Costs-effectiveness and cost components of pharmaceutical and non-pharmaceutical interventions affecting antibiotic resistance outcomes in hospital patients: A systematic literature review

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Abstract

Introduction. Limited information on costs and the cost-effectiveness of hospital interventions to reduce antibiotic resistance (ABR) hinder efficient resource allocation.

Methods. We conducted a systematic literature review for studies evaluating costs and cost-effectiveness of pharmaceutical and non-pharmaceutical interventions' aimed at reducing, monitoring, and controlling ABR in patients. Articles published until December 12, 2023, were explored utilising EconLit, EMBASE, and PubMed. We focused on critical or high-priority bacteria, as defined by the World Health Organization, and intervention costs and incremental cost-effectiveness ratio (ICER). Following PRISMA guidelines, we extracted unit costs, ICERs, and essential study information including country, intervention, bacteria-drug combination, discount rates, type of model, and outcomes. Costs were reported in 2022 USD, adopting the healthcare system perspective. Country willingness-to-pay (WTP) thresholds from Woods *et al.* 2016 guided cost-effectiveness assessments. We assessed studies' reporting check-list utilising Drummond's method.

Results. Among 20,958 articles, 59 (32 pharmaceutical and 27 non-pharmaceutical interventions) met the inclusion criteria. Non-pharmaceutical interventions, such as hygiene measures, had unit costs as low as $1 per patient, contrasting with generally higher pharmaceutical intervention costs. Several studies found that linezolid-based treatments for methicillin-resistant *Staphylococcus aureus* (MRSA) were cost-effective compared to vancomycin (ICER up to $21,488 per treatment success, all 16 studies' ICERs<WTP). Infection control measures such as hand hygiene and gown usage (ICER=$1,160/QALY or $4,949 per ABR case averted, all ICERs<WTP) and PCR or chromogenic agar screening for ABR detection were highly cost-effective (e.g., ICER=$1,206 and $1,115 per life-year saved in Europe and the United States). Comparisons were hindered by within-study differences.

Conclusion. Robust information on ABR interventions is critical for efficient resource allocation. We highlight cost-effective strategies for mitigating ABR in hospitals, emphasising substantial knowledge gaps, especially in low- and middle-income countries. Our study serves as a resource for guiding future cost-effectiveness study design and analyses.

Keywords: Antibiotic resistance, cost-effectiveness, cost ingredients, pharmaceutical interventions, non-pharmaceutical interventions

What is already known on the topic?

► Pharmaceutical and non-pharmaceutical interventions play a crucial role in global antibiotic resistance (ABR) control and prevention

►There is a paucity of data on the comprehensive health economic costs and outcomes, with most existing literature reviews targeting specific interventions, such as antimicrobial stewardship

What this study adds?

► We synthesised global literature on unit costs and effectiveness of pharmaceutical and non-pharmaceutical interventions among hospitalised patients

► Despite substantial heterogeneity and some studies lacking fundamental cost and methodological considerations (e.g., discounting, risk-scenarios, and outcomes including hospital stay or mortality), we identified several interventions with robust evidence supporting their benefit, translated into cost or utility-adjusted life years averted

How this study might affect research, practice, or policy?

► Our results aid decision-making by guiding the allocation of scarce resources for combating ABR in hospitals

► Further investigations, empirical and methodological, is essential to advance the economic evaluation of interventions to progress towards optimising antibiotic usage and reducing ABB rates in hospitals, especially in low-and middle-income countries

Introduction

Antibiotic resistance (ABR) causes an enormous burden on health systems and the global economy.[1-4] According to a recent study by the Global Burden of Disease, approximately 1.27 million deaths worldwide in 2019 were attributable to ABR if all ABR infections would be replaced by drug-susceptible infections.[2] The World Bank projects an annual global cost of up to $3.4 trillion by 2030 if no action is taken.[5] The US Centers for Disease Control and Prevention has estimated an annual impact of ABR infections on healthcare and societal costs approximately US$25 billion in the United States.[6] While these estimates are based on limited data, they underscore the severity of ABR. Setting- and population-specific strategies designed to alleviate ABR burden by reducing antibiotic usage and resistance transmission are crucial to reducing loss of life and minimizing costs.

Economic evaluations provide critical insights for decision-makers about how to allocate limited healthcare budgets to optimise overall population health. Despite finances underlying healthcare management strategy,[7] economic evaluations of alternative interventions are surprisingly scarce. Those that are conducted often fail to capture key costs and outcomes required to decide whether to retain the status quo or take up a novel alternative. For example, daptomycin was the first cyclic lipopeptide with demonstrable activity against vancomycin-resistant gram-positive pathogens. It was shown to have equivalent clinical effectiveness in treating complicated skin infections compared with semi-synthetic penicillin, while resulting in shorter hospital stays for patients.[8] Even in this economic evaluation of daptomycin compared to penicillin, however, treatment costs were not explicitly considered, so ambiguity remained over daptomycin's economic dominance.

Studies synthesising the economic evidence base for alternative ABR-mitigating strategies are equally rare. Previous reviews reporting on economic evaluations of interventions to prevent and control ABR are limited.[9-12] Naylor *et al.* reviewed the cost-effectiveness of antimicrobial stewardship programmes, with estimates ranging from $540 in inpatient net savings to $24,231 for each prevented death.[9] In a similar review, Huebner *et al.* found that targeted control of appropriate antimicrobial agents could save up to $2,403 in total antibiotic costs per 100 patient-days.[12] Niewiadomska *et al.* reviewed mathematical modelling studies on population-level transmission of ABR; however, only 9% of reviewed models included details of cost-effectiveness analyses.[10] Among these, universal surveillance and decolonisation programs were cost-saving in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infections.[12] Wilton *et al.*'s review of studies of the (cost-)effectiveness of interventions for ABR control, including restricting antimicrobials use, prescriber education, use of guidelines for ABR, combination therapies and vaccination,[11] highlighted the paucity of evidence as a key limitation in delivering definitive and actionable recommendations for ABR control.[11]

Our study aims to systematically synthesise the economic evidence for pharmaceutical and non-pharmaceutical interventions to reduce, monitor, and control ABR of critical or high-priority bacteria, as defined by the World Health Organization (WHO), including colonisation, infection and antibiotic usage, in hospital settings globally from a health system or payer perspective.[13] To our knowledge, this is the first review contrasting all available economic and effectiveness components for both intervention types while focusing on key ABR pathogens. By formalising costs and effectiveness for both intervention types in hospital patients, we offer a comprehensive synthesis of ABR interventions conducted within healthcare settings.

Methods

We conducted a systematic literature review of the costs and cost-effectiveness of pharmaceutical and non-pharmaceutical interventions to reduce, monitor, and control ABR levels in hospitalised patients. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[14] and the ISPOR (The Professional Society for Health Economics and Outcomes Research)[15] guidelines, and our study was prospectively registered with PROSPERO (ID numbers: CRD42020341827 and CRD42022340064).[14] The search was conducted on Econlit, EMBASE, and PubMed concluding on December 12, 2023.

Search strategy

We used three key concepts to perform our literature search: (1) "Interventions for antibiotic resistance", (2) "Hospital" and (3) "Cost-effectiveness and Economic evaluation". Economic evaluation filters from InterTASC Information Specialists' Sub-Group (ISSG) search filters were used to capture the cost-effectiveness aspect of the search. The final literature search strategy and details of studies from initial screening are presented in Supplementary Tables SM1-4.

Study selection – inclusion and exclusion criteria

We followed the Patient Population, Intervention, Comparator, Outcome, Setting, Timing (PICOST) framework to present our inclusion and exclusion criteria[16] (Supplementary Table SM1-2). Titles and abstracts of identified articles were screened using Rayyan (https://www.rayyan.ai) by two reviewers for eligibility, and a third reviewer checked them for final inclusion. We contrasted our results with the 'ASReview' tool for potential misclassification.[17] The study population was limited to hospital settings; community-settings and acquired infections were excluded. We did not restrict our search by language and years. Studies were included only if the intervention targeted antibiotic-resistant bacterial pathogens listed as critical or high priority by the WHO[18] (Supplementary Table SM3). Bacterial pathogens not on the WHO's list was excluded. Pharmaceutical interventions were defined as those that directly involve the use of medication, while all other interventions were classified as non-pharmaceutical. Economic evaluations included only complete evaluations (e.g., cost-effectiveness, cost-utility, cost-benefit) and defined as a comparative analysis of the costs and reported effectiveness of alternative programmes, following Drummond *et al.*[19] Only evaluations using a healthcare or payer perspective were included; very few studies used a societal perspective (n=2). While both perspectives are similar, the healthcare perspective focuses on the costs incurred by providers in delivering medical care and health services to patients and the payer perspective includes the financial aspects of healthcare from the viewpoint of the organization that funds or reimburses costs to providers. Conference abstracts, editorials, and systematic literature reviews were excluded. Papers had to present measures of costs and an incremental cost-effectiveness ratio 'ICER' or incremental net monetary and health benefit analyses (i.e., comparison between strategies presenting an ICER).

Data extraction

We extracted study characteristics and outcomes, including unit costs, effectiveness, and cost-effectiveness rates following the Campbell & Cochrane Economic Methods group and a recent protocol for economic appraisal to address ABR which include specific guidance on reporting health economic data in systematic reviews.[13, 20] For study characteristics, we retrieved the study's year, author, title, perspective, country, currency, pathogen, intervention, comparator, type of economic evaluation, source of effectiveness data, source of costing, and primary outcome.

Implementation costs, such as training, were excluded. We also extracted information on the analytical model used, time horizon, discount rate, measure of effectiveness, results of the base-case analysis (e.g., ICER), and sensitivity analyses (e.g., univariate or multivariate analyses and parameter effects on outcomes). Costs were first converted to USD (utilising currency-specific exchange rates) and inflated to 2022 USD based on Gross Domestic Product (GDP) deflators.[21] We utilised the reported costs year, or, if absent, using the publication year instead for exchange rate conversion and subsequent inflation.

Data synthesis and analysis

We summarise the included data by providing disaggregated unit costs and effectiveness per study and intervention type (pharmaceutical and non-pharmaceutical). Cost-effectiveness estimates were primarily characterised as ICER, including (i) $/(quality-adjusted life-years 'QALY' gained), (ii) $/(disability-adjusted life-years 'DALYs' gained), (iii) $/ABR infection averted, or (iv) $/life-year gained. A dominant strategy refers to a scenario where the incremental cost of the intervention is less than the comparator, and the incremental efficacy is greater than the comparator. Willingness-to-pay (WTP) thresholds per efficiency outcomes were also included, if provided. We identified the gap between individuals' WTP and intervention's real cost-effectiveness to determine feasibility of the program in the setting where it was evaluated. Cost-effectiveness thresholds (CTE) , based on countries' opportunity costs, were employed for strategy comparative purposes and to define resource gaps following Woods *et al.*[22]

Assessment of quality of reporting and risk of bias

We used Drummond *et al.*'s checklist for assessing economic evaluations.[23] The checklist comprises ten questions for evaluating reporting quality in economic evaluations, assigning a 1 (or 0) to each question if the article included the safeguard (Supplementary Table SM5). The aggregate results provided an economic reporting quality appraisal of below average (1-7 points), average (8 points), and above average (9–10 points).

Microsoft Excel was used to create a database of the study characteristics, unit costs and appraisal of studies following the checklist (see https://bit.ly/SR_amrCEingredients).

Patient and public involvement

The patients and the public were not involved in the design, conduct, or reporting of our research.

Results

Study identification and selection

Figure 1 describes the PRISMA chart for the results of our literature review. We found 20,958 articles in Econlit, EMBASE, and PubMed, of which 1,744 were duplicated. We excluded 18,811 records due to not fulfilling our inclusion criteria (Figure 1). Finally, 406 studies were assessed for full eligibility and 59 (32 on pharmaceutical and 27 on non-pharmaceutical interventions) presented a complete cost-effectiveness analysis and were included in our analytical sample.

Characterisation of studies included

Most reports on pharmaceutical interventions were focused on MRSA (20 of 32 studies, 63%). The remaining studies analysed carbapenem-resistant gram-negative pathogens contrasting ceftazidime

avibactam versus colistin or alternative drug-based treatments. MRSA interventions were focused on comparing linezolid, or any relatively new drug (e.g., daptomycin), with vancomycin, the established treatment. Studies on non-pharmaceutical interventions were wide-ranging but most explored surveillance or screening methods. Reports included improved surveillance and wide Polymerase Chain Reaction (PCR) or chromogenic-based surveillance and testing (n=11),), multiple surveillance schemes including testing, decolonisation, and/or isolation (n=8), infection control and hygiene including use of gowns and hand hygiene practices (n=3), and miscellaneous (n=5; e.g., antibiotic stewardship, pre-emptive isolation, whole-genome sequencing, etc.). Generally, these interventions targeted MRSA (n=16, 59%), carbapenem-resistant Enterobacteriaceae (CRE) (n=4, 13%), and vancomycin-resistant Enterococci (VRE) (n=4), and compared the intervention's effectiveness with current practice, which was typically the absence of the intervention. Most studies were conducted in high-income countries, mainly the USA (n=26, 44%; see Figure 2). We found two regional studies; one utilising European data and the second in Africa. Decision analytic models were usually employed for the analyses (e.g., decision trees, Markov, and stochastic simulation models), often using a one-way sensitivity analysis. Time horizons and discount rates were reported inconsistently, and target populations usually consisted of all hospital patients and patients with pneumonia. See Supplementary Tables SM6-7 for a full description of the studies' characteristics.

Unit costs of interventions

Supplementary Table SM8 provides a cost breakdown for pharmaceutical interventions. Economic costs varied based on factors such as drug components, dosage, length of hospital stay (LOS), and study scale. Bed-day expenses, associated with admissions to general wards and ICU, constituted the largest portion of total economic costs (~50% to 90%). Drugs represented about 10% of total costs (adjacent therapies, rehabilitation, and diagnostic were costlier), with drugs like daptomycin and linezolid being notably more expensive, approximately 200% greater than vancomycin[24, 25] (Supplementary Table SM8). For instance, Niederman *et al.* reported the cost of intravenous linezolid (600mg) as $107 per dose, while vancomycin costed $5.8 for 1g intravenous administration.[26]

Supplementary Table SM9 shows an itemised breakdown of the non-pharmaceutical interventions' unit costs. Hospitalisation and additional costs were the highest cost component. Test or intervention unit costs varied widely, ranging from $1 per patient (e.g., use of gown or gloves[27]) to as high as $108 for genome sequencing,[28] $103 for decolonisation,[29] $598 for isolation,[30] and $652 for infection control bundles[31] per patient. The lowest costs among non-pharmaceutical interventions were also those involving screening or surveillance, due to their being single-step procedures incurring no overhead or operating costs (e.g., PCRs, chromogenic agar, or electronic registry).

Cost-effectiveness and outcomes

Supplementary Table SM6 displays studies' strategies and cost-effectiveness (ICERs) of the pharmaceutical (I) and non-pharmaceutical (II) interventions.

1. Pharmaceutical interventions

1.1. Linezolid vs. vancomycin

For patients with complicated skin and skin structure infections (cSSSI), linezolid consistently emerged as a cost-effective and dominant strategy compared to vancomycin (Supplementary Table SM6, panel I).[24, 32-35] For instance, Mackinnon *et al.*[32] reported a mean cost of $7,077 (SD=$5,752) for linezolid versus $8,709 (SD=$7,307) for vancomycin treatment among cSSSI

patients reporting MRSA infections, with a mean cost difference of $2,756 (p-value=0.041) due a 2.5-days longer LOS for vancomycin-treated patients. Bounthavong *et al.*[34], De Cock *et al.*[33] and Schurmann *et al.*[35] estimated lower hospitalisation costs for linezolid (incremental costs were -$7,791, -$1,827 and -$1,749, respectively) along with higher cure rates (incremental cure rates for first-line MRSA were 13%, 10%, and 10%, respectively), compared to vancomycin in cSSSI patients. Differences were explained by reduced LOS and improved treatment failures due to linezolid oral formulation compared to intravenous vancomycin therapy.

In studies focusing on nosocomial pneumonia,[25, 26, 36-43] linezolid showed a dominant ICER or ICER ranging from $5,726 to $84,823 per death averted or life saved, and between $3,179 and $21,488 per cure or treatment success among MRSA infected patients, compared to vancomycin (Supplementary Table SM6, section I). Variations in LOS and its associated economic costs across study settings accounted for differences in ICER. Mullins *et al.* predicted an ICER of $5,726 for linezolid per life saved, balancing the higher acquisition costs with enhanced survival rates.[36] De Cock *et al.* designed a decision–analytic model using clinical trial data that again favoured linezolid over vancomycin with greater clinical cure (+8.7%) and survival (+13.2%) rates at an additional incremental cost of $420 per treatment cycle.[37] However, Collins *et al.*[25] reported a higher ICER per life saved ($84,823) due to limited variation in incremental mortality (≈1%) between linezolid and vancomycin.

Figure 3A shows that the linezolid strategy is beneficial compared to vancomycin at country-specific WTP thresholds (ICER<WTP).

1.2. Ceftazidime avibactam vs. colistin or other drugs

Six studies evaluated the use of *Ceftazidime avibactam* (CZA) versus colistin or other drugs (Supplementary Table SM6).[44-49] ICERs ranged between $693 and $113,423 per QALY gained. Gourdarzi *et al.*[45] and Simon *et al.[47]* calculated ICERs equal to $798 and $113,423 per QALY gained among patients infected with CRE, respectively, comparing CZA versus colistin therapy. Incremental QALYs were similar (≈0.5) in both studies, but costs differed. In Gourdazi *et al.*, CZA therapy costs were 1.5-times greater for CZA compared to colistin according to Iran health system tariffs. Simon *et al.* employed a healthcare system perspective in the USA, estimating 4-times greater daily therapy costs for CZA compared to colistin after accounting for LOS, which increased the ICER. In comparison to colistin + meropenem, Gutierrez *et al.*[48] and Varon-Vega *et al.*[49] reported ICERs of $1,340 and $3,797 per QALY gained for CZA, respectively. This difference is attributed to CZA showing increased incremental QALYs (+2.3 and +1.8, respectively), while incremental costs were similar ($3,151 and $2,886, respectively). The slight variation in additional concomitant treatments reported (amikacin + fosfomycin and tigecycline + fosfomycin) played a minor role.

Four studies presented an ICER below the WTP threshold (Figure 3B), except Bolaños-Diaz *et al*[44] and Simon *et al.*[47]

1.3. Miscellaneous: other combination drug comparison types

Laohavaleeson *et al.*[50] found an estimated 0.5-day shorter LOS and savings of $478 favouring telavancin (dominant strategy compared to vancomycin) among MRSA patients, regardless of sensitivity analyses on MRSA drug acquisition costs. Favourable results were shown for IMI/REL (Imipenem/cilastatin/relebactam) compared to CMS+IMI (colistin plus imipenem) usage for gram-negative infections (+3.7 QALYs and lower mortality rates; 15.2% compared to 39%). However, the clinical response rate was limited among the IMI/REL group[51]. Additionally, treating patients with complicated intra-abdominal infections following ceftolozane/tazobactam + metronidazole was found

to be cost-effective (ICER=$8,551 per QALY gained), compared to piperacillin/tazobactam,[52]. Mennini *et al.*[53] and Vlachaki *et al.*[54] assessed meropenem-vaborbactam versus the best available treatment for CRE patients, revealing ICERs of $11,813 and $20,486 per QALY, respectively. The disparity arises from three times higher drug costs for meropenem-vaborbactam compared to the best available therapy in the UK,[54] while in the Italy-based study,[53] it was only 1.5 times higher. Furthermore, the UK-based study attributed higher costs to long-term care tariffs associated with increased survivability among meropenem-vaborbactam.

All miscellaneous interventions presented ICERs below country-specific WTP thresholds (Figure 3C).

2. Non-pharmaceutical interventions

2.1. Testing schemes: chromogenic-based agar or PCR

Rapid PCR testing for MRSA detection compared to standard hospital treatments was found to be cost-effective (ICER=$55 and $39 per life-year saved in Europe and the United States, respectively[55]), with ICER=$20,401 per hospital-acquired MRSA case detected in the United States[27], ICER=$38,911 per MRSA infection averted in Switzerland[56], and ICER=$243 per life year saved in Spain.[57] Single-culture of an anterior nares specimen for universal screening of MRSA patients resulted in an ICER of $14,766 per QALY gained, compared to a "change nothing" scenario, producing better MRSA control and lower losses attributed to hospital bed-day costs.[58] One study showed that screening for carbapenemase-producing Enterobacteriaceae was cost-saving (ICER= $32,049 per QALY gained) at prevalence levels above 0.3% or if one additional patient were exposed for every infected patient (i.e., highly dependent on local transmission settings).[59] Similarly, active PCR among CRE patients, compared to do nothing, was cost-effective at $100 per QALY gained in surgical ICU patients in Hong Kong[60] due to cheaper PCR unit costs compared to an inadequate empirical antibiotic treatment for CRE. Hubben *et al.*[61] found selective chromogenic-based agar cost-effective for MRSA detection compared to taking no action (ICER: $5,787-$14,538, with 622 infections averted in a moderate MRSA prevalence scenario). Selective PCR was also cost-effective versus chromogenic agar (ICER: $18,349-$51,095). However, universal screening was not cost-effective, as it incurred substantial costs for screening and isolation ($9.2 million incremental costs, with only 28 infections averted; ICER: $184,902-$328,448), surpassing the country WTP threshold (Figure 4A).

2.2 Hygiene and sanitation

Interventions including proactive infection control, hand hygiene, and gown usage were cost effective at country WTP thresholds (Figure 4B).[62-64] For instance, Luangasanatip *et al.* found that 20% compliance in healthcare hygiene protocol, versus 10%, was associated with reductions in MRSA BSIs and ICERs of $1,160 and $835 per QALY in paediatric and adult ICUs, respectively.[62] Gown usage for 18 months was linked to 58 VRE cases averted in a hospital ICU in the USA (ICER=$2,939 per case averted).[64]

2.3. Utilising combination of multiple surveillance schemes and other methods

Combination schemes containing decolonisation, isolation, testing and surveillance were evaluated.[29, 30, 65-70] Robotham *et al.* combined screening, decolonisation and isolation techniques versus a do-nothing scenario.[29] Universal PCR/chromogenic agar plus decolonisation with mupirocin was cost-effective finding up to $11,005 per QALY gained; however, most interventions involving patient isolation plus PCR for identification were costly due to infrastructure requirements (Supplementary Table SM6, panel II; Figure 4C). Universal decolonization for ICU

patients with MRSA infections emerged as a dominant strategy in the USA[68] and in Hong Kong[69], leading to cost savings of $737 and reductions in infection and mortality rates by 0.9% and 0.2%, respectively. Similarly, Nelson *et al.*[30] estimated that PCR screening and decolonisation (dominant strategy), had cost-savings of $14,433 and $47,762 and reduced 0.38 and 3.13 MRSA infections per 100 patients compared to PCR screening alone or do-nothing scenarios, respectively. However, in the same veteran hospital in the USA, more comprehensive strategies, comprising screening, contact precautions, and infection control combined were more cost-effective, particularly in scenarios with high MRSA transmission rate rather than low transmission in subsequent periods (ICER: $13,904[66] and $34,201[67] per life years gained; as shown in Supplementary Table SM6, panel II, and Figure 4C). Last, real-time blood culturing and evidence-based antimicrobial consumption among ampicillin-resistant *Salmonella enterica* and *Streptococcus pneumoniae* infections was cost-effective in Africa (ICER=$3,531 per life saved, averting 934 deaths per 100,000 patients), compared to generic antimicrobial management.[70]
Most of these strategies were cost-effective based on country WTP thresholds (Figure 3C), but consideration of local costs were essential in scenarios with low MRSA prevalence and transmission.[65]

2.4. Miscellaneous single strategies

Interventions in this category included antibiotic stewardship, single surveillance schemes, test-guided decontamination, and pre-emptive isolation.[28, 31, 71-73] Voermans *et al.* estimated that procalcitonin-led antibiotic stewardship reduced average expenses per patient, specifically, 49% reduction from standard care for sepsis and 23% reduction for lower respiratory tract infections associated with ABR (cost savings of $29,197 and $4,138 per each group).[72] Active surveillance (current standards and screening of previously hospitalised) for patients with VRE was the most medically and economically beneficial, resulting in $4 screening cost per patient admitted, lowering admission costs ($792) and improving survival rates.[71] Whole genome sequencing as a surveillance alternative resulted in 14.3 additional QALYs gained among MRSA patients.[28] The use of a state-wide electronic registry reduced CRE by 18.8 cases per year (95%CI= 5.8, 31.7) and by 6.3% (95%CI= 2.0%,10.6%; p-value<0.05) compared to the “do nothing” scenario (ICER=$27,000 per infection averted).[31] Test-guided selective digestive decontamination among CRE patients in the ICU was cost-effective in reducing CRE (ICER=$688 per QALY, reduction of 0.2% and 0.3% in CRE cases and mortality, respectively).[73] Most strategies were cost-effective according to country-specific WTP thresholds (Figure 4D), except for Robotham *et al.*'s study on universal pre-emptive isolation in the UK's hospital ICU for high MRSA risk patients,[29] which reported substantial hospital costs due to necessary infrastructure investments.

Quality of reporting and risk of bias

A substantial proportion of the pharmaceutical (25%) and non-pharmaceutical studies (33%) failed to report important costs and their potential consequences (Supplementary Table SM10). The type of costing methodology was dissimilar along studies, resulting in costs for drug acquisition reported, for instance, in cost per day, patient, or dose. Discounting varied among studies in magnitude and usage (61% failed to report discounting Supplementary Table SM10). Despite most studies achieving average high-quality scores of 8.2 and 8.0 out of 10 for pharmaceutical and non-pharmaceutical interventions,[74] timeframes and year of economic evaluation were not always reported.

Discussion

We identified 59 studies investigating the cost-effectiveness of pharmaceutical or non-pharmaceutical interventions reducing ABR among WHO's global priority pathogen list in hospital settings.[18] We flag the reduced data among critical pathogens, such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, and the scarcity of standardised cost-effectiveness methods, ingredient costs, and limited data from low- and middle-income countries indicated the need for more consistent approaches in the future.

More studies found that, compared to vancomycin, linezolid was more effective and less costly for the treatment of MRSA infections. Despite pharmaceutical costs being a highly predictable line item in hospital budgets (e.g., diagnostic tests, treatment), LOS often constitutes a higher proportion of the cost for hospital stay and should be considered in cost-effectiveness analyses and decisions related to formulary and drug reimbursement. For example, Kauf *et al.* reported that drug costs drove 6.4% of the total inpatient cost compared to LOS accounting for 85.9% of total inpatient cost for patients with cSSSI.[75] Treatment resulting in expedited infection resolution will likely be more cost-effective even when drug costs are much higher. This is also seen with linezolid compared to vancomycin. Vancomycin can be taken orally (as opposed to intravenously) meaning that patients can be discharged earlier, potentially offsetting higher drug acquisition costs.[36] De Cock *et al.* noted that in a scenario analysis between linezolid and vancomycin, when the most conservative treatment durations were applied rather than those estimated by the physician panel, linezolid was dominant over vancomycin based on the shorter LOS.[33]

The appropriateness of initial antibiotic therapy and the possibility of switching treatments during hospitalization also play crucial roles, by affecting length of hospital stay and treatment outcome. One key question is whether being on vancomycin during hospitalisation and switching to linezolid for outpatient care is cost-saving.[36] De Cock *et al.* suggest that most patients are cured after treatment with two lines of antibiotic therapy.[37] Empirical therapy with linezolid was considered most cost-effective in unconfirmed MRSA patients, as LOS for unconfirmed patients is lower.[33]

A recent meta-analysis indicates that ceftazidime-avibactam offers advantages over colistin, including lower mortality rates, improved clinical cure rates, and reduced kidney deterioration in CRE infections.[76] Comparing ceftazidime-avibactam to colistin plus meropenem revealed high efficacy and lower nephrotoxicity in CRE patients in Chile[48] and Colombia[49] (ICER=$1,340 and $3,797 per QALY gained, both falling below the country's WTP thresholds). This finding holds relevance for a region where kidney disease burden is substantial.[77] Moreover, considering the complex dosing requirements and close monitoring associated with colistin plus meropenem, along with the region's higher prevalence of carbapenemase-producing Enterobacterales[78, 79] and antibiotic-resistant gram-negative pathogens[80], the potential for expanded treatment coverage is substantial.

Non-pharmaceutical interventions were generally less cost-effective than pharmaceutical interventions. For instance, one of the most expensive non-pharmaceutical interventions was a mandatory full NHS-level screening programme modelled by Robotham and colleagues.[65] Other infrastructure-demanding interventions, such as whole genome sequencing (WGS), were only cost-effective if applied at a specific UK tertiary research hospital where MRSA prevalence was significant and sequencing infrastructure already existed.[28] Although the effectiveness of WGS surveillance is highly dependent on infrastructure, the study's modelling estimate found that WGS was not sensitive to simulated reduced efficacy in colonisation/mortality reduction.[28] Nevertheless,

the limited evidence renders universal screening strategies for reducing MRSA inconclusive.[81] Literature on MRSA demonstrates limited capacity to account for confounding and temporal trends when assessing the burden of disease and resource utilisation associated with MRSA screening.

Costs associated with the required professional training often lead to the perception that antimicrobial stewardship is not cost-effective. However, there might be unaccounted outcomes and positive spillover effects not captured by economic evaluation. Although not specifically targeting ABR, Scheetz, *et al.*[82] presented an ICER of $3,219 per QALY gained in antimicrobial stewardship programs attributed to substantial fixed operating costs required to maintain the stewardship team and the reduction in patient inflow. Antimicrobial stewardship prove more economically efficient in larger hospitals with higher inpatient volume, presenting increased risks and expanded economic returns of scale, specifically for persuasive and structural programs.[9] Notwithstanding, some studies have shown mixed results, with increased consumption of antibiotics not targeted or restricted by the antimicrobial stewardship program leading to higher global ABR rates and worsening patient outcomes.[83] Decreased resistance may not be expected if antimicrobial stewardships only target certain antibiotics. LOS and mortality could be affected beyond antibiotic control, changes in pre- and post-intervention populations, including existing comorbidities and disease severity, might lead to poorer health outcomes despite the stewardship program.[83] Comprehensive antimicrobial stewardship programs, including physiological monitoring, therapy review, and antibiotic restrictions are essential to avoid ABR and associated disease burden.

Procalcitonin (PCT) has demonstrated the ability to increase specificity and sensitivity for different bacterial infections at the point-of-care, even in the earliest phases of inflammation. PCT has been shown to reduce LOS and improve appropriateness of antibiotic treatment at low costs compared to no-PCT.[72, 84-86] Similar to a study in Europe avoiding antibiotic-days in European settings,[85] we found support for PCT-guided healthcare in the USA, contributing to halving sepsis with cost-savings of $29,197 compared to costs for standard care.[72] These results are mainly driven by the associated reduction in ICU-admitted patients, which results in shorter antibiotic treatment and exposure time. These findings are corroborated by studies by Mewes *et al.* 2019, Harrison and Collins 2015, and Huang *et al.* 2018, showing PCT to be a cost-saving strategy in hospitalised patients with lower respiratory tract infections or suspected sepsis,[87-89] although not specifically targeting ABR pathogens. Furthermore, a recent study suggests that these interventions among emergency departments in low-resource settings are feasible if PCT is applied simultaneously with C-reactive protein through a fluorescence reader-based duplex lateral flow assay.[90] This has direct implications for applications in low- and middle-income countries for rapid and accurate viral and bacterial infection differentiation, with an estimated rounded cost per patient below $70.[90]

Reducing the time interval between a positive test for MRSA and the implementation of appropriate infection control measures during hospitalisation is achievable using diagnostic technologies such as PCR.[91] PCR assays were cost-effective in Europe and the UK, with the lowest ICER values per life-saved, ranging from $1,100 and 1,200, compared to standard treatment.[55] Although the costs are low, PCR is only feasible as an intervention when the hospital has appropriate facilities and when the additional delay incurred poses little-to-no threat to patient wellbeing. PCR-based interventions may only be cost-effective in highly endemic settings where targeted screening is likely to detect a large number of MRSA cases.[27] Despite potential drawbacks, studies have shown that PCR may prevent adverse events and toxicity due to treating patients empirically,[92] reducing LOS and economic costs.[93, 94]

Limitations

Our review has highlighted important deficiencies in the health economics literature pertaining to pharmaceutical and non-pharmaceutical interventions aimed at reducing, monitoring, and controlling ABR levels, particularly concerning critical or high-priority bacteria. We included literature from three major search engines, potentially overlooking publications in interdisciplinary journals and grey literature like government reports, particularly from low- and middle-income countries. Our primary sources were PubMed, which comprehensively indexes biomedical and life sciences literature, including health economics; Embase, which specializes in biomedical and pharmacological content, with a specific emphasis on drug and pharmaceutical research; and EconLit, which is dedicated to economics. Second, we found significant heterogeneity in the costs and effectiveness units reported across studies, which may have been affected by the lack standardization in analysis, illustrated by the scarcity of cost-utility analyses considering the difficulty of measuring quality of life for acute events). Therefore, comparing results was challenging given the range of resistant bacterial types, intervention types, populations studied, and the lack of consistency in study design. Our study focused on the health systems perspective to report unit costs and cost-effectiveness, which fails to take account of a societal perspective. However, most studies did not report a specific perspective of analysis. Finally, many articles failed to report discounting and a risk-scenario for the associated consequences. This may be explained because due to the short time horizons used, often under a year and mostly under a month, which may not capture all relevant cost and benefits of the interventions. While we used Woods *et al.'s* cost-effectiveness or WTP thresholds,[22] some literature suggests wider thresholds, such as $100,000 or $150,000 per QALY, as more appropriate for evaluating interventions in the USA. This variation might impact the generalisability of our results.[95, 96] It is relevant to recall that cost-effectiveness thresholds are contingent upon the locally-relevant WTP thresholds.

Conclusion

Most economic evaluations on ABR interventions have focused on MRSA, revealing a significant gap for other priority pathogens. Even when available, most studies lack a comprehensive economic analysis, even though such analysis would require readily available components such as intervention costs, bed-day expenses, and patient outcomes, such as LOS or ICU admission. Data on bed-day expenses for primary, secondary and tertiary hospitals are freely available for most countries from the WHO-CHOICE[97]. This is important because, as Nathwani *et al.*[83] showed, more effective antimicrobial control does not necessarily translate into improved cost-effectiveness due to population heterogeneity and decisions in resource allocation. Many studies were based on non-randomised designs that did not adequately account for potential confounders and antimicrobial regulations or guidelines (e.g., stewardship programs could reduce antibiotic consumption of a targeted component while increasing others). This issue could be rectified by strengthening intervention designs through a priori examination of biases and ensuring consistency. We have synthesised evidence supporting pharmacological and non-pharmacological interventions from the limited available scientific literature using economic analysis. Still, for many interventions, hospital-level considerations (e.g. laboratory capacity, prevalence of resistance in the local community, therapy review, and population features) need to be considered to optimise healthcare expenditure and address the costs of inaction. We recommend future economic evaluations consider the CHEERs checklist[98] using the healthcare sector and societal perspectives simultaneously as benchmarks[99] and for consistency across studies.

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Data availability and ethics: Data are fully available in the main manuscript and supplementary material. The project was considered exempt from ethical review.

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Figure legends

Figure 1. PRISMA flowchart for the inclusion and exclusion of relevant studies

Notes: ABR=antibiotic resistance; CEA=cost-effectiveness analysis. "n" stands for the number of articles included/excluded at each stage. ICER=Incremental cost-effectiveness ratio. Source: Moher *et al.* 2009.

Figure 2. Geographical distribution of the included studies (N=59)

Notes: Geographic Information System Open-Source Geospatial Foundation Project (QGIS) version 2022 was used for map visualisation.

Figure 3. Incremental cost-effectiveness ratios and willingness-to-pay country thresholds among pharmaceutical interventions (in 2022 USDs), by study†

Notes: †Studies with letters in brackets (e.g., [a]) indicate different strategy evaluations, detailed in Supplementary Table SM6 under the strategy column. K=thousands or 1,000 units. Interpretation of the incremental cost-effectiveness ratio 'ICER" should be taken with caution as outcomes (e.g., deaths averted, cured patients, quality-adjusted life years 'QALYs") used to calculate ICERs varied from study to study. Supplementary Table SM6 contains detailed information by study and outcomes utilised. WTP=Willingness-to-pay threshold. ⁂WTP thresholds were extracted from country estimates provided by Woods *et al.* 2016 [22] and adjusted to 2022 USD. A dominant strategy means that interventions is more effective and less costly (ICER<0). "vs."= versus. We excluded ICER per life saved from Collins *et al.*[25] and only ICER$ per QALY was included (ICER per life saved was far beyond the WTP threshold for this study, see Supplementary Table SM6). + ICERs were capped at $75,000 but values are higher (see Supplementary Table SM6). CZA= Ceftazidime avibactam.

Figure 4. Incremental cost-effectiveness ratios and willingness-to-pay country thresholds among non-pharmaceutical interventions (in 2022 USDs), by study†

Notes: †Studies with letters in brackets (e.g., [a]) indicate different strategy evaluations, detailed in Supplementary Table SM6 under the strategy column. K= thousands or 1,000 units. Interpretation of the incremental cost-effectiveness ratio 'ICER" should be taken with caution as outcomes (e.g., deaths averted, cured patients, quality-adjusted life years 'QALYs") used to calculate ICERs varied from study to study. Supplementary Table SM6 contains detailed information by study and outcomes utilised. WTP= Willingness-to-pay threshold. ⁂WTP thresholds were extracted from country estimates provided by Woods *et al.* 2016 [22] and adjusted to 2022 USD. A dominant strategy means that interventions is more effective and less costly (ICER<0). PCR= polymerase chain reaction. "vs."= versus. + ICERs were capped at $75,000 but values are higher (see Supplementary Table SM6).