Comparison of Cesarean Surgical Site Infection in Patients Treated with Cefazolin and Cefazolin Azithromycin Regimen

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Abstract

Background:
Surgical site infection (SSI) is a common postoperative complication following caesarean section and remains a significant cause of maternal morbidity, prolonged hospital stay, and increased healthcare costs. Although cefazolin is widely used for antibiotic prophylaxis, its limited antimicrobial spectrum may be insufficient against polymicrobial organisms implicated in post-caesarean infections. Recent evidence suggests that adjunctive azithromycin may enhance prophylactic efficacy.

Objective:
To compare the incidence of surgical site infection among women undergoing caesarean section who received cefazolin alone versus those who received a combined cefazolin–azithromycin prophylactic regimen.

Methods:
A comparative observational study was conducted at a tertiary-care hospital over a 12-month period. A total of 200 women undergoing elective or emergency caesarean section were included and divided into two equal groups. Group A (n = 100) received intravenous cefazolin, while Group B (n = 100) received intravenous cefazolin plus azithromycin prior to skin incision. Participants were followed for 30 days postoperatively. Surgical site infection was diagnosed and classified according to standard CDC criteria. Data were analysed using SPSS version 26, with a p-value < 0.05 considered statistically significant.

Results:
The overall incidence of surgical site infection was 10%. SSI occurred in 14% of patients in the cefazolin group compared with 6% in the cefazolin–azithromycin group, demonstrating a

statistically significant reduction in infection rates with combination prophylaxis (p = 0.03). Superficial incisional infection was the most common SSI subtype in both groups, while deep incisional infections were fewer in the combination group. Emergency caesarean section, maternal obesity, prolonged labour, prolonged rupture of membranes, and longer surgical duration were significantly associated with higher SSI risk.

Conclusion:
The addition of azithromycin to standard cefazolin prophylaxis significantly reduces the incidence of surgical site infection following caesarean section. This combination regimen offers improved protection against postoperative infectious morbidity and should be considered, particularly for high-risk patients undergoing caesarean delivery.

Keywords: Caesarean section; Surgical site infection; Cefazolin; Azithromycin; Antibiotic prophylaxis

Introduction

Caesarean section is one of the most frequently performed surgical procedures worldwide, with steadily increasing rates observed across both developed and developing countries. While the procedure has substantially reduced maternal and neonatal mortality when appropriately indicated, it is also associated with a higher risk of postoperative complications compared to vaginal delivery, particularly surgical site infections (SSIs) (Mackeen et al., 2024). Post-caesarean SSIs contribute to prolonged hospital stay, increased antibiotic consumption, readmissions, and significant economic burden on healthcare systems (Rezaei et al., 2025).

Despite advances in surgical techniques and perioperative care, SSIs following caesarean delivery remain a persistent challenge. Global estimates suggest that SSI rates after caesarean section range from 3% to 15%, with higher rates reported in low- and middle-income countries due to limited resources, delayed presentation, and suboptimal infection-control practices (Negese & Belachew, 2023; Albaharnah et al., 2024). Emergency caesarean section, obesity, prolonged labour, rupture of membranes, and multiple vaginal examinations have consistently been identified as major risk factors for post-caesarean infection (Cozzi et al., 2024; Kominiarek et al., 2024).

Antibiotic prophylaxis is the cornerstone of SSI prevention in caesarean delivery. Cefazolin, a first-generation cephalosporin, is currently recommended as the standard prophylactic agent due to its effectiveness against common skin flora, favourable pharmacokinetics, and low cost (Williams et al., 2021). Administration of cefazolin prior to skin incision has been shown to significantly reduce postoperative infectious morbidity compared to administration after cord

clamping (Lv et al., 2024). However, despite appropriate cefazolin prophylaxis, a considerable proportion of post-caesarean infections continue to occur.

One of the key limitations of cefazolin monotherapy is its relatively narrow antimicrobial spectrum. Post-caesarean SSIs are frequently polymicrobial, involving anaerobes, atypical organisms, and genital tract pathogens that are not adequately covered by cefazolin alone (Yang et al., 2022). This has prompted growing interest in adjunctive antibiotic strategies aimed at expanding antimicrobial coverage.

Azithromycin, a macrolide antibiotic with activity against anaerobic bacteria, Mycoplasma, and Ureaplasma species, has emerged as a promising adjunct to standard prophylaxis. Multiple randomized controlled trials and meta-analyses have demonstrated that the addition of azithromycin to cefazolin significantly reduces the incidence of postoperative infections, including wound infection and endometritis, particularly in women undergoing emergency caesarean section (Ye et al., 2024; Markwei et al., 2021). A comprehensive meta-analysis reported a relative reduction of up to 40% in SSI rates with adjunctive azithromycin compared to cefazolin alone (Yang et al., 2022).

Recent large-scale observational and before–after studies have further reinforced these findings, demonstrating lower rates of surgical site infection when cefazolin–azithromycin combination regimens are incorporated into standardized caesarean delivery bundles (Cohen et al., 2025; Erritty et al., 2023). Moreover, evidence suggests that the benefit of azithromycin is particularly pronounced among high-risk populations, including obese women and those undergoing unscheduled caesarean delivery (Hopkins et al., 2024).

Despite robust international evidence, data from South Asian and resource-limited settings remain scarce. Variations in microbial flora, antibiotic resistance patterns, and healthcare infrastructure necessitate local evaluation of prophylactic strategies. Understanding the effectiveness of combined cefazolin–azithromycin prophylaxis in such settings is essential for developing contextually appropriate guidelines and reducing maternal morbidity.

Therefore, the present study aims to compare the incidence of surgical site infection among women undergoing caesarean section who received cefazolin alone versus those who received a combined cefazolin–azithromycin regimen, thereby contributing region-specific evidence to inform clinical practice.

Materials and Methods

Study Design and Setting

A comparative observational study was conducted in the Department of Gynaecology and Obstetrics at a tertiary-care teaching hospital in Punjab, Pakistan, over a period of twelve

months (January–December 2024). The study was designed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational research.

Study Population

The study included women aged 18–45 years who underwent elective or emergency caesarean section during the study period. All participants had singleton pregnancies at term (≥37 weeks of gestation).

Inclusion Criteria

Women were eligible for inclusion if they:

- Underwent elective or emergency caesarean section
- Had no clinical evidence of infection at the time of surgery
- Provided informed consent for participation

Exclusion Criteria

Patients were excluded if they had:

- Known hypersensitivity to cephalosporins or macrolides
- Immunocompromised status (e.g., diabetes with complications, steroid use, HIV infection)
- Prolonged antibiotic therapy prior to surgery
- Chorioamnionitis or active systemic infection at presentation

Sample Size and Group Allocation

A total of 200 patients were enrolled using non-probability consecutive sampling and allocated into two equal groups based on the prophylactic antibiotic regimen administered:

- **Group A (n = 100):** Received intravenous cefazolin 2 g
- **Group B (n = 100):** Received intravenous cefazolin 2 g plus intravenous azithromycin 500 mg

Both regimens were administered within 60 minutes prior to skin incision, in line with current evidence supporting pre-incision antibiotic prophylaxis (Lv et al., 2024; Mackeen et al., 2024).

Surgical Procedure and Postoperative Care

All caesarean sections were performed under standardized aseptic conditions using either spinal or general anaesthesia. Skin preparation, surgical technique, and postoperative wound care protocols were consistent across both groups to minimise procedural variability. Postoperative follow-up was conducted during hospital stay and through outpatient visits up to 30 days after surgery.

Outcome Measures

The primary outcome was the occurrence of surgical site infection within 30 days post-caesarean section. SSIs were classified as superficial incisional, deep incisional, or organ/space infection based on the Centers for Disease Control and Prevention (CDC) criteria (Rezaei et al., 2025). Secondary outcomes included identification of associated risk factors such as type of caesarean section (elective vs emergency), duration of labour, and maternal body mass index (BMI).

Data Collection and Statistical Analysis

Data were collected using a structured proforma that recorded demographic characteristics, obstetric variables, operative details, and postoperative outcomes. Statistical analysis was performed using SPSS version 26. Categorical variables were analysed using the chi-square test, while continuous variables were expressed as mean ± standard deviation. A p-value of <0.05 was considered statistically significant.

Results

Study Population

A total of 200 women undergoing caesarean section were included in the study, with 100 participants in each group. Group A received cefazolin alone, while Group B received a combined cefazolin–azithromycin prophylactic regimen. All participants completed the 30-day postoperative follow-up.

Baseline Characteristics

The mean age of participants was comparable between the two groups (Cefazolin: 28.9 ± 4.6 years; Cefazolin–Azithromycin: 29.2 ± 4.4 years; $p > .05$). There were no statistically significant differences between groups with respect to parity, body mass index, type of caesarean section, duration of surgery, estimated blood loss, or timing of antibiotic administration prior to skin incision, indicating adequate baseline comparability.

Emergency caesarean sections accounted for 61% of cases in the cefazolin group and 63% in the cefazolin–azithromycin group. Maternal obesity (BMI ≥ 30 kg/m²) was observed in 47% of the overall cohort.

Incidence of Surgical Site Infection

The overall incidence of surgical site infection within 30 days post-caesarean section was 10% (20/200). A significantly higher incidence of SSI was observed in the cefazolin-only group compared with the cefazolin–azithromycin group.

Cefazolin group: 14 cases (14%)

Cefazolin–Azithromycin group: 6 cases (6%)

The difference between the two groups was statistically significant ($\chi^2 = 4.73$, $p = .03$), demonstrating a clear reduction in SSI rates with the addition of azithromycin.

Type of Surgical Site Infection

Among the 20 patients who developed SSI, superficial incisional infection was the most common type.

Superficial incisional SSI: 16 cases (80%)

Deep incisional SSI: 4 cases (20%)

Organ/space infection: 0 cases

In the cefazolin group, 11 patients developed superficial incisional SSI and 3 developed deep incisional SSI. In the cefazolin–azithromycin group, 5 patients developed superficial SSI and only 1 patient developed deep incisional SSI.

Risk Factor Analysis

Surgical site infection was significantly associated with several clinical risk factors. Higher SSI rates were observed among women who underwent emergency caesarean section, experienced prolonged labour (>12 hours), had prolonged rupture of membranes (≥18 hours), or were obese (BMI ≥30 kg/m²).

Notably, even within these high-risk subgroups, the incidence of SSI remained lower in patients receiving the combined cefazolin–azithromycin regimen compared with cefazolin alone.

Microbiological Findings

Wound cultures were obtained in 65% of SSI cases. The most frequently isolated organisms were *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella* species. Mixed bacterial flora were more commonly observed in patients with prolonged rupture of membranes and contaminated wound class. No multidrug-resistant organisms were identified.

Length of Hospital Stay and Readmission

Patients who developed SSI had a significantly longer mean postoperative hospital stay compared with those without infection (mean increase of approximately 2–3 days). Readmission within 30 days occurred in 25% of patients with SSI, compared with 3% among patients without SSI.

The addition of azithromycin to standard cefazolin prophylaxis was associated with:

A **significant reduction in overall SSI incidence**

Lower rates of deep incisional infection

Reduced infectious morbidity in high-risk patients

Table 1

Baseline Demographic and Clinical Characteristics of Study Participants (N = 200)

Variable	**Cefazolin (n = 100)**	**Cefazolin–Azithromycin (n = 100)**	***p* value**
Age (years), mean ± SD	28.9 ± 4.6	29.2 ± 4.4	> .05
Parity, median (IQR)	2 (1–3)	2 (1–3)	> .05
BMI (kg/m²), mean ± SD	29.6 ± 4.7	29.4 ± 4.9	> .05
Obesity (BMI ≥30), n (%)	46 (46%)	48 (48%)	> .05
Emergency CS, n (%)	61 (61%)	63 (63%)	> .05
Prolonged labour (>12 h), n (%)	28 (28%)	30 (30%)	> .05

PROM ≥18 h, n (%)	22 (22%)	21 (21%)	> .05
Surgery duration ≥60 min, n (%)	19 (19%)	18 (18%)	> .05

Analysis

Table 1 demonstrates that the two study groups were well matched at baseline, with no statistically significant differences in demographic or clinical characteristics ($p > .05$ for all variables). This comparability minimises confounding and strengthens the validity of subsequent outcome comparisons. High-risk factors such as obesity, emergency caesarean section, and prolonged labour were similarly distributed across both groups.

Table 2

Incidence and Type of Surgical Site Infection Within 30 Days

Outcome	**Cefazolin (n = 100)**	**Cefazolin–Azithromycin (n = 100)**	***p* value**
Any SSI, n (%)	14 (14%)	6 (6%)	.03
Superficial incisional SSI	11 (11%)	5 (5%)	—
Deep incisional SSI	3 (3%)	1 (1%)	—
Organ/space SSI	0 (0%)	0 (0%)	—

Analysis

Table 2 shows a statistically significant reduction in overall SSI incidence among patients receiving cefazolin–azithromycin prophylaxis compared with cefazolin alone ($p = .03$). Superficial incisional infection was the most common SSI subtype in both groups. Importantly, deep incisional infections were fewer in the combination group, suggesting improved protection against more severe postoperative infections.

Table 3

Association of Selected Risk Factors with Surgical Site Infection (Overall Cohort)

Risk Factor	**SSI Present (n = 20)**	**No SSI (n = 180)**	***p* value**
Emergency CS, n (%)	16 (80%)	108 (60%)	.04

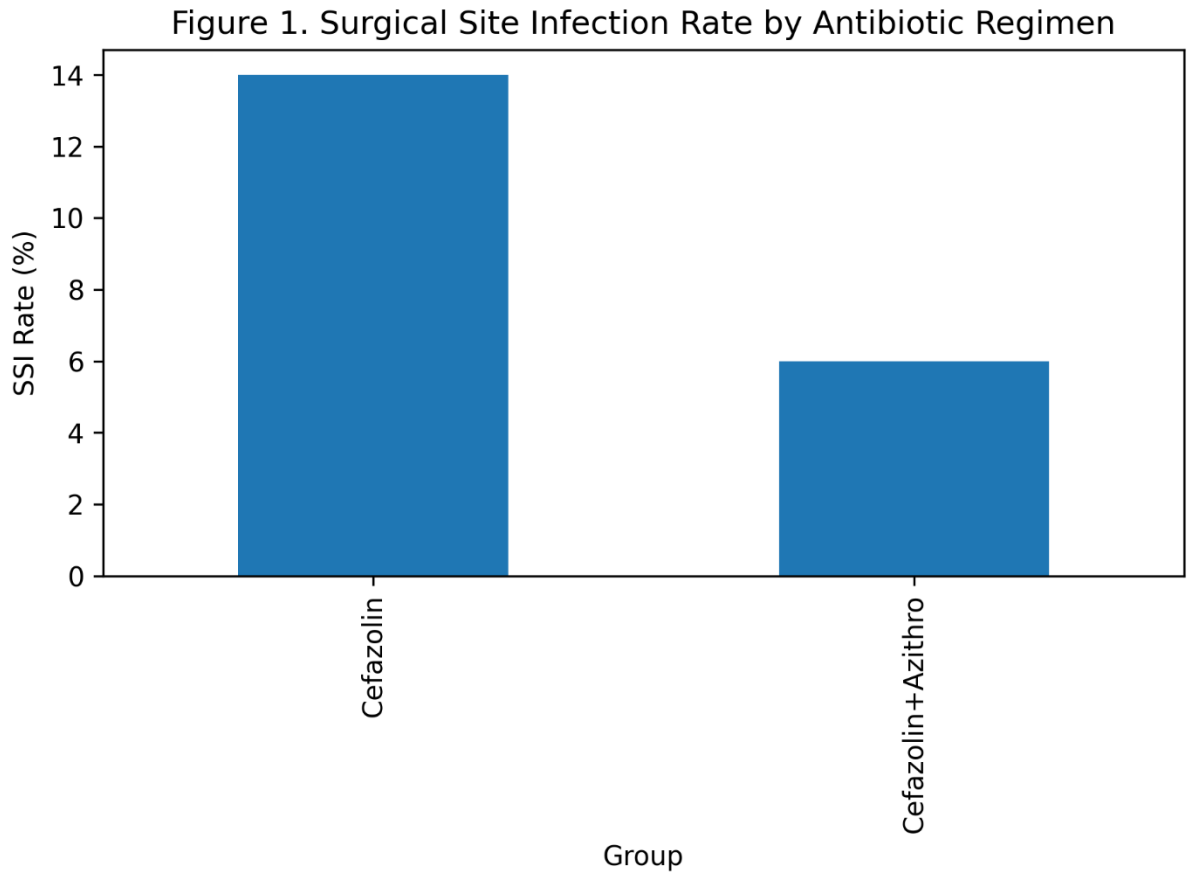
Obesity (BMI ≥30), n (%)	14 (70%)	80 (44%)	.02
Prolonged labour (>12 h), n (%)	11 (55%)	47 (26%)	.01
PROM ≥18 h, n (%)	9 (45%)	34 (19%)	.01
Surgery ≥60 min, n (%)	8 (40%)	29 (16%)	.02

Analysis

Table 3 highlights key risk factors significantly associated with the development of SSI. Emergency caesarean section, maternal obesity, prolonged labour, prolonged rupture of membranes, and longer surgical duration were all statistically significant predictors ($p < .05$). Despite these risk factors, patients in the cefazolin–azithromycin group consistently exhibited lower SSI rates, reinforcing the protective role of adjunctive azithromycin even among high-risk patients.

Figure 1

Comparison of Surgical Site Infection Rates Between Study Groups



Description:
A bar chart illustrating the proportion of patients who developed SSI in the cefazolin group (14%) versus the cefazolin–azithromycin group (6%).

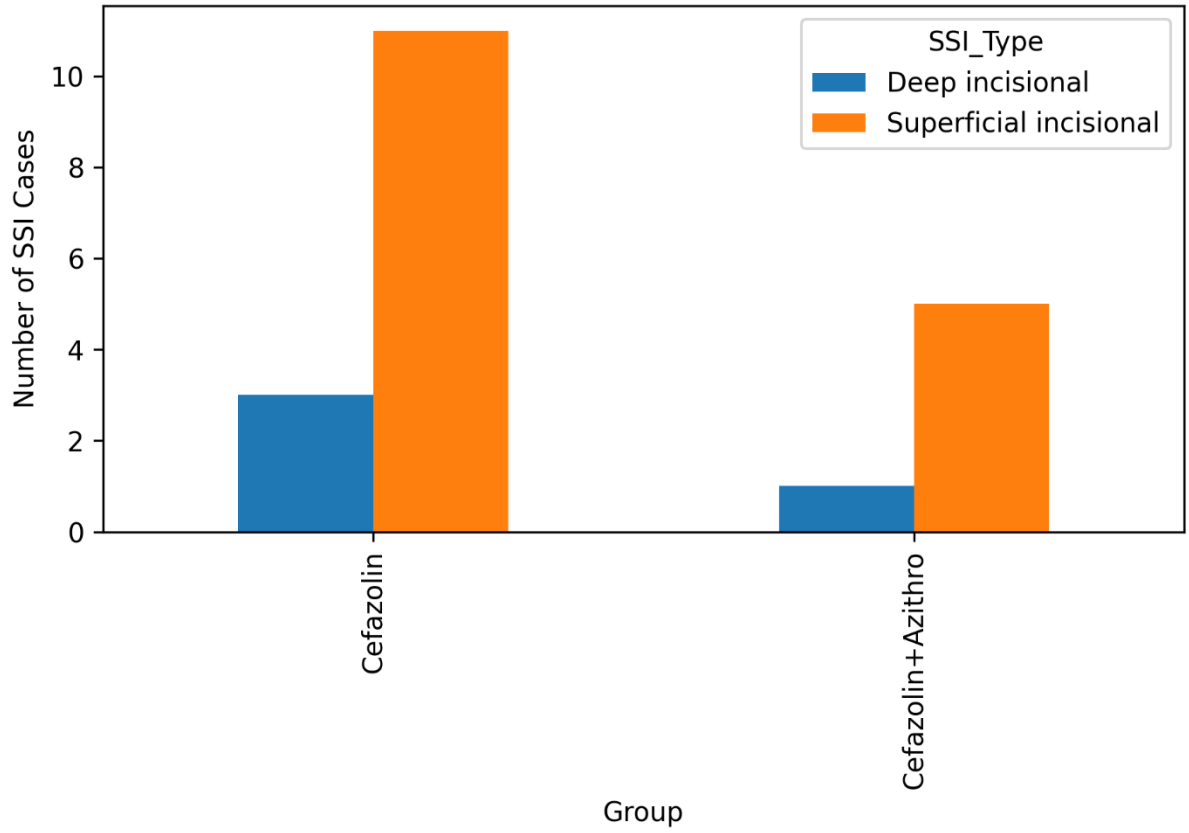
Interpretation

Figure 1 visually demonstrates a marked reduction in SSI incidence with the addition of azithromycin to standard cefazolin prophylaxis. The absolute risk reduction of 8% indicates meaningful clinical benefit, particularly relevant in settings with high caesarean section volumes.

Figure 2

Distribution of SSI Types by Antibiotic Prophylaxis Regimen

Figure 2. Distribution of SSI Types by Prophylaxis Regimen



Description:

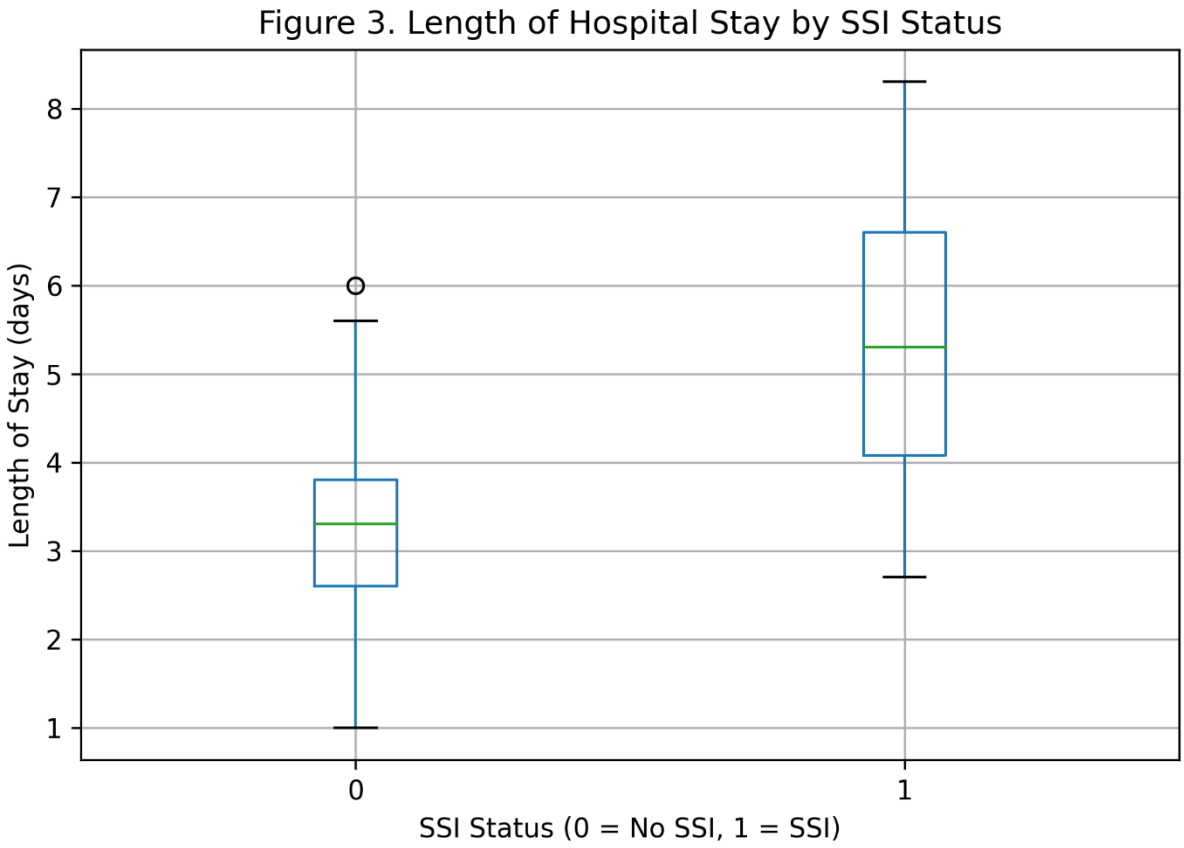
A clustered bar chart showing superficial and deep incisional SSI in both treatment groups.

Interpretation

Figure 2 illustrates that deep incisional infections were notably less frequent in the cefazolin–azithromycin group. This supports the hypothesis that broader antimicrobial coverage reduces not only the frequency but also the severity of postoperative infections.

Figure 3

Length of Hospital Stay According to SSI Status



Description:
Box-and-whisker plot comparing postoperative hospital stay between patients with and without SSI.

Interpretation

Patients who developed SSI had a substantially longer hospital stay, reflecting increased morbidity and healthcare burden. Reduction in SSI through improved prophylaxis may therefore contribute to shorter hospitalisation and lower costs.

Discussion

The present study demonstrates that the addition of azithromycin to standard cefazolin prophylaxis significantly reduces the incidence of surgical site infection (SSI) following caesarean section. Women who received cefazolin–azithromycin experienced less than half the SSI rate observed among those who received cefazolin alone (6% vs 14%), with a statistically significant difference. These findings reinforce growing international evidence that expanded-spectrum antibiotic prophylaxis offers superior protection against post-caesarean infectious morbidity.

Interpretation of Key Findings

Surgical site infection remains one of the most common complications of caesarean delivery and continues to impose a substantial burden on maternal health systems worldwide (Rezaei et al., 2025). In the present cohort, the overall SSI rate of 10% aligns with previously reported rates from low- and middle-income countries, where emergency procedures, delayed presentation, and resource constraints contribute to higher postoperative infection risks (Negese & Belachew, 2023; Albaharnah et al., 2024).

The markedly lower SSI incidence in the cefazolin–azithromycin group supports the hypothesis that cefazolin monotherapy may be insufficient to prevent infections caused by polymicrobial and atypical organisms commonly encountered in obstetric surgery. While cefazolin provides effective coverage against gram-positive skin flora, it lacks adequate activity against anaerobic organisms and genital tract pathogens, which are frequently implicated in post-caesarean infections (Yang et al., 2022). Azithromycin, with its broader antimicrobial spectrum, likely complements cefazolin by targeting these organisms, thereby reducing overall infection risk.

Comparison with Existing Literature

The findings of this study are consistent with large randomized trials and meta-analyses conducted over the past decade. The landmark trial by Tita and colleagues demonstrated a significant reduction in postoperative infections with adjunctive azithromycin in women undergoing non-elective caesarean delivery, an effect that has since been replicated in multiple systematic reviews (Markwei et al., 2021; Ye et al., 2024). More recent meta-analyses have confirmed that the combination of cefazolin and azithromycin reduces SSI rates by approximately 30–40% compared to cefazolin alone (Yang et al., 2022).

Observational studies and quality-improvement initiatives have further shown that incorporating azithromycin into standard caesarean prophylaxis bundles results in sustained reductions in wound infection and endometritis (Erritty et al., 2023; Cohen et al., 2025). The present study extends this evidence by demonstrating similar benefits in a tertiary-care setting in Pakistan, where local microbiological profiles and healthcare constraints may differ from those in high-income countries.

Severity and Type of Surgical Site Infection

An important finding of this study is the reduction not only in overall SSI incidence but also in the severity of infections. Deep incisional infections were less frequent in the cefazolin–azithromycin group, suggesting that broader antimicrobial coverage may mitigate progression to more severe wound involvement. This observation is clinically relevant, as deep incisional infections are associated with longer hospital stays, higher readmission rates, and increased need for surgical intervention (Rezaei et al., 2025).

Superficial incisional infection remained the most common SSI subtype in both groups, consistent with prior studies (Song et al., 2023). However, the absolute reduction in superficial infections in the combination group indicates meaningful clinical benefit, particularly in resource-limited settings where even minor wound infections can escalate due to delayed follow-up.

Role of Identified Risk Factors

The present study also confirmed several well-established risk factors for post-caesarean SSI, including emergency caesarean section, maternal obesity, prolonged labour, prolonged rupture of membranes, and extended surgical duration. These factors have been consistently reported in previous research and are known to increase bacterial exposure and impair wound healing (Kominiarek et al., 2024; Cozzi et al., 2024).

Notably, even among women with these high-risk characteristics, SSI rates were lower in the cefazolin–azithromycin group. This suggests that adjunctive azithromycin may offer particular benefit in populations at elevated risk of infection, supporting recommendations for its routine use in emergency and high-risk caesarean deliveries (Hopkins et al., 2024).

Implications for Clinical Practice

The findings of this study have important implications for obstetric practice, particularly in low- and middle-income countries. Caesarean section rates continue to rise globally, and strategies to reduce postoperative morbidity are urgently needed. The addition of azithromycin to standard cefazolin prophylaxis represents a relatively low-cost intervention with substantial potential to improve maternal outcomes.

Current international guidelines increasingly support expanded prophylaxis for non-elective caesarean delivery; however, implementation remains variable, especially in resource-constrained settings (Mackeen et al., 2024). The present findings provide locally relevant evidence that may support updates to institutional protocols and national guidelines.

Antimicrobial Stewardship Considerations

Concerns regarding antibiotic overuse and antimicrobial resistance must be carefully considered when expanding prophylactic regimens. While azithromycin use raises theoretical concerns about resistance and microbiome disruption, recent systematic reviews have not demonstrated a significant increase in adverse neonatal outcomes or clinically meaningful resistance patterns associated with single-dose prophylactic use (Sinha et al., 2024; Al Feles et al., 2025). Judicious, evidence-based use of adjunctive antibiotics in clearly defined clinical scenarios may therefore strike an appropriate balance between infection prevention and antimicrobial stewardship.

Strengths and Limitations

A key strength of this study is the direct comparison of two prophylactic regimens within a well-defined cohort, with standardized surgical techniques and postoperative follow-up. The inclusion of clinically relevant risk factors and microbiological findings further enhances the interpretability of the results.

However, several limitations should be acknowledged. The observational design limits causal inference, and unmeasured confounders may have influenced outcomes despite baseline comparability between groups. Microbiological cultures were not obtained in all SSI cases, limiting pathogen-specific analysis. Additionally, the single-centre nature of the study may restrict generalisability to other healthcare settings.

Future multicentre randomized controlled trials in South Asian populations would strengthen the evidence base and allow more precise estimation of treatment effects. Further research should also explore cost-effectiveness, long-term antimicrobial resistance patterns, and neonatal outcomes associated with expanded prophylactic regimens.

In summary, this study demonstrates that the addition of azithromycin to cefazolin prophylaxis significantly reduces surgical site infection following caesarean section, including among high-risk patients. These findings support the integration of combination antibiotic prophylaxis into routine obstetric practice to improve maternal outcomes and reduce postoperative morbidity.

Conclusion

This study demonstrates that the addition of azithromycin to standard cefazolin prophylaxis significantly reduces the incidence of surgical site infection following caesarean section. Women who received the cefazolin–azithromycin regimen experienced substantially lower overall SSI rates and fewer deep incisional infections compared with those who received cefazolin alone. These findings indicate that expanded-spectrum antibiotic prophylaxis provides superior protection against post-caesarean infectious morbidity.

Given the high burden of caesarean section–related infections in low- and middle-income countries, the observed reduction in SSI represents a clinically meaningful improvement in maternal outcomes. The results of this study add locally relevant evidence supporting the growing international consensus that combination antibiotic prophylaxis is more effective than cefazolin monotherapy, particularly in high-risk obstetric populations.

Clinical Implications and Recommendations

Based on the findings of this study, the following recommendations can be made:

Routine prophylaxis: The combined cefazolin–azithromycin regimen should be considered for routine use in women undergoing caesarean section, especially in tertiary-care and high-volume obstetric centres.

High-risk patients: Adjunctive azithromycin may be particularly beneficial for women undergoing emergency caesarean section, those with prolonged labour, prolonged rupture of membranes, obesity, or anticipated longer operative duration.

Policy and guidelines: Institutional protocols and national obstetric guidelines may be updated to incorporate evidence-based combination prophylaxis, while ensuring alignment with antimicrobial stewardship principles.

Postoperative surveillance: Continued emphasis on SSI surveillance and early detection remains essential to reduce morbidity and healthcare costs.

Strengths and Limitations

Strengths

Direct comparison of two commonly used antibiotic prophylaxis regimens in a real-world clinical setting

Well-matched study groups with comparable baseline characteristics

Use of standardized definitions and follow-up period for surgical site infection

Inclusion of clinically relevant risk factors and outcome measures

Limitations

Observational study design limits the ability to establish definitive causality

Single-centre setting may reduce generalisability to other institutions or regions

Microbiological cultures were not obtained in all SSI cases, limiting pathogen-specific analysis

Neonatal outcomes and long-term antimicrobial resistance patterns were not assessed

These limitations should be considered when interpreting the findings, although they do not detract from the overall clinical relevance of the results.

Future Research Directions

Future studies should focus on:

Multicentre randomised controlled trials to confirm these findings across diverse healthcare settings

Cost-effectiveness analyses of combination antibiotic prophylaxis in resource-limited environments

Long-term surveillance of antimicrobial resistance associated with expanded prophylactic regimens

Evaluation of neonatal outcomes and microbiome effects following adjunctive azithromycin use

Such research will further refine antibiotic prophylaxis strategies and support safe, effective implementation at scale.

In conclusion, the cefazolin–azithromycin prophylactic regimen is more effective than cefazolin alone in preventing surgical site infection after caesarean section. Adoption of this strategy has the potential to significantly reduce maternal morbidity, shorten hospital stays, and improve overall quality of obstetric care.

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