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ORIGINAL RESEARCH

Impact of a Pharmacist-Led Grid-Based Stewardship Program on the Association Between Antimicrobial Use and Resistance: A 7.5-Year Interrupted Time-Series Analysis in a Chinese Tertiary Hospital

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Background: Whether antimicrobial stewardship programs (ASPs) modulate the association between antimicrobial use and resistance remains uncertain. Long-term evidence for precision stewardship models in Chinese tertiary hospitals is scarce.

Methods: A 7.5-year interrupted time-series analysis (2018–2025) was conducted at a 1900-bed Chinese tertiary hospital. A pharmacist-led, grid-based precision ASP—stratifying 29 departments via Boston Matrix and integrating four synergistic pillars—was implemented in July 2020. Segmented regression models, adjusted for seasonality and autocorrelation, evaluated changes in antimicrobial use density (AUD), clinical/economic outcomes, and the temporal association (R^2) between AUD and multidrug-resistant organism (MDRO) detection rates.

Results: The ASP was associated with an immediate AUD reduction (−25.6%, $\beta_2 = -14.55$ DDDs/100 patient-days, $P < 0.001$) and a sustained decline in antimicrobial use rate ($\beta_3 = -0.003$, $P < 0.001$). Key antimicrobial classes showed marked reductions (fluoroquinolones: −40.2%; carbapenems: −16.1%). The ASP was also associated with improved clinical outcomes, including shorter median length of stay (10.9 to 8.8 days), 52% lower all-cause mortality (0.79% to 0.38%, $P < 0.001$), and declining per capita antimicrobial costs ($\beta_3 = -19.39$ CNY/month, $P < 0.001$). Notably, the AUD-MDRO temporal association varied across pathogens: R^2 for MRSA, CREco, and CRAB decreased by 71.8% to 87.0%, moderately weakened for CRKP (49.8%), but paradoxically strengthened for CRPA (+78.3%).

Conclusion: This grid-based precision ASP was associated with sustained reductions in antimicrobial use and costs, and improved clinical outcomes. It was also associated with changes in the temporal relationship between AUD and MDRO detection rates. These alterations suggest this approach may mitigate selective pressure driving resistance, although causality cannot be established in this observational study. This framework may serve as a policy-aligned reference for large tertiary hospitals and provide useful insights to inform local and national antimicrobial stewardship initiatives.

Keywords: temporal association, antimicrobial stewardship, pharmacist-led intervention, grid-based precision management, interrupted time-series analysis, multidrug-resistant organism

Introduction

Antimicrobial resistance (AMR) constitutes a paramount global public health threat, with projections estimating over 39 million cumulative deaths and an economic burden of up to US$100 trillion by 2050.[1,2] As a leading consumer of antimicrobials, China's healthcare system, particularly its tertiary hospitals, faces intense pressure to curb inappropriate

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use—a primary driver of resistance.[3,4] In response, national policies mandate the implementation of antimicrobial stewardship programs (ASPs) in tertiary hospitals, with pharmacist-led, multidisciplinary models recognized as a cornerstone strategy.[5,6]

Despite this policy impetus, critical evidence gaps in ASP evaluation persist. Most published evaluations of ASPs are limited to short follow-up durations, predominantly employ simple pre-post designs, and rarely account for inter-departmental heterogeneity in clinical practice.[7–9] More critically, evidence remains limited regarding whether ASPs are associated with changes in the temporal relationship between antimicrobial consumption and resistance.[10] Exploring potential shifts in the temporal correlation between antimicrobial use density (AUD) and multidrug-resistant organism (MDRO) detection rates may provide additional observational insights into antimicrobial resistance patterns.

To address these gaps, we designed and implemented a novel, pharmacist-led ASP structured around a grid-based framework for precision management. This model stratifies clinical departments into distinct risk categories using the validated Boston Matrix—which has proven feasible for identifying high-priority departments[11]—with pre-intervention AUD and guideline compliance rates as two core dimensions directly linked to stewardship optimization. We hypothesized that this precision, stratified approach would be associated with optimized antimicrobial use and changes in clinical and economic indicators, while also potentially altering temporal correlations between antimicrobial consumption and MDRO detection at the institutional level.

We employed a 7.5-year interrupted time-series (ITS) analysis, a robust quasi-experimental design well-suited for evaluating sustained, policy-driven interventions in healthcare settings while controlling for underlying secular trends.[12] This study evaluated intervention effects across four sequential domains: (1) antimicrobial consumption (AUD and antimicrobial use rate [AUR]); (2) department-level heterogeneity; (3) clinical safety and economic impact; and (4) ecological patterns, including observational changes in the temporal correlation between AUD and MDRO detection. This structured assessment thus aims to provide a replicable framework for large tertiary hospitals and empirical evidence to inform the refinement of national stewardship policies.

Materials and Methods

Study Design

A retrospective, single-center ITS analysis was conducted at Yichang Central People's Hospital, a 1900-bed tertiary Grade A teaching hospital in central China. The study period spanned 90 months from January 2018 to June 2025, divided into a pre-intervention phase (January 2018–June 2020) and a post-intervention phase (July 2020–June 2025). The intervention—a hospital-wide, pharmacist-led, grid-based precision ASP—was implemented in July 2020. We included discharged inpatients who received at least one dose of systemic antibacterial or antifungal agents (therapeutic or prophylactic). Excluded were outpatients, emergency visits not resulting in hospitalization, and records with missing discharge dates.

ASP Intervention

The ASP was built upon four synergistic, interdependent pillars, with the overall workflow and risk stratification framework visualized in Figure 1.

Grid-Based Precision Management

Clinical departments (n=29) were stratified into a 2×2 matrix using two dimensions derived from 30 months of pre-intervention data: AUD (Defined Daily Doses [DDDs] per 100 patient-days [PD]) and institutional antimicrobial guideline compliance rate. High/low thresholds were defined at the 75th and 25th percentiles, respectively, creating four risk grids: High-Use/Low-Compliance (key target), High-Use/High-Compliance (optimization focus), Low-Use /Low-Compliance, and Low-Use/High-Compliance. Dedicated clinical pharmacists provided tailored education, differentiated audit intensity, and targeted feedback based on the specific profile of each risk grid.

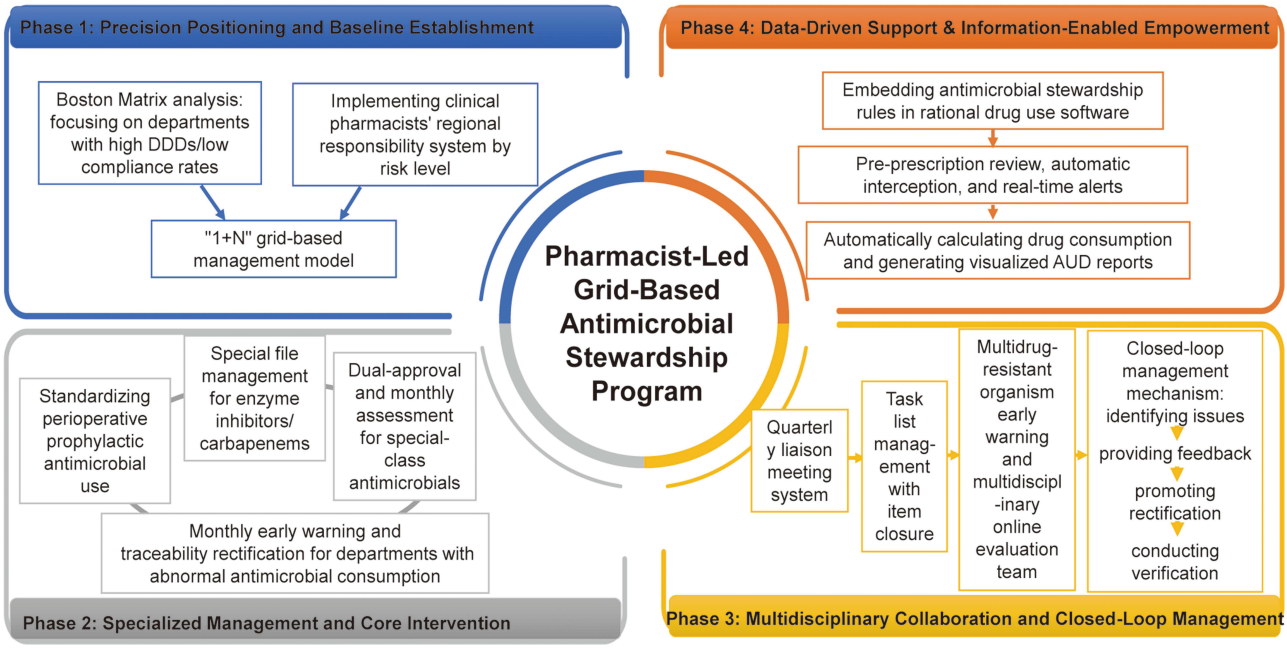

Figure 1 Four-Phase Implementation Framework of the Pharmacist-Led Grid-Based Antimicrobial Stewardship Program (ASP) for the 7.5-Year Interrupted Time Series (ITS) Study.

Targeted Control of Key Antimicrobials and High-Risk Processes

Standardized, evidence-based protocols for perioperative antimicrobial prophylaxis were implemented and enforced across all surgical departments.[13] For broad-spectrum and restricted agents (eg, carbapenems, enzyme-inhibitor combinations), a mandatory prospective audit-and-feedback (PAF) process with a dual-approval system (requiring authorization from both the prescribing physician and a clinical pharmacist) was instituted prior to therapy initiation, ensuring real-time review of antimicrobial indications, dosage, and duration.

Multidisciplinary Closed-Loop Feedback Cycle

A stewardship multidisciplinary team (MDT) was established, convened and chaired by a chief clinical pharmacist, with representation from medical administration, infection control, and clinical departments. The MDT met quarterly to perform three key activities: review department-level performance dashboards, analyze electronic alerts for non-compliant prescriptions, and investigate units with elevated MDRO rates. Findings were translated into action via a structured "task-list system," which formally mandated corrective actions from respective department heads. These actions were then followed by a pharmacist-led re-audit, thereby closing the feedback loop. An MDRO early-warning mechanism was integrated into this cycle to trigger immediate MDT consultations for mitigating emerging resistance risks.

IT-Enabled Stewardship

Customized stewardship rules developed by the pharmacy team were embedded within the hospital's computerized physician order entry (CPOE) system. This integration enabled prospective, pharmacist-led prescription review and triggered real-time alerts for non-compliant orders (eg, missing indications, excessive duration, guideline deviations). Furthermore, the system generated dynamic, visualized dashboards that displayed key metrics—including AUD, AUR, MDRO detection rates, and cost data—to support continuous quality improvement and data-driven decision making.

Data Collection

De-identified monthly aggregate data (January 2018–June 2025) were independently extracted by two investigators from the hospital's electronic medical record and microbiology laboratory systems. To protect patient privacy, all personal identifiers

were permanently de-identified, and dates were generalized to month and year. Discrepancies in data extraction were resolved by consensus between investigators, and a random 10% sample was cross-checked to validate extraction accuracy.

Collected variables included: (1) Demographic and clinical characteristics: age, sex, surgical status, length of stay (LOS), discharge status (cured, improved, died, others); (2) Antimicrobial use: agent name, formulation, quantity, and DDDs for systemic antibacterial and antifungal agents; (3) Economic indicators: per capita total hospitalization cost and antimicrobial cost (Chinese Yuan, CNY); (4) Microbiological surveillance: monthly detection rates of methicillin-resistant *Staphylococcus aureus* (MRSA) and carbapenem-resistant Gram-negative bacilli (CR-GNB), including *Escherichia coli* (CREco), *Klebsiella pneumoniae* (CRKP), *Pseudomonas aeruginosa* (CRPA), and *Acinetobacter baumannii* (CRAB). Susceptibility testing followed CLSI M100-S35 standards.[14] Only the first non-duplicate clinical isolate per patient per hospitalization was included. Monthly MDRO detection rates were calculated as the percentage of non-duplicate targeted multidrug-resistant isolates among the total number of isolates for the same bacterial species (the complete raw datasets of all collected variables are provided in Supplementary Table S1.1–S1.5).

Outcome

Primary outcomes were AUD and AUR. AUD was calculated as (total cumulative DDDs of systemic antimicrobials / total PD) × 100, consistent with the WHO ATC/DDD index (2025 edition).[15] Total PD was defined as the sum of daily inpatient counts at midnight for the month. AUR was defined as (number of discharged inpatients receiving at least one systemic antimicrobial agent / total discharged inpatients) × 100%.

Secondary outcomes included the consumption of key antimicrobial classes (fluoroquinolones, third-/fourth-generation cephalosporins, enzyme-inhibitor combinations, carbapenems); clinical outcomes (median LOS, all-cause in-hospital mortality rate); economic outcomes (per capita antimicrobial cost, proportion of total hospitalization costs attributed to antimicrobials); and monthly MDRO detection rates.

Statistical Analysis

Descriptive statistics were used to summarize participant characteristics, with continuous variables presented as median (interquartile range, IQR) and categorical variables as frequencies (percentages). Between-group comparisons were performed using the Wilcoxon rank-sum test for continuous variables and Pearson's χ^2 test or Fisher's exact test for categorical variables.

The impact of the ASP was assessed using segmented linear regression for ITS data. The model was specified as:

$$Y_t = \beta_0 + \beta_1 \times \text{time} + \beta_2 \times \text{intervention} + \beta_3 \times \text{post} - \text{time} + \Sigma\delta_i \cdot \text{month}_\text{i} + \varepsilon_t$$

where: Y_t = outcome at month t; β_0 = baseline intercept; β_1 = pre-intervention trend; β_2 = immediate level change following intervention; β_3 = post-intervention trend change; $\Sigma\delta_i \cdot \text{month}_\text{i}$ = monthly dummy variables for seasonal adjustment (January as the reference month); ε_t = random error term. Autocorrelation was assessed using the Durbin–Watson statistic and residual ACF/PACF plots, while heteroskedasticity was examined via the Breusch–Pagan test. Newey–West standard errors (lag order 4, selected by comparing fit across lags 1–8) were applied to address violations, with sensitivity analyses confirming robustness to alternative lags and seasonal specifications (monthly dummies vs unadjusted).[16,17] Given the aggregated data structure, conventional multivariable adjustment for case-mix shifts was not feasible. We therefore compared key demographic and clinical characteristics between periods and performed a quantitative bias analysis to assess confounding related to observed differences. Model fit was assessed using R^2, and standardized effect sizes were quantified with Cohen's d (interpreted as small [< 0.5], moderate [0.5–0.8], or large [≥ 0.8]).[18]

For exploratory department-level analysis, annual AUD values (pre- vs post-intervention) were compared using the Wilcoxon rank-sum test, reporting unadjusted P values without correction for multiple testing.

To evaluate the impact of stewardship on the ecological dynamics between antimicrobial use and MDRO detection rates, the temporal association between AUD and MDRO detection rates was assessed using simple linear regression (MDRO rate as the dependent variable and AUD as the independent variable). The primary outcome was the change in the strength of this association before and after the intervention. The optimal lag period (1–6 months) was selected via cross-correlation analysis to maximize model fit. We quantified changes in the strength of the association by calculating

the percentage change in R^2: [(R^2 *post* − R^2 *pre)* / R^2 *pre*] × 100%. A substantial reduction in R^2 reflected a change in the temporal correlation between AUD and MDRO rates, indicating a shift in the co-occurrence trends of antimicrobial consumption and resistance.

All analyses were performed using STATA/MP 17.0 (Stata Corp LLC, College Station, TX, USA). A two-tailed P value < 0.05 was considered statistically significant.

Results

Participant Characteristics

A total of 427,619 inpatient admissions were analyzed (126,356 pre-intervention; 301,263 post-intervention). The post-intervention cohort was significantly older (median age, 56 vs 53 years; $P < 0.001$) with a higher proportion of surgical patients (42.49% vs 36.71%; $P < 0.001$), reflecting increasing case complexity over time. Sex distribution was comparable between periods ($P = 0.591$). Key characteristics are summarized in Table 1.

Hospital-Wide Antimicrobial Use

ITS analysis showed immediate and sustained reductions in antimicrobial use: AUD decreased by 25.6% ($\beta_2 = -14.55$ DDDs/100 PD, $P < 0.001$) with no significant post-intervention trend shift, while AUR declined by 8.6% immediately ($\beta_2 = -0.052$, $P < 0.001$) and continued to decrease ($\beta_3 = -0.003$, $P < 0.001$). Both models, adjusted for seasonality and autocorrelation, demonstrated excellent fit ($R^2 = 0.81$) with large effect sizes (Cohen's d: 2.60–3.74) (Table 2 and Figure 2; see Supplementary Table S2 for model adjustment details).

Department-Level Heterogeneity

Exploratory analysis showed heterogeneous AUD changes across 29 clinical departments: 19 (65.5%) exhibited significant reductions, with the most pronounced decreases observed in Otorhinolaryngology (−72.8%), Ophthalmology (−68.6%), and Endocrinology (−48.3%). Hematology showed a non-significant reduction (−7.4%, $P = 0.302$). In contrast, the intensive care unit (ICU) demonstrated a significant AUD increase (+34.2%, $P = 0.020$), alongside its high-acuity case mix characterized by severe sepsis and multi-organ dysfunction, while Stomatology showed a non-significant upward trend (+24.0%, $P = 0.302$) (Table 3 and Figure 3).

Table 1 Baseline Characteristics and Key Outcomes Pre- vs Post-ASP Intervention

Characteristics	Pre-Intervention (n = 126,356)	Post-Intervention (n = 301,263)	*P*
Demographic			
Age (years), median (IQR)	53 (32–68)	56 (37–69)	< 0.001
Male sex, n (%)	57,759 (45.71)	136,878 (45.43)	0.591
Surgical patients, n (%)	46,380 (36.71)	128,020 (42.49)	< 0.001
Clinical outcomes, n (%)			
Cure	50,286 (39.80)	104,964 (34.84)	< 0.001
Improvement	68,325 (54.07)	173,819 (57.70)	< 0.001
Death	997 (0.79)	1,145 (0.38)	< 0.001
Others	6,748 (5.34)	21,335 (7.08)	< 0.001
Process measures			
LOS (days), median (IQR)	10.9 (10.5–11.1)	8.8 (7.9–9.8)	< 0.001
AUR (%), median (IQR)	59.43 (58.44–61.29)	50.51 (47.51–53.31)	< 0.001
AUD (DDDs/100 PD), median (IQR)	56.19 (53.27–58.00)	36.15 (32.93–39.50)	< 0.001
Economic outcomes			
Per capita hospitalization cost (CNY), median (IQR)	3,685.84 (3,485.61–4,027.90)	2,718.48 (1,622.82–3,117.94)	<0.001
Per capita antimicrobial cost (CNY), median (IQR)	742.19 (671.27–813.45)	312.81 (169.10–528.86)	< 0.001
Antimicrobial cost ratio (%), median (IQR)	19.95 (18.67–21.62)	11.86 (10.27–16.55)	< 0.001

Notes: Others include transfer, untreated, and voluntary discharge. Antimicrobial cost ratio = (Per capita antimicrobial cost / Per capita hospitalization cost) × 100%.
Abbreviations: LOS, length of stay; AUR, antimicrobial use rate; AUD, antimicrobial use density; PD, patient-days; IQR, interquartile range; CNY, Chinese Yuan.

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Table 2 Segmented Regression Analysis Results for Antimicrobial Use, Key Class, and Secondary Outcomes

Outcome (Unit)	Level Change Post-Intervention		Trend Change Post-Intervention		Relative Decrease (%)	Cohen's *d*	R^2
	β_2 (95% CI)	*P*	β_3 (95% CI)	*P*			
Hospital-wide antimicrobial use							
AUD (DDDs/100 PD)	−14.55 (−19.34, −9.76)	< 0.001	−0.14 (−0.31, 0.03)	0.104	25.6	3.74	0.81
AUR (proportion, 0–1)	−0.052 (−0.077, −0.027)	< 0.001	−0.003 (−0.004, −0.002)	< 0.001	8.6	2.60	0.81
Key antimicrobial classes (AUD, DDDs/100 PD)							
Fluoroquinolones	−3.39 (−5.56, −1.22)	0.003	−0.01 (−0.10, 0.08)	0.851	40.2	0.71	0.09
Third-/fourth-generation cephalosporins	−2.19 (−3.64, −0.75)	0.003	−0.06 (−0.15, 0.03)	0.170	23.3	2.53	0.69
Enzyme-inhibitor combinations	−2.70 (−4.22, −1.17)	0.001	−0.25 (−0.32, −0.18)	< 0.001	28.6	0.66	0.43
Carbapenems	−0.25 (−0.49, −0.01)	0.039	−0.01 (−0.03, −0.00)	0.014	16.1	0.62	0.13
Secondary outcomes							
Per capita LOS (days)	−0.44 (−1.15, 0.26)	0.215	−0.07 (−0.10, −0.04)	< 0.001	4.1	2.09	0.87
Per capita hospitalization cost (CNY)	−362.66 (−969.24, 243.93)	0.245	−59.96 (−92.04, −27.88)	< 0.001	9.4	1.90	0.84
Per capita antimicrobial cost (CNY)	−270.96 (−407.48, −134.44)	< 0.001	−19.39 (−25.95, −12.83)	< 0.001	34.9	2.37	0.85
Antimicrobial cost ratio	−0.041 (−0.063, −0.018)	< 0.001	−0.003 (−0.004, −0.002)	< 0.001	20.2	2.29	0.84

Notes: Baseline trend (β_1): AUD = −0.03 (95% CI: −0.19 to 0.13), *P* = 0.716; AUR = 0.0007 (95% CI: −0.0002 to 0.0015), *P* = 0.112. Relative reduction = $|\beta_2|$ / pre-intervention mean × 100%, (AUD pre-mean = 56.94 DDDs/100 PD; AUR pre-mean = 0.6049). Models adjusted for seasonality and autocorrelation (Newey-West SE, lag = 4). Cohen's *d* interpretation: <0.5 = small, 0.5–0.8 = moderate, ≥0.8 = large.

Abbreviations: AUD, antimicrobial use density; AUR, antimicrobial use rate; DDDs, defined daily doses; PD, patient-days; CI, confidence interval; LOS, length of stay.

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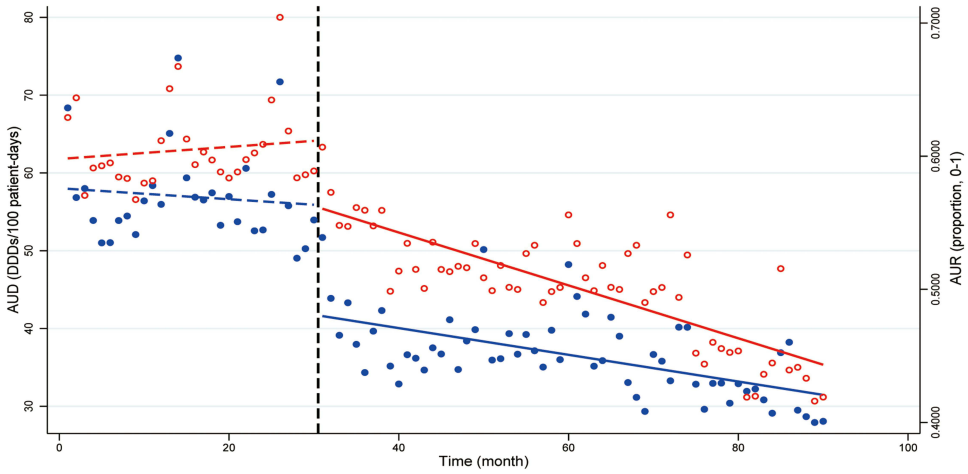

Figure 2 ITS Analysis of Hospital-Wide Antimicrobial Use Density (AUD) and Antimicrobial Use Rate (AUR). Blue: AUD; red: AUR. Points: monthly observed values; dashed lines: pre-intervention fitted trends; solid lines: post-intervention fitted trends. Vertical dashed line: ASP implementation (Month 30).

Key Antibacterial Class Consumption

Significant immediate reductions were observed in the use of key antibacterial classes: fluoroquinolones (−40.2%, $\beta_2 = -3.39$ DDDs/100 PD, $P = 0.003$), third-/fourth-generation cephalosporins (−23.3%, $\beta_2 = -2.19$ DDDs/100 PD, $P = 0.003$), enzyme-inhibitor combinations (−28.6%, $\beta_2 = -2.70$ DDDs/100 PD, $P = 0.001$), and carbapenems (−16.1%, $\beta_2 = -0.25$ DDDs/100 PD, $P = 0.039$). Furthermore, enzyme-inhibitor combinations and carbapenems exhibited significant sustained downward trends in the post-intervention period (both $P < 0.05$) (Table 2 and Figure 4).

Table 3 Changes in Annual Antimicrobial Use Density (AUD) Across 29 Clinical Departments

Department	Median AUD_Pre (IQR)	Median AUD_Post (IQR)	Change (%)	*P*
Otorhinolaryngology	121.24 (109.11–130.25)	32.94 (23.17–40.41)	−72.8	0.020
Ophthalmology	89.44 (83.28–92.20)	28.11 (8.70–37.86)	−68.6	0.020
Endocrinology	23.52 (20.66–24.51)	12.16 (8.52–20.54)	−48.3	0.039
Inpatient Nuclear Medicine	18.69 (4.75–20.00)	10.32 (4.04–11.66)	−44.8	0.439
General Practice	53.35 (43.98–55.74)	30.66 (28.78–33.92)	−42.5	0.020
Emergency Intensive Care Unit	167.57 (138.67–168.77)	98.16 (95.22–114.79)	−41.4	0.020
Obstetrics	67.71 (54.39–68.08)	40.74 (39.14–43.48)	−39.8	0.020
Gastroenterology	63.68 (59.71–65.20)	38.91 (23.91–45.44)	−38.9	0.020
Orthopedics	48.09 (31.09–58.22)	29.45 (27.93–30.44)	−38.8	0.020
Cardiothoracic Surgery	55.50 (50.98–60.25)	34.21 (32.63–39.66)	−38.4	0.020
Pediatrics	73.79 (54.81–77.92)	45.57 (30.40–57.59)	−38.2	0.071
Oncology	22.57 (22.39–26.51)	14.10 (13.14–15.10)	−37.5	0.020
Rheumatology and Immunology	33.49 (31.48–40.52)	21.11 (18.15–32.55)	−37.0	0.197
General Surgery	81.95 (80.91–101.54)	52.31 (50.47–56.96)	−36.2	0.020
Urology	78.50 (73.52–89.43)	53.65 (50.51–55.51)	−31.7	0.020
Neurosurgery	71.52 (63.45–74.29)	50.20 (40.80–51.53)	−29.8	0.020
Nephrology	43.46 (32.46–45.12)	30.90 (28.19–31.31)	−28.9	0.039
Geriatrics	43.98 (40.07–55.74)	31.45 (29.03–32.38)	−28.5	0.020
Cardiology	24.05 (20.22–26.36)	17.29 (13.62–17.36)	−28.1	0.020
Dermatology	31.30 (13.78–35.25)	22.98 (21.20–23.63)	−26.6	0.439
Breast and Thyroid Surgery	15.84 (15.55–23.59)	11.68 (5.08–14.30)	−26.2	0.071
Gynecology	57.23 (56.38–59.96)	43.33 (42.07–45.15)	−24.3	0.020
Neurology	21.87 (21.30–23.39)	16.73 (11.77–19.64)	−23.5	0.020

(*Continued*)

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Table 3 (Continued).

Department	Median AUD_Pre (IQR)	Median AUD_Post (IQR)	Change (%)	*P*
Burns and Plastic Surgery	68.77 (55.72–70.00)	52.82 (43.19–68.87)	−23.2	0.302
Respiratory and Critical Care Medicine	122.71 (116.49–123.88)	94.85 (93.77–96.53)	−22.7	0.020
Rehabilitation Medicine	6.13 (5.63–6.43)	5.07 (4.91–5.75)	−17.3	0.121
Hematology	53.71 (50.71–70.25)	49.74 (46.47–58.24)	−7.4	0.302
Stomatology	60.00 (58.24–111.85)	74.39 (66.78–86.46)	+24.0	0.302
Intensive Care Unit (ICU)	116.25 (98.24–130.70)	155.97 (140.24–167.26)	+34.2	0.020

Notes: Change (%) = [(Median AUD_post - Median AUD_pre) / Median AUD_pre] × 100% (negative = reduction, positive = increase). This subgroup analysis is unadjusted for multiple comparisons (type I error inflation risk); findings are exploratory/hypothesis-generating, not confirmatory.
Abbreviations: AUD, antimicrobial use density; IQR, interquartile range.

Clinical and Economic Outcomes

Concurrent changes were observed in secondary outcomes: a sustained monthly reduction in LOS (β_3 = −0.07 days/month, $P < 0.001$), per capita antimicrobial cost (β_3 = −19.39 CNY/month, $P < 0.001$), and the ratio of antimicrobial cost to total hospitalization cost (β_3 = −0.003/month, $P < 0.001$). A 52% reduction in all-cause in-hospital mortality was observed (from 0.79% to 0.38%, $P < 0.001$). Models for these outcomes showed high goodness-of-fit (R^2 = 0.84–0.87) and moderate-to-large effect sizes (Cohen's d = 1.90–2.37) (Table 2 and Figure 5).

MDRO Detection and AUD-MDRO Association

The explanatory power of AUD on MDRO detection rates was markedly reduced in the post-intervention period. Linear regression analysis revealed altered temporal correlations across key pathogens: MRSA, CREco, and CRAB showed the most pronounced reduction in R^2 (a 71.8–87.0% decrease), reflecting that AUD explained much less of the variance in detection rates post-intervention. CRKP showed a moderate reduction in association strength (49.8% decrease in R^2). In

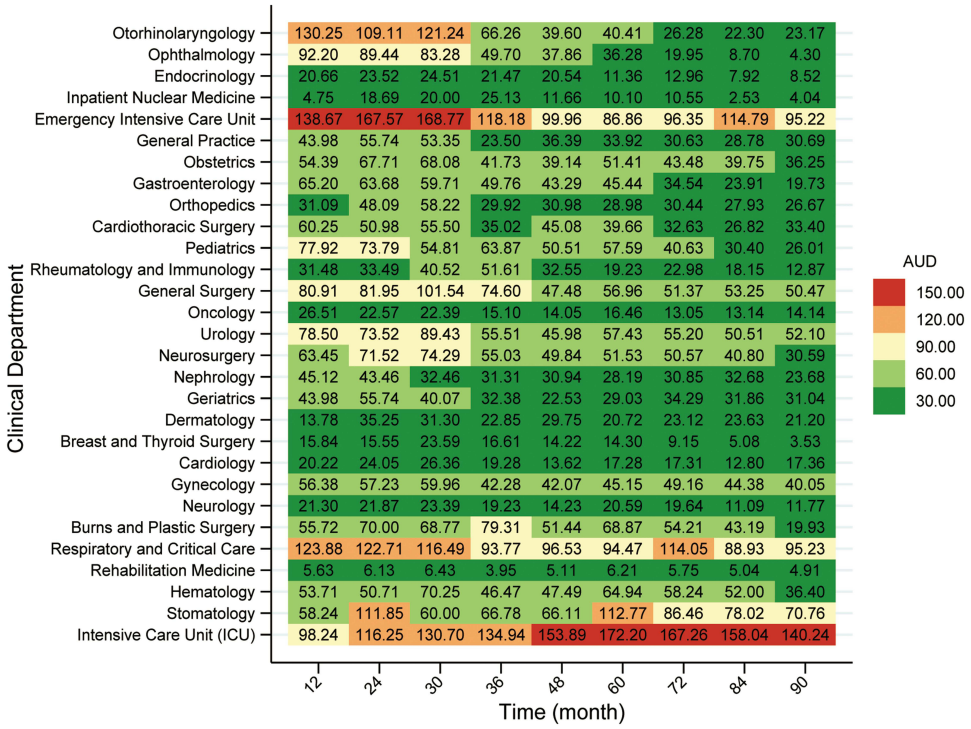

Figure 3 Heatmap of Heterogeneous Antimicrobial Use Density (AUD) Changes Across 29 Clinical Departments. Color gradient (blue = low AUD, red = high AUD) shows heterogeneous ASP effects. AUD unit: Defined Daily Doses (DDDs)/100 patient-days.

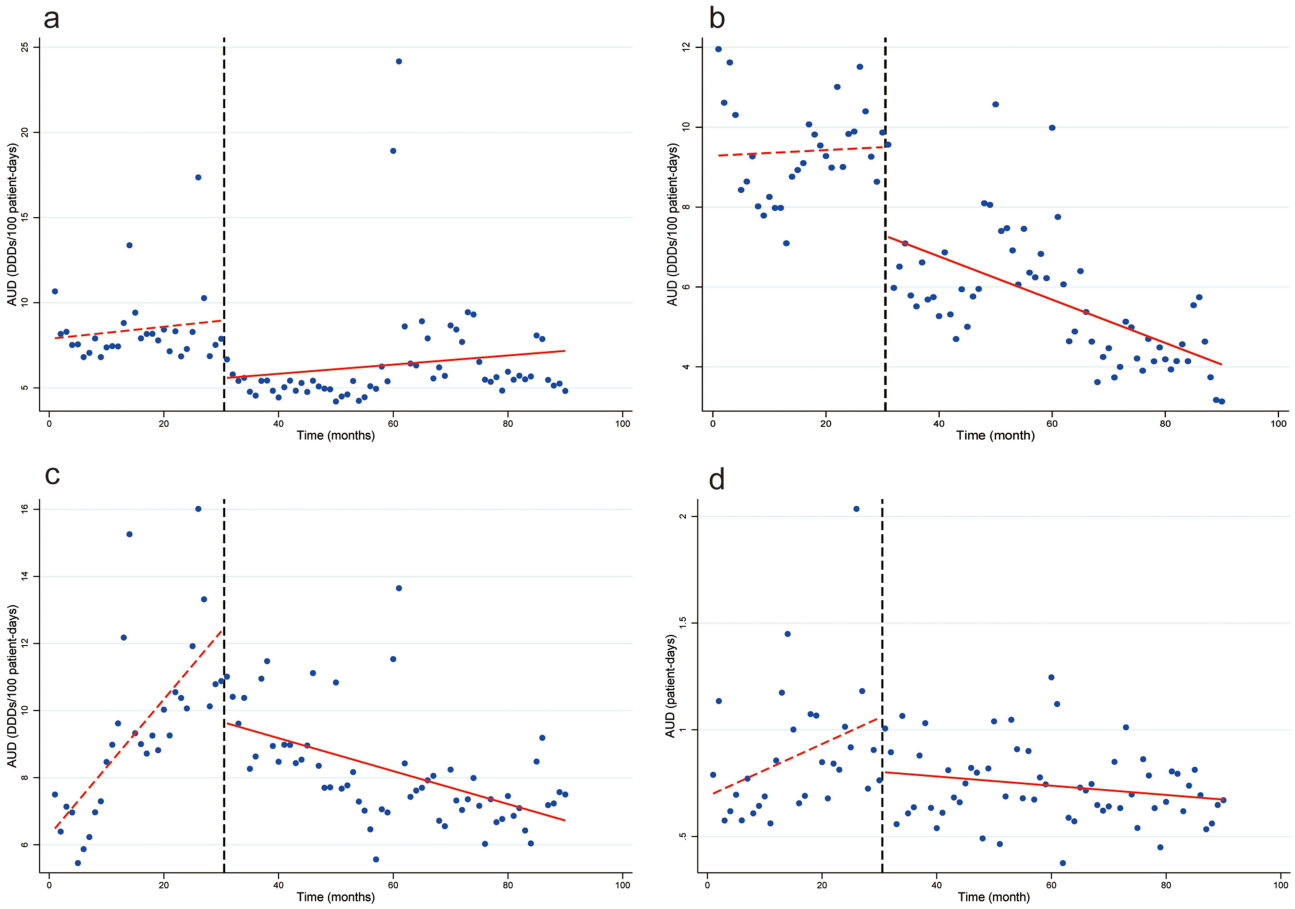

Figure 4 ITS Analysis of Consumption Trends for Key Antimicrobial Classes. (**a**) Fluoroquinolones; (**b**) Third-/fourth-generation cephalosporins; (**c**) Enzyme-inhibitor combinations; (**d**) Carbapenems. Points: monthly observed values; dashed lines: pre-intervention fitted trends; solid lines: post-intervention fitted trends. Vertical dashed line: ASP implementation (Month 30).

contrast, the association for CRPA paradoxically strengthened (+78.3% change in R^2), with an observed shift in temporal correlation despite stable detection rates. Concurrently, crude monthly detection rates decreased significantly for MRSA (P = 0.016) and CRAB (P = 0.008), while no significant changes were observed for CREco (P = 0.127), CRKP (P = 0.800), and CRPA (P = 0.273) (Table 4 and Figure 6).

Discussion

This 7.5-year ITS analysis reveals that a pharmacist-led, grid-based precision ASP was associated with sustained reductions in antimicrobial use and an altered temporal association between antimicrobial consumption and MDRO detection rates. Four key findings emerged: (1) sustained reductions in antimicrobial use were observed despite increasing patient complexity; (2) substantial department-level heterogeneity was noted, consistent with adaptive, targeted stewardship; (3) parallel changes in clinical and economic outcomes were identified; and (4) the temporal association between AUD and MDRO detection rates was markedly altered. These findings address key gaps in the long-term observational evaluation of hospital-based antimicrobial stewardship programs.

Our key contribution lies in the empirical observation of a shift in temporal association patterns between antimicrobial consumption and MDRO detection rates. Unlike most ASP studies, which only report declines in antimicrobial use or MDRO prevalence and fail to address the dynamic temporal relationship between antimicrobial consumption and MDRO detection rates—the core relationship that ASPs seek to influence—our analysis reveals a notable change in this long-term relationship.[10] For example, Xia et al reported optimized pre-therapy pathogen identification and corresponding CRKP declines but observed no consistent correlation shifts for other MDROs.[19] Similarly, Zhang et al documented

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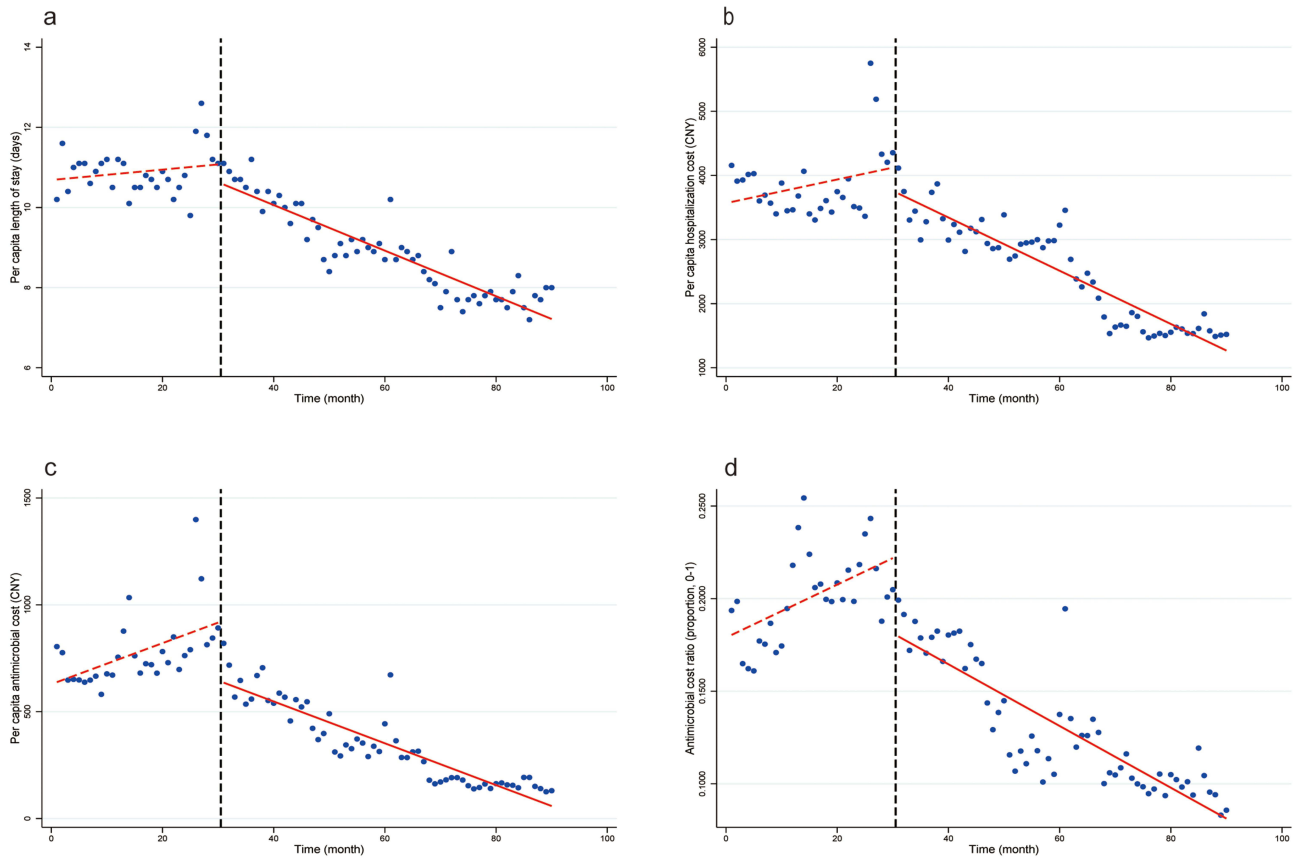

Figure 5 ITS Analysis of Secondary Clinical and Economic Outcomes. (**a**) Length of stay; (**b**) Total hospitalization cost; (**c**) Per capita antimicrobial cost; (**d**) Antimicrobial cost ratio (0–1). Points: monthly observed values; dashed lines: pre-intervention fitted trends; solid lines: post-intervention fitted trends. Vertical dashed line: ASP implementation (Month 30).

a 15.2% AUD reduction over 3 years in a Chinese hospital but did not quantify such ecological associations.[20] In contrast, our grid-based ASP was associated with a marked reduction in R^2 (explanatory power) for MRSA, CREco, and CRAB (71.8–87.0%), suggesting that antimicrobial use became less predictive of MDRO detection trends. These findings highlight that precision stewardship can mitigate inappropriate antimicrobial exposure rather than promote indiscriminate antimicrobial restriction—a critical distinction rarely quantified in long-term ASP evaluations.[12,21,22]

In comparison with international experiences, the present intervention documents sustained trends over an extended follow-up period. Ford et al achieved 24–47% azithromycin reduction via clinical decision support, but only for a single drug class and over a short follow-up.[21] Sangiorgi et al reported 11% inappropriate carbapenem reduction in Italy, but without departmental

Table 4 MDRO Detection Rates and Temporal Association with Antimicrobial Use Density (AUD)

Pathogen	Pre-Intervention Detection Rate (Median [IQR])	Post-Intervention Detection Rate (Median [IQR])	*P*	Optimal Lag/ Lead Period	R^2 *pre*	R^2 *post*	Change in R^2 (%)	Association Grade
MRSA	0.290 (0.211–0.357)	0.212 (0.137–0.286)	0.016	5-month lag	0.097	0.013	−86.1	Substantially Weakened
CREco	0.000 (0.000–0.029)	0.000 (0.000–0.021)	0.127	2-month lead	0.003	0.000	−87.0	Substantially Weakened
CRKP	0.118 (0.059–0.200)	0.136 (0.044–0.262)	0.800	5-month lead	0.108	0.054	−49.8	Moderately Weakened
CRPA	0.154 (0.111–0.250)	0.143 (0.098–0.212)	0.273	1-month lead	0.007	0.013	+78.3	Strengthened
CRAB	0.785 (0.556–0.889)	0.571 (0.500–0.732)	0.008	6-month lag	0.022	0.006	−71.8	Substantially Weakened

Notes: Change in Coefficient of Determination (R^2) (%) = [(R^2 *post* - R^2 *pre*) / R^2 *pre*] × 100% (negative = weakened association, positive = strengthened association). Association grade: Substantially Weakened (R^2 reduction ≥70%), Moderately Weakened (40–70%), Strengthened (positive values). Optimal lag/lead periods determined via cross-correlation analysis. This subgroup analysis is unadjusted for multiple comparisons (type I error inflation risk); findings are exploratory/hypothesis-generating, not confirmatory.
Abbreviations: MDRO, multidrug-resistant organism; MRSA, methicillin-resistant *Staphylococcus aureus*; CREco, carbapenem-resistant *Escherichia coli*; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; IQR, interquartile range.

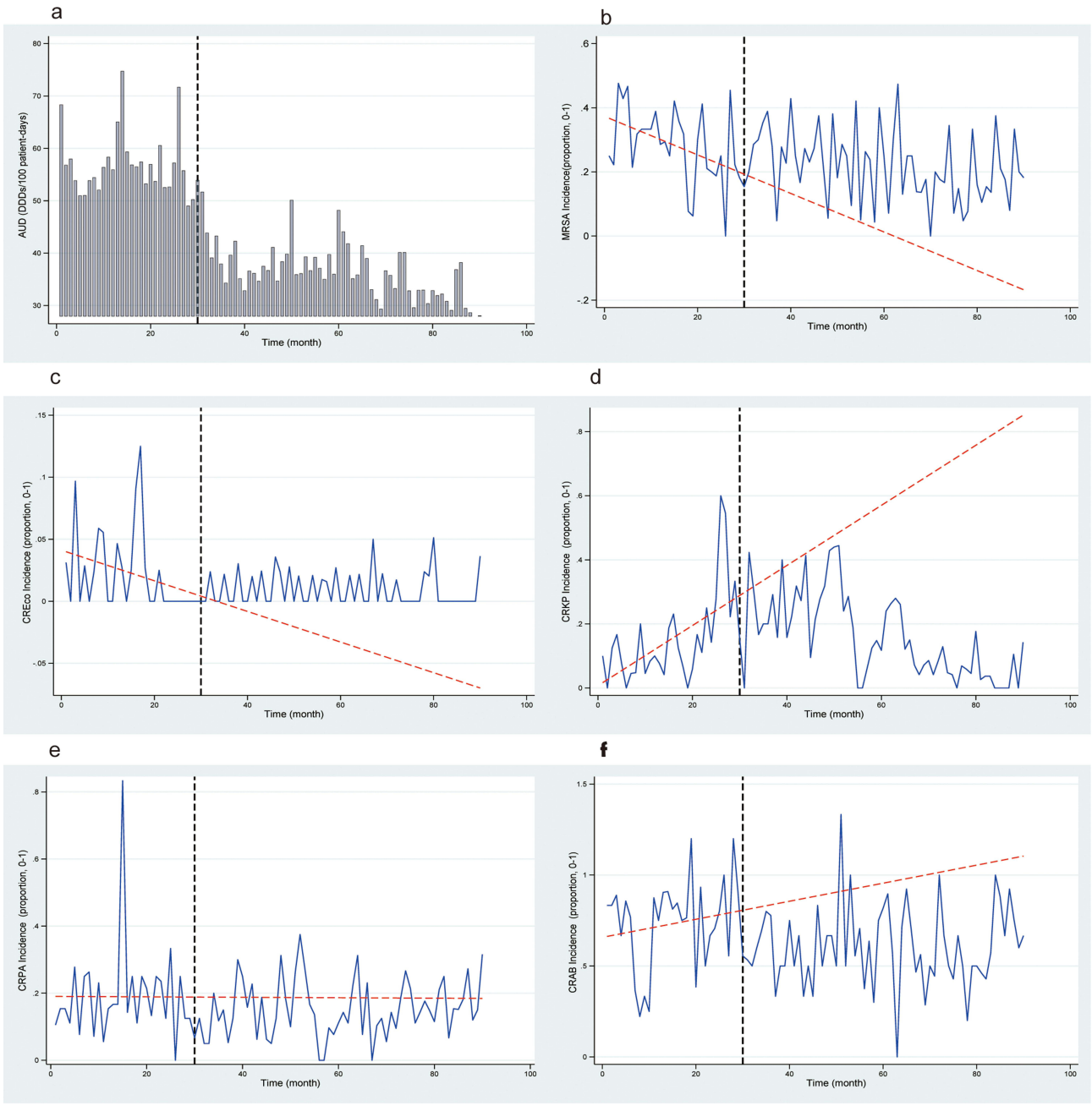

Figure 6 Temporal Association between Antimicrobial Use Density (AUD) and Multidrug-Resistant Organism (MDRO) Detection Rates. (**a**) AUD; (**b**) Methicillin-resistant *Staphylococcus aureus* (MRSA); (**c**) Carbapenem-resistant *Escherichia coli* (CREco); (**d**) Carbapenem-resistant *Klebsiella pneumoniae* (CRKP); (**e**) Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA); (**f**) Carbapenem-resistant *Acinetobacter baumannii* (CRAB). Blue lines: monthly observed values; red lines: counterfactual trends (expected values without ASP intervention). Vertical dashed line: ASP implementation (Month 30).

stratification—resulting in uneven effectiveness across care areas.[22] By contrast, our 7.5-year intervention was associated with sustained reductions across multiple high-priority antimicrobial classes (fluoroquinolones: −40.2%; carbapenems: −16.1%) while accounting for departmental heterogeneity. The 34.2% increase in ICU AUD—rather than indicating an undesired outcome—reflects the adaptive, tailored design of the intervention: in this high-acuity setting (characterized by severe sepsis and multi-organ dysfunction), antimicrobial use was guided by clinical appropriateness rather than blanket restriction, illustrating a "precision over restriction" approach[23] and addressing known limitations of uniform restriction strategies.[24] This pattern of heterogeneous response—reductions in low-acuity departments and appropriateness-driven adjustments in the ICU—supports the potential value of grid-based stratification in supporting sustainable program implementation.

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Moving beyond one-size-fits-all strategies enables more efficient and targeted resource allocation. Substantial reductions in lower-complexity, high-use departments—Otorhinolaryngology (−72.8%) and Ophthalmology (−68.6%)—paired with appropriateness-focused ICU management, illustrate the value of tailored stewardship. Such heterogeneity, often masked in hospital-wide aggregate analyses, is critical to sustaining frontline clinician engagement and long-term compliance. Targeted interventions for "High-Use/Low-Compliance" departments (eg, General Surgery), including monthly pharmacist-led education and real-time prescription auditing, contributed to a 36.2% AUD reduction—further validating the practical utility of grid-based stratification.

The program's four-pillar synergistic design—supported by a modest resource investment (≈ 1 full-time equivalent pharmacist per 100–300 beds),[25] consistent with international sustainable ASP staffing benchmarks—was key to its sustained performance. Mandatory prospective audit and dual approval for restricted antimicrobials balanced consumption reduction with continued appropriate access for high-risk patients[26]—an approach more durable than rigid restriction alone.[24] The pharmacist-chaired multidisciplinary team and closed-loop feedback mechanism drove a 23.3% sustained reduction in third-/fourth-generation cephalosporin use (β_2 = −2.19 DDDs/100 PD; 95% CI: −3.64 to −0.75; P = 0.003; Table 2 and Figure 4). Embedding stewardship rules into the CPOE system enabled scalable real-time decision support and dynamic performance dashboards,[27] curbing non-compliant prescribing. This multifaceted integrated approach likely explains five years of durable post-implementation effectiveness, with large effect sizes (Cohen's d = 1.90–3.74) that compare favorably with other long-term ITS evaluations,[21,22,28] and these findings were corroborated by sensitivity analyses (Supplementary Table S2).

The paradoxical 78.3% strengthening of the AUD–CRPA association—despite stable crude detection rates—may arise from three interrelated mechanisms. First, PA has an intrinsic resistance profile, including efflux pump overexpression and OprD porin deficiency, which reduces its responsiveness to volume-focused stewardship.[29,30] Second, shifts in pathogen distribution may have occurred: the significant reduction in CRAB (P = 0.008) likely opened a niche favorable to CRPA expansion.[31] Of note, CRPA isolates were concentrated in respiratory and neurosurgical ICUs, where continued appropriate broad-spectrum antipseudomonal use may have altered local microbial dynamics. Third, the environmental persistence of CRPA and prolonged antipseudomonal courses for ventilator-associated pneumonia can inadvertently support ongoing transmission. These observations highlight important limitations of antimicrobial stewardship alone: pathogen-specific strategies and enhanced infection control—including rigorous environmental disinfection and contact precautions—are necessary to control persistent environmental pathogens such as CRPA.[32]

This study has several limitations. First, as an ecological time-series analysis, we cannot establish individual-level causality or adjust for patient-specific confounders such as disease severity. However, the increased proportion of surgical patients after intervention represents a negative confounder that biases results toward the null, suggesting our findings are conservative. Second, the linear ITS model cannot fully capture the complex non-linear biological dynamics of antimicrobial resistance evolution, though our results still provide valuable population-level observational trends. Third, subgroup and pathogen-specific analyses were not adjusted for multiple comparisons, which may inflate type I error; these findings should therefore be interpreted as exploratory and hypothesis-generating rather than confirmatory. Finally, the single-center, retrospective design limits generalizability, although the 7.5-year duration and ICU's divergent trend help reduce bias from secular trends.

This grid-based precision ASP may offer preliminary policy and clinical translational insights. Observations from this single-center program suggest potential alignment with tertiary hospital quality improvement initiatives and DRG-based payment reform, as the intervention was associated with reduced unnecessary antimicrobial consumption and improved key quality metrics.[7,33] For tertiary care settings, this framework may warrant further evaluation for potential scalability, given its relatively modest resource requirements, compatibility with existing CPOE systems, and adaptability to local antimicrobial prescribing guidelines.

Three priorities for future research emerge: (1) to conduct the planned multi-center stepped-wedge randomized controlled trial (RCT) to evaluate generalizability across diverse healthcare settings;[34] (2) to implement AI-powered real-time decision support in high-risk units, integrating machine learning models to predict CRPA risk and personalize antipseudomonal therapy;[35] and (3) to use whole-genome sequencing to clarify whether the altered AUD—CRPA association reflects evolutionary adaptation, unmeasured confounding, or differential transmission

dynamics.[36] For future translational research, we will develop a DRG-aligned pharmacoeconomic framework and implement targeted infection control bundles for high-priority MDROs such as CRPA.

Conclusion

This pharmacist-led, grid-based precision ASP was associated with sustained reductions in antimicrobial consumption, concurrent shifts in clinical and economic indicators, and altered temporal correlations between antimicrobial use and MDRO detection at a single tertiary hospital. These observational findings reflect parallel resistance trends alongside decreased antimicrobial consumption, without implying causal ecological relationships. This integrated, data-driven stewardship model merits further evaluation for scalability and may inform local and national antimicrobial stewardship strategies targeting antimicrobial resistance and rational prescribing.

AI-Assisted Statement

Limited AI-assisted language editing and grammatical refinement were performed using Doubao solely to improve manuscript readability. No artificial intelligence tools were used for study design, data analysis, result interpretation, or core manuscript writing. All authors retain full responsibility for the final content and conclusions of this study.

Data Sharing Statement

The complete primary raw datasets supporting the conclusions of this study are available as Supplementary Table S1 with this manuscript, and supplementary materials for ITS model adjustment and robustness tests are provided in Supplementary Table S2.

Ethics Approval and Informed Consent

The study was approved by the Medical Ethics Committee of Yichang Central People's Hospital (Approval No. 2026-021-01). Informed consent was waived due to the retrospective nature of the study and use of fully anonymized, aggregated data. All procedures were conducted in accordance with the ethical standards outlined in the Declaration of Helsinki, with strict patient data confidentiality maintained.

Consent for Publication

The study used fully anonymized, aggregated data with all personal identifiers permanently removed. Informed consent for publication was waived by the Medical Ethics Committee of Yichang Central People's Hospital, consistent with the study's ethical approval.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests.

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