Infection and Drug Resistance

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Impact of an Antimicrobial Stewardship Program on Pre-Therapy Pathogen Detection Specimen Submission, Antimicrobial Use, and Resistant Pathogens: An Interrupted Time Series Analysis

Suirui Xia, Qiankun Jiang, Yijun Liu, Ruijuan Huang, Jianmei Li, Wei Yu, Hongxu Pan

Department of Healthcare-Associated Infection Management, Nanxishan Hospital of Guangxi Zhuang Autonomous Region, Guilin, Guangxi Zhuang Autonomous Region, People's Republic of China

Correspondence: Hongxu Pan, Department of Healthcare-associated Infection Management, Nanxishan Hospital of Guangxi Zhuang Autonomous Region, Guilin, Guangxi Zhuang Autonomous Region, People's Republic of China, Email tgyx130@163.com

Background: Inappropriate antibiotic use drives antimicrobial resistance (AMR). Performing pathogen detection before initiating antimicrobial therapy is essential for antimicrobial stewardship (AMS), enabling targeted treatment. Robust evidence on multifaceted interventions' sustained impact on pre-therapy pathogen detection specimen submission rates, AMS metrics, and multidrug-resistant organisms (MDROs) is limited.

Methods: Interrupted time series analysis evaluated a comprehensive AMS intervention (April 2023) at a tertiary care hospital in China (April 2022–May 2025). Interventions included: team establishment, lab expansion, education, electronic restrictions for restricted/special use-levels antibiotics (mandating pre-therapy pathogen detection specimen submission rate), audit/feedback, and monitoring. Segmented regression assessed level (immediate) and slope (trend) changes in pre-therapy pathogen detection specimen submission rate, antimicrobial use, costs, and MDRO isolate rates.

Results: Post-intervention, overall pre-therapy pathogen detection specimen submission rate increased immediately (+9.82%, P=0.009) with sustained monthly growth (+1.21%, P<0.001); increases occurred across all antimicrobial classes (all P<0.05). Antimicrobial use intensity reversed significantly from a pre-intervention upward trend (β_1 = +1.22 DDDs/100PD, P=0.002) to a sustained downward trajectory (β_3 = −1.36, P=0.001), with non-restricted agents showing the steepest decline (net slope = −0.16). Concurrently, antimicrobial utilization rate, per capita costs, and cost proportion reversed to downward trends (all P<0.05), while testing costs remained stable Only carbapenem-resistant *Klebsiella pneumoniae* (CRKP) exhibited sustained reduction (−0.87%/month, P=0.013); other MDROs showed no significant changes.

Conclusion: The intervention significantly improved pre-therapy pathogen detection specimen submission rate and optimized antimicrobial use (reduced intensity/costs), but demonstrated limited resistance impact beyond CRKP reduction. Sustainable AMR control requires integrating diagnostic stewardship with infection prevention programs.

Keywords: pre-therapy pathogen detection specimen submission, multifaceted intervention, antimicrobial stewardship, multidrug-resistant organism isolate rate, interrupted time series analysis

Introduction

The relentless global spread of antimicrobial resistance (AMR) poses a critical public health threat, predominantly fueled by inappropriate antibiotic use.[1] A key driver of this crisis is the systematic omission of pre-therapy pathogen detection specimen submission, which perpetuates empirical prescribing practices—often resulting in overly broad, ineffective, or unnecessary regimens—that accelerate the evolution of multidrug-resistant organisms (MDROs).[2] In response, health authorities worldwide have prioritized rational antibiotic use as a strategic imperative, advancing standardized stewardship initiatives.[3,4]

Infection and Drug Resistance downloaded from https://www.dovepress.com/
For personal use only.

Received: 3 September 2025
Accepted: 1 November 2025
Published: 12 December 2025

© 2025 Xia et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v4.0) License (http://creativecommons.org/licenses/by-nc/4.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php).

Within antimicrobial stewardship (AMS) frameworks, pre-therapy pathogen detection constitutes a foundational diagnostic target, with the pre-therapy pathogen detection specimen submission rate serving as its core performance metric.[5] However, despite the global consensus on its importance, significant heterogeneity characterizes practical implementation across regions with varying economic development levels. Disparities in diagnostic resource accessibility, clinical decision-making pathways, and risk mitigation priorities distinguish high-income countries from low- to middle-income countries: the former face challenges of over-testing and overtreatment driven by resource surplus, while the latter prioritize addressing under-testing and the arbitrariness of empirical prescribing due to constrained resources.[6] Confronting pervasive antibiotic misuse in which 51% of outpatient prescriptions in tertiary hospitals are deemed inappropriate,[7] China's health authorities have consecutively prioritized enhanced pre-therapy pathogen detection specimen submission rate as a core stewardship objective to mitigate antimicrobial resistance driven by non-evidence-based prescribing.[8]

Although pre-therapy pathogen detection specimen submission rate focused interventions are advocated, evidence for their sustainable, system-wide implementation remains limited. Existing studies frequently assess isolated tactics (eg, education-only) or rely solely on simple before-after comparisons or short-term observations lacking longitudinal rigor.[9,10] Critically, these conventional approaches cannot disentangle genuine intervention effects from pre-existing upward or downward trends already manifesting prior to implementation, nor can they adequately address concurrent contextual confounders. This fundamental limitation severely undermines causal inference. Interrupted Time Series (ITS) analysis—a robust quasi-experimental design widely implemented in public health research—was strategically employed in this study to account for underlying temporal trends. This approach enabled rigorous quantification of both immediate intervention effects and sustained outcome trajectory changes through comparative assessment of pre- and post-intervention regression slopes, strengthening causal inference for policy impact evaluation.[11,12] Therefore, this study employs an ITSA framework to rigorously model the underlying pre-intervention trend, test for significant discontinuities in both level and slope at the implementation point, and thereby evaluate the true effectiveness of the multifaceted intervention strategy with enhanced internal validity.

To address these gaps, we implemented a multidimensional intervention exclusively targeting pre-therapy pathogen detection specimen submission rate barriers at a tertiary hospital in Southern China. This pre-therapy pathogen detection specimen submission rate centric initiative integrated team-based accountability with defined goals, implemented staffed extended microbiology laboratory operating hours, expanded testing capacity, enforced electronic mandates requiring pre-therapy pathogen detection specimen submission rate documentation for restricted/special-class antibiotics, and established clinician audit/feedback mechanisms. Using ITSA, we evaluated immediate and sustained changes in pre-therapy pathogen detection specimen submission rate (overall and stratified by antibiotic class/pathogen), downstream impacts on antimicrobial utilization (rate, intensity, cost), and exploratory trends in MDRO isolate to contextualize resistance implications.

Materials and Methods

Study Design

This interrupted time series analysis included inpatients receiving systemic therapeutic antibiotics at a tertiary general hospital with 2,120 beds in Southern China between April 2022 and May 2025.The study period commenced in April 2022 following a critical enhancement of the hospital's electronic health record system, which fundamentally transformed data capture methodology: whereas pre-April 2022 data relied on medical order entry timestamps, post-implementation data utilized actual specimen submission and antibiotic administration times as temporal anchors. This methodological harmonization ensured rigorous temporal consistency in outcome measurement throughout the study period, satisfying a core validity requirement for interrupted time series analysis. According to the implementation timeline of the hospital's comprehensive interventions to improve pre-therapy pathogen detection specimen submission rate, we defined the pre-intervention period as from April 2022 to March 2023 and the post-intervention period as from April 2023 to May 2025.

Comprehensive Interventions

Building upon existing antimicrobial stewardship infrastructure—including hierarchical prescribing privileges, prescription and order audits, stewardship team consultations, and performance-based incentives,[13] We implemented the following measures: (1) A multidisciplinary task force with defined responsibilities conducting regular strategy meetings; (2) Program management optimization using evidence-based frameworks with quantifiable targets; (3) Institutionalization of the pre-therapy pathogen detection specimen submission rate as a tier-1 quality indicator with monthly departmental reporting linked to performance incentives; (4) Laboratory capacity enhancement through: recruitment of two additional microbiology laboratory staff, addition of night shifts (previously 8:00–17:30 without night coverage), and implementation of advanced diagnostics (respiratory pathogen nucleic acid amplification tests [NAAT], next-generation sequencing [NGS]); (5) Promotion of specimen submission compliance via: department-specific, face-to-face workshops by the Hospital Infection Management Department (replacing centralized hospital-wide training), standardized specimen-handling training (Clinical Laboratory and Nursing Departments), and antimicrobial stewardship education (Pharmacy Department); (6) Enforcement of rational prescribing through: EHR-embedded mandatory pre-therapy pathogen detection specimen submission rate orders for restricted and special-use antimicrobials, monthly audits of discharged records with disciplinary actions for violations, and mandatory consultation for special-use antimicrobials; (7) Implementation of real-time pre-therapy pathogen detection specimen submission rate surveillance featuring: corrective action plans for underperforming units, targeted interventions (departmental discussions and retraining) for high-priority departments with documented low pre-therapy pathogen detection specimen submission rate and elevated therapeutic antimicrobial usage, and formal root-cause analysis for continuous process refinement.A detailed, narrative description of each intervention component is provided in Supplementary File 1.

Data Definitions

The impact of the antimicrobial stewardship (AMS) interventions was evaluated using a comprehensive set of indicators, including pre-therapy pathogen detection specimen submission rate, antimicrobial use metrics, and economic indicators, all extracted from the hospital information system (HIS).Pathogen detection metrics included: pre-therapy pathogen detection specimen submission rate: The proportion of patients receiving therapeutic antimicrobials who had pathogen detection tests performed before the first antimicrobial dose. Stratified Pre-therapy Specimen Submission Rate: Calculated according to China's three-tier antimicrobial classification system (Guiding Principles for Clinical Application of Antimicrobials, 2015): overall, unrestricted use-level antimicrobials, Restricted use-level antimicrobials, Special use-level antimicrobials, calculated using the same formula but stratified by antimicrobial classification.[13] Targeted pathogen detection rate: Proportion of patients undergoing pathogen-specific tests before first antimicrobial dose (eg, blood cultures, CSF cultures, Legionella/Streptococcus antigen tests). Antimicrobial use metrics included: Antimicrobial use density (AUD): expressed as DDDs/100 patient-days, Defined Daily Doses (DDDs) in accordance with the guidelines for Anatomical Therapeutic Chemical (ATC) classification and DDD assignment,[14] and stratified AUD reported across the three-tier antimicrobial classification strata (overall, unrestricted, restricted, and special use-level antimicrobials) using an identical calculation method. Antimicrobial utilization rate: The percentage of hospitalized patients receiving antimicrobial therapy during their admission. Antimicrobial injection utilization rate: The percentage of hospitalized patients receiving injectable antimicrobial therapy. Economic indicators included: Per capita antimicrobial cost: Antimicrobial expenditure per patient in the antimicrobial-treated cohort. Antimicrobial cost proportion: Total antimicrobial costs as a percentage of total medical costs. Per capita laboratory cost: Laboratory testing expenditure per discharged patient. The multidrug-resistant organism (MDRO) isolate rate represents the percentage of non-duplicate clinical isolates resistant to ≥3 antimicrobial classes among all identified pathogens, calculated separately for key species: carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenem-resistant *Klebsiella pneumoniae* (CRKP), carbapenem-resistant *Escherichia coli* (CREC), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), and methicillin-resistant *Staphylococcus aureus* (MRSA).[15] For duplicate pathogen test results from the same patient during the same hospitalization, only the initial result was included in the analysis to avoid data redundancy.

Statistical Analysis

Interrupted time series analysis was conducted using segmented linear regression:

$Y = \beta_0 + \beta_1 \times \text{time} + \beta_2 \times \text{intervention} + \beta_3 \times \text{posttime} + \varepsilon$, where β_0 represents the baseline intercept, β_1 the pre-intervention slope, β_2 the immediate level change following intervention implementation, and β_3 the post-intervention slope change ($\beta_1 + \beta_3 =$ post-intervention slope).[12] In this model, the outcome variable (Y) represented the monthly value for each indicator assessed in this study, including the overall and stratified pre-therapy pathogen detection specimen submission rates, antimicrobial use density (overall and by class), antimicrobial utilization rate, antimicrobial injection utilization rate, per capita antimicrobial cost, antimicrobial cost proportion, per capita laboratory cost, and the isolate rates for CRAB, CREC, CRKP, CRPA, and MRSA. Time was coded as a sequential index (time = n - 1), intervention as a binary indicator (0 = pre-intervention; 1 = post-intervention), and posttime as the post-intervention time counter (0 during pre-intervention; 0–25 during post-intervention). Autocorrelation was assessed using the Durbin-Watson statistic; models with DW ≈ 2 (indicating no autocorrelation) were fitted using ordinary least squares (OLS) regression, while models with autocorrelation were fitted using Newey-West heteroscedasticity- and autocorrelation-consistent (HAC) standard errors. Analyses were performed using Stata/MP 18.0 (StataCorp LLC, College Station, TX, USA) with statistical significance defined as $P < 0.05$.

Results

Regression Analysis Results for Pre-Therapy Pathogen Detection Specimen Submission Rate

Segmented regression analysis results and monthly trends are presented in Table 1 and Figure 1. For the overall pre-therapy pathogen detection specimen submission rate, the pre-intervention trend was non-significant ($\beta_1 = -0.07$, $P = 0.734$), with a significant immediate increase in the first intervention month ($\beta_2 = 9.82$, $P = 0.009$); the post-intervention slope change was significantly positive ($\beta_3 = 1.21$, $P < 0.001$), yielding a post-intervention slope of $-0.07 + 1.21 = 1.14$, demonstrating an upward trend.

Table 1 ITSA Results for Pathogen Detection Specimen Submission Rates (Pre-Therapy SSR) for Antimicrobial Agents

	Parameter Evaluated	**Parameter Values**	**t**	**95% CI**		***P***
Overall antimicrobials Pre-therapy SSR (%)	Baseline Level(β_0)	43.42	40.31	41.23	45.61	<0.001
	Pre-intervention trend (β_1)	−0.07	−0.34	−0.52	0.37	0.734
	Level Change(β_2)	9.82	2.76	2.58	17.05	0.009
	Post-intervention slope change (β_3)	1.21	4.34	0.64	1.78	<0.001
Unrestricted use-level antimicrobials Pre-therapy SSR (%)	Baseline Level(β_0)	37.30	24.52	34.21	40.40	<0.001
	Pre-intervention trend (β_1)	0.50	1.43	−0.21	1.22	0.161
	Level Change(β_2)	2.81	0.63	−6.27	11.89	0.534
	Post-intervention slope change (β_3)	0.82	2.07	0.01	1.62	0.046
Restricted use-level antimicrobials Pre-therapy SSR (%)	Baseline Level(β_0)	53.67	84.32	52.37	54.96	<0.001
	Pre-intervention trend (β_1)	−0.42	−3.26	−0.69	−0.16	0.003
	Level Change(β_2)	10.30	3.24	3.83	16.76	0.003
	Post-intervention slope change (β_3)	1.53	7.54	1.12	1.94	<0.001
Special use-level Antimicrobials Pre-therapy SSR (%)	Baseline Level(β_0)	85.63	78.60	83.42	87.85	<0.001
	Pre-intervention trend (β_1)	−0.16	−1.09	−0.46	0.14	0.283
	Level Change(β_2)	−8.42	−2.16	−16.35	−0.49	0.038
	Post-intervention slope change (β_3)	0.62	2.34	0.08	1.16	0.025
Targeted Pre-therapy SSR (%)	Baseline Level(β_0)	35.10	35.52	33.09	37.11	<0.001
	Pre-intervention trend (β_1)	−0.17	−0.83	−0.61	0.26	0.415
	Level Change(β_2)	8.26	3.75	3.79	12.74	0.001
	Post-intervention slope change (β_3)	0.70	3.19	0.25	1.14	0.003

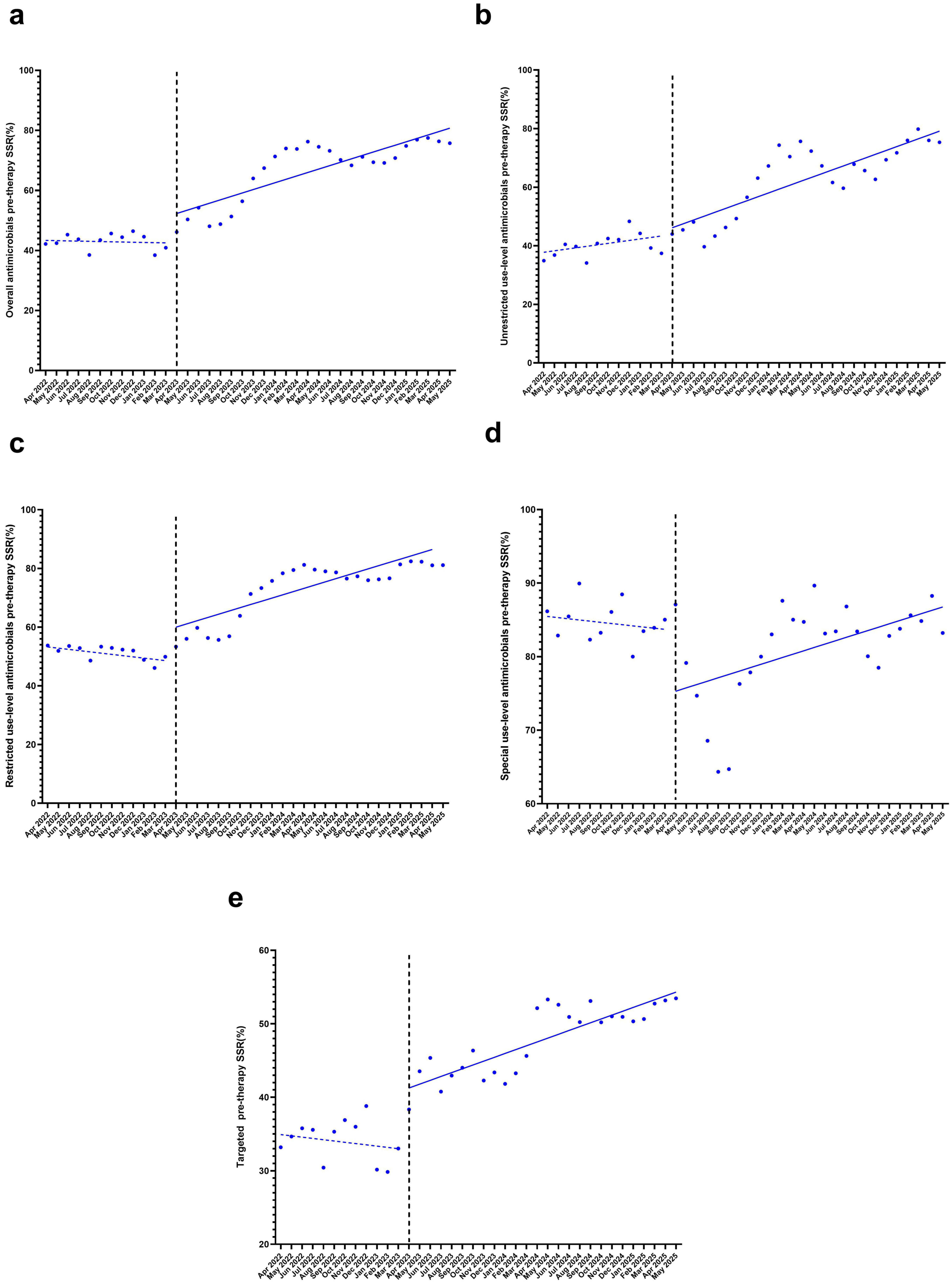

Figure 1 Temporal trends in pre-therapy specimen submission rates by antimicrobial category. (**a**) Overall antimicrobials, (**b**) Unrestricted use-level antimicrobials, (**c**) Restricted use-level antimicrobials, (**d**) Special use-level antimicrobials, (**e**) Targeted pathogen detection. Data points represent observed monthly values (SSR, %). Dashed line: pre-intervention fitted trend (segmented linear regression); Solid line: post-intervention fitted trend; Vertical dashed line: intervention timepoint (April 2023).
Abbreviation: SSR, specimen submission rate.

For unrestricted use-level antimicrobials, neither the pre-intervention trend ($\beta_1 = 0.50$) nor the immediate change ($\beta_2 = 2.81$) was significant (both $P > 0.05$); a positive post-intervention slope change ($\beta_3 = 0.82$, $P = 0.046$) resulted in a post-intervention slope of 0.50 + 0.82 = 1.32, showing an upward trend.

For restricted use-level antimicrobials, a significant pre-intervention decline ($\beta_1 = -0.42$, $P = 0.003$) was reversed by an immediate increase ($\beta_2 = 10.30$, $P = 0.003$); a positive post-intervention slope change ($\beta_3 = 1.53$, $P < 0.001$) established an upward trend (post-intervention slope = −0.42 + 1.53 = 1.11).

For special use-level antimicrobials had a non-significant pre-intervention trend ($\beta_1 = -0.16$, $P = 0.283$) with an initial reduction ($\beta_2 = -8.42$, $P = 0.038$); nevertheless, a positive post-intervention slope change emerged ($\beta_3 = 0.62$, $P = 0.025$), confirming an upward trend (post-intervention slope = −0.16 + 0.62 = 0.46). Targeted pathogen detection exhibited a non-significant pre-intervention trend ($\beta_1 = -0.17$, $P = 0.415$), a significant immediate increase ($\beta_2 = 8.26$, $P = 0.001$), and a positive post-intervention slope change ($\beta_3 = 0.70$, $P = 0.003$), establishing an upward trend (post-intervention slope = −0.17 + 0.70 = 0.53).

Regression Analysis Results for Antimicrobial Use Intensity

Segmented regression analysis results and monthly trends are presented in Table 2 and Figure 2. Overall antimicrobial use density exhibited a significant pre-intervention increase ($\beta_1 = 1.22$, P = 0.002), with non-significant immediate change ($\beta_2 = -1.63$, P = 0.619), transitioning to a sustained downward trend through a significantly negative slope change ($\beta_3 = -1.36$, P = 0.001; net slope = −0.14).

Unrestricted antimicrobials demonstrated heightened responsiveness: a significant pre-intervention increase ($\beta_1 = 0.41$, P < 0.001) reversed through an immediate reduction ($\beta_2 = -1.27$, P = 0.031) and accelerated decline ($\beta_3 = -0.57$, P < 0.001), yielding the steepest negative slope among categories (net = −0.16).

Table 2 ITSA Results for Antimicrobial Use Intensity by Class (DDDs/100 Patient-Days)

Antimicrobial Class	**Parameter Evaluated**	**Parameter Values**	**t**	**95% CI**		***P***
Overall antimicrobials	Baseline Level(β_0)	26.85	18.24	23.86	29.84	<0.001
	Pre-intervention trend (β_1)	1.22	3.38	0.49	1.95	0.002
	Level Change(β_2)	−1.63	−0.5	−8.21	4.96	0.619
	Post-intervention slope change (β_3)	−1.36	−3.64	−2.12	−0.6	0.001
Unrestricted use-level antimicrobials	Baseline Level(β_0)	9.97	18.57	8.88	11.06	<0.001
	Pre-intervention trend (β_1)	0.41	5.61	0.26	0.56	<0.001
	Level Change(β_2)	−1.27	−2.25	−2.41	−0.13	0.031
	Post-intervention slope change (β_3)	−0.57	−7.41	−0.73	−0.41	<0.001
Restricted use-level antimicrobials	Baseline Level(β_0)	14.09	17.92	12.50	15.69	<0.001
	Pre-intervention trend (β_1)	0.47	2.35	0.06	0.87	0.025
	Level Change(β_2)	1.80	0.83	−2.61	6.22	0.412
	Post-intervention slope change (β_3)	−0.52	−2.26	−0.98	−0.05	0.031
Special use-level Antimicrobials	Baseline Level(β_0)	2.80	7.07	1.99	3.60	<0.001
	Pre-intervention trend (β_1)	0.34	5.52	0.21	0.46	<0.001
	Level Change(β_2)	−2.11	−3.99	−3.18	−1.03	<0.001
	Post-intervention slope change (β_3)	−0.27	−4.25	−0.40	−0.14	<0.001

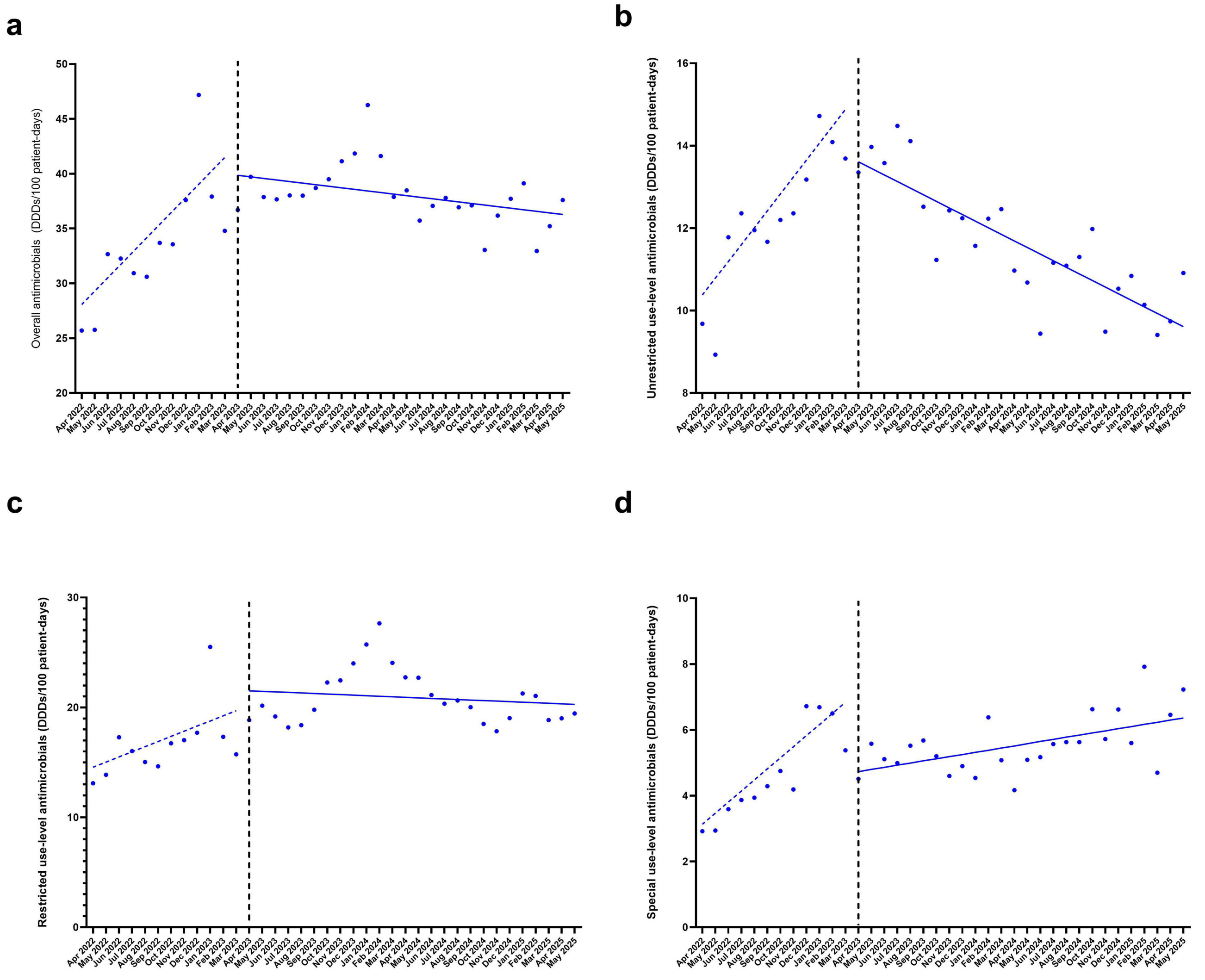

Figure 2 Temporal Trends in Antimicrobial Use Intensity by Category (DDDs/100 patient-days). (**a**) Overall antimicrobials, (**b**) Unrestricted use-level antimicrobials, (**c**) Restricted use-level antimicrobials, (**d**) Special use-level antimicrobials. Data points represent observed monthly values. Dashed line: pre-intervention fitted trend (segmented linear regression); Solid line: post-intervention fitted trend; Vertical dashed line: intervention timepoint (April 2023).
Abbreviation: DDD, defined daily dose.

Restricted antimicrobials showed moderated effects—significant pre-intervention growth ($\beta_1 = 0.47$, $P = 0.025$), non-significant immediate change ($\beta_2 = 1.80$, $P = 0.412$), but subsequent decline through negative slope change ($\beta_3 = -0.52$, $P = 0.031$; net slope = −0.05).

Special-use antimicrobials exhibited a significant pre-intervention increase ($\beta_1 = 0.34$, $P < 0.001$), followed by an immediate reduction ($\beta_2 = -2.11$, $P < 0.001$) and negative post-intervention slope change ($\beta_3 = -0.27$, $P < 0.001$), resulting in a net post-intervention slope of +0.07, indicating growth deceleration.

Regression Analysis Results for Other Process Indicators and Economic Benefit Indicators of Antimicrobial Stewardship

Segmented regression analysis results and monthly trends are presented in Table 3 and Figure 3. For antimicrobial utilization rate, a non-significant pre-intervention trend ($\beta_1 = 0.46$, $P = 0.117$) and a non-significant immediate change ($\beta_2 = 0.59$, $P = 0.814$); a significantly negative slope change ($\beta_3 = -0.68$, $P = 0.031$) yielded a post-intervention slope of $0.46 + (-0.68) = -0.22$, confirming a downward trend.

Table 3 ITSA Results for Additional Process Metrics and Economic Outcomes in Antimicrobial Stewardship

	Parameter Evaluated	Parameter Values	t	95% CI		*P*
Antimicrobial Use Rate (%)	Baseline Level(β_0)	32.53	17.46	28.74	36.32	<0.001
	Pre-intervention trend (β_1)	0.46	1.61	−0.12	1.04	0.117
	Level Change(β_2)	0.59	0.24	−4.46	5.64	0.814
	Post-intervention slope change (β_3)	−0.68	−2.25	−1.29	−0.07	0.031
Antimicrobial injection utilization rate (%)	Baseline Level(β_0)	31.43	16.91	27.65	35.21	<0.001
	Pre-intervention trend (β_1)	0.47	1.66	−0.11	1.06	0.107
	Level Change(β_2)	0.32	0.13	−4.72	5.36	0.897
	Post-intervention slope change (β_3)	−0.68	−2.25	−1.28	−0.07	0.031
Per Capita Antimicrobial Cost(CNY)	Baseline Level(β_0)	178.63	15.70	155.52	201.75	<0.001
	Pre-intervention trend (β_1)	6.96	2.51	1.32	12.59	0.017
	Level Change(β_2)	−24.41	−0.90	−79.62	30.81	0.375
	Post-intervention slope change (β_3)	−10.00	−3.45	−15.90	−4.11	0.002
Antimicrobial cost proportion (%)	Baseline Level(β_0)	1.78	13.72	1.52	2.05	<0.001
	Pre-intervention trend (β_1)	0.09	4.42	0.05	0.13	<0.001
	Level Change(β_2)	−0.27	−1.56	−0.62	0.08	0.127
	Post-intervention slope change (β_3)	−0.12	−5.82	−0.16	−0.08	<0.001
Per capita laboratory cost (CNY)	Baseline Level(β_0)	1572.81	91.10	1537.72	1607.89	<0.001
	Pre-intervention trend (β_1)	−3.32	−0.74	−12.48	5.85	0.467
	Level Change(β_2)	−88.66	−1.61	−200.65	23.33	0.117
	Post-intervention slope change (β_3)	0.59	0.12	−9.48	10.66	0.906

For antimicrobial injection utilization rate, a non-significant pre-intervention trend ($\beta_1 = 0.47$, $P = 0.107$) and a non-significant immediate change ($\beta_2 = 0.32$, $P = 0.897$); a significantly negative slope change ($\beta_3 = -0.68$, $P = 0.031$) established a downward trend (post-intervention slope = 0.47 + (−0.68) = −0.21).

For antimicrobial cost proportion, an upward pre-intervention trend ($\beta_1 = 0.09$, P < 0.001) with a non-significant immediate change ($\beta_2 = -0.27$, P = 0.127); a significantly negative slope change ($\beta_3 = -0.12$, P < 0.001) confirmed a downward trend (post-intervention slope = 0.09 + (−0.12) = −0.03).

For per capita antimicrobial cost, a significant upward pre-intervention trend ($\beta_1 = 6.96$, $P = 0.017$) with a non-significant immediate change ($\beta_2 = -24.41$, $P = 0.375$); a significantly negative slope change ($\beta_3 = -10.00$, $P = 0.002$) demonstrated a downward trend (post-intervention slope = 6.96 + (−10.00) = −3.04). Per capita laboratory cost showed no significant changes in pre-intervention trend, immediate change, or post-intervention slope (all $P > 0.05$).

Regression Analysis Results for MDRO Isolate Rates

Segmented regression analysis revealed pathogen-specific responses to antimicrobial stewardship (Table 4 and Figure 4). Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) exhibited a significant pre-intervention upward trend ($\beta_1 = 1.32$, P < 0.001), immediate reduction post-intervention ($\beta_2 = -16.97$, P < 0.001), and sustained declining trajectory ($\beta_3 = -0.87$, P = 0.013). For other multidrug-resistant organisms, while no statistically significant changes were observed (all

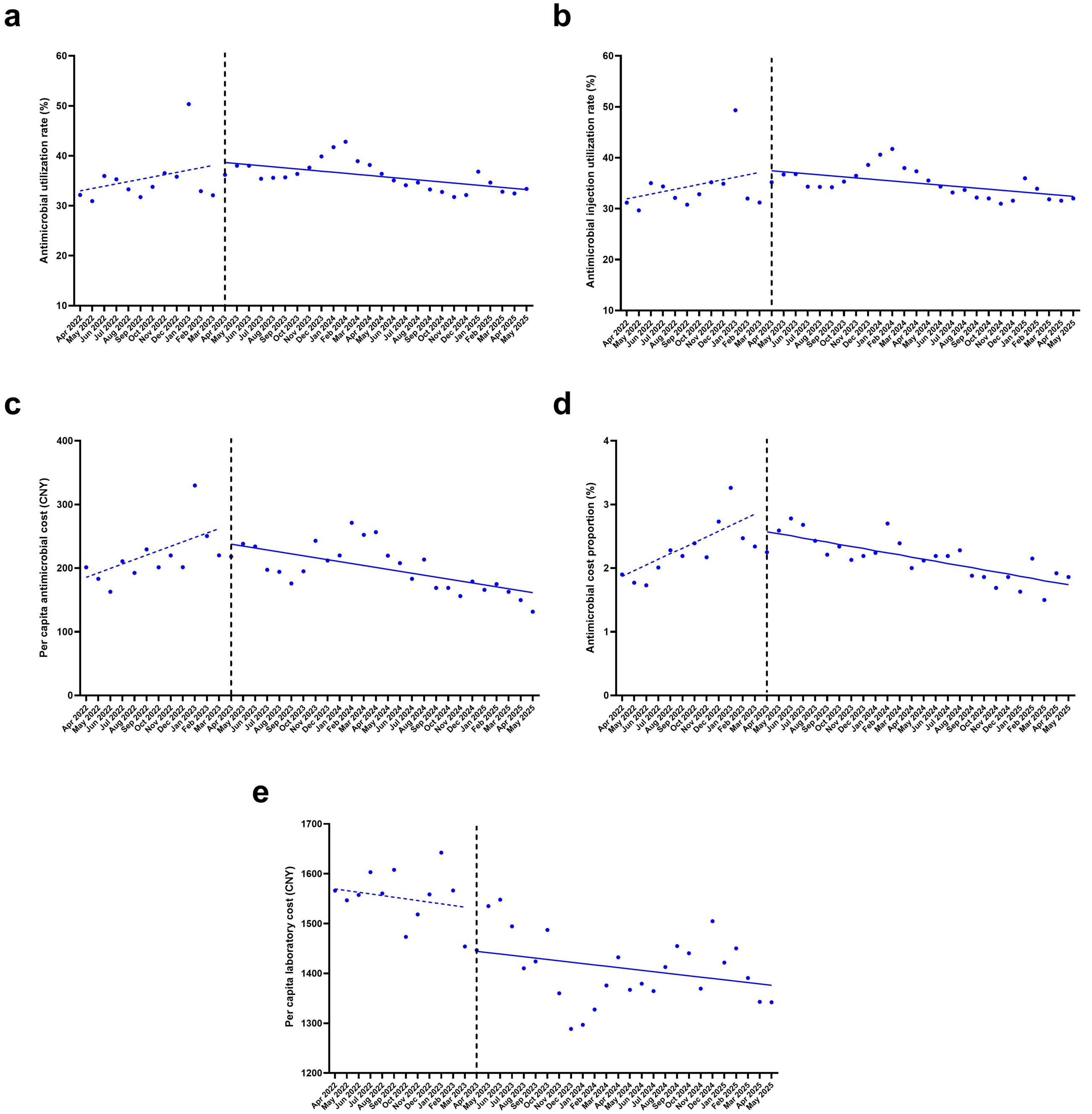

Figure 3 Temporal Trends in Additional Process Metrics and Economic Outcomes of Antimicrobial Stewardship. (**a**) Antimicrobial utilization rate (%), (**b**) Antimicrobial injection utilization rate (%), (**c**) Per capita antimicrobial cost (CNY), (**d**) Antimicrobial cost proportion (%), (**e**) Per capita laboratory cost (CNY). Data points represent observed monthly values. Dashed line: pre-intervention fitted trend (segmented linear regression); Solid line: post-intervention fitted trend; Vertical dashed line: intervention timepoint (April 2023).

Abbreviation: CNY, Chinese Yuan.

$P > 0.05$), carbapenem-resistant *Acinetobacter baumannii* (CRAB) and methicillin-resistant *Staphylococcus aureus* (MRSA) demonstrated directional shifts from pre-intervention upward tendencies to post-intervention decline, whereas carbapenem-resistant *Escherichia coli* and carbapenem-resistant *Pseudomonas aeruginosa* showed post-intervention upward trajectories.

Table 4 ITSA Results for Multidrug-Resistant Organism (MDRO) Isolate Rates

	Parameter Evaluated	**Parameter values**	**t**	**95% CI**		***P***
CRAB Isolate Rate (%)	Baseline Level(β_0)	53.59	6.37	36.49	70.69	<0.001
	Pre-intervention trend (β_1)	1.75	1.4	−0.80	4.30	0.171
	Level Change(β_2)	−14.20	−1.37	−35.34	6.94	0.181
	Post-intervention slope change (β_3)	−1.13	−0.9	−3.70	1.43	0.376
CREC Isolate Rate (%)	Baseline Level(β_0)	4.86	6.92	3.43	6.28	<0.001
	Pre-intervention trend (β_1)	−0.04	−0.58	−0.20	0.11	0.567
	Level Change(β_2)	−1.71	−1.91	−3.53	0.11	0.065
	Post-intervention slope change (β_3)	0.12	1.39	−0.06	0.30	0.174
CRKP Isolate Rate (%)	Baseline Level(β_0)	21.73	14.80	19.46	24.00	<0.001
	Pre-intervention trend (β_1)	1.32	4.04	0.91	1.73	<0.001
	Level Change(β_2)	−16.97	−4.24	−23.73	−10.21	<0.001
	Post-intervention slope change (β_3)	−0.87	−2.05	−1.55	−0.19	0.013
CRPA Isolate Rate (%)	Baseline Level(β_0)	23.29	8.02	17.40	29.17	<0.001
	Pre-intervention trend (β_1)	0.02	0.04	−0.93	0.97	0.965
	Level Change(β_2)	−0.005	0	−8.76	8.75	0.999
	Post-intervention slope change (β_3)	0.50	0.99	−0.49	1.48	0.312
MRSA Isolate Rate (%)	Baseline Level(β_0)	24.37	4.33	12.57	36.17	<0.001
	Pre-intervention trend (β_1)	0.69	0.93	−0.80	2.18	0.352
	Level Change(β_2)	−0.85	−0.17	−9.16	7.47	0.837
	Post-intervention slope change (β_3)	−0.78	−1.00	−2.36	0.80	0.325

Discussion

This study evaluated the impact of China's compulsory national antimicrobial stewardship policy on optimizing pre-therapy pathogen detection specimen submission rate, reducing nonessential antimicrobial utilization, and mitigating antimicrobial resistance at a tertiary care hospital.[16,17] The multifaceted intervention significantly enhanced diagnostic stewardship efficacy, inducing concurrent declines in antimicrobial utilization intensity and cost burdens. Selective reductions in key resistant pathogens were observed, though overall multidrug-resistant organism prevalence exhibited heterogeneous responses. Nevertheless, containing the emergence and dissemination of drug-resistant bacteria critically depends on optimized antibiotic use and minimized nonessential antimicrobial exposure.[18,19] Elevating the pre-therapy specimen submission rate constitutes a fundamental prerequisite: standardized etiological testing enables pathogen identification and susceptibility profiling, thereby establishing an objective diagnostic foundation to facilitate the accelerated shift from empirical to targeted therapy.[20]

This study demonstrates that comprehensive interventions significantly improved pre-therapy pathogen detection specimen submission rate—consistent with Zhang et al's multicenter findings on the efficacy of collaborative stewardship.[21,22] Notably, the transition from perfunctory compliance to precision diagnostics was evidenced by sustained gains in targeted pathogen detection, establishing critical foundations for evidence-based anti-infective therapy. Whereas Du et al reported homogeneous pre-therapy specimen submission rate improvements across antimicrobial

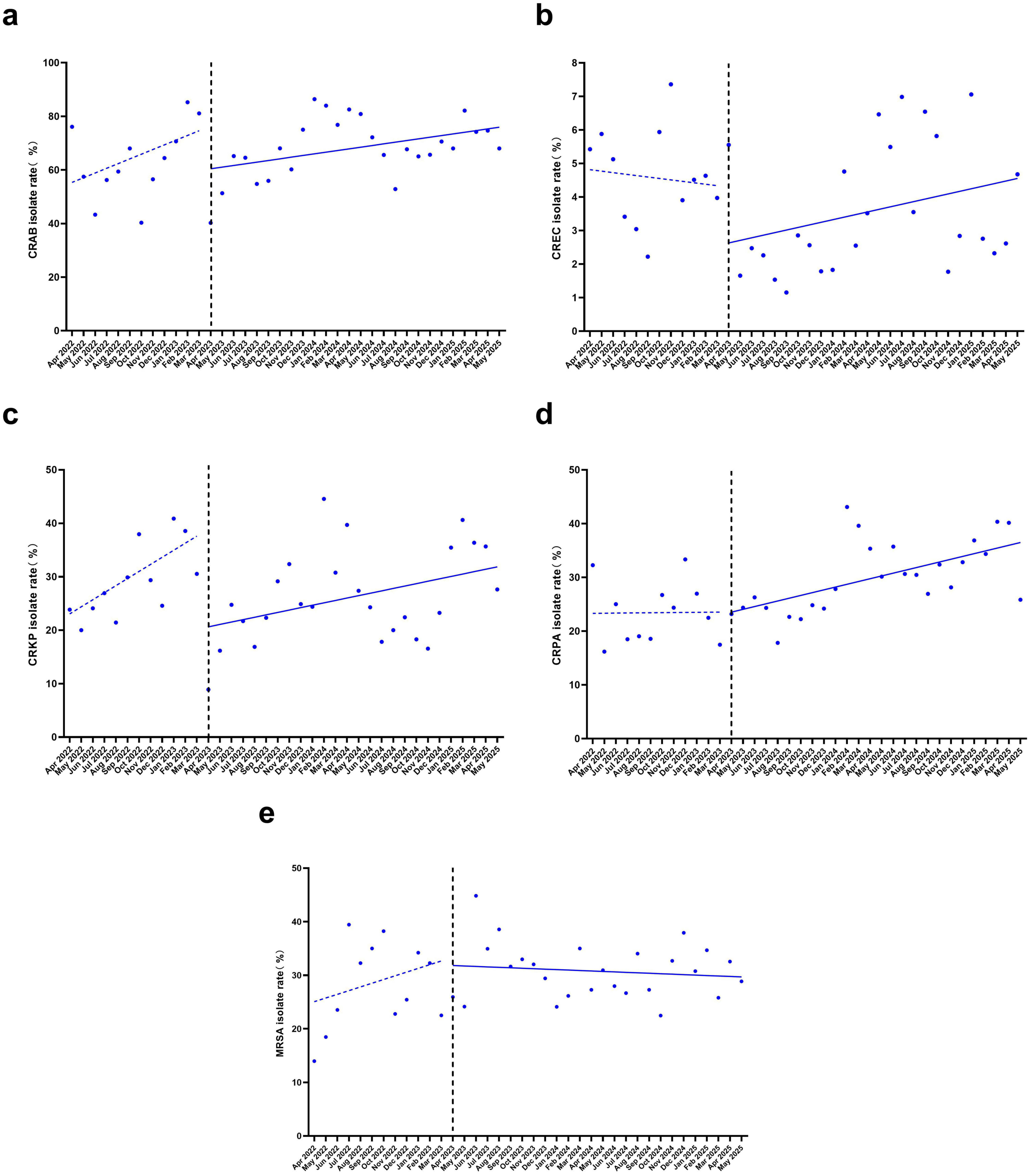

Figure 4 Temporal Trends in Multidrug-Resistant Organism (MDRO) Isolate Rates. (**a**) CRAB isolate rate (%), (**b**) CREC isolate rate (%), (**c**) CRKP isolate rate (%), (**d**) CRPA isolate rate (%), (**e**) MRSA isolate rate (%). Data points represent observed monthly values. Dashed line: pre-intervention fitted trend (segmented linear regression); Solid line: post-intervention fitted trend; Vertical dashed line: intervention timepoint (April 2023).

classes,[23] our stratified analysis revealed divergent response patterns: restricted-use agents exhibited maximal improvement, aligning with their status as stewardship priorities and reflecting successful clinical standardization. In contrast, special-use antimicrobials exhibited a characteristic J-curve response: a significant initial reduction reflecting clinician adaptation during regulatory intensification, followed by progressive normalization as interventions matured—highlighting the necessity for phased implementation balancing regulatory stringency with clinical feasibility.[24]

Consistent with Xiao et al's nationwide analysis,[25] our intervention achieved significant reductions in antimicrobial consumption across all drug classes—potentially attributable to optimized prescribing driven by enhanced infection identification.[26] In contrast to Garwan et al,[27,28] who observed compensatory intravenous-to-oral substitution during stewardship implementation, we documented parallel declines in both the overall antimicrobial utilization rate and the antimicrobial injection utilization rate. This divergence likely reflects the role of our hospital-wide electronic mandate system in simultaneously constraining prescribing behaviors across all administration routes—representing a structural distinction from education-focused interventions.

Notably, class-specific response patterns emerged: unrestricted antimicrobials demonstrated the steepest decline, a trend aligned with their role as frontline therapeutic agents, while special-use antimicrobials exhibited adaptive prescribing dynamics amid intensified regulatory oversight. These differential trajectories remained undetected in aggregated analyses—a limitation characterizing prior studies relying solely on such data.[25] Our stratified interrupted time series (ITS) methodology, however, successfully identified these patterns, demonstrating its distinctive capacity to capture antimicrobial stewardship's heterogeneous impacts. Economically, per capita laboratory costs remained stable ($P > 0.05$) despite rising testing volumes, indicating controlled cost-shifting risks. This outcome aligns with the reduction in patient financial burdens achieved through rational antimicrobial use.[29] It may be attributed to sustained increases in the targeted pre-therapy pathogen detection specimen submission rate. By enabling precise resource allocation and reducing non-essential laboratory tests, this practice optimizes diagnostic efficiency while containing expenditures.

The intervention achieved limited reduction in multidrug-resistant organism (MDRO) isolate rates overall, despite increased specimen submission rates theoretically curbing resistance.[15,30] Segmented regression confirmed only carbapenem-resistant *Klebsiella pneumoniae* (CRKP) achieved statistically significant immediate and sustained declines. Although CRAB, CREC, CRPA, and MRSA exhibited non-significant changes, these findings suggest that initial stewardship effects may require an extended observation period to achieve statistical significance. This is consistent with previous studies: Against the backdrop of established high resistance levels, reduced antibiotic consumption primarily slows down the growth rate of resistance. In the short term, the core value of antimicrobial stewardship measures lies in "decelerating growth" rather than "reversing trends".[31,32] Throughout this study, the institution prioritized elevating pre-therapy pathogen detection specimen submission rate while neglecting concurrent reinforcement of critical infection control pillars—including enhanced environmental disinfection, monitored contact-isolation compliance, and improved hand hygiene—despite multidrug-resistant organism (MDRO) persistence being governed by the interdependent triad of antimicrobial selective pressure, host immunity, and environmental reservoirs.[33]

Our data reveal recurrent winter (December–February) increases in antimicrobial use and select multidrug-resistant organism (MDRO) rates, as illustrated in Figures 2 (antimicrobial use intensity), 3 (process and economic metrics), and 4a/c (CRAB and CRKP). This pattern is attributable to well-characterized seasonal surges in bacterial respiratory tract infections, particularly community-acquired pneumonia (CAP). Heightened admissions for CAP and other severe respiratory syndromes prompt the initiation of empirical antimicrobial therapy—a standard clinical approach to managing potential bacterial pathogens such as *Streptococcus pneumoniae* and *Haemophilus influenzae* before definitive microbiological results are available.[34,35] This established seasonal practice accounts for the observed transient peaks in antimicrobial consumption and the associated selective pressure on resistant pathogens, a dynamic consistent with established seasonal epidemiology.The entire study period (April 2022–May 2025) coincided with the later stages of the COVID-19 pandemic, during which our institution maintained stabilized operational conditions. Importantly, institutional infection control surveillance identified no discrete notifiable disease outbreaks or major public health disruptions during this interval, thereby ruling out emergent epidemic shocks as a plausible cause for the observed fluctuations and reinforcing the attribution of the significant long-term trends to the April 2023 antimicrobial stewardship intervention.

A critical evaluation identified key systemic and operational barriers to the intervention's effectiveness, with the primary challenge centering on diagnostic stewardship optimization. While the EHR mandate successfully increased overall specimen submission rates, promoting consistent use of high-quality targeted testing encountered a fundamental paradox: conventional culture methods were perceived as having limited clinical utility due to slow turnaround times, whereas rapid advanced diagnostics remained financially inaccessible under prevailing reimbursement policies.[36] This constraint impeded meaningful improvements in targeted pathogen detection—an outcome essential for reducing empirical antimicrobial use. Our integrated strategy combined department-specific, face-to-face education sessions focused on antimicrobial optimization through targeted testing with systematic sharing of outcome data demonstrating the relationship between testing adherence and improved clinical outcomes, including reduced time to effective therapy and lower hospitalization costs. These targeted initiatives fostered shared accountability among clinicians and mitigated the principal implementation barriers.

This study has several limitations that should be considered. First, its monocentric design may affect generalizability, necessitating future multicentric validation. Second, while the ITS design controls for underlying trends, we did not perform formal sensitivity analyses for confounders such as seasonal epidemics. Third, although we present promising economic data, a formal cost-effectiveness analysis would strengthen the argument for policymakers. Finally, and most critically from an evolving methodological perspective, our intervention demonstrates the benefits of a traditional stewardship program but does not include a direct comparison with emerging artificial intelligence (AI) and machine learning (ML) approaches. Recent systematic reviews document the superior predictive performance of AI/ML models for optimizing therapy compared to conventional methods.[37] Therefore, a pivotal future direction lies in integrating AI-based clinical decision support within multicentric stewardship frameworks to enable more proactive and personalized interventions.

These methodological considerations reinforce our central conclusion. The findings robustly demonstrate that a diagnostic stewardship intervention can significantly optimize antimicrobial prescribing. However, the modest impact on most MDROs empirically validates that enhancing the pre-therapy pathogen detection specimen submission rate alone is insufficient for comprehensively disrupting the ecological chain of resistant pathogen transmission. Consequently, sustainable containment necessitates an integrated, long-term strategy that synergistically combines surveillance, robust infection control, antimicrobial stewardship, and education.

Conclusion

This study demonstrates that a multifaceted intervention successfully enhanced the pre-therapy pathogen detection specimen submission rate, which was followed by sustained reductions in antimicrobial utilization, intensity, and cost. However, the limited impact on antimicrobial resistance—with a significant reduction observed only for CRKP—indicates that improving the specimen submission rate alone cannot comprehensively curb the transmission of resistant pathogens. Our findings therefore advocate for a strategic shift toward an integrated model. Achieving sustainable containment of antimicrobial resistance will require synchronizing reinforced infection prevention and control with antimicrobial stewardship, augmented by AI-driven clinical decision support within multicentric validation frameworks.

Ethics Approval

This study was reviewed and approved by the Ethics Committee of Nanxishan Hospital of Guangxi Zhuang Autonomous Region (Approval No: NXSYY-2025-180Y). The Committee formally approved the waiver of informed consent, which was applied for and granted based on the retrospective nature of the study and the use of anonymized patient data. All procedures were performed in accordance with the ethical standards of the Declaration of Helsinki. All patient data were maintained under strict confidentiality.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Collaborators GAR. Global burden of bacterial antimicrobial resistance 1990-2021: a systematic analysis with forecasts to 2050. *Lancet*. 2024;404(10459):1199–1226. doi:10.1016/S0140-6736(24)01867-1
2. Lina Z, Jinyi L, Yafang L, Zongjiu Z. Current situation, problems and development strategies of antimicrobial stewardship in China. *Chin J Infect Control*. 2025;24(1):6–14.
3. ASPE. National action plan for combating antibiotic-resistant bacteria, 2020-2025. Available from: https://aspe.hhs.gov/reports/national-action-plan-combating-antibiotic-resistant-bacteria-2020-2025. Accessed October 11, 2025.

4. WHO. Global action plan on antimicrobial resistance. publicaciones de la organización Mundial de la Salud. Available from: https://www.who.int/publications/i/item/9789241509763. Accessed October 11, 2025.
5. Zhang M, Zhang X, Ye Y, Gao L. Effect of PDCA cycle in the management of pathogenic examination before antibiotic therapy. *Zhonghua Yi Yuan Gan Ran Za Zhi*. 2023;33(16):2523–2527.
6. Morgan DJ, Malani P, Diekema DJ. Diagnostic stewardship-leveraging the laboratory to improve antimicrobial use. *JAMA*. 2017;318(7):607–608. doi:10.1001/jama.2017.8531
7. Liu C. Antibiotic stewardship challenges in an evolving health-care market in China. *The Lancet. Infectious Diseases*. 2021;21(6):753–754. doi:10.1016/S1473-3099(20)30685-X
8. NHC. Notice of the gene-ral office of the national health commission on issuing the 2021 national medical quality and safety improvement goals: national health office medical letter. Available from: https://www.nhc.gov.cn/wjw/c100175/202102/6823244e8de14e8fbc8dbfbcc928bbc5.shtml. Accessed October 11, 2025.
9. Phan QTN, Le TD, Do QK, et al. Impact of antimicrobial stewardship intervention in clean and clean-contaminated surgical procedures at a Vietnamese national hospital. *Tropical Med Inter Health*. 2022;27(4):454–462. doi:10.1111/tmi.13738
10. Strumann C, Steinhaeuser J, Emcke T, Sönnichsen A, Goetz K. Communication training and the prescribing pattern of antibiotic prescription in primary health care. *PLoS One*. 2020;15(5):e0233345. doi:10.1371/journal.pone.0233345
11. Turner SL, Karahalios A, Forbes AB, Taljaard M, Grimshaw JM, McKenzie JE. Comparison of six statistical methods for interrupted time series studies: empirical evaluation of 190 published series. *BMC Med Res Methodol*. 2021;21(1):134. doi:10.1186/s12874-021-01306-w
12. SC Y, QQ W, Mao F, et al. The design of interrupted time series and its analytic methods. *Zhonghua Yu Fang Yi Xue Za Zhi*. 2019;53(8):858–864. doi:10.3760/cma.j.issn.0253-9624.2019.08.012
13. Council NH. Guiding principles for clinical application of antimicrobials 2015. Available from: https://www.nhc.gov.cn/yzygj/c100068/201508/9f7136d6fb034339a7c9348c72a8a1fd.shtml. Accessed October 11, 2025.
14. Norwegian Institute of Public Health. Guidelines for ATC classification and DDD assignment 2025. *ATC/DDD Index* Available from: https://atcddd.fhi.no/atc_ddd_index/. Accessed October 11, 2025.
15. Zhang X, Zhou L, Peng P, Zhang W, Liang C. Role of antimicrobial stewardship in modulating antibiotic use and mitigating bacterial resistance in a tertiary care setting during COVID-19. *Infect Drug Resist*. 2025;18:1647–1656. doi:10.2147/IDR.S500379
16. NHC. Notice of the gene-ral office of the national health commission on issuing the 2022 national medical quality and safety improvement goals: national health office medical letter. Available from: https://www.nhc.gov.cn/yzygj/c100068/202203/d5e4af0c96814da3974d25df0bfad607.shtml. Accessed October 11, 2025.
17. NHC. Notice of the gene-ral office of the national health commission on issuing the 2023 national medical quality and safety improvement goals: national health office medical letter. Available from: https://www.nhc.gov.cn/yzygj/c100068/202302/5d9f7e4ef1d8472fa9ac6d19140dfb83.shtml. Accessed October 11, 2025.
18. Bassetti S, Tschudin-Sutter S, Egli A, Osthoff M. Optimizing antibiotic therapies to reduce the risk of bacterial resistance. *Eur J Intern Med*. 2022;99:7–12. doi:10.1016/j.ejim.2022.01.029
19. Razzaque MS. Implementation of antimicrobial stewardship to reduce antimicrobial drug resistance. *Expert Rev Anti Infect Ther*. 2021;19(5):559–562. doi:10.1080/14787210.2021.1840977
20. Keij FM, Kornelisse RF, Tramper-Stranders GA, Allegaert K. Improved pathogen detection in neonatal sepsis to boost antibiotic stewardship. *Future Microbiol*. 2020;15(7):461–464. doi:10.2217/fmb-2019-0334
21. Su-xia X, Ke-wen J, Xin-xin H, Shan-shan Z, Hui-li Z. Impact of the RCA method combined with the PDCA cycle management model on the rate of pathogenic delivery before antimicrobials treatment in hospitalized patients. *Zhonghua Yi Yuan Gan Ran Za Zhi*. 2024;34(2):272–276.
22. Wang A, Qin K, Ma S. Improving antimicrobial utilization and infection control in ophthalmology: an information-assisted transparent supervision and multidisciplinary team model. *Infect Drug Resist*. 2024;17:5061–5072. doi:10.2147/IDR.S481050
23. Du K, Wushouer H, Huang T, et al. The changes of different restriction level adjustments on antibiotic use in China. *Int J Antimicrob Agents*. 2024;63(2):107073. doi:10.1016/j.ijantimicag.2023.107073
24. Yoo JS, Park JY, Chun H, et al. Impact of prolonged carbapenem use-focused antimicrobial stewardship on antimicrobial consumption and factors affecting acceptance of recommendations: a quasi-experimental study. *Sci Rep*. 2023;13(1):14501. doi:10.1038/s41598-023-41710-4
25. Xiao Y, Shen P, Zheng B, Zhou K, Luo Q, Li L. Change in antibiotic use in secondary and tertiary hospitals nationwide after a national antimicrobial stewardship campaign was launched in China, 2011-2016: an observational study. *J Infect Dis*. 2020;221(Suppl 2):S148–S155. doi:10.1093/infdis/jiz556
26. Trevas D, Caliendo AM, Hanson K, Levy J, Ginocchio CC. Diagnostic tests can stem the threat of antimicrobial resistance: infectious disease professionals can help. *Clin Infect Dis*. 2021;72(11):e893–e900. doi:10.1093/cid/ciaa1527
27. Garwan YM, Alsalloum MA, Thabit AK, Jose J, Eljaaly K. Effectiveness of antimicrobial stewardship interventions on early switch from intravenous-to-oral antimicrobials in hospitalized adults: a systematic review. *Am J Infect Control*. 2023;51(1):89–98. doi:10.1016/j.ajic.2022.05.017
28. Hermes VC, Loureiro AP, Assis MP, et al. Pharmacoeconomic and antimicrobial stewardship analysis in waste management: beyond switching drug administration route. *Am J Infect Control*. 2023;51(12):1334–1338. doi:10.1016/j.ajic.2023.06.003
29. Wang Y, Zhou C, Liu C, Liu S, Liu X, Li X. The impact of pharmacist-led antimicrobial stewardship program on antibiotic use in a county-level tertiary general hospital in China: a retrospective study using difference-in-differences design. *Front Public Health*. 2022;10:1012690. doi:10.3389/fpubh.2022.1012690
30. Yusef D, Hayajneh WA, Bani Issa A, et al. Impact of an antimicrobial stewardship programme on reducing broad-spectrum antibiotic use and its effect on carbapenem-resistant acinetobacter baumannii (CRAb) in hospitals in Jordan. *J Antimicrob Chemotherap*. 2021;76(2):516–523. doi:10.1093/jac/dkaa464
31. Rahman S, Kesselheim AS, Hollis A. Persistence of resistance: a panel data analysis of the effect of antibiotic usage on the prevalence of resistance. *J Antibiotic*. 2023;76(5):270–278. doi:10.1038/s41429-023-00601-6
32. Naito Y, Maeda M, Nagatomo Y, et al. Impact of the antimicrobial stewardship team intervention focusing on changes in prescribing trends and the rate of carbapenem-resistant P. aeruginosa. *Yakugaku Zasshi*. 2022;142(5):527–534. doi:10.1248/yakushi.21-00202

33. Ji B, Ye W. Prevention and control of hospital-acquired infections with multidrug-resistant organism: a review. *Medicine*. 2024;103(4):e37018. doi:10.1097/MD.0000000000037018
34. Cheysson F, Brun-Buisson C, Opatowski L, et al. Outpatient antibiotic use attributable to viral acute lower respiratory tract infections during the cold season in France, 2010-2017. *Int J Antimicrob Agents*. 2021;57(6):106339. doi:10.1016/j.ijantimicag.2021.106339
35. Singer R, Abu Sin M, Tenenbaum T, et al. The increase in invasive bacterial infections with respiratory transmission in Germany, 2022/2023. *Dtsch Arztebl Int*. 2024;121(4):114–120. doi:10.3238/arztebl.m2023.0261
36. Peri AM, Harris PNA, Paterson DL. Culture-independent detection systems for bloodstream infection. *Clin Microbiol Infect*. 2022;28(2):195–201. doi:10.1016/j.cmi.2021.09.039
37. Pinto A, Pennisi F, Ricciardi GE, Signorelli C, Gianfredi V. Evaluating the impact of artificial intelligence in antimicrobial stewardship: a comparative meta-analysis with traditional risk scoring systems. *Infect Dis Now*. 2025;55(5):105090. doi:10.1016/j.idnow.2025.105090

Infection and Drug Resistance

Dovepress
Taylor & Francis Group

Publish your work in this journal

Infection and Drug Resistance is an international, peer-reviewed open-access journal that focuses on the optimal treatment of infection (bacterial, fungal and viral) and the development and institution of preventive strategies to minimize the development and spread of resistance. The journal is specifically concerned with the epidemiology of antibiotic resistance and the mechanisms of resistance development and diffusion in both hospitals and the community. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: https://www.dovepress.com/infection-and-drug-resistance-journal