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ARTHROPLASTY

National variation in prophylactic antibiotic use for elective primary total joint replacement

AN ANALYSIS OF GUIDELINES ACROSS HOSPITALS AND TRUSTS IN THE UK

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Aims

Prophylactic antibiotic regimens for elective primary total hip and knee arthroplasty vary widely across hospitals and trusts in the UK. This study aimed to identify antibiotic prophylaxis regimens currently in use for elective primary arthroplasty across the UK, establish variations in antibiotic prophylaxis regimens and their impact on the risk of periprosthetic joint infection (PJI) in the first-year post-index procedure, and evaluate adherence to current international consensus guidance.

Methods

The guidelines for the primary and alternative recommended prophylactic antibiotic regimens in clean orthopaedic surgery (primary arthroplasty) for 109 hospitals and trusts across the UK were sought by searching each trust and hospital's website (intranet webpages), and by using the MicroGuide app. The mean cost of each antibiotic regimen was calculated using price data from the British National Formulary (BNF). Regimens were then compared to the 2018 Philadelphia Consensus Guidance, to evaluate adherence to international guidance.

Results

The primary choice and dosing of the prophylactic antimicrobial regimens varied widely. The two most used regimens were combined teicoplanin and gentamicin, and cefuroxime followed by two or three doses of cefuroxime eight-hourly, recommended by 24 centres (22.02%) each. The alternative choice and dosing of the prophylactic antimicrobial regimen also varied widely across the 83 centres with data available. Prophylaxis regimens across some centres fail to cover the likeliest causes of surgical site infection (SSI). Five centres (4.59%) recommend co-amoxiclav, which confers no *Staphylococcus* coverage, while 33 centres (30.28%) recommend cefuroxime, which confers no *Enterococcus* coverage. Limited adherence to 2018 Philadelphia Consensus Guidance was observed, with 67 centres (61.50%) not including a cephalosporin in their guidance.

Conclusion

This analysis of guidance on antimicrobial prophylaxis in primary arthroplasty across 109 hospitals and trusts in the UK has identified widespread variation in primary and alternative antimicrobial regimens currently recommended.

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Introduction

Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are the two most common elective orthopaedic procedures performed in the UK. While excellent long-term outcomes are observed in the vast

majority of patients, infections continue to present a substantial clinical challenge.[1] Surgical site infection (SSI), which often precedes periprosthetic joint infection (PJI), poses a potentially devastating complication after elective joint arthroplasty, and is associated with high morbidity, poor quality of life, and increased mortality risk.[2–7] Previous research has highlighted the prevalence of PJIs in THA to range from 0.79% to 2.18%, and in TKA from 0.51% to 2.18%, respectively,[8–12] with levels of infection on the rise internationally.[13,14]

The pathophysiology of PJI is multifactorial, with both patient and non-patient factors modulating the overall risk of this surgical complication.[15–17] Previous research has indicated that over half of PJIs are caused by *Staphylococcus* species of bacteria, principally *Staphylococcus aureus* and coagulase-negative staphylococci, with methicillin-resistant *S. aureus* (MRSA) the cause of around 8% of infections, with previous research showing that over one-third of infections are polymicrobial.[1,18–20] Infection may be caused by transfer of commensal flora from the skin at implantation as occurs in a SSI or, less frequently, haematogenous spread from distant sites.[18,21] SSI prevention is multifaceted, with skin decolonization, implant and instrument sterilization, and preoperative medical optimization all important interventions.[22] Central to SSI prevention is the use of prophylactic antibiotics.

Best practice on the use of prophylactic antibiotics in the UK is informed by National Institute for Health and Care (NICE) guidelines, which recommend giving antibiotics before, and a single dose of antibiotic prophylaxis intravenously at the start of surgery in surgeries involving the placement of a prosthesis or implant, such as elective primary arthroplasty.[23] Current international guidance is based on the 2018 Philadelphia Consensus Guidance, and states that a single intravenous dose of a first- or second-generation cephalosporin, given within 30 to 60 minutes prior to surgical incision, should be the first-line prophylactic antibiotic regimen for patients undergoing elective lower limb arthroplasty.[24]

Despite the importance of single-dose prophylactic antibiotics to SSI prevention, previous research has highlighted substantial variation across trusts in England in the preferred prophylactic regimen, and dose and duration of prophylactic antibiotic, for elective THA and TKA, despite identifying only seven organisms as being causative for 89% of all SSIs.[18]

Given the increasing clinical burden of PJIs and the importance of antibiotic prophylaxis in the prevention of SSIs, there is a need to understand the contemporary landscape of current practice guidance across the NHS hospitals in the UK.

In light of this, the aims of this study were: to identify the antibiotic prophylaxis regimens currently in use for elective primary arthroplasty across hospitals in the UK; to establish the variations in antibiotic prophylaxis regimens in use for elective primary arthroplasty across the UK, and their impact on the risk of PJI in the first-year post-index procedure; and to compare current antibiotic prophylaxis regimens across hospitals in the UK to current international consensus guidance, to evaluate degree of adherence.

Methods

The guidelines for prophylactic antibiotic regimens in clean orthopaedic surgery (primary arthroplasty) in 109 hospitals and trusts across the UK were sought through a search of each trust and hospital's website. The data were collected from the prophylaxis antibiotic policy for each trust, published on its intranet webpage. Additionally, the MicroGuide app was used to access the prophylaxis antibiotic policy for trusts where there was difficulty in getting the information through the intranet webpage.

Guidelines were reviewed to identify the primary antibiotic choice, dose, and number of subsequent doses recommended.

Information on the alternative recommended prophylactic antibiotic regimen in patients allergic to penicillin, where MRSA was suspected, or when the primary choice was unavailable, was also sought, noting the recommended antibiotic(s), dosage, and the number of subsequent doses.

This information was then collated and recorded via Microsoft Excel (Microsoft, USA) and analyzed. Excel graphing software was then used to analyze trends in the preferred antibiotics and alternative antibiotics for trusts with information available (Supplementary Figures a and b, Figures 1 and 2).

This information was then used to calculate the number of trusts using a first- or second-generation intravenous cephalosporin as their recommended primary antimicrobial prophylaxis regimen (2018 Philadelphia Consensus Guidance) to evaluate the degree of adherence to current international guidance. This was presented graphically (Figure 3).

The cost of each antibiotic was calculated from the mean of all the available prices in the British National Formulary (BNF).[25] The mean cost of each antibiotic regimen was then determined and used to calculate the overall cost of each primary antibiotic regimen across hospitals with data available (Supplementary Figure c).

Hospital data on the number of elective primary THAs and TKAs were sought and found for 105/109 (96.30%) hospitals and trusts. This information was then collated and paired with the recommended primary antimicrobial prophylaxis regimen recommended for each centre, to calculate the frequency of use of each antimicrobial prophylaxis regimen nationally (Supplementary Figure d).

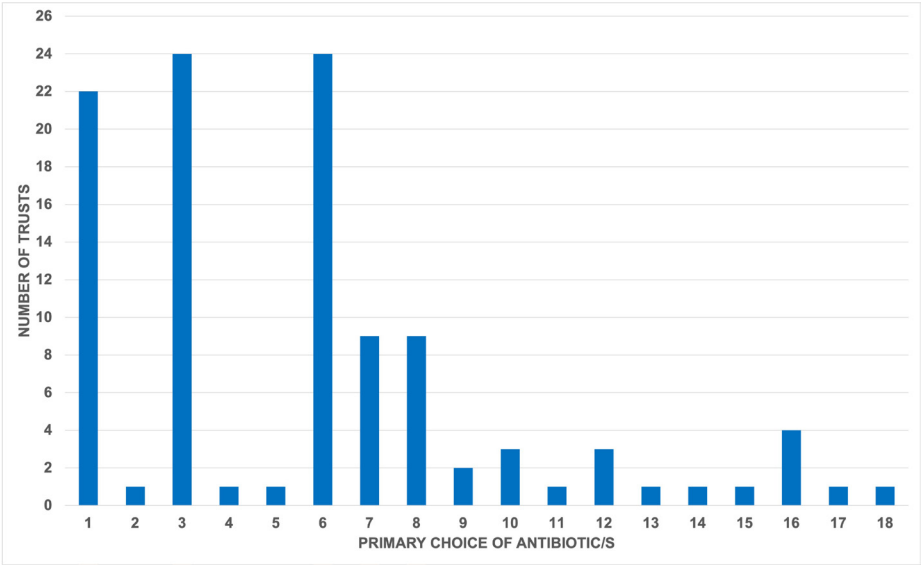

Fig. 1

Primary antibiotic(s) across centres. The antibiotics are described as follows. 1) Flucloxacillin and gentamicin, then flucloxacillin after six hours. 2) Cefuroxime and gentamicin, then cefuroxime after eight hours. 3) Cefuroxime, then hourly cefuroxime. 4) Flucloxacillin only, then hourly flucloxacillin. 5) Flucloxacillin 1 g, flucloxacillin 2 g, gentamicin 160 mg, gentamicin 240 mg, then two doses of flucloxacillin 1 g six-hourly. 6) Teicoplanin and gentamicin. 7) Flucloxacillin and gentamicin. 8) Cefuroxime. 9) Cefalozin. 10) Ceftriaxone. 11) Co-amoxiclav. 12) Teicoplanin. 13) Cefuroxime and gentamicin. 14) Cefuroxime and gentamicin, then three times more eight-hourly. 15) Teicoplanin and gentamicin, then teicoplanin after 12 hours. 16) Co-amoxiclav, then two doses of co-amoxiclav eight-hourly. 17) Teicoplanin and gentamicin, then teicoplanin after 12 hours. 18) Cefuroxime and teicoplanin.

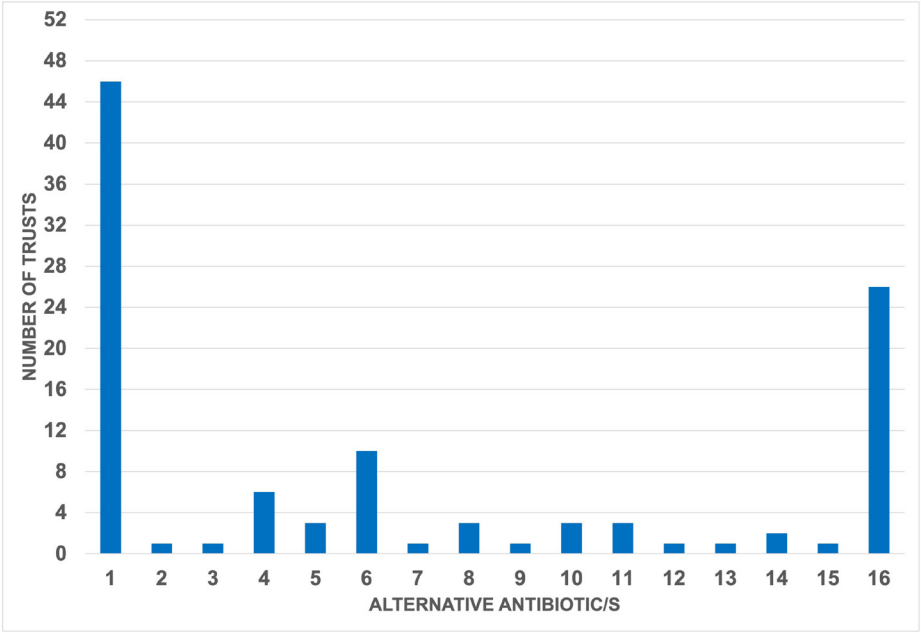

Fig. 2

Alternative antibiotic(s) across centres. The regimens are described as follows. 1) Teicoplanin and gentamicin. 2) Cefuroxime and gentamicin, followed by cefuroxime hourly. 3) Vancomycin and gentamicin. 4) Teicoplanin and gentamicin, followed by teicoplanin hourly. 5) Clarithromycin followed by clarithromycin hourly. 6) Teicoplanin. 7) Clindamycin and gentamicin, followed by clindamycin hourly. 8) Vancomycin. 9) Teicoplanin followed by teicoplanin hourly. 10) Teicoplanin and gentamicin, followed by teicoplanin and gentamicin hourly. 11) Teicoplanin and ciprofloxacin followed by ciprofloxacin hourly. 12) Vancomycin and ciprofloxacin followed by ciprofloxacin hourly. 13) Teicoplanin and gentamicin, followed by vancomycin hourly. 14) Teicoplanin and gentamicin. 15) Teicoplanin and gentamicin and metronidazole, followed by teicoplanin hourly. 16) No data.

Results

Guidelines for the preferred antibiotic regimen and dose for primary arthroplasty were available for 109 centres across the UK. Data on the preferred alternative

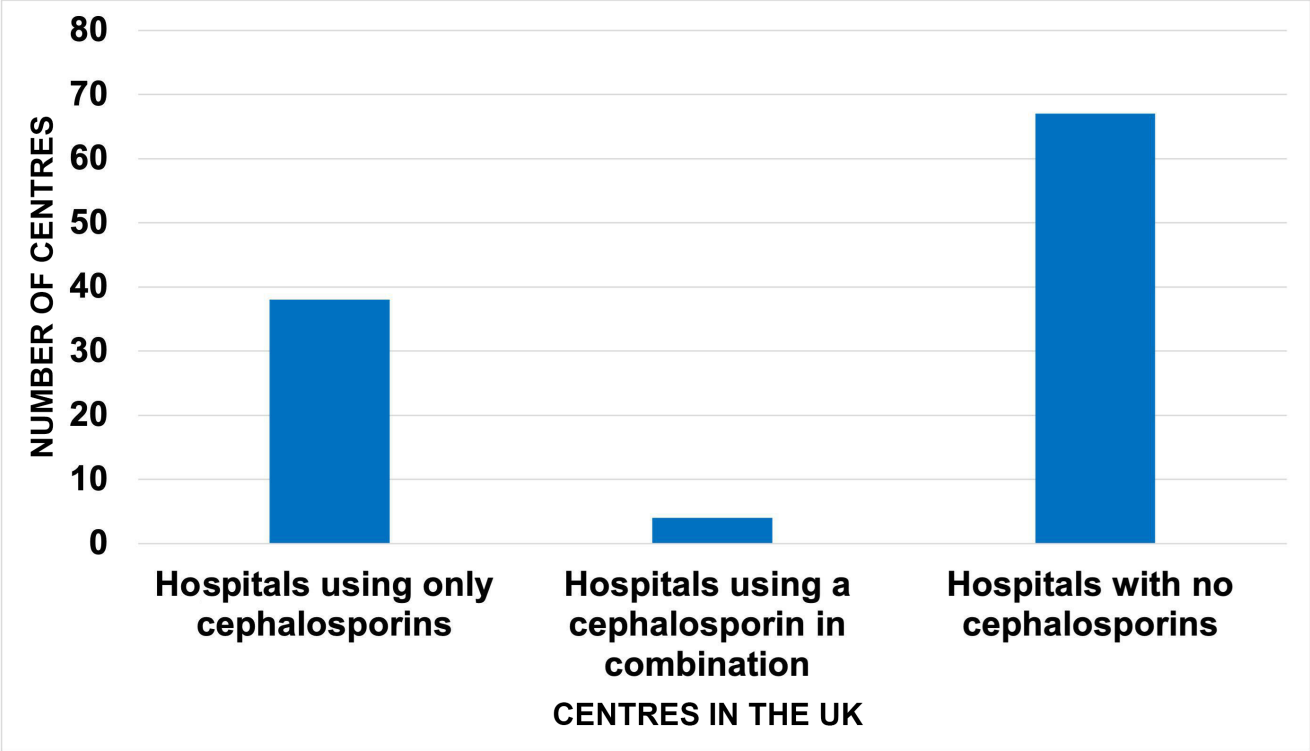

Fig. 3
Adherence of centres in the UK to 2018 Philadelphia Consensus Guidance.

antibiotic and dose (for patients with penicillin allergy, MRSA prevalence, or unavailability of the preferred choice) were available for 83/109 hospitals and trusts (76.20%).

Primary choice of prophylactic antimicrobial regimen. The primary choice and dosing of prophylactic antimicrobial regimen for elective primary arthroplasty varied widely. The most used regimen was cefuroxime 1.5 g followed by three doses of cefuroxime 750 mg eight-hourly, used by 20 centres (18.40%). Cefuroxime 1.5 g only was used in 9/109 (8.26%) of centres, while teicoplanin 600 mg and gentamicin 3 mg/kg were recommended by five centres (4.6%), and flucloxacillin 2 g and gentamicin 160 mg were recommended by four centres (3.70%). Flucloxacillin 2 g and gentamicin 160 mg, followed by flucloxacillin 1 g three times six-hourly were recommended by another four centres (3.70%). Guidance across the remaining centres varied widely, with many regimens distinct to the 67 centres (61.50%) (Supplementary Figure a).

The choice or combination of primary antibiotic(s) also ranged widely. The two most used regimens were a combination of teicoplanin and gentamicin, recommended by 24 centres (22%), and cefuroxime followed by two or three doses of cefuroxime eight-hourly, recommended by 24 centres (22%). A combination of flucloxacillin and gentamicin, followed by additional flucloxacillin after six hours, was recommended by 22 trusts (20.2%). A combination of flucloxacillin and gentamicin and cefuroxime-only treatment were recommended by nine trusts each (8.3%). Co-amoxiclav, followed by additional co-amoxiclav eight hours later, was recommended by four trusts (3.7%), while a further six trusts (5.5%) recommended teicoplanin only or ceftriaxone only. Across the remaining centres, the choice of antibiotics varied widely and was distinct across most of the remaining ten trusts (9.2%) (Figure 1).

Alternative choice of antimicrobial regimen. The alternative choice and dosing of the prophylactic antimicrobial regimen for elective primary joint arthroplasty also varied widely across the 83 centres for which the data were available. The most commonly recommended regimen was teicoplanin 600 mg and gentamicin 160 mg, which formed the guidance of six trusts (7.2%). A combination of teicoplanin 800 mg and gentamicin 2 mg/kg was recommended by five trusts (6%), while teicoplanin 600 mg alone was recommended by four trusts (4.8%). Across the remaining 67 centres (80.7%), guidance varied very widely and was distinct to most individual trusts (Supplementary Figure b). There was a greater consensus when comparing the choice or combination of alternative antibiotic(s) across the 83 centres (76.2%) for which data were available. A total of 46 trusts (55.4%) recommended teicoplanin and gentamicin. Ten centres (12.1%) recommended teicoplanin only, while

six trusts (7.2%) recommended teicoplanin and gentamicin, followed by hourly teicoplanin. Across the remaining 21 centres (25.3%), the range of the recommended prophylactic antibiotic(s) varied widely (Figure 2).

Adherence to 2018 Philadelphia Consensus Guidance. Comparing primary antimicrobial prophylaxis regimens to the 2018 Philadelphia Consensus Guidance, limited adherence was observed. A total of 67 centres (61.5%) did not include any cephalosporins in their primary prophylactic regimens, whereas four (3.7%) recommended a cephalosporin in combination with other antibiotics. The remaining 38 centres (34.9%) recommended a cephalosporin only (in accordance with 2018 Philadelphia Consensus Guidance), although often multiple doses were recommended, which deviates from the guidance (Figure 3).

Mean spend per patient on primary antimicrobial prophylaxis regimen. When comparing the 105 centres for which the mean pricing data were available, heterogeneity was observed. The greatest spend per patient was £47 on primary antimicrobial prophylaxis regimen, and the lowest spend per patient was £2.57 (Supplementary Figure c).

Number of operations performed for each antimicrobial regimen. Two regimens emerged as those used for the majority of total hip and total knee arthroplasties. The most frequently used regimen was a combination of flucloxacillin 1 g and gentamicin 3 mg/kg, followed by three doses of flucloxacillin 1 g six-hourly, used for 21,125 THAs and TKAs (16.6% of all total hip and knee arthroplasties performed annually).

The second most used regimen was a combination of cefuroxime 1.5 g followed by three doses of cefuroxime 750 mg eight-hourly, used for 18,004 total hip and knee arthroplasties (14.2%). This was used across 20 centres, public and private, mostly across London and Wales. A single dose of cefuroxime 1.5 g was used for 7,833 patients (6.2%), across nine centres. A regimen of teicoplanin 800 mg combined with gentamicin 3 mg/kg was used for 4,769 patients (3.8%), used across three centres: two in northern England and one in southern England. A combination of cefuroxime 1.5 g followed by two doses of cefuroxime 1.5 g eight-hourly was used for 4,634 patients (3.6%) (Supplementary Figure d).

Antibiotic prophylaxis regimens and their impact on the risk of PJI in the first-year post-index procedure. Most centres provided prophylactic antibiotic regimens that conferred protection against the leading causes of SSI: *Staphylococcus* and *Enterococcus* species. However, guidelines from five centres (4.59%) recommend co-amoxiclav as their primary antibiotic regimen, which does not cover *Staphylococcus* species of bacteria, which causes 18.6% of SSI infections.[19] Guidelines from 33 centres (30.28%) recommend cefuroxime only as their primary antibiotic regimen, which confers no *Enterococcus* coverage.

Discussion

This analysis of guidance on antimicrobial prophylaxis in primary arthroplasty across 109 hospitals and trusts in the UK has identified widespread variation in primary and alternative antimicrobial regimens currently being recommended, with no clear trends by geographical area, consensus on the antibiotic dose, or consensus on the number of follow-up doses, with limited adherence to NICE and international consensus guidance (Supplementary Figures a to c, Figures 1 to 3).

This analysis highlights the substantial variation in primary choice and dosage of prophylactic antimicrobial regimens across the 109 centres. The most commonly used regimen was a combination of cefuroxime 1.5 g followed by three eight-hourly doses of 750 mg cefuroxime, recommended in 20/109 centres (18.4%). A single dose of cefuroxime 1.5 g was recommended by nine trusts (8.3%), while other regimens varied very widely across trusts and were distinct for most of the remaining 67 centres (61.5%). This variation is notable, given recent research by Badge et al[26] showing that adequate weight-based dosage and early administration of the prophylactic antibiotics may reduce the risk of SSI in total hip and total knee arthroplasty.

When excluding antibiotic dosage, greater commonality was observed across centres. A combination of teicoplanin and gentamicin was recommended by 24 trusts (22%), while cefuroxime, followed by two or three eight-hourly doses of cefuroxime, was also recommended by 24 trusts (22%). Antibiotics recommended across the remaining trusts were varied and distinct for most. Given the importance of an effective dose to eradicate *Staphylococcus* species of bacteria, the leading cause of SSIs, it is unclear why so much variance in the antibiotic dose and the number of doses was observed (Supplementary Figure a). Previous research has indicated that antibiotic doses below the minimum inhibitory concentration (MIC) can stimulate the formation of biofilms, increasing the likelihood of infection. Therefore, the wide variance in dose size and dose number in guidance across hospitals is concerning.[27]

Greater consensus was observed when comparing guidance across hospitals for preferred alternative antibiotic prophylaxis, although there was still major variance in recommended dosages across the 83 centres with data available. The most recommended regimen was teicoplanin 600 mg and gentamicin 160 mg, followed by a combination of teicoplanin 800 mg and gentamicin 2 mg/kg and teicoplanin 600 mg alone. Across the remaining 67 centres (80.8%), guidance varied very widely and was distinct to most individual trusts. When comparing the overall cost of each antibiotic regimen per patient, major variance was also observed across the 105 centres with data available. Most centres fell into two groups: those spending £15 to £25 per patient (50

centres – 47.61% of 105 centres), and those spending £5 to £15 per patient (46 centres – 43.80% of 105 centres). However, a notable variation between trusts in overall spending on antimicrobial prophylaxis was observed (Figure 3). Adjusting for the number of elective THAs and TKAs performed per antibiotic regimen, two regimens are used for the majority of THAs and TKAs. The most frequently used regimen was a combination of flucloxacillin 1 g and gentamicin 3 mg/kg, followed by three doses of flucloxacillin 1 g six-hourly, then a combination of cefuroxime 1.5 G followed by three doses of cefuroxime 750 mg eight-hourly.

When evaluating the adherence of centres to the internationally recognized 2018 Philadelphia Consensus Guidelines, limited adherence was observed, with only 34.9% of centres having a cephalosporin as their primary prophylactic antibiotic regimen, while 61.5% of centres did not include a cephalosporin in their primary antimicrobial regimen at all (Figure 3). These findings are concerning and highlight the widespread, limited adherence to current NICE and international guidelines.

The findings of this review are in accordance with previous research by Hickson et al,[18] whose 2015 paper identified widespread variation in trust guidance for antimicrobial prophylaxis for elective hip and knee arthroplasty across trusts in England.[18] The results of this analysis highlight that little has changed since this paper was published. Similar research evaluating adherence to antimicrobial prophylaxis guidelines in the management of patients sustaining open tibial fractures has also highlighted similarly poor adherence in the trauma setting, suggesting that this problem extends across orthopaedic subspecialties.[28]

Recent research by Public Health England has highlighted that most SSIs are caused by Enterobacterales and *Staphylococcus* species, constituting 33.1% and 18.6% of SSIs in 2021 respectively, while coagulase-negative staphylococci constituted one-quarter of infections.[1,19] Reviewing trust guidelines, there is also concern that current prophylaxis regimens fail to cover the likeliest causes of SSI. Guidelines from five centres (4.59%) recommend co-amoxiclav as their primary antibiotic regimen. Co-amoxiclav, however, does not cover *Staphylococcus* species of bacteria, which make up 18.6% of SSI infections.[19] Guidelines from 33 centres (30.28%) recommend cefuroxime only as their primary antibiotic regimen; however, this confers no *Enterococcus* coverage. Given that *Enterococcus* infections are implicated in over 25% of SSIs, this is another point of concern.[1,19] The variation in antibiotic usage is neither evidence-based nor advantageous to patients or the NHS. Indeed, different antibiotics have different safety profiles, and this unwanted variation is against the philosophy of "getting it right first time".[29] In addition, inappropriate usage of antibiotics is likely to further increase the risks of antimicrobial resistance.

The lack of consensus across hospitals included in this analysis has highlighted the need for further research. There is a need to understand how decisions are being made across different trusts for the preferred antibiotic prophylactic regimen for patients undergoing primary arthroplasty. Due to a lack of present data, we are unable to comment on the relationship between recommended prophylactic antibiotic regimens and more widespread bacteria in individual geographical areas. Contemporary research, mapping geographical variations in causative bacteria for SSIs across the UK and comparing with antibiotic strategies in local hospitals, would allow antibiotic strategies to be better matched to purpose. This analysis has evaluated differences in guidance on the use of antibiotic prophylaxis across hospitals. There is, however, also a need to understand how closely followed guidance is in current practice, with scope for an audit on antibiotic stewardship in the prevention and management treatment of SSIs in primary arthroplasty surgery across hospitals in the UK.

This analysis of hospital guidelines has certain limitations. It only focused on guidance for antibiotic prophylaxis in clean orthopaedic surgery for primary arthroplasty. Guidance for other clean orthopaedic procedures, such as arthroscopy, and open reduction and internal fixation (ORIF) for closed fractures, have not been assessed. Other procedures, such as spinal surgery and ORIF for open fractures – which present the greatest risk of subsequent infection – have been excluded from this analysis. This review was also solely of guidelines, and may not reflect true practice. Antibiotic use in practice varies widely, at the discretion of the treating consultant and multidisciplinary team.

We are not able to comment on which antibiotic regime is optimal for prophylactic use in patients undergoing elective joint arthroplasty (based on these data). This is in part due to the lack of information on adherence to trust guidelines and patient and surgical factors (BMI, comorbidities, duration of surgery, type of surgery, etc), and in part due to lack of details about antibiotic prescription in primary healthcare for patients who have undergone joint arthroplasty and post-discharge consult their GP for wound issues.

In conclusion, current guidance from NHS trusts across the UK regarding antimicrobial prophylaxis in patients undergoing primary hip or knee arthroplasty shows major variation in terms of choice of antibiotic and recommended dosage. This does not seem to be evidence-based and is also associated with important cost implications. Future studies should assess adherence to the antimicrobial policy, reasons for the variations noticed, and the policy's impact on the risk of SSIs.

Take home message

- There is major variance across NHS trusts in recommended antimicrobial prophylaxis regimens for primary total hip and knee arthroplasty, with guidelines often deviating from internationally agreed best practice.
- Future research is required to understand the reasons for the variations in current guidelines, and their impact on clinical outcomes.

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- J. Palan: Conceptualization, Supervision.
- H. Pandit: Project administration, Writing – review & editing.

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