling PJI incidence across studies, the incidence (estimated from the number of PJI outcomes within period of follow-up/total number of participants or procedures as reported) with 95% confidence intervals (CIs) was used as the summary measure. Given that the data was binary with low rates, the Freeman-Tukey variance stabilising double arcsine transformation (29) was used in calculating the rates as done in previous reports.(30-32) Temporal trends in incidence were evaluated using the median year of data collection/surgery reported by studies, as previously reported.(33) The measures of association were presented as RRs with 95% CIs. Following Cornfield's rare disease assumption(34), HRs and ORs were assumed to approximate the same measure of RR. Multivariable-adjusted risk estimates were used for pooling when reported, otherwise crude RRs were calculated from studies that provided raw counts. Different BMI cut-offs were reported by the eligible studies, hence to ensure consistency in the pooling approach and enhance comparability and interpretation of findings, we employed the following risk comparisons based on the data available and to maintain consistency with previous reports: ≥ 25 vs. < 25 , ≥ 30 vs. < 30 , ≥ 40 vs. < 40 kg/m² and per unit increase in BMI.(19, 27) Random-effects models by DerSimonian and Laird which takes into account heterogeneity both within and between studies, were used to combine RRs and account for the effect of heterogeneity.(35) In the absence of substantial heterogeneity, fixed-effect models were employed. We estimated 95% prediction intervals to determine the degree of heterogeneity, as they provide a range in which the underlying true effects of future studies will lie with 95% certainty.(36, 37) We conducted stratified analyses and random effects meta-regression to assess several pre-defined study level characteristics which could explain heterogeneity between the studies.(38) All statistical analyses were conducted using STATA SE 15.1 (Stata Corp, College Station, Texas, USA).

Results

Study identification and selection

The study selection progress is summarised in **Fig. 1**. A total of 244 potential citations were identified after the literature search and manual screening of relevant articles. Of these, 153 seemed to satisfy the review inclusion criteria based on titles and abstracts. Following detailed evaluation of full texts, 48 citations were excluded due to the following reasons: (i) population was not relevant (n=21); (ii) duplicate of another study included in review (n=14); (iii) the outcome was not relevant (n=9); (iv) study design was not relevant (n=3); and (v) full text not accessible (n=1). The remaining 105 citations which comprised of 108 non-overlapping studies were eligible to be included in the review (**Fig. 1; Supplementary Material 4**).

Study characteristics and study quality

The 108 distinct studies comprised of 24 studies of TSRs and 84 of TERs. Publication dates of included studies ranged from 1989 to 2019. **Table 1** is a summary table of relevant study characteristics for both types of joint replacements.

Supplementary Material 5 provides details of the key characteristics and quality assessment scores of the individual studies. Overall, there were 631,854 TSRs and 1,751 PJIs; the corresponding figures for TERs were 17,485 and 525 respectively.

Patient populations were recruited from North America (Canada and USA), Europe (Belgium, Czech, Denmark, Finland, France, Germany, Italy, The Netherlands, Norway, Switzerland, Spain and Sweden, UK), Asia (China, Korea and Japan) and the Pacific (Australia). For TSRs, the weighted mean age and mean follow-up duration was 68.8 and 1.3 years respectively and that for TERs was 59.5 and 3.3 years respectively. Prosthetic joint infection outcomes were reported in a variety of ways which included infection, deep infection, surgical site infection, and revision for infection (**Supplementary Material 5**). Registry studies reported this outcome as revision due to infection, which was defined as removal or exchange of the whole or part of the prosthesis with infection reported as the cause of revision. The majority of studies did not provide details on the definition of infection or its diagnosis. However, a few studies defined PJI based on findings by the surgeon at preoperative assessment and during surgery. The majority of studies did not provide information on bacterial profiles responsible for infection; however, for the few studies that reported these data, the most predominant bacteria were *Cutibacterium acnes* and *Staphylococcus aureus* (**Supplementary Material 5**). Methodological quality of all included studies ranged from 6-9.

Incidence of infection following primary TSR

Across 22 studies of TSR with relevant data, the incidence of PJI over a weighted mean follow-up duration of 1.1 years ranged from 0.00% to 4.56%. The pooled random effects incidence (95% CI) over this follow-up duration was 0.61% (0.34-0.93) (**Fig. 2**). The 95% prediction interval for the summary incidence was 0.00 to 2.32%, suggesting that the true incidence for any single new study will usually fall within this range. The pooled incidence of superficial wound infection of three studies over a weighted mean follow-up duration of 7.4 years was 0.08% (0.00-0.42). Comparing PJI outcome by TSR procedure type, the PJI incidence for anatomic TSR was 0.48% (0.28-0.73) over a weighted mean follow-up duration of 2.4 years and that for reverse TSR was 0.78% (0.06-2.02) over a weighted mean follow-up duration of approximately 1 year (**Supplementary Material 6**). The pooled incidence of PJI at specific

average follow-up periods reported by studies was 0.10% (0.07-0.14) at < 30 days, 0.34% (0.11-0.67) at 30 days, 0.16% (0.12-0.22) at 60 days, 0.34% (0.12-0.64) at 3 months, 0.59% (0.49-0.72) at 6 months, 0.39% (0.03-0.99) at 1 year, 1.29% (0.72-2.01) at 2 years, 1.18% (0.37-2.32) at 3 years, 1.21 (0.88-1.58) at 5 years, 1.05% (0.79-1.39) at 10 years, and 1.51% (1.22-1.87) at 15 years (**Supplementary Material 7**). Based on the median year of data collection/surgery, the pooled incidence of PJI was 1.51% (1.22-1.87) in the 1990s, 0.61% (0.26-1.07) in 2000-2009 and 0.63% (0.22-1.18) in 2010 and beyond (**Fig. 3A**). In meta-regression analysis, there was no significant association between PJI incidence and median year of data collection/surgery ($p=0.801$) (**Fig. 3B**).

Incidence of infection following primary TER

Across 82 studies of TER with relevant data, PJI incidence over a weighted mean follow-up duration of 3.3 years ranged from 0.00% to 11.76%. The pooled random effects incidence (95% CI) over this follow-up period was 2.53% (1.99-3.12) (**Fig. 4**). In pooled analysis of 11 studies, the incidence of superficial wound infection over a weighted mean follow-up duration of 9.4 years was 1.45% (0.19-3.44). Comparing PJI outcome by type of elbow prosthesis (linked vs. unlinked), the PJI incidence for linked elbow prosthesis was 2.35% (1.55-3.28) over a weighted mean follow-up duration of 6.2 years and that for unlinked prosthesis was 2.01% (1.39-2.72) over a weighted mean follow-up duration of 8.8 years (**Supplementary Material 8**). The pooled incidence of PJI at specific average follow-up periods reported by studies was 1.59% (0.54-4.56) at 30 days, 2.67% (2.10-3.31) at 90 days, 2.00% (0.35-10.50) at 1 year, 5.89% (1.56-12.03) at 2 years, 1.86% (0.91-3.04) at 3 years, 3.22 (2.22-4.35) at 5 years, 1.49% (0.61-2.64) at 10 years, and 0.50% (0.00-3.00) at 15 years (**Supplementary Material 9**). There seemed to be a temporal decline in PJI incidence from the 1980s to 2010 and beyond based on median year of data collection (**Fig. 3C**), but the decline was not statistically significant in a meta-regression analysis ($p=0.683$) (**Fig. 3D**).

Potential risk factors for PJI following primary TSR

The associations of sociodemographic, BMI comparisons, medical and surgical history characteristics with the risk of PJI following TSR are summarised in **Fig. 5**. Older age was associated with a decreased risk of PJI: RRs (95% CIs) of 0.62 (0.48-0.79) and 0.95 (0.92-0.98) comparing age ≥ 75 years vs. < 75 years and per one-year increase respectively. Comparing males with females in three studies, the pooled RR (95% CI) for PJI was 1.95 (1.52-2.48) (**Fig. 5**). There was no strong evidence of associations of other sociodemographic characteristics such as race and smoking status with the risk of PJI following TSR. None of the BMI comparisons was associated with PJI risk; however, there was a

marginally significant increase in PJI risk comparing BMI ≥ 30 vs. <30 kg/m² RR (95% CI) of 1.60 (0.99-2.56). A history of sleep apnoea and previous shoulder surgery were each associated with an increased risk of PJI, RRs (95% CIs) of 1.33 (1.15-1.54) and 1.92 (1.14-3.23) respectively. In evaluation of surgical indications for TSR, neither rheumatoid arthritis nor inflammatory arthritis was associated with PJI risk; however, rotator cuff arthropathy was associated with an increased risk of PJI when compared with osteoarthritis, RR (95% CI) of 3.13 (2.01-4.87) (**Fig. 5**). The associations of surgery- and hospital-related factors with risk of PJI following TSR are summarised in **Fig. 6**. Comparing reverse TSR vs. anatomic TSR and outpatient TSR vs inpatient TSR, RRs (95% CIs) were 2.19 (1.66-2.89) and 0.38 (0.21-0.69) respectively. Other factors such as implant fixation, surgeon experience and period or seasonality of surgery were not found to be associated with PJI risk following TSR (**Fig. 6**). In a retrospective study that compared an innovative supplemental UV-C air decontamination technology plus standard HEPA-filtered HVAC versus standard HEPA-filtered HVAC for the incidence of PJI following TSR, no cases of PJI occurred in either group after 12 months of follow-up.(39)

Potential risk factors for PJI following primary TER

Only two studies were identified to have quantitatively assessed potential risk factors for PJI following primary TER. The RR (95% CI) for PJI comparing BMI ≥ 30 vs <30 and ≥ 40 vs <40 kg/m² was 2.20 (1.60-3.10) and 2.50 (1.89-3.29) respectively (**Supplementary Material 10**). A history of psychiatric illness and a previous elbow surgery were each associated with increased PJI risk.

Discussion

Key findings

Over a weighted average follow-up period of about a year, the incidence rates for PJI following primary TSR ranged from 0.00 to 4.56% across individual studies and averaged approximately 0.61% in pooled analysis. The PJI incidence was higher following reverse TSR compared with anatomic TSR. For TER, the PJI incidence rate ranged from 0.00% to 11.76% across individual studies and averaged 2.53% over an average follow-up period of approximately 3 years. The PJI incidence rates for linked and unlinked elbow prosthesis were similar, ranging from 2.01% to 2.35%. For both shoulder and elbow joints, the risk of PJI is not constant in the post-operative period but appears to be higher at 2 years postoperative. There appeared to be a temporal decline in both shoulder and elbow PJI rates from the 1980s/1990s to 2010 and beyond, but findings were not robust. On the role of patient-related factors and their

associations with the risk of PJI following TSR, younger patients, males, and patients with a previous shoulder surgery, each had an increased risk of PJI. The increased PJI risk associated with younger patients is unclear,(40) but that in males has been attributed to a higher bacterial load of *Cutibacterium acnes*.(41) The findings in males may reflect the observation that *Cutibacterium acnes* was the predominant bacteria in one of the studies contributing to the pooled analysis.(41) The finding of an increased risk of PJI associated with rotator cuff arthropathy compared to osteoarthritis probably reflects less protection of the implant by vascularised tissue, hence more haematoma formation which increases the risk of infection;(42) on the other hand, this finding may reflect the use of reverse TSR in treating rotator cuff arthropathy rather than the surgical indication itself. Compared to anatomic TSR, reverse TSR is commonly used in treating rotator cuff arthropathy(43) and is also associated with higher incidence of PJIs as confirmed in our aggregate review. Patients with a history of sleep apnoea also had an increased risk of PJI. Sleep apnoea might be a surrogate measure for obesity, smoking, or cardiopulmonary complications,(44, 45) which are factors known to increase the risk of PJI in hip and knee joints.(19-21) In the current study, obesity was potentially associated with an increased risk of PJI following TSR, but the result was marginally significant. Compared to inpatient TSR, outpatient TSR was associated with a reduced risk of PJI, which likely reflects a patient selection effect. For TER, high BMI, psychiatric illness, and previous elbow surgery increased the risk of PJI.

Comparison with previous work

A number of previous reviews have attempted to synthesise the evidence on incidence rates of PJI following TER, but these reports have either been based on few studies or did not employ meta-analytic approaches to summarise the evidence. Voloshin and colleagues reported the deep infection rate to be 3.3%.(46) Welsink and colleagues recently reviewed 73 articles comprising a total of 9,379 TERs in an attempt to summarise survival rates, functional results and complication rates of TER implants.(47) The authors reported a deep infection rate of 3.4% (207 of 6,091 TERs). van der Lugt and colleagues have also reported infection rates ranging from 0.7% to 4.0% according to the type of elbow prosthesis used.(48) Though these previous reports provide relevant findings, a major limitation in their approach was that incidence rates were estimated from the number of infections divided by the total number of joint procedures and expressed as a percentage; hence, such findings do not account for time. By employing relevant statistical approaches and taking into account the period of follow-up (weighted means), our review represents the first attempt at evaluating and synthesising overall PJI incidence rates, period-specific PJI risk and its temporal trends. We did not identify any previous review that has summarised or synthesized evidence on the incidence of PJI following TSR. Furthermore,

this is the first aggregate analysis to evaluate the associations of patient-, surgery-, and hospital-related factors with PJI risk following TSR. The current review has also identified large gaps in the existing literature – though TERs are associated with higher incidence of PJIs compared with hip, knee or shoulder replacements,(15-17) only a few studies have evaluated the role of potential risk factors for PJI development in these joint and this may reflect the fact that relatively few elbow replacements are performed compared to shoulders, hips or knees.(8) Furthermore, existing cases series are small and have low event rates, hence do not have adequate power to investigate potential associations.

Implications of our findings

With increase in life expectancy and a growing burden due to degenerative conditions such as rotator cuff arthropathy and osteoarthritis, there will be an increase in demand for joint replacements. Though relatively few total shoulder and elbow replacements are performed compared with hip or knee replacements,(8) recent data suggests that there will be a sharp increase in demand for TSRs over the next decade.(24) The temporal decline in the incidence of PJI suggested by our findings is not unexpected and this likely reflects innovations in surgical procedures and behaviour, as well as antibiotic prophylaxis. However, with the increase in demand for shoulder replacements especially, it is likely there will be a proportionate rise in the overall burden of PJIs. The social, health and economic costs associated with shoulder and elbow PJI and its treatment are substantial and potentially devastating.(22, 49-51) Our data on the incidence rates and temporal trends of PJI is a valuable data resource for clinicians and policy makers, as it enables quantification of the societal impact of PJIs and assists in planning purposes. The high PJI rates following TSR and TER at 2 years postoperative compared to the immediate postoperative period, suggests that patients should have at least a minimum follow-up of 2 years following primary surgery. We have also shown that the aetiology of PJI following TSR is multifactorial and is influenced by several modifiable factors which can be optimised prior to joint surgery. Recognition of unmodifiable factors such as younger age and male sex could be used to counsel patients regarding their individual risk for PJI when undergoing joint replacement. In cases where it is felt that there is a high risk of needing to carry out a joint replacement in the near future, patients may prefer to avoid other, temporising surgical procedures that would lead to an increase in their risk of subsequent PJI. Finally, our findings provide insight on the large gaps in the existing literature regarding definitive evidence on the role of potential risk factors for PJI following total shoulder and elbow replacements. Investigators of case series on these upper extremity joint replacements are encouraged to publish their findings in relation to follow-up for PJI outcomes.

Study strengths and limitations

To our knowledge, this is the first aggregate analysis to assess the overall and period-specific incidence of and temporal trends in PJI following primary total shoulder and elbow replacement and evaluate the associations of patient-, surgery-, and hospital-related factors with PJI risk in one single comprehensive investigation. Appropriate meta-analytic approaches were utilised in all analyses and which included accounting for heterogeneity between contributing studies and ensuring that studies with zero rates were not excluded from the pooled analysis as well as the use of meta-regression techniques. We conducted quality assessments using a validated tool and employed comprehensive data checks to ensure that participants were not double during pooling, given that some of the articles were based on the same database or study. There were a number of limitations: (i) there was absence of clear definitions for PJI in the majority of studies and these were reported in a variety of ways for studies that reported these data; we acknowledge that this did not enhance consistency of the pooling approach and could have limited the validity of the findings. In addition, a number of registry studies were included in our analyses and these are known to under-report revision for PJI and thus their incidence estimates of PJI are potentially lower;(52) (ii) furthermore, incidence rates for PJI following TSR may be underestimates, given that PJI in the shoulder is difficult to diagnose especially when associated with low virulence infections caused by *Cutibacterium acnes*;(22) (iii) it is acknowledged that the associations could be influenced by the particular prevalence of bacteria associated with PJI in the data used; however, we were unable to explore this because majority of studies did not provide profiles of the bacteria causing PHI; (iv) though an eligibility criterion was to include only studies that recruited patients who had undergone elective TJR, a number of studies included a mix of elective and trauma indications for TJR, hemiarthroplasties, and resurfacing arthroplasties whose data could not be disentangled, hence the effect estimates may be biased; (v) the majority of studies did not adjust for confounding and for those that adjusted for confounding, there was a potential for residual confounding; (vi) findings on the temporal trends in PJI rates were based on median year of data collection reported by studies, which may not accurately capture specific periods of surgery and follow-up; and (vii) several of the findings on risk factor evaluations were based on single study reports with imprecise estimates, hence need interpretation with caution.

Conclusions

Over an average period of 1 year, the average incidence of PJI following TSR is less than 1%. Following TER, the incidence of PJI averages about 3% over an average duration of approximately 3 years. The risk of PJI following TSR

and TER is higher at 2 years postoperative compared to the immediate postoperative period. There appears to be a temporal decline in PJI rates following both primary total shoulder and joint replacements from the 1980s/1990s through to 2010 and beyond, though the evidence is not robust. The risk of PJI following primary TSR has a multifactorial aetiology and is influenced by a number of patient-, surgery-, and hospital-related factors. Particular caution should be taken for patients at high risk of PJI following primary TSR such as younger males and patients with a previous shoulder surgery or rotator cuff arthropathy and they should be counselled accordingly.

Conflict of interest

None.

Acknowledgements

This article presents independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research program (RP-PG-1210-12005). This study was supported by the NIHR Biomedical Research Centre at University Hospitals Bristol NHS Foundation Trust and the University of Bristol (BRC-1215-20011). RSC acknowledges support from the NIHR Oxford Biomedical Research Centre. The views expressed in this publication are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

We thank the following investigators for providing additional information or data on request: Professor Simon P Frostick, Department of Molecular and Clinical Cancer Medicine, Cancer Research Centre, 200 London Road, Liverpool L3 9TA; Prof Thomas (Quin) Throckmorton, MD, FAAOS, Shoulder and Elbow Surgery, Residency Program Director, University of Tennessee-Campbell Clinic, Department of Orthopaedic Surgery; and Armin Arshi, MD, Department of Orthopaedic Surgery, David Geffen School of Medicine, University of California, Los Angeles, 10833 Le Conte Ave, 76-143 CHS, Los Angeles, CA 90095-6902

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Figure Legends

Figure 1. PRISMA flow diagram

Figure 2. Incidence rates of infection following primary TSR across eligible studies

The summary incidence rate estimate presented was calculated using random effects models; CI, confidence interval (bars); PJI, prosthetic joint infection; TSR, total shoulder replacement

Figure 3. Temporal trends in PJI rates following primary TSR and TER

A, Incidence of TSR PJI by median year of data collection; B, Meta-regression bubble plot of incidence of TSR PJI against median year of study data collection; C, Incidence of TER PJI by median year of data collection; D, Meta-regression bubble plot of incidence of TER PJI against median year of study data collection; capped vertical bars represent 95% confidence intervals; PJI, prosthetic joint infection; TER, total elbow replacement; TSR, total shoulder replacement

Figure 4. Incidence rates of infection following primary TER across eligible studies

The summary incidence rate estimate presented was calculated using random effects models; CI, confidence interval (bars); PJI, prosthetic joint infection; TER, total elbow replacement

Figure 5. Sociodemographic characteristics, body mass index comparisons, medical and surgical history characteristics and risk of PJI following primary TSR

ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval (bars); IA, inflammatory arthritis; OA, osteoarthritis; PJI, prosthetic joint infection; RA, rheumatoid arthritis; RR, relative risk; TSR, total shoulder replacement

Figure 6. Surgery- and hospital-related factors and risk of PJI following primary TSR

CI, confidence interval (bars); PJI, prosthetic joint infection; RR, relative risk; TSR, total shoulder replacement

Table 1. Summary characteristics of the 109 unique studies

Characteristics	Total shoulder replacement (24 studies)	Total elbow replacement (85 studies)
Population	N	N
Participants/procedures	627,326	17,485
Prosthetic joint infection	1,751	525
Superficial wound infection	16	19
Study characteristics		
Location	N studies (N participants/procedures)	N studies (N participants/procedures)
<i>North America</i>	18 (613,434)	20 (10,773)
<i>Europe</i>	5 (18,380)	51 (5,795)
<i>Asia</i>	1 (40)	12 (889)
<i>Pacific</i>	-	1 (28)
Study design	N studies (N participants/procedures)	N studies (N participants/procedures)
<i>Retrospective cohorts</i>	19 (608,980)	72 (14,212)
<i>Prospective cohorts</i>	5 (22,874)	12 (3,273)
Weighted mean follow-up (min-max), years	1.27 (0.01-20.00)	3.31 (0.08-18.00)
Median (IQR) study quality score for observational studies	8 (7-9)	7 (6-7)
Study level participant characteristics		
Weighted mean age (min-max), years	68.8 (66.0-72.7)	59.5 (28.0-70.0)
Median (IQR) % males	43.6 (36.7-45.0)	22.6 (16.7-29.3)

IQR=interquartile range; N, number

Supplementary Material

Supplementary Material 1	PRISMA checklist
Supplementary Material 2	MOOSE checklist
Supplementary Material 3	Literature search strategy
Supplementary Material 4	Reference list of 106 included articles
Supplementary Material 5	Characteristics of studies included in review
Supplementary Material 6	Incidence rate of PJI by TSR procedure type
Supplementary Material 7	Incidence of PJI following primary TSR at specific average follow-up periods
Supplementary Material 8	Incidence rate of PJI by TER prosthesis type
Supplementary Material 9	Incidence of PJI following primary TER at specific average follow-up periods
Supplementary Material 10	Patient-related risk factors and risk of PJI following primary TER

Supplementary Material 1. PRISMA checklist

Section/topic	Item No	Checklist item	Reported on page No
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	Introduction
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	Methods
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	Methods
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	Methods
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	Supplementary Material 3
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	Methods
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	Methods
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made	Methods
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	Methods
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	Methods
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis	Methods
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	Methods
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	Methods
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	Results, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	Results, Table 1, Supplementary Material 5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	Results, Supplementary Material 5
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	Results, Figures 2-6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	Results, Figures 2-6; Supplementary Materials 6-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	Not applicable
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)	Results
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)	Discussion
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	Discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	Discussion
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	14

Supplementary Material 2. MOOSE checklist

Prosthetic joint infection following 649,376 primary total shoulder and elbow replacements: meta-analyses of incidence rates, temporal trends and potential risk factors

Criteria		Brief description of how the criteria were handled in the review
Reporting of background		
✓	Problem definition	Data on incidence rates of prosthetic joint infection (PJI) following upper extremity joint replacement is variable. Whether risk factors for PJI following hip and knee replacements influence the risk for PJI following upper extremity joint replacement in a similar manner is uncertain. We conducted a systematic meta-analysis to evaluate the incidence and its temporal trends as well as potential risk factors for PJI following primary total shoulder replacement (TSR) and elbow replacement (TER).
✓	Hypothesis statement	Several patient-, surgery-, implant-, and hospital-related factors influence the risk of PJI following primary TSR or TER
✓	Description of study outcomes	PJI and superficial wound infection
✓	Type of exposure	Patient-, surgery-, implant-, and hospital-related factors
✓	Type of study designs used	Longitudinal studies (prospective or retrospective case control, prospective cohort, retrospective cohort, case-cohort, nested-case control, or clinical trials)
✓	Study population	Patients followed for PJI following primary TSR or TER
Reporting of search strategy should include		
✓	Qualifications of searchers	
✓	Search strategy, including time period included in the synthesis and keywords	Time period: from inception to June 2019 The detailed search strategy can be found in Supplementary Material 3
✓	Databases and registries searched	MEDLINE, EMBASE, and Cochrane databases
✓	Search software used, name and version, including special features	OvidSP was used to search EMBASE and MEDLINE EndNote used to manage references
✓	Use of hand searching	We searched bibliographies of retrieved papers
✓	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the flow chart. The citation list for excluded studies are available on request.
✓	Method of addressing articles published in languages other than English	Not applicable
✓	Method of handling abstracts and unpublished studies	Abstracts with no full text publications were not included.
✓	Description of any contact with authors	We contacted authors of studies that did not provide adequate data in their studies
Reporting of methods should include		
✓	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria are described in the Methods section.
✓	Rationale for the selection and coding of data	Data extracted from each of the studies were relevant to the population characteristics, study design, exposure, and outcome.
✓	Assessment of confounding	We assessed confounding by ranking individual studies on the basis of different adjustment levels and performed sub-group analyses to evaluate differences in the overall estimates according to levels of adjustment.
✓	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Study quality was assessed based on the nine-star Newcastle–Ottawa Scale using pre-defined criteria namely: population representativeness, comparability (adjustment of confounders), ascertainment of outcome.
✓	Assessment of heterogeneity	Heterogeneity of the studies was quantified with I^2 statistic that provides the relative amount of variance of the summary effect due to the between-study heterogeneity and explored using meta-regression and stratified analyses
✓	Description of statistical methods in sufficient detail to be replicated	Description of methods of meta-analyses, sensitivity analyses, and meta-regression are detailed in the methods. We performed random effects meta-analysis with Stata 15.
✓	Provision of appropriate tables and graphics	Table 1; Figures 1-6; Supplementary Materials 1-10
Reporting of results should include		
✓	Graph summarizing individual study estimates and overall estimate	Figures 2-6; Supplementary Materials 6-10

√	Table giving descriptive information for each study included	Supplementary Material 5
√	Results of sensitivity testing	Not applicable
√	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary estimates, I ² values and results of sensitivity analyses
Reporting of discussion should include		
√	Quantitative assessment of bias	Sensitivity analyses indicate heterogeneity in strengths of the association due to most common biases in observational studies. The systematic review is limited in scope, as it involves published data. Individual participant data is needed. Limitations have been discussed.
√	Justification for exclusion	All studies were excluded based on the pre-defined inclusion criteria in methods section.
√	Assessment of quality of included studies	Brief discussion included in 'Methods' section
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	Discussion
√	Generalization of the conclusions	Discussed in the context of the results.
√	Guidelines for future research	We recommend analyses of individual participant data
√	Disclosure of funding source	In "Acknowledgement" section

Supplementary Material 3. Literature search strategy

Relevant studies, published from inception to 20 June 2019 (date last searched), were identified through electronic searches limited to the English language using MEDLINE, Embase, Web of Science, and Cochrane databases. Electronic searches were supplemented by scanning reference lists of articles identified for all relevant studies (including review articles), by hand searching of relevant journals and by correspondence with study investigators.

- 1 exp Arthroplasty, Replacement, Shoulder/ (761)
- 2 exp Arthroplasty, Replacement, Elbow/ (349)
- 3 periprosthetic joint infection.mp. (1171)
- 4 prosthetic joint infection.mp. (1173)
- 5 prosthetic infection.mp. (415)
- 6 exp Wound Infection/ (45091)
- 7 deep infection.mp. (2901)
- 8 exp Surgical Wound Infection/ (34798)
- 9 1 or 2 (1107)
- 10 3 or 4 or 5 or 6 or 7 or 8 (49918)
- 11 9 and 10 (64)
- 12 limit 11 to humans (64)

Each part was specifically translated for searching the other databases (EMBASE, Web of Science, and Cochrane databases)

Supplementary Material 4. Reference list of 106 included articles

1. Weiland AJ, Weiss AP, Wills RP, Moore JR. Capitellocondylar total elbow replacement. A long-term follow-up study. *J Bone Joint Surg Am.* 1989;71(2):217-22.
2. Morrey BF, Adams RA. Semiconstrained arthroplasty for the treatment of rheumatoid arthritis of the elbow. *J Bone Joint Surg Am.* 1992;74(4):479-90.
3. Ruth JT, Wilde AH. Capitellocondylar total elbow replacement. A long-term follow-up study. *J Bone Joint Surg Am.* 1992;74(1):95-100.
4. Ewald FC, Simmons ED, Jr., Sullivan JA, Thomas WH, Scott RD, Poss R, et al. Capitellocondylar total elbow replacement in rheumatoid arthritis. Long-term results. *J Bone Joint Surg Am.* 1993;75(4):498-507.
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8. Sjoden GO, Lundberg A, Blomgren GA. Late results of the Souter-Strathclyde total elbow prosthesis in rheumatoid arthritis. 6/19 implants loose after 5 years. *Acta Orthop Scand.* 1995;66(5):391-4.
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10. Allieu Y, Meyer zu Reckendorf G, Daude O. Long-term results of unconstrained Roper-Tuke total elbow arthroplasty in patients with rheumatoid arthritis. *J Shoulder Elbow Surg.* 1998;7(6):560-4.
11. Verstreken F, De Smet L, Westhovens R, Fabry G. Results of the Kudo elbow prosthesis in patients with rheumatoid arthritis: a preliminary report. *Clin Rheumatol.* 1998;17(4):325-8.
12. Gschwend N, Scheier NH, Baehler AR. Long-term results of the GSB III elbow arthroplasty. *J Bone Joint Surg Br.* 1999;81(6):1005-12.
13. Kudo H, Iwano K, Nishino J. Total elbow arthroplasty with use of a nonconstrained humeral component inserted without cement in patients who have rheumatoid arthritis. *J Bone Joint Surg Am.* 1999;81(9):1268-80.
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15. P. R. Souter-Strathclyde total elbow arthroplasty. 2000;82-B(8):1129-34.
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Supplementary Material 5. Characteristics of studies included in review

Author, year of publication	Country	Year of study	Type of implant	Study design	Mean/median age (years)	% males	Mean/median follow-up (yrs)	No. of participants	No. of infections	Endpoint used by report (Definition)	Predominant bacteria for infection	Study quality
TSR												
Singh, 2012	USA	1976-2008	NR	Prospective cohort	65.0	47.0	7.0	2588	32	Deep prosthetic infection (Surgeon reported)	<i>S. aureus</i> (31%); <i>Cutibacterium acnes</i> (19%)	8
Berth, 2013	Germany	2006-2009	NR	Prospective cohort	67.0	34.1	2.7	82	1	Superficial wound infection (NR)	NR	8
Richards, 2014	USA	2005-2011	NR	Retrospective cohort	69.7	44.0	2.7	4528	45	Deep infection (Modified NHSN/CDC guidelines)	<i>Cutibacterium acnes</i> (27.5%); CN <i>S. aureus</i> (13.7)	9
Chalmers, 2014	USA		NR	Retrospective cohort	66.3	42.0	> 90 days	127	0	Infection (NR)	NA	8
Griffin, 2014b	USA	1998-2008	NR	Retrospective cohort	68.8	44.0	2.57 days	31924	32	Infection (NR)	NR	7
Caceres-Sanchez, 2015	Spain	2004-2012	NR	Retrospective cohort	70.2	16.0	3.0	52	2	Deep infection (NR)	NR	7
Churchill, 2016	USA	2011-2012	Simpliciti canal-sparing	Prospective cohort	66.0	71.3	2.0	157	1	Infection (NR)	NR	8
Leschinger, 2016	Germany	1998-2009	Aequalis Total Shoulder	Prospective cohort	68.0	27.6	3.6	275	3	Infection (NR)	NR	9
Leroux, 2016	USA	2005-2014	NR	Retrospective cohort	NR	51.3	30 days	7197	48	Infection (NR)	NR	7
Villacis, 2016	USA	2011-2013	NR	Retrospective cohort	70.1	45.0	2.0	10844	140	Infection (NR)	NR	6
Anakwenze, 2017	USA	2007-2013	NR	Prospective cohort	70.1	47.4	2.6	4630	36	Deep SSI (NR)	NR	9
Basques, 2017	USA	2005-2012	NR	Retrospective cohort	NR	38.4	90 days	123347	633	SSI (NR)	NR	8
Cho, 2017	Korea	2010-2015	NR	Retrospective cohort	72.7	17.5	2.2	40	1	Deep infection (NR)	NR	6
Everhart, 2017	USA	2000-2011	NR	Retrospective cohort	NR	NR	30 days	485	16	SSI (Surgeon reported)	<i>Cutibacterium acnes</i> (42.9%)	8
Johansson, 2017	Sweden	2008-2012	NR	Retrospective cohort	NR	45.2	2.0	241	11	PJI (Microbiology)	<i>Cutibacterium acnes</i> (72.7%)	9
Rao, 2017	USA	2005-2012	NR	Retrospective cohort	NR	NR	30 days	1591	2	Deep infection (NR)	NR	8
Wagner, 2017	USA	1970-2013	NR	Retrospective cohort	68.0	45.0	10.0	4567	48	Deep infection (NR)	NR	9
Wagner, 2017b	USA	1970-2012	NR	Retrospective cohort	67.0	45.0	20.0	5494	83	PJI (NR)	NR	8
Werthel, 2017b	USA	1970-2012	NR	Retrospective cohort	66.2	45.0	6.8-7.4	4577	68	PJI (Surgeon reported)	NR	9
Arshi, 2018	USA	2007-2016	NR	Retrospective cohort	70-74	40.3	1.0	17542	118	Infection (NR)	NR	8
Chand, 2018	USA	2010-2016	NR	Retrospective cohort	71.7	46.7	90 days	184	4	SSI (NR)	NR	6
Nelson, 2018	USA	2009-2012	NR	Retrospective cohort	NR	NR	5.0	80	1	Deep infection (NR)	NR	7
Saltzman, 2018	USA	2002-2011	NR	Retrospective cohort	66-70.8	40.3	NR	372753	373	SSI (NR)	NR	8
Koh, 2018	USA	2006-2015	NR	Retrospective cohort	NR	43.6	30 days	11450	16	Deep infection (NR)	NR	8

Author, year of publication	Country	Year of study	Type of implant	Study design	Mean/median age (years)	% males	Mean/median follow-up (yrs)	No. of participants	No. of infections	Endpoint used by report (Definition)	Predominant bacteria for infection	Study quality
Scott, 2019	USA	2014	NR	Retrospective cohort	72.3	36.7	90 days	25196	45	Infection (NR)	NR	8
Cook, 2019	USA	2016-2017	NR	Retrospective cohort	NR	NR	1.0	24	0	PJI (MSIS criteria)	NA	7
Walters, 2019	USA	2009-2014	NR	Retrospective cohort	67.0	52.0	3.0	102	3	PJI (NR)	NR	6
Wang, 2019	USA	2005-2014	NR	Retrospective cohort	NR	48.9	2.0	33366	726	PJI (NR)	NR	7
Moeini, 2019	Denmark	2004-2013	NR	Prospective cohort	NR	30.4	3.8	17730	188	Revision for PJI (Surgeon reported)	NR	9
Yin, 2019	USA	2006-2015	NR	Retrospective cohort	63.9	39	30 days	2785	10	Deep SSI (NR)	NR	8
TER												
Weiland, 1989	USA	1976-1984	Capitellocondylar TER	Retrospective cohort	56.0	28.6	7.2	45	2	Deep infection (NR)	NR	7
Wolfe, 1990	USA	1974-1986	NR	Retrospective cohort	18-78	32.0	6.0	164	12	Deep infection (Culture findings)	<i>S. aureus</i> (75%)	7
Ruth, 1992	USA	1976-1986	Capitellocondylar TER	Retrospective cohort	56.0	12.2	6.5	51	4	Infection (NR)	CNSA (50%)	7
Morrey, 1992	USA	1982-1988	Coonrad/Morrey Total Elbow	Retrospective cohort	NR	NR	3.8	68	4	Infection (NR)	NR	7
Ewald, 1993	USA	1974-1987	Capitellocondylar TER	Retrospective cohort	NR	NR	5.8	312	7	Deep infection (NR)	NR	7
Ewald, 1993	USA	1974-1987	Capitellocondylar TER	Retrospective cohort	NR	NR	5.8	312	2	Superficial wound infection (NR)	NR	7
Kasten, 1993	USA	1974-1988	NR	Retrospective cohort	NR	NR	7.6	34	4	Infection (NR)	NR	7
Alnot, 1994	France	1986-1991	Guepar	Retrospective cohort	58.0	16.1	2.7	33	2	Deep infection (NR)	NR	6
Lyall, 1994	UK	1987-1990	Souter-Strathclyde	Retrospective cohort	60.0	23.5	3.4	19	0	Infection (NR)	NA	7
Kraay, 1994	USA	1983-1989	Semiconstrained prosthesis	Retrospective cohort	53.0	76.8	8.3	113	7	Deep infection (NR)	NR	7
Ljung, 1995	Sweden	1989-1993	Capitellocondylar TER	Prospective cohort	62.0	9.5	1.0	50	1	Infection (NR)	NR	5
Sjoden, 1995	Sweden	1982-1992	Souter-Strathclyde	Prospective cohort	62.0	16.7	5.0	19	0	Infection (NR)	NA	6
Risung, 1997	Norway	1987-1996	Norway Elbow	Prospective cohort	62.1	NR	4.3	118	2	Deep infection (NR)	NR	7
Allieu, 1998	France	1983-1989	Roper-Tuke	Retrospective cohort	52.8	NR	9.5	21	1	Infection (NR)	NR	7
Verstreken, 1998	Belgium	1991-1996	Kudo	Prospective cohort	56.0	26.7	3.0	16	1	Deep infection (NR)	NR	7
Gschwend, 1999	Switzerland	1978-1986	GSB III prosthesis	Retrospective cohort	NR	NR	13.5	59	3	Deep infection (NR)	NR	6
Kudo, 1999	Japan	1993-1999	Kudo type-5	Prospective cohort	55.0	13.5	3.8	43	0	Infection (NR)	NA	7
Schneeberger, 2000	Switzerland	1988-1995	GSB III prosthesis	Retrospective cohort	57.6	28.6	6.0	14	1	Infection (NR)	<i>Streptococcus Pneumoniae</i>	7
Hildebrand, 2000	Canada	1989-1996	Coonrad/Morrey Total Elbow	Retrospective cohort	64.0	28.6	4.2	51	3	PJI (NR)	NR	6
Rozing, 2000	Netherlands	1982-1993	Souter-Strathclyde	Retrospective cohort	60.0	37.3	7.8	66	3	Infection (NR)	NR	7

Author, year of publication	Country	Year of study	Type of implant	Study design	Mean/median age (years)	% males	Mean/median follow-up (yrs)	No. of participants	No. of infections	Endpoint used by report (Definition)	Predominant bacteria for infection	Study quality
Wright, 2000	USA	1985-1997	Mayo-Coonrad	Retrospective cohort	62.8	42.9	3.0	14	0	Infection (NR)	NA	7
Wright, 2000	USA	1985-1997	Ewald	Retrospective cohort	63.1	16.7	6.1	12	1	Infection (NR)	<i>Acinetobacter</i>	7
Dainton, 2002	UK	1987-1996	Souter-Strathclyde	Retrospective cohort	59.0	16.7	6.0	44	1	Deep infection (NR)	NR	6
Ikävalko, 2002	Finland	1982-1997	Souter-Strathclyde	Retrospective cohort	57.0	8.4	15.0	525	12	Deep infection (NR)	NR	7
Ikävalko, 2002	Finland	1982-1997	Souter-Strathclyde	Retrospective cohort	57.0	8.4	15.0	525	3	Superficial wound infection (NR)	NR	7
Rahme, 2002	Sweden	1992-1998	Kudo	Retrospective cohort	63.0	21.4	5.0	30	2	Deep infection (NR)	NR	7
Mansat, 2003	France	1988-1996	Guepar	Retrospective cohort	58.0	6.3	5.6	19	1	Deep infection (NR)	NR	6
Mansat, 2003	France	1988-1996	Guepar	Retrospective cohort	58.0	6.3	5.6	19	1	Superficial wound infection (NR)	NR	6
Lo, 2003	China	1992-2002	Coonrad/Morrey Total Elbow	Retrospective cohort	58.0	NR	3.0	23	1	Deep infection (NR)	MRSA	7
Espag, 2003	UK	1991-2000	Souter-Strathclyde	Retrospective cohort	NR	NR	5.7	11	0	Deep infection (NR)	NA	7
Espag, 2003	UK	1991-2000	Souter-Strathclyde	Retrospective cohort	NR	NR	5.7	11	2	Superficial wound infection (NR)	NR	7
Potter, 2003	UK	1993-1996	Kudo type-5	Retrospective cohort	60.0	NR	6.0	35	0	Infection (NR)	NA	5
Reinhard, 2003	Netherlands	1990-1997	Kudo type-4	Retrospective cohort	53.0	NR	7.0	57	1	Superficial wound infection (NR)	NR	7
Kelly, 2004	Australia	1988-1995	GSB III prosthesis	Retrospective cohort	NR	4.3	7.6	28	1	Deep infection (NR)	NR	6
Kelly, 2004	Australia	1988-1995	GSB III prosthesis	Retrospective cohort	NR	4.3	7.6	28	2	Superficial wound infection (NR)	NR	6
Willems, 2004	Belgium	1991-2002	Kudo	Retrospective cohort	57.5	34.3	4.8	36	1	Deep infection (NR)	NR	7
Ovesen, 2005	Denmark	1994-2000	Capitellocondylar TER	Retrospective cohort	56.4	29.3	6.9	51	3	Deep infection (NR)	NR	7
Little, 2005	UK	1992-1998	Souter-Strathclyde	Retrospective cohort	63.0	18.2	5.1	33	1	Infection (NR)	NR	7
Little, 2005	UK	1993-1997	Kudo	Retrospective cohort	60.0	33.3	5.6	33	0	Infection (NR)	NA	7
Little, 2005	UK	1997-1999	Coonrad/Morrey Total Elbow	Retrospective cohort	65.0	24.2	5.7	33	2	Infection (NR)	NR	7
Khatri, 2005	UK	1991-1996	Souter-Strathclyde	Retrospective cohort	61.0	19.1	6.8	47	3	Deep infection (NR)	<i>S. epidermidis</i> (33.3%)	7
van der Lugt, 2005	Netherlands	1982-2000	Souter-Strathclyde	Prospective cohort	NR	NR	6.4	204	10	Infection (NR)	NR	6
Landor, 2006	Czech	1988-2000	Souter-Strathclyde	Retrospective cohort	53.0	14.3	9.5	58	1	Deep infection (NR)	NR	7
Jensen, 2006	Denmark	1990-1997	GSB III prosthesis	Retrospective cohort	NR	15.8	5.0	23	0	Infection (NR)	NA	6
Rauhaniemi, 2006	Finland	1997-2001	Kudo type-5	Retrospective cohort	58.0	18.5	4.8	28	0	Infection (NR)	NA	7
Thillemann, 2006	Denmark	1992-1993	Kudo type-3	Retrospective cohort	60.3	18.8	9.5	17	1	Deep infection (NR)	NR	7
Bassi, 2007	UK	2000-2002	Acclaim	Prospective cohort	64.0	25.0	3.0	36	1	Deep infection (NR)	NR	6
Schmidt, 2007	Germany	1987-2005	Mixture of several prosthesis	Retrospective cohort	63.5	NR	5.5	195	22	Infection (NR)	NR	7

Author, year of publication	Country	Year of study	Type of implant	Study design	Mean/median age (years)	% males	Mean/median follow-up (yrs)	No. of participants	No. of infections	Endpoint used by report (Definition)	Predominant bacteria for infection	Study quality
Cesar, 2007	France	1993-2002	GSB III prosthesis	Retrospective cohort	55.7	NR	6.2	58	0	Deep infection (NR)	NA	7
Shi, 2007	USA	1990-2003	Coonrad/Morrey Total Elbow	Retrospective cohort	61.0	24	7.2	37	3	Infection (NR)	NR	9
Tachira, 2008	Japan	1998-2006	J-alumina ceramic elbow	Retrospective cohort	59.7	NR	4.6	3	1	Deep infection (NR)	<i>Enterobacter cloacae</i>	6
Tachira, 2008	Japan	1998-2006	STABLE	Retrospective cohort	60.6	NR	5.0	13	0	Deep infection (NR)	NA	6
Tachira, 2008	Japan	1998-2006	Kudo	Retrospective cohort	62.7	NR	2.4	32	2	Deep infection (NR)	<i>S. aureus; Pseudomonas aeruginosa</i>	6
Hilker, 2009	Germany	1987-2005	Mixture of several prosthesis	Retrospective cohort	63.5	15.3	5.5	195	21	Deep infection (NR)	NR	7
Hilker, 2009	Germany	1987-2005	Mixture of several prosthesis	Retrospective cohort	63.5	15.3	5.5	195	1	Superficial wound infection (NR)	NR	7
Celli, 2009	USA	1982-2003	Coonrad/Morrey Total Elbow	Retrospective cohort	32.0	22.4	7.6	55	2	Deep infection (NR)	NR	7
Patil, 2009	USA	1994-2001	Solar Total Elbow	Retrospective cohort	63.4	NR	8.4	17	1	Deep infection (NR)	NR	7
Amirfeyz, 2009	UK	1996-2004	GSB III prosthesis	Retrospective cohort	69.0	24.4	4.5	54	0	Deep infection (NR)	NA	7
Skytta, 2009	Finland	1982-2006	Mixture	Prospective cohort	59.0	13.0	7.5	1457	25	Revision for PJI (Surgeon reported)	NR	9
Naqui, 2010	UK	2000-2006	Acclaim	Retrospective cohort	65.4	72.7	4.8	13	0	Deep infection (NR)	NA	7
Corradi, 2010	Italy	2000-2007	Coonrad/Morrey Total Elbow	Retrospective cohort	69.0	NR	5.0	18	1	Superficial wound infection (NR)	NR	7
Prasad, 2010	UK	1993-2000	Souter-Strathclyde	Retrospective cohort	60.0	20.0	9.0	44	1	Infection (NR)	NR	6
Prasad, 2010	UK	1997-2010	Coonrad/Morrey	Retrospective cohort	62.0	33.3	5.0	55	1	Infection (NR)	NR	6
Qureshi, 2010	UK	1993-1996	Kudo-5	Retrospective cohort	56.0	NR	11.9	34	2	Infection (NR)	NR	6
Guttler, 2011	Czech	1988-2000	Souter-Strathclyde	Retrospective cohort	53.0	NR	9.5	58	1	Deep infection (NR)	NR	6
Guttler, 2011	Czech	2000-2009	Coonrad/Morrey Total Elbow	Retrospective cohort	54.0	NR	4.21	63	2	Deep infection (NR)	NR	6
Sorbie, 2011	Canada	1995-2002	Sorbie-QUESTOR	Retrospective cohort	51.0	50.0	7.5	51	7	Infection (NR)	NR	7
Gay, 2012	USA	1997-2006	NR	Retrospective cohort	58.3	28.8	90 days	1155	36	Infection (NR)	NR	7
Ishii, 2012	Japan	2001-2009	GSB III prosthesis	Retrospective cohort	66.0	0.0	6.3	36	0	Deep infection (NR)	NA	7
Maheshwari, 2012	UK	NR	Coonrad/Morrey Total Elbow	Retrospective cohort	65.0	32.1	4.6	31	1	Deep infection (NR)	NR	7
Park, 2013	Korea	1984-2010	Pritchard ERS; Kudo	Retrospective cohort	53.0	20.0	8.0	35	1	Infection (NR)	NR	7
Park, 2013	Korea	1984-2010	Pritchard Mark II; Coonrad-Morrey	Retrospective cohort	61.0	38.8	14.0	49	0	Infection (NR)	NA	7
Kodde, 2013	Belgium	2006-2011	Coonrad/Morrey Total Elbow	Prospective cohort	70.0	23.5	2.7	17	1	Infection (NR)	NR	6
Kodde, 2013	Belgium	2006-2011	Coonrad/Morrey Total Elbow	Prospective cohort	70.0	23.5	2.7	17	1	Superficial wound infection (NR)	NR	6
Jenkins, 2013	UK	1991-2008	NR	Prospective cohort	16->74	NR	90 days	1146	22	Infection (NR)	NR	7

Author, year of publication	Country	Year of study	Type of implant	Study design	Mean/median age (years)	% males	Mean/median follow-up (yrs)	No. of participants	No. of infections	Endpoint used by report (Definition)	Predominant bacteria for infection	Study quality
Baghdadi, 2014	USA	1987-2006	Coonrad/Morrey Total Elbow	Retrospective cohort	62.3	24.0	5.8	723	20	Revision for deep infection (NR)	NR	8
Cross, 2014	USA	1988-1995	Osteonics Total Elbow	Retrospective cohort	28.0	30.0	18.0	10	1	Deep infection (NR)	NR	6
Hastings, 2014	USA	2002-2009	Discovery Elbow System	Prospective cohort	63.9	22.8	4.1	92	2	Deep infection (NR)	NR	7
Hastings, 2014	USA	2002-2009	Discovery Elbow System	Prospective cohort	63.9	22.8	4.1	92	2	Superficial wound infection (NR)	NR	7
Large, 2014	UK	2008-2011	Discovery Elbow System	Retrospective cohort	69.2	37.0	3.4	51	4	PJI (NR)	NR	7
Plaschke, 2014	Denmark	1981-2006	Souter Strathclyde, Capitellocondylar, Pritchard ERS, Kudo-3	Retrospective cohort	62.0	19.2	8.7	172	2	Revision for infection	NR	7
Plaschke, 2014	Denmark	1990-2008	Coonrad-Morrey, GSB III, Discovery	Retrospective cohort	64.0	17.8	8.7	152	3	Revision for infection	NR	7
Alizadehkhayat, 2015	UK	2003-2010	Discovery Elbow System	Prospective cohort	NR	NR	4.0	75	1	Deep infection (NR)	NR	7
Kiran, 2015	UK	NR	Coonrad/Morrey Total Elbow	Retrospective cohort	67.3	34.0	8.1	50	2	Deep infection (NR)	NR	9
Kiran, 2015	UK	NR	Coonrad/Morrey Total Elbow	Retrospective cohort	67.3	34.0	8.1	50	3	Superficial wound infection (NR)	NR	9
Griffin, 2015	USA	2005-2011	NR	Retrospective cohort	<65->80	18.6	90 days	7580	218	Infection (NR)	NR	7
Williams, 2016	UK	2000-2012	Coonrad/Morrey Total Elbow	Retrospective cohort	59.1	42.9	5.3	22	1	Deep infection (NR)	NR	6
Toulemonde, 2016	France	1997-2008	Coonrad/Morrey	Retrospective cohort	63.0	18.7	5.0	100	4	Deep infection (NR)	NR	7
Kodama, 2017	Japan	1994-2003	Kudo type-5	Retrospective cohort	58.9	3.2	11.8	41	1	Deep infection (NR)	NR	9
Lovy, 2017	USA	2007-2013	NR	Retrospective cohort	63.3	25.0	30 days	189	3	Deep infection (NR)	NR	7
Nishida, 2018	Japan	2003-2012	J-alumina ceramic elbow	Retrospective cohort	62.0	4.0	9.0	87	1	Deep infection (NR)	NR	7
Minami, 2018	Japan	1982-2007	Kudo	Retrospective cohort	56.6	17.6	12.3	421	8	Deep infection (NR)	MRSA (37.5%); <i>S. aureus</i> (25%)	6
Kondo, 2019	Japan	1998-2014	Niigata- Senami-Kyocera modular system	Retrospective cohort	64.0	11.0	5.2	75	3	PJI (NR)	<i>S. aureus</i> (66.7%); <i>Cutibacterium acnes</i> (33.3%)	6

CDC, Center for Disease Control; CNSA, Coagulase Negative *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; MSIS, Musculoskeletal Infection Society; NHSN, National Healthcare Safety Network; NR, not reported; PJI, prosthetic joint infection; *S*, *Staphylococcus*; SSI, surgical site infection; TER, total elbow replacement; TSR, total shoulder replacement

Supplementary Material 6. Incidence rate of PJI by TSR procedure type

CI, confidence interval; PJI, prosthetic joint infection; TSR, total joint replacement

Supplementary Material 7. Incidence of PJI following primary TSR at specific average follow-up periods

PJI, prosthetic joint infection; TSR, total shoulder replacement; capped vertical bars represent 95% confidence intervals

Supplementary Material 8. Incidence rate of PJI by TER prosthesis type

CI, confidence interval; PJI, prosthetic joint infection; TER, total elbow replacement

Supplementary Material 9. Incidence of PJI following primary TER at specific average follow-up periods

PJI, prosthetic joint infection; TER, total elbow replacement; capped vertical bars represent 95% confidence intervals

Supplementary Material 10. Patient-related risk factors and risk of PJI following primary TER

BMI, body mass index; CI, confidence interval; PJI, prosthetic joint infection; RR, relative risk; TER, total elbow replacement