

## ■ INFECTION

# Mortality and re-revision following single-stage and two-stage revision surgery for the management of infected primary knee arthroplasty in England and Wales

EVIDENCE FROM THE NATIONAL JOINT REGISTRY



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## Aims

We compared the risks of re-revision and mortality between two-stage revision surgery and single-stage revision surgery among patients with infected primary knee arthroplasty.

## Methods

Patients with a periprosthetic joint infection (PJI) of their primary knee arthroplasty, initially revised with a single-stage or a two-stage procedure in England and Wales between 2003 and 2014, were identified from the National Joint Registry. We used Poisson regression with restricted cubic splines to compute hazard ratios (HR) at different postoperative periods. The total number of revisions and re-revisions undergone by patients was compared between the two strategies.

## Results

A total of 489 primary knee arthroplasties were revised with single-stage procedure (1,390 person-years) and 2,377 with two-stage procedure (8,349 person-years). The adjusted incidence rates of all-cause re-revision and for infection were comparable between these strategies (HR overall five years, 1.15 (95% confidence interval (CI) 0.87 to 1.52),  $p = 0.308$ ; HR overall five years, 0.99 (95% CI 0.70 to 1.39),  $p = 0.949$ , respectively). Patients initially managed with single-stage revision received fewer revision procedures overall than after two-stage revision (1.2 vs 2.2,  $p < 0.001$ ). Mortality was lower for single-stage revision between six and 18 months postoperative (HR at six months, 0.51 (95% CI 0.25 to 1.00),  $p = 0.049$ ; HR at 18 months, 0.33 (95% CI 0.12 to 0.99),  $p = 0.048$ ) and comparable at other timepoints.

## Conclusion

The risk of re-revision was similar between single- and two-stage revision for infected primary knee arthroplasty. Single-stage group required fewer revisions overall, with lower or comparable mortality at specific postoperative periods. The single-stage revision is a safe and effective strategy to treat infected knee arthroplasties. There is potential for increased use to reduce the burden of knee PJI for patients, and for the healthcare system.

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## Article focus

■ The two-stage revision strategy has traditionally been considered the gold standard, but there has been an increasing

interest in the use of the single-stage revision strategy, as the patient only requires one surgical procedure with potentially better patient outcomes such as shorter

overall hospital stay, quicker recovery, and significant cost-benefits.

- Several meta-analyses have not shown the superiority of one surgical strategy over the other, but evidence suffers from data scarcity on one-stage periprosthetic joint infection (PJI) revision, heterogeneity between pooled studies, and small sample sizes.
- Patients undergoing revision for PJI have a higher risk of mortality compared to national age-adjusted population or patients undergoing non-septic revision, but no study has compared the risk of post-operative mortality following single- and two-stage revision for PJI.

### Key messages

- The risk of re-revision for PJI or for any cause was comparable between single-stage and two-stage revision, but patients treated with single-stage revision underwent fewer planned and unplanned operations in total.
- The mortality following single-stage revision for PJI was comparable or lower at specific postoperative periods compared to two-stage revision, but higher for both PJI revision approaches than the mortality rate following primary knee arthroplasty and non-septic revision.

### Strengths and limitations

- These results are based on observational data, and therefore subject to potential biases contrary to findings from a randomized controlled trial.
- Our results are based on the National Joint Registry data from all orthopaedic units in England and Wales, providing findings that can be directly generalizable to any orthopaedic practices in the NHS.

### Introduction

Total knee arthroplasty is a commonly performed elective procedure.<sup>1,2</sup> While most knee arthroplasties will last for more than 25 years,<sup>3</sup> one of the most severe complications is infection affecting the tissues around the implant,<sup>4-6</sup> or periprosthetic joint infection (PJI), which affects approximately 1%.<sup>7-10</sup> In PJI, bacteria rapidly form biofilms on implants;<sup>4</sup> therefore, antibiotic treatment alone cannot cure PJI, merely suppress it, and surgical treatment is required if the aim is to achieve a cure. Debridement, antibiotics and implant retention with exchange of modular components (DAIR) may successfully treat PJI in about 60% of cases.<sup>11</sup> However, the majority of patients undergoing revision for PJI require either single- or two-stage revision, and the outcomes for these procedures differ.<sup>7</sup> Two-stage revision is more commonly used, and requires two distinct planned major surgeries and an interim period, usually of several months,<sup>9</sup> during which patients experience limited knee function, pain, disability, and uncertainty.<sup>6</sup>

Comparable risk of re-revision for PJI (8% to 9%) following single- and two-stage revisions has been

observed.<sup>12-14</sup> Systematic reviews suffer from a lack of any randomized controlled trial (RCT) evidence, data scarcity on one-stage PJI revision, heterogeneity between pooled studies, and generally small sample size and patient selection. A subsequent observational study of over 8,300 patients with knee PJI revised with single-stage or two-stage found higher risk of re-revision for PJI following single-stage revision.<sup>10</sup> The risk of further surgery and complications following management of knee PJI with a two-stage approach has been previously highlighted.<sup>15</sup> It is therefore still unclear which surgical option is superior to manage knee PJI. No study has investigated potential postoperative time-specific disparities. In hip PJI, most surgical practices, throughout the world, are not following the advocated criteria,<sup>16</sup> leading to uncertainty in the choice of the best management strategy.<sup>17</sup> Patients undergoing revision for PJI also have a higher risk of mortality compared to national age-adjusted population or patients undergoing aseptic revision.<sup>18-20</sup> No study has compared mortality outcomes between the two PJI revision strategies.

Given the current evidence gaps, we aimed to use a prospective nationally representative comprehensive cohort to compare the revision burden, all-cause risk and PJI-specific risk of re-revision, and the risk of mortality after single-stage or two-stage revision procedures performed for PJI of primary knee arthroplasty.

### Methods

**Study design and data sources.** In this retrospective analysis of prospectively collected data, we used information for England and Wales from the National Joint Registry (NJR) for England, Wales, Northern Ireland, and the Isle of Man recorded between 1 April 2003 and 31 December 2014. Personal Demographics Service data from the Office for National Statistics (ONS) were linked to obtain date of death where patients had died following treatment. Patient consent was obtained for data collection and linkage by the NJR. According to the NHS Health Research Authority, separate consent and ethical approval were not required for this study.

**Procedures and outcomes.** We included patients with a primary knee arthroplasty, subsequently reported to be revised for PJI with a single- or two-stage procedure by the operating team. Those revised with DAIR procedures and excision arthroplasties were excluded (Supplementary Figure a).

We used the NJR component level data to identify which implants were recorded as being removed and/or implanted, and therefore to identify the precise type of revision procedure. We considered an initial revision for PJI as re-revised if a subsequent procedure that was in addition to the planned one (single-stage) or two (two-stage) procedures performed, where an implant was added, changed, or removed, was recorded in the NJR between 1 April 2003 and 31 December 2014. The individual and distinct procedures of a two-stage revision were labelled "stage 1" and "stage 2". We also considered two-stage

**Table 1.** Characteristics and outcomes of initial revision procedures performed to managed primary knee arthroplasty with periprosthetic joint infection.

Variable	Single-stage				Two-stage				p-value		
	Person-years	Cases	Rate*	95% CI	Person-years	Cases	Rate*	95% CI			
<b>Total, n</b>	489				2,377						
<b>Male, n (%)</b>	269 (55.0)				1,361 (57.3)				0.361†		
<b>Mean age, yrs (SD)</b>	68 (10.0)				69 (9.0)				0.184‡		
< 60 yrs, n (%)	84 (17.2)				369 (15.5)				0.616†		
60 to 69 yrs, n (%)	176 (36.0)				829 (34.9)						
70 to 79 yrs, n (%)	166 (34.0)				876 (36.9)						
≥ 80 yrs, n (%)	63 (12.9)				303 (12.8)						
<b>ASA grade, n, %</b>											
1	36 (7.4)				160 (6.7)				0.064†		
2	322 (65.9)				1,452 (61.1)						
3 to 5	131 (26.8)				765 (32.0)						
<b>Knee procedure, n (%)</b>											
CLR	277 (56.6)				1,498 (63.0)				< 0.001†		
PS	132 (27.0)				670 (28.2)						
UKA	63 (12.9)				127 (5.3)						
CC	4 (0.8)				28 (1.2)						
Other	13 (2.7)				54 (2.3)						
<b>Re-revised (all cause)</b>	489	1,390	70	50.4	39.2 to 63.6	2,377	8,349	327	39.1	35.0 to 43.7	0.119§
Single-stage, n, %			41 (58.6)					111 (33.9)			
Two-stage, n (%)¶			29 (41.4)					136 (41.6)			
Repeated stage 1**			-					59 (18.0)			
Other			0 (0.0)					21 (6.5)			
<b>Re-revised (PJI only)</b>	489	1,390	45	32.4	23.6 to 43.3	2,377	8,349	246	29.5	25.9 to 33.4	0.749§
Single-stage, n, %			16 (35.6)					36 (14.6)			
Two-stage			29 (64.4)					131 (53.3)			
Repeated stage 1			-					59 (24.0)			
Other			0 (0.0)					20 (8.1)			
<b>Deceased</b>	489	1,597	41	25.7	18.4 to 34.8	2,880**	10,721	328	30.6	27.4 to 34.1	0.369§
≤ 90 days	489	1,597	5	3.1	1.0 to 7.3	2,880	10,721	239	2.1	1.4 to 3.2	0.602§

N = 2,880 two-stage procedures, including 1,526 procedures with both one stage 1 and one stage 2 operations recorded in the NJR, 59 procedures with multiple stage 1 prior to stage 2 (the repeated stage 1 procedure is counted as a re-revision), 792 procedures with only stage 2 operations recorded (1,526 + 59 + 792 = 2,377), and 503 procedures for which only the stage 1 procedure was performed.

\*Per 10,000 person-years.

†Chi-squared test.

‡Independent-samples *t*-test.

§Likelihood-ratio test.

¶54 (18/29 and 36/136) of the 165 (29 + 136) two-stage re-revision procedures had no stage 1 operation recorded in the National Joint Registry.

\*\*42 patients received an additional stage 1 procedure prior to stage 2, and 17 patients received multiple stage 1 procedures but no stage 2.

ASA, American Society of Anesthesiologists; CC, constrained condylar; CI, confidence interval; CLR, cruciate ligament retaining; PJI, periprosthetic joint infection; PS, posterior-stabilized; UKA, unicompartmental knee arthroplasty.

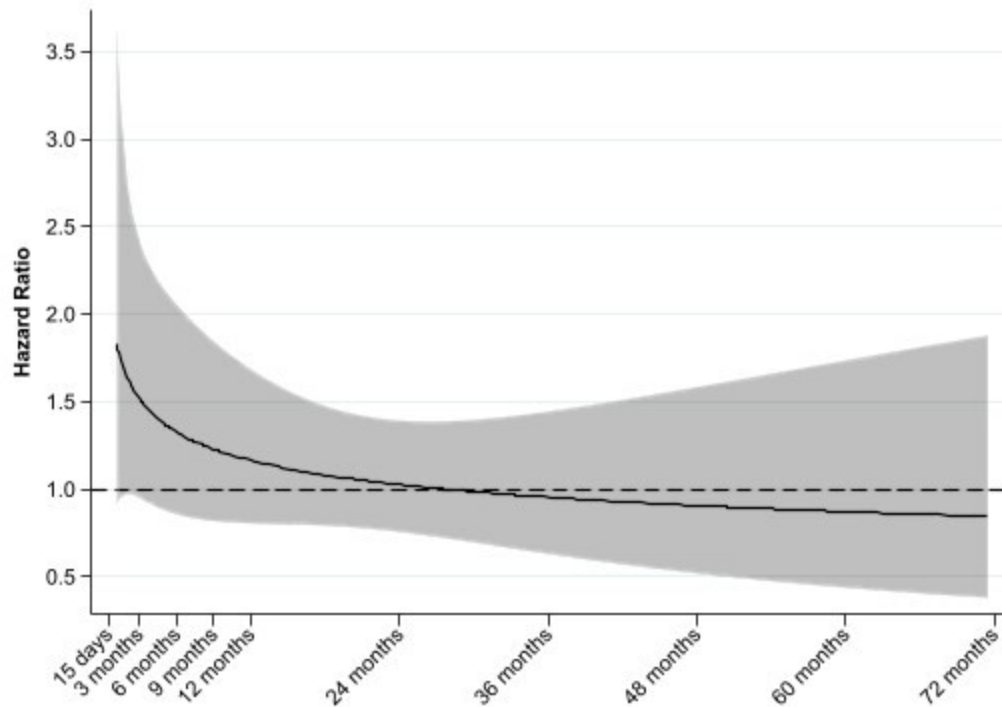


Fig. 1

Hazard ratios (95% confidence interval) of all-cause re-revision between revision procedures performed to manage infected primary knee arthroplasty. The hazard ratios are adjusted for age, sex, American Society of Anesthesiologists grade, and type of primary knee arthroplasty. The hazard ratios are reported between one month and six years postoperative due to small number of reoperations and/or person-years observed thereafter.

revision to have undergone an additional revision if the patient underwent repeated stage 1 procedures before a stage 2 procedure. We considered single-stage revisions and complete two-stage revisions (after a stage 1 and stage 2 of two-stage revision was performed) re-revised if the planned revision procedures were followed by any further revision episode where implants were changed as defined above.

We considered all-cause re-revision, and re-revision specifically for PJI. The indication for surgery was recorded by the surgical team at the time of the procedure.

Primary arthroplasties not revised or revised for a non-septic indication were used as comparators in the mortality analysis, excluding from the “non-septic revision” comparator group primary procedures initially revised for a non-septic indication prior to a re-revision for PJI.

Incomplete two-stage revisions, where patients only received a single stage 1 but no stage 2 of a two-stage revision procedure, or no further stage 1 reoperation, were excluded from the re-revision analyses but included in the mortality analysis.

**Statistical analysis.** Kaplan–Meier analyses were performed to assess the cumulative re-revision incidence for any cause, for PJI and mortality incidence by study group. The derivation of the time at risk is detailed in the Supplementary Material. We also compared the

statistics for the single- and two-stage surgeries using independent-samples *t*-test for continuous variables, independent chi-squared test for binary variables, and likelihood-ratio test for the other categorical variables. We used Cox shared frailty models to account for within-hospital correlation and compute overall hazard ratios (HRs) of re-revision/mortality for the first two years following the single-stage revision, and for the first five years (two-stage used as the reference).

We then produced time-dependent HRs using Poisson regressions, modelling the baseline hazard function with restricted cubic splines to capture time-specific disparities throughout the postoperative period between the two PJI revision procedures (Supplementary Table i).<sup>21</sup> These regressions were adjusted for age, sex, and American Society of Anesthesiologists (ASA) grade.<sup>22</sup> Further details are provided in the Supplementary Material. Patients with a primary procedure not revised, or revised for a non-septic indication, were used as comparator groups in the mortality analysis.

We performed a sensitivity analysis for each of the above models without patients with incomplete two-stage revision, i.e. no stage 1 recorded and only a stage 2 procedure recorded for their first PJI revision following the primary hip arthroplasty. We compared the revision burden by type of PJI revision (single- or two-stage) using zero-truncated Poisson model. The revision

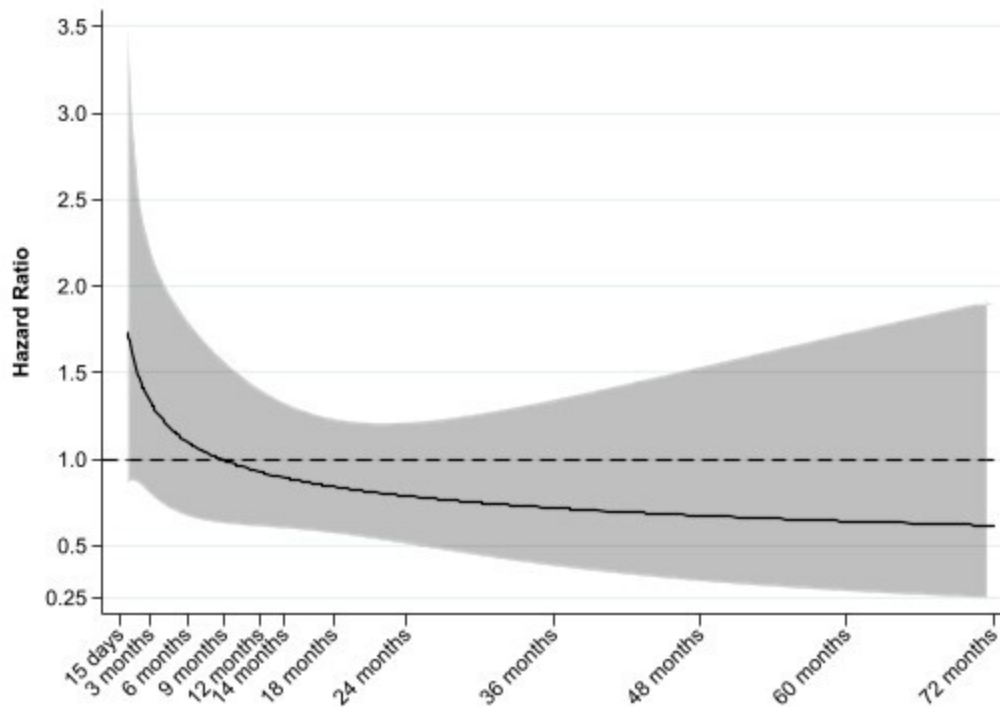


Fig. 2

Hazard ratios (95% confidence interval) of re-revision for periprosthetic joint infection between revision procedures performed to manage infected primary knee arthroplasty. a) The hazard ratios are adjusted for age, sex, American Society of Anesthesiologists grade, and type of primary knee arthroplasty. b) The hazard ratios are reported between one month and six years\* postoperative due to small number of reoperations and/or person-years observed thereafter.

burden included all procedures recorded in the NJR from the first single-stage or first stage 1 of two-stage procedure for PJI following the primary procedure to the last recorded re-revision procedures. We conducted the analyses with Stata 15.1 (StataCorp, USA). The level of significance was set at  $p < 0.05$ , and comparisons were performed using likelihood-ratio test.

## Results

Between 2003 and 2014, 3,369 primary knee arthroplasties were revised for PJI, 489 with a single-stage procedure and 2,880 with a two-stage procedure, and 2,377 with a second-stage procedure (Supplementary Figure a). Patients revised with a single-stage procedure were more likely to have an ASA grade  $\leq 2$  (27% vs 32%), and more likely to have undergone a unicompartmental rather than total primary knee arthroplasty (13% vs 5%), than patients revised with two-stage procedure (Table I). The median time elapsed between stage 1 and stage 2 for two-stage revision was three months (interquartile range (IQR) 2 to 5).

**All-cause re-revision.** Of the 3,369 primary knee arthroplasties revised for PJI, 397 subsequently underwent re-revision for any cause (Table I). The incidence of all-cause re-revision following single-stage revision was 50/10,000 person-years (95% CI 39 to 64) compared to 39/10,000 (95% CI 35 to 44) following two-stage revision ( $p = 0.119$ ).

The overall adjusted risk of re-revision for the first two postoperative years was higher, but not statistically different, between single-stage revision and two-stage revision (HR overall two years, 1.32 (95% CI 0.97 to 1.81);  $p = 0.082$ ); the risk was also comparable for the first five postoperative years (HR overall five years, 1.15 (95% CI 0.87 to 1.52);  $p = 0.308$ ). The cumulative probability of revision is shown in Supplementary Figure b. Compared to two-stage revision for knee PJI (Figure 1), the adjusted risks of all-cause re-revision for single-stage revision were comparable throughout the postoperative periods (HR at three months, 1.51 (95% CI 0.95 to 2.41);  $p = 0.081$ ; HR at 12 months, 1.16 (95% CI 0.80 to 1.68);  $p = 0.418$ ; Supplementary Table ii).

**PJI re-revision.** Of the re-revisions performed, 291 (73%) were performed for an indication of PJI (Table I). The incidence of PJI re-revision following single-stage revision was 32/10,000 person-years (95% CI 24 to 43) and 30/10,000 (95% CI 26 to 33) following two-stage revision ( $p = 0.738$ ). The adjusted risks of PJI re-revision for the first two postoperative years and first five postoperative years were similar (HR overall two years, 1.09 (95% CI 0.76 to 1.57);  $p = 0.664$ ; HR overall five years, 0.99 (95% CI 0.70 to 1.39);  $p = 0.995$ ). The cumulative probability of revision is shown in Supplementary Figure c. The incidence of re-revision for PJI was comparable between the two revision strategies (Figure 2) throughout the postoperative periods (HR at three months, 1.33 (0.80 to 2.20),

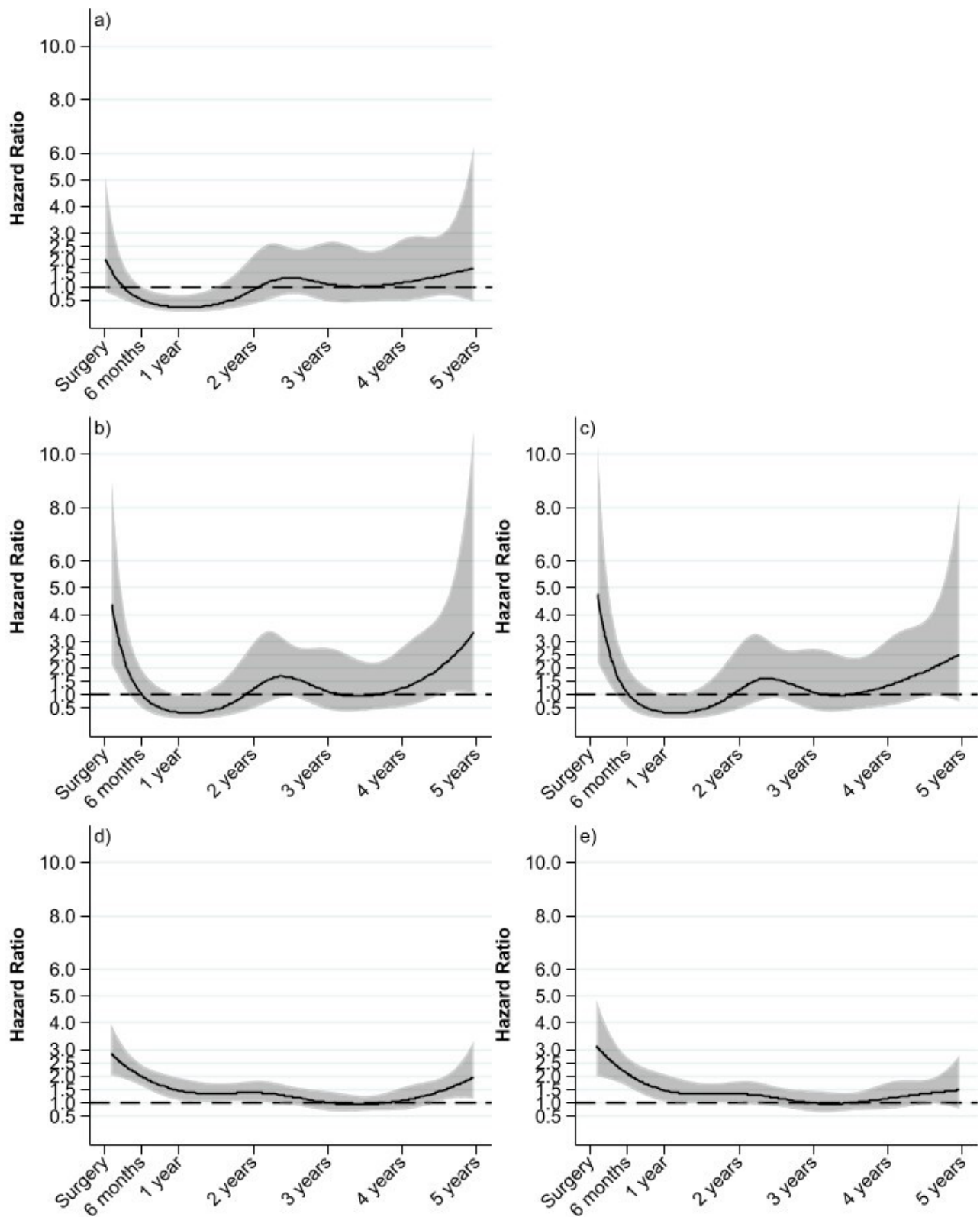


Fig. 3

Mortality hazard ratios between revision procedures performed to manage infected primary knee arthroplasty and other arthroplasty procedures. a) Single-stage versus two-stage (reference). b) Single-stage versus primary (reference). c) Single-stage versus non-septic revision (reference). d) Two-stage versus primary (reference). e) Two-stage versus non-septic revision (reference). f) The hazard ratios are adjusted for age, sex, American Society of Anesthesiologists grade, and type of primary knee arthroplasty. g) The hazard ratios are reported between one month and six years postoperative due to small number of reoperations and/or person-years observed thereafter. h) Non-septic revisions are primary knee arthroplasties revised for any other indication than periprosthetic joint infection.

**Table II.** Number of revision procedures performed to manage primary knee arthroplasty with periprosthetic joint infection.\*

Number of surgeries	Single-stage (n = 489)	Two-stage (n = 2,377)	p-value
Median (IQR)	1 (1 to 1)	2 (2 to 2)	< 0.001†
One, n (%)	419 (85.7)	0 (0.0)	< 0.001‡
Two, n (%)	33 (6.8)	2,079 (87.5)	
Three, n (%)	31 (6.3)	160 (6.7)	
Four to five, n (%)	6 (1.2)	124 (5.2)	
Six to eight, n (%)	0 (0.0)	14 (0.6)	

\*The number of revision procedures includes the first single-stage procedure/first stage 1 of two-stage procedure and any subsequent procedures recorded thereafter in the National Joint Registry.

†Zero-truncated Poisson regression.

‡Chi-squared test.

IQR, interquartile range.

$p = 0.274$ ; HR at 12 months, 0.93 (95% CI 0.61 to 1.40);  $p = 0.719$ ; Supplementary Table iii).

**Mortality.** A total of 369 patients who underwent revision for knee PJI died (Table I). The mortality rates for single- and two-stage procedures were 26/10,000 person-years (95% CI 18 to 35) and 31/10,000 (95% CI 27 to 34), respectively ( $p = 0.436$ ).

The cumulative probability of mortality for single-stage and two-stage revision for knee PJI is shown in Supplementary Figure d. The adjusted risks of mortality in the first two years and first five postoperative years were comparable (HR single-stage (ref) vs two-stage overall two years, 1.21 (95% CI 0.72 to 2.03),  $p = 0.469$ ; HR overall five years, 1.06 (95% CI 0.74 to 1.51),  $p = 0.760$ ). Time-specific differences were identified with lower risk of mortality between six months and around 1.5 years after the surgery for patients who had undergone a single-stage revision (Figure 3a). This reduced risk was only observed between six months and one year in the sensitivity analysis (Supplementary Table iv).

Compared to patients who had undergone a primary arthroplasty (21.7/10,000 (95% CI 21.6 to 21.9)), the mortality was not different following single-stage revision for PJI (HR primary (ref) vs single-stage overall two years, 1.37 (95% CI 0.84 to 2.23),  $p = 0.211$ ; HR overall five years, 1.32 (95% CI 0.94 to 1.85),  $p = 0.103$ ; Figure 3b), but was higher following two-stage revision for PJI (HR primary (ref) vs two-stage overall two years, 1.66 (95% CI 1.40 to 1.96),  $p < 0.001$ ; HR overall five years, 1.40 (95% CI 1.24 to 1.58),  $p < 0.001$ ).

Compared to patients who had undergone a revision for a non-septic indication (15.3/10,000 (95% CI 14.3 to 16.3)), there was no or weak evidence of higher mortality following single-stage revision for PJI (HR non-septic revision (ref) vs single-stage overall two years, 1.40 (95% CI 0.84 to 2.31),  $p = 0.192$ ; HR overall five years, 1.40 (95% CI 0.99 to 1.98),  $p = 0.054$ ), but higher mortality for those who underwent a two-stage revision for PJI (HR non-septic revision (ref) vs two-stage overall two years,

1.69 (95% CI 1.38 to 2.08),  $p < 0.001$ ; HR overall five years, 1.48 (95% CI 1.29 to 1.71),  $p < 0.001$ ).

These differences were not constant throughout the postoperative period (Supplementary Table iv). In the first three postoperative months, patients revised for knee PJI with a single-stage procedure were at higher risk of mortality than those who had undergone a primary arthroplasty (Figure 3b, HR at three months, 2.93 (95% CI 1.59 to 5.41),  $p < 0.001$ ) or a revision for non-septic indication (Figure 3c; HR at three months, 3.17 (95% CI 1.66 to 6.04),  $p < 0.001$ ). In the first 24 postoperative months, the mortality was also higher following revision for PJI with a two-stage procedure than following primary arthroplasty (Figure 3d; HR at 12 months, 1.44 (95% CI 1.10 to 1.95),  $p = 0.009$ ; HR at 24 months, 1.38 (95% CI 1.05 to 1.83),  $p = 0.022$ ). Two-stage revision also had a higher risk of mortality in the first 18 postoperative months compared to revision for a non-septic indication (Figure 3e; HR at 18 months, 1.33 (95% CI 1.01 to 1.75),  $p = 0.044$ ). This was only evident in the first six postoperative months in the sensitivity analysis (Supplementary Table iv).

**Number of revision surgeries performed.** The two-stage group underwent more operations than those initially managed with a single-stage procedure (mean number of procedures 2.2 vs 1.2;  $p < 0.001$ , Table II). Overall 14.3% of single-stage patients required additional revision procedures (i.e. more than one), with 7.5% re-revised three to five times. Around 11.5% of two-stage patients required additional procedures (i.e. at least three procedures), with 6% re-revised four to eight times.

## Discussion

Our study of over 3,300 single- and two-stage revisions for the management of infected primary knee arthroplasty has shown comparable risk of re-revision for PJI or for any cause. Patients managed with single-stage revision underwent 45% fewer operations. The length of time between stage 1 and stage 2 was higher than three months for 50% of the patients treated with two-stage procedures. The risk of mortality following single-stage revision for PJI was comparable or lower (between six and 18 postoperative months) compared to two-stage revision, but both were higher than for patients undergoing primary knee arthroplasty, or revision for indications other than infection.

Current evidence synthesis suggests similar rates of re-revision for PJI between single- and two-stage revision for PJI of the knee;<sup>12-14</sup> our findings are consistent with this. The evidence published previously is limited by small study sizes, lack of studies on single-stage revision, and lack of head-to-head comparisons (Table III). One large cohort study, based on Medicare patients, found a 34% higher risk of reinfection following single-stage revision compared to two-stage revision.<sup>10</sup> It is unclear to what extent this study is directly comparable to our data, given the much higher incidence of PJI seen, partly but not entirely explained by the inclusion of patients managed

**Table III.** Sample size and nature of the comparison between main studies on outcomes following one-stage and two-stage revision surgeries for the management of knee prosthesis infection.

Author	Publication year	Study type	Type of revision	Study year	Sample size	Number of studies by sample size						
						< 20	20 to 30	30 to 50	50 to 100	100 to 200	200 to 500	≥ 500
Masters et al <sup>13</sup>	2013	Systematic review	1-stage only	1985 to 2012	110	2	1	0	1	1	0	0
			2-stage only	1987 to 2012	1,597	0	0	4	12	3	1	1
Cochran et al <sup>10</sup>	2016	Cohort	1-stage only	2001 to 2005	3,069	0	0	0	0	0	0	1
			2-stage only	2001 to 2005	5,364	0	0	0	0	0	0	1
			Comparison 1- vs 2-stage	2001 to 2005	3,069 + 5,364	0	0	0	0	0	0	1
Kunutsor et al <sup>12</sup>	2016	Systematic review	1-stage only	1976 to 2010	423	2	3	3	1	1	0	0
			2-stage only	1969 to 2011	5,129	27	31	24	20	2	4	0
Nagra et al <sup>14</sup>	2016	Systematic review	1-stage only	1987 to 2014	46	4	1	0	0	0	0	0
			2-stage only	1987 to 2014	185	3	0	0	2	0	0	0
			Comparison 1- vs 2-stage	1987 to 2014	46 + 185	3	0	0	1	1	0	0

with incision and drainage alone or with DAIR, and much higher rates of reinfection (29% to 38% vs 13% to 15% in our study).

No study has reported on the risk of re-revision for any cause following single- and two-stage revision for knee PJI. Despite the potential for further bone loss and a second insult to the soft tissues associated with a two-stage revision strategy, this did not lead to an increased risk of subsequent problems such as aseptic loosening. This is also the first study to have explored time-specific differences in the risk of re-revision for PJI or any cause, and we observed no overall or time-specific difference when comparing single- or two-stage revision for knee PJI.

No study has compared the risk of mortality between these two approaches. Previous studies have compared knee revision for PJI to the risk observed in the general population, following primary knee arthroplasty or non-infectious revision.<sup>18-20</sup> While our overall findings are comparable to these previous findings, we have shown that this increase is particularly marked in the first three months following single-stage revision compared to both primary and non-septic revision, whereas patients treated with a two-stage revision retained a higher risk of mortality for at least the first two years compared to these procedures. Mortality is therefore higher in patients revised for infection; the type of procedure used to manage the infection seems to have a marginal effect except during the first six to 18 months, during which the mortality of patients operated with a two-stage revision was higher in England and Wales compared to those managed with a single-stage revision.

PJI treatment is expensive and protracted, and both the infection and the treatment have profoundly negative effects on patients and their families, particularly

if complications occur between stages.<sup>4-6,19</sup> Currently, over 70% of knee PJIs are managed with a two-stage approach,<sup>9</sup> and in hip PJI the cost of a two-stage procedure is 1.6 to 1.7 times more than a single-stage revision.<sup>23,24</sup> Our study has shown equivalent re-revision and mortality outcomes, but lower numbers of revision procedures for single-stage revision compared to the current “gold-standard” two-stage approach for revision of knee PJI.

This is the largest study to compare the incidence of re-revision after single-stage and two-stage revision for knee PJI. We used a standardized data collection process and adjustment approach, examining component level data to precisely define and group comparable procedures. It is the first to map the time-varying risks throughout the postoperative period, the importance of which is demonstrated by the patterns observed. We have also used modelling to best account for the time elapsed between the initial management of PJI and the first following re-revision for PJI or death.

Only procedures where an implant is added, removed, or modified are captured in the NJR. We are therefore not able to explore the risks for knee PJI treated with antibiotics or incision and drainage alone, but the reoperation outcomes are substantially worse for this strategy.<sup>10</sup> Like any other observational study, and the entirety of the international literature published so far on knee PJI, our results are subject to selection bias. However, this study is based on the NJR, capturing most if not all knee revision PJI procedures performed in England and Wales, and such bias is likely to be small. We also excluded DAIR procedures due to different indications for the procedure compared to single- or two-stage revision and worse infection control rates seen, which means that they cannot be considered to be equivalent interventions and cannot be directly



compared.<sup>11</sup> The NJR does not capture data on the presence of a sinus or the microorganism(s) causing the PJI; the choice of surgical strategy to treat PJI may depend on the perceived complexity of the infection management.<sup>25</sup> Information on immunocompromised patients, previous surgical management, bony defects, types of organisms, and duration of surgery are also not captured in the NJR. Patients managed with single-stage revision were less likely to have a higher ASA grade, and more likely to have received a unicompartmental primary knee arthroplasty, but were comparable in terms of sex and age; adjustment for these factors did not affect the results. The NJR does not capture data on soft-tissue coverage procedures, the requirement for which is associated with a higher risk of failure,<sup>26</sup> and may be more amenable to planning with a two-stage approach. The risks of mortality and re-revision for any cause, or specifically for PJI, were comparable between single- and two-stage revision for PJI, and those who underwent single-stage revision had a lower number of operations. With appropriate selection, single- and two-stage revision have comparable results, and when considered alongside the results of recent evidence synthesis, the single-stage revision strategy for knee PJI is a reasonable option to reduce the distress experienced by patients having to undergo multiple PJI surgeries and the burden of knee PJI on the healthcare system.

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## Supplementary material



Further methodological information, tables on the model goodness of fit and hazard ratios underpinning the figures presented in the main manuscript, and additional figures.

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**ICMJE COI statement:**

- We declare that we have no conflict of interest. M. R. Reed is the chair of the NJR Editorial Board, and reports institutional payments from Stryker, Zimmer Biomet, Heraeus, Link, Depuy, Smith & Nephew, Implantcast, and Biocomposites, and speaker payments from Zimmer Biomet, all of which are unrelated to this study.
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**Data sharing:**

- E. Lenguerrand and A. W. Blom had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. The authors have conformed to the NJR's standard protocol for data access and publication. The views expressed represent those of the authors and do not necessarily reflect those of the NJR Steering Committee or Healthcare Quality Improvement Partnership (HQIP), who do not vouch for how the information is presented.
- The data used in these analyses cannot be accessed without permission from the NJR scientific committee. Further details are available at <http://www.njrcentre.org.uk/njr-centre/Research/Research-requests>. Once the required permissions are secured, the authors will be able to share the data and analytical approaches used in this manuscript.

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**Ethical review statement:**

- With support under Section 251 of the NHS Act 2006, the Ethics and Confidentiality Committee (ECC), (now the Health Research Authority Confidentiality Advisory Group) allows the NJR to collect patient data where consent is indicated as 'Not Recorded'. Before Personal Data and Sensitive Personal Data are recorded, express written patient consent is provided. The NJR records patient consent as either 'Yes', 'No', or 'Not Recorded'. Consent for publication, using anonymization strategy, has been obtained via the NJR patient consent and a Section 251. This manuscript has also been approved for publication by the NJR scientific committee.

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