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Incidence, associated disease burden and healthcare utilization due to *Staphylococcus aureus* prosthetic joint infection in European hospitals: the COMBACTE-NET ARTHR-IS multi-centre study

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SUMMARY

Background: The aim of this study was to estimate the incidence, associated disease burden and healthcare utilization due to *Staphylococcus aureus* prosthetic joint infections (SA-PJI) after primary hip and knee arthroplasty in European centres.

Methods: This study was conducted in patients who underwent primary hip and knee arthroplasty in 19 European hospitals between 2014 and 2016. The global incidence of PJI and SA-PJI was calculated. The associated disease burden was measured indirectly as infection-related mortality plus loss of function. For healthcare utilization, number and duration of hospitalizations, number and type of surgical procedures, duration of antibiotic treatments, and number of outpatient visits were collected. Subgroup and regression analyses were used to evaluate the impact of SA-PJI on healthcare utilization, controlling for confounding variables.

Results: The incidence of PJI caused by any micro-organism was 1.41%, and 0.40% for SA-PJI. Among SA-PJI, 20.7% were due to MRSA with substantial regional differences, and were more frequent in partial hip arthroplasty (PHA). Related deaths and loss of function occurred in 7.0% and 10.2% of SA-PJI cases, respectively, and were higher in patients with PHA. Compared with patients without PJI, patients with SA-PJI had a mean of 1.4 more readmissions, 25.1 more days of hospitalization, underwent 1.8 more surgical procedures, and had 5.4 more outpatient visits, controlling for confounding variables. Healthcare utilization was higher in patients who failed surgical treatment of SA-PJI.

Conclusions: This study confirmed that the SA-PJI burden is high, especially in PHA, and provided a solid basis for planning interventions to prevent SA-PJI.

Introduction

Increased life expectancy has led to an increase in the indications for primary joint replacements with a corresponding proportional increase in the number of patients affected by prosthetic joint infections (PJIs) [1]. *Staphylococcus aureus* is the most important micro-organism causing PJI and has been associated with high rates of therapeutic failure, including loss of joint function and infection-associated mortality [2,3].

Measures to prevent *S. aureus* surgical site infection (SSI) have been based on antibiotic prophylaxis, hygiene measures, and decolonization of carriers. Implementation of the latter has been low level, due to the logistical barriers to universal, pre-procedure screening for *S. aureus*. Interestingly, new alternatives based on vaccines and monoclonal antibodies are being developed that could reduce the incidence of *S. aureus* SSI [4,5]. Patients undergoing primary arthroplasty have been identified as a target population to benefit from the new preventive approaches [6]. Efficiency in the implementation of any preventive intervention should be supported by robust incidence data. In a review of the literature covering the period 2003–2013 that included 81 studies, *S. aureus* SSI rates in patients undergoing knee and hip arthroplasty ranged from 0.2 to 2.4% and 0.18–3.8%, respectively [7]. Given the variability of these estimates, probably due to differences in study design, studies are needed that provide reliable incidence estimates of *S. aureus* PJI (SA-PJI) in European countries.

PJI is costly, both in terms of its high healthcare consumption and because it results in significant disability [8]. Studies assessing healthcare utilization found that the occurrence of postoperative *S. aureus* SSI following orthopaedic procedures increased the length of hospital stay (LOS) by a factor of two to three, increased the likelihood of readmission, and tripled the costs compared with no SSI [7]. The results of studies assessing the cost of SA-PJI are difficult to extrapolate from one country to another due to different ways of measuring and equating costs. Furthermore, these studies often do not estimate factors that determine costs such as comorbidities and age. Given the scarcity of estimations of costs and disability associated with PJI in Europe, as well as the predominance of *S. aureus* as the cause of PJI, better estimates of the costs and health burden of SA-PJI in European centres are also needed.

The present study aimed to estimate the attributable burden and outcomes of SA-PJI following primary hip and knee

replacement. This included estimating the incidence of SA-PJI, the disease burden in terms of death and loss of function, and the associated healthcare utilization, providing parameters for future estimations of cost savings associated with different scenarios of reduction in SA-PJI rates.

Methods

Study design and sites

ARTHR-IS was a multi-centre case—control study carried out in 19 hospitals in six European countries (Spain, Italy, France, Germany, UK and the Netherlands) to investigate the incidence, risk factors, predictors of treatment failure and healthcare utilization associated with SA-PJI following primary hip arthroplasty (HA) and knee arthroplasty (KA). The study protocol was registered at clinicaltrials.gov (NCT03826108). The results on risk factors and predictors of SA-PJI treatment failure have been published elsewhere [3,9]. In the current article, the results on incidence, associated disease burden and healthcare utilization are presented.

Study population, period, and data sources

All patients undergoing primary HA or KA (partial or total) at participating hospitals between 1st January 2014 and 31st December 2016 were identified through the arthroplasty register at each hospital. Those who developed postoperative PJI in the first year after primary arthroplasty were detected through the discharge records of patients admitted for PJI or any joint procedure; records from local SSI surveillance programmes in patients undergoing primary arthroplasty; or by matching the list of patients undergoing arthroplasty with the microbiological records for PJI. Patients with SA-PJI were retrospectively followed up for 18 months after the first procedure performed to treat the infection.

For each case of SA-PJI, three patients without PJI were selected as controls and matched by hospital, arthroplasty joint (knee/hip) and date of surgery (nearest to the date of surgery of the corresponding case). For SA-PJI, the following information was collected: (1) meticillin-resistant SA-PJI (MRSA-PJI) and SA-PJI presenting with bacteraemia; (2) number of SA-PJI-related deaths and number of cases with total loss of joint function as indicators of associated disease burden; (3) number and days of hospital admission, days of antibiotic treatment for SA-PJI (intravenous and oral); (4) number and type of surgical procedures (debridement, partial prosthesis removal, total prosthesis removal, re-implantation), and number of outpatient consultations with orthopaedic surgeons and infectious diseases specialists, as indicators of healthcare resources used to treat SA-PJI. For patients without PJI, number and days of hospital admission, number and type of new surgical procedures after primary arthroplasty, and number of outpatient consultations were collected. Data on healthcare utilization was compiled by reviewing patient medical charts.

Definitions

PJIs were defined according to standard criteria [10] and were considered to be caused by *S. aureus* if this organism was isolated from $\geq$1 joint aspirate sample, $\geq$2 periprosthetic tissue samples, and/or blood cultures with no other obvious source of infection.

Treatment failure was defined as a composite variable including related mortality, clinical failure and functional failure, as previously reported [3]. Related mortality was defined as mortality resulting from SA-PJI. Clinical failure was defined as persistence or recurrence of signs or symptoms of infection, the need for long-term suppressive antibiotic therapy, and removal of the prosthesis if not performed as the initial surgical procedure due to prosthetic loosening. Functional failure was defined as significantly impeded or impaired ability to walk due to prosthetic loosening or the need for a Girdlestone procedure or arthrodesis.

Healthcare utilization for patients with SA-PJI included the use of healthcare resources during and after the first procedure performed to treat the infection, additional procedures if the patient had complications related to the procedure, or if the initial treatment failed. For patients without PJI, healthcare utilization included the standard resources used in the follow up of patients undergoing arthroplasty or its non-infectious complications.

Data were entered into an anonymized electronic case report form and monitored for data coherence and completeness. The study was approved by the ethics committees at each site according to local regulations. Due to the retrospective nature of the study, the need to obtain written informed consent was waived (except in French hospitals where informed consent was requested).

Statistical analysis

One-year cumulative incidence (referred from now on as incidence, for the sake of brevity) data were calculated using a cohort design. The number of primary arthroplasties for each calendar year (2014—2016) constituted the annual aggregated cohorts. For each calendar year, the cumulative incidence of PJI, SA-PJI, MRSA-PJI and bacteraemic SA-PJI with their 95% confidence intervals (CIs) were calculated. The disease burden associated with SA-PJI was calculated as the proportion of SA-PJI patients who died from SA-PJI-related infection and/or experienced severe loss of function, overall and stratified by type of prosthesis.

For healthcare resource utilization, qualitative variables were presented as percentages, and quantitative variables as median and interquartile ranges (IQRs). Resource utilization was compared between patients with SA-PJI versus patients without PJI, and in patients with SA-PJI, between those with and without treatment failure, using the chi-squared and Mann—Whitney U tests or the Kruskal—Wallis test for qualitative and quantitative variables, respectively. Stratified analyses were performed for patients aged $<$65 years and $\geq$65 years, patients with Charlson index $<$3 and $\geq$3, by sex of patient, and type of joint prosthesis. To determine the use of healthcare utilization attributable to SA-PJI, controlling for age, sex, Charlson index and type of prosthesis, multi-variable linear regression analyses were performed; generalized linear mixed models controlled for the effect of study site, considered as a random effect. Regression coefficients (β) and their 95% CIs were calculated to reflect the fixed-effects relationship between each healthcare utilization variable and SA-PJI or its absence. Statistical analyses were conducted using SPSS 26.0 (SPSS Inc.).

Results

Cumulative incidence of SA-PJI after primary hip and knee arthroplasty

During the three-year study period, 39,261 arthroplasties were performed, of which 23,545 (60.0%) were of the hip (50.6% total hip, 9.3% partial hip) and 15,716 (40.0%) of the knee (Table I). Supplementary Table S1 shows the number of procedures by country.

In total, 553 patients developed a PJI due to any type of micro-organism (incidence, 1.41%; 95% CI: 1.30–1.53), of which 159 (28.8%) were due to *S. aureus* (SA-PJI incidence, 0.40%; 95% CI: 0.35–0.47). Stratified by type of arthroplasty, patients who underwent partial hip arthroplasty (PHA) had the highest incidence: 2.55% (95% CI: 2.10–3.13) for PJI caused by any type of micro-organism, and 0.96% (95% CI: 0.69–1.33) for SA-PJI (Table I).

Supplementary Table S2 shows the incidence of MRSA-PJI and cases of SA-PJI with associated bacteraemia. Of the total number of SA-PJI cases, 33 (20.7%) were caused by MRSA, with significant differences between countries, being highest in Spain and Italy, and with no cases at centres in the Netherlands (Supplementary Table S1). There were also significant differences according to the location of the prosthesis: the highest proportions of MRSA-PJI among SA-PJI cases occurred in patients who underwent HA (25.8% total HA and 37.1% PHA) compared with 6.4% in patients with KA (Supplementary Table S2). Bacteraemia occurred in 27 patients with SA-PJI and was also more frequent in PHA (31.4%) than total HA (16.1%) and KA (9.7%) (Supplementary Table S2).

Disease burden and healthcare utilization associated with SA-PJI

Table II shows the associated disease burden (including infection-related mortality and functional loss in survivors) and healthcare utilization for 128 patients with SA-PJI versus 380 patients without PJI, both overall and stratified by type of prosthesis. Among patients with SA-PJI, related mortality and functional loss were higher in those with PHA compared with those with total hip and knee prostheses, after controlling for confounding factors (Supplementary Table S3). Overall, the 128 patients with SA-PJI had 196 hospital admissions for a total of 4848 days (median per admission, 26 days), underwent 236 surgical procedures, had a median of eight consultations with an orthopaedic surgeon or infectious diseases specialist, and received 13,476 days of antibiotic treatment, including 4923 days of intravenous antibiotic treatment (median, 21 days) and 8553 days of oral antibiotic treatment (median, 56 days). Patients with PHA had significantly fewer outpatient visits and fewer days of antibiotic treatment than patients with total hip or knee prostheses. These differences were maintained after excluding patients who died due to SA-PJI or underwent prosthesis resection as the first procedure (data not shown). Patients with SA-PJI had significantly more admissions, hospital days, additional procedures, and outpatient visits compared with those without PJI (Table II). The differences remained when patients were stratified by type of prosthesis (Table III), age >65 years, sex, and Charlson index ≥3 (Supplementary Table S4). After adjusting for all these variables and controlling for hospital site, mean resource consumption for patients with SA-PJI was higher than for those without PJI: 1.4 more

Table I
Primary arthroplasty procedures, post-surgical prosthetic joint infection and cumulative incidence (total and *Staphylococcus aureus*) during 2014–2016 by type of arthroplasty and year of procedure

	Number of procedures	PJI	1-year cumulative incidence of PJI (95% CI)	SA-PJI	1 year cumulative incidence of SA-PJI (95% CI)	Proportion SA-PJI/PJI (95% CI)
Total hip arthroplasty						
2014	6630	95	1.43 (1.17–1.75)	30	0.45 (0.32–0.65)	31.6 (23.1–41.5)
2015	6625	76	1.15 (0.92–1.43)	14	0.21 (0.13–0.35)	18.4 (11.3–28.6)
2016	6602	69	1.05 (0.83–1.32)	18	0.27 (0.17–0.43)	26.1 (17.2–37.5)
Total	19,857	240	1.21 (1.07–1.37)	62	0.31 (0.24–0.40)	25.8 (20.7–31.7)
Partial hip arthroplasty						
2014	1234	33	2.67 (1.91–3.73)	15	1.22 (0.74–2.00)	45.5 (29.8–62.0)
2015	1269	35	2.76 (1.99–3.81)	13	1.02 (0.60–1.74)	37.1 (23.2–53.7)
2016	1185	26	2.19 (1.50–3.20)	7	0.60 (0.29–1.24)	26.9 (13.7–46.1)
Total	3688	94	2.55 (2.10–3.13)	35	0.96 (0.69–1.33)	37.2 (28.1–47.3)
Knee arthroplasty						
2014	5107	74	1.45 (1.14–1.82)	27	0.53 (0.35–0.77)	36.5 (25.6–48.5)
2015	5089	68	1.34 (1.04–1.69)	16	0.31 (0.18–0.51)	23.53 (14.1–35.4)
2016	5520	77	1.39 (1.10–1.74)	19	0.34 (0.21–0.54)	24.7 (15.6–35.8)
Total	15,716	219	1.39 (1.21–1.59)	62	0.39 (0.31–0.51)	28.3 (22.4–34.8)
All arthroplasties						
2014	12,971	202	1.56 (1.35–1.79)	72	0.56 (0.43–0.70)	35.6 (29.1–42.7)
2015	12,983	179	1.38 (1.19–1.59)	43	0.33 (0.24–0.45)	24.0 (18.0–31.0)
2016	13,307	172	1.29 (1.11–1.50)	44	0.33 (0.24–0.44)	25.6 (19.2–32.8)
Total	39,261	553	1.41 (1.30–1.53)	159	0.40 (0.35–0.47)	28.8 (25.1–32.7)

PJI, prosthetic joint infection caused by any micro-organism; SA-PJI, prosthetic joint infection caused by *S. aureus*. Procedures: number of primary arthroplasties (hip/knee) during the years 2014–2016. PJI and SA-PJI are expressed as number of cases.

Table II
Healthcare utilization and disease burden of prosthetic joint infection caused by *Staphylococcus aureus* (SA-PJI) at 18-month follow up, and healthcare utilization for patients without prosthetic joint infection (PJI)

	Cases of SA-PJI *N*=128					Controls (no PJI) *N*=380					*P* [a] total
	Partial hip *N*=27	Total hip *N*=50	Knee *N*=51	*P*	Total	Partial hip *N*=42	Total hip *N*=190	Knee *N*=148	*P*	Total	
Hospital admissions	37	68	91	0.106	196	2	11	9	0.949	22	<0.001
Median (IQR)	1 (1–2)	1 (1–1)	1 (1–2)		1 (1–2)	0 (0–0)	0 (0–0)	0 (0–0)		0 (0–0)	
Days of hospitalization	1051	1456	2341	0.284	4848	31	123	77	0.9711	231	<0.001
Median (IQR)	28 (23–50)	22.5 (16–37)	25 (15–62)		26 (16.2–41.5)	0 (0–0)	0 (0–0)	0 (0–0)		0 (0–0)	
Total procedures	45	80	111	0.555	236	2	3	2	0.774	7	<0.001
Median (IQR)	1 (1–2)	1 (1–2)	1 (1–3)		1 (1–2)	0 (0–0)	0 (0–0)	0 (0–0)		0 (0–0)	
Consultation with specialist	118	538	540	0.004	1196	118	804	669	0.001	1591	<0.001
Median (IQR)	3 (0–8)	10 (6–12)	8 (7–15)		8 (5–12)	2 (1–3)	3 (2–5)	4 (2–6)		3 (2–5)	
Days of IV antibiotic treatment	963	1242	2718	<0.001	4923	–	–	–		–	
Median (IQR)	21 (12–48)	17.5 (12–28)	30 (14–62)		21 (13.0–43.5)						
Days of oral antibiotic treatment	1068	3005	4480	<0.001	8553	–	–	–		–	
Median (IQR)	33 (6–61)	54 (42–78)	69 (40–142)		56 (33.5–84.0)						
Total days of antibiotic treatment	2031	4247	7198	<0.001	13476						
Median (IQR)	64 (48–85)	73.5 (56–107)	117 (73–188)		83.5 (56.5–120)						
Death-related (%)	7 (25.9)	2 (4.0)	0	<0.001	9 (7.0)						
Loss of functionality (%)	6 (22.2)	2 (4.0)	5 (9.8)	<0.001	13 (10.2)						
Overall treatment failure (%)	13 (48.1)	4 (8.0)	5 (9.8)	<0.001	22 (17.2)						

Data expressed as median and interquartile range (IQR).
[a] Comparison of totals for cases and controls.

Table III
Adjusted multi-variate generalized linear mixed models of patient healthcare utilization after primary hip or knee arthroplasty

Variable	Hospital admissions		Days of hospitalization		Total procedures		Consultations with specialist	
	β [95% CI] [a]	*P*	β [95% CI] [a]	*P*	β [95% CI] [a]	*P*	β [95% CI] [a]	*P*
SA-PJI (vs no PJI)	1.442 [1.332; 1.553]	<0.001	25.081 [10.063; 40.099]	0.001	1.781 [1.622; 1.941]	<0.001	5.432 [4.548; 6.316]	<0.001
Age <65 years	0.137 [0.031; 0.244]	0.011	3.422 [-8,602; 15,446]	0.575	0.132 [-0,030; 0,293]	0.110	0.892 [0.042; 1.742]	0.040
Charlson ≥3	0.200 [0.052; 0.349]	0.008	14.159 [0.499; 27.820]	0.042	0.222 [-0.001; 0.445]	0.051	-0.243 [-1.431; 0.944]	0.687
Sex male	0.045 [-0.540; 0.143]	0.374	4.721 [-6.225; 15.697]	0.387	0.168 [0.018; 0.317]	0.028	0.020 [0.768; 0.807]	0.961
Type of prosthesis								
Total knee	Ref		Ref		Ref		Ref	
Total hip	-0.129 [-0.232; -0.027]	0.014	-12.788 [-24.311; -1.265]	0.030	-0.181 [-0.337; -0.025]	0.023	-0.358 [-1.181; 0.465]	0.393
Partial hip	-0.146 [-0.301; 0.009]	0.064	-6.351 [-21.537; 8.836]	0.410	-0.140 [-0.381; 0.102]	0.256	-3.099 [-4.336; -1.862]	<0.001

No-PJI, patients without prosthetic joint infection; SA-PJI, prosthetic joint infection caused by *Staphylococcus aureus*.
[a] Estimated fixed-effects regression coefficients (β) with 95% confidence interval (CI) reflecting the differences in each healthcare utilization variable (hospital admission, days of hospitalization, total procedures performed, consultation with specialist) between patients with SA-PJI versus no-PJI, patients younger vs older than 65 years, Charlson index ≥3 vs <3, sex male vs female, and type of prosthesis. In univariate mixed model analyses, the β regression coefficient and 95% CI of SA-PJI for hospital admissions was 1.473 (1.364–1.583); for days of hospitalization, 27.375 (12.517–42.233); for total procedures, 1.834 (1.677–1.991); and for consultations with specialist, 5.157 (4.265–6.048).

admissions, 25.1 more days of hospitalization, 1.8 more surgical procedures, and 5.4 more outpatient visits (Table III).

Supplementary Table S5 shows the different surgical procedures performed to treat SA-PJI according to type of prosthesis. Debridement, antibiotics, and implant retention (DAIR) was performed in 153 (64.8%) of the SA-PJI cases and was the most common procedure in all types of arthroplasty. For total hip and knee SA-PJI, the second most frequent procedure was two-stage removal, and for PHA, resection. Supplementary Table S6 shows resource utilization and associated disease burden according to each surgical procedure.

Finally, healthcare utilization was higher in patients who failed their first procedure. Supplementary Table S7 compares patients who failed with those who were cured, according to conservative treatment with DAIR or prosthesis removal, and excluding deaths and resection of prosthesis without reimplantation as first procedure. Patients who failed (compared with those who were cured) had 37 and 67.5 more days of hospitalization after undergoing DAIR or prosthesis removal, respectively; consumed 38 and 175 more days of antibiotics, respectively; and had four and nine times more outpatient consultations, respectively.

Discussion

In this multi-national cohort study, we estimated the disease burden caused by PJI and SA-PJI. The study provides an updated picture of the incidence of PJI and SA-PJI after primary HA and KA treated in six European countries. The disease burden associated with infection was measured in terms of associated mortality, severe loss of function, rehospitalizations, reinterventions and medical treatment, controlling for confounding factors. The overall incidence of PJI was 1.41%, and 0.40% for SA-PJI, 20.7% of which was due to MRSA; all of these were higher in PHA. Infection-related deaths and severe loss of function occurred in 7.0% and 10.2% of SA-PJI cases, respectively, and were higher in PHA patients. Healthcare resource utilization was significantly higher in patients with SA-PJI, especially in those who failed after the first surgical procedure performed.

Cumulative incidence of postsurgical PJI and SA-PJI

The rate of SSI after HA and KA has not changed significantly in recent years. In the European Centre for Disease Prevention and Control (ECDC) annual epidemiological report for 2014, the rates of SSI were 1.1% (range, 0.3–3.8) and 0.6% (0.0–3.4) for HA and KA, respectively, and for 2017, they were 1.0% (range 0.4–2.2) and 0.5% (0.2–2.7) [11]. Of these infections, only 10–25% were PJI (organ/space). In our study of primary arthroplasties, the incidences of PJI for total HA, PHA, and KA were 1.21 (range 1.07–1.37), 2.55 (2.1–3.13), and 1.39 (1.21–1.59), respectively. The slightly higher rates observed compared with ECDC surveillance data may be due to the longer observation period in our study (up to one year after surgery instead of 90 days) and possible gaps and weaknesses in the surveillance reporting systems. The incidences of SA-PJI for total HA, PHA, and KA were 0.31, 0.96 and 0.34, respectively, with a downward trend between 2014 and 2016 (0.45–0.27, 1.22–0.60, 0.53–0.34 for total HA, PHA, and KA, respectively). These incidences are lower than those reported by Dreyfus

et al. in a study conducted between 2010 and 2015 in US hospitals [12]. This may be explained by the inclusion in the latter study of all types of SSI (superficial, deep, and organ or space), the overall decrease in the incidence of PJI, and the implementation of preventive measures, as discussed below.

MRSA caused about one in five cases of SA-PJI, and was more frequent in total and PHAs. The frequency of MRSA-PJI was heterogenous across countries, which is consistent with ECDC data [13]. The higher percentages of both SA-PJI and MRSA-PJI in PHA in our study suggest that this is a potential target population for additional preventive measures. PHA is generally an urgent procedure, thus there may often be suboptimal compliance with standard preventive measures. In addition, screening and decolonization are not always possible and patients undergoing PHA are older and have more comorbidities [14]. This could therefore be a target population for innovative preventive approaches.

Morbidity and healthcare utilization associated with SA-PJI

The purpose of cost-of-illness (COI) studies is to assess the economic burden of a particular disease on the population, taking into account direct costs (use of healthcare-related and other resources), indirect costs (productivity losses related to morbidity and mortality), and intangible costs (losses in the quality and length of life) [15]. In traditional COI studies, all these impacts are conventionally referred to as 'costs', converted into monetary values wherever possible. In the field of PJI, many studies have tried to evaluate the economic cost of different surgical strategies used to treat infection [16], or have separately assessed hospital stay [17], antibiotic consumption [18,19] or quality of life [20]. The great variety of health and reimbursement systems, not only between countries but also in different regions of the same country, precludes extrapolation of the results of economic costs. With information on the incidence, related morbidity and mortality, and consumption of resources, each health system can calculate avoidable costs in its own population.

To our knowledge, there have been no previous published assessments of the burden of SA-PJI in Europe including mortality (days of life lost), functional loss, and healthcare resource utilization. Mponponsuo *et al*. [16] performed an interesting analysis to evaluate the monetary costs, hospitalizations and LOS of different surgical strategies (DAIR, DAIR with liner exchange, two-stage revision, one-stage revision) for complex SSI following hip and knee arthroplasty in Canada, stratifying and controlling for age, sex and comorbidities. They found that two-stage revision was the most expensive procedure compared with DAIR and one-stage revision. However, they studied all types of PJI, did not include a control group without SSI, and only calculated the cost of the first surgical procedure performed to treat the SSI. A German study compared healthcare resource utilization, direct costs, and mortality at 90 days and one year between patients with and without orthopaedic SA-SSI (hip and knee arthroplasties, and spine surgery) using multivariable analyses to control for confounding factors. Direct all-cause healthcare costs in the SA-SSI group were nearly two times higher and there was a 1.72 times increased risk of death from all causes; however, the results cannot be generalized to other healthcare systems due to differences in insurance reimbursement. Furthermore the data was drawn from a health insurance fund registry [21].

Although we provide data on healthcare resource utilization in patients with SA-PJI, we did not consider estimation of monetary cost per procedure because the healthcare and insurance systems vary from country to country, and even from centre to centre. This information is useful to estimate avoidable expenses if infections are prevented. We also calculated days of antibiotics used, which is relevant for drug-related adverse effects and antimicrobial resistance. In this context, it is noteworthy that duration of antibiotic therapy was not as long as in North America [22] where reported treatments usually exceed three to six months. We also calculated other indirect costs, such as severe loss of function and related mortality. Overall, the consumption of healthcare resources and use of antibiotics was significantly higher in patients who experienced treatment failure after the first procedure than in those who did not. For this reason, in addition to the development of new preventive measures to reduce the incidence of SA-PJI, another top priority should be to identify the factors associated with treatment failure and the best therapeutic strategy to deal with these infections, in order to reduce the impact on the healthcare system and the personal cost to patients.

This study has limitations that should be taken into account when interpreting the results. The first concerns the generalizability of the study outcomes; the SA-PJI cohort cannot be considered representative of SA-PJI in Europe, as only six countries were included, and the number of hospitals among participating countries was not well balanced. Due to the multi-centre, multi-national design of the study, case identification strategies were not uniform in all participating hospitals, each of which had to adapt data extraction depending on the databases available. It is possible therefore that the number of cases of SA-PJI in some hospitals was underreported. The sample size, especially for procedures other than DAIR for SA-PJI, was also limited. The number of MRSA-PJI cases was also too low to be able to calculate associated morbidity and healthcare utilization. The retrospective nature of the study made it impossible to assess quality of life, pain, non-severe functional deficits and adverse reactions related to long-term antibiotic use. As all controls followed during observation survived, it was not possible to compare the overall mortality of cases and controls. Finally, we were unable to calculate the monetary costs associated with SA-PJI, although our aim was not to provide the economic burden of SA-PJI, which has already been discussed in other publications [16,17].

In conclusion, the incidence of SA-PJI in this multi-national study was slightly lower than that previously published, except in PHA, where the incidence, including that of MRSA, was higher and was also associated with higher related mortality and greater loss of function. Healthcare resource utilization was significantly higher in patients with SA-PJI compared with controls, even after adjusting for confounding factors, and was especially higher in patients who failed treatment after the first surgical procedure.

The incidence and healthcare resource utilization data generated in this study will serve as benchmarks to measure the impact of strategies to reduce the risk of post-surgical infection due to *S. aureus* after primary HA or KA.

Quantification of the impact of treatment failure on personal cost and medical resources will be useful to evaluate the implementation of strategies to reduce the rate of SA-PJI failure.

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Author contributions

R.E., V.V., J.R.-B., M.D.D.T. contributed to the conception and design of the study, analysis and interpretation of data and drafting the article. N.B., I.M., S.T., E.Z., J.G.E.H, L.S., O.M., L.S., M.S., C.S., J.K., M.C.F, M.W.P., I.M., R.E.-S., C.A., C.B., F.-A.D., W.-Y.L., J.L.-T., J.P., and J.U. contributed to the acquisition of data and revising the article. E.C., M.P. and F.B. participated in the analysis and interpretation of data and revision the article. All authors gave their final approval of the version to be submitted.

Conflicts of interest statement

V.V., E.C., M.P. and F.B. are employees of the GSK group of companies. V.V., M.P. and F.B. hold shares in the GSK group of companies. F.B. holds pending and issued patents on *Staphylococcus aureus* vaccine formulations. V.V., E.C., M.P. and F.B. declare no other financial or non-financial relationships and activities. All other authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

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References

[1] Kurtz S1, Ong K, Lau E, Mowat FHM. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Jt Surg Am 2007;89:780—5.

[2] Lora-Tamayo J, Murillo O, Iribarren JA, Soriano A, Sánchez-Somolinos M, Baraia-Etxaburu JM, et al. A large multicenter study of methicillin-susceptible and methicillin-resistant staphylococcus aureus prosthetic joint infections managed with implant retention. Clin Infect Dis 2013;56:182—94.

[3] Espíndola R, Vella V, Benito N, Mur I, Tedeschi S, Zamparini E, et al. Rates and predictors of treatment failure in Staphylococcus aureus prosthetic joint infections according to different management strategies: a multinational cohort study — The ARTHR-IS Study Group. Infect Dis Ther 2022;11:2177—203.

[4] Giersing BK, Dastgheyb SS, Modjarrad K, Moorthy V. Status of vaccine research and development of vaccines for Staphylococcus aureus. Vaccine 2016;34:2962—6.

[5] Speziale P, Pietrocola G. Monoclonal antibodies targeting surface-exposed and secreted proteins from Staphylococci. Vaccines 2021;9:459.

[6] Gustin M-P, Giard M, Bénet T, Vanhems P. Use of surveillance data to identify target populations for Staphylococcus aureus vaccines and prevent surgical site infections: a pilot study 2015;10:3517—21.

[7] Patel H, Khoury H, Girgenti D, Welner S, Yu H. Burden of surgical site infections associated with arthroplasty and the contribution of Staphylococcus aureus. Surg Infect (Larchmt) 2016;17:78—88.

[8] Parvizi J, Pawasarat IM, Azzam KA, Joshi A, Hansen EN, Bozic KJ. Periprosthetic joint infection: the economic impact of methicillin-resistant infections. J Arthroplasty 2010;25:103—7.

[9] Espindola R, Vella V, Benito N, Mur I, Tedeschi S, Rossi N, et al. Preoperative and perioperative risk factors, and risk score development for prosthetic joint infection due to Staphylococcus aureus: a multinational matched case—control study. Clin Microbiol Infect 2022;28:1359—66.

[10] Parvizi J, Gehrke T. Definition of periprosthetic joint infection. J Arthroplasty 2014;29:1331.

[11] Healthcare-associated infections: surgical site infections — Annual Epidemiological Report for 2017. Available at: https://www.ecdc.europa.eu/en/publications-data/healthcare-associated-infections-surgical-site-infections-annual-1 [last accessed April 2023].

[12] Dreyfus J, Yu H, Begier E, Gayle J, Olsen MA. Clinical infectious diseases incidence of Staphylococcus aureus infections after elective surgeries in US hospitals. Am Acad Orthop Surg 2021;73:e2635—46.
[13] Surveillance Atlas of Infectious Diseases. Available at: http://atlas.ecdc.europa.eu/public/index.aspx [last accessed April 2023].
[14] Del Toro MD, Nieto I, Guerrero F, Corzo J, Del Arco A, Palomino J, et al. Are hip hemiarthroplasty and total hip arthroplasty infections different entities? The importance of hip fractures. Eur J Clin Microbiol Infect Dis 2014;33:1439—48.
[15] Larg A, Moss JR. Cost-of-illness studies: a guide to critical evaluation. Pharmacoeconomics 2011;29:653—71.
[16] Mponponsuo K, Leal J, Puloski S, Chew D, Chavda S, Au F, et al. Economic burden of surgical management of surgical site infections following hip and knee replacements in Calgary, Alberta, Canada. Infect Control Hosp Epidemiol 2022;43:728—35.
[17] Kapadia BH, McElroy MJ, Issa K, Johnson AJ, Bozic KJ, Mont MA. The economic impact of periprosthetic infections following total knee arthroplasty at a specialized tertiary-care center. J Arthroplasty 2014;29:929—32.
[18] Haenle M, Skripitz C, Mittelmeier W, Skripitz R. Economic impact of infected total knee arthroplasty. ScientificWorldJournal 2012;2012:196515.
[19] Klouche S, Sariali E, Mamoudy P. Total hip arthroplasty revision due to infection: a cost analysis approach. Orthop Traumatol Surg Res 2010;96:167—75.
[20] Aboltins C, Dowsey M, Peel T, Lim WK, Choong P. Good quality of life outcomes after treatment of prosthetic joint infection with debridement and prosthesis retention. J Orthop Res 2016;34:898—902.
[21] Hardtstock F, Heinrich K, Wilke T, Mueller S, Yu H. Burden of Staphylococcus aureus infections after orthopedic surgery in Germany. BMC Infect Dis 2020;20:233.
[22] Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2013;56:e1—25.