BMJ Open

Implementation of antimicrobial stewardship programmes in hospitals of the Brazilian public health system: PeGASUS study protocol

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To cite: Cortez AL, Fachi MM, Boszczowski I, *et al*. Implementation of antimicrobial stewardship programmes in hospitals of the Brazilian public health system: PeGASUS study protocol. *BMJ Open* 2026;**16**:e124811. doi:10.1136/bmjopen-2026-124811

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2026-124811).

Received 26 June 2026
Accepted 13 October 2026

Check for updates

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ABSTRACT

Introduction Antimicrobial resistance represents a global threat, making antimicrobial stewardship programmes (ASPs) essential yet underutilised in many hospitals. Therefore, the PeGASUS study evaluates a structured intervention to strengthen ASPs in Brazilian public hospitals.

Methods and analysis PeGASUS is a nationwide, multicentre, quasi-experimental before-after study (2025–2026) with historical within-hospital controls and no concurrent control group evaluating a multifaceted intervention (web-based training (WBT), leadership engagement and mentoring). Eligible sites are medium-to-large Brazilian public hospitals with adult intensive care units (ICU), infection control committees, infectious disease specialists and inadequate, basic or absent ASPs. For the selected hospitals, the study will be conducted over an estimated period of 21 months and comprises four phases: (1) pre-intervention (baseline), (2) intervention, (3) follow-up and (4) wrapping up. The primary outcome will be ASP organisational performance, while secondary outcomes will include antimicrobial consumption measured as defined daily dose, clinical and healthcare utilisation outcomes and cost-effectiveness. Populations analysed will be as-assigned (total consented), modified as-assigned (baseline completed) and completers-only (formal ASP team, ≥2 meetings, ≥50% WBT completion).

Ethics and dissemination The study was approved by the Research Ethics Committee of Hospital Alemão Oswaldo Cruz (Committee No. 0070; CAAE 84285924.0.0000.0070; Approval No. 7.221.341); separate local ethics approval at participating sites was not required. Findings will be disseminated through peer-reviewed publications, scientific conferences and communication materials targeting healthcare professionals, hospital managers, policymakers and the general public. Results will be reported transparently regardless of study outcomes.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This nationwide multicentre study evaluates the implementation of antimicrobial stewardship programmes (ASPs) across diverse Brazilian public hospitals, enhancing the generalisability of findings.
⇒ The intervention combines web-based training, leadership engagement, quality-improvement tools and specialist mentoring, reflecting a pragmatic and scalable implementation strategy.
⇒ The study assesses organisational, clinical, antimicrobial consumption and economic outcomes, providing a comprehensive evaluation of ASP implementation.
⇒ Variability in hospital infrastructure, local resources and adherence to intervention components may influence implementation outcomes across participating sites.
⇒ As a quasi-experimental before-after evaluation without a concurrent control group, observed changes in antimicrobial consumption and clinical metrics may be influenced by background temporal trends or concurrent local initiatives, which will be acknowledged as a study limitation.

INTRODUCTION

Antimicrobial resistance (AMR) represents a growing global public health threat, compromising the effectiveness of treatments and increasing the morbidity and mortality associated with infections.[1 2] In 2019, approximately 4.95 million deaths were associated with antimicrobial resistance, and without effective action, AMR could cause up to 10 million deaths annually by 2050, surpassing diseases such as cancer and diabetes.[2 3]

The implementation of antimicrobial stewardship programmes (ASPs) is widely recognised as a key strategy to optimise antimicrobial use and reduce the spread

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of AMR. These programmes promote the rational and evidence-based use of antimicrobials in healthcare settings, improving patient outcomes while minimising the selective pressure that drives resistance.[4] A recent umbrella review synthesising 55 systematic reviews from diverse geographical regions found that ASPs consistently reduce antibiotic consumption—with reported reductions in defined daily doses (DDDs) ranging from 7.2 to 290 per 1000 patient-days and decreases of up to 91% in some settings—while improving adherence to prescribing guidelines (gains of 6.5%–74%).[5] Significant declines in resistant pathogens were documented, including methicillin-resistant Staphylococcus aureus and extended-spectrum β-lactamase-producing organisms, alongside reductions in *Clostridioides difficile* infection.[6–8]

However, the implementation of ASPs can be challenging. Recent literature indicates that while the clinical and economic value of ASPs is well demonstrated, the priorities differ by context: reducing overuse predominates in high-income settings, with behaviour changes being the main challenge, whereas low- and middle-income countries must simultaneously balance rational use with equitable access, address infrastructure and workforce shortages and adopt context-adapted, standardised evaluation methods to generate policy-relevant evidence.[6–8]

In a global survey of 660 hospitals across 67 countries, it was identified that 42% lacked a formal ASP. In Brazil, approximately 47.3% of hospitals do not have an established ASP.[9] While the country possesses a vast hospital network with over 65 000 intensive care unit (ICU) beds, the specialised workforce traditionally required to lead ASPs is critically scarce and unequally distributed, with only 4801 infectious diseases physician specialists nationwide, mostly concentrated in southeastern capitals.[10 11]

Additional knowledge gaps persist regarding the optimal design, adaption and integration of ASP into routine clinical practice. Specifically, the role of contextual determinants and implementation strategies in ensuring long-term sustainability remains poorly understood. Nevertheless, recent large-scale initiatives demonstrate that structured and context-sensitive frameworks can effectively strengthen ASP. Evidence from low- and middle-income settings suggests that coordinated, multi-site approaches (integrating baseline assessments, tailored action plans and iterative monitoring) can improve core stewardship elements across diverse healthcare systems.[12 13] Furthermore, recent evidence from large-scale regional and national implementation initiatives highlights that structured, multi-site stewardship frameworks supported by appropriate governance, standardised approaches, multidisciplinary collaboration, training and continuous monitoring are essential for driving system-wide improvements in hospital prescribing practices.[14 15] These experiences also indicate that implementation at regional and national levels may be affected by variability in organisational structures, resources, professional capacity and local practices, underscoring the need for strategies that can be adapted to different contexts while maintaining common stewardship objectives. In addition, sustained improvements may require ongoing assessment and adaptation, as the establishment of a structured framework alone may not be sufficient to ensure continuous implementation and long-term effectiveness.

Despite growing global awareness, the worldwide development and implementation of ASPs vary considerably. Workforce shortages and resistance from prescribing clinicians have been consistently identified as key barriers to implementation.[8] Furthermore, prospective measurement of ASP impact remains limited, as most evidence is derived from cross-sectional surveys, including national ASP assessment conducted by the Brazilian National Health Regulatory Agency (Anvisa).[16]

While national guidelines provide the regulatory architecture for ASPs, Brazilian public hospitals face profound implementation barriers, including a critical scarcity of infectious disease specialists and highly heterogeneous diagnostic capacities. Traditional, resource-intensive stewardship models are often unfeasible in these environments. The PeGASUS study, supported by the National Surveillance Agency—Anvisa, hypothesises that a decentralised, capacity-building framework—web-based training (WBT), leadership engagement, structured implementation toolkits and multiprofessional mentoring—can empower existing lean infection control teams to overcome these structural constraints, transitioning institutions from passive antimicrobial surveillance to active stewardship.

Accordingly, this paper aims to describe the PeGASUS protocol. The primary outcome is the change in ASP organisational implementation level; secondary outcomes are antimicrobial consumption (DDD/1000 patient-days), intervention acceptance, clinical and healthcare-utilisation outcomes and incremental cost-effectiveness.

METHODS AND ANALYSIS

The design of this study was reported according to StaRI[17] guidelines to ensure transparency and reproducibility (online supplemental material table S1).

Study design, site selection and study timeline

The PEGASUS is a nationwide, multicentre, quasi-experimental before-after study with historical within-hospital controls and without a concurrent control group. Because the intervention will be evaluated under real-world conditions without a concurrent unexposed comparator, potential confounding by secular trends, background epidemiological shifts or concurrent health system initiatives will be acknowledged as a study limitation. To mitigate these effects, hospital-level antimicrobial consumption data collected during the 3 month baseline period will serve as internal historical controls in the generalised estimating equation (GEE) models. Although the initial PeGASUS study design did not

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explicitly incorporate the Reach, Effectiveness, Adoption, Implementation and Maintenance (RE-AIM) implementation framework a priori,[18] a pragmatic adaptation was made to evaluate real-world translation. In the final quarter of Phase 2 (Intervention), a formative and implementation evaluation was introduced, requiring local ASPs to complete monthly Monitoring Reports. These reports will focus on implementation barriers and facilitators, and their subsequent analysis will provide qualitative and quantitative data that indirectly addresses RE-AIM dimensions, thus complementing the primary numerical outcomes.

Hospitals across all Brazil's five geographic regions will be included in the study if they meet the following criteria: (i) the presence of an established Hospital Infection Prevention and Control (IPC) committee; (ii) either the absence of an ASP or an ASP classified as inadequate or basic according to the ASP Level Assessment Questionnaire (online supplemental material table S2), based on the National Evaluation of Antimicrobial Stewardship Programmes in Health Services conducted by Anvisa[16]; (iii) the availability of either an infectious diseases physician or a physician with expertise in infectious diseases, or a clinical pharmacist with expertise in infectious diseases; (iv) the presence of at least one adult ICU (medical, surgical or coronary) and (v) classification as a medium- or large-sized public hospital.

Hospitals will be excluded if they meet any of the following criteria: (i) failure to obtain authorisation for participation from local, municipal or state health authorities or (ii) involvement of their adult ICU in other concurrent projects related to ASP, healthcare-associated infections or AMR.

Hospitals interested in participating in the study will be required to complete a feasibility questionnaire, which included information on institutional identification and infrastructure, and to submit a Letter of Agreement signed by the hospital director and other institutional leaders.

Following participant allocation, pre-intervention data collection was initiated in March 2025. The study timeline is projected to be concluded in October 2026, encompassing a total follow-up period of approximately 21 months across all phases.

Sample size and pragmatic rationale

Because the hospital is the unit of analysis, the target sample size was pragmatically set at 54 public hospitals (two medium-to-large public hospitals in each of Brazil's 27 federative units), optimising national geographic representation within available project resources. Statistical power was estimated through Monte Carlo simulations (5000 iterations per scenario) modelling hospital transitions across four ASP maturity tiers (nonexistent or inadequate, basic, intermediate and advanced) under pre-specified baseline tier distributions, tier-specific improvement probabilities and a 5% regression probability. With a significance level of 0.05, a sample of 54 hospitals achieves 98.8% power (95% CI 98.5% to 99.1%) for the McNemar-Bowker test to detect shifts in ASP maturity tiers. Under attrition scenarios reducing the cohort to 40 hospitals, power remains 86.9% (95% CI 86.0% to 87.9%), above the conventional 80% threshold, while power for the Wilcoxon signed-rank and binomial sign tests exceeds 98%. Simulation parameters and results for all scenarios are provided in the online supplemental material table S3.

Intervention: The PeGASUS study intervention and phases

For the selected hospitals, the study will be conducted in four phases over an estimated period of 21 months: (1) pre-intervention (baseline), (2) intervention, (3) follow-up and (4) wrapping up.

Following hospital selection, participating hospitals will be formally notified, and an in-person inaugural meeting will mark the official start of the intervention phase. This meeting will serve as a key milestone to align study objectives, formalise institutional engagement and integrate hospital reference professionals with the PeGASUS technical team. Hospital representatives and state-level IPC coordinators will also participate remotely.

Phase 1 - pre-intervention data collection (baseline)

The objective of this phase is to establish a comprehensive baseline of institutional characteristics, ASP maturity and antimicrobial use indicators, while ensuring formal institutional engagement and leadership alignment prior to the start of the intervention. This phase will be conducted over a 3 month period.

During this phase, participating hospitals will complete the Hospital Characterisation Form (online supplemental material table S4), to document infrastructure, human resources and institutional characteristics. In addition, hospitals will complete the Cost Form (online supplemental material table S5) and the ASP Implementation Level Assessment Questionnaire (online supplemental material table S2); for the latter, mandatory supporting documentation will be required to substantiate the information provided. In parallel, informed consent will be obtained from professionals at participating hospitals.

During the baseline phase, hospitals will collect data using standardised indicator collection forms routinely applied for antimicrobial monitoring. Baseline indicators will include ICU antimicrobial consumption measured in DDDs, available prescription intervention data, surgical antibiotic prophylaxis indicators (when applicable) and cost-related indicators.

Phase 2 - Intervention

This phase aims to facilitate the development of a context-adapted ASP implementation plan, provide continuous technical support from the PeGASUS team, strengthen local capacity and monitor implementation and antimicrobial use indicators over a 10-month period.

The ASP implementation plan will be developed according to the Brazilian National Guideline for ASP

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issued by Anvisa[19] and structured around the six core components: (i) institutional leadership commitment, (ii) accountability and defined responsibilities, (iii) stewardship actions to optimise antimicrobial use, (iv) education and training of healthcare professionals, (v) monitoring of antimicrobial use and resistance and (vi) feedback and reporting of stewardship activities and indicators.

For each component, a set of mandatory elements has been predefined (online supplemental material table S2) to ensure standardisation across participating hospitals. These elements guide hospitals toward measurable progress in ASP maturity, supporting advancement across the classification levels of the ASP Implementation Level Assessment Questionnaire.

The plan will be tailored through individualised meetings between the PeGASUS team and each hospital to address local structures, resources and specific barriers. To support this process, we developed a structured toolkit based on quality-improvement methodologies, specifically the model for improvement and Plan-Do-Study-Act cycles (figure 1).

This toolkit provides stepwise guidance for defining priorities and designing improvement cycles aligned with institutional goals and local epidemiological patterns, such as AMR profiles. A driver diagram illustrates the logical framework connecting the intervention's primary drivers to its operational goals (table 1).

Participating hospitals will be required to establish two groups: a leadership team (including a representative of institutional management) and an operational team (responsible for daily ASP planning, implementing and monitoring ASP activities; ideally comprising an infectious diseases specialist, an IPC nurse, a clinical pharmacist and a laboratory professional.

Throughout the 10-month intervention period, the PeGASUS teams will provide a hybrid support model. This will include at least one on-site visit by specialists (physician, nurse or pharmacist) to assess local workflows and monthly virtual meetings for technical support and progress monitoring. Additionally, monthly group sessions will promote collaborative learning and benchmarking among hospitals. As part of the capacity-building component, a 6-month training programme will be implemented, consisting of web-based self-instructional training (WBT) developed by the multidisciplinary PeGASUS team. The course features 5 monthly interactive modules delivered via a digital platform with attendance tracking and formative assessments. Certification is granted on successful completion of all modules and fulfilment of the following criteria: completion of assessment activities and completion of the course evaluation via the Net Promoter Score.

During the intervention period, hospitals will perform monthly data collection using standardised forms to monitor ICU antimicrobial consumption measured in DDDs, the number and acceptance rate of ASP interventions, surgical antibiotic prophylaxis indicators (when applicable) and clinical and resource utilisation data in the online supplemental material table S6.

Phase 3 – follow-up

This phase will assess the sustainability of the ASP in participating hospitals, monitoring the continuity of implemented actions under routine conditions for 6 months. This phase will encompass local implementation, conducted by each hospital's own teams, without scheduled support meetings from the coordinating centre.

Throughout this phase, hospitals are expected to maintain the routine monthly collection of data related to antimicrobial consumption and intervention related indicators in the online supplemental material table S6. At the conclusion of the phase, the ASP Implementation Level Assessment Questionnaire in the online supplemental material table S2 will be reapplied, accompanied by the collection of supporting documentation and the completion of the cost form in the online supplemental material table S5, allowing evaluation of the consolidation of implemented practices and the outcomes achieved throughout the project.

Phase 4 – wrapping up

This phase is estimated to last 2 months and will be dedicated to the analysis of results and the conduct of the final event. This event aims to convene, in person, one representative of the multidisciplinary team and one representative of the leadership from each participating hospital, as well as technical staff from Anvisa. The final meeting will focus on the joint evaluation of the intervention periods, action plans and improvements achieved, as

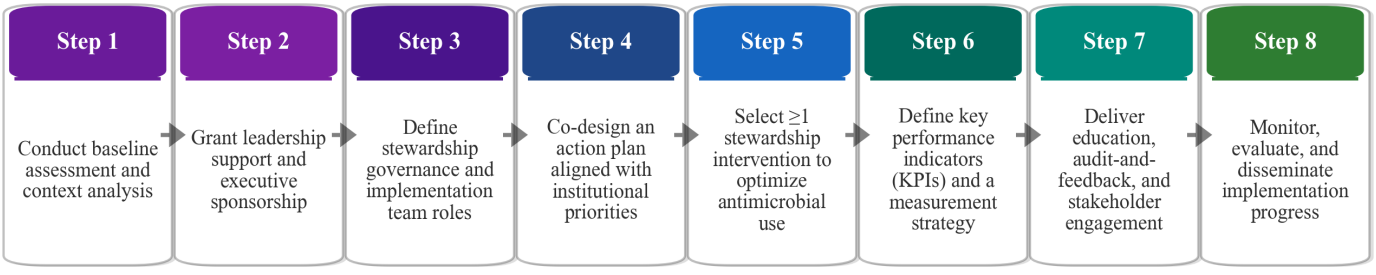


Figure 1 Implementation and Operational Toolkit for the PeGASUS Antimicrobial Stewardship Study.

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Table 1 Driver diagram: primary and secondary drivers for the implementation of antimicrobial stewardship programmes in Brazilian public hospitals

Overall aim	**To promote and strengthen the implementation of antimicrobial stewardship Programmes (ASPs) in Brazilian public hospitals.**
Primary driver	Secondary drivers (specific interventions/activities)
Institutional leadership commitment	► Formal engagement of institutional leadership ► Formal appointment of ASP team endorsed by hospital management
Accountability and defined responsibilities	► Establishment of dedicated leadership and operational teams ► Operational team should include, at minimum, a physician, an IPC nurse and a pharmacist
Stewardship actions to optimise antimicrobial use	► Development of an ASP implementation plan tailored to the local hospital context ► Use of a structured implementation toolkit based on quality-improvement and implementation science methods
Education and training of healthcare professionals	► Implementation of a 6-month e-learning training programme on antimicrobial stewardship ► Monthly group virtual sessions for shared learning and targeted education ► Microlearning sessions developed and delivered by local hospital teams, tailored to specific local contexts ► Integrated benchmarking and learning sessions
Monitoring of antimicrobial use and resistance	► Monthly data collection using standardised forms for indicators (eg, ICU antimicrobial consumption in DDDs and prescription intervention data) ► Triggering the development of local action plans through facility-level data
Feedback and reporting of stewardship activities and indicators	► Monthly virtual meetings for monitoring progress and ongoing technical support ► At least one on-site visit from the coordinating centre ► Structured feedback to prescribers and multidisciplinary teams, incorporating insights derived from ASP data

Primary drivers represent the core components of an ASP aligned with national and international guidelines. Secondary drivers describe the specific interventions and activities designed within this implementation initiative.
ASP, antimicrobial stewardship programme; DDD, defined daily dose; ICU, intensive care unit; IPC, infection prevention and control.

well as on disseminating the results obtained and formally concluding the study.

Variables and data collection

The evaluation of the PeGASUS intervention is based on a set of outcomes and variables, with data collected and aggregated at the hospital level across all study phases. Data collection will be managed using the Research Electronic Data Capture system and will employ standardised instruments. These include:

- The Hospital Characterisation Form, which captures structural, organisational and human resource data in the online supplemental material table S4.
- The ASP Implementation Level Assessment Questionnaire, adapted from the National Assessment of Antimicrobial Stewardship Programmes conducted by Anvisa in the online supplemental material table S2.
- Monthly Indicator Forms for tracking antimicrobial consumption (DDD per 1000 patient-days metric) and stewardship interventions in the online supplemental materail table S6.
- Cost forms for economic sub-study in the online supplemental material table S5.

For the ASP assessments, mandatory supporting documentation will be required and centrally audited to ensure data accuracy and reliability.

Evaluation and data analysis

ASP Implementation level assessment

Based on the total score obtained in the ASP Implementation Level Assessment Questionnaire, hospitals with an established ASP will be categorised into four groups: Group 1 (0–239 points), classified as Inadequate, comprising institutions without an established and implemented ASP or with deficient implementation of essential components, requiring significant improvements; Group 2 (240–509 points), classified as basic, corresponding to hospitals that have the essential elements of the programme with some strategic actions initiated but still insufficiently implemented; Group 3 (510–724 points), classified as Intermediate, including institutions that have adequately implemented most of the essential elements and strategic actions, but that should further improve the scope and quality of implementation and develop long-term plans to sustain and expand ongoing activities and Group 4 (725–1020 points), classified as Advanced,

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encompassing hospitals with full implementation of essential and strategic actions, as well as complementary initiatives aimed at strengthening the programme. Institutions that report that do not have an ASP will be categorised in the study as having a nonexistent ASP.[16]

The ASP Implementation Level Assessment Questionnaire was adapted from Anvisa's national assessment tool, which underwent expert face and content validation during national monitoring cycles. Because the intervention targets the same organisational structures that the questionnaire evaluates, assessor and self-reporting bias may occur. To minimise this bias, baseline and post-intervention assessments will require mandatory submission of supporting administrative documents (eg, formal appointment letters, meeting minutes and audit logs), which will be independently audited by central study reviewers.

Antimicrobial consumption

Antimicrobial consumption will be stratified by antimicrobial classes, according to the data collection instrument provided by the research team. The number of patient-days will be calculated as the daily sum of hospitalised patients in each unit/ward during the evaluated period.[9]

Statistical analysis

At the conclusion of the project, indicators and metrics will be compared between the baseline and post-intervention periods for each participating hospital. All statistical analyses will be conducted at the hospital level. Descriptive statistics will be used to summarise all variables. Categorical variables will be presented as absolute and relative frequencies, while continuous variables will be expressed as means and SD or as medians and IQRs, depending on the data distribution assessed by the Shapiro-Wilk test. All analyses will adopt a two-tailed significance level of $p<0.05$.

Data will be analysed using three distinct populations to ensure the robustness of the findings: as-assigned, modified as-assigned and completers-only populations with hospitals as the unit of analysis.

All hospitals deemed eligible to receive the intervention will comprise the as-assigned population, representing the full group initially allocated to the intervention, regardless of adherence to the protocol or completeness of the data. This approach maintains the original assignment structure and enables the evaluation of the programme's effectiveness under real-world implementation conditions.

The modified as-assigned population will include only the hospitals that effectively initiated the intervention and provided the minimum essential data required for analysis, even in the presence of occasional missing information.

Finally, the completers-only population will consist of hospitals that (1) formally appointed the ASP team with written documentation endorsed by hospital leadership, (2) conducted at least two ASP meetings and (3) achieved a minimum approval rate of 50% among enrolled participants in the web-based self-training. This analysis will enable the estimation of the intervention's efficacy under ideal implementation conditions, considering only the hospitals that fully met the established criteria.

Outcomes

The evaluated outcomes will include the level of organisation of the ASP, the number of interventions performed by the ASP team, the acceptance rate of these interventions, antimicrobial consumption, clinical and healthcare utilisation outcomes and the incremental cost-effectiveness ratio associated with PeGASUS.

The primary outcome will be the change in the ASP organisational level, analysed using a before-and-after design with paired data. For the dichotomous classification, McNemar's test will be applied.

Secondary outcomes will include: (1) an expanded categorical analysis considering the absence of an ASP and transitions between inadequate, basic, intermediate and advanced levels, which will be analysed using the McNemar-Bowker test for paired multicategory data and (2) comparison of the ASP score before and after the intervention, which will be assessed using paired t tests or Wilcoxon signed-rank tests, depending on data distribution. Additionally, improvement rates in ASP organisational level will be presented as frequencies and 95% CIs. The outcome of change in antimicrobial consumption will be analysed using GEEs for repeated measures, including institution and baseline antimicrobial consumption (DDD) as covariates. χ^2 tests will be used for categorical variables, and paired t tests or Wilcoxon signed-rank tests will be applied to numerical variables, as appropriate.

The level of organisation of the ASPs will be applied during the pre-intervention phase and will be re-applied in Phase 3 of the study. In addition, these results will be compared with those obtained from the National Assessment of Antimicrobial Stewardship Programmes in Healthcare Services, conducted by the Department of Surveillance and Monitoring in Healthcare Services of the Anvisa in 2022.[16] The objective of this comparison will be to determine whether a hospital's ASP classifications were consistent across both assessments.

Clinical, healthcare utilisation outcomes and cost-effectiveness analysis

The length of stay in general wards and ICUs will be measured, according to the type of ICU available (eg, clinical, surgical or coronary), as well as 30-day mortality, to assess clinical and healthcare utilisation outcomes. For this analysis, aggregated information collected by the operational team will be used, referring to patients admitted during the study period who initiated antimicrobial treatment in adult ICUs of any type, as well as to the hospital units in which these patients were subsequently hospitalised.

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Based on this information, a subset of hospitals will participate in a cost-effectiveness analysis, considering availability of cost data.

A comparison will be made between the models previously implemented in the institutions and those observed after its implementation. The result will be expressed as the incremental cost-effectiveness ratio, considering the relationship between the costs associated with ASP and the benefit obtained in terms of 30-day deaths avoided. Furthermore, if sufficient data are available, incremental cost-effectiveness ratio may also be estimated in terms of life-years gained or quality-adjusted life-years.

The costs considered will encompass all hospital sectors through which patients who were admitted to the participating ICUs passed. Depending on the adopted perspective (health public system or hospital), the following cost categories will be included: (1) length of hospital stay (cost per patient-day), (2) cost of DDDs per patient, (3) resources used for microbiological and imaging diagnostics related to infections and (4) workload of the multidisciplinary team per hospitalisation day.

The hospitalisation (1) cost will be defined as the average cost per patient-day in the ICU and/or in other hospital wards where patients with ICU admissions were treated. This cost will include human resources, medical supplies and other relevant inputs, excluding costs directly related to antibiotic therapy, which will be assessed separately using the DDD metric.

The DDD (2) will be calculated based on pharmacy dispensing records, with each DDD unit multiplied by the corresponding drug cost. Thus, antimicrobial therapy will be expressed as the 'cost per DDD per patient.'

Costs associated with bacterial infection diagnostics (3) will also be considered. For this purpose, information will be collected on the prevalence and topography of infections. The costs of microbiological tests (cultures, antibiograms and other laboratory tests) and imaging exams may be obtained directly from participating hospitals or through micro-costing approaches.

Finally, the cost of the multidisciplinary team's workload (4) will be estimated based on the average time spent by each professional category involved in the ASP activities.

To assess the robustness of the findings, both deterministic and probabilistic sensitivity analyses will be conducted, exploring uncertainty surrounding parameter estimates and assessing the impact of alternative assumptions on the incremental cost-effectiveness ratio results.

In the probabilistic sensitivity analysis, 1000 simulations will be conducted, simultaneously varying all parameters according to statistical functions widely accepted in the literature: beta distribution for variables ranging from 0 to 1 (such as proportions and utility parameters) and gamma distribution for variables ranging from zero to infinity (such as costs and days of productivity lost). The results may be presented as scatter plots on incremental cost-effectiveness planes and as cost-effectiveness acceptability curves, accompanied by descriptive analysis.

The univariate deterministic analysis will be presented using a tornado diagram, in which the variation of each parameter will be defined based on available data or by applying a standard variation of ±20%. Sub-analyses may also be conducted to account for potential heterogeneity in data obtained from different hospitals.

Patient and public involvement

Patients and members of the public were not involved in the design, conduct, reporting or dissemination plans of this study.

Ethics and dissemination

The study was approved on 12 November 2024, by the Research Ethics Committee of Hospital Alemão Oswaldo Cruz (Committee No. 0070; CAAE 84285924.0.0000.0070; Approval No. 7.221.341). Separate local ethics approval from the participating public hospitals of the Brazilian Unified Health System (SUS) was not required, as the protocol was reviewed and approved by the central Research Ethics Committee. Informed consent will be obtained from participating healthcare professionals, and individual patient consent was waived because only aggregated hospital-level administrative, pharmacy and infection control data will be analysed.

Findings from this study will be disseminated through multiple strategies tailored to key stakeholder groups. Results will be published in peer-reviewed scientific journals and presented at national and international conferences relevant to infectious diseases, antimicrobial stewardship and public health. Executive summaries written in accessible language will be provided to hospital managers and policymakers to support evidence-based implementation and sustainability of ASPs.

Lay summaries, infographics and audiovisual materials will be made available to the general public through institutional communication channels and social media platforms to enhance awareness of antimicrobial stewardship.

The Study Publications Committee ensures that findings will be reported transparently, regardless of whether results are positive, negative or inconclusive. The success of this initiative is founded on the dedication of the participating healthcare professionals and the collaborative efforts of the hospitals involved.

Acknowledgements This study was supported by the Unified Health System Institutional Development Support Program (PROADI-SUS) of the Brazilian Ministry of Health, under the coordination of the Brazilian Health Regulatory Agency (ANVISA). Furthermore, we are grateful to the coordinating hospital team for their essential support in research logistics, mentoring and educational guidance. We also extend our sincere appreciation to the State Centers for Infection Control and Antimicrobial Resistance (CECIRAS) for their strategic support and contributions to implementation. Finally, we thank the teams at the participating hospitals for their cooperation and for providing the institutional data necessary for this study.

Contributors All authors contributed to manuscript revision, approved the final version and agreed to be accountable for all aspects of the work. Study conception and design: ALC, IB, BDMT, KCCB, MRSG, MMDMC, RL and FTP. Protocol development and methodological framework: ALC, IB, BDMT, MYC, KCCB, MRSG, MMDMC, RL and FTP. Data management and statistical planning: ALC, MMF, RL and FTP. Manuscript writing: ALC and MMF. Critical revision of the manuscript for important intellectual content: MYC, IB, BDMT, KCCB, PCZ, LMAM, MRSG, MMDMC,

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RL and FTP. Study supervision and coordination: IB, BDMT, MYC, KCCB, PCZ, LMAM, MRSG, MMDMC, RL and FTP. FTP acted as guarantor and is responsible for the overall content of the manuscript.

Funding The study received funding from the Unified Health System - Institutional Development Support Programme (PROADI-SUS) of the Ministry of Health of Brazil, under the coordination of the Brazilian Health Regulatory Agency (ANVISA).

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The study data will be presented in aggregate form in the publication of the results, with no provision for sharing individual-level data. Aggregate data supporting the findings of this study may be made available upon reasonable request to the corresponding author. In addition, the analysis scripts will be made publicly available in a repository to be specified (e.g., GitHub or a similar platform).

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