Short Against Long Antibiotic Therapy for Infected Orthopaedic Sites - 2nd Interim Analysis of the SALATIO Trials

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Article

Short Against Long Antibiotic Therapy for Infected Orthopaedic Sites - 2nd Interim Analysis of the SALATIO Trials

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Abstract

Background/Objectives: The optimal duration of postoperative antibiotic therapy for bone and orthopaedic implant infections remains undefined. The SALATIO Trials are prospective randomised trials investigating whether shorter antibiotic courses are non-inferior to standard durations across different infection strata. This report presents the second interim analysis. **Methods:** Two unblinded non-inferiority RCTs were conducted (intention-to-treat population). Primary outcomes were remission, clinical failure, and microbiologically identical recurrence. In SALATIO 1 (material arm), participants with infected implants, retained or replaced during initial surgery, were randomised to short-course (six weeks) or long-course (twelve weeks) targeted systemic antibiotic therapy following debridement. In SALATIO 2 (non-material arm), participants undergoing implant removal or two-stage exchange were randomised to either a short-course (three weeks) or a long-course (six weeks) of antibiotic therapy. **Results**: We analysed 175 infections with a minimum follow-up period of one-year from October 2022 until July 2025: 69 (39%) in the material arm (38 short-course [55%], 31 long-course [45%]) and 106 (61%) in the non-material arm (44 short-course [42%], 62 long-course [58%]). No significant differences in clinical failure (19% overall) or microbiological recurrence (7%) were observed between treatment arms in either stratum. Multivariate analysis identified diabetes mellitus and number of debridements—but not antibiotic duration—as independent risk factors for clinical failure. Patients receiving short-course therapy experienced significantly fewer adverse events (median 0 versus 1; p=0.01). Formal non-inferiority has not yet been achieved due to limited statistical power. **Conclusion:** This interim analysis suggests no disadvantage of shorter antibiotic regimens in surgically treated orthopaedic infections, whilst reducing adverse events. Patient comorbidities and surgical factors appear to be more relevant to treatment outcomes than antibiotic duration. The SALATIO Trials are ongoing and may support improved antibiotic stewardship without compromising outcomes. **Trials Registration:** NCT05499481.

Keywords: orthopaedic infections; short-course antibiotic therapy; antibiotic stewardship; infection recurrence; randomised clinical trial

1. Introduction

The optimal duration of postoperative systemic antibiotic therapy for bone and orthopaedic implant infections remains undefined [1]. Current guidelines recommend twelve weeks of treatment when an infected implant is retained or replaced, and six weeks following implant removal [1–5]. However, the rationale for precisely doubling the antibiotic duration for retained implants—

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regardless of debridement technique or implant characteristics—lacks scientific justification. These recommendations are largely derived from historical osteomyelitis practices and expert consensus from the previous century, established in the absence of randomised data [4]. Furthermore, the management of osteoarticular infections is inherently challenging, frequently complicated by recurrences, new infections, mechanical failures, implant loosening, gait disturbances, treatment-related adverse events, diminished quality of life, and substantial costs.

To date, these expert-driven recommendations for bone and implant infections have not undergone the same rigorous scrutiny applied to treatment protocols for other infectious diseases. Given the demonstrated success of antibiotic stewardship programmes in reducing adverse events and antimicrobial resistance across various clinical fields, there is compelling reason to pursue similar initiatives in orthopaedics, where supportive evidence remains limited [6–8]. Retrospective studies suggest that six weeks of treatment is as effective as prolonged courses [9–13], even with implant retention [9,11,13]. Additionally, these evaluations consistently fail to identify a minimum antibiotic duration threshold - irrespective of oral or parenteral antibiotic administration - below which the risk of infection recurrence rises. Concurrently, the prevalence of resistant pathogens in bone and implant infections appears to be rising worldwide [14,15]. Hence antibiotic stewardship has been designated a priority by government agencies, regulatory bodies, professional societies, and healthcare systems alike [16]. Such stewardship is equally imperative in orthopaedic surgery, especially given that orthopaedic patients are frequently hospitalised in other departments due to advanced age, frailty, and multiple comorbidities.

At our university orthopaedic centre, we are conducting several prospective randomised trials to reduce excessive antibiotic use and improve antibiotic stewardship within the field of orthopaedic surgery [8,16,17]. The SALATIO Trials [1] extend these efforts to all bone-related infections, excluding spinal and diabetic foot infections, which are being addressed in two separate ongoing trials. For a trial of this scale and duration, interim analyses are mandatory, especially considering the theoretical risk of increased recurrence rates associated with shortened antibiotic regimens. The first interim analysis was presented at the Swiss National Congress for Orthopaedic Surgery in Lausanne (26 June 2024) [18]. The conclusion was that shorter antibiotic therapy is non-inferior compared to standard treatment regimens. This report presents the second interim analysis, performed two years after trial commencement.

1.1. Main Hypothesis

Based on our experience and retrospective data, we hypothesised that the duration of postsurgical antibiotic therapy does not independently influence treatment outcomes in bone and implant infections. Rather, adequate surgical management is the more critical determinant. Furthermore, we posit that current standard durations are excessive for most routine cases, and that halving these durations would remain non-inferior to conventional prolonged courses in terms of clinical failure and microbiological recurrence rates. While this second interim analysis is not expected to achieve formal statistical non-inferiority within the predefined 10% margin, we anticipate no significant imbalance favouring either the short or long treatment arm. Additionally, we hypothesised that shorter antibiotic regimens will be associated with fewer antibiotic-related adverse events.

2. Materials and Methods

The methods employed in this interim analysis are identical to those described in our published SALATIO study protocol [1]. This section provides a condensed summary with modifications for clarity.

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2.1. Study Setting and Objectives

We aimed to optimise postoperative antibiotic use in adult patients with orthopaedic infections. Two non-inferiority RCTs were conducted to evaluate whether shorter systemic antibiotic courses are non-inferior to conventional regimens. The primary outcomes were remission rate ("remission") and recurrent infections with the same pathogen(s) as the index episode ("microbiological recurrences"). The secondary outcomes were antibiotic-related adverse events.

2.2. Definitions and Eligibility Criteria for Participants

An "orthopaedic infection" was defined as the concordant microbiological evidence of bacteria in at least two deep intraoperative tissue samples together with radiological (osteomyelitis, collections, inflammation) and/or clinical evidence of infection (pus, discharge, sinus tracts, rubor, color, pain). Histological proof was facultative for this study. Implants were defined as any foreign material, except for allografts, transient wires, or fixator pins outside of the infected bone. Remission of infection was defined as the absence of clinical, and/or radiological, and/or laboratory signs of the (former) infection after the minimal follow-up time of 12 months. Inversely, a clinical failure was any problem leading to unplanned revision surgeries, including surgeries for persistent infection during antibiotic therapy, non-infectious reasons (i.e., seroma, haematoma, implant failure, wound dehiscence, fractures), or a new infection at the same site. A microbiological recurrence was a recurrence with the same pathogen(s) after completion of antibiotic therapy.

An adverse event (AE) was defined as any unexpected medical occurrence, with emphasis on antibiotic-related events. A serious adverse event (SAE) was defined as any life-threatening occurrence or one requiring rehospitalisation or significant prolongation of hospitalisation.

2.3. Study Conduct

Eligible patients were screened according to predefined inclusion and exclusion criteria [1], and randomisation was performed at a 1:1 ratio using sealed envelopes.

- SALATIO 1, material arm: Participants with infected implants retained or replaced during initial surgery were randomised to a short-course (six weeks) or a long-course (twelve weeks) of targeted systemic antibiotic therapy (±5 days) following first debridement.
- SALATIO 2, non-material arm: Participants undergoing implant removal or two-stage exchange were randomised to a short-course (three weeks) or a long-course (six weeks) of antibiotic therapy (±5 days).

All cases required curative surgical intent from the start; patients undergoing inadequate debridement were excluded. The choice of antibiotic agent, dosage, and route of administration (oral or parenteral) was at the discretion of treating clinicians, selected from a predefined list of approved antibiotics [1,19–21].

2.4. Statistical Analyses and Sample Size

Both RCTs (material arm (SALATIO 1) and non-material arm (SALATIO 2)) are independent non-inferiority trials with a 10% margin for remission, 80% power, and two-sided α=0.05 [1]. Group comparisons were performed using the Pearson χ^2 test, Fisher's exact test, or Wilcoxon rank-sum test, as appropriate. Futility was assessed according to established methods [22]. Multivariate logistic regression was employed to adjust for case-mix heterogeneity [23]. Formal non-inferiority was evaluated using a one-sided p-value threshold of <0.025 for "remission" only, as "microbiological recurrences" were too infrequent for meaningful analysis. Data were exported from REDCap® to EXCEL™ and analysed using STATA™ (Version 18; StataCorp, College Station, TX, USA).

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3. Results

3.1. Study Population

This second interim analysis included 175 independent infection episodes documented from October 2022 until July of 2025 with a minimum follow-up of one year (intention-to-treat population (ITT)). Of the 175 infections, 69 (39.4%) were in the material arm and 106 (60.6%) were in the non-material arm. The cohort included 64 women (37%) with a median age of 66 years and median body mass index of 25.8 kg/m². Immunocompromised status was present in 38 patients (21.7%), including diabetes mellitus (n=20; 11.4%), active malignancy (n=5; 2.9%), and immunosuppressive medication (n=13; 7.4%). Approximately half of the patients (n=89; 51%) had an American Society of Anesthesiologists (ASA) score of more than 2 points. The median C-reactive protein at admission was 91 mg/L (interquartile range [IQR], 51–161 mg/L).

The most common infection sites were the foot in the non-material arm and the hip and knee in the material arm. The predominant pathogens were methicillin-sensitive *Staphylococcus aureus* (MSSA), *Cutibacterium acnes*, and methicillin-resistant *Staphylococcus epidermidis* (MRSE), isolated from a median of three intraoperative samples. Bacteraemia was present in only five cases (2.9%). Most patients (n=156; 89.1%) presented with a first infection episode, whilst 19 (10.9%) had experienced one previous infection at the same site. The median length of hospital stay was 8 days (IQR, 4–21). Median sick leave duration following discharge was 54 days (IQR,0–56).

3.2. Treatment

Randomisation achieved adequate balance, with 82 infections (47%) allocated to short-course and 93 (53%) to long-course antibiotic therapy (p=0.08) (Table 1). Baseline characteristics did not differ significantly between treatment arms, including sex, age, body mass index, ASA score, diabetes mellitus, active malignancy, C-reactive protein level, bacteraemia, and length of hospitalisation (all p>0.05) (Table 1). The median number of surgical debridements was 1 (IQR, 1–1), there was no statistical difference between the long- and short course (p=0.72). A total of 23 different intravenous regimens were administered for a median duration of 6 days (IQR, 2 - 8) followed by 36 different oral regimens for a median of 41 days. Rifampicin was added in ten cases. The most frequently prescribed agents were amoxicillin-clavulanate, levofloxacin, and clindamycin.

Table 1. Baseline characteristics of participants by treatment arm.

	Category	n (%)	Short Treatment Arm	Long Treatment Arm	p value *
Total patients		175 (100%)	82 (47%)	93 (53%)	
	Sex, female[b]	64 (37%)	34 (53%)	30 (47%)	0.21
	Age[a]		63 years	67 years	0.08
	Body Mass Index[a]		25.3 kg/m²	26.7 kg/m²	0.27
	ASA-Score ≥ 3 points[b]	74 (42%)	33 (45%)	41 (55%)	0.1
	Diabetes mellitus [b]	20 (100%)	6 (30%)	14 (70%)	0.11
	Active malignancy[b]	5 (100%)	3 (60%)	2 (40%)	0.55
	C-reactive protein level[a]		62.2 mg/l	108.7 mg/l	0.51
	Bacteraemia[b]	5 (100%)	1	4	0.22

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	Length of hospitalisation[a]		7 days	9.5 days	0.09
Infection type	Material arm[b]	69 (39%)	38 (55%)	31 (45%)	0.08
	Non-Material arm[b]	106 (61%)	44 (42%)	62 (58%)	

[a] Values are expressed as the median. The Mann-Whitney U test was used to analyse the differences between the short treatment arm and the long treatment arm. [b] Values are expressed as absolute numbers with percentages in parentheses. The Fisher-exact or Chi-square-test was used to analyse the difference between the short treatment arm and the long treatment arm. *A p value <.05 was considered significant.

3.3. Outcomes

At one year, 142 of 175 episodes (81.1%) achieved "remission", while 33 (18.9%) experienced "clinical failure" and 13 (7.4%) had a "microbiological recurrence". Amongst the 69 material arm infections, clinical failure occurred in 9 of 38 patients (24%) in the short-course arm (six weeks) versus 7 of 31 (23%) in the long-course arm (twelve weeks), with no significant difference between groups (p=0.91). Similarly, within the 106 non-material arm infections, clinical failure rates did not differ significantly between treatment arms: 4 of 44 (9%) in the short-course arm (three weeks) versus 13 of 62 (21%) in the long-course arm (six weeks) (p=0.10) (Table 2). In the material arm group, no significant differences were observed between patients who achieved remission and those experiencing clinical failure with respect to sex, diabetes mellitus, or number of debridements. However, patients with clinical failure were significantly older (median 78 vs. 63 years; p=0.001). In the non-material arm group, the rate of diabetes mellitus was higher amongst patients with clinical failure than amongst those who had achieved remission (29% versus 6%; p=0.01). Furthermore, the number of debridements was significantly higher in the clinical failure group (p=0.01).

Table 2. Baseline demographic and clinical characteristics by treatment allocation.

Material Arm (SALATIO 1)	**Remission**	**Clinical failure+**	**p-value ***	**Non-material Arm (SALATIO 2)**	**Remission**	**Clinical failure+**	**p-value***
n = 69 (100%)	n = 53 (77%)	n = 16 (23%)		n = 106 (100%)	n = 89 (84%)	n = 17 (16%)	
Female sex[b]	18 (34%)	7 (44%)	0.48	Female sex[b]	33 (37%)	6 (35%)	0.89
Age[a]	63 years	78 years	***0.001***	Age[a]	64 years	63 years	0.24
Diabetes mellitus[b]	8 (15%)	2 (13%)	0.80	Diabetes mellitus[b]	5 (6%)	5 (29%)	***0.01***
ASA score[a]	3	3	0.33	ASA score[a]	3	3	*0.98*
Number of debridement[a]	1 intervention	1 intervention	0.08	Number of debridement[a]	1 intervention	1 intervention	***0.0004***
Six weeks of antibiotic therapy[b] (n=38) (100%)	29 (76%)	9 (24%)	0.91	Three weeks of antibiotic therapy[b] (n=44) (100%)	40 (91%)	4 (9%)	0.10
Twelve weeks of antibiotic therapy[b] (n=31) (100%)	24 (77%)	7 (23%)		Six weeks of antibiotic therapy[b] (n=62) (100%)	49 (79%)	13 (21%)	

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[a]Values are expressed as the median. The Mann-Whitney U test was used to analyse the differences between the groups. [b] Values are expressed as absolute numbers with percentages in parentheses. The Fisher exact or Chi-square-test was used to analyse the difference between the groups. * A p value <0.05 was considered significant. Significant results are indicated ***in bold and italic*** + Clinical failure = any unplanned clinical condition requiring re-hospitalisation (including revision) such as new infection, hematoma, wound dehiscence, seroma, implant-loosening, fracture, segment degeneration.

3.4. Multivariate Adjustment

To adjust for case-mix heterogeneity and contextualise antibiotic duration within the broader clinical setting, we performed unconditional logistic regression with clinical failure as the dependent variable (Table 3). The final model included randomisation arm (antibiotic duration), age, ASA score, number of debridements, and diabetes mellitus; no significant interactions were observed amongst these covariates. For material arm infections, shorter antibiotic treatment did not increase the risk of clinical failure in either univariate or multivariate analysis (Table 3). Likewise, in the non-material arm group, antibiotic duration was not a significant predictor of outcome. However, diabetes mellitus (OR 7.6; p=0.04) and number of debridements (OR 13.6; p=0.002) were identified as independent risk factors for clinical failure in this group. However, the wide confidence intervals reflect limited statistical power inherent to interim analyses. Goodness-of-fit tests were non-significant for both models, indicating adequate fit.

Table 3. Univariate and multivariate predictors of clinical failure.

Material arm infections	**Univariate**			**Multivariate**		
n = 69	Odds Ratio	95%CI	p-Value*	Odds Ratio	95%CI	p-Value*
Age	1.1	1.0-1.2	0.01	-		
Diabetes mellitus	0.8	0.2-4.2	0.8	0.6	0.1-3.6	0.58
° ASA-Score	1.5	0.7-3.3	0.36	-		
Short (6-week) antibiotic therapy	1.1	0.3-3.3	0.91	1.2	0.3-4.4	0.8
Number of debridement	2.9	0.9-9.3	0.07	3.2	0.9-11.3	0.08
Non-material arm infections	**Univariate**			**Multivariate**		
n = 106	Odds Ratio	95%CI	p-Value*	Odds Ratio	95%CI	p-Value*
Age	1.0	0.9-1.0	0.25	-		
Diabetes mellitus	***7.0***	***1.8-27.8***	***0.01***	***7.6***	***1.0-55.0***	***0.04***
° ASA-Score	1.2	0.3-10.2	0.67	-		
Short (6-week) antibiotic therapy	0.4	0.1-1.2	0.11	0.1	0.1-1.6	0.11
Number of debridement	***3.9***	***1.6-9.7***	***0.003***	***13.6***	***2.6-71.0***	***0.002***

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* A p-value < 0.05 was considered significant. Statistically significant results are displayed ***in bold and italic***. " - " = not included in the multivariate model due to interaction or few cases ° ASA = American Society of Anaesthesiologists.

3.5. Formal Non-Inferiority Assessment

Consistent with the wide confidence intervals, formal non-inferiority within the predefined 10% margin was not yet achieved in the ITT population (unidirectional t-test mean 0.01, 90%CI ranging from -0.18 to +0.16 for "material arm" and 0.11, 90%CI -0.01 to +0.23 for "no material arm", respectively). A formal futility analysis was not required [22]. The independent "Data Reviewer" recommended continuation of the SALATIO Trials.

3.6. Adverse Events

Adverse events (AEs) occurred in 92 of 175 patients (52.6%), with a median onset of 22 days following debridement. Of these, 41 (49.4%) were classified as serious adverse events (SAEs). Half of all AEs were unrelated to antibiotic therapy. The median AE duration was 23 days (IQR, 9–53). Patients in the long-course treatment arm experienced significantly more AEs than those receiving short-course therapy (median 1 versus 0 AEs, p=0.01).

4. Discussion

This second interim analysis of the SALATIO Trials [1] yielded no unexpected findings. Consistent with the first interim analysis [18], no significant differences in remission or clinical failure were observed between short- and long-course antibiotic regimens. These findings were consistent across both strata; material arm (SALATIO 1) and non-material arm (SALATIO 2) infections. The overall clinical failure rate was high (19%), as anticipated in this population of frail patients with orthopaedic infections. Notably, this risk was not influenced by antibiotic duration. This suggests that other clinical variables are more important determinants of treatment success than antibiotic duration alone. This observation is supported by our multivariate analysis, which identified diabetes mellitus (OR 7.6; 95% CI, 1.0–55.0; p=0.04) and number of debridements (OR 13.6; 95% CI, 2.6–71.0; p=0.002) as independent risk factors for clinical failure in the non-material arm group, whereas antibiotic duration showed no significant effect. In the material arm group, patients with clinical failure were significantly older than those achieving remission (median 78 versus 63 years; p=0.001), highlighting the role of patient-related factors over treatment duration. Adverse events occurred more frequently in long-course treatment arms (median 1 versus 0 AEs; p=0.01), although no major safety concerns emerged. As expected for an interim analysis, statistical power was limited, and formal non-inferiority was not yet demonstrated. The SALATIO Trials are ongoing.

The objective of the SALATIO Trials is to reduce standard postoperative antibiotic duration by half in surgically treated orthopaedic infections, in accordance with antibiotic stewardship principles. Prior to these trials, considerable evidence suggested that such a reduction may be feasible. Retrospective case-control studies across diverse orthopaedic infections—including sacral osteomyelitis [24], long-bone osteomyelitis [25], fracture-related infections [25–27], prosthetic joint infections [9], and diabetic foot osteomyelitis [28] —have consistently demonstrated that longer treatment durations do not correlate with improved remission rates. Studies evaluating a standardised six-week treatment duration have shown promising results, with success rates up to 91.5% [11,29]. For sacral osteomyelitis limited to cortical bone, some authors advocate courses as short as two weeks [24]. Historically, recommended durations for bone infections ranged from four to six weeks during the twentieth century [30], with numerous case reports documenting successful outcomes with even shorter courses [31]. The current six-week standard was established in the twenty-first century, based primarily on expert consensus [4,5,25].

Our interim data aligns with these findings. The overall remission rate of 81% in our cohort is comparable to published success rates of up to 91.5% [9–11,26,29,32] despite halving antibiotic

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duration in the short-course arms. Notably, in the non-material arm, the short-course group showed a numerically lower failure rate than the long-course group (9% versus 21%), although this difference did not reach statistical significance (p=0.10). This observation, while requiring confirmation in the final analysis, suggests that shorter treatment may be at least as effective as conventional durations. Preliminary RCTs have addressed similar questions in diabetic foot osteomyelitis [28] and spinal infections [33,34], with promising results supporting a reduction of antibiotic treatment duration. Studies from other institutions have reported comparable findings. Prospective randomised trials suggest that three to four weeks of systemic antibiotic therapy are sufficient following implant removal [25]. For debridement, antibiotics, and implant retention (DAIR) procedures in prosthetic joint infections, prospective data indicate that six to eight weeks of therapy may achieve outcomes equivalent to the currently recommended twelve weeks, even for virulent pathogens such as *Staphylococcus aureus* [35,36]. Only one RCT demonstrated superior outcomes with twelve-week treatment, and this benefit was limited to DAIR cases [32]. A study of fracture-related infections reported fewer adverse events with shortened antibiotic courses, without increased risk of treatment failure [37]. The SOLARIO Trial, a non-inferiority study of 500 patients with a design comparable to the SALATIO Trials, demonstrated that reducing antibiotic duration is feasible and associated with fewer AEs [38]. Further trials addressing this question have been proposed [39].

Our findings regarding adverse events further support this trend. Patients in the short-course arm experienced significantly fewer AEs (median 0 versus 1; p=0.01), consistent with the SOLARIO Trial findings [38] and underscoring an important secondary benefit of reduced antibiotic exposure. Given that 52.6% of our patients experienced at least one adverse event, and half of these were antibiotic-related, the potential to reduce treatment-associated morbidity through shortened courses is clinically meaningful. In the SALATIO Trials [1], we did not control for the duration of initial parenteral therapy. This decision was based on consistent evidence from our own studies, including trials in diabetic foot osteomyelitis [28], as well as the broader literature [19–21], demonstrating no benefit of prolonged parenteral therapy in surgically treated, haemodynamically stable orthopaedic infections. The median duration of parenteral administration in our cohort was six days, consistent with the landmark OVIVA Trial [19]. Furthermore, our multivariate analysis identified patient comorbidities (diabetes mellitus) and surgical complexity (number of debridements) as the primary determinants of treatment failure, while antibiotic duration showed no significant effect. In the material arm, advanced age was the only factor significantly associated with clinical failure. These findings reinforce the concept that adequate surgical debridement and optimisation of patient-related factors may be more critical to treatment success than prolonged antibiotic therapy.

This study has several limitations. First, as an interim analysis, statistical power was limited, precluding definitive conclusions regarding non-inferiority. The wide confidence intervals reflect this underpowering and necessitate cautious interpretation of the findings. Second, randomisation imbalance was observed, with more patients allocated to the long-course arm (53% versus 47%), which may introduce bias. Third, this is a single-centre study conducted at a tertiary referral hospital specialising in orthopaedic infections, which may limit generalisability to other settings with different patient populations, surgical expertise, or microbiological profiles. Fourth, anatomical categories are not mutually exclusive, and overlap exists. We intentionally refrained from establishing a hierarchy to include all orthopaedic infections and to avoid underpowering of the subgroup analyses. Fifth, the definition of clinical failure was broad, encompassing both infectious and non-infectious complications; this may have diluted the effect of antibiotic duration on infection-specific outcomes. Finally, long-term outcomes beyond one year were not assessed; late recurrences, particularly in implant-related infections, may occur beyond this follow-up period. However, the primary purpose of our interim analysis is to identify unanticipated safety signals or futility that would warrant early trial termination. Neither concern was identified. This second interim analysis corroborates the findings of the first. The SALATIO Trials will continue, with a third interim analysis planned for late 2025, prior to the scheduled completion of follow-up in mid-2026.

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5. Conclusions

This second interim analysis suggests no disadvantage of shorter postoperative systemic antibiotic regimens in surgically treated orthopaedic infections, while adverse events were reduced. Although formal non-inferiority within the prespecified margin cannot yet be confirmed at this stage, no safety signal indicating harm of the short-course approach was observed. The overall pattern of findings indicates that patient comorbidities and surgical factors are more relevant determinants of treatment outcome than antibiotic duration alone. These results may support improved antibiotic stewardship by reducing unnecessary antibiotic exposure without compromising clinical outcomes. The SALATIO Trials are ongoing, and final results will be reported in multiple publications, with stratified analyses of surgical and microbiological parameters presented separately.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

Author Contributions: Conceptualization, I.U.; methodology, I.U.; software, S.K. and N.K..; validation, F.Z. and I.U.; formal analysis, S.K. and I.U.; investigation, S.K., N.K., M.S., F.Z., P.R.F., and I.U; resources, S.K., I.U.; data curation, S.K., N.K., and I.U.; writing-original draft preparation, S. K., F.Z., and I.U.; writing-review and editing, I.U., M.S., and F.Z; visualization, S.K.; F.Z.; supervision, I.U.; project administration, N.K., I.U. All authors agreed to this published version.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and the guidelines of Good Clinical Practice (GCP). It is approved by the Swiss regulatory authority's requirements. The collection, disclosure and storage of data is carried out in accordance with Swiss data protection regulations and the Human Research Act.

Ethics approval and consent to participate: The study protocol is approval by the Cantonal Ethical Commission of Zurich Canton, Stampfenbachstrasse 121, 8090 Zürich (BASEC 2022-01012) on 8 July 2022 and internationally registered in ClinicalTrials.gov (Number NCT05499481).

Informed consent statement: Informed consent was obtained from all participants.

Availability of data and materials: We may provide anonymized key elements of the datasets upon reasonable scientific request.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

SALATIO	Short Against Long Antibiotic Therapy for Infected Orthopaedic Sites
RCT	Randomised Controlled Trial
AE	Adverse event
DAIR	Debridement, antibiotics, implant retention
SAE	Serious adverse event
MSSA	Methicillin-sensitive *Staphylococcus aureus*
MRSE	Methicillin-resistant *Staphylococcus epidermidis*

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