Antibiotic prophylaxis in breast cancer surgery (PAUS trial)

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Randomized Clinical Trial

Antibiotic prophylaxis in breast cancer surgery (PAUS trial): randomised clinical double-blind parallel-group multicentre superiority trial

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Abstract

Background: Participants were patients with invasive breast cancer undergoing primary surgery. The aim was to test whether a single dose of amoxicillin–clavulanic acid would reduce wound infection at 30 days postoperatively, and to identify risk factors for infection.

Methods: Participants were randomised to either a single bolus of 1.2 g intravenous amoxicillin–clavulanic acid after the induction of anaesthesia (intervention) or no antibiotic (control). The primary outcome was the incidence of wound infection at 30 days postoperatively.

Results: There were 871 evaluable patients. Of these, 438 received prophylactic antibiotic and 433 served as controls. Seventy-one (16.2 per cent) patients in the intervention group developed a wound infection by 30 days, while there were 83 (19.2 per cent) infections in the control group. This was not statistically significant (odds ratio (OR) 0.82, 95 per cent c.i. 0.58 to 1.15; $P = 0.250$). The risk of infection increased for every 5 kg/m^2 of BMI (OR 1.29, 95 per cent c.i. 1.10 to 1.52; $P = 0.003$). Patients who were preoperative carriers of *Staphylococcus aureus* had an increased risk of postoperative wound infection; however, there was no benefit of preoperative antibiotics for patients with either a high BMI or who were carriers of *S. aureus*.

Conclusion: There was no statistically significant or clinically meaningful reduction in wound infection at 30 days following breast cancer surgery in patients who received a single dose of amoxicillin–clavulanic acid preoperatively.

Registration number: N0399145605 (National Research Register).

Introduction

A postoperative wound infection is not only a significant complication for an individual patient, but also leads to human, financial, and resource costs to health services. An infection after breast cancer surgery may also cause delays in the initiation of adjuvant therapy, with potential effects on survival[1]. Although wound infection rates after breast cancer surgery are higher than expected (0 to 29 per cent), when compared to other clean surgeries (1 to 2 per cent)[2,3], there still remains controversy regarding the value of prophylactic antibiotics[4,5]. The majority of postoperative wound infections occur in the first 30 days following surgery (98 per cent)[6].

The Association of Breast Surgery and the Scottish Intercollegiate Guideline Network (SIGN) currently recommends that antibiotics should be 'considered' in breast cancer surgery[3,7]. The National Institute of Health and Care Excellence (NICE) recommends that local protocols should apply[5,8]. In clinical practice there is currently no consensus about prophylactic antibiotics in breast cancer surgery, and there have been no new trials published in the last 15 years[2,9]. Moreover, there are no current recommendations about what specific antibiotic should be used for prophylaxis in breast cancer surgery.

Antibiotic prophylaxis in surgery carries a risk of adverse events, including *Clostridium difficile* infection, and it increases the prevalence of multiresistant organisms[2,9–11]. Over the last 15 years, global antibiotic overuse has accelerated antimicrobial resistance[12]. This has led to a growing number of common infections becoming harder to treat[13]. The UK Department of Health antimicrobial resistance strategy (2013 to 2018) encourages evidence-based antibiotic use[14]. It is therefore very important to avoid prophylactic antibiotics in surgery unless they have a proven benefit. The present study set out to clarify whether, in patients undergoing primary breast cancer surgery, a single dose of amoxicillin–clavulanic acid would reduce wound infection at 30 days after surgery, and to identify risk factors for postoperative infection.

Methods

The Prophylactic Antibiotic Use in Surgery (PAUS) trial was carried out between June 2002 and March 2005. It was a randomised

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double-blind parallel-group multicentre superiority trial. PAUS was carried out in 11 of 13 in breast units in the west of Scotland, covering a source population of 2.5 million. The Robertson Centre of Biostatistics (RCB), University of Glasgow, was involved from the outset in study design and grant applications (*Appendix S1*). Data collection, form planning and printing, data entry, and queries were carried out through the RCB. The RCB was designated as the study centre, and performed the randomisation, administration, maintenance, and statistical analysis of the final database. The analysis was carried out according to the predetermined statistical analysis plan (*Appendix S2*). The study received ethical approval from local ethics committees, as well as the regional committee (Multi Research Ethics Committee for Scotland: MREC0310013). The trial was carried out in accordance with good clinical practice guidelines for clinical trials[15].

Patients were screened preoperatively by a research nurse, breast care nurse, or consultant surgeon. If there were no excluding criteria, the patient provided written consent after full discussion.

Primary outcome

The primary outcome of the trial was to test whether a single dose of amoxicillin–clavulanic acid 1.2 g given intravenously during the induction of anaesthesia would reduce the incidence of wound infections at 30 days after breast cancer surgery. The trial was therefore designed to show superiority for antibiotics (intervention) *versus* no antibiotics (control).

Secondary outcome

A prespecified secondary outcome was the time to wound infection. The incidence of wound infection was recorded at day 1 postoperatively, days 3 to 5, days 7 to 10, and at 30 days.

Inclusion criteria

Patients over the age of 18 years with invasive breast cancer undergoing primary surgery were recruited. Patients either had mastectomy or breast-conserving surgery, with either nodal sampling or axillary lymph node dissection.

Exclusion criteria

Patients with a local infection at the time of surgery or who were taking antibiotics for any reason were excluded. Further exclusion criteria were allergy to penicillin or amoxicillin–clavulanic acid, pregnancy, and breastfeeding. Patients who were operated on with immediate breast reconstruction with either an implant, pedicle, or free flap at the time of mastectomy were also excluded, as were those having any type of oncoplastic breast conservation.

Randomisation method

Randomisation was stratified by hospital and operation type (mastectomy or wide local excision) in permuted blocks of four. Each study participant was allocated the next available sequential identifier according to the study protocol. This unique identifier (identifying both the hospital and the participant) determined which treatment the patient received. Patients were randomised to either 1.2 g intravenous amoxicillin–clavulanic acid or no antibiotic. The anaesthetist opened wage slip-type envelope A in the anaesthetic room and gave antibiotic, if this was the allocation. This was given intravenously as a single bolus after the induction of anaesthesia, and before the patient was moved to the operating room. The anaesthetist then signed the enclosed slip in envelope A and returned it in a prepaid envelope to the study centre. A duplicate sealed envelope B was kept in the notes in the event of unblinding becoming necessary. No other study personnel or the patient knew which allocation they had received and the comment 'patient in PAUS study' was recorded on the anaesthetic sheet, regardless of whether or not the patient had been given the antibiotic.

Definition of wound infection

Wound infection was defined as pus exuding from the wound; surgeon-diagnosed infection; a wound that needed to be opened in the presence of fever, local pain, or an abscess; or the presence of a single cultured organism from the wound. This was done in accordance with the Centers for Disease Control criteria[16]. The presence, absence, and severity of each sign or symptom was recorded.

Prognostic model

The prespecified subgroup analysis for the PAUS study was to build a prognostic model to assess the baseline and perioperative characteristics that influenced 30-day wound infection rates. Patient characteristics included age, smoking status (recorded as current, past, or never), BMI, and Carstairs deprivation index (DepCat). The latter is the Scottish Index of Deprivation, based on a patient's postcode. Operative characteristics included type of operation (mastectomy or wide local excision), wire localization, axillary surgery, and bilateral surgery. Duration of surgery and blood loss, as well as ASA grade were recorded, as were the number of postoperative seroma drainages. Background information was collected on a baseline form, including medical and drug history.

Preoperative *Staphylococcus aureus* carriage was determined by nose, axilla, and perineal screening swabs, which were sent to a single laboratory. Any coagulase-positive swabs were forwarded to the Scottish methicillin-resistant *S. aureus* (MRSA) reference laboratory for characterization and storage. In patients with a postoperative wound infection who had had screening swabs taken, coagulase-positive swabs were sent to the same laboratory for comparison with screening swabs. Comparisons were made with culture morphology, antibiogram, standard phage typing, and pulsed-field gel electrophoresis.

The patients' general practitioners (GP) were informed, but patients were encouraged to return to the hospital with any wound problems. If patients required further surgery, they were evaluated up to the date of reoperation. Unscheduled visits to the hospital, the GP, or the breast care nurse prior to the 30-day follow-up visit were recorded.

Safety

Adverse events were monitored, including reactions to amoxicillin–clavulanic acid.

Statistical analysis

The efficacy population was defined as all randomised patients with at least one scheduled postoperative examination. The safety population was defined as all the patients screened, recruited, and randomised into the trial. Baseline characteristics were reported as a whole and by treatment group. Categorical variables were summarized as frequencies and percentages. Continuous variables were summarized as mean and standard deviation (s.d.) or median and interquartile range (i.q.r., defined as the 25th and 75th percentiles).

The primary analysis compared the proportion of patients with wound infection diagnosed at any visit up to and including the 30-day follow-up, using a mixed-effects logistic regression

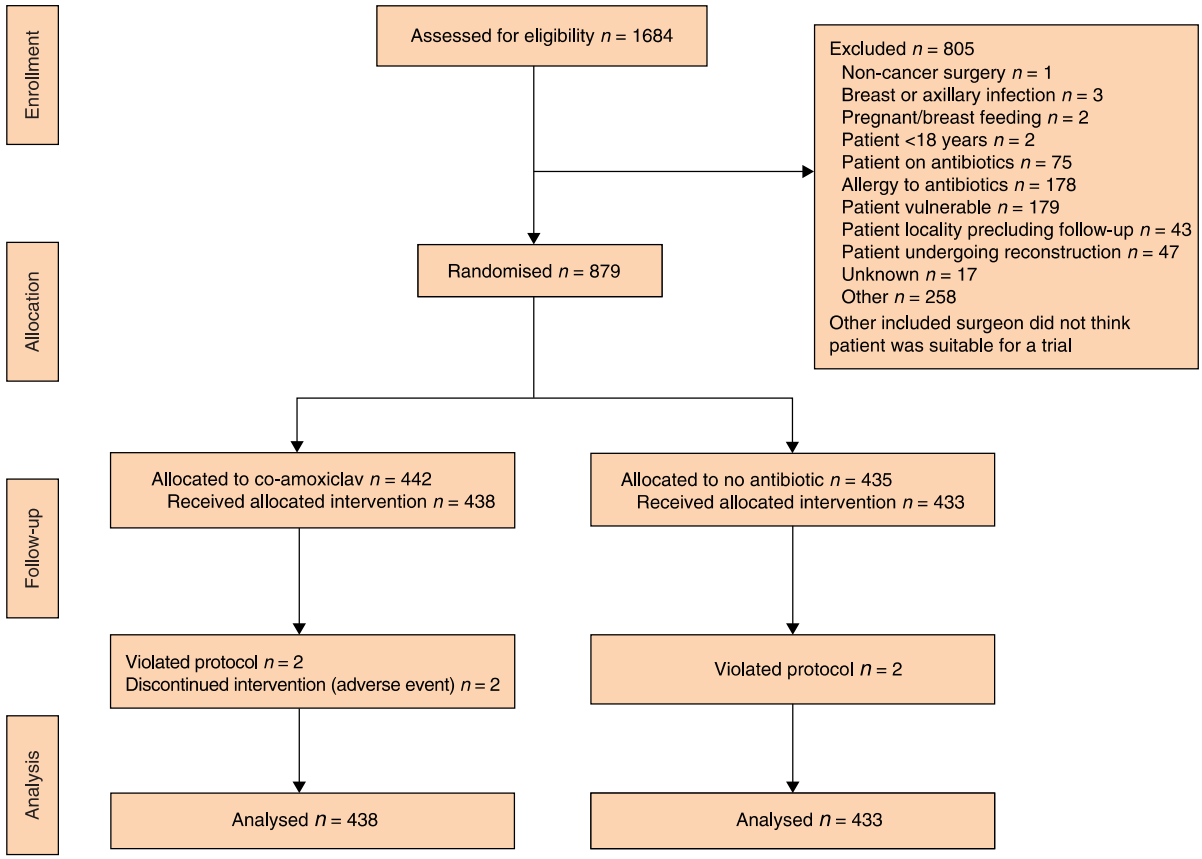

Fig. 1 CONSORT diagram
Adapted from Moher *et al.*[18]

model. The analysis adjusted for the type of surgery (mastectomy or wide local excision) and site (as a random effect), and was carried out according to an intention-to-treat principle. Treatment effects were estimated as odds ratios (ORs) between the amoxicillin–clavulanic acid and control groups with 95 per cent confidence intervals.

Moderation of the treatment effects were explored by prespecified baseline subgroups of *S. aureus* carriage, age, and BMI. Treatment-by-subgroup interactions were added to the mixed-effects logistic regression.

For the secondary outcome of wound infection by time of follow-up (at days 1, 2 to 5, 6 to 10, and 11 to 30), separate mixed-effects logistic regression models were fitted. Follow-up was divided into time periods, and proportional hazard models were used to estimate the treatment effect. These models were then extended to incorporate patient and surgical characteristics as covariates. Treatment and covariate effects are reported as hazard ratios (HRs) with 95 per cent confidence intervals. A *P* value of less than 0.05 was taken to indicate statistical significance, and no adjustment for multiple comparisons were made. Formal significance tests were not applied to other analyses.

Data were prepared for analysis using SAS for Windows v 8.02 (SAS Institute, Cary, NC, USA). Analysis was carried out with S-Plus for Windows v6.1 (TIBCO Software, Palo Alto, CA, USA). Recent analysis was carried out using R for Windows v4.05 (R Foundation, Vienna, Austria).

Sample size and power

The postoperative wound infection rate was estimated to be 15 per cent in untreated patients, and that an absolute 6 per cent decrease in wound infection rates would be a clinically useful benefit for the intervention. Using a χ^2 test, for 80 per cent power at a 5 per cent level of significance, to detect a wound infection reduction from 15 per cent to 9 per cent would require 914 participants, so we targeted a total sample size of 1000 to allow for a 9 per cent loss to follow up at 30 days. The recruitment period was 18 months.

Results

A total of 1684 patients were screened, and 805 (47.8 per cent) patients were excluded after screening (*Table S1*). The most common reasons for exclusion were allergy to penicillin or amoxicillin–clavulanic acid (11 per cent), taking antibiotics at the time of surgery (5 per cent), or the patient being vulnerable (11 per cent; *Fig. 1* and *Table S1*)[17].

A total of 879 patients (including two male patients) were randomised; of these, 871 were evaluable and included in the analysis. A total of 438 patients received the intervention and 433 patients served as controls. In total, 822 of 871 randomised patients completed the 30-day follow-up (94.3 per cent). Forty-three patients required further surgery before 30 days, and two patients withdrew consent due to a non-fatal adverse event; four patients were protocol violators, with no follow-up information recorded.

Safety

Apart from two patients who had a mild reaction to the antibiotic (transient rash), there were no adverse events seen in the trial.

Table 1 Baseline patient characteristics

Characteristic	Prophylactic antibiotic ($n = 438$)	Control ($n = 433$)
Mean (s.d.) age (years)	59.1 (10.5)	58.9 (10.4)
Mean (s.d.) BMI (kg/m^2)	26.8 (5.1)	26.6 (5.0)
Never smokers	234 (53.4)	238 (55.0)
Former smoker	111 (25.3)	84 (19.4)
Current smoker	93 (21.2)	111 (25.6)
DepCat score 1–3	139 (31.7)	140 (32.8)
DepCat score 4–5	174 (40.1)	165 (38.6)
DepCat score 6–7	121 (27.9)	122 (28.6)
Diabetes	18 (4.1)	12 (2.8)
CRP >12 mg/dl*	31 (14.1)	24 (12.5)
White cell count >10 mg/dl	43 (9.9)	40 (9.3)

Data are *n* (%) unless otherwise indicated. DepCat score: Scottish Index of Multiple Deprivation. In DepCat. score 1–3 indicates affluent and 6–7 deprived. *C-reactive protein (CRP) data missing in 50 per cent of patients overall.

Baseline characteristics

Baseline patient characteristics were well matched between the intervention and control groups (*Table 1*). Of the 871 evaluable patients 322 (37 per cent) had a mastectomy and 549 (63 per cent) a wide local excision. Seventy-nine patients (29 per cent of those operated with breast conservation) had a wire localization for non-palpable disease.

The two study populations were also well matched for duration of surgery, blood loss, and ASA grade. Equivalent numbers had surgery lasting for longer than 90 minutes (12.2 per cent in the intervention group and 10.3 per cent in the control group), and 1.6 per cent of patients in both groups had more than 300 ml of blood loss (*Table S2*). Axillary lymph node dissection was performed in 766 (90 per cent) patients, and 84 underwent axillary sampling (*Table S2*), with patients equally distributed between the intervention and control groups. Drains were used after mastectomy and/or axillary lymph node dissection and were removed before discharge.

Preoperative carriage rates for *S. aureus* showed that 128 patients (15.2 per cent) of patients were *S. aureus* carriers at any site (16.2 per cent in the intervention group and 14.5 per cent in the control group). These numbers included patients who were positive at more than one site (*Table S3*). Of those who were carriers, 126 patients had methicillin-susceptible *S. aureus* in their screening swabs, and two had MRSA, meaning that 0.23 per cent were MRSA carriers. The *S. aureus* carriage rates overall were lower than expected for the population (expectation of 20 per cent), and about the same as expected for MRSA carriage[18].

Primary outcome

There were 154 (17.7 per cent) wound infections among 871 randomised evaluable patients in this trial, which exceeded the estimated 15 per cent used in the power calculation. Of the 438 patients in the intervention group, 71 (16.2 per cent) developed a wound infection. In the control group, 83 of 433 patients (19.2 per cent) developed a wound infection. This difference was not statistically significant (OR 0.82, 95 per cent c.i. 0.58 to 1.15). The lower 95 per cent confidence interval of 0.58 was unable to rule out a benefit of the equivalent of an absolute 6 per cent reduction in the 30-day wound infection rate.

There was no significant difference in the risk of wound infection at 30 days after surgery when stratifying patients according to type of surgery (mastectomy *versus* wide local excision). In the mastectomy group, 27 of 53 patients who received prophylactic antibiotic developed a wound infection, while 26 of those without antibiotics had the same outcome ($P = 0.921$). Among those who underwent wide local excision, 44 patients in the antibiotic group *versus* 57 in the control group developed a wound infection ($P = 0.152$).

Table 2 Treatment effect of prophylactic antibiotic at four time points

	OR (95% c.i.)	*P* value
Wound infection at 1 day	1.99 (0.39–14.38)	0.429
Wound infection at day 3–5	0.43 (0.17–0.96)	0.049
Wound infection at day 7–10	0.57 (0.33–0.97)	0.041
Wound infection at 30 days	1.13 (0.66–1.93)	0.665

Odds ratios (OR) for treatment effect at each time point, adjusting for type of surgery.

Secondary outcomes

A significantly lower rate of wound infection for the antibiotic group was recorded at days 3 to 5. This significant difference was maintained at days 7 to 10; however, there was no significant difference between the antibiotic group and the controls at day 30. Sixty per cent of infections had occurred by day 10 (*Table 2*).

The prognostic model showed that there was no treatment effect seen in the subgroup analysis of baseline demographic and operative details. This included no effect for smoking or deprivation. However, a BMI of 30 or higher was significantly associated with wound infection (OR 1.67, 95 per cent c.i. 1.04 to 2.66; $P = 0.038$). Despite the increased risk of a postoperative wound infection in these patients, there was no benefit of the antibiotic prophylaxis (*Fig. 2*, *Table S4*).

The presence of *S. aureus* in preoperative screening swabs was significantly associated with a postoperative wound infection (OR 2.43, 95 per cent c.i. 1.54 to 3.80; $P < 0.001$). The odds of a wound infection was around 143 per cent higher when *S. aureus* was present *versus* absent. When comparing treatment effect for patients both carrying *S. aureus* and having a BMI of 30 or higher (OR 0.73, 95 per cent c.i. 0.18 to 2.94; $P = 0.656$) with other study participants (OR 0.82, 95 per cent c.i. 0.57 to 1.18; $P = 0.288$), no significant effect of prophylactic antibiotic was seen (interaction *P* value= 0.874).

Infecting organisms

Of the 154 patients with wound infections there was no information about the infecting organism in 44 cases, as no swab had been taken. In the remaining 110 patients, 81 (74 per cent) had a *S. aureus* infection. Of these, 40 were in the intervention group and 41 in the control group (OR 0.68, 95 per cent c.i. 0.42 to 1.10; $P = 0.120$). Of the 81 patients with *S. aureus* infections, nine were due to MRSA infections. Of these, six were in the antibiotic group, while three were in the control group (OR 1.98, 95 per cent c.i. 0.49 to 7.96; $P = 0.32$). Other organisms were identified in 14 antibiotic patients *versus* 15 in the control group (OR 0.9, 95 per cent c.i. 0.55 to 1.45; $P = 0.66$). Two patients with MRSA isolated from pus from postoperative wound swabs had these organisms typed alongside preoperative screening swabs with MRSA, and they were shown to be indistinguishable by pulsed-field gel electrophoresis.

Discussion

Antimicrobial resistance to common pathogens has been a growing concern in recent decades[11]. There is a lack of robust,

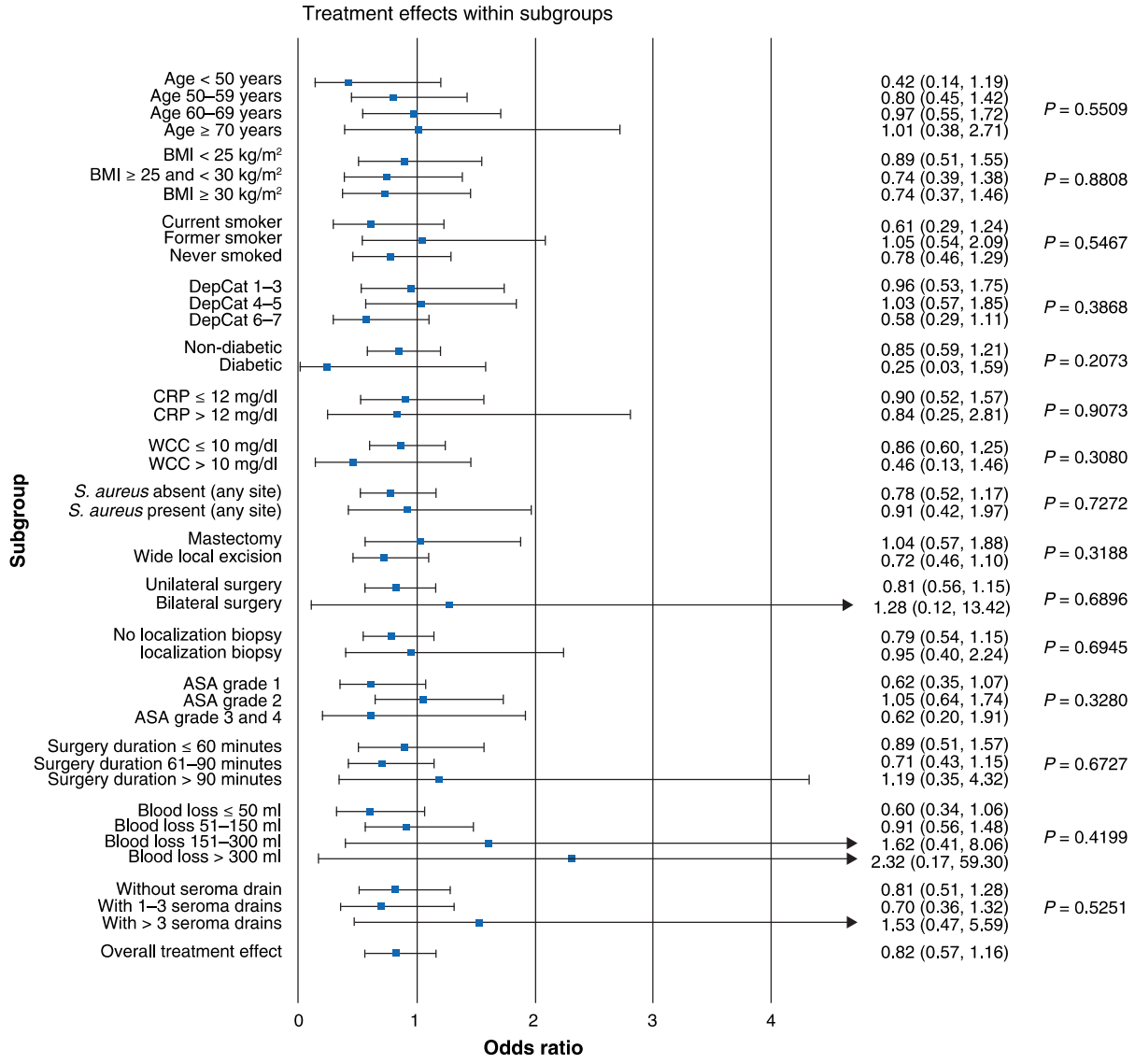

Fig. 2 Forest plot of subgroups (some upper confidence limits cut off due to large values)

CRP, C-reactive protein; WCC, white cell count.

worldwide surveillance and reporting of antibiotic use in human, veterinary, and agricultural practice, and their patterns of resistance. Antimicrobial resistance poses a worldwide threat of 'a post-antibiotic era', when antibiotics would be unavailable to treat common illnesses[12,19]. It is with this in mind and in the spirit of sharing valuable data that the results of this randomised clinical trial are being published, several years after the original primary study data were collected.

This trial demonstrated neither a statistical nor a clinical benefit for a single dose of amoxicillin–clavulanic acid in preventing wound infection at 30 days after breast cancer surgery. Despite not meeting our target recruitment figure of 1000 patients within the 18-month recruitment period, the trial was sufficiently powered to show an effect for the antibiotic as the overall wound infection rate was higher than predicted in the power calculation (17.6 per cent observed in the trial *versus* 15 per cent predicted).

This study identified a significant and clinically meaningful benefit for prophylactic antibiotics in the first 10 days postoperatively, although this was not the primary outcome of the study. As sixty per cent of infections had occurred by day 10, it is useful to note that preoperative antibiotics reduced wound infection in the early postoperative period.

The observed wound infection rate of 17.6 per cent is high compared with other studies, and one may argue that ascertainment can introduce bias in studies of wound infection. However, in this trial the fact that the presence or absence of infection was recorded for each patient should have mitigated this risk. In addition, the patient population was homogeneous compared with many other studies. The trial was pragmatic, carried out in working breast units in the west of Scotland, meaning that the results are likely to be applicable to everyday practice for clinicians in similar western medical environments. The choice of the antibiotic amoxicillin–clavulanic acid reflects how this antibiotic was the most common routinely used antibiotic for breast cancer surgery at the time of this trial. Given that *S. aureus* was the most common organism causing wound infections indicates that flucloxacillin may have been a

better choice of antibiotic, particularly when there are concerns of broad-spectrum antibiotic resistance.

There are no previous studies comparing *S. aureus* carriage with the final infecting organism in patients with breast cancer. There were only two such patients in this study, but the fact that the organism was identical supports the concept of wound infection by the patients' own carrier *S. aureus*[20]. Twenty per cent of patients in the west of Scotland at the time of this study would have been expected to be nasal *S. aureus* carriers in the community[18]. The preoperative screening carriage rate was lower than expected in this study (15 per cent). Since this trial, community *S. aureus* carriage has fallen[21,22]. It is unclear therefore whether routine preoperative screening and potential eradication measures would be useful in breast cancer surgery.

In the wider surgical setting, a recent systematic review by O'Connor *et al.* suggested that in the 17 included studies reporting culture results in patients with surgical site infection (SSI), *S. aureus* remained the major isolated organism[21]. A recent, 2056-patient retrospective/prospective comparative study by Zhang *et al.* also noted that *S. aureus* was the predominant microorganism isolated in patients with SSI following breast cancer surgery[24]. However, only 23 (1.1 per cent) of their study population developed SSIs and only eight had *S. aureus* isolated from screening swabs, making any correlation between the effects of *S. aureus* carriage rate and infection risks difficult[23]. Moreover, no effect was identified for the use of antibiotic in prevention of SSI[23].

The effect of antibiotics in breast surgery has been studied before, and there are four Cochrane reviews on this topic[9,10,25,26]. The first 'Prophylactic antibiotics to prevent surgical site infection after breast cancer surgery' was published in 2005[26]. Since then, there have been three updates, the last one in September 2019[10]. In the latest review there had been no new trials since 2014. Eleven randomised trials were included in the 2014 Cochrane review and in pooling the data there were 2867 patients in randomised trials of antibiotics *versus* no antibiotics or placebo[26–36]. Overall, there were 105 infections per 1000 in the placebo or no-antibiotic patients and 71 per 1000 in the patients who received antibiotics. None of the trials in the review was powered to show an effect of antibiotics, and in some trials the patient populations were highly heterogeneous. These data are the basis of current guidelines recommending that surgeons should 'consider' antibiotics in breast cancer surgery[3,5,7].

The present study has shown increased wound infection rates with increasing BMI but with no effect of prophylactic antibiotics, which is in line with what has previously been reported[30,37,38]. Some studies suggest that a lack of titration of the antibiotic dose may result in relative insufficient treatment to patients with a high BMI[30,32]. Recently, a large study by Pastoriza *et al.*[38], observing the National Surgical Quality Improvement Program (NSQIP) suggested, from a retrospective review of 30 544 lumpectomies and 23 494 mastectomies, that the SSI rate was higher in patients with a BMI higher than 35 kg/m^2. In the same study, smoking was also identified as a risk factor for SSI after breast surgery[37]. No such association between smoking and postoperative infection within 30 days of surgery was observed in the present trial. Similarly, no effect of deprivation was shown[37].

Although beyond the scope of this paper, it is relevant to note that other factors apart from antimicrobial therapy are important in attempting to reduce postoperative wound infection rates. Patient warming, hydration, and tissue oxygen delivery are factors that have been implicated in perioperative infection rates[39,40]. Postoperative infection has been identified as a possible risk factor for recurrence and is known to affect survival for a number of cancers, most notably in colorectal cancer[41]. However, more recently, a systematic review and meta-analysis by Savioli *et al.* identified that the available literature on breast cancer remains equivocal[43].

This trial would support the fact that most patients undergoing breast cancer surgery without complex oncoplastic techniques do not require routine prophylactic antibiotics[43,44].

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Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

Data availability

The authors are willing to make the data, analytical methods, and study materials available to other researchers. The authors had complete access to the study data. The data are archived at Glasgow University, Robertson Centre for Biostatistics.

References

1. Morante Z, Ruiz R, De la Cruz - Ku G, Namuche F, Mantilla R, Lujan M *et al.* Abstract GS2-05: Impact of the delayed initiation of adjuvant chemotherapy in the outcomes of triple negative breast cancer. *Cancer Research* 2019;**79**:GS2–05
2. Phillips BT, Bishawi M, Dagum AB, Khan SU, Bui DT. A systematic review of antibiotic use and infection in breast reconstruction: what is the evidence? *Plast Reconstr Surg* 2013; **131**:1–13
3. SIGN. *Antibiotic Prophylaxis in Surgery. A National Clinical Guideline*. http://medicinainterna.net.pe/images/guias/GUIA_PARA_LA_PROFILAXIS_ANTIBIOTICA_EN_CIRUGIA.pdf (accessed 26 July 2022)
4. Espin Basany E, Solís-Peña A, Pellino G, Kreisler E, Fraccalvieri D, Muinelo-Lorenzo M *et al.* Preoperative oral antibiotics and surgical-site infections in colon surgery (ORALEV): a multicentre, single-blind, pragmatic, randomised controlled trial. *Lancet Gastroenterol Hepatol* 2020;**5**:729–738
5. NICE. *Surgical Site Infections: Prevention and Treatment*. https://www.nice.org.uk/guidance/ng125 (accessed 29 July 2022)

6. Mitchell DH, Swift G, Gilbert GL. Surgical wound infection surveillance: the importance of infections that develop after hospital discharge. *Aust N Z J Surg* 1999;**69**:117–120
7. Association of Breast Surgery. *Association of Breast Surgery Summary Statement: Antibiotic Prophylaxis in Breast Surgery*. https://associationofbreastsurgery.org.uk/media/64256/final-antibiotic-prophylaxis.pdf (accessed 29 July 2022)
8. National Collaborating Centre for Women's and Children's Health (UK). *Surgical Site Infection: Prevention and Treatment of Surgical Site Infection*. London: RCOG Press, 2008
9. Bunn F, Jones DJ, Bell-Syer S. Prophylactic antibiotics to prevent surgical site infection after breast cancer surgery. *Cochrane Database Syst Rev* 2012:Issue 1. DOI: 10.1002/14651858.CD005360.pub3
10. Gallagher M, Jones DJ, Bell-Syer SV. Prophylactic antibiotics to prevent surgical site infection after breast cancer surgery. *Cochrane Database Syst Rev* 2019;**9**. DOI: 10.1002/14651858:CD005360.pub5
11. NICE. Clostridium difficile *Infection: Risk with Broad Spectrum Antibiotics*. https://www.nice.org.uk/advice/esmpb1/resources/clostridium-difficile-infection-risk-withbroadspectrum-antibiotics-1502609568697285 (accessed 26 July 2022)
12. O'Neill J. *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*. Review on Antimicrobial Resistance 2016
13. World Health Organization. *Antimicrobial Resistance: Global Report on Surveillance*. Geneva: World Health Organization, 2014
14. World Health Organization. *Antibiotic Resistance*. https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance (accessed 29 July 2020)
15. Department of Health. UK 5 Year Antimicrobial Resistance Strategy 2013 to 2018. https://www.gov.uk/government/publications/uk-5-year-antimicrobial-resistance-strategy-2013-to-2018 (accessed 26 July 2022)
16. National Institute for Health and Care Research. Good Clinical Practice (GCP). Available from: https://www.nihr.ac.uk/health-and-care-professionals/learning-and-support/good-clinical-practice.htm (accessed 7 January 2022)
17. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. *Infect Control Hosp Epidemiol* 1999;**20**:247–280
18. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ *et al.* CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *Int J Surg* 2012;**10**:28–55
19. den Heijer CD, van Bijnen EM, Paget WJ, Pringle M, Goossens H, Bruggeman CA *et al.* Prevalence and resistance of commensal *Staphylococcus aureus*, including methicillin-resistant S *aureus*, in nine European countries: a cross-sectional study. *Lancet Infect Dis* 2013;**13**:409–415
20. McEwen SA, Collignon PJ. Antimicrobial resistance: a one health perspective. *Microbiol Spectr* 2018;**6**:1–26
21. O'Connor RI, Kiely PA, Dunne CP. The relationship between post-surgery infection and breast cancer recurrence. *J Hosp Infect* 2020;**106**:522–535
22. Hunt AC, Edwards B, Girvan EK, Cosgrove B, Edwards GFS, Gould IM. Methicillin-resistant *Staphylococcus aureus* in Northeastern Scotland in 2003 to 2007: evolving strain distribution and resistance patterns. *J Clin Microbiol* 2011;**49**:1975–1978
23. Wyllie D, Paul J, Crook D. Waves of trouble: MRSA strain dynamics and assessment of the impact of infection control. *J Antimicrob Chemother* 2011;**66**:2685–8
24. Zhang H, Wang Y, Yang S, Zhang Y. Peri-operative antibiotic prophylaxis does not reduce surgical site infection in breast cancer. *Surg Infect (Larchmt)* 2020;**21**:268–274
25. Jones DJ, Bunn F, Bell-Syer SV. Prophylactic antibiotics to prevent surgical site infection after breast cancer surgery. *Cochrane Database Syst Rev* 2014:Issue 3. DOI: 10.1002/14651858.CD005360.pub4
26. Cunningham M, Bunn F, Handscomb K. Prophylactic antibiotics to prevent surgical site infection after breast cancer surgery. *Cochrane Database Syst Rev* 2005:Issue 1. DOI: 10.1002/14651858.CD005360
27. Amland PF, Andenaes K, Samdal F, Lingaas E, Sandsmark M, Abyholm F *et al.* A prospective, double-blind, placebo-controlled trial of a single dose of azithromycin on postoperative wound infections in plastic surgery. *Plast Reconstr Surg* 1995;**96**:1378–1383
28. Bold RJ, Mansfield PF, Berger DH, Pollock RE, Singletary SE, Ames FC *et al.* Prospective, randomized, double-blind study of prophylactic antibiotics in axillary lymph node dissection. *Am J Surg* 1998;**176**:239–243
29. Cabaluna ND, Uy GB, Galicia RM, Cortez SC, Yray MDS, Buckley BS. A randomized, double-blinded placebo-controlled clinical trial of the routine use of preoperative antibiotic prophylaxis in modified radical mastectomy. *World J Surg* 2013;**37**:59–66
30. Chow LW, Yuen KY, Woo PC, Wei WI. Clarithromycin attenuates mastectomy-induced acute inflammatory response. *Clin Diagn Lab Immunol* 2000;**7**:925–931
31. Gulluoglu BM, Guler SA, Ugurlu MU, Culha G. Efficacy of prophylactic antibiotic administration for breast cancer surgery in overweight or obese patients: a randomized controlled trial. *Ann Surg* 2013;**257**:37–43
32. Gupta R, Sinnett D, Carpenter R, Preece PE, Royle GT. Antibiotic prophylaxis for post-operative wound infection in clean elective breast surgery. *Eur J Surg Oncol* 2000;**26**:363–366
33. Hall JC, Willsher PC, Hall JL. Randomized clinical trial of single-dose antibiotic prophylaxis for non-reconstructive breast surgery. *Br J Surg* 2006;**93**:1342–1346
34. Paajanen H, Hermunen H. Does preoperative core needle biopsy increase surgical site infections in breast cancer surgery? Randomized study of antibiotic prophylaxis. *Surg Infect (Larchmt)* 2009;**10**:317–321
35. Platt R, Zaleznik DF, Hopkins CC, Dellinger EP, Karchmer AW, Bryan CS *et al.* Perioperative antibiotic prophylaxis for herniorrhaphy and breast surgery. *N Engl J Med* 1990;**322**:153–160
36. Wagman LD, Tegtmeier B, Beatty JD, Kloth DD, Kokal WA, Riihimaki DU *et al.* A prospective, randomized double-blind study of the use of antibiotics at the time of mastectomy. *Surg Gynecol Obstet* 1990;**170**:12–16
37. Yetim I, Özkan OV, Dervişoglu A, Erzurumlu K, Canbolant E. Effect of local gentamicin application on healing and wound infection in patients with modified radical mastectomy: a prospective randomized study. *J Int Med Res* 2010;**38**:1442–1447
38. Pastoriza J, McNelis J, Parsikia A, Lewis E, Ward M, Marini CP *et al.* Predictive factors for surgical site infections in patients undergoing surgery for breast carcinoma. *Am Surg* 2020:3134820949996
39. Olsen MA, Lefta M, Dietz JR, Brandt KE, Aft R, Matthews R *et al.* Risk factors for surgical site infection after major breast operation. *J Am Coll Surg* 2008;**207**:326–335
40. Ban KA, Minei JP, Laronga C, Harbrecht BG, Jensen EH, Fry DE *et al.* Executive Summary of the American College of Surgeons/

Surgical Infection Society Surgical Site Infection Guidelines – 2016 Update. *Surg Infect (Larchmt)* 2017;**18**:379–382
41. Greif R, Akça O, Horn E-P, Kurz A, Sessler DI. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. *N Engl J Med* 2000;**342**:161–167
42. McSorley ST, Horgan PG, McMillan DC. The impact of the type and severity of postoperative complications on long-term outcomes following surgery for colorectal cancer: a systematic review and meta-analysis. *Crit Rev Oncol Hematol* 2016;**97**:168–177
43. Savioli F, Edwards J, McMillan D, Stallard S, Doughty J, Romics L. The effect of postoperative complications on survival and recurrence after surgery for breast cancer: a systematic review and meta-analysis. *Crit Rev Oncol Hematol* 2020;**155**: 103075
44. Mansell J, Weiler-Mithoff E, Stallard S, Doughty JC, Mallon E, Romics L. Oncoplastic breast conservation surgery is oncologically safe when compared to wide local excision and mastectomy. *Breast* 2017;**32**:179–185