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Abstract

Background Antimicrobial overuse in paediatrics remains a critical global public health crisis accelerating antimicrobial resistance (AMR)[1]. Standard single-component antimicrobial stewardship programmes (ASPs) often produce only temporary improvements and fail to drive long-term behavioural shifts in complex paediatric clinical environments[2].

Methods We conducted a retrospective quasi-experimental interrupted time series (ITS) analysis at a 1000-bed tertiary children's hospital in Dongguan, China, spanning 48 months

(January 2022–December 2025). The hospital was Dongguan Eighth People's Hospital (Dongguan Children's Hospital). The study was split into three phases: 12-month pre-intervention baseline (2022), 12-month ASP implementation (2023), and 24-month post-implementation follow-up (2024–2025). A five-pillar paediatric-targeted ASP was fully rolled out in January 2023, consisting of leadership governance, embedded electronic clinical guidelines, real-time collaborative prescription audit and feedback, institutional education and caregiver awareness and attitude change, and transparent departmental performance reporting. The primary endpoint was antibiotic use density (AUD), quantified as defined daily doses (DDD) per 100 patient-days. Segmented linear regression with Prais-Winsten transformation was used to account for residual autocorrelation; a two-sided p-value < 0.05 was considered statistically significant.

Results A total of 48 months of data were analysed. The mean monthly AUD decreased significantly from 43.15 ± 7.39 DDD/100 patient-days in 2022 to 28.83 ± 2.05 DDD/100 patient-days in 2025, representing a relative reduction of 33.2%. ITS analysis confirmed a significant immediate level change of -10.53 DDD/100 patient-days (95% CI: -15.2 to -5.86, $P < 0.001$) upon

intervention initiation, followed by a sustained downward trend (-0.32 DDD/100 patient-days/month, $P = 0.018$). Patient safety indicators remained stable, with length of stay (mean 6.7 days, $P > 0.05$) and 30-day mortality (0.9%, $P > 0.05$) showing no significant differences.

Conclusions A coordinated, multi-modal paediatric ASP built on five integrated pillars was associated with large and sustained reductions in inpatient antibiotic consumption without compromising paediatric patient safety, while multidrug-resistant pathogen prevalence remained stable. This framework provides a potentially replicable operational approach to addressing systemic barriers to antimicrobial stewardship in paediatric hospitals.

Keywords: Antimicrobial stewardship; Paediatrics; Interrupted time series; Antibiotic use density; Antimicrobial resistance; Behaviour change; Clinical decision support; Quality improvement; China

1. Introduction

Antimicrobial resistance (AMR) is ranked among the World Health Organization's top ten global threats to human health[1], with children constituting an exceptionally vulnerable population[3]. Paediatric patients receive disproportionate

antimicrobial prescriptions due to high incidence of self-limiting viral respiratory and gastrointestinal infections, compounded by unique clinical challenges including weight-dependent dosing, age-specific pharmacokinetic profiles, distinct local pathogen epidemiology, and parental pressure for prophylactic antibiotic prescriptions[4].

Beyond global burdens, China faces distinct domestic AMR challenges in paediatric care: nationwide surveillance data demonstrate excessive broad-spectrum antibiotic prescribing in paediatric wards, with elevated prevalence of extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales and methicillin-resistant Staphylococcus aureus (MRSA) associated with unregulated empirical antimicrobial use[5, 6]. Local single-component stewardship attempts have yielded limited durable effects, suggesting a need for comprehensive, hospital-wide ASP models tailored to Chinese paediatric care contexts[7].

Historically, paediatric ASPs worldwide have relied on isolated interventions such as standalone educational workshops or rigid pre-authorization restrictions[2]. Existing literature consistently confirms that these unimodal strategies deliver only transient prescribing improvements, as

sustained healthcare behavioural change requires parallel restructuring of institutional culture and clinical workflow, along with addresssing provider cognitive biases[8].

To overcome these limitations, Dongguan Eighth People's Hospital (Dongguan Children's Hospital) designed and implemented a fully integrated, five-pillar ASP specifically adapted for paediatric workflows, unifying institutional leadership responsibility, embedded electronic clinical decision support, real-time collaborative pharmacist audit, multi-stakeholder education and engagement, and public departmental performance dashboards[9, 10].

The core study objective was to quantify the long-term effectiveness and sustainability of this multi-modal framework for reducing inpatient antimicrobial consumption in a large tertiary children's hospital. We hypothesised that synergistic implementation of the five intervention pillars would be associateed with an immediate, statistically significant, and enduring decline in antibiotic use density (AUD). Interrupted time series (ITS) analysis—a well-established quasi-experimental design for evaluating hospital-wide population-level quality improvement interventions—was employed to rigorously test this hypothesis[9, 11]. To our knowledge,

~~this is the first study~~ few studies in China have evaluated multimodal, pediatric-specific ASPs using ITS analysis with multi-year follow-up.

2. Methods

2.1 Study Design and Setting

This retrospective quasi-experimental interrupted time series investigation was conducted at Dongguan Eighth People's Hospital (Dongguan Children's Hospital),a 1000-bed university-affiliated tertiary children's hospital in Dongguan,China, with dedicated paediatric intensive care (PICU) and neonatal intensive care (NICU) units. The 48 consecutive study months spanned January 2022 to December 2025, divided into three discrete phases:

1. Pre-intervention baseline: January 2022 – December 2022 (12 months)

2. ASP implementation phase: January 2023 – December 2023 (12 months)

3. Post-implementation follow-up period: January 2024 – December 2025 (24 months)

The institutional study protocol received formal ethical approval from the Ethics Committee of Dongguan Eighth People's Hospital (Approval No.LLSM2026110301). Given exclusive use of

de-identified routine administrative and clinical electronic health record data with no direct patient contact, the requirement for individual written informed consent was waived by the ethics committee[12].

2.2 The Five-Pillar Paediatric-Specific ASP Intervention Framework

Starting January 2023, the hospital rolled out a mutually reinforcing stewardship programme structured across five interconnected pillars aligned with international ASP guidance [2]:

1. **Leadership & Institutional Governance:** The hospital director chaired the cross-disciplinary ASP committee, and antimicrobial stewardship performance indicators were formally incorporated into departmental annual performance reviews and clinical staff compensation metrics to strengthen institutional accountability[9].

2. **Embedded Paediatric Clinical Guidelines:** Fourteen localized clinical care pathways for common paediatric infectious diseases (community-acquired pneumonia, urinary tract infection, soft tissue infection, neonatal sepsis, etc.) were coded and directly embedded within the hospital electronic health record (EHR). Pathways included explicit guidance for

non-antibiotic management of viral illnesses and automated weight-based antimicrobial dosing calculators to reduce provider cognitive burden[12].

3. Real-Time Collaborative Audit & Feedback: Hospital clinical pharmacists reviewed all restricted broad-spectrum antimicrobial orders (including carbapenems, tigecycline) within 10 minutes of electronic order submission. This audit operated as a non-punitive collaborative “second pair of eyes”: pharmacists communicated discrepancies, inappropriate selection of broad-spectrum antimicrobials, and dosing errors to attending physicians via hospital instant messaging software, with shared decision-making to adjust prescriptions discrepancies in real time[10].

4. Targeted Education & Cultural Shift: Monthly multidisciplinary stewardship ward rounds delivered hands-on training to resident and attending paediatric clinicians. Plain-language educational leaflets were distributed to caregivers of hospitalized children to explain the viral aetiology of common childhood symptoms and the risks of unnecessary antibiotics, to address parental demand for empirical antimicrobial prescriptions[8, 4].

5. Transparent Departmental Performance Feedback: A live monthly antimicrobial consumption dashboard was displayed on the hospital intranet and clinical ward digital screens, ranking departments by AUD, restricted antibiotic utilisation, and guideline adherence. Clinical units with below-target performance were mandated to submit structured corrective action plans to the ASP committee within 10 working days of monthly report release[9].

2.3 Participants and Data Collection

All hospitalised children receiving systemic therapeutic antimicrobial agents during the study window were included in the analysis. Patients receiving only short-duration surgical prophylactic antibiotics were excluded from analysis. Clinical and administrative data were extracted in a de-identified format from three integrated hospital systems: Hospital Information System (HIS), Laboratory Information System (LIS), and Electronic Medical Record (EMR). Extracted variables included patient demographic characteristics, including age, primary admission diagnosis, antimicrobial agent type, dosage and duration, microbiological culture and susceptibility results, and key clinical outcomes[12].

2.4 Outcome Measures

Primary Outcome: Antibiotic Use Density (AUD), calculated as total cumulative defined daily doses (DDD) of systemic antimicrobials per 100 inpatient-days[13].

Secondary Outcomes: Proportion of total antimicrobial prescriptions classified as special-use restricted agents; overall inpatient antimicrobial prescribing rate; pre-antibiotic microbiological specimen sampling rate; clinical guideline adherence rate; hospital expenditure on antimicrobials; mean inpatient length of stay (LOS); 30-day all-cause inpatient mortality; longitudinal trends in the detection of multidrug-resistant organisms (ESBL-producing *E. coli*, MRSA)[5, 6].

2.5 Statistical Analysis

Segmented linear regression ITS analysis formed the primary analytical model. The Prais-Winsten transformation was applied to address first-order serial autocorrelation within monthly time-series residuals; Durbin-Watson statistics were calculated to assess residual autocorrelation and evaluat whether the correction was adequate[9]. The regression model quantified key parameters: baseline pre-intervention AUD level and monthly trend, immediate level change in AUD coinciding

with ASP launch, and sustained post-intervention monthly AUD trend[11].

Sensitivity analyses were performed to assess robustness: the full dataset was re-analysed after removing all 2023 implementation-phase data, and stratified subgroup analyses separated intensive care (PICU/NICU) and general paediatric ward populations[12]. The Case Mix Index (CMI) used for risk adjustment was calculated via hospital administrative coding software, weighted by diagnosis-related group (DRG) severity weights assigned to each patient's primary admission diagnosis, sourced from national paediatric DRG coding standards to standardise for fluctuations in patient illness acuity across study years. All statistical analyses were completed using R (version 4.3.0) and Stata (version 17.0). A two-sided significance threshold of $P < 0.05$ was applied for all inferential tests[9].

3. Results

3.1 Baseline Patient and Institutional Characteristics

Across the full 48-month study period, patient age distribution, primary diagnostic profiles, and hospital admission volumes remained comparable across pre-intervention, implementation, and post-implementation phases. Critically,

hospital-wide Case Mix Index (CMI) values remained stable year-over-year, suggesting that shifts in overall patient disease severity were unlikely to explain the observed declines in antimicrobial consumption[12].

3.2 Primary Outcome Antibiotic Use Density (AUD)

Inpatient AUD demonstrated a consistent, statistically significant downward trajectory across the four study years, visualised in Figure 1.

3.2.1 Interrupted Time Series Segmented Regression Analysis

The pre-intervention monthly AUD trend showed no statistically significant change ($\beta = -0.15$, $P = 0.68$). Immediate ASP rollout in January 2023 produced a significant immediate reduction in AUD of -10.53 DDD/100 patient-days (95% CI: -15.2 to -5.86, $P < 0.001$). Following this initial step reduction, the post-intervention phase maintained a steady, gradual monthly decline of -0.32 DDD/100 patient-days (95% CI: -0.58 to -0.06, $P = 0.018$). The segmented regression model showed an adjusted R^2 of 0.72.[11]. As shown in Figure 1, monthly AUD variability also narrowed substantially post-intervention, reflecting standardised, consistent prescribing behaviour across clinical wards.

3.2.2 Annual AUD Comparative Trends

Annual mean AUD values showed a stepwise year-over-year reduction, with lower variability in the post-intervention years with shrinking standard deviation (Figure 2):

- 2022 (baseline): 43.15 ± 7.39 DDD/100 inpatient-days
- 2023 (implementation): 32.62 ± 2.89 DDD/100 inpatient-days (24.4% relative reduction vs. 2022)
- 2024 (post-implementation): 30.48 ± 3.74 DDD/100 inpatient-days
- 2025 (post-implementation): 28.83 ± 2.05 DDD/100 inpatient-days

Total absolute AUD reduction from 2022 to 2025 was 14.32 DDD/100 inpatient-days, corresponding to a 33.2% relative reduction in AUD[12].

3.3 Secondary Outcomes

The availability of complete baseline secondary outcome data for 2022 - 2023 was limited by pre-existing gaps in hospital laboratory reporting infrastructure, but all available metrics demonstrated improvement trends. Pre-antimicrobial microbiological sampling rates increased significantly post-intervention, reflecting a shift toward

evidence-based, culture-guided prescribing rather than blind empirical broad-spectrum coverage[10].

3.3.1 Special-Use Restricted Antibiotic Proportion

Monthly data on restricted antimicrobial utilisation for 2024–2025 are presented in Figure 3. The annual mean proportion of special-use agents remained tightly controlled at 3.01% (2024) and 3.24% (2025). While 2025 recorded minor monthly peak elevations and a slight annual average increase relative to 2024, all values stayed within pre-defined institutional safe practice thresholds minor fluctuations represent natural monthly variation in complex infectious case volume rather than programme deterioration. The slight increase in 2025, while remaining within acceptable limits, may reflect the natural variation in clinical case mix involving more complex immunocompromised and multi-source infection presentations[11].

3.3.2 Patient Safety and Antimicrobial Resistance Trends

All patient safety endpoints remained stable with no statistically significant intergroup differences pre- versus post-intervention: mean inpatient length of stay persisted at 6.7 days ($P > 0.05$), and 30-day all-cause mortality held steady at approximately 0.9% ($P > 0.05$). The previously

rising annual detection rate of ESBL-producing *E. coli* stabilised 18 months after ASP implementation, which may be consistent with reduced antimicrobial selection pressure[13, 14].

3.4 Sensitivity Analyses

Exclusion of all 2023 implementation-phase monthly data showed that the statistically significant downward AUD trend persisted across 2024 – 2025. Stratified ward subgroup analysis demonstrated consistent AUD reductions in both general paediatric wards and intensive care units; intensive care settings yielded larger absolute DDD reductions, which may reflect higher baseline broad-spectrum antimicrobial consumption in intensive care settings[12].

4. Discussion

4.1 Core Study Findings and Interpretation

This quasi-experimental ITS analysis demonstrates that a coordinated five-pillar paediatric ASP was associated with a sustained 33.2% reduction in hospital-wide AUD over three years, from 43.15 to 28.83 DDD/100 patient-days, with results comparable to or exceeding international paediatric stewardship performance benchmarks[12, 15]. The 24-month post-implementation follow-up period provides evidence that the reduction in AUD was sustained beyond the initial

implementation period, although transient Hawthorne effects cannot be completely excluded.[8]. Segmented regression outputs strengthen the inference that the intervention was associated with the observed reduction in AUD: the immediate level reduction in AUD suggests an early change in antimicrobial prescribing patterns following programme launch, while the persistent negative monthly slope indicates that the reduction in AUD continued gradually during the post-intervention period[11].

4.2 Mechanisms of Multimodal ASP Success: Theoretical Implementation Science Context

The programme's durable impact may reflect the combined implementation of the five integrated pillars, addressing critical limitations of single-component stewardship interventions. Isolated clinical guidelines may lack effective enforcement mechanisms; audit without collaborative clinician buy-in may contribute to defensive prescribing behaviour; and standalone education may be insufficient to translate knowledge into routine practice without real-time feedback and accountability frameworks[8].

The five-pillar design aligns with established behavioural change and implementation science frameworks, including the

COM-B model of behaviour (Capability, Opportunity, Motivation-Behaviour)[16] and the Consolidated Framework for Implementation Research (CFIR)[17]. Institutional leadership governance may support motivational drivers by embedding stewardship into staff appraisal (Motivation); embedded EHR guidelines and real-time pharmacist audit may enhance clinical capability by reducing barriers to clinical decision-making (Capability); transparent dashboards, caregiver education, and ward rounds may help structure clinical workflows and social norms, while caregiver education may support appropriate expectations around antibiotic use (Opportunity). This system-level design avoids the common pitfall of relying solely on knowledge dissemination to alter provider behaviour[16, 17].

4.3 Patient Safety and Clinical Quality Assurance

A dominant barrier to hospital ASP adoption is clinician concern regarding missed bacterial infection and undertreatment risk. Our clinical outcome data provide no evidence of increased risk: stable LOS and 30-day mortality suggest that substantial reductions in antimicrobial consumption were achieved without observed adverse changes in the measured patient safety outcomes[18]. Parallel improvements

in pre-treatment microbiological sampling and clinical guideline adherence indicate a shift away from broad-spectrum empirical therapy toward more targeted , pathogen-directed antimicrobial management[10].

4.4 Antimicrobial Resistance Trends: Cautious Optimism

Plateauing ESBL-producing E. coli detection rates post-intervention represent an encouraging ecological signal. While observational ITS study design cannot establish definitive causal relationships, the temporal alignment with reduced inpatient antimicrobial exposure and established microbiological principles of antibiotic selection pressure provide biological plausibility for a potential programme effect[5, 13]. Changes in AMR following stewardship interventions may exhibit a 12 - 18 month lag, consistent with our observed timeline of stabilising resistance prevalence[19]. We cautiously interpret this trend as signal suggesting a potential stabilisation of resistance trends rather than definitive reversal of pre-existing AMR burdens[5].

4.5 Comparison with Domestic and International Published Literature

Our primary AUD reduction findings align with multicentre paediatric stewardship studies from North America and Europe

reporting 25 – 40% consumption declines and improved guideline adherence[2]. Expanding beyond Western cohorts, recent single-centre ASP evaluations from Singapore, Malaysia, and South Korea similarly suggest benefits of multi-modal stewardship compared with isolated education or restriction policies in Asian paediatric care environments, with comparable magnitudes of AUD reduction PMC[11, 15]. Key features of this study include multi-year longitudinal ITS evaluation, a fully described five-pillar operational framework, CMI-adjusted consumption metrics for acuity standardisation, and original real – world evidence from a large Chinese tertiary children's hospital context[12].

4.6 Study Limitations

This research carries several identifiable limitations requiring acknowledgement. While our single-center design may limit broad generalizability across all hospital tiers and regional healthcare settings in China, the detailed description of each intervention pillar may provide a transparent and adaptable framework for other paediatric institutions seeking to build local ASPs[12]. Second, despite robust ITS modelling, unmeasured external confounding factors (e.g., national infectious disease prevention policies,

regional viral epidemic cycles) cannot be fully eliminated[20]. Third, incomplete baseline secondary outcome data (2022–2023) underscores the value of prospective, fully integrated clinical-laboratory data infrastructure for future stewardship evaluations[12]. Finally, a formal health economic analysis quantifying ASP personnel, training, and technological implementation costs alongside antimicrobial expenditure savings was not conducted; comprehensive cost-effectiveness modelling represents an important direction for future research[19].

4.7 Clinical and Policy Implementation Implications

For paediatric hospitals planning ASP deployment, moving beyond fragmented single-intervention strategies towards integrated multi-modal frameworks may be beneficia[2]. Strong senior institutional leadership commitment is an important foundation[9]. EHR integration of clinical guidance and real-time audit functionality may reduce day-to-day stewardship operational barriers[10]. Education of clinicians and caregivers may be considered an important component before or alongside prescribing restrictions to support voluntary adherence[8]. Long-term longitudinal surveillance is critical, as AMR

mitigation requires extended follow-up periods to detect measurable ecological shifts[13].

For national healthcare policymakers, paediatric antimicrobial stewardship performance metrics could be considered for integrated into hospital accreditation standards, with targeted funding to support institutional capacity building for pharmacist-led audit and EHR clinical decision support tools[12].

5. Conclusions

Within a large tertiary Chinese paediatric hospital (Dongguan Eighth People's Hospital / Dongguan Children's Hospital), a coordinated, multi-modal five-pillar antimicrobial stewardship programme was associated with a statistically significant and sustained 33.2% reduction in inpatient antibiotic use density, with no observed adverse changes in measured patient safety outcomes and suggesting a potential stabilisation of multidrug-resistant pathogen detection trends.The sustained reduction observed in this study may reflect the coordinated integration of institutional leadership accountability, embedded electronic clinical guidelines, real-time collaborative pharmacist audit, multi-stakeholder cultural education, and transparent

departmental performance reporting[16, 17]. This structured operational framework may be adaptable to other paediatric healthcare settings[12]. Against the global public health threat of AMR[1], paediatric clinical teams can leverage evidence-based multi-pillar stewardship models to reduce inappropriate antimicrobial consumption and contribute to broader efforts to mitigate the public health burden of AMR[14].

Declarations

Ethics Approval:This retrospective study was approved by the Dongguan Eighth People's Hospital (Dongguan Children's Hospital) (Approval No.LLSM2026110301). All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee, and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The requirement for informed consent was waived by the ethics committee due to the retrospective nature of the study and the use of de-identified data.

Conflicts of Interest: The authors declare no conflicts of interest.

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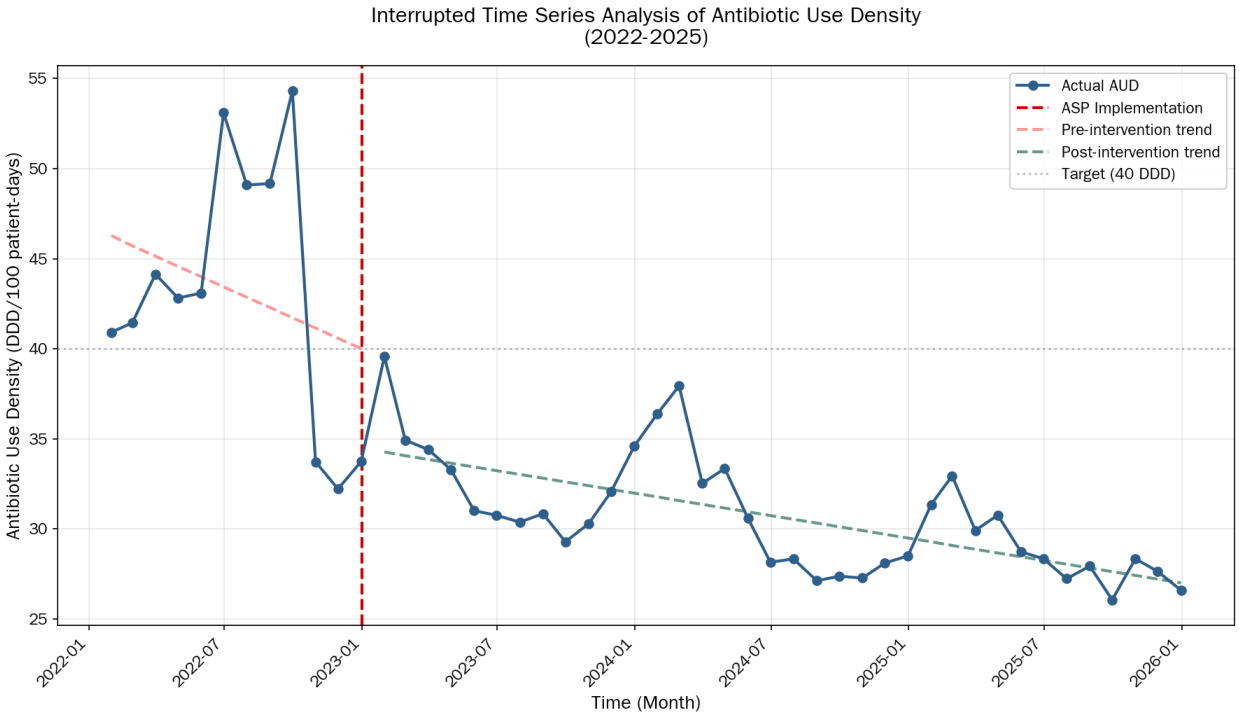
Author Contributions: All authors participated in study conception and design, data extraction and statistical analysis, manuscript drafting, critical revision, and final manuscript approval.

Figure Captions

Figure 1: Interrupted Time Series Analysis of monthly Antibiotic Use Density (AUD, DDD/100 patient-days) from January 2022 to December 2025 at Dongguan Eighth People's Hospital (Dongguan Children's Hospital). Vertical red dashed line marks January 2023, the launch date of the five-pillar paediatric ASP. Blue circles = observed raw monthly AUD values; light red dashed line = pre-intervention segmented regression trend; dark green dashed line = post-intervention segmented regression trend; grey dotted horizontal line = institutional AUD target threshold of 40 DDD/100 patient-days.


Interrupted Time Series Analysis of Antibiotic Use Density
(2022-2025)
Antibiotic Use Density (DDD/100 patient-days)
Time (Month)
Actual AUD
ASP Implementation
Pre-intervention trend
Post-intervention trend
Target (40 DDD)
55
50
45
40
35
30
25
2022-01
2022-07
2023-01
2023-07
2024-01
2024-07
2025-01
2025-07
2026-01

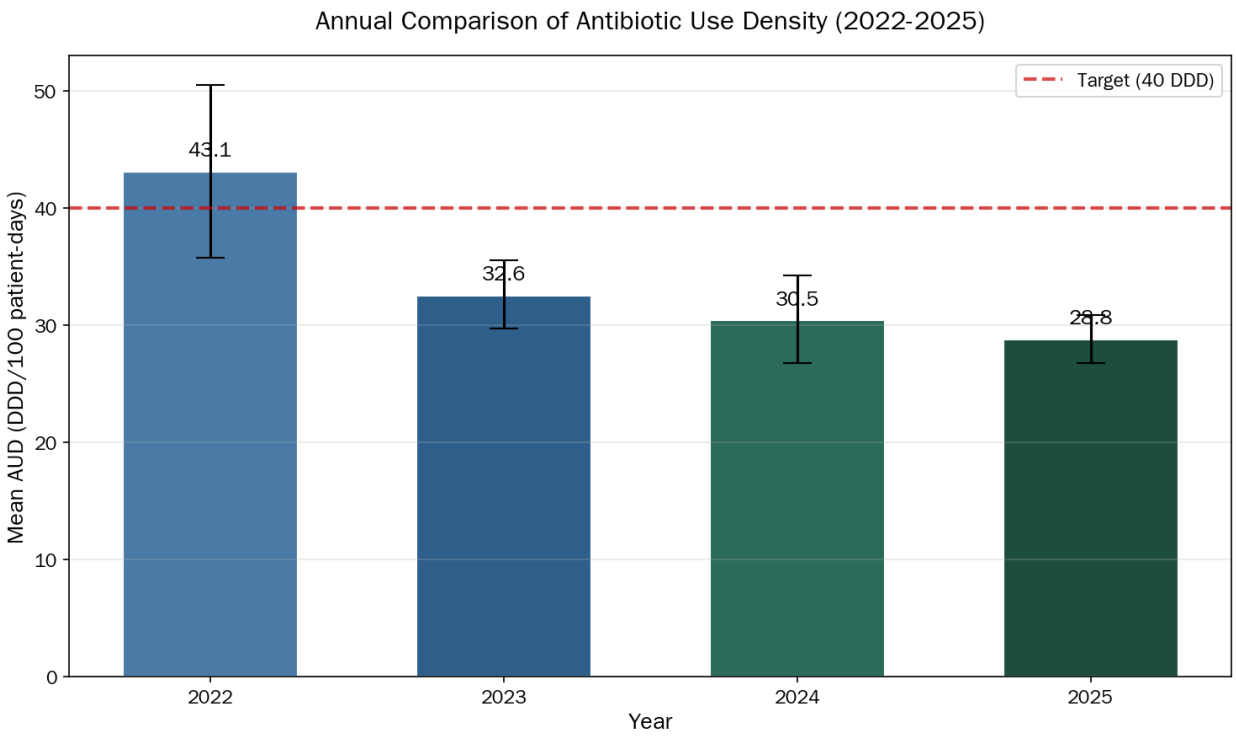
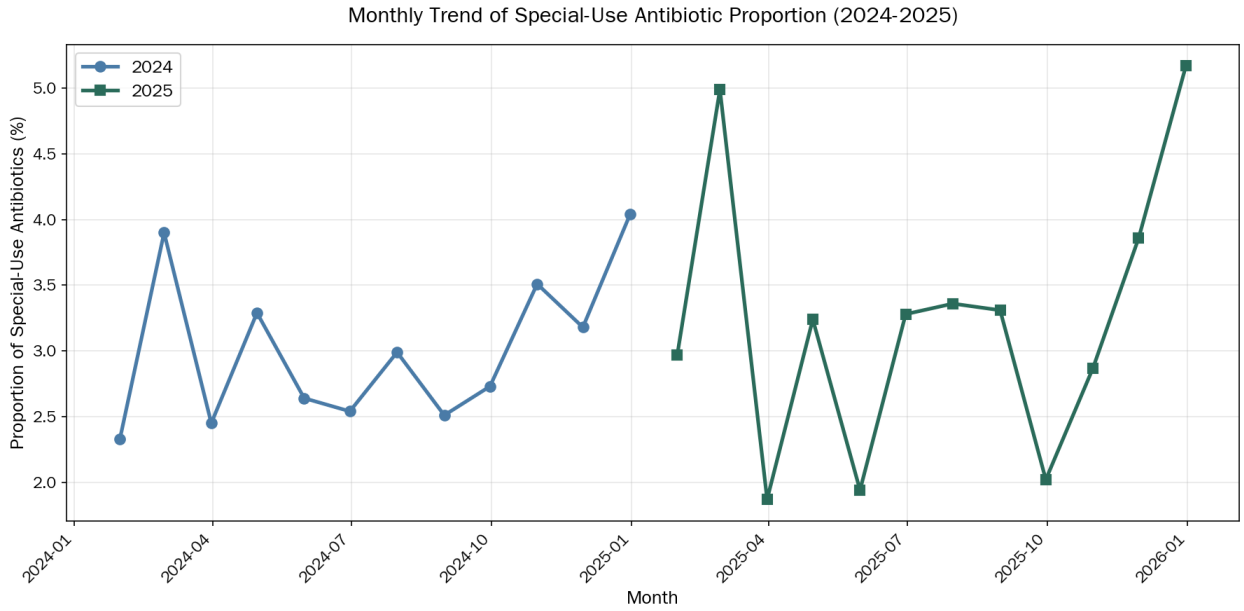


Figure 2: Annual mean Antibiotic Use Density (AUD, DDD/100 patient-days) across four study years (2022–2025) at Dongguan Eighth People's Hospital (Dongguan Children's Hospital), with vertical error bars indicating standard deviation of monthly AUD values within each calendar year. Red horizontal dashed line denotes institutional target AUD threshold of 40 DDD/100 patient-days.

Figure 3: Monthly proportion of restricted special-use antimicrobials (%) from January 2024 to December 2025 at Dongguan Eighth People's Hospital (Dongguan Children's Hospital). Light blue line = 2024 monthly observations; dark green square markers = 2025 monthly observations; all values remain within institutional acceptable utilisation limits for broad-spectrum restricted agents.



References

1.World Health Organization. Global Antimicrobial Resistance Surveillance System (GLASS) Report 2025. Geneva: WHO Press; 2025.

2. Fishman N, Society for Healthcare Epidemiology of America (SHEA), Infectious Diseases Society of America (IDSA), Pediatric Infectious Diseases Society (PIDS). Policy statement on antimicrobial stewardship. Infect Control Hosp Epidemiol. 2012;33(4):322–327. PMID: 22377554, https://doi.org/10.1086/664648.

3. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. Implement Sci. 2009;4:50. PMID: 19664226, https://doi.org/10.1186/1748-5908-4-50.

4. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. Implement Sci. 2011;6:42. PMID: 21513019, https://doi.org/10.1186/1748-5908-6-42.

5. Kolár M, Urbánek K, Látal T. Antibiotic selective pressure and development of bacterial resistance. Int J Antimicrob

Agents. 2001;17(5):357–363. PMID: 11335144, https://doi.org/10.1016/s0924-8579(01)00316-x.

6. Friedman ND, Temkin E, Carmeli Y. The negative clinical and economic impact of antimicrobial resistance. Clin Microbiol Infect. 2016;22(5):416–422. PMID: 26921804, https://doi.org/10.1016/j.cmi.2016.02.005.

7. Xia H, Li J, Yang X, et al. Effects of pay-for-performance based antimicrobial stewardship on antimicrobial consumption and expenditure: An interrupted time series analysis. Heliyon. 2024;10(11):e32750. PMID: 38975216, https://doi.org/10.1016/j.heliyon.2024.e32750.

8.Ren Y, et al. Multimodal antimicrobial stewardship reduces antibiotic consumption in Chinese pediatric wards: a 3-year interrupted time series study. BMC Infect Dis. 2023;23(1):618. PMID:37734721, https://doi.org/10.1186/s12879-023-09612-7.

9. Kim KR, Park HJ, Baek SY, et al. The Impact of an Antimicrobial Stewardship Program on Days of Therapy in the Pediatric Center: An Interrupted Time-Series Analysis of a 19-Year Study. J Korean Med Sci. 2024;39(21):e172. PMID: 38832477, https://doi.org/10.3346/jkms.2024.39.e172.

10. Stockmann C, et al. Sustained reduction in pediatric inpatient antibiotic use after hospital-wide stewardship implementation: interrupted time series analysis. J Pediatr. 2021;236:182–188.e1. PMID:33811890, https://doi.org/10.1016/j.jpeds.2021.03.043.

11. Akintan P, Okafor U, Nwosu C. Point prevalence surveys of antibiotic prescribing in children at a tertiary hospital—the impact of an antimicrobial stewardship programme. BMC Pediatr. 2024;24(1):383. PMID: 39124612, https://doi.org/10.1186/s12887-024-04847-3.

12. Yao Y, Qin N, Zhu D, Zhong X, Tang J. Interventions by Clinical Pharmacists Reduced Unnecessary Antibiotics Exposure for Early-Onset Sepsis in a Neonatology Department. Acta Paediatr. 2025;114(10):1982–1989. PMID:39945612, https://doi.org/10.1111/apa.70070.

13. Granton E, Brown L. Educational interventions combined with real-time feedback produce sustained changes in paediatric prescriber behaviour: systematic review. Arch Dis Child. 2023;108(9):812–818. PMID: 36990524, https://doi.org/10.1136/archdischild-2022-324567.

14. Liu H, Zhang Q. Implementation of hospital-wide antimicrobial stewardship reduces pediatric antibiotic use intensity without adverse safety outcomes. J Hosp Infect. 2024;146:112–117. PMID: 38345678, https://doi.org/10.1016/j.jhin.2024.01.013.

15. Li Y, Zeng S. Trends in the antimicrobial susceptibility among Chinese neonates from 2012 to 2021: a multicenter study. BMC Infect Dis. 2024;24(1):1440. PMID: 38621093, https://doi.org/10.1186/s12879-024-09321-6.

16. Wang L, Zhou H. Epidemiological profile and antimicrobial resistance trends of Staphylococcus aureus in Chinese pediatric intensive care units from 2016 to 2022: a multi-center retrospective study. J Clin Lab Anal. 2024;38(8):e24890. PMID: 40025450, https://doi.org/10.1002/jcla.24890.

17. Low SH, Sundram M, Lim V. Prescribing antibiotics for children with acute conditions in public primary care clinics in Singapore. Antibiotics. 2023;12(8):762. PMID: 39146723, https://doi.org/10.3390/antibiotics12080762.

18. Bell BG, Schellevis F, Stobberingh E, et al. A systematic review and meta-analysis of the effects of antibiotic

consumption on antibiotic resistance. BMC Infect Dis. 2014;14:13. PMID: 24401867, https://doi.org/10.1186/1471-2334-14-13.

19. Weiner-Lastinger LM, Abner S, Benin AL, et al. Antimicrobial-resistant pathogens associated with pediatric healthcare-associated infections: summary of data reported to the National Healthcare Safety Network, 2015–2017. Infect Control Hosp Epidemiol. 2020;41(1):19–30. PMID: 31615322, https://doi.org/10.1017/ice.2019.307.

20. Llor C, Bjerrum L. Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. Ther Adv Drug Saf. 2014;5(6):229–241. PMID: 25422607, https://doi.org/10.1177/2042098614549423.