

Economic evaluations of antibiotic stewardship programmes 2015–2024: a systematic review

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Summary

BACKGROUND: Numerous studies have demonstrated the effectiveness of Antibiotic Stewardship Programmes in reducing antibiotic resistance and healthcare costs. However, the use of different methods to assess these costs, along with the uncertainty regarding which interventions are cost-effective, hampers the comparison of results and the formulation of clear recommendations. The aim of this systematic review was to provide a comprehensive overview of the available evidence on economic evaluations of Antibiotic Stewardship Programmes and to assess their impact on healthcare costs.

METHODS: The systematic review analysed articles indexed in Medline, Embase, Cochrane Reviews and Trials, Business Source Premier or EconLit that assessed the attributed economic impact of Antibiotic Stewardship Programme interventions in acute care settings and were published between 2015 and 2024. Studies identifying as economic analyses, cost-benefit analyses, cost-effectiveness analyses, cost-consequence analyses, cost analyses or cost-minimisation analyses and that fulfilled the essential parameters required for an economic analysis were included. A descriptive analysis was conducted to examine the impact of the interventions on overall costs, length of stay and antimicrobial costs. We also analysed the different kinds of interventions and the type of costs considered in the analyses. Study quality was evaluated using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist, version 2022.

RESULTS: A total of 2965 publications were identified, of which 411 underwent full-text screening. The 27 studies ultimately included involved 20,232 patients in total and consistently demonstrated savings in antibiotic costs ranging from 2% to 95% relative cost savings, in length of stay costs (3% to 85%) and in overall hospital costs (3% to 86%). The intervention most frequently implemented was “therapy evaluation, review and/or feedback” (23/27, 85%), followed by “alteration of therapy guidelines” (8/27, 30%) and “education” (6/27, 22%). While operational costs were reported by all studies, implementation costs (8/27, 30%) and societal costs (3/27, 11%) were less frequently analysed. By CHEERS category, 9 (33%) of the included studies were rated as low-quality (<60%), 16 (59%) as medium-quality (60–80%) and 2 (7%) as high-quality (>80%).

CONCLUSIONS: Our results emphasise that Antibiotic Stewardship Programmes may contribute to a substantial reduction in healthcare costs for a hospital. While the economic reporting in the field has recently improved, certain cost categories should be accounted for more consistently. There remains considerable potential for further improvement and standardisation to enhance the comparability of studies and facilitate the implementation of effective Antibiotic Stewardship Programmes.

Background

As early as the 1990s, the misuse and overuse of antibiotics and the resulting development of antibiotic-resistant bacteria highlighted the need for systematic approaches to managing antibiotic use [1]. As reported by the Organisation for Economic Co-operation and Development (OECD) in 2023, the issue of antibiotic resistance has reached a critical point, with the financial burden estimated to exceed US\$ 28.9 billion per year worldwide [2].

Antibiotic Stewardship Programmes represent systematic efforts within healthcare facilities to promote the appropriate use of antimicrobials through targeted measures adapted to the local context [3]. A number of studies, such as those by Lee et al. [4] and Baur et al. [5], have demonstrated that Antibiotic Stewardship Programmes can contribute to a reduction of antibiotic resistance by minimising unnecessary prescriptions. In accordance with the Centers for Disease Control and Prevention (CDC), this objective is complemented by the need to mitigate the numerous other adverse effects on society, the environment and the economy [6].

From a societal perspective, Antibiotic Stewardship Programmes represent a logical approach to reducing antibiotic resistance, as they have the potential to lower antibiotic resistance-related mortality and associated costs [7–10]. In addition to the well-documented health impact, the economic benefits of Antibiotic Stewardship Programmes are increasingly being recognised. A growing field of research indicates that Antibiotic Stewardship Programmes contribute to healthcare cost savings by reducing the length

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ABBREVIATIONS

CHEERS: Consolidated Health Economic Evaluation Reporting Standards

DRG: Diagnosis-Related Group

of hospital stays, overall cost savings and antibiotic expenses. These metrics serve as indicators of cost-effectiveness, with the objective of determining whether Antibiotic Stewardship Programmes represent an economically viable solution for hospitals. This leads to the important question of who should bear the financial responsibility for implementing Antibiotic Stewardship Programme measures: policymakers or individual facilities?

Previous literature reviews, such as those by Dik et al. [11] or Nathwani et al. [8], demonstrated significant discrepancies in the methodologies employed to assess costs and frequently observed the lack of a standardised approach to documenting expenses. The complexity of determining all relevant costs led to expenses, such as implementation costs, not being considered. Such discrepancies, along with the uncertainty regarding which interventions are cost-effective, made comparisons challenging and precluded the formulation of clear recommendations for action. Furthermore, there have also been significant developments since these reviews. For instance, the WHO has accorded antibiotic resistance the status of a public health threat since 2015 and has developed a Global Action Plan to combat antimicrobial resistance. As part of this plan, a series of campaigns were initiated, including the GLASS report, the TrACSS website and the World Antimicrobial Resistance Awareness Week [12, 13]. These initiatives emphasise the increase in global awareness about antibiotic resistance and underscore the need to evaluate the economic aspects of Antibiotic Stewardship Programmes as a component of these efforts.

The present study builds on previous findings by Dik et al. [11], which covered the period between 2000 and 2014, and aims to provide a comprehensive and updated overview of the literature published between 2015 and 2024 to examine the impact of these various developments on the economic analysis of Antibiotic Stewardship Programmes. The review also assesses the quality of the included studies using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist, to identify trends in the documentation of economic outcomes and provide recommendations for future research.

Materials and methods

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA-P) statement and has been registered with the international prospective register for systematic reviews (PROSPERO) (registration number: CRD42023441237), available at <https://www.crd.york.ac.uk/prospero/> [11, 14]. A full study protocol was not prepared beforehand.

Eligibility criteria

Studies published between 2015 and June 2024 and explicitly labelled as economic analyses examining the economic impact of Antibiotic Stewardship Programmes in the acute care setting were included. Only full-length publications in peer-reviewed journals, written in English and designed as randomised controlled trials, observational studies (cohort and case-control studies) or quasi-experimental studies (before-and-after studies) were considered eligible. Other study types and any studies with a sample size lower

than five were excluded. Finally, studies investigating paediatric populations or patients in long-term care were not considered. This was done to enhance the comparability of results as the specificities of these populations might not only be reflected in the choice of interventions, but also the cost structure of these settings may differ considerably from adult acute care facilities, potentially distorting the economic analysis.

Search methods

Search strategy

The search was conducted with the assistance of an information specialist librarian (AB) from the University of Zurich medical library. The electronic databases Medline (via Ovid), Embase (via Elsevier), Cochrane Reviews and Trials (via Cochrane Library), Business Source Premier (via EBSCOhost) and EconLit (via EBSCOhost) were searched using a combination of medical indexing terms and free-text terms. The full search strategies for all databases are reported in the appendix (tables S1–S5). The initial searches were performed in August 2023 and an update search was performed in June 2024. In addition, we performed citation searching using Scopus and Web of Science (forward and backward citation searching). The seed references were the articles included for analysis following full-text screening.

Study selection

Search results from each database (including update searches and citation searching results) were exported and uploaded individually to Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org). Deduplication was performed using Covidence. Title and abstract screening was conducted independently by three authors (AB, TD, JH). All records were screened by JH. The concurrent screening performed by AB and TD was split, with the initial 100 being done by AB and the remainder by TD. Disagreements were resolved by a fourth review author (SK).

Eligibility was determined by a two-stage full-text screening process, performed independently by two authors (TD and JH), with disagreements again resolved by SK. Initially, exclusion criteria were applied, and then, in a second step, relevant studies for the economic evaluation identified.

For this analysis, we only included studies that were labelled as economic analyses and could be clearly categorised as Cost-Benefit Analyses (CBA), Cost-Effectiveness Analyses (CEA), Cost-Consequence Analyses (CCA), Cost-Utility Analyses (CUA), Cost Analyses (CA) or Cost-Minimisation Analyses (CMA) [11, 15]. A more detailed explanation of the categories can be found in table 1.

In accordance with the recommendations of Drummond et al., the studies were required to include the implementation and/or operating costs associated with the interventions [15].

Data extraction

Data extraction was conducted by two authors (TD and JH). Major disagreements were resolved by discussion with a third author (SK). Besides bibliographic data (i.e. publication year, journal, authors), we extracted information on study characteristics (i.e. study design, setting, hospital size, number of patients included, time horizon), details about the interventions (categorised as “giving education”, “therapy evaluation, review and/or feedback”, “alteration of therapy guidelines”, “pre-analytic consultations” and “rapid diagnostic tools”), classification as an Antibiotic Stewardship Programme (i.e. structured programme promoting the appropriate use of antibiotics, requiring the involvement of qualified personnel) and financial outcomes (i.e. type of economic analysis). For the latter, the framework used by Dik et al. [11] was applied, measuring impact in monetary units per type of cost accounted for. The following cost categories were extracted: Antibiotic Stewardship Programme implementation costs, Antibiotic Stewardship Programme operational costs (personnel and/or equipment), morbidity and/or mortality costs, and societal costs. Also, data regarding cost changes attributed to Antibiotic Stewardship Programmes, such as length-of-stay costs, overall antimicrobial costs and overall costs, were collected, along with data on implemented price adjustments and/or discounting measures.

Analysis

All statistics were descriptive, including differences, medians with ranges and percentages. To ensure comparability of outcomes, data were converted to US dollars (USD) per year. While this approach facilitates standardised reporting across studies from different countries, it does not account for variations in local purchasing power or economic conditions, which may influence cross-country comparisons. In studies that did not employ inflation-adjusted values during the intervention period, the inflation adjustment was performed separately. To assess the effectiveness of the interventions, the aim was to achieve a percentage reduction in costs between the pre- and post-intervention periods for the outcomes length of stay, antimicrobial costs and overall costs. The cost reduction was calculated by determining the difference between the costs before and after the intervention. This difference was then divided by the pre-intervention costs and expressed as a percentage by multiplying by 100.

The variability in cost reporting was minimised by dividing the assessed costs and Antibiotic Stewardship Pro-

gramme measures into subgroups and tabulating categories such as study design, geographical region and hospital size, and making inflation adjustments for values from previous currency years. Nevertheless, due to the considerable heterogeneity among the included studies, particularly in relation to the methods employed for cost reporting and the measures utilised for outcomes, sensitivity analyses could not be performed. Furthermore, the risk of bias resulting from incomplete results was not formally evaluated. However, for studies with incomplete data, missing data were documented as “not available” and no assumptions or imputations were made. Studies that exhibited significant data gaps were excluded during the data extraction process (see tables S1–S5).

Quality assessment

The quality of studies was evaluated by two reviewers independently (TD and JH) using the CHEERS checklist, version 2022 [16]. Discrepancies were discussed and resolved by consensus. The CHEERS checklist assesses the fulfilment of 28 quality criteria. For each, a score of 1 point was allocated if information was adequately disclosed and documented. In cases of incomplete or absent information, 0.5 or 0 points, respectively, were assigned. The category “not applicable (N/A)” was used if the criterion did not apply to the included study. The values were converted into a scale ranging from 0 to 1, with higher numbers indicating better quality. To enable a more precise quality assessment of the included studies, we adopted the quality classification standard by Degeling et al. [17], which divides quality into three categories: high quality (>80%), moderate quality (60–80%), and low quality (<60%). A detailed description of the CHEERS checklist items is provided in table S6 in the appendix.

Ethics approval and consent to participate

Not applicable.

Results

Study selection

A total of 2596 publications were detected in our literature search after deduplication. After title and abstract review, 411 papers were included in the full-text review of which 194 studies matched the eligibility criteria. Based on their fulfilment of the essential parameters required for an economic analysis, 27 were selected and included in the sys-

Table 1:
Overview of economic analysis methods and their applications. The cost measurement for all categories is expressed in monetary units.

Type of economic analysis	Outcome measures (effect)	Application
Cost-effectiveness analysis (CEA)	Clinical parameters (e.g. life years gained)	Compares relative costs and health outcomes to determine the most efficient option.
Cost-benefit analysis (CBA)	Monetary value	Evaluates costs and benefits by converting outcomes into monetary terms to assess economic impact.
Cost-consequence analysis (CCA)	Various outcomes presented separately	Examines both the varying costs and effects associated with two methods.
Cost-minimisation analysis (CMA)	Assumes effects are equal; compares costs only	Analyses cost differences under the assumption of similar effects across methods.
Cost analysis (CA)	Not applicable	Focuses only on the cost aspect, without evaluating the outcomes.
Cost-utility analysis (CUA)	Utility measures (e.g. quality-adjusted life years [QALYs])	Measures outcomes based on their benefits, focusing on the quality and quantity of life.

tematic review [18–44]. The review process is summarised in figure 1.

Characteristics of the studies

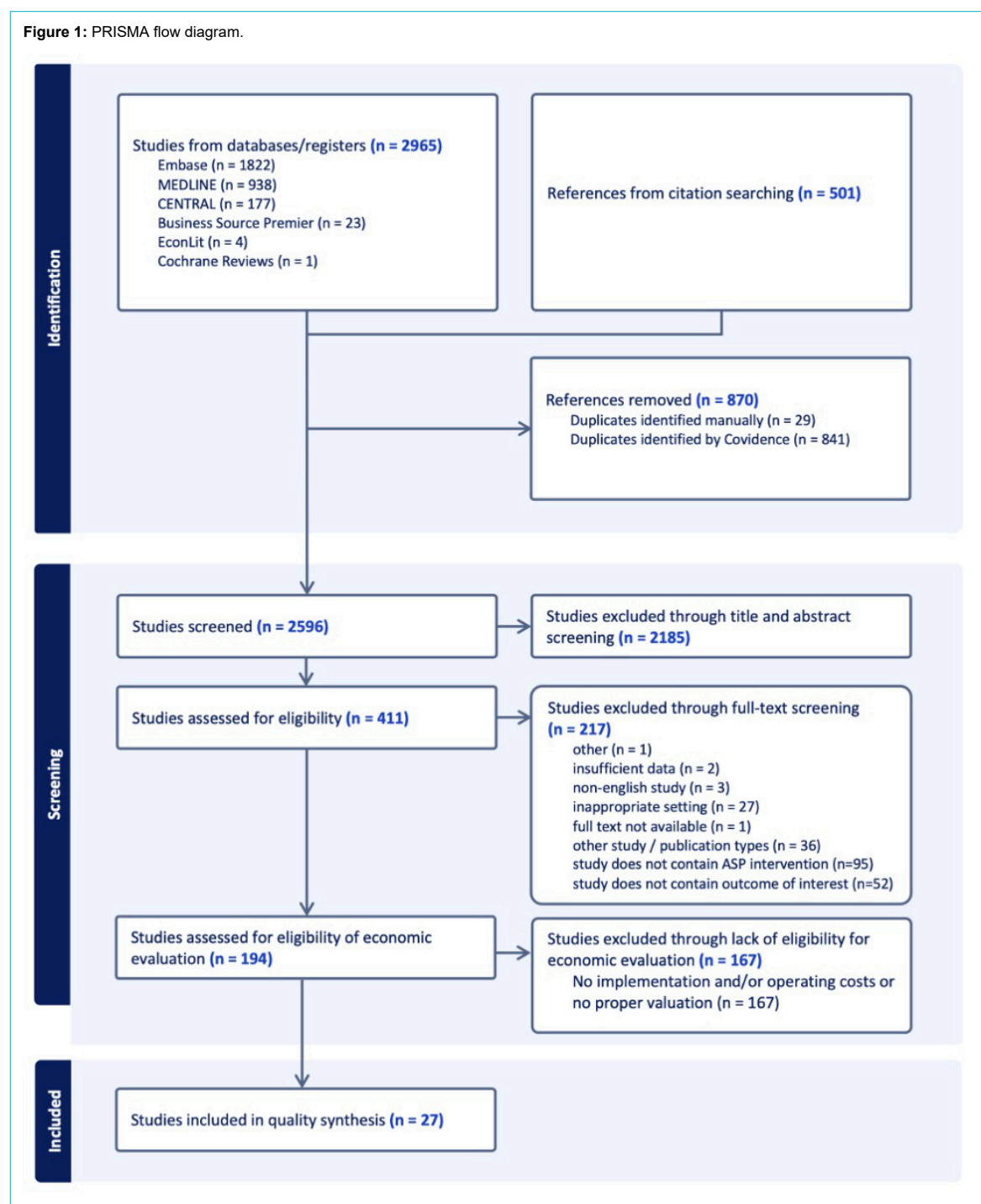
Population, setting and design

Overall, the 23 studies focusing on an economic analysis included a total of 10,827 patients undergoing Antibiotic Stewardship Programme interventions and 9405 in the comparison groups. In four studies, the exact number of patients or the distinction between the two groups was unclear [21, 25, 30, 41].

Most of the studies were conducted in North America (10/27, 37%) [25–28, 35, 36, 38–40, 44] or Europe (8/27, 30%)

[19–21, 23, 24, 30, 34, 42]. The most common study period was 2015–2017 (9/27, 33%) [21, 23, 30, 33, 36, 39, 40, 42, 43]. Observational studies, including cohort and case-control studies, were the most common study design (8/27, 30%) [23–27, 29, 32, 35], followed by retrospective evaluations (6/27, 22%) [18, 20, 28, 33, 40, 41] or quasi-experimental studies (5/27, 19%) [22, 30, 36, 39, 43]. One study (1/27, 4%) employed a randomised controlled trial (RCT) methodology, specifically a stepped-wedge cluster RCT conducted by van Daalen et al. [42]. Table S7 in the appendix provides a summary of the general characteristics of the 27 included studies.

Figure 1: PRISMA flow diagram.



Types of intervention

Therapy evaluation, review and/or feedback (23/27, 85%) [18, 20, 21, 23–34, 36–41, 43, 44] were the most frequently used interventions, followed by alteration of therapy guidelines (9/27, 33%) [18, 19, 21, 22, 26, 31, 35, 39, 42] and education (6/27, 22%) [22, 27, 28, 34, 42, 43]. Pre-analytic consultations (3/27, 11%) [20, 26, 43] and rapid diagnostic tools (3/27, 11%) [28, 36, 38] were less often utilised. Out of the 27 studies, 14 (52%) combined multiple interventions, qualifying them as “service bundles” [18, 20–22, 26–28, 31, 34, 36, 38, 39, 42, 43]. Of these, 12 (86%) contained the intervention “therapy evaluation, review and/or feedback”. In contrast, all studies that considered only one intervention (13/27, 48%) analysed the intervention category “therapy evaluation, review and/or feedback” [19, 23–25, 29, 30, 32, 33, 35, 37, 40, 41, 44].

Types of economic outcome analysis

The majority of the identified studies (19/27, 70%) were categorised as cost analyses [18–20, 24, 27, 28, 30, 31, 33–36, 38–44] in general. Furthermore, 19% (5/27) of the studies conducted cost-benefit analyses [21, 22, 25, 26, 35], with an equivalent number (5/27, 19%) categorised as cost-effectiveness analyses [20, 28, 29, 35, 42]. Cost-minimisation analyses were reported (2/27, 7%) [23, 32]. Only Psaltikidis et al. [37] conducted a cost-utility analysis (1/27, 4%), while Durojaiye et al. [24] employed a cost-consequence analysis. Some studies addressed multiple categories (5/27, 19%) [20, 24, 28, 35, 42].

Cost outcome measures

Costs were measured in various currencies, including USD (18/27, 67%) [18, 19, 25–29, 31–33, 35–41, 43], Euros (EUR) (4/27, 15%) [21, 23, 34, 42], Canadian Dollars (CAD) (1/27, 4%) [44], Turkish Lira (TRY) (1/27, 4%) [20], Swedish Krona (SEK) (1/27, 4%) [30] and British Pounds (GBP) (1/27, 4%) [24]. Only the cost-benefit study of Butt et al. used a benefit-to-cost ratio [22]. The methods used to estimate costs in the 27 studies varied widely, including “per patient”, “per year”, “per bloodstream infection”, “per five years”, “per 1000 cases”, “per month”, “average cost” and no specific method. Only one third (9/27, 33%) considered inflation and performed price adjustments [18, 20, 23, 24, 29–31, 37, 42].

In all studies, the costs and benefits were analysed from the perspective of the hospital (27/27, 100%). While all studies reported operational costs, implementation costs were only reported in 8/27 (30%) of the studies [22–24, 28–30, 36, 42]. Additionally, only 14/27 (52%) papers examined morbidity/mortality costs [18, 20–24, 26, 28, 29, 35, 37, 40, 43, 44] and societal costs were considered in only 3 of the 27 studies (11%) [22, 36, 37]. While the need for inclusion of social costs was highlighted in a few studies, only Psaltikidis et al. also evaluated costs and benefits from a societal perspective (1/27, 4%) [37]. A comprehensive analysis of the efficacy of length of stay, antimicrobial cost savings and overall cost savings is presented in table 2.

Overall cost savings

Overall cost savings were reported by 24 studies (89%) [18, 20–38, 41–44]. Only 12 (44%) quantified the effectiveness of their interventions in terms of overall cost savings [18–20, 24, 25, 28–32, 36, 37, 43, 44]. Yadav et al. [44] reported a significant reduction in total costs of 80% and, similarly, Durojaiye et al. [24] achieved a relative cost reduction of 85%. Karimaghaei et al. [28] also showed a substantial total cost reduction of 86%. Cost reductions in the remaining nine studies ranged from 3% to 50% [20, 25, 29–32, 36, 37, 43].

Antimicrobial cost savings

The cost of antimicrobials was analysed in 16/27 studies (59%) [18–23, 25–27, 29–31, 33, 34, 39–41, 43], and all showed a reduction, with figures ranging from 23% [30] to 95% [43]. Furthermore, the study by Jaggar et al. [27] identified differences in costs between academic and non-academic hospitals and Dik et al. presented minimal differences in percentage reduction in antibiotic costs based on Diagnosis-Related Groups (DRGs) [23, 27].

Length of stay cost savings

Of the seven studies that assessed length of stay [20, 22, 29, 30, 33, 34, 42], six reported that an Antibiotic Stewardship Programme intervention led to a reduction in costs. Kim et al. [29] reported that although the intervention group had higher hospitalisation costs (USD +266.8 or +21%), the overall hospital length of stay was reduced from 10.8 to 9.5 days, yielding an overall cost saving. Three studies demonstrated cost savings between 2.9% and 85% [20, 22, 30] and in three studies [33, 34, 42], it was not possible to quantify cost savings attributable to change in length of stay.

Quality assessment

The quality assessment yielded a median score of 64% (range 43–87%). The reporting quality of the included studies varied significantly. As illustrated in table 2, nine studies (33%) scored 60% or lower [22, 25, 27, 28, 36, 38–41], placing them in the low-quality category and 16 studies (59%) fell into the moderate-quality category [19–21, 23, 24, 26, 29–35, 42–44]. Only Psaltikidis et al. [37] and Abushanab et al. [18] (2/27, 7%) achieved the high-quality category, scoring 83% and 87%, respectively. Furthermore, there were several aspects for which the studies often lacked the required reporting according to the CHEERS checklist criteria. For instance, item 16, “Rationale and description of the model”, was only assessable in four studies (15%), as most of the economic evaluations were not model-based [23, 37, 41, 42]. A plan for health economic analyses was developed but not fully reported in three studies (11%) [18, 42, 43]. Of the 27 studies included, only van Daalen et al. [42] mentioned their approach to involving patients and other stakeholders in the study, while none of the studies addressed the impact of this involvement in the results section. Of note, none of the 27 studies had a complete abstract, with information on discount rate, perspective, currency year and time horizon mostly missing. Only two studies (7%) characterised the distributional effects completely [24, 44] and three (11%)

considered the discount rate [18, 31, 37]. Figure 2 shows the proportions of fulfilment categories per item.

Discussion

In the present systematic literature review, focusing on economic studies examining Antibiotic Stewardship Programme interventions in the acute care setting and their attributed economic impact for a hospital, published between 2015 and 2024, we observe that Antibiotic Stewardship Programmes are consistently associated with reduction of overall costs, length of stay costs and antimicrobial costs. Furthermore, the intervention category “evaluation, review and feedback of therapeutic interventions” was most com-

mon and was consistently shown to be effective in reducing costs. Additionally, the implementation of rapid diagnostic tools and educational programmes contributed to these reductions. Similar to Dik et al. [11], we observed significant heterogeneity between studies. However, with the increasing efforts in papers such as those by Psaltikidis et al. [37] and Abushanab et al. [18] to document cost changes in a standardised manner, we noted that the quality of studies evaluating economic aspects of Antibiotic Stewardship Programme interventions has improved over time. This improvement in comparison with the publications before 2015 allowed us to apply the recommended CHEERS checklist for quality assessment in the updated period from 2015 to 2024.

Table 2:

Overview of relative cost savings for different interventions. An en dash (–) indicates that the study did not consider the particular value. “Unquantifiable” means the effectiveness of the measures regarding overall cost savings could not be quantified due to insufficient data. Studies are organised alphabetically by first author.

Author(s) (Year)	Intervention category	Length of stay reduction	Antimicrobial reduction	Overall cost reduction
Abushanab et al. (2024)	Altered therapy guidelines, Therapy evaluation, review and/or feedback	–	–2%	unquantifiable
Asilturk et al. (2024)	Altered therapy guidelines	–	–37%	–
Bastug et al. (2021)	Therapy evaluation, review and/or feedback, Pre-analytic consultations	–85%	–	–25%
Borde et al. (2016)	Therapy evaluation, review and/or feedback, Altered therapy guidelines	–	–67%	unquantifiable
Butt et al. (2019)	Giving education, Altered therapy guidelines	–35%	–26%	unquantifiable
Dik et al. (2015)	Therapy evaluation, review and/or feedback	–	DRG1: –23.4% / DRG2: –26.6%	unquantifiable
Durojaiye et al. (2018)	Therapy evaluation, review and/or feedback	–	–	–85%
Howell et al. (2019)	Therapy evaluation, review and/or feedback	–	unquantifiable	–20%
Hyland et al. (2022)	Therapy evaluation, review and/or feedback, pre-analytic consultations, altered therapy guidelines	–	unquantifiable	unquantifiable
Jaggar et al. (2023)	Therapy evaluation, review and/or feedback, Giving education	–	–32% (academic hospital) –63% (non-academic hospital)	unquantifiable
Karimaghaei et al. (2022)	Therapy evaluation, review and/or feedback, Giving education, Rapid diagnostic tools	–	–	–86%
Kim et al. (2022)	Therapy evaluation, review and/or feedback	+21%	–39%	–27%
Lanbeck et al. (2016)	Therapy evaluation, review and/or feedback	–3%	–23%	–3%
Lester et al. (2020)	Altered therapy guidelines, Therapy evaluation, review and/or feedback	–	–69%	–30%
Loesch et al. (2021)	Therapy evaluation, review and/or feedback	–	–	–50%
Malone et al. (2015)	Therapy evaluation, review and/or feedback	unquantifiable	unquantifiable	unquantifiable
Mouwens et al. (2020)	Giving education, Therapy evaluation, review and/or feedback	unquantifiable	unquantifiable	unquantifiable
Olson et al. (2023)	Altered therapy guidelines	–	–	unquantifiable
Patel et al. (2017)	Rapid diagnostic tools, Therapy evaluation, review and/or feedback	–	–	–5%
Psaltikidis et al. (2019)	Therapy evaluation, review and/or feedback	–	–	–47%
Ramsey et al. (2020)	Therapy evaluation, review and/or feedback, Rapid diagnostic tools	–	–	unquantifiable
Ross et al. (2015)	Therapy evaluation, review and/or feedback, Giving education, Altered therapy guidelines	–	unquantifiable	–
Ruh et al. (2015)	Therapy evaluation, review and/or feedback	–	–92% / –81%	–
Salman et al. (2021)	Therapy evaluation, review and/or feedback	–	–	unquantifiable
van Daalen et al. (2017)	Giving education, Altered therapy guidelines	unquantifiable	–	unquantifiable
Wang et al. (2015)	Giving education, Therapy evaluation, review and/or feedback, Pre-analytic consultations	–	–95%	–20%
Yadav et al. (2022)	Therapy evaluation, review and/or feedback	–	–	–80%

DRG: Diagnosis-related group.

Despite the potential for cost reduction, the quantitative documentation of overall costs, length of stay costs and antimicrobial costs varied considerably. Among the included studies, length of stay costs were less frequently documented than antimicrobial costs and overall savings. Dik et al. [11] emphasised the financial importance of reducing length of stay costs, noting that in addition to the financial benefit for a hospital resulting from the freed-up beds, there can also be a positive effect on patients by allowing them to leave hospital earlier.

Furthermore, it was challenging to ascertain the financial benefits of specific interventions, as so-called “service bundles” were frequently implemented. While the intervention “therapy evaluation, review and/or feedback” was the most prevalent intervention in our review, accounting for 23 of the 27 studies (85%), its actual cost-effectiveness could not be clearly determined, as in most cases it was

combined with other interventions such as education or alteration of therapy guidelines. Van Dorst et al. [45] highlight the need to evaluate the economic impact of individual Antibiotic Stewardship Programme interventions. This is essential to facilitate comparisons and determine the most effective intervention in each setting. This may prove to be especially important in settings with limited resources and not only guide health policy stakeholders in the selection of Antibiotic Stewardship Programme interventions but also provide motivation for their implementation.

As became evident when applying the CHEERS checklist, economic reporting quality is not consistent, preventing comparability of study results. The variations in the quality of the studies summarised in table 2 are principally due to discrepancies in adherence to methodological rigour. For instance, high-quality studies provided comprehensive jus-

Figure 2: Overview of reported items from the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist among the 27 included studies. Numbers are percentages and have been rounded.



tifications for the selection of economic models and contained clear information on discount rates and sensitivity analyses. Conversely, lower-quality studies frequently exhibited deficiencies in these aspects and demonstrated a lack of transparency in cost reporting and valuation approaches. In general, the absence and heterogeneity of crucial information on parameters such as study design, number of patients or beds, currency, and inflation or price adjustment posed a significant challenge during data synthesis and indicates that the improvements and recommendations proposed by Dik et al. [11] have not yet been widely implemented in the economic evaluation of Antibiotic Stewardship Programmes. In particular, the inclusion of all relevant cost types, including implementation, operating and societal costs, was considered in a few studies in our review. Our results are consistent with those reported by Dik et al. [11], which also found that only 11% of the included studies considered implementation costs, and none of them considered societal costs.

Recent literature supports this observation. Elshenawy et al. [46] identified that numerous studies lacked comprehensive consideration of all relevant costs, limiting their broader applicability. Similarly, Painter et al. [47] emphasised that the variability in cost calculation methods and the inconsistent reporting of implementation costs continue to hinder the comparability of Antibiotic Stewardship Programme studies. Nevertheless, it is evident that interventions require time, resources and specific equipment, which could represent a significant challenge for small hospitals. Stenehjem et al. [48] identified practical challenges that small hospitals face in implementing Antibiotic Stewardship Programmes and notes that these costs are often underreported, which affects the comparability of study results. In addition to insufficient funding, these challenges include limited access to infectious diseases specialists and difficulties in collecting and analysing data on antibiotic use due to inferior data infrastructure. Telemedical support, optimisation of resource allocation within healthcare networks and training of non-specialised healthcare professionals to assume leadership roles in Antibiotic Stewardship Programmes are potential approaches to meet these challenges. Furthermore, the CDC [49] emphasised the need for robust implementation strategies tailored to the capabilities of small and critical access hospitals.

Therefore, the need to improve the quality of economic evaluations of Antibiotic Stewardship Programmes persists. The implementation of simplified measures, including antibiotic time-outs, clinical algorithms and regional collaborations, has the potential to further facilitate the implementation of Antibiotic Stewardship Programmes in resource-limited settings [48]. These improvements are of paramount importance to ensure the comparability of different interventions, facilitate transferability of results to other settings and motivate both small and large hospitals to invest in Antibiotic Stewardship Programmes on their own.

Our study has several limitations. First and foremost, our review was limited to studies that explicitly categorised their economic evaluations as cost-benefit analyses, cost-effectiveness analyses, cost-consequence analyses, cost analyses or cost-minimisation analyses. Nevertheless, it is possible that other studies addressing costs and their conse-

quences may also have been pertinent, but did not explicitly identify themselves as such economic analyses and were therefore not included in the present review. Second, it is possible that publication bias may have influenced the results: all the selected studies reported cost reductions and it may be that studies in which no effects on cost reduction could be demonstrated were not published. This has the potential to result in an overestimation of the cost-saving potential of Antibiotic Stewardship Programme interventions. Furthermore, the paucity of access to unpublished data makes it difficult to comprehensively assess the true extent of this cost effect. Thirdly, the considerable variability in study design, as well as the geographical representation of mainly high-income countries such as North America and Europe, may limit the generalisability of our results to low-resource settings. This emphasis on high-income settings has the potential to introduce a bias by overestimating the feasibility and cost-effectiveness of Antibiotic Stewardship Programmes in resource-limited contexts, where specific challenges, such as limited infrastructure and higher implementation costs, may be of critical importance. Fourthly, it is important to acknowledge the implications of the exclusion criteria, paediatric populations, studies not in English and long-term care facilities, on the generalisability and external validity of the results.

It is important to note that cost measures might be influenced by external factors, such as disease severity or events such as pandemics. Thus, the evaluation of costs does not allow for measuring the appropriateness of the interventions or clinical results. The cost calculations and timeframe of the intervention that led to the observed cost reductions were highly heterogeneous and not always clearly stated, which could affect the external validity of our results. Finally, the factor “loss to follow-up” in the original studies could be indirectly relevant for our systematic review as a significant loss of participants in the original studies could cause systematic bias and affect the robustness of the results. However, this potential bias is reflected in the quality analysis using the CHEERS checklist, which takes aspects such as inadequate reporting or methodological weaknesses into account.

In summary, our systematic review provides a comprehensive and transparent overview of the current state of knowledge and demonstrates that Antibiotic Stewardship Programmes represent, in addition to the known social benefits, a promising approach to reducing costs in acute care facilities. These findings have the potential to motivate both small and large hospitals to independently invest in the implementation of Antibiotic Stewardship Programmes. Nevertheless, there remain unanswered questions regarding the long-term impact on overall healthcare costs and the methods used to assess this impact. Further studies should aim to address these limitations by employing standardised economic evaluation methodologies, thus facilitating the comparability of research results and ensuring the attainment of more robust and generally valid outcomes. Furthermore, the reporting process should be transparent, and the long-term economic impact of Antibiotic Stewardship Programmes should be analysed comprehensively. This will further reinforce the evidence base for the economic evaluation of Antibiotic Stewardship Programmes and facilitate the formulation of well-informed

decisions regarding the implementation of such programmes.

Availability of data and materials

Datasets used and/or analysed in this study are available on request from the corresponding author.

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Author contributions: JH, TD and SK were involved in the conception and design of the work. JH, TD, SK and AB were involved in study selection and data extraction. JH contributed as first author and drafted the original version of the manuscript. SK contributed as final author. TD, AB, PK and SPK critically reviewed and approved the final manuscript.

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Appendix

Table S1. Medline (Ovid) search strategy

No.	Query
1	*Antimicrobial Stewardship/ or ((Antimicrob* or antibiotic* or antiinfective*) and steward*).ti,ab,kw. or ((Antimicrob* or antibiotic* or antiinfective*) adj4 (reduc* or optimiz* or optimis* or control* or access* or audit* or feedback*) adj3 (program* or framework*).ti,ab,kw. or ((Antimicrob* or antibiotic* or antiinfective*) adj6 (optimal or misuse or underdos* or de-escalation or "IV/PO-switch" or "intravenous-to-oral" or narrowing)).ti,ab,kw. or ((Antimicrob* or antibiotic* or antiinfective*) adj6 "use" adj2 (responsible or resource* or surveillance or management or appropriate* or rational)).ti,ab,kw. or ((Antimicrob* or antibiotic* or antiinfective*) and ("diagnostic stewardship" or "drug utilization review" or "decision support system*" or "therapeutic drug monitoring" or "infecti* disease specialist*")).ti,ab,kw. or (OPAT or "outpatient parenteral antibiotic therapy").ti,ab,kw.
2	exp "Costs and Cost Analysis"/ or exp "Economics, Hospital"/ or exp "Economics, Pharmaceutical"/ or exp "Fees, Pharmaceutical"/ or exp "Financial Management, hospital"/ or exp "Health Care Sector"/ or exp "Models, Econometric"/ or (((Cost* or expenditure* or financial* or economic* or dollar* or euro or euros or money) adj6 (analysis or analyz* or assess* or evaluat* or impact or model* or compar* or direct or indirect or consequence or reduc* or increase* or calculate* or investigat* or quantif* or saving*)) or "health resource utilization").ti,ab,kw.
3	1 and 2
4	limit 3 to yr=2015-Current
5	limit 4 to english
6	5 not (animals not humans).sh.
7	6 not ((exp child/ or exp infant/ or exp adolescent/) not exp adult/)
8	limit 7 to (congress or editorial or letter or preprint)
9	7 not 8

Table S2. Embase (Elsevier) search strategy

No.	Query
#1	'antimicrobial stewardship'/mj OR 'antimicrobial stewardship program'/syn OR 'antibiotic stewardship program'/syn OR ((antimicrob*:ti,ab,kw OR antibiotic*:ti,ab,kw OR antiinfective*:ti,ab,kw) AND steward*:ti,ab,kw) OR (((antimicrob* OR antibiotic* OR antiinfective*) NEAR/4 (reduc* OR optimiz* OR optimis* OR control* OR access* OR audit* OR feedback*) NEAR/3 (program* OR framework*)):ti,ab,kw) OR (((antimicrob* OR antibiotic* OR antiinfective*) NEAR/6 (optimal OR misuse OR underdos* OR 'de escalation' OR 'iv/po-switch' OR 'intravenous-to-oral' OR narrowing)):ti,ab,kw) OR (((antimicrob* OR antibiotic* OR antiinfective*) NEAR/6 use NEAR/2 (responsible OR resource* OR surveillance OR management OR appropriate* OR rational)):ti,ab,kw) OR ((antimicrob*:ti,ab,kw OR antibiotic*:ti,ab,kw OR antiinfective*:ti,ab,kw) AND ('diagnostic stewardship':ti,ab,kw OR 'drug utilization review':ti,ab,kw OR 'decision support system':ti,ab,kw OR 'therapeutic drug monitoring':ti,ab,kw OR 'infecti* disease specialist':ti,ab,kw)) OR opat:ti,ab,kw OR 'outpatient parenteral antibiotic therapy':ti,ab,kw
#2	'economic evaluation'/syn OR 'health care cost'/exp OR 'health care utilization'/exp OR (((cost* OR expenditure* OR financial* OR economic* OR dollar* OR euro OR euros OR money) NEAR/6 (analysis OR analyz* OR assess* OR evaluat* OR impact OR model* OR compar* OR direct OR indirect OR consequence OR reduc* OR increase* OR calculate* OR investigat* OR quantif* OR saving*)):ti,ab,kw) OR 'health resource utilization':ti,ab,kw
#3	#1 AND #2
#4	#3 AND [2015-2023]/py
#5	#4 AND [english]/lim
#6	#5 NOT (('animal'/de OR 'animal experiment'/exp OR 'nonhuman'/de) NOT ('human'/exp OR 'human experiment'/de))
#7	#6 NOT (([infant]/lim OR [child]/lim OR [adolescent]/lim) NOT ([adult]/lim OR [aged]/lim))
#8	#7 NOT ([conference abstract]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim OR [preprint]/lim)

Table S3. Cochrane search strategy

No.	Query
#1	((Antimicrob* OR antibiotic* OR antiinfective*) AND steward*):ti,ab,kw OR ((Antimicrob* OR antibiotic* OR antiinfective*) NEAR/4 (reduc* OR optimiz* OR optimis* OR control* OR access* OR audit* OR feedback*) NEAR/3 (program* OR framework*)):ti,ab,kw OR ((Antimicrob* OR antibiotic* OR antiinfective*) NEAR/6 (optimal OR misuse OR underdos* OR de-escalation OR "IV/PO-switch" OR "intravenous-to-oral" OR narrowing)):ti,ab,kw OR ((Antimicrob* OR antibiotic* OR antiinfective*) NEAR/6 use NEAR/2 (responsible OR resource* OR surveillance OR management OR appropriate* OR rational)):ti,ab,kw OR ((Antimicrob* OR antibiotic* OR antiinfective*) AND ("diagnostic stewardship" OR "drug utilization review" OR ("decision support" NEXT system*) OR "therapeutic drug monitoring" OR ("infectious disease" NEXT specialist*)):ti,ab,kw OR (OPAT OR "outpatient parenteral antibiotic therapy"):ti,ab,kw
#2	(((Cost* OR expenditure* OR financial* OR economic* OR dollar* OR euro OR euros OR money) NEAR/6 (analysis OR analyz* OR assess* OR evaluat* OR impact OR model* OR compar* OR direct OR indirect OR consequence OR reduc* OR increase* OR calculate* OR investigat* OR quantif* OR saving*)) OR "health resource utilization"):ti,ab,kw
#3	#1 AND #2
#4	#3 NOT (([mh "infant"] OR [mh "child"] OR [mh "adolescent"])) NOT [mh "adult"])
#5	#4 with Cochrane Library publication date Between Jan 2015 and Dec 2023

Table S4. Business Source Premier (EBSCOhost) search strategy

No.	Query
S1	DE "ANTIMICROBIAL stewardship" OR ((DE "ANTIBIOTICS" OR DE "Anti-infective agents") AND (DE "infection prevention" OR DE "Hospital pharmacies" OR DE "Health services administration"))
S2	(TI ((Antimicrob* OR antibiotic* OR antiinfective*) AND steward*)) OR (AB ((Antimicrob* OR antibiotic* OR antiinfective*) AND steward*))
S3	(TI ((Antimicrob* OR antibiotic* OR antiinfective*) N4 (reduc* OR optimiz* OR optimis* OR control* OR access* OR audit* OR feedback*) N3 (program* OR framework*))) OR (AB ((Antimicrob* OR antibiotic* OR antiinfective*) N4 (reduc* OR optimiz* OR optimis* OR control* OR access* OR audit* OR feedback*) N3 (program* OR framework*)))
S4	(TI ((Antimicrob* OR antibiotic* OR antiinfective*) N6 (optimal OR misuse OR underdos* OR de-escalation OR "IV/PO-switch" OR "intravenous-to-oral" OR narrowing))) OR (AB ((Antimicrob* OR antibiotic* OR antiinfective*) N6 (optimal OR misuse OR underdos* OR de-escalation OR "IV/PO-switch" OR "intravenous-to-oral" OR narrowing)))
S5	(TI ((Antimicrob* OR antibiotic* OR antiinfective*) N6 use N2 (responsible OR resource* OR surveillance OR management OR appropriate* OR rational)) OR AB ((Antimicrob* OR antibiotic* OR antiinfective*) N6 use N2 (responsible OR resource* OR surveillance OR management OR appropriate* OR rational)))
S6	(TI ((Antimicrob* OR antibiotic* OR antiinfective*) AND ("diagnostic stewardship" OR "drug utilization review" OR "decision support system*" OR "therapeutic drug monitoring" OR "infecti* disease specialist*"))
S7	(AB ((Antimicrob* OR antibiotic* OR antiinfective*) AND ("diagnostic stewardship" OR "drug utilization review" OR "decision support system*" OR "therapeutic drug monitoring" OR "infecti* disease specialist*"))
S8	(TI (OPAT OR "outpatient parenteral antibiotic therapy") OR AB (OPAT OR "outpatient parenteral antibiotic therapy"))
S9	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
S10	DE "Cost effectiveness" OR DE "Medical care costs" OR DE "Cost control" OR DE "Value-based healthcare" OR TI ((Cost* OR expenditure* OR financial* OR economic* OR dollar* OR euro OR euros OR money) N6 (analysis OR analyz* OR assess* OR evaluat* OR impact OR model* OR compar* OR direct OR indirect OR consequence OR reduc* OR increase* OR calculate* OR investigat* OR quantif* OR saving*)) OR "health resource utilization")) OR AB ((Cost* OR expenditure* OR financial* OR economic* OR dollar* OR euro OR euros OR money) N6 (analysis OR analyz* OR assess* OR evaluat* OR impact OR model* OR compar* OR direct OR indirect OR consequence OR reduc* OR increase* OR calculate* OR investigat* OR quantif* OR saving*)) OR "health resource utilization"))
S11	S9 AND S10
S12	S11 NOT (DE "farm management" OR DE "dairy farm management" OR DE "dairy farms" OR DE "dairy cattle" OR DE "bovine mastitis" OR DE "animal herds" OR DE "cows" OR DE "poultry" OR DE "poultry farms" OR DE "poultry farm management")
S13	S12 with EBSCOhost Limiter PublishedDate: 20150101-20231231

Table S5. EconLit (EBSCOhost) search strategy

No.	Query
S1	(TI ((Antimicrob* OR antibiotic* OR antiinfective*) AND steward*)) OR (AB ((Antimicrob* OR antibiotic* OR antiinfective*) AND steward*)) OR (TI ((Antimicrob* OR antibiotic* OR antiinfective*) N4 (reduc* OR optimiz* OR optimis* OR control* OR access* OR audit* OR feedback*) N3 (program* OR framework*))) OR (AB ((Antimicrob* OR antibiotic* OR antiinfective*) N4 (reduc* OR optimiz* OR optimis* OR control* OR access* OR audit* OR feedback*) N3 (program* OR framework*))) OR (TI ((Antimicrob* OR antibiotic* OR antiinfective*) N6 (optimal OR misuse OR underdos* OR de-escalation OR "IV/PO-switch" OR "intravenous-to-oral" OR narrowing))) OR (AB ((Antimicrob* OR antibiotic* OR antiinfective*) N6 (optimal OR misuse OR underdos* OR de-escalation OR "IV/PO-switch" OR "intravenous-to-oral" OR narrowing))) OR (TI ((Antimicrob* OR antibiotic* OR antiinfective*) N6 use N2 (responsible OR resource* OR surveillance OR management OR appropriate* OR rational)) OR AB ((Antimicrob* OR antibiotic* OR antiinfective*) N6 use N2 (responsible OR resource* OR surveillance OR management OR appropriate* OR rational))) OR (TI ((Antimicrob* OR antibiotic* OR antiinfective*) AND ("diagnostic stewardship" OR "drug utilization review" OR "decision support system" OR "therapeutic drug monitoring" OR "infecti* disease specialist*"))) OR (AB ((Antimicrob* OR antibiotic* OR antiinfective*) AND ("diagnostic stewardship" OR "drug utilization review" OR "decision support system" OR "therapeutic drug monitoring" OR "infecti* disease specialist*"))) OR (TI (OPAT OR "outpatient parenteral antibiotic therapy") OR AB (OPAT OR "outpatient parenteral antibiotic therapy"))
S2	TI ((Cost* OR expenditure* OR financial* OR economic* OR dollar* OR euro OR euros OR money) N6 (analysis OR analyz* OR assess* OR evaluat* OR impact OR model* OR compar* OR direct OR indirect OR consequence OR reduc* OR increase* OR calculate* OR investigat* OR quantif* OR saving*)) OR "health resource utilization") OR AB ((Cost* OR expenditure* OR financial* OR economic* OR dollar* OR euro OR euros OR money) N6 (analysis OR analyz* OR assess* OR evaluat* OR impact OR model* OR compar* OR direct OR indirect OR consequence OR reduc* OR increase* OR calculate* OR investigat* OR quantif* OR saving*)) OR "health resource utilization")
S3	S1 AND S2
S4	S3 with EBSCOhost Limiters PublishedDate: 20150101-20231231; Publication Type: Collective Volume Article, Journal Article

Table S6. Quality of included studies according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist 2022.

Section/Item	Mouwen et al. (2020)	Ramsey et al. (2020)	Salman et al. (2021)	Yadav et al. (2022)	Wang et al. (2015)	vanDaalen et al. (2017)	Ruh et al. (2015)	Ross et al. (2015)	Psaltikidis et al. (2019)	Patel et al. (2017)	Malone et al. (2015)	Loesch et al. (2021)	Lester et al. (2020)	Lanbeck et al. (2016)	Kim et al. (2022)	Karimaghvaei et al. (2022)	Jaggar et al. (2023)	Hyland S. et al. (2022)	Howell et al. (2019)	Durojaiye et al. (2018)	Dik et al. (2015)	Butt et al. (2019)	Borde et al. (2016)	Bastug et al. (2021)	Olson et al. (2023)	Asilturk et al. (2024)	Abushanab et al. (2024)
Title	0.5	0	0.5	1	1	1	1	0.5	1	1	1	1	0.5	1	0.5	1	0.5	0	0	1	1	0.5	1	1	1	1	1
Abstract	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Background and objectives	0.5	0.5	0.5	1	0.5	0.5	0.5	0.5	1	0.5	0.5	0.5	0.5	0.5	0.5	1	0.5	1	0.5	0.5	1	0.5	0.5	0.5	0.5	0.5	1
Health economic analysis plan	0	0	0	0	0.5	0.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Study population	1	1	0	1	1	0.5	1	1	1	1	0.5	1	1	0.5	1	1	1	1	1	1	1	1	N/A	1	1	1	1
Setting and location	1	1	1	1	1	0.5	1	1	1	1	1	1	1	1	1	0.5	0.5	0.5	0.5	1	1	1	1	1	1	1	1
Comparators	1	1	0.5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Perspective	1	0	0	1	1	1	0	0	1	0.5	0	0	0	0	0	0	0	1	0	1	0	0	1	0.5	1	0	1
Time horizon	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Discount rate	0	0	0	0	0	0	0	0	1	0	0	0	0.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0.5
Selection of outcome	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

<i>Measurement of outcomes</i>	0.5	1	1	0	1	1	1	0.5	1	1	1	1	1	1	1	1	1	1	1	0.5	1	1	1	1	1	1	1
<i>Valuation of outcomes</i>	1	1	1	1	1	1	0.5	0	1	1	1	0	1	1	1	0	1	1	0	0	1	1	1	0.5	1	1	1
<i>Measurement and valuation of resources and costs</i>	1	1	1	1	0.5	1	0	1	1	1	1	0	1	1	0	1	1	1	0	1	1	1	1	1	1	1	1
<i>Currency, price date, and conversion</i>	0	0	0	1	0.5	1	0	0	1	0	0.5	0.5	1	1	1	0	0.5	0	0	0.5	1	0	0.5	1	1	1	1
<i>Rationale and description of model</i>	N/A	N/A	1	N/A	N/A	0.5	N/A	N/A	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A	N/A	N/A	N/A	N/A	N/A
<i>Analytics and assumptions</i>	1	0.5	0	1	1	0.5	1	0.5	1	1	1	0.5	1	1	1	0	0	1	N/A	0	1	1	1	1	1	1	1
<i>Characterizing heterogeneity</i>	0.5	0	0	1	0.5	0	0	0	1	0	1	1	0.5	1	0	0	1	0	0	0	0.5	0	N/A	0	0	0	1
<i>Characterising distributional effects</i>	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	N/A	0	0	0	0.5
<i>Characterising uncertainty</i>	1	0	0	1	1	0	0.5	1	1	1	1	1	1	1	0	0	0	0.5	N/A	0	1	1	1	1	0.5	0.5	1
<i>Approach to engagement with patients and others affected by the study</i>	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<i>Study parameters</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	N/A	1	1	0.5	1	1	1	1	1
<i>Summary of main results</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
<i>Effect of uncertainty</i>	0	0	0	0	1	0	1	0	1	0	0	1	0.5	1	1	0	0	0	N/A	1	1	0	0	0	0	0	1
<i>Effect of engagement with patients and others affected by the study</i>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<i>Study findings and limitations</i>	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0.5	1	1	1	1	0.5	1	1	1

Source of funding	1	0	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	
Conflicts of interest	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Overall quality	17. 5	13. 5	14	20. 5	20	18. 5	16	14. 5	23. 5	15. 5	17	17	19	19. 5	16. 5	14	15. 5	16. 5	10	17	21	16	16. 5	17. 5	18. 5	17. 5	23. 5
Score %	64	50	50	76	74	66	59	53	83	57	63	63	70	72	61	51	57	61	43	63	75	59	69	65	69	65	87

Table S7. Characteristics of included studies. The symbol “x” indicates that the study reported on the particular outcome. Studies are organised alphabetically by first author.

Author(s) (year)	Number of patients (pre- /post- intervention)	Study design (as reported)	Country – Setting	Intervention	Study period	Type of economic evaluation	Overall costs	Length of stay costs	Antimicrobial costs	Operational costs	Morbidity/mortality costs	Implementation costs	Societal costs	Inflation/price adjustment	Currency
Abushanab et al. (2024) [18]	250/250	Retrospective evaluation	Qatar – General medicine wards in three central hospitals	Introduction of guidelines, daily data collection by pharmacists and physicians, regular Antibiotic Stewardship Programme committee meetings and daily clinical rounds.	2015–2020	Cost analysis	x		x	x	x			Yes	USD
Asilturk et al. (2024) [19]	339/233	Unclear	Turkey – ICU of Ankara bilkent city hospital	Implementation of carbapenem restriction if sepsis, septic shock or carbapenem-only susceptible microorganisms are present.	2020–2021	CA			x	x				No	USD
Bastug et al. (2021) [20]	594/594	Retrospective evaluation	Turkey – Tertiary care hospital	Reviewing and comparing Outpatient Parenteral Antibiotic Therapy service to inpatients.	2013–2017	CA, CEA	x	x		x	x			Yes	TRY
Borde et al. (2016) [21]	Not reported	Interrupted time-series analysis	Germany – Community-based hospital	Weekly ID rounds, phone consultations, guideline revision and dissemination of new recommendations with feedback.	2012–2015	CBA	x		x	x	x			No	EUR
Butt et al. (2019) [22]	225/225	Quasi-experimental study	Pakistan – Tertiary care hospital	Educational and training sessions were conducted to brief and discuss the standard treatment guidelines regarding the use of antibiotics for surgical prophylaxis.	2016–2017	CBA	x	x	x	x	x	x	x	No	PKR
Dik et al. (2015) [23]	114/357	Cohort study	The Netherlands – Academic medical centre	Implementation of an Antibiotic Stewardship Team (A-Team), performing ward visits and discussing patients.	2013–2014	CMA	x		x	x	x	x		Yes	USD

Durojaiye et al. (2018) [24]	3004/3004	Cohort study	United Kingdom – Large teaching hospital	Outpatient Parenteral Antibiotic Therapy service run by multidisciplinary team including weekly review of progress and management.	2006–2016	CA, CCA	x			x	x	x		Yes	GBP
Howell et al. (2019) [25]	Not reported	Observational study	USA – Small community hospital	Daily alerts by a clinical decision support application triggered a chart review for possible AS intervention including feedback on the recommendation.	2016–2017	CBA	x		x	x				No	USD
Hyland et al. (2022) [26]	57/1220	Cohort study	USA – Tertiary community teaching hospital	Implementing 11 antimicrobial recommendations, screening patients for <i>Staphylococcus aureus</i> colonisation, evaluating beta-lactam allergies, new protocol for intra- and postoperative antibiotic use.	2018–2019	CBA	x		x	x	x			No	USD
Jaggar et al. (2023) [27]	1068/1065	Observational study	USA – Five adult acute care facilities	Review and revision of the i.v. to p.o. conversion eligibility criteria including educational computerised training modules.	2021–2022	CA	x		x	x				No	USD
Karimaghaei et al. (2022) [28]	91/91	Retrospective evaluation	USA – Two public hospitals	Implementation of a disposable elastomeric continuous infusion pump (eCIP) for self-administered i.v. antibiotics (s-Outpatient Parenteral Antibiotic Therapy) at home including evaluation, recommendations, education and follow-up.	2018–2021	CA, CEA	x			x	x	x		No	USD
Kim et al. (2022) [29]	1094/850	Observational study	South Korea – National university hospital	Performing vancomycin therapeutic drug monitoring by reviewing clinical history, dosing regimen and laboratory tests.	2009–2013	CEA	x	x	x	x	x	x		Yes	USD
Lanbeck et al. (2016) [30]	Not reported	Quasi-experimental study	Sweden – University hospital	Auditing and feedback of antibiotic therapy by an ID specialist.	2012–2013	CA	x	x	x	x		x		Yes	SEK
Lester et al. (2020) [31]	203/300	Not reported	Malawi – Central hospital	Implementation of a consensus-based antibiotic guideline with clinician review, distribution using booklets, posters, and smartphone application, prescriber feedback.	2016–2018	CA	x		x	x				Yes	USD
Loesch (2021) [32]	225/225	Observational study	Brazil – Tertiary care hospital	Evaluation and review of Outpatient Parenteral Antibiotic Therapy comparing to in-hospital situation.	2017–2020	CMA	x			x				No	USD

Malone et al. (2015) [33]	26/26	Retrospective evaluation	Australia – Tertiary care hospital	Outpatient i.v. antibiotic therapy of patients with diabetic foot infection including feedback and follow-up.	2007–2012	CA	x	x	x	x					No	USD
Mouwen et al. (2020) [34]	54/84	Prospective study	The Netherlands – Non-academic teaching hospital	Education and pocket-sized cards regarding early antibiotic switch from intravenous to oral, evaluation of patients and switch advice provision in electronic patient records.	2017–2018	CA	x	x	x	x					No	EUR
Olson et al. (2023) [35]	72/72	Observational study	USA – Skilled nursing facility	Implementation of an automated, standardised probiotic Antibiotic Stewardship Programme policy.	2009–2021	CA, CBA, CEA	x			x	x				No	USD
Patel et al. (2017) [36]	243/233	Quasi-experimental study	USA – University health System	Implementation of MALDI-TOF pathogen identification with real-time notification, giving antibiotic recommendations to prescribers.	2011–2012	CA	x			x		x	x		No	USD
Psaltikidis et al. (2019) [37]	40/40	Prospective study	Brazil – Tertiary university hospital	Outpatient Parenteral Antibiotic Therapy for eligible cases as determined and supervised by multidisciplinary team.	2015–2016	CUA, cost-saving percentage	x			x	x		x		Yes	USD
Ramsey et al. (2020) [38]	53/48	Prospective study	USA – Tertiary care hospital	3-step direct challenge for patients reporting penicillin allergy and receiving antibiotics by ID pharmacist or skin testing.	2018–2019	CA	x			x					No	USD
Ross et al. (2015) [39]	39/73	Quasi-experimental study	USA – Tertiary care academic hospital	Development of a daptomycin dosing algorithm, hospital approval and education of ID specialists.	2013–2014	CA			x	x					No	USD
Ruh et al. (2015) [40]	85/85	Retrospective evaluation	USA – Veterans Affairs healthcare system	Outpatient Parenteral Antibiotic Therapy including review of patients and initial treatment decision with dosing and follow-up appointments, overview of pharmacist work.	2011–2013	CA			x	x	x				No	USD
Salman et al. (2021) [41]	Not reported	Retrospective evaluation	Oman – University hospital	Dose modifications, stopping prolonged duration, de-escalation, addition of antibiotics if indicated, therapeutic drug monitoring initiation, information of healthcare providers, i.v. to p.o. switch, other.	2018	CA	x		x	x					No	USD

Van Daalen et al. (2017) [42]	853/1207	RCT	The Netherlands – Seven teaching hospitals, two university hospitals	Checklist for antimicrobial stewardship (visible display in workplaces and pocket versions) with educational briefing at implementation.	2014–2015	CA, CEA	x	x		x		x		Yes	EUR
Wang et al. (2015) [43]	206/204	Quasi-experimental study	China – Tertiary hospital	Education, real-time monitoring of clinical records and making recommendations to obstetricians, Pre-reviewing and reviewing the prescriptions of antibiotics with feedback.	2012	CA	x		x	x	x			No	USD
Yadav et al. (2022) [44]	467/341	Not reported	Canada – Two tertiary care hospitals	Evaluation and review of Outpatient Parenteral Antibiotic Therapy referral from the emergency department for cellulitis compared to hospital admission.	2015	CA	x			x	x			No	CAD

Abbreviations. RCT, randomised controlled trial; CA, cost analysis; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; CMA, cost-minimisation analysis; CBA, cost-benefit analysis; CCA, cost-consequence analysis; LOS, length of stay; EUR, Euro; USD, United States Dollar; CAD, Canadian Dollar; PKR, Pakistani Rupee; GBP, British Pound Sterling; TRY, Turkish Lira; OPAT, Outpatient Parenteral Antibiotic Therapy.