Strategies in prevention and treatment of prosthetic joint infections

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CHAPTER

3

Similar risk of complete revision for infection with single-dose versus multiple-dose antibiotic prophylaxis in primary arthroplasty of the hip and knee: results of an observational cohort study in the Dutch Arthroplasty Register in 242,179 patients

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ABSTRACT

Background and purpose

The optimal type and duration of antibiotic prophylaxis for primary arthroplasty of the hip and knee are subject to debate. We compared the risk of complete revision (obtained by a 1- or 2-stage procedure) for periprosthetic joint infection (PJI) after primary total hip or knee arthroplasty between patients receiving a single dose of prophylactic antibiotics and patients receiving multiple doses of antibiotics for prevention of PJI.

Methods A cohort of 130,712 primary total hip and 111,467 knee arthroplasties performed between 2011 and 2015 in the Netherlands was analysed. We linked data from the Dutch arthroplasty register to a survey collected across all Dutch institutions on hospital-level antibiotic prophylaxis policy. We used restricted cubic spline Poisson models adjusted for hospital clustering to compare the risk of revision for infection according to type and duration of antibiotic prophylaxis received.

Results For total hip arthroplasties, the rates of revision for infection were 31/10,000 person-years (95% CI 28–35), 39 (25–59), and 23 (15–34) in the groups that received multiple doses of cefazolin, multiple doses of cefuroxime, and a single dose of cefazolin, respectively. The rates for knee arthroplasties were 27/10,000 person-years (95% CI 24–31), 40 (24–62), and 24 (16–36). Similar risk of complete revision for infection among antibiotic prophylaxis regimens was found when adjusting for confounders.

Interpretation In a large observational cohort we found no apparent association between the type or duration of antibiotic prophylaxis and the risk of complete revision for infection. This does question whether there is any advantage to the use of prolonged antibiotic prophylaxis beyond a single dose.

INTRODUCTION

Annually around 1 million patients receive a total hip or total knee prosthesis in the United States and over 190,000 hip and knee replacements are performed in England and Wales.[1, 2] The incidences of prosthetic replacement of the hip and knee are expected to increase.[3] Prosthetic joint infection (PJI) following total hip or knee arthroplasty and the treatment thereof are catastrophic for patients and pose tremendous costs to healthcare systems.[4-6] Perioperative antibiotic prophylaxis remains an effective method of reducing the risk of PJI.[7, 8] The type and duration of antibiotic prophylaxis are subject to debate.

Both single dose and multiple dose antibiotic prophylaxis regimens have been advocated with comparable results.[8, 9] The recommendations provided by the Second International Consensus Meeting of the MusculoSkeletal Infection Society (MSIS) and the European Bone and Joint Infection Society (EBJIS) advise that antibiotic prophylaxis should be administered 30-60 minutes before incision and discontinued within 24 hours after surgery.[10, 11] Large variations in prophylaxis regimens has been observed in the United Kingdom.[12] The Dutch national orthopaedic association advises administration of antibiotic prophylaxis using a first or second generation cephalosporin starting 30-60 minutes preoperatively and discontinuing the antibiotic prophylaxis within 24 hours.[13, 14] The World Health Organisation and, in the USA, the Center for Disease Control and Prevention (CDC) recommends against the use of postoperative continuation of antibiotic prophylaxis and advocate for a single dose of antibiotics delivered pre-operatively.[15] This recommendation is vehemently challenged by the American Association of Hip and Knee Surgeons and the International Consensus Meeting which encourage their members to proceed with the current common practice of multiple dose antibiotic prophylaxis protocols until more evidence is available.[16]

We compared the risk of complete revision for infection in the 1st year following primary hip and knee arthroplasty according to the perioperatively administered antibiotic prophylaxis regimen by using data from the Dutch Arthroplasty Register (LROI).

METHODS

This study was structured using the STROBE guideline. In this observational cohort study, we report analyses of data for the Netherlands from the Dutch Arthroplasty Register (LROI) between January 1st 2011 and December 31st 2015. We included all patients who had a primary hip or knee replacement during this period in the study. Patient consent was obtained for data collection and linkage by the LROI. Using data on patient level was not possible due to the legislation of the General Data Protection Regulation.

In absence of individual patient level data on antibiotic prophylaxis, we performed an national audit of hospital perioperative antibiotic prophylaxis regimens in the Netherlands.[17] All 99 Dutch hospitals or clinics performing primary total hip arthroplasty (THA) or total knee arthroplasty (TKA) were contacted and all completed a survey to identify existence of treatment protocols concerning primary joint replacement, existence of protocols regarding treatment strategy in case of suspected early postoperative infection and tendency to register procedures in the LROI database. We asked, in particular, about type and duration of antibiotic prophylaxis. This survey showed a variance in postoperative duration of antibiotic prophylaxis. 10 Dutch hospitals administered a single shot antibiotic prophylaxis, while the remaining 89 administered a multiple shot antibiotic prophylaxis. This variance facilitated an observational cohort study using the LROI. The LROI has a completeness of over 95% for primary hip and knee arthroplasties and of 91% and 92% for the hip and knee revision procedures respectively.[18-20] The translated survey form can be found in Appendix 1, supplementary data.

Each patient who had a primary THA or TKA was followed up for a minimum of 12 months until the end of the observation period (December 31st, 2015) or until the date of 1- or 2-stage revision for infection, revision for another indication, death or end of follow-up (January 1st 2018). Revisions for infection included only complete revision of the total system, obtained by a 1- or 2-stage revision procedure. All partial revisions (e.g. debridement, antibiotics and implant retention procedures (DAIR)) were excluded because these partial revisions are inconsistently recorded compared to total revisions.[17, 18] We chose to end the follow-up period at 1 year after surgery as with longer follow-up the influence of hematogenous infections on the measured outcome may increase to become larger than the influence of the duration of antibiotic prophylaxis at primary surgery.

We defined infection status using the surgical indication reported in the LROI revision arthroplasty form following surgery by the treating orthopaedic surgeon. We included patients whom had undergone complete revision captured by the LROI where the reason for revision was defined as infection in the infected group and patients in whom the reason for revision was not reported, or reason for revision other than infection was reported, in the non-infected group. The diagnosis and treatment strategy for complete revision for infection was at the discretion of the surgeon and treating unit and it reflected contemporary practice over the study period, with raised inflammatory markers, joint specific symptoms, sinuses, and positive microbiological cultures being common diagnostic features over that period.[21]

We compared the risk of complete revision surgery for infection in the 1st year following primary arthroplasty by the type and duration of antibiotic prophylaxis regimen administered at primary surgery. We considered the patient characteristics age, sex, BMI, ASA grade, and previous surgery. We considered surgical factors such as indication for surgery, surgical approach, type of fixation and bearing surface. Data from the LROI database were combined at hospital level with the results of the national survey on antibiotic prophylaxis. Results of the survey show there were 3 types of antibiotic regimens that are used in the Netherlands: multiple dose of cefazolin (MCZ), multiple dose of cefuroxime (MCX), and single dose of cefazolin (SCZ), which are all in concordance with the Dutch guideline for perioperative antibiotics in total hip and knee arthroplasty.[17] No other antibiotic regimens were encountered in the survey. Patients were divided into 3 groups (MCZ, MCX and SCZ) according to the antibiotic prophylaxis protocol of the hospital they were treated.

Statistics

We investigated the association between hospital antibiotic prophylaxis regimen policies (MCZ used as the reference) and the risk of complete revision for infection in the first 12 months following the index primary surgery with Poisson regression to account for time at risk and to produce hazard ratios including 95% confidence intervals (CI). The baseline hazard rate was modelled with restricted cubic splines. The optimum numbers of knots (3 degrees of freedom (d.f.) for the hip models, 4 d.f. for the knee models) was identified with AIC and BIC criteria (Appendix Table 1, supplementary data). Interaction terms between the splines and the main exposure covariates were included to estimate the time-dependent hazard ratio for complete revision for infection of the different antibiotic prophylaxis regimens.[22] Huber-White-sandwich estimate of variance were computed to adjust for within-hospital correlation. The models were stratified by surgical site and adjusted for age, sex, BMI and ASA classification. Multiple imputation by chained equations (5 imputations sets) under a missing at random framework was used to account for missing data. The imputation model incorporated the PJI status, time at risk, the main exposure, the aforementioned adjustment factors and indication for surgery, surgical approach, method of fixation, bearing surface, and year of surgery as ancillary variables. All statistical analyses were performed using Stata, version 15.1.

Ethics, funding, and potential conflicts of interest

The study protocol was registered on ClinicalTrials.gov with reference NCT03348254.

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The National Institute for Health Research had no role in study design, data collection analysis, interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

During 2011 to 2015, 130,712 primary total hip arthroplasties and 111,467 primary total knee arthroplasties were performed across 99 centers. 399 hips and 303 knees were revised within 1 year of the primary arthroplasty for an indication of infection (Tables 2 and 3, see supplementary data). Multiple dose cefazolin (MCZ), multiple dose cefuroxime (MCX), or single dose cefazolin (SCZ) antibiotic prophylaxes were respectively administrated to 87%, 4% and 9% of patients. Hereafter, 'revision' refers to '1 and 2-stage revisions'.

For total hip arthroplasties, the 1-year rates of revision for infection (CI) were respectively 31/10,000 person-years (28-35), 39 (25-59), and 23 (15-34) in the groups that received MCZ, MCX, and SCZ; the rates for knee arthroplasties were 27 (24-31), 40 (24-62), and 24 (16-36) respectively. The rates of revision for infection over time according to antibiotic prophylaxis regimen are shown in Figures 1 and 2. Revision for infection was performed most frequently in the first 3 months postoperatively for both hip and knee replacements.

While the risk of complete revision for infection appeared to differ over time, no or little evidence of differences between antibiotic prophylaxis regimens were found (Figures 3 and 4). In the first 11 months after primary hip arthroplasty, the risk of revision was comparable between SCZ and MCZ (adjusted $HR_{SCZ\ vs.\ MCZ}$ at 3 months 0.59 [0.19-1.79], at 6 months 1.02 [0.43-2.39]), but the risk of revision was higher in the SCZ group thereafter (HR 2.21 [1.12-4.38]). No evidence of difference was found between MCZ and MCX following hip arthroplasty (adjusted $HR_{MCX\ vs.\ MCZ}$ at 3 months 1.54 [0.77-3.08], at 6 months 1.00 [0.60-1.68], at 12 months 0.61 [0.20-1.81]). For patients receiving a primary total knee arthroplasty revision rates between SCZ and MCZ were comparable (adjusted $HR_{SCZ\ vs.\ MCZ}$ at 3 months 1.81 [0.87-3.76], at 6 months 0.89 [0.15-5.31], at 12 months 0.47

[0.09-2.37]). The risk of revision for infection was also comparable between MCZ and MCX (adjusted $HR_{MCX\ vs.\ MCZ}$ at 3 months 1.71 [0.54-5.37], at 6 months 1.15 [0.65-2.02], at 12 months 1.88 [0.56-6.31]). The patterns observed were comparable in the unadjusted and adjusted models (Tables 1 and 2).

Figure 1: Rate of complete revision for infection in the first 12 months following primary hip replacement by type of antibiotics regimen.

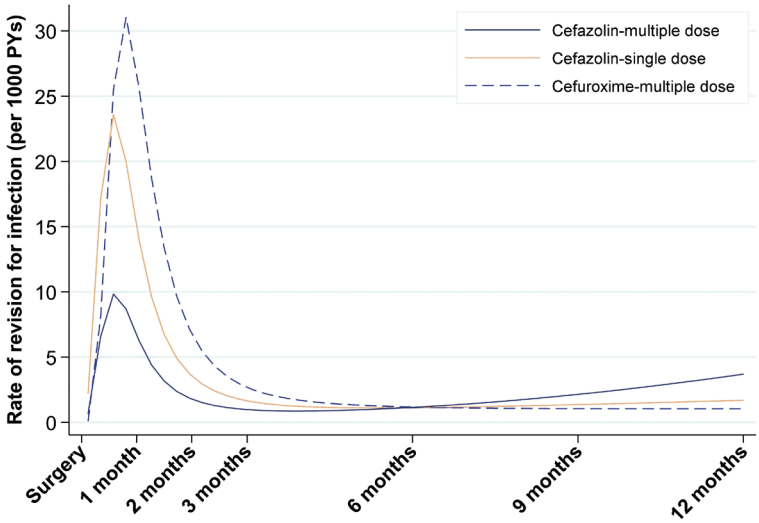

Figure 2: Rate of complete revision for infection in the first 12 months following primary knee replacement by type of antibiotics regimen.

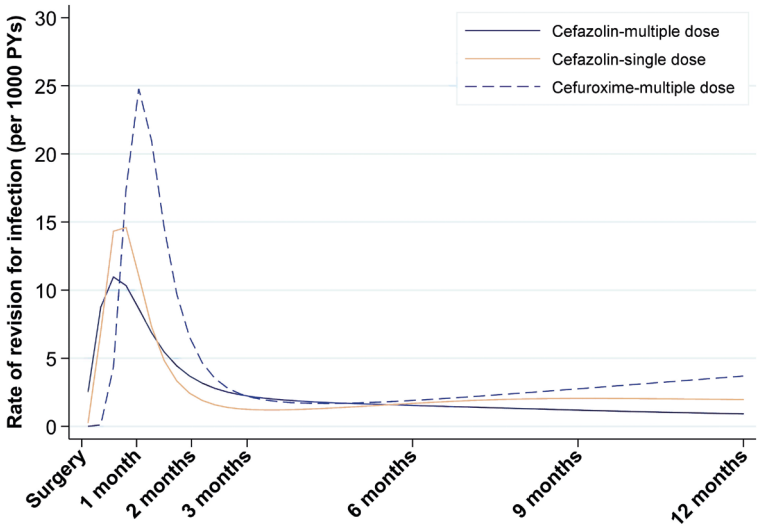

Figure 3: Hazard ratio and 95% CI* of complete revision for infection in the first 12 months following primary hip replacement by type of antibiotics regimen (reference: cefazolin multiple dose). *Derived from unadjusted Poisson model with restricted cubic splines (3 degrees of freedom) (see Appendix Table 2).

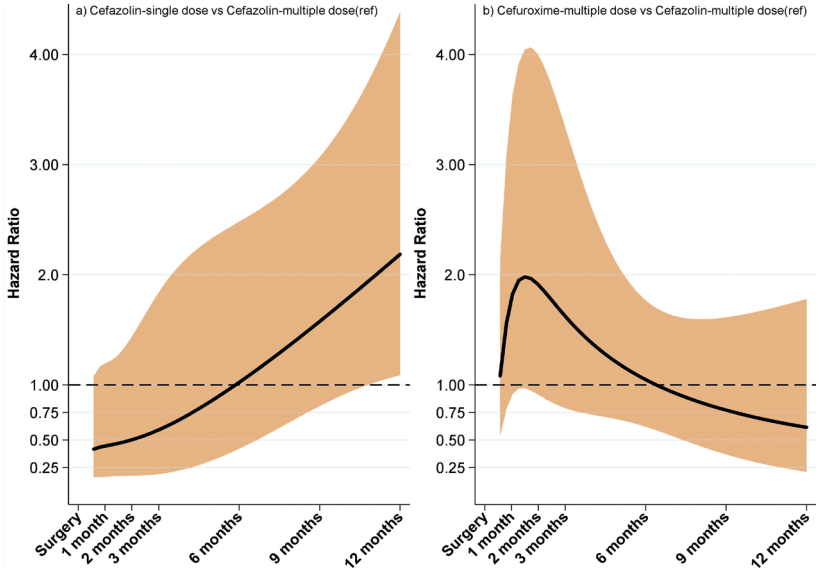

Figure 4: Hazard ratio and 95% CI* of complete revision for infection during the first 12 months following primary knee replacement by type of antibiotics regimen (reference: cefazolin multiple dose). *Derived from unadjusted Poisson model with restricted cubic splines (3 degrees of freedom) (see Appendix Table 3).

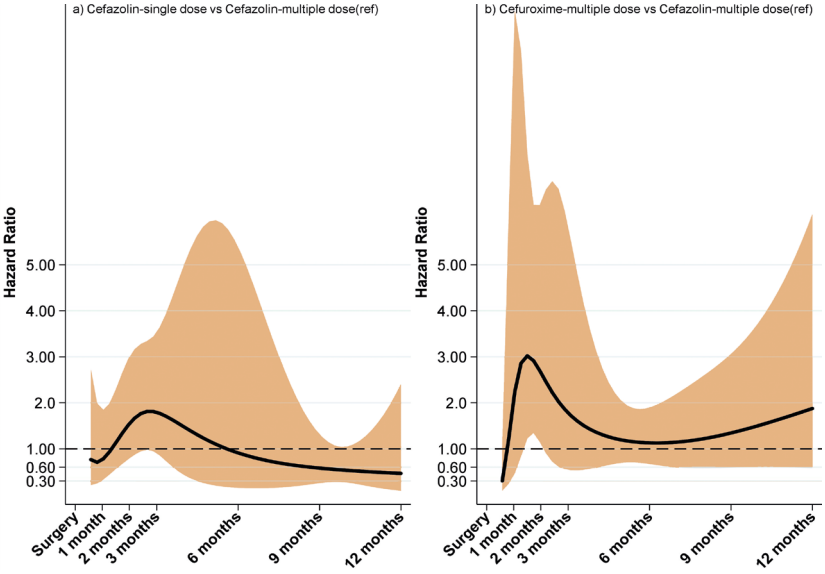

Table 1: Unadjusted Hazard-Ratio (HR) of revision for PJI infection in the first 12 months following primary hip replacement (Reference: Cefazolin multiple dose)

Time*	HR $_{\text{Cefazoline-single dose}}$	95%CI	HR $_{\text{Cefuroxime-multiple dose}}$	95%CI
1 month	0.45	[0.17, 1.20]	1.82	[0.92, 3.62]
2 months	0.50	[0.17, 1.42]	1.92	[0.92, 4.01]
3 months	0.60	[0.19, 1.87]	1.59	[0.78, 3.25]
6 months	1.04	[0.43, 2.49]	1.03	[0.61, 1.74]
9 months	1.59	[0.82, 3.09]	0.76	[0.36, 1.61]
12 months	2.18	[1.09, 4.38]	0.61	[0.21, 1.78]

*Time from primary procedure

Adjusted Hazard-Ratio (HR)** of revision for PJI infection in the first 12 months following primary hip replacement (Reference: Cefazolin multiple dose)

Time*	HR $_{\text{Cefazoline-single dose}}$	95%CI	HR $_{\text{Cefuroxime-multiple dose}}$	95%CI
1 month	0.45	[0.17, 1.20]	1.80	[0.92, 3.52]
2 months	0.49	[0.17, 1.38]	1.88	[0.92, 3.86]
3 months	0.59	[0.19, 1.79]	1.54	[0.77, 3.08]
6 months	1.02	[0.43, 2.39]	1.00	[0.60, 1.68]
9 months	1.59	[0.83, 3.02]	0.75	[0.35, 1.61]
12 months	2.21	[1.12, 4.38]	0.61	[0.20, 1.81]

*Time from primary procedure, **adjusted for age, sex, BMI and ASA grade

Table 2: Unadjusted Hazard-Ratio (HR) of revision for PJI infection in the first 12 months following primary knee replacement (Reference: Cefazolin multiple dose)

Time*	HR $_{\text{Cefazoline-single dose}}$	95%CI	HR $_{\text{Cefuroxime-multiple dose}}$	95%CI
1 month	0.78	[0.33, 1.84]	2.24	[0.48, 10.52]
2 months	1.52	[0.78, 2.95]	2.70	[1.15, 6.30]
3 months	1.77	[0.86, 3.63]	1.72	[0.54, 5.50]
6 months	0.89	[0.15, 5.26]	1.13	[0.66, 1.91]
9 months	0.58	[0.26, 1.26]	1.36	[0.59, 3.11]
12 months	0.47	[0.09, 2.40]	1.88	[0.58, 6.10]

*Time from primary procedure

Adjusted Hazard-Ratio (HR)** of revision for PJI infection in the first 12 months following primary knee replacement (Reference: Cefazolin multiple dose)

Time*	HR $_{\text{Cefazoline-single dose}}$	95%CI	HR $_{\text{Cefuroxime-multiple dose}}$	95%CI
1 month	0.78	[0.33, 1.83]	2.34	[0.49, 11.20]
2 months	1.55	[0.80, 3.02]	2.70	[1.16, 6.29]
3 months	1.81	[0.87, 3.76]	1.71	[0.54, 5.37]
6 months	0.89	[0.15, 5.31]	1.15	[0.65, 2.02]
9 months	0.58	[0.26, 1.28]	1.38	[0.58, 3.30]
12 months	0.47	[0.09, 2.37]	1.88	[0.56, 6.31]

DISCUSSION

In this large observational cohort study of primary total hip and knee replacement, our findings suggest a comparable risk of complete revision for infection between the antibiotic prophylaxis regimens in terms of type of antibiotic and duration of prophylaxis during the first 12 months following surgery. When examining the hazard ratios, it is important to note that the majority of infections occurred within the first 3 months of surgery. Comparing single and multi-dose prophylaxis with Cefazolin for hip replacement, the hazard ratio for complete revision for infection following single dose prophylaxis steadily increased over time from less than half of that with multi-dose to over double the incidence of infection by month 12. It may be due to low virulence micro-organisms that are more susceptible to multi-dose therapy presenting with infection later. In case this is true, the differences between the different regimes should become more apparent with longer follow-up. This was not the case following knee replacement and alternatively may simply reflect either a chance occurrence, differences in patient- and surgery related factors, or residual confounding. Adjustment for established confounding variables (age, sex, BMI, ASA grade) did not change these results.

We observed that the highest risk of complete revision for infection in the year following surgery occurred within the first 3 months after the operation. Rates then appear to rise again towards the end of the follow up period. These patterns are consistent with contemporary patterns found in other registries.[23-25] This may be due to the effect of more virulent microorganisms presenting during the first 3 months and less virulent microorganisms presenting later. Since the LROI does not provide data on which microorganism is causing the PJI, this remains speculative. Another reason might be a genuine increase in the incidence of PJI or may reflect more rapid diagnosis and aggressive treatment of PJI in recent years. We have not analysed procedures where only debridement or partial revision (including debridement and implant retention (DAIR) with modular exchanges) were performed as these procedures are not reliably captured by the LROI registry.[17] DAIR has been shown to effectively treat infection in approximately 46-76% of cases.[26] We have no reason to believe that the use of DAIR is related to type or duration of antibiotic prophylaxis, but it is a possible cause of residual confounding.

It has been suggested that the most appropriate perioperative prophylactic antibiotic is a first or second generation cephalosporin (i.e. cefazolin or cefuroxime) administered intravenously within 30 to 60 minutes prior to incision as single and weight adjusted dose.[27-29] This policy is part of antibiotic stewardship, performed in countries with a

low prevalence of MRSA.[7, 30] While consensus exists on type of antibiotic prophylaxis, the postoperative duration of antibiotic prophylaxis remains subject to discussion.[11]

A recent systematic review and meta-analysis by Thornley et al. (2015) explored whether or not a single preoperative antibiotic dose is adequate for arthroplasty patients.[8] The review included 4 RCTs including 4,036 patients.[31-34] They concluded that additional postoperative antibiotic doses did not reduce the rates of infections (3.1% versus 2.3% postoperative PJI for multiple dose and single dose prophylaxis respectively). However, they reported that the quality of the included studies was very low. 3 of these studies were performed more than 20 years ago, while the other study used Teicoplanin, which is no longer recommended for use as antibiotic prophylaxis.[34] Heydemann and Nelson (1986) randomised 211 patients between single dose and 48-hour multiple dose prophylaxis, but found no cases of PJI in either group.[31] Ritter et al. (1989) compared a single dose of cefuroxime to 24 hours of postoperative prophylaxis in 196 patients, and found no cases of PJI in either group.[32] Wymenga et al. (1992) randomised 3,013 patients in a multicenter RCT comparing a single preoperative dose of cefuroxime to a group receiving three doses and found no significant differences in PJI rates between groups.[33] Engesaeter et al. (2003) reported the lowest rate of infection for patients who received four doses of antibiotic prophylaxis in 24 hours, compared to patients who received one, two or three doses in their study of the Norwegian Arthroplasty Register.[35] All authors of these studies recognized their study sample to be underpowered for determining a difference in PJI rates and recommended further studies to provide a definite answer. Based on these studies, the CDC has recently recommended against the use of postoperative continuation of antibiotic prophylaxis.[15] The recent International Consensus meeting advises to continue antibiotics postoperatively for 24 hours until better quality evidence is available.[11] A protocol for a RCT randomizing patients receiving a total knee arthroplasty between single dose versus multiple dose antibiotic prophylaxis has been registered on clinicaltrials.gov (NCT03283878). The study aims to definitively answer which duration of antibiotic prophylaxis is best. However, the planned follow-up of 90 days seems too short to capture all relevant infections. Also, the sample size is not justified in the trial registration, but with the aim of including 8000 patients the study seems underpowered.

Our study has several strengths. The large numbers studied allows adequate power to detect rare outcomes such as complete revision for infection. Data capture represents over 98% of national activity.[18] This rate of coverage provides excellent external validity and generalizability of our findings. The rate of complete revision for infection within

1 year of primary arthroplasty is higher for males, patients with higher BMI, or higher ASA grade in all groups, independent of the type of antibiotic prophylaxis.[23, 36] This is in concordance with the literature and highlights the comparability of this Dutch arthroplasty cohort to other studied cohorts.[23, 36, 37]

In order to establish the current practice for antibiotic prophylaxis regimes, we conducted a comprehensive national survey to determine current practice. The outcome of interest is a binary endpoint, whilst this may mean that not all cases of PJI are captured, as many may be treated without complete revision surgery, it does make the end point easily defined.[38] In the absence of randomized controlled trials on the type and duration of antibiotic prophylaxis, this natural experiment in a large and generalizable national registry represents the best data currently available to determine if there is a difference in the risk of complete revision for infection according to the antibiotic prophylaxis regimen.

The study does have limitations. The LROI database was established as an arthroplasty register, whilst one of the outcomes of interest is complete revision for infection, the register was not designed to capture all infection outcomes and thus there is likely to be underreporting of infection as may also be the case in other national arthroplasty registries.[37, 39] The most notable effect of this is the lack of capture of further procedures performed after the primary surgery to manage infection, such as DAIR procedures. The Dutch survey showed only 64% of hospitals registered DAIR procedures in the LROI, thus we did not include these in our analysis. As about 50% of PJI may be only treated with DAIR and arthroplasty registries are known to provide an underestimation of the rate of prosthetic revisions due to PJI of 20%, we may be missing as much as 70% of all treated infections.[39, 40] Although prospectively collected, our data are observational and we can only draw conclusions on the nature and magnitude of the associations but cannot establish causative relation due to the possibility of residual confounding and estimation uncertainty. Whilst we conducted a comprehensive survey to establish the current practice in terms of antibiotic prophylaxis regimes, it is likely that for various reasons, including allergy, intolerance, and surgeons' preference, not all patients received the antibiotics as per hospital protocol. However, a recent large retrospective study in the USA showed that 95% of patients received standard antibiotic prophylaxis.[41] The three types of antibiotics all are cephalosporins with the same allergy profile, therefore the percentage of patients with allergies should be comparable in all groups. Changes to the local antibiotic protocols during the study period have not been captured by the survey. The Dutch guideline for antibiotic prophylaxis around primary

hip and knee arthroplasty did not change during the time period. However, changes to the antibiotic protocols can have occurred between the groups in all directions. Due to the quasi-randomized allocation of our patients, this should not introduce systematic bias.

Thus, this study resembles a natural experiment. Rather than controlling for observed confounders and expecting no unobserved confounders to be present (as in multiple regression, matching, and reweighting), natural experiments identify variation in the exposure, known to be independent of other confounders.[42] In our study quasi-random variation in the exposure (antibiotic prophylaxis regimen after total hip or knee arthroplasty) arises from naturally occurring random variation due to allocation of patients to the regional hospital near their residence. Natural experiments minimize the risk of confounding due to selective exposure to the intervention or residual confounding, have internal validity and transparency of assumptions.[42] To establish true causality, a superiority or non-inferiority randomized controlled trial is still needed. However, as PJI is rare, the numbers needed for such a trial would be very large. Nonetheless, as the impact of PJI is so devastating,[6] we recommend that such a trial is undertaken and suggest that embedding such a trial in a national arthroplasty registry may reduce costs and improve feasibility. Until such time, the data represented here is the best available evidence and it does question whether there is any advantage to the use of prolonged antibiotic prophylaxis beyond a single dose.

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AUTHOR CONTRIBUTIONS

ESV, EL, DJM and RWP designed the study. The data were extracted from the LROI database by Liza van Steenbergen of the LROI. ESV performed the literature search. EL performed the data analysis. All authors interpreted data, drafted, and reviewed the final manuscript. All authors approved the submitted manuscript and take responsibility for the integrity of the work.

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APPENDIX TABLES

Appendix table 1: Model fit
The models that minimised the AIC and BIC criteria were selected to identify the number of optimal knots for the spline function (number of degrees of freedom-1). The log of follow-up time was modelled to obtain better fitting models.

	d.f. [1]	AIC[2]	BIC[3]
Hip model			
	2	2570	2586
	3	***2429***	***2447***
	4	2431	2452
	5	2432	2456
Knee model			
	2	2218	2234
	3	2133	2151
	4	***2111***	***2132***
	5	2114	2139

1. Degrees of freedom
2.Akaike information criterion
3.Bayesian information criterion

Appendix Table 2: Description of hip procedures by antibiotics regimen. * Revision rate for infection per 10,000 person-years

		Cefazolin multi dose					Cefazolin single dose					Cefuroxime multi dose				
		Revision	n	Person-years	Rate*	95%CI	Revision	n	Person-years	Rate*	95%CI	Revision	n	Person-years	Rate*	95%CI
Overall		350	113285	111562	31.4	[28.2, 34.8]	26	11455	11314	23	[15, 33.7]	23	5972	5830	39.4	[25, 59.2]
Year of surgery	2011	22	20238	19986	11	[6.9, 16.7]	1	2225	2201	4.5	[0.1, 25.3]	4	1101	1075	37.2	[10.1, 95.2]
	2012	40	21580	21256	18.8	[13.4, 25.6]	3	2270	2241	13.4	[2.8, 39.1]	5	1132	1109	45.1	[14.6, 105.2]
	2013	53	22418	22080	24	[18, 31.4]	2	2225	2203	9.1	[1.1, 32.8]	4	1140	1117	35.8	[9.8, 91.7]
	2014	94	24232	23861	39.4	[31.8, 48.2]	10	2353	2324	43	[20.6, 79.1]	4	1262	1231	32.5	[8.9, 83.2]
	2015	141	24817	24379	57.8	[48.7, 68.2]	10	2382	2344	42.7	[20.5, 78.4]	6	1337	1299	46.2	[17, 100.5]
Sex	Male	173	37855	37115	46.6	[39.9, 54.1]	17	3920	3856	44.1	[25.7, 70.6]	12	2065	2003	59.9	[31, 104.7]
	Female	175	75122	74144	23.6	[20.2, 27.4]	9	7526	7448	12.1	[5.5, 22.9]	11	3898	3819	28.8	[14.4, 51.5]
	Missing	2	308	304	65.9	[8, 238]	0	9	9	0	[0, 4086.5]	0	9	9	0	[0, 4086.5]
Age	Missing	0	178	176	0	[0, 209.1]	0	4	4	0	[0, 9194.6]	0	8	7	0	[0, 5047.4]
	<60	68	19092	18859	36.1	[28, 45.7]	8	2172	2156	37.1	[16, 73.1]	5	1127	1110	45	[14.6, 105.1]
	60-65	58	19156	18936	30.6	[23.3, 39.6]	4	1889	1871	21.4	[5.8, 54.7]	8	986	968	82.7	[35.7, 162.9]
	66-70	79	21791	21536	36.7	[29, 45.7]	7	2105	2084	33.6	[13.5, 69.2]	3	1137	1114	26.9	[5.6, 78.7]
	71-75	55	21076	20809	26.4	[19.9, 34.4]	2	2143	2122	9.4	[1.1, 34.1]	3	1120	1094	27.4	[5.7, 80.1]
	76-80	56	18104	17790	31.5	[23.8, 40.9]	2	1788	1763	11.3	[1.4, 41]	3	881	848	35.4	[7.3, 103.4]
	>80	34	13888	13457	25.3	[17.5, 35.3]	3	1354	1313	22.8	[4.7, 66.8]	1	713	689	14.5	[0.4, 80.9]
BMI	Missing	91	57099	56295	16.2	[13, 19.8]	6	6344	6268	9.6	[3.5, 20.8]	10	2981	2922	34.2	[16.4, 62.9]
	<18.5	3	477	460	65.2	[13.4, 190.4]	0	40	36	0	[0, 1011.1]	0	41	37	0	[0, 991.9]
	18.5-24.9	36	17623	17346	20.8	[14.5, 28.7]	5	1639	1618	30.9	[10, 72.1]	3	1013	990	30.3	[6.3, 88.6]
	25-29.9	106	24280	23916	44.3	[36.3, 53.6]	9	2201	2175	41.4	[18.9, 78.6]	4	1208	1172	34.1	[9.3, 87.4]
	30-39.9	100	13109	12872	77.7	[63.2, 94.5]	5	1153	1140	43.9	[14.2, 102.3]	6	694	675	88.8	[32.6, 193.3]
	40+	14	697	673	208	[113.7, 349]	1	78	76	131.6	[3.3, 733.1]	0	35	34	0	[0, 1081.5]

Appendix Table 2: Description of hip procedures by antibiotics regimen. * Revision rate for infection per 10,000 person-years (continued)

		Cefazolin multi dose					Cefazolin single dose					Cefuroxime multi dose				
		Revision	n	Person-years	Rate*	95%CI	Revision	n	Person-years	Rate*	95%CI	Revision	n	Person-years	Rate*	95%CI
ASA	Missing	5	1138	1118	44.7	[14.5, 104.3]	0	333	332	0	[0, 111.1]	1	88	83	120.6	[3.1, 671.7]
	ASA I	49	23602	23411	20.9	[15.5, 27.7]	4	2428	2411	16.6	[4.5, 42.5]	3	1177	1170	25.6	[5.3, 75]
	ASA II	217	73177	72235	30	[26.2, 34.3]	16	7269	7198	22.2	[12.7, 36.1]	13	3743	3669	35.4	[18.9, 60.6]
	ASA III-IV	79	15368	14797	53.4	[42.3, 66.5]	6	1425	1372	43.7	[16, 95.2]	6	964	909	66	[24.2, 143.7]
Surgical indication	Missing	5	978	952	52.5	[17, 122.5]	0	156	153	0	[0, 241.3]	0	55	49	0	[0, 754.4]
	Osteoarthritis	297	98160	96929	30.6	[27.3, 34.3]	18	9761	9666	18.6	[11, 29.4]	19	5001	4910	38.7	[23.3, 60.4]
	Trauma	22	6718	6424	34.2	[21.5, 51.9]	5	689	662	75.6	[24.5, 176.3]	2	415	384	52.1	[6.3, 188.3]
	Other indication	26	7429	7257	35.8	[23.4, 52.5]	3	849	833	36	[7.4, 105.3]	2	501	488	41	[5, 148.1]
Surgical approach	Missing	3	667	656	45.8	[9.4, 133.7]	0	109	107	0	[0, 345.3]	0	22	22	0	[0, 1681.8]
	Posterolateral	250	69871	68737	36.4	[32, 41.2]	18	7675	7580	23.7	[14.1, 37.5]	16	3311	3234	49.5	[28.3, 80.3]
	Anterior	23	12948	12822	17.9	[11.4, 26.9]	2	288	287	69.7	[8.4, 251.8]	0	612	598	0	[0, 61.7]
	Anterolateral	74	29799	29348	25.2	[19.8, 31.7]	6	3383	3340	18	[6.6, 39.1]	7	2027	1977	35.4	[14.2, 73]
Fixation	Missing	1	469	460	21.7	[0.6, 121.1]	0	34	34	0	[0, 1099.9]	0	10	8	0	[0, 4543.1]
	Cemented	101	29191	28638	35.3	[28.7, 42.9]	18	5685	5606	32.1	[19, 50.7]	7	1293	1254	55.8	[22.5, 115.1]
	Hybrid	43	9829	9654	44.5	[32.2, 60]	1	1685	1665	6	[0.2, 33.5]	4	921	903	44.3	[12.1, 113.4]
	Uncemented	205	73796	72811	28.2	[24.4, 32.3]	7	4051	4008	17.5	[7, 36]	12	3748	3665	32.7	[16.9, 57.2]
Bearings surface	Missing	34	10459	10227	33.2	[23, 46.5]	0	603	590	0	[0, 62.6]	0	129	125	0	[0, 296.1]
	Ceramic on PE	181	56009	55231	32.8	[28.2, 37.9]	11	5943	5876	18.7	[9.3, 33.5]	11	1587	1557	70.6	[35.3, 126.4]
	Metal on PE	110	31121	30585	36	[29.6, 43.3]	14	2721	2683	52.2	[28.5, 87.5]	7	2809	2729	25.6	[10.3, 52.8]
	Ceramic on Ceramic	10	8231	8159	12.3	[5.9, 22.5]	1	2069	2046	4.9	[0.1, 27.2]	2	818	797	25.1	[3, 90.7]
	Zirconium on PE	14	6486	6395	21.9	[12, 36.7]					[,]	0	507	503	0	[0, 73.3]
	Metal on metal	1	979	966	10.4	[0.3, 57.7]	0	119	118	0	[0, 311.7]	3	122	119	251.6	[51.9, 735.3]

Appendix Table 3: Description of knee procedures by antibiotics regimen. * Revision rate for infection per 10,000 person-years

		Cefazolin multiple dose					Cefazolin single dose					Cefuroxime multiple dose				
		Revision	n	Person-years	Rate	95%CI	Revision	n	Person-years	Rate	95%CI	Revision	n	Person-years	Rate	95%CI
Overall		260	96791	96237	27	[23.8, 30.5]	24	9880	9826	24.4	[15.6, 36.3]	19	4796	4767	39.9	[24, 62.2]
Year of surgery	2011	19	16735	16652	11.4	[6.9, 17.8]	2	1785	1775	11.3	[1.4, 40.7]	2	927	924	21.7	[2.6, 78.2]
	2012	48	18740	18643	25.7	[19, 34.1]	1	1925	1915	5.2	[0.1, 29.1]	2	948	945	21.2	[2.6, 76.5]
	2013	55	19288	19162	28.7	[21.6, 37.4]	3	1911	1909	15.7	[3.2, 45.9]	1	977	970	10.3	[0.3, 57.4]
	2014	53	20920	20814	25.5	[19.1, 33.3]	6	2170	2154	27.9	[10.2, 60.6]	6	1018	1008	59.5	[21.8, 129.5]
	2015	85	21108	20966	40.5	[32.4, 50.1]	12	2089	2073	57.9	[29.9, 101.1]	8	926	920	87	[37.5, 171.3]
Sex	Male	143	33501	33244	43	[36.3, 50.7]	16	3317	3293	48.6	[27.8, 78.9]	7	1539	1532	45.7	[18.4, 94.1]
	Female	115	62932	62638	18.4	[15.2, 22]	8	6558	6528	12.3	[5.3, 24.1]	12	3250	3228	37.2	[19.2, 64.9]
	Missing	2	358	355	56.3	[6.8, 203.2]	0	5	5	0	[0, 7355.7]	0	7	7	0	[0, 5254.1]
Age	Missing	1	152	150	66.8	[1.7, 372]	0	4	4	0	[0, 9194.6]	0	7	7	0	[0, 5254.1]
	<60	47	17104	17038	27.6	[20.3, 36.7]	5	1726	1721	29.1	[9.4, 67.8]	6	769	761	78.8	[28.9, 171.6]
	60-65	55	19282	19216	28.6	[21.6, 37.3]	3	1951	1949	15.4	[3.2, 45]	6	948	942	63.7	[23.4, 138.7]
	66-70	53	19483	19414	27.3	[20.4, 35.7]	7	1905	1899	36.9	[14.8, 76]	2	983	980	20.4	[2.5, 73.7]
	71-75	43	17982	17892	24	[17.4, 32.4]	3	1893	1885	15.9	[3.3, 46.5]	2	938	938	21.3	[2.6, 77]
	76-80	37	13566	13455	27.5	[19.4, 37.9]	4	1367	1351	29.6	[8.1, 75.8]	1	664	661	15.1	[0.4, 84.3]
	>80	24	9222	9072	26.5	[17, 39.4]	2	1034	1017	19.7	[2.4, 71]	2	487	479	41.8	[5.1, 150.9]
BMI	Missing	97	48461	48194	20.1	[16.3, 24.6]	6	5458	5435	11	[4.1, 24]	4	2518	2508	16	[4.3, 40.8]
	<18.5	0	96	95	0	[0, 386.8]	1	15	15	673.8	[17.1, 3754.3]	0	2	2	0	[0, 18389.2]
	18.5-24.9	20	7664	7601	26.3	[16.1, 40.6]	1	727	720	13.9	[0.4, 77.4]	2	370	369	54.3	[6.6, 196]
	25-29.9	74	19919	19791	37.4	[29.4, 46.9]	8	1815	1801	44.4	[19.2, 87.5]	6	890	882	68	[25, 148.1]
	30-39.9	60	18701	18620	32.2	[24.6, 41.5]	7	1687	1679	41.7	[16.8, 85.9]	7	931	925	75.7	[30.4, 156]
	40+	9	1950	1935	46.5	[21.3, 88.3]	1	178	177	56.6	[1.4, 315.4]	0	85	83	0	[0, 446.4]

Appendix Table 3: Description of knee procedures by antibiotics regimen. * Revision rate for infection per 10,000 person-years (continued)

		Cefazolin multiple dose					Cefazolin single dose					Cefuroxime multiple dose				
		Revision	n	Person-years	Rate	95%CI	Revision	n	Person-years	Rate	95%CI	Revision	n	Person-years	Rate	95%CI
ASA	Missing	3	1350	1340	22.4	[4.6, 65.4]	0	314	314	0	[0, 117.6]	0	78	78	0	[0, 471.5]
	ASA I	41	16189	16138	25.4	[18.2, 34.5]	5	1509	1503	33.3	[10.8, 77.6]	4	636	633	63.2	[17.2, 161.9]
	ASA II	167	65977	65649	25.4	[21.7, 29.6]	13	6749	6722	19.3	[10.3, 33.1]	12	3276	3259	36.8	[19, 64.3]
	ASA III-IV	49	13275	13109	37.4	[27.7, 49.4]	6	1308	1288	46.6	[17.1, 101.4]	3	806	798	37.6	[7.8, 109.9]
Surgical indication	Osteoarthritis	234	92427	91909	25.5	[22.3, 28.9]	19	9232	9183	20.7	[12.5, 32.3]	19	4548	4521	42	[25.3, 65.6]
	Trauma	11	1495	1480	74.3	[37.1, 133]	0	135	135	0	[0, 273.2]	0	105	104	0	[0, 354.8]
	Rheumatic	7	1380	1369	51.1	[20.6, 105.3]	1	186	185	54	[1.4, 301]	0	65	65	0	[0, 566.5]
	Other indication	8	1489	1479	54.1	[23.4, 106.6]	4	327	323	123.8	[33.7, 317]	0	78	78	0	[0, 475.7]
Surgical approach	Missing	3	1241	1237	24.3	[5, 70.9]	0	89	89	0	[0, 413.3]	0	19	19	0	[0, 1935.7]
	Medial parapatellar	243	90617	90100	27	[23.7, 30.6]	21	9628	9578	21.9	[13.6, 33.5]	17	4169	4144	41	[23.9, 65.7]
	Mid/sub vastus	9	3715	3698	24.3	[11.1, 46.2]	1	90	89	112.4	[2.8, 626.2]	1	592	589	17	[0.4, 94.7]
	Other approach	5	1218	1203	41.6	[13.5, 97]	2	73	70	285.2	[34.5, 1030.2]	1	16	16	624.3	[15.8, 3478.6]
Fixation	Missing	1	882	880	11.4	[0.3, 63.3]	0	42	42	0	[0, 875.7]	0	20	20	0	[0, 1838.9]
	Cemented	247	86406	85905	28.8	[25.3, 32.6]	21	9202	9154	22.9	[14.2, 35.1]	19	4763	4735	40.1	[24.2, 62.7]
	Hybrid	3	5145	5113	5.9	[1.2, 17.1]	0	16	16	0	[0, 2351.3]	0	1	0	0	[0, 13000000]
	Uncemented	9	4358	4338	20.7	[9.5, 39.4]	3	620	615	48.8	[10.1, 142.6]	0	12	12	0	[0, 3064.9]