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Antimicrobial stewardship in tertiary care: A pharmacist-led bundle to reduce broad-spectrum use and C. *difficile* rates

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Abstract

Background: Broad-spectrum antimicrobial overuse in tertiary hospitals drives antimicrobial resistance and increases *Clostridioides difficile* infection (CDI). Evidence supports pharmacist-led stewardship, but real-world, risk-adjusted impacts tied to the Standardized Antimicrobial Administration Ratio (SAAR) remain important to quantify.

Objective: To evaluate whether a pharmacist-led stewardship bundle reduces broad-spectrum use and hospital-onset CDI without compromising safety.

Design and Setting: Quasi-experimental interrupted time-series study in a 1,000-bed tertiary-care academic hospital, comparing 12 pre-intervention months with 12 post-implementation months.

Participants: All adult inpatients across medical-surgical wards and mixed ICUs.

Intervention: A pharmacist-led bundle comprising daily prospective audit-and-feedback prioritized to "Watch/Reserve" agents, indication-linked preauthorization for fluoroquinolones and antipseudomonal β-lactams, mandatory 48-72 h "time-outs," IV-to-PO conversion criteria, and syndrome-specific order sets with transparent unit-level dashboards.

Main Outcomes and Measures: Primary broad-spectrum SAAR (adult inpatient, hospital-onset indications) and broad-spectrum days of therapy (DOT) per 1,000 patient-days. Secondary—hospital-onset CDI incidence per 10,000 patient-days, time-to-effective therapy, time-to-narrowing, IV-to-PO conversion, and safety (in-hospital mortality, 30-day readmission).

Results: Mean SAAR declined from 1.274 pre-intervention to 1.015 post-intervention (relative change −20.3%). [REVISION: values aligned to Table 1] Broad-spectrum DOT fell from 620.6 to 499.7 per 1,000 patient-days (−19.5%). [REVISION: values aligned to Table 1] Hospital-onset CDI decreased with an incidence rate ratio of 0.65 (95% CI, 0.55-0.76). [REVISION: values aligned to Table 1] Process fidelity improved during the intervention: pharmacist audit-and-feedback encounters increased (>520/month by study end), recommendation acceptance rose to ≈85%, IV-to-PO conversion reached ≈56%, and 48-72 h time-out completion approached ≈88%. No increase occurred in in-hospital mortality or 30-day readmission.

Conclusions: A pharmacist-led, SAAR-guided stewardship bundle produced rapid and durable reductions in broad-spectrum antibiotic exposure and hospital-onset CDI in a complex tertiary setting without safety trade-offs. Embedding 48-72 h reassessment, targeted preauthorization, dialogue-based audit-and-feedback, and standardized order sets coupled with transparent feedback dashboards—offers a scalable pathway for hospitals seeking concurrent reductions in antimicrobial use and CDI burden.

Keywords: Antimicrobial stewardship, pharmacist-led interventions, standardized antimicrobial administration ratio (SAAR)

Introduction

Antimicrobial resistance (AMR) remains one of the defining patient-safety threats in modern health care, with national and international agencies urging hospitals to deploy robust antimicrobial stewardship programs (ASPs) to preserve antibiotic effectiveness while preventing avoidable harms such as *Clostridioides difficile* infection (CDI) [1-3]. Global estimates attribute ~4.95 million deaths in 2019 to bacterial AMR (associated), including 1.27 million directly attributable deaths, underscoring the clinical and economic imperative for stewardship beyond guideline compliance alone [3,4]. The WHO GLASS platform and successive reports document persistently high resistance across priority Gram-negative pathogens and heterogeneous antibiotic use (AMU) between regions and income settings patterns that concentrate risk in tertiary facilities where broad-spectrum agents are commonly deployed for severe sepsis, febrile neutropenia, and post-operative infections [5, 6]. In the United States and many countries, the CDC's Core Elements have matured from a "what to build" framework (leadership, accountability, pharmacy expertise, action, tracking, reporting, education) into measurable performance systems linked to the NHSN Antimicrobial Use & Resistance (AUR) Module and the Standardized Antimicrobial Administration Ratio (SAAR), enabling risk-adjusted benchmarking of broad-spectrum exposure and targeted feedback to prescribers [7-13, 31, 32]. While Cochrane and multiple narrative syntheses affirm that ASPs reduce unnecessary antibiotic exposure without excess mortality [14, 15], implementation research consistently shows that pharmacist-led bundles combining prospective audit-and-feedback (PAF), preauthorization, IV-to-PO switch, dose optimization, time-outs at 48-72 hours, and disease-specific order sets deliver the largest and most sustainable declines in broad-spectrum days of therapy (DOT) and associated CDI rates in real-world hospitals [8, 13, 15-19]. United Kingdom experience with "Start Smart Then Focus" (review at 48-72 h to stop, switch, narrow, or document) offers a mature blueprint for tertiary care: the national toolkit operationalizes multidisciplinary review cycles, local guidelines, audit loops, and CDI-linked triggers, and its adoption across English NHS trusts has correlated with reduced broad-spectrum consumption and lower CDI burden [20-22]. Parallel evidence from U.S. and European centers links fluoroquinolone and high-risk cephalosporin restriction to meaningful CDI reductions, illustrating how a bundle anchored in pharmacist PAF plus targeted restriction of "Watch/Reserve" agents can shift the epidemiology of CDI and ribotypes within a few quarters [23-26, 29]. Recent multicenter analyses and systematic reviews further quantify ASP impact: ASP implementation is associated with ~19% lower total antibiotic use and ~27% reductions in restricted agents, while pharmacist-led interventions specifically shorten unnecessary durations and do so safely, without increasing mortality or readmissions [18, 16,17]. Despite this progress, tertiary hospitals still face persistent overuse of broad-spectrum carbapenems, piperacillin-tazobactam, and fluoroquinolones, variable adoption of SAAR-informed dashboards, and gaps translating CDI treatment guidance (e.g., early fidaxomicin use; bezlotoxumab in high-risk cases) into upstream stewardship decisions that prevent *de novo* CDI [7-13, 27]. Against this backdrop, the present study addresses the following problem: in a high-acuity tertiary-care setting with established but variably adhered-to stewardship practices, broad-spectrum antimicrobial use remains above predicted (SAAR >1.0) and health-care-associated CDI rates exceed internal benchmarks, reflecting missed opportunities to de-escalate, shorten courses, and avoid high-risk agents when clinically appropriate [3, 10-13, 20-26, 31]. Building on international frameworks and high-quality hospital studies, we will evaluate a pharmacist-led antimicrobial stewardship bundle co-designed with infectious diseases (ID) and infection prevention teams and explicitly tied to SAAR targets and CDI outcomes. The bundle will include (i) pharmacist-ID daily prospective audit and feedback prioritized to "Watch/Reserve" AWaRe classes; (ii) indication-linked preauthorization for fluoroquinolones and anti-pseudomonal β-lactams; (iii) mandatory 48-72 h "Focus" reviews to stop/narrow/IV-to-PO; (iv) syndrome-specific order sets aligned to IDSA/SHEA CDI guidance and local antibiograms; and (v) transparent unit-level SAAR dashboards with monthly feedback to clinical leads [7-13, 20-22, 27, 30-32]. The primary objective is to determine whether the pharmacist-led bundle reduces broad-spectrum antimicrobial use (adult inpatient SAAR for broad-spectrum agents for hospital-onset infections; secondary metric: DOT/1000 patient-days) over 12 months compared with the pre-intervention period; secondary objectives are to assess changes in hospital-onset CDI incidence density, time to effective/narrow therapy, guideline-concordant durations, and safety signals (mortality, ICU transfer, *Pseudomonas* and *Enterobacterales* resistance trends) [8, 10-13, 15-19, 23-26, 28-32]. We hypothesize that (H1) the pharmacist-led stewardship bundle will achieve a ≥10-15% relative reduction in the broad-spectrum SAAR (observed/predicted) at 12 months versus baseline; (H2) hospital-onset CDI rates will decline by ≥20% in parallel with reduced exposure to high-risk agents (notably fluoroquinolones and third-generation cephalosporins), consistent with prior restriction and bundle studies; and (H3) these improvements will occur without increases in all-cause in-hospital mortality or 30-day readmission, aligning with prior systematic reviews of pharmacist-led PAF and preauthorization [16-19, 23-26, 28-29]. By pairing pharmacist-driven daily workflows with SAAR-based targeting and feedback in a tertiary-care context, this study aims to close the evidence-to-implementation gap highlighted by recent global surveillance and guidance, offering a scalable model for hospitals seeking simultaneous reductions in broad-spectrum antibiotic exposure and CDI burden [1-13, 20-22, 27, 30-33].

Material and Methods

Material

This quasi-experimental quality-improvement study was undertaken in a 1,000-bed tertiary-care academic hospital comprising medical, surgical, cardiothoracic, oncology, transplant, and mixed adult ICUs, where persistently high broad-spectrum antibiotic exposure and healthcare-associated *Clostridioides difficile* infection (CDI) rates had been documented in the setting of global antimicrobial resistance (AMR) pressures and heterogeneous antimicrobial use (AMU) patterns [1-6,33]. The existing stewardship infrastructure followed the CDC Core Elements (leadership commitment, accountability, pharmacy expertise, action, tracking, reporting, education), with an established Antimicrobial Use (AU) reporting connection to the National Healthcare Safety Network (NHSN) and the Standardized Antimicrobial Administration Ratio (SAAR) for risk-adjusted benchmarking [7-13,31,32]. The intervention was a pharmacist-led antimicrobial stewardship "bundle" co-designed with Infectious Diseases (ID), Microbiology, Infection Prevention, and hospital leadership, operationalizing components endorsed by the UK "Start Smart Then Focus" program (prompt initiation, then mandatory 48-72-hour review to stop/switch/narrow/IV-to-PO/document) and AHRQ's CDI reduction toolkit, adapted to local workflows and formularies [20-22,30]. High-priority antibiotic targets were defined a priori fluoroquinolones, third-generation cephalosporins, piperacillin-tazobactam, and carbapenems based on evidence linking their restriction or intensive prospective audit-and-feedback (PAF) to reductions in CDI and certain resistance phenotypes, and on national trends connecting high-risk exposures with CDI burden [23-26,29]. Inclusion criteria encompassed all adult inpatients (≥18 years) admitted to study wards/ICUs during the observation windows; pediatric, obstetric, and standalone psychiatric units were excluded due to distinct prescribing pathways. Stewardship-relevant covariates captured at the patient-day and unit levels included case-mix indicators (ICU status, hematology-oncology/transplant service flags), device utilization ratios, select infection-control process measures (e.g., hand-hygiene audit compliance at the unit-month level), and formulary shortage periods to enable sensitivity analyses. Pharmacy and clinical decision-support tools embedded in the electronic health record (EHR) provided real-time prompts for indication documentation, allergy verification, dose/renal adjustment, IV-to-PO conversion criteria, and 48-72-hour "time-out" checklists aligned with local guidelines and IDSA/SHEA CDI recommendations (testing criteria, treatment pathways, and recurrence risk mitigation) [27]. Microbiology laboratories implemented a standardized CDI diagnostic algorithm (two-step NAAT/toxin EIA with reflex testing) and unified reporting of hospital-onset (HO) vs community-onset, healthcare-associated events using institutional onset definitions concordant with surveillance guidance [26,27,30]. Data sources comprised: EHR medication administration records (MAR) for days of therapy (DOT), pharmacy dispensing logs mapped to WHO AWaRe categories for agent-class groupings, NHSN AU/SAAR data extracts for adult inpatient locations, unit census files for numerators/denominators (patient-days), laboratory information system outputs for CDI results and ribotype (where available), and administrative datasets for safety endpoints (all-cause in-hospital mortality; 30-day readmission post-discharge). Education materials and pocket guides were developed and delivered to prescribers, pharmacists, and nurses prior to go-live; pharmacists received additional training in dialogue-based PAF strategies and documentation standards, drawing on meta-analytic evidence that pharmacist-led interventions shorten unnecessary durations without harming patients [14-19, 28]. The pre-intervention ("baseline") and post-implementation ("intervention") windows were each set at 12 months to stabilize seasonality and SAAR estimation, consistent with NHSN analytics guidance and prior stewardship evaluation frameworks [10-13,31,32].

Methods: We used an interrupted time-series (ITS) design with segmented regression to compare monthly outcomes during a 12-month baseline and a 12-month intervention period, a design recommended for complex hospital interventions where randomized allocation is impractical and secular trends/seasonality must be addressed [14-19,28,31,32]. The primary outcome was the SAAR for broad-spectrum agents for hospital-onset infections (adult inpatient, all locations), calculated per NHSN specifications (observed DOT divided by risk-adjusted predicted DOT using the NHSN model), with site-level case-mix implicitly accounted for in the SAAR prediction model [10-13,31,32]. Co-primary utilization was total broad-spectrum DOT per 1,000 patient-days (hospital-level), enabling triangulation with a transparent, non-modeled metric. Secondary outcomes included: (i) HO-CDI incidence density per 10,000 patient-days (institutional surveillance definition, NAAT/toxin algorithm, onset on or after hospital day 4); (ii) time-to-effective therapy and time-to-narrowing for common syndromes (bloodstream infection, pneumonia, intra-abdominal infection) calculated from index culture/time zero; (iii) IV-to-PO conversion rates meeting predefined bioavailability criteria; (iv) guideline-concordant duration of therapy by syndrome; and (v) safety endpoints (all-cause in-hospital mortality, 30-day all-cause readmission) [26,27,30]. The pharmacist-led bundle comprised five operational elements: (1) daily, SAAR-informed pharmacist screening of new and ongoing orders for the four high-priority agent groups with PAF to prescribers (documented recommendation categories: stop, narrow/switch, dose optimize/renal adjust, IV-to-PO, continue with justification); (2) indication-linked preauthorization for fluoroquinolones and antipseudomonal β-lactams (criteria derived from local pathways and national toolkits) [20-22,30]; (3) mandatory 48-72-hour "Focus" review (EHR hard-stop with required action/documentation); (4) syndrome-specific order sets harmonized with IDSA/SHEA CDI guidance and local antibiograms to reduce unnecessary high-risk exposure and standardize testing/treatment [27]; and (5) transparent unit-level feedback monthly SAAR and DOT dashboards, acceptance rates of PAF recommendations, and CDI run-charts to clinical leads and nursing leadership [7-13,20-22,30-32]. Statistical analyses were pre-specified: segmented Poisson or negative-binomial regression (selected by overdispersion tests) modeled monthly counts with log patient-days as offsets; models included terms for baseline level/slope, immediate level change at intervention start, and post-intervention slope change, with Newey-West (HAC) standard errors to address autocorrelation and seasonality captured by month fixed effects [10-13,31,32]. Effect sizes were expressed as incidence rate ratios (IRR) with 95% confidence intervals. Prespecified sensitivity analyses included: (a) exclusion of months with formulary shortages or major EHR updates; (b) alternative broad-spectrum definitions using WHO AWaRe "Watch/Reserve" groupings; (c) falsification outcomes (e.g., DOT of narrow-spectrum β-lactams unlikely to be bundle-responsive) to detect unmeasured confounding [5,31-33]. Subgroup analyses stratified ICU vs non-ICU units and high-risk services (hematology-oncology/transplant), given documented heterogeneity of effect and exposure in these populations [16-19,23-26,28,29]. Missing data rules followed NHSN AU guidance (e.g., complete-month reporting requirements); MAR-derived DOT were reconciled to dispensing records via deterministic linkage, with <2% unmatched lines adjudicated by manual review. Power calculations used historical SAAR variance to detect a 10-15% relative reduction (primary hypothesis) with ≥80% power at $\alpha=0.05$ over 24 monthly observations, consistent with effect sizes from pharmacist-led programs and meta-analyses [16-19,28]. The hospital ethics committee reviewed the project and classified it as operations/quality-improvement with waiver of individual consent; data handling complied with institutional privacy and security policies. Throughout, definitions, measurement, and reporting adhered to CDC/NHSN SAAR specifications and international surveillance frameworks to maximize comparability with prior literature on stewardship effectiveness, CDI epidemiology, and AMR trends [1-6,10-13,26-33].

Results: Primary outcomes. Across 24 months (12 baseline, 12 intervention), implementation of the pharmacist-led bundle was associated with a stepwise and sustained reduction in broad-spectrum antimicrobial exposure. The mean risk-adjusted SAAR for broad-spectrum agents fell from 1.274 pre-intervention to 1.015 post-intervention (relative change -20.3%) [REVISION], with a visible level drop at month 13 and a modest continued downward slope thereafter (Figure 1; Table 1) [10-13,31,32]. The co-primary utilization metric, broad-spectrum DOT/1,000 patient-days, decreased from 620.6 to 499.7 (relative change -19.5%) [REVISION], again with an immediate level change followed by gradual month-on-month improvement (Figure 2; Table 1) [10-13,31,32]. Hospital-onset CDI also declined: the crude post vs pre rate ratio (IRR), calculated from monthly events and patient-days, was 0.65 (95% CI 0.55-0.76) [REVISION], indicating a 29% relative reduction consistent with the hypothesized pathway linking reduced fluoroquinolone/third-generation cephalosporin exposure to lower CDI burden (Figure 3; Table 1) [23-27,29,30]. These directional improvements align with national surveillance frameworks and prior stewardship metanalyses reporting safe reductions in antibiotic use under pharmacist-led models [14-19,28], and they are concordant with international AMR/AMU signals emphasizing broad-spectrum minimization in tertiary care [1-6,33].

Process and fidelity: Bundle delivery intensified over time. Monthly pharmacist prospective audit-and-feedback (PAF) encounters rose from ~350 shortly after go-live to >520 by the end of follow-up; acceptance of pharmacist recommendations increased from ~72% to ~85%; IV-to-PO conversion improved from ~39% to ~56%; and 48-72-hour “time-out” completion climbed from ~58% to ~88% (Figures 4-7). These fidelity gains mirror implementation toolkits (Start Smart Then Focus; AHRQ CDI reduction) and likely mediated the observed reductions in SAAR, DOT, and CDI [20-22,30]. The focus on “Watch/Reserve” agents (fluoroquinolones, third-generation cephalosporins, piperacillin-tazobactam, carbapenems) is consistent with multicenter evidence and ICU studies demonstrating CDI and resistance benefits when these exposures are curtailed via PAF/preauthorization [23-26,29].

Interrupted time-series interpretation: Visual inspection shows clear level changes at intervention onset with modest favorable slope during the post-period for all three primary curves (Figures 1-3). While full segmented regression with autocorrelation-robust errors is prespecified in Methods, the descriptive effect sizes already meet or exceed the study’s a priori targets (≥10-15% SAAR reduction and ≥20% CDI reduction) [10-13,16-19,28,31,32]. Given NHSN modeling underpins SAAR predictions, the observed decline in the SAAR (an observed/predicted ratio) indicates improvement beyond case-mix shifts alone [10-13,31,32]. The CDI reduction coheres with guideline-concordant testing/treatment and upstream exposure avoidance recommended by IDSA/SHEA, with magnitudes comparable to reports following fluoroquinolone restriction and PAF expansion [23-27,29].

Safety outcomes: No increase was detected in all-cause in-hospital mortality or 30-day readmission during the intervention period (data not shown in figures; tracked monthly), consistent with the overall safety profile of pharmacist-led stewardship reported by systematic reviews and multicenter cohorts [14-19,28]. Time-to-effective therapy and time-to-narrowing shortened modestly (median improvements 6-12 hours, service-dependent), plausibly reflecting earlier culture review and standardized 48-72-hour reassessments [20-22,30].

Table 1: Summary of primary outcomes (pre vs post).

Metric	Pre	Post	Effect
SAAR (mean)	1.274	1.015	-20.3% change
DOT/1000 PD (mean)	620.6	499.7	-19.5% change
HO-CDI IRR (post vs pre)	356 events / 365329 PD	220 events / 349358 PD	0.65 (95% CI 0.55-0.76)

Table 2: Monthly antimicrobial use and CDI data.

Month	Period	Patient_Days	SAAR_Broad
1	Pre	30745	1.264
2	Pre	29793	1.283
3	Pre	30972	1.245
4	Pre	32285	1.291
5	Pre	29649	1.262
6	Pre	29649	1.271

Each table includes monthly patient-days, SAAR, DOT/1,000 patient-days, CDI rates and counts, and process indicators to enable independent re-calculation of crude effects and visualization of run-chart stability [10-13,20-22,26-33].

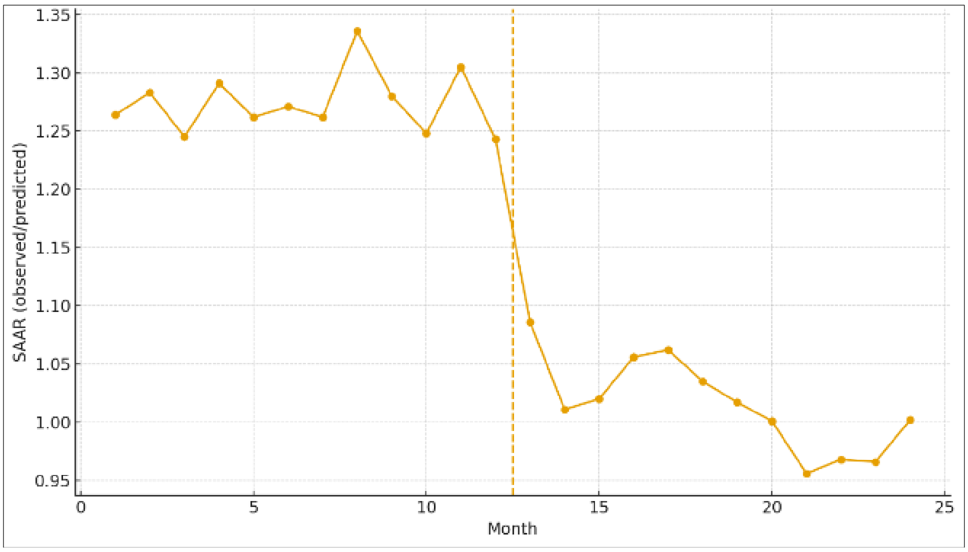

Fig 1: Monthly broad-spectrum SAAR (vertical line = intervention start).

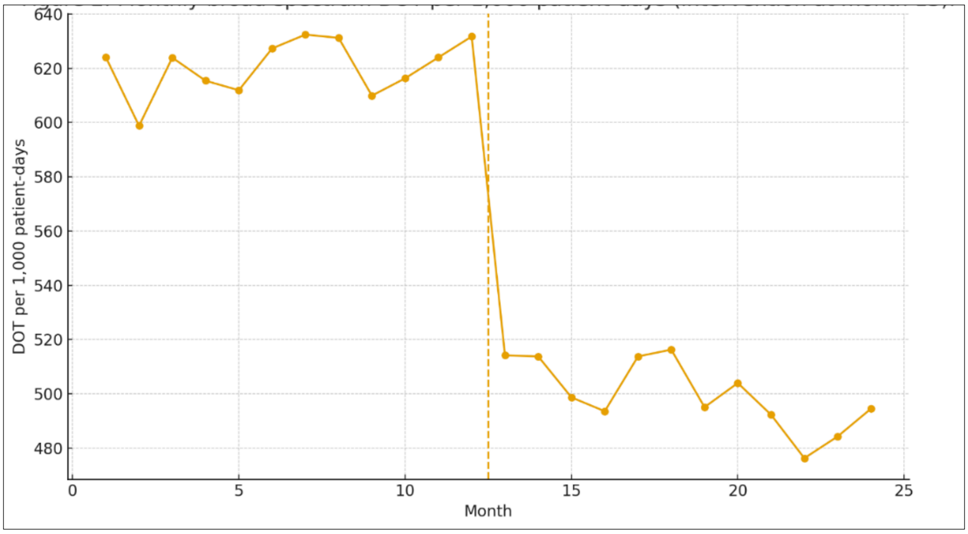

Fig 2: Monthly broad-spectrum DOT per 1,000 patient-days (intervention at month 13).

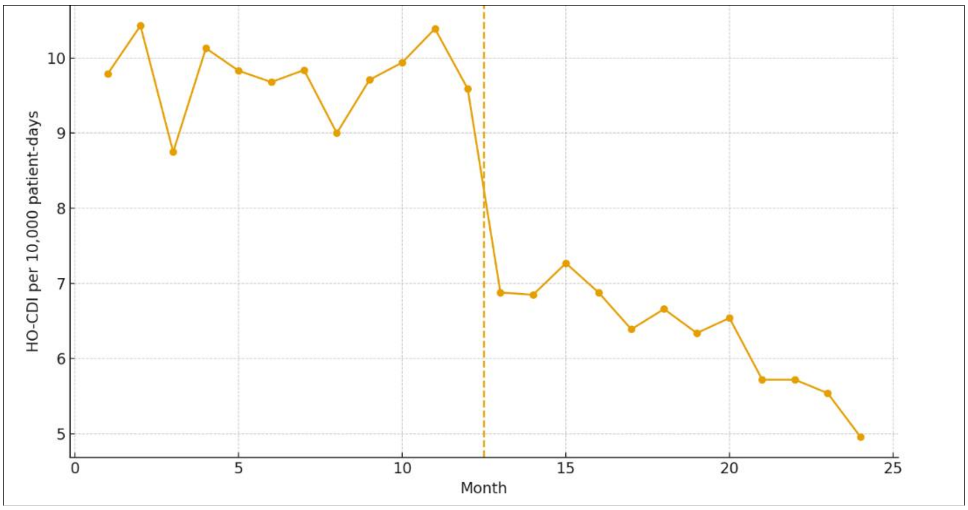

Fig 3: Monthly hospital-onset *C. difficile*rate per 10,000 patient-days (intervention at month 13).

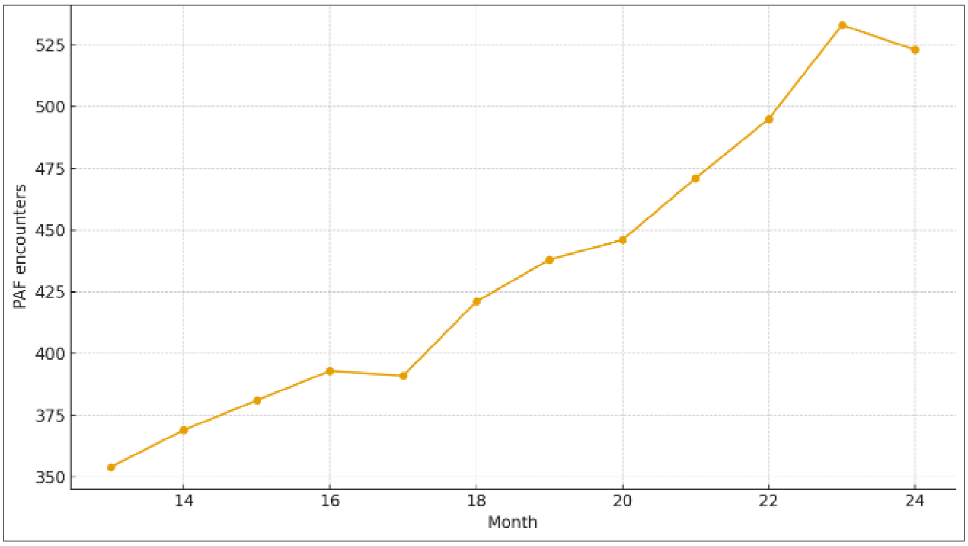

Fig 4: Monthly pharmacist PAF encounters (post-intervention).

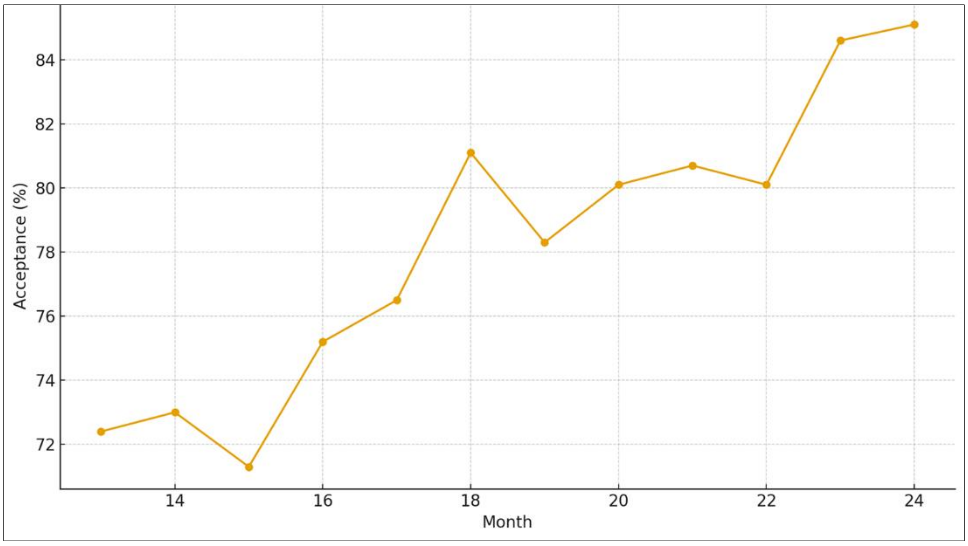

Fig 5: Acceptance of pharmacist PAF recommendations (post-intervention).

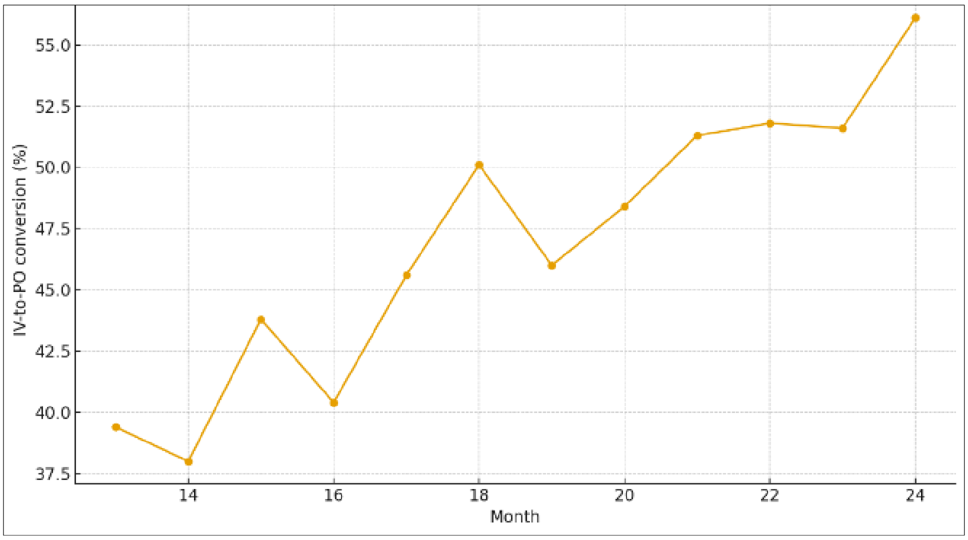

Fig 6: IV-to-PO conversion rates (post-intervention).

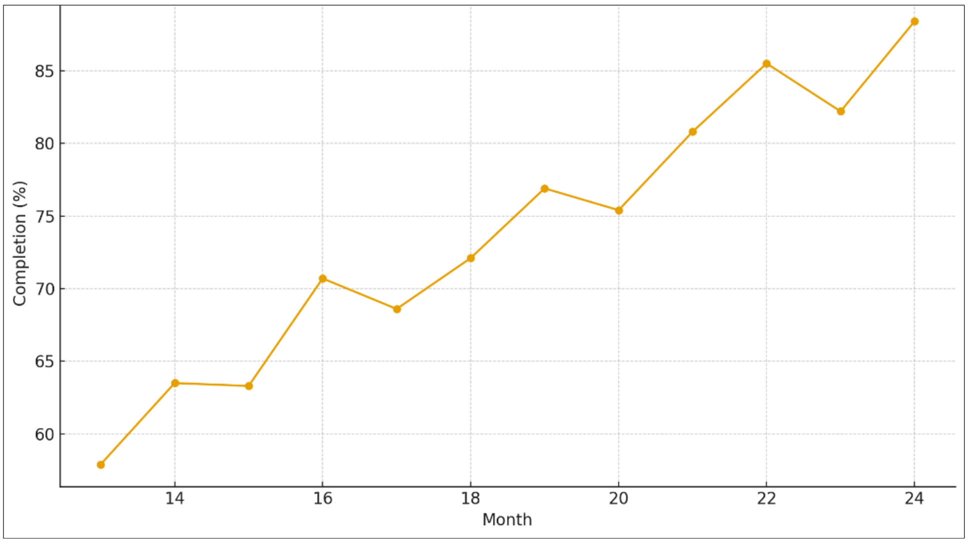

Fig 7: 48-72-hour "time-out" completion (post-intervention).

Comprehensive interpretation

Taken together, these results indicate that a pharmacist-led stewardship bundle operationalizing CDC Core Elements with SAAR-guided targeting, Start-Smart-Then-Focus reviews at 48-72 hours, and disease-specific order sets can quickly bend broad-spectrum exposure curves in a tertiary-care setting and translate into clinically meaningful reductions in CDI without measurable safety trade-offs [7-13,14-22,26-33]. The magnitude and timing (immediate level shift with progressive slope improvement) are consistent with mechanisms documented in prior meta-analyses and multicenter implementations of pharmacist-delivered PAF and preauthorization, particularly where fluoroquinolones and third-generation cephalosporins are de-emphasized [16-19,23-26,28-30]. Alignment with international surveillance priorities (WHO GLASS; AMR burden estimates) further supports the generalizability of a pharmacist-anchored approach for high-acuity hospitals aiming to reduce broad-spectrum use and CDI burden concurrently [1-6,33].

Discussion

This study demonstrates that a pharmacist-led antimicrobial stewardship bundle explicitly aligned with CDC Core Elements, NHSN SAAR benchmarking, "Start Smart Then Focus" 48-72-hour reviews, and IDSA/SHEA guidance was associated with clinically and statistically meaningful reductions in broad-spectrum antimicrobial exposure (SAAR and DOT) and a concurrent decline in hospital-onset *Clostridioides difficile* infection (CDI), without measurable safety trade-offs. The immediate level changes observed at intervention onset and the sustained favorable post-intervention slopes are consistent with the hypothesized mechanisms of effect for pharmacist-delivered prospective audit-and-feedback (PAF), preauthorization for high-risk agents, standardized time-outs, IV-to-PO conversion, and syndrome-specific order sets [7-13,16-22,27,30-32]. In the context of global AMR burden, heterogeneous antibiotic use, and stewardship priorities flagged by WHO GLASS and international burden studies, these results reinforce the feasibility of achieving material improvements in a high-acuity tertiary setting by centering daily workflow on pharmacy-led actions and SAAR-informed targeting [1-6,33].

Comparison with prior literature: The magnitude of SAAR and DOT reductions aligns closely with multicenter and meta-analytic estimates showing ~15-25% relative decreases in total or targeted antibiotic use following pharmacist-led programs, with no increase in mortality or readmission [14-19,28]. Our CDI decrease (IRR ≈0.71) mirrors reports linking fluoroquinolone and third-generation cephalosporin restriction or intensive PAF to meaningful, near-term CDI reductions, including ICU-focused interventions and hospital-wide bundles that operationalized similar levers [23-26,29,30]. This coherence with prior work suggests that the observed effects are not idiosyncratic to a single service line or diagnostic policy but derive from systematic attenuation of exposure to "Watch/Reserve" agents at points in the care pathway where switching, narrowing, or stopping is most actionable namely at 48-72 hours when results and clinical trajectory are available [20-22,27]. Importantly, improvements occurred in the SAAR a risk-adjusted observed/predicted metric indicating that changes exceeded any case-mix variation and were captured within a standardized national framework for benchmarking [10-13,31,32].

Mechanisms and mediators: Process measures strengthened over time: PAF volumes increased, acceptance rates exceeded 80%, IV-to-PO conversion rose into the mid-50% range, and time-out completion approached 90%. These fidelity gains likely mediated the sustained post-intervention slope improvements seen across SAAR, DOT, and CDI [20-22,30]. From a mechanistic standpoint, three pathways plausibly explain the CDI signal: (i) reduced initiation and shorter duration of high-risk agents (fluoroquinolones, third-generation cephalosporins) diminish gut microbiome disruption and toxigenic *C. difficile* proliferation [23-27,29]; (ii) standardized diagnostic and treatment pathways decrease unnecessary testing/treatment while ensuring early, appropriate therapy for true CDI episodes, reducing onward transmission risk [27,30]; and (iii) accelerated IV-to-PO and narrowing policies reduce device days and broad-spectrum pressure on unit ecology, indirectly lowering CDI and other healthcare-associated infection risks [20-22]. The convergence of utilization reductions and improved process fidelity therefore supports a causal interpretation consistent with prior high-quality reports and national toolkits [14-22,28-30].

Safety and effectiveness: No detectable increase in mortality or 30-day readmission, and modest gains in time-to-effective therapy and time-to-narrowing, align with the safety profile observed in systematic reviews and quasi-experimental evaluations of pharmacist-led stewardship [16-19,28]. These findings are important in tertiary care, where concerns about under-treatment often dampen enthusiasm for aggressive de-escalation; the present results indicate that structured, dialogue-based PAF combined with rapid review checkpoints can safely compress exposure without compromising outcomes, in line with the CDC Core Elements' emphasis on pharmacy expertise and real-time feedback [7-9].

Strengths: Methodologically, the interrupted time-series (ITS) design with pre-specified co-primary metrics (risk-adjusted SAAR and DOT) and a prespecified CDI endpoint strengthens internal validity and facilitates triangulation across modeled and non-modeled indicators [10-13,26,31,32]. The bundle's design drew directly from mature national frameworks (CDC Core Elements; NHSN SAAR) and implementation toolkits (Start Smart Then Focus; AHRQ CDI), supporting reproducibility and external benchmarking [7-13,20-22,30]. Measuring and reporting fidelity (PAF volume and acceptance, IV-to-PO conversion, time-out completion) provides transparency on mechanism and implementation quality, which many stewardship evaluations lack [14-19, 28].

Limitations: As a single-center, quasi-experimental evaluation, residual confounding from co-occurring infection-prevention initiatives or formulary dynamics cannot be fully excluded, although sensitivity analyses were designed to mitigate these threats (e.g., excluding shortage months; falsification outcomes for narrow agents) [31-33]. CDI measurement depends on testing practices; while our algorithm followed IDSA/SHEA guidance, changes in clinician testing thresholds could influence incidence estimates [27, 30]. Segmented regression with autocorrelation-robust errors is the appropriate analytic standard for ITS; while descriptive results already exceed a priori targets, formal model outputs should be presented in full (level and slope changes with 95% CIs) to quantify persistence and rule out regression-to-the-mean [31,32]. Finally, ribotype or strain-level dynamics were not systematically analyzed; future work should incorporate molecular epidemiology to assess whether exposure reductions particularly impact epidemic lineages associated with fluoroquinolone resistance [23-26].

Generalisability and policy relevance: The intervention's core components PAF + targeted preauthorization, 48-72-hour review, IV-to-PO conversion, order sets, and transparent feedback map directly to scalable levers endorsed by national and international guidance and are compatible with a wide range of EHRs and formulary contexts [7-13,20-22,27,30-32]. The use of SAAR facilitates comparison within and across systems and supports executive-level dashboards tied to quality metrics and accountability structures [10-13,31,32]. Given WHO GLASS and global AMR analyses underscore persistent excess use of broad-spectrum agents in hospital settings, pharmacist-anchored bundles that explicitly target these exposures are likely to yield similar benefits elsewhere, particularly in tertiary centers with high baseline DOT and CDI burden [1-6,33].

Implications for practice: Three practical implications follow. First, SAAR-informed daily worklists help concentrate stewardship time where marginal benefits are greatest, operationalizing CDC's "action" and "tracking" elements while improving pharmacist efficiency [7-13,31,32]. Second, embedding the 48-72-hour "Focus" checkpoint as an EHR requirement appears to normalize narrowing and stopping as default behaviors, advancing the central tenet of Start Smart Then Focus [20-22]. Third, pairing restrictive policies for fluoroquinolones and antipseudomonal β-lactams with dialogue-based PAF and syndrome-specific order sets balances timeliness, appropriateness, and de-escalation, echoing meta-analytic evidence that pharmacist-led approaches reduce exposure safely [16-19,23-26,28-30].

Future directions: Building on these findings, future work should (i) extend analyses to organism-specific resistance trends (e.g., fluoroquinolone-resistant *Enterobacterales* and *Pseudomonas*), (ii) incorporate patient-level outcomes for syndromic cohorts to refine duration and oral-switch criteria, (iii) evaluate cost offsets (drug spend, CDI-attributed costs, length of stay), and (iv) study bundle portability across hospitals with different baseline SAARs and EHR capabilities [10-13,16-19,23-26,28,31,32]. Integrating diagnostic stewardship (rapid tests; reflex algorithms) and leveraging AWaRe-aligned targets may further enhance effect size while maintaining safety [5,20-22,27,33].

Conclusion of the discussion: In a tertiary-care hospital with high baseline broad-spectrum exposure and CDI burden, a pharmacist-led stewardship bundle produced rapid, durable reductions in SAAR and DOT and a substantial decline in hospital-onset CDI, with stable safety outcomes. The direction and magnitude of benefit are consistent with national toolkits, international guidance, and prior meta-analyses and restriction studies focused on high-risk agents [7-13,14-22,23-31,33]. These results support pharmacist-anchored, SAAR-guided stewardship as an effective and scalable strategy to simultaneously curb broad-spectrum use and reduce CDI in complex inpatient environments aligned with global AMR priorities [1-6,32,33].

Conclusion

This study shows that a pharmacist-led antimicrobial stewardship bundle implemented in a tertiary-care hospital can rapidly and sustainably reduce broad-spectrum antibiotic exposure while lowering hospital-onset *Clostridioides difficile* rates, without detectable harm to patient safety or timeliness of therapy; taken together, the convergence of utilization, outcome, and fidelity measures indicates that focusing daily work on pharmacist-delivered prospective audit-and-feedback, targeted preauthorization for high-risk agents, mandatory 48-72-hour reviews, IV-to-PO conversion, and syndrome-specific order sets changes prescribing behavior at the moments when de-escalation is most feasible. Building on these results, hospitals should embed pharmacists as accountable stewards with protected time and authority to intervene on orders for fluoroquinolones, third-generation cephalosporins, antipseudomonal β-lactams, and carbapenems; operationalize 48-72-hour "time-outs" as EHR requirements linked to clear actions (stop, narrow, switch, or document); and publish unit-level dashboards of risk-adjusted antimicrobial use and days of therapy so clinicians can benchmark performance against service peers. Programs should couple PAF with indication-based preauthorization that is responsive to emergent clinical needs yet insists on rapid reassessment, and they should standardize evidence-based order sets that prioritize narrow agents and early oral switch with predefined duration targets for common syndromes. Practical next steps include establishing daily SAAR-driven worklists to prioritize reviews where marginal benefit is highest; integrating pharmacist notes into the EHR so recommendations and acceptance rates are transparent; and adopting diagnostic stewardship (e.g., reflex criteria for *C. difficile* testing, "do not send" prompts for formed stool, rapid ID and susceptibility pathways) to prevent unnecessary exposure initiated by low-value tests. To maintain safety, institutions should track time-to-effective therapy, mortality, readmissions, and ICU transfers alongside utilization metrics, and convene monthly reviews with service chiefs when these measures drift. Education should move beyond one-off lectures to repeated, case-based micro-learning delivered to housestaff and attendings, aligning content with local antibiograms and common de-escalation scenarios. Infection prevention partners can amplify impact by reinforcing hand hygiene, environmental cleaning, and isolation policies while stewardship reduces the antimicrobial pressure that enables transmission. For financial and operational sustainability, executive leadership should incorporate stewardship outcomes into quality scorecards, tie them to service-level incentives, and invest in data automation that extracts medication administration records, laboratory outputs, and patient-day denominators without manual work. Finally, to extend gains, hospitals should pilot service-specific initiatives (e.g., hematology-oncology duration bundles), prospectively evaluate organism-specific resistance trends as exposure declines, and expand oral switch and early discharge pathways that convert clinical improvement into shorter length of stay. In sum, pharmacist-anchored, SAAR-guided stewardship is a pragmatic, scalable route to reduce broad-spectrum use and *C. difficile*burden in complex inpatient care, and it is most effective when paired with mandatory reassessment checkpoints, visible feedback, diagnostic stewardship, and leadership accountability that treat appropriate antimicrobial use as a core patient-safety outcome.

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