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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 the costs and cost-effectiveness of pharmaceutical and non-pharmaceutical interventions aimed at reducing, monitoring and controlling ABR in patients. Articles published until 12 December 2023 were explored using EconLit, EMBASE and PubMed. We focused on critical or high-priority bacteria, as defined by the WHO, and intervention costs and incremental cost-effectiveness ratio (ICER). Following Preferred Reporting Items for Systematic review and Meta-Analysis 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 US dollars ($), adopting the healthcare system perspective. Country willingness-to-pay (WTP) thresholds from Woods *et al* 2016 guided cost-effectiveness assessments. We assessed the studies reporting checklist using 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* were cost-effective compared with 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=$1160/QALY or $4949 per ABR case averted, all ICERs<WTP) and PCR or chromogenic agar screening for ABR detection were highly cost-effective (eg, ICER=$1206 and $1115 per life-year saved in Europe and the USA). 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-income and middle-income countries. Our study

WHAT IS ALREADY KNOWN ON THIS 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 (eg, 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, are essential to advance the economic evaluation of interventions to progress toward optimising antibiotic usage and reducing ABB rates in hospitals, especially in low-income and middle-income countries.

serves as a resource for guiding future cost-effectiveness study design and analyses.

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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 were 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 of approximately $25 billion in the USA.[6] While these estimates are based on limited data, they underscore the severity of ABR. Setting-specific and population-specific strategies designed to alleviate ABR burden by reducing antibiotic usage and resistance transmission are crucial to reducing loss of life and minimising 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 semisynthetic penicillin while resulting in shorter hospital stays for patients.[8] Even in this economic evaluation of daptomycin compared with 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 $2403 in total antibiotic costs per 100 patient-days.[12] Niewiadomska *et al* reviewed mathematical modelling studies on the population-level transmission of ABR; however, only 9% of reviewed models included details of cost-effectiveness analyses.[10] Among these, universal surveillance and decolonisation programmes 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 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.[14] The search was conducted on EconLit, EMBASE and PubMed concluding on 12 December 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 search filters were used to capture the cost-effectiveness aspect of the search. The final literature search strategy and details of studies from the initial screening are presented in online supplemental 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] (online supplemental tables SM1 and 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] (online supplemental table SM3). Bacterial pathogens not on the WHO's list were excluded. Pharmaceutical interventions were defined as those that directly involved the use of medication, while all other interventions were classified as non-pharmaceutical. Economic evaluations included only complete evaluations (eg, cost-effectiveness, cost-utility, cost-benefit) and were defined as a comparative analysis of the costs and reported the 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 organisation 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 (ie, a 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 and Cochrane Economic Methods group and a recent protocol for economic appraisal to address ABR which includes 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 (eg, ICER) and sensitivity analyses (eg, univariate or multivariate analyses and parameter effects on outcomes). Costs were first converted to US dollars (using currency-specific exchange rates) and inflated to 2022 US dollars based on Gross Domestic Product deflators.[21] We used 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 (1) $/(quality-adjusted life-years 'QALY' gained), (2) $/(disability-adjusted life-years 'DALYs' gained), (3) $/ABR infection averted or (4) $/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 the intervention's real cost-effectiveness to determine the feasibility of the programme in the setting where it was evaluated. Cost-effectiveness thresholds, 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 10 questions for evaluating reporting quality in economic evaluations, assigning a 1 (or 0) to each question if the article included the safeguard (online supplemental 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 1744 were duplicated. We excluded 18 811 records due to not fulfilling our inclusion criteria (figure 1). Finally, 403 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 (eg, 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 PCR or chromogenic-based surveillance and testing (n=11), multiple surveillance schemes including testing, decolonisation and/or isolation (n=8), infection control

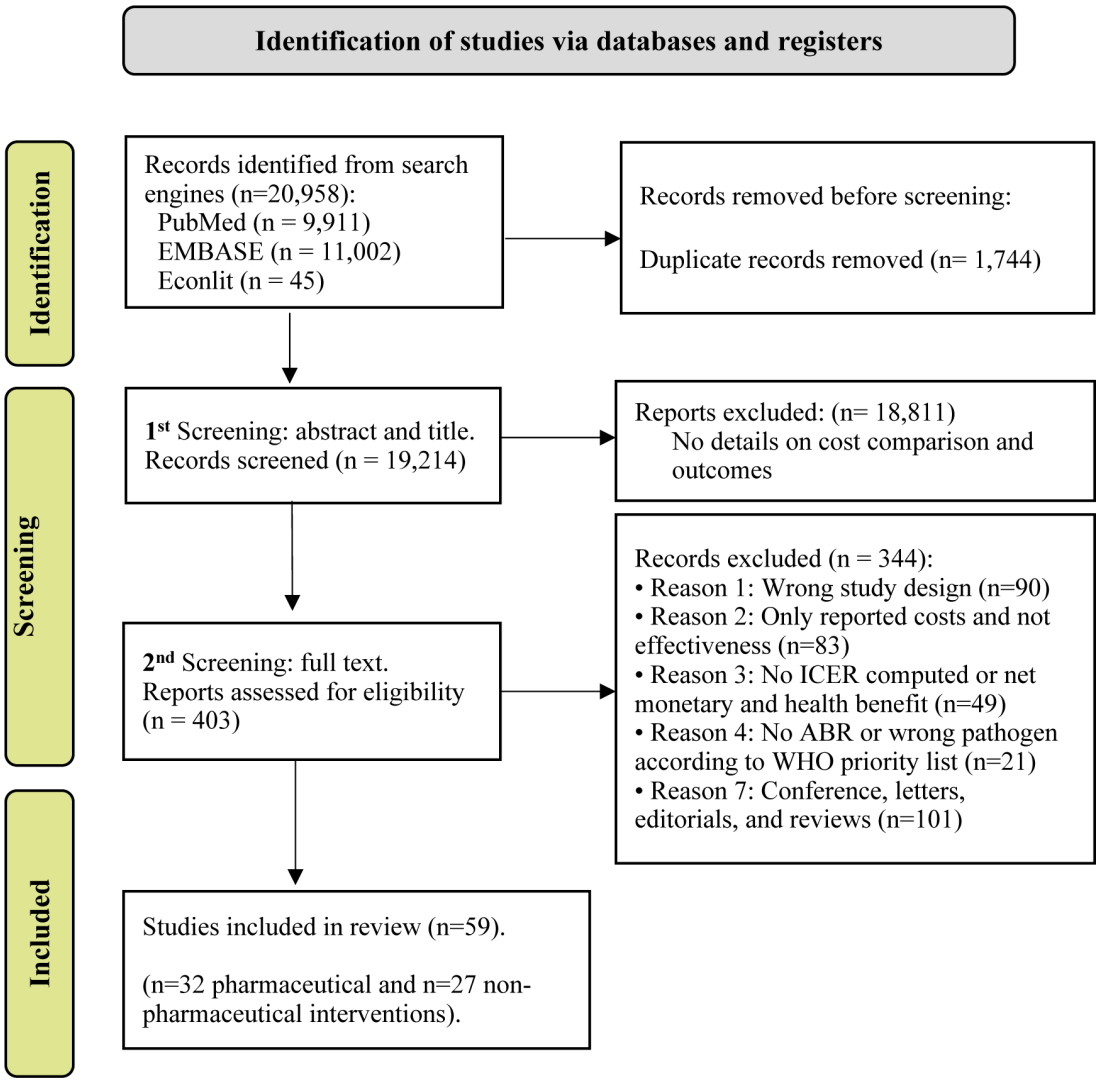

Figure 1 Preferred Reporting Items for Systematic review and Meta-Analysis flowchart for the inclusion and exclusion of relevant studies. 'n' stands for the number of articles included/excluded at each stage. ABR, antibiotic resistance; ICER, incremental cost-effectiveness ratio. Source: Moher *et al* 2009.

and hygiene including use of gowns and hand hygiene practices (n=3) and miscellaneous (n=5; eg, antibiotic stewardship, pre-emptive isolation, whole-genome sequencing). 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 using European data and the second in Africa. Decision analytical models were usually employed for the analyses (eg, 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 online supplemental tables SM6 and 7 for a full description of the studies' characteristics.

Unit costs of interventions

Online supplemental 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 intensive care unit (ICU), constituted the largest portion of total economic costs (~50%–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] (online supplemental table SM8). For instance, Niederman *et al* reported the cost of intravenous linezolid (600 mg) as $107 per dose, while vancomycin costed $5.8 for 1 g intravenous administration.[26]

Online supplemental 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

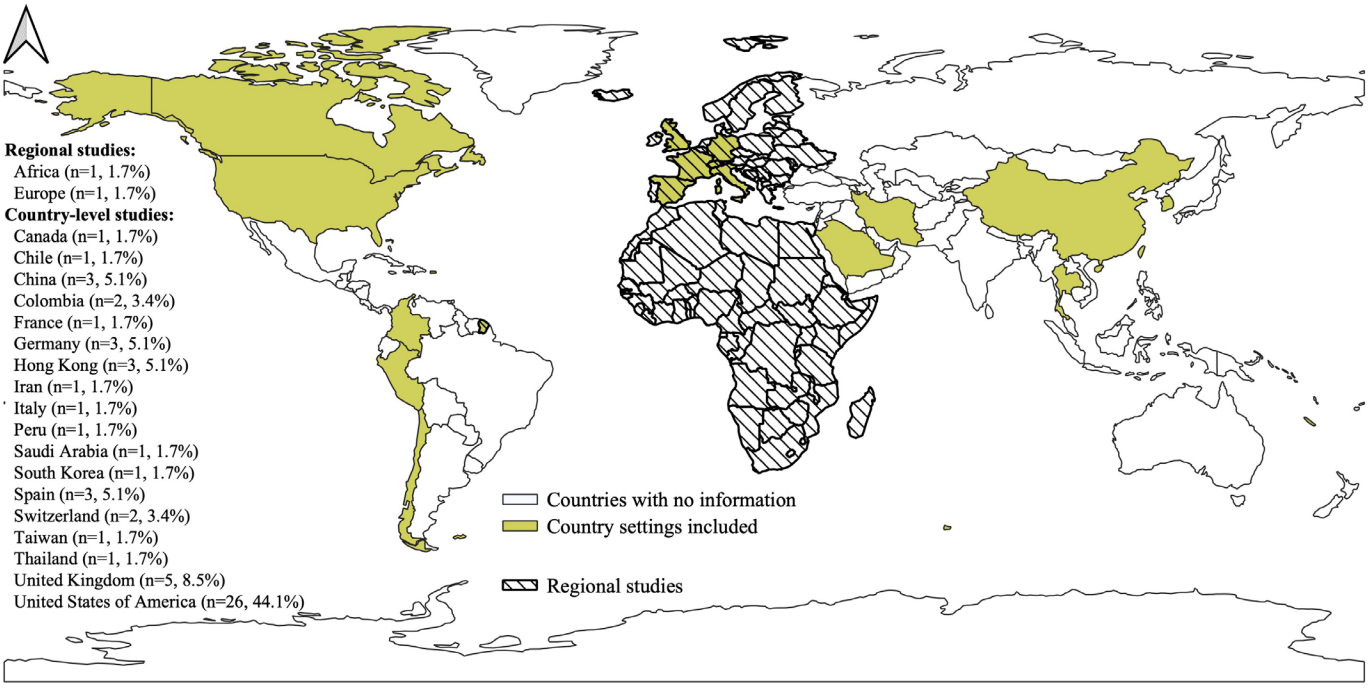

Figure 2 Geographical distribution of the included studies (N=59) Notes: Geographical Information System Open-Source Geospatial Foundation Project (QGIS) V.2022 was used for map visualisation.

varied widely, ranging from $1 per patient (eg, 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 (eg, PCRs, chromogenic agar or electronic registry).

Cost-effectiveness and outcomes

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

Pharmaceutical interventions

Linezolid versus vancomycin

For patients with complicated skin and skin structure infections (cSSSI), linezolid consistently emerged as a cost-effective and dominant strategy compared with vancomycin (online supplemental table SM6, panel I).[24 32–35] For instance, McKinnon *et al*[32] reported a mean cost of $7077 (SD=$5752) for linezolid versus $8709 (SD=$7307) for vancomycin treatment among patients with cSSSI reporting MRSA infections, with a mean cost difference of $2756 (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 Schürmann *et al*[35] estimated lower hospitalisation costs for linezolid (incremental costs were −$7791, −$1827 and −$1749, respectively) along with higher cure rates (incremental cure rates for first-line MRSA were 13%, 10% and 10%, respectively), compared with vancomycin in patients with cSSSI. Differences were explained by reduced LOS and improved treatment failures due to linezolid oral formulation compared with intravenous vancomycin therapy.

In studies focusing on nosocomial pneumonia,[25 26 36–43] linezolid showed a dominant ICER or ICER ranging from $5726 to $84 823 per death averted or life saved, and between $3179 and $21 488 per cure or treatment success among MRSA-infected patients, compared with vancomycin (online supplemental table SM6, section I). Variations in LOS and its associated economic costs across study settings accounted for differences in ICER. Daniel Mullins *et al* predicted an ICER of $5726 for linezolid per life saved, balancing the higher acquisition costs with enhanced survival rates.[36] De Cock *et al* designed a decision–analytical 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 with vancomycin at country-specific WTP thresholds (ICER<WTP).

Ceftazidime avibactam *versus colistin or other drugs*

Six studies evaluated the use of ceftazidime avibactam (CZA) versus colistin or other drugs (online supplemental table SM6).[44–49] ICERs ranged between $693 and $113 423 per QALY gained. Goudarzi *et al*[45] and Simon *et al*[47] calculated ICERs equal to $798 and $113 423 per QALY gained among patients infected with CRE,

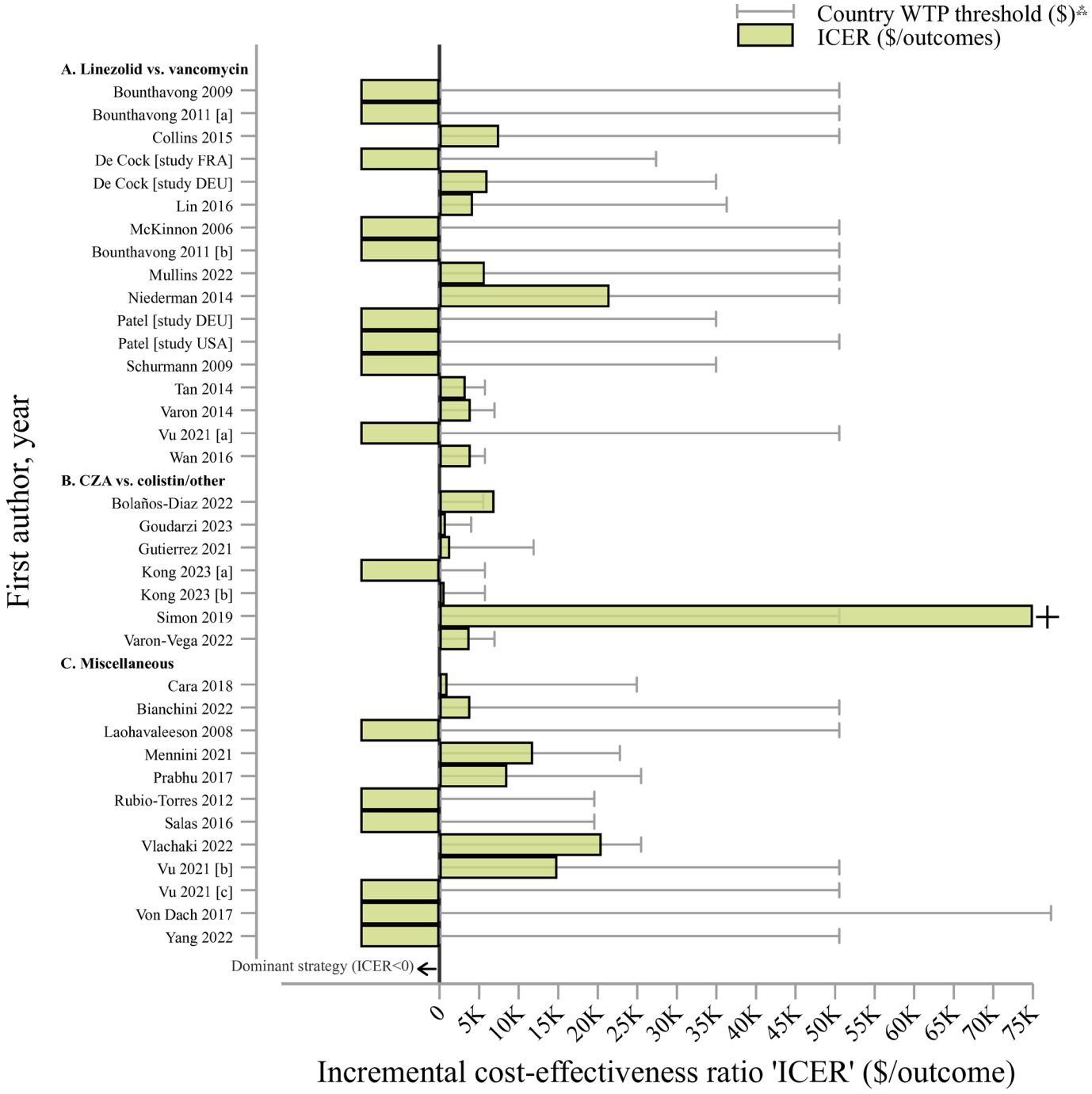

Figure 3 Incremental cost-effectiveness ratios and willingness-to-pay country thresholds among pharmaceutical interventions (in 2022 US dollars, '$'), by study†. Notes: †Studies with letters in brackets (eg, (a)) indicate different strategy evaluations, detailed in online supplemental table SM6 under the strategy column. K=thousands or 1000 units. Interpretation of the incremental cost-effectiveness ratio 'ICER' should be taken with caution as outcomes (eg, deaths averted, cured patients, quality-adjusted life years 'QALYs') used to calculate ICERs varied from study to study. Online supplemental table SM6 contains detailed information by study and outcomes used. **WTP thresholds were extracted from country estimates provided by Woods *et al*[22] and adjusted to 2022 US dollars. A dominant strategy means that interventions are more effective and less costly (ICER<0). We excluded ICER per life saved from Collins *et al*[25] and only ICER$ per QALY was included (ICER per life saved was far beyond the WTP threshold for this study, see online supplemental table SM6). + ICERs were capped at US$75 000 but values are higher (see online supplemental table SM6). CZA, ceftazidime avibactam; 'vs', versus; WTP, willingness-to-pay.

respectively, comparing CZA versus colistin therapy. Incremental QALYs were similar (≈0.5) in both studies, but costs differed. In Goudarzi *et al*, CZA therapy costs were 1.5-times greater for CZA compared with colistin according to Iran health system tariffs. Simon *et al* employed a healthcare system perspective in the USA,

estimating four times greater daily therapy costs for CZA compared with colistin after accounting for LOS, which increased the ICER. In comparison to colistin+meropenem, Gutiérrez and Fandiño[48] and Varón-Vega *et al*[49] reported ICERs of $1340 and $3797 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 ($3151 and $2886, 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]

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 with vancomycin) among MRSA patients, regardless of sensitivity analyses on MRSA drug acquisition costs. Favourable results were shown for IMI/REL (imipenem/cilastatin/relebactam) compared with CMS+IMI (colistin plus imipenem) usage for gram-negative infections (+3.7 QALYs and lower mortality rates; 15.2% compared with 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=$8551 per QALY gained), compared with 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 with 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).

Non-pharmaceutical interventions

Testing schemes: chromogenic-based agar or PCR

Rapid PCR testing for MRSA detection compared with standard hospital treatments was found to be cost-effective (ICER=$55 and $39 per life-year saved in Europe and the USA, respectively[55]), with ICER=$20 401 per hospital-acquired MRSA case detected in the USA,[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 with 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 (ie, highly dependent on local transmission settings).[59] Similarly, active PCR among CRE patients, compared with 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 with an inadequate empirical antibiotic treatment for CRE. Hubben *et al*[61] found selective chromogenic-based agar cost-effective for MRSA detection compared with taking no action (ICER= $5787–$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).

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 bloodstream infections (BSIs) and ICERs of $1160 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=$2939 per case averted).[64]

Using a 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 (online supplemental table SM6, panel II; figure 4C). Universal decolonisation 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 with 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 rates rather than low transmission in subsequent periods (ICER= $13 904[66] and

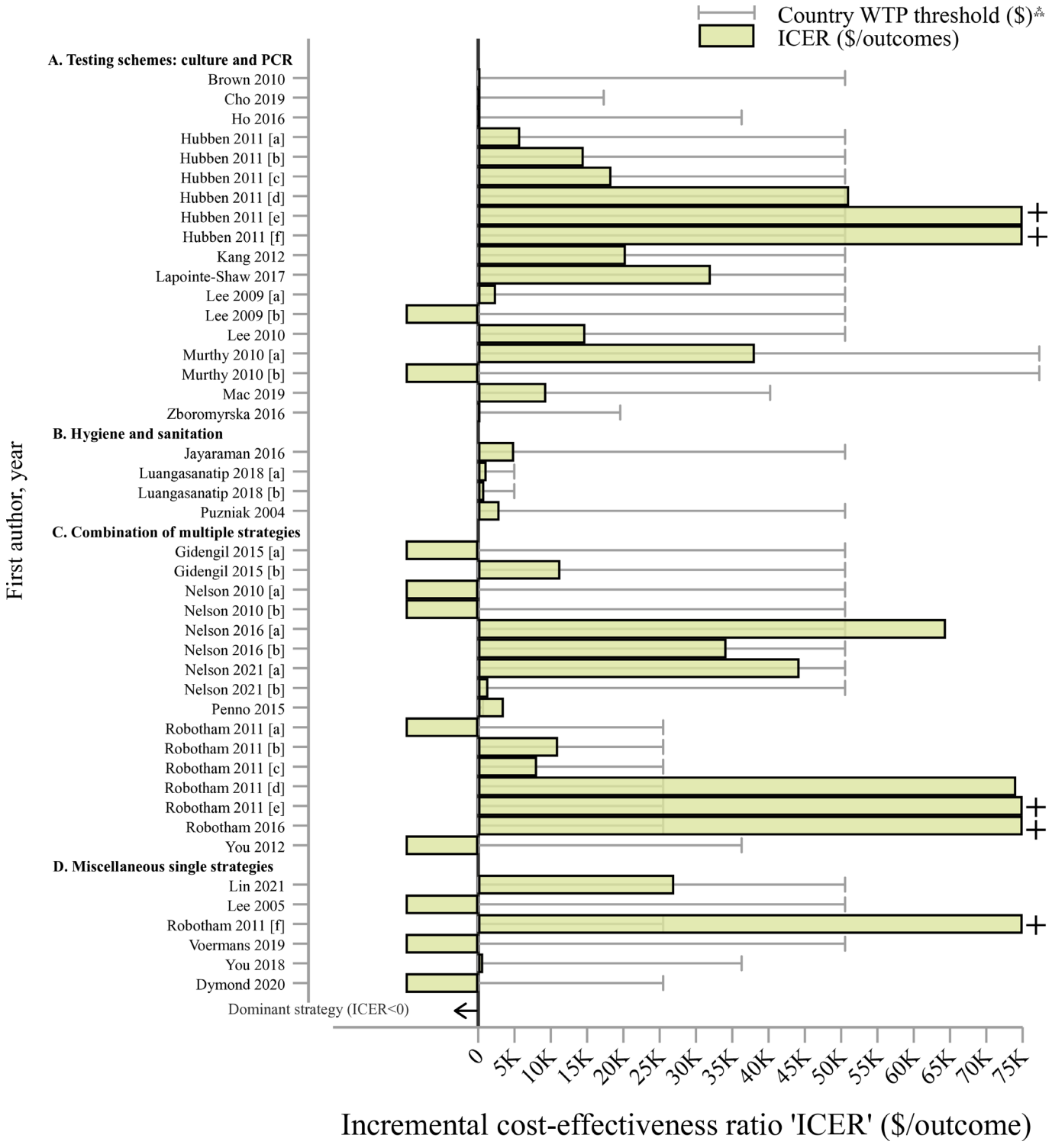

Figure 4 Incremental cost-effectiveness ratios and willingness-to-pay country thresholds among non-pharmaceutical interventions (in 2022 US dollars, '$'), by study†. Notes: †Studies with letters in brackets (eg, (a)) indicate different strategy evaluations, detailed in online supplemental table SM6 under the strategy column. K=thousands or 1000 units. Interpretation of the incremental cost-effectiveness ratio 'ICER' should be taken with caution as outcomes (eg, deaths averted, cured patients, quality-adjusted life years 'QALYs') used to calculate ICERs varied from study to study. Online supplemental table SM6 contains detailed information by study and outcomes used. **WTP thresholds were extracted from country estimates provided by Woods *et al*[22] and adjusted to 2022 US dollars. A dominant strategy means that interventions is more effective and less costly (ICER<0). + ICERs were capped at US$75 000 but values are higher (see online supplemental table SM6). PCR, PCR chain reaction; 'vs', versus; WTP, willingness-to-pay.

$34 201[67] per life years gained; as shown in online supplemental 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 were cost-effective in Africa (ICER=$3531 per life saved, averting 934 deaths per 100 000 patients), compared with generic antimicrobial management.[70]

Most of these strategies were cost-effective based on country WTP thresholds (figure 3C), but consideration of local costs was essential in scenarios with low MRSA prevalence and transmission.[65]

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, a 49% reduction from standard care for sepsis and 23% reduction for lower respiratory tract infections associated with ABR (cost savings of $29 197 and $4138 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 a $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 to 31.7) and by 6.3% (95% CI=2.0% to 10.6%; p value<0.05) compared with 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 (online supplemental table SM10). The type of costing methodology was dissimilar in 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 online supplemental 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] time frames and years 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-income and middle-income countries indicated the need for more consistent approaches in the future.

More studies found that, compared with 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 (eg, 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 with 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 with 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 hospitalisation 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=$1340 and $3797 per QALY gained, both falling below the country's WTP thresholds). This finding holds relevance for a region where the 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 National Health Service-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 the 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 evaluations. Although not specifically targeting ABR, Scheetz, *et al*[82] presented an ICER of $3219 per QALY gained in antimicrobial stewardship programmes attributed to substantial fixed operating costs required to maintain the stewardship team and the reduction in patient inflow. Antimicrobial stewardship proves more economically efficient in larger hospitals with higher inpatient volume, presenting increased risks and expanded economic returns of scale, specifically for persuasive and structural programmes.[9] Notwithstanding, some studies have shown mixed results, with increased consumption of antibiotics not targeted or restricted by the antimicrobial stewardship programme 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 preintervention and post-intervention populations, including existing comorbidities and disease severity, might lead to poorer health outcomes despite the stewardship programme.[83] Comprehensive antimicrobial stewardship programmes, 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 the appropriateness of antibiotic treatment at low costs compared with 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 with 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*, Harrison and Collins and Huang *et al*, 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-income 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 $1100 to $1200, compared with 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 well-being. 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-income and middle-income countries. Our primary sources were PubMed, which comprehensively indexes biomedical and life sciences literature, including health economics; Embase, which specialises 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 of standardisation 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 costs 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 on 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 (eg, stewardship programmes 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 (eg, laboratory capacity, the 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 Consolidated Health Economic Evaluation Reporting Standards checklist[98] using the healthcare sector and societal perspectives simultaneously as benchmarks[99] and for consistency across studies.

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SUPPLEMENTARY MATERIAL

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

Kasim Allel*, María José Hernández-Leal, Nichola Naylor, Eduardo A. Undurraga, Gerard Joseph Abou Jaoude, Priyanka Bhandari, Ellen Flanagan, Hassan Haghparast-Bidgoli, Koen B. Pouwels, Laith Yakob

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† Supplementary file containing cost ingredients per study is located in https://bit.ly/SR_amrCEingredients.

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Table SM1: Search strategy

Research question	**What is the economic impact (cost-effectiveness) of pharmaceutical and non-pharmaceutical interventions for reducing AMR levels among critical pathogens within hospital inpatients?**		
Keywords	Economic evaluation	Population	Antimicrobial
Search terms	Economics Costs Cost Analysis Fees and Charges Budgets Pharmacoeconomic Expenditure Finance	Hospital Patient Inpatient	Antimicrobial Microbial Antibiotic + Resistance

Table SM2: Study inclusion and exclusion criteria

Criteria	Inclusion Criteria	Exclusion Criteria
Population	Hospitalised patients, no age restrictions	Patients outside hospital
Geography	All countries	None
Period	Until December 2023	After December 2023
Setting	Inpatients care setting, hospital infections, nosocomial infections (infections occurring within the hospital)	Nursing home, long-term care studies, community settings.
Interventions	Pharmaceutical or non-pharmaceutical interventions targeting infections from the WHO critical and high-priority AMR bacterial pathogens only	All other interventions or pathogens.
Outcomes	Studies must have at least an incremental cost-effectiveness measure, e.g., dollars per QALY gained, however, other measures were included ,e.g. cost per patient cured	All other outcomes (non-incremental cost per gain in hospital outcomes).
Publication language	All languages	None
Publication Type	Peer-reviewed articles	Conference proceedings, case reports, grey literature, magazine entries, protocols, literature reviews, commentaries, and abstracts
Study design	Cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses, piggyback economic evaluation alongside RCTs, case reports	All other study designs (e.g., literature review,; systematic reviews; meta-analyses not using primary data)

Notes: QALY: quality-adjusted life year. RCT= randomised controlled trial.

Table SM3: WHO global priority pathogens list of antibiotic-resistant bacteria

Priority 1: CRITICAL
• *Acinetobacter baumannii*, carbapenem-resistant • *Pseudomonas aeruginosa*, carbapenem-resistant • *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing
Priority 2: HIGH
• *Enterococcus faecium*, vancomycin-resistant • *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate, and resistant • *Helicobacter pylori*, clarithromycin-resistant • *Campylobacter spp.*, fluoroquinolone-resistant • *Salmonellae*, fluoroquinolone-resistant • *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant
Priority 3: MEDIUM
• *Streptococcus pneumoniae*, penicillin-non-susceptible • *Haemophilus influenzae*, ampicillin-resistant • *Shigella spp.*, fluoroquinolone-resistant

Notes: Adapted from the World Health Organization 'WHO' priority pathogen report[1].

Table SM4: Final literature search strategy (search codes) in three search engines (12th of December 2023)

I. PubMed

('Economic' OR 'Budget' OR 'cost' OR 'cost analysis' OR 'pharmacoeconomic' OR 'pharmaco-economic' OR 'economic evaluation' OR 'economic analysis' OR 'economic modelling' OR 'cost utility' OR 'cost minimi*' OR 'cost' OR 'cost saving' OR 'cost-saving' OR 'cost allocation' OR 'expenditure' OR 'expense' OR 'financ*' OR 'healthcare cost' OR 'unit cost' OR 'money' OR 'monetary' OR 'cost-effectiv*' OR 'cost-benefit') AND ('Drug resistance' OR 'antimicrobial drug resistan*' OR 'drug resistan*' OR 'antibiotic resistan*' OR 'antimicrobial resistan*' OR 'multi-drug resistan*' OR 'drug-resistance' OR 'carbapenem-resistant Escherichia coli' OR 'carbapenem-resistant Klebsiella pneumoniae' OR 'cephalosporin-resistant Escherichia coli' OR 'cephalosporin-resistant Klebsiella pneumoniae' OR 'carbapenem-resistant Enterobacteral*' OR 'carbapenem-resistant Enterobacteriaceae' OR 'cephalosporin-resistant Enterobacteral*' OR 'cephalosporin-resistant Enterobacteriaceae' OR 'Penicillin-resistant Streptococcus pneumoniae' OR 'vancomycin-resistant Staphylococcus aureus' OR 'methicillin-resistant Staphylococcus aureus' OR 'carbapenem-resistant Pseudomonas aeruginosa' OR 'carbapenem-resistant Acinetobacter baumanii' OR 'vancomycin-resistant Enterococcus' OR 'vancomycin-resistant Enterococcus faecium' OR 'clarithromycin-resistant Helicobacter pylori' OR 'fluoroquinolone-resistant Campylobacter' OR 'fluoroquinolone-resistant Salmonella' OR 'fluoroquinolone-resistant Neisseria gonorrhoeae' OR 'cephalosporin-resistant Neisseria gonorrhoeae' OR 'fluoroquinolone-resistant Shigella' OR 'ampicillin-resistant Haemophilus influenzae') AND ('hospital' OR 'inpatient' OR 'patient' OR 'healthcare' OR 'ICU' OR 'intensive care unit' OR 'ward' OR 'clinic' OR 'medical' OR 'nursing') NOT ('HIV' OR 'Tuberculosis' OR 'TB' OR 'virus' OR 'fungus' OR 'fungal' OR 'conference' OR 'letter to the editor')

II. EMBASE

((('Economic' or 'Budget' or 'cost' or 'cost analysis' or 'pharmacoeconomic' or 'pharmaco-economic' or 'economic evaluation' or 'economic analysis' or 'economic modelling' or 'cost utility' or 'cost minimi*' or 'cost' or 'cost saving' or 'cost-saving' or 'cost allocation' or 'expenditure' or 'expense' or 'financ*' or 'healthcare cost' or 'unit cost' or 'money' or 'monetary' or 'cost-effectiv*' or 'cost-benefit') and ('Drug resistance' or 'antimicrobial drug resistan*' or 'drug resistan*' or 'antibiotic resistan*' or 'antimicrobial resistan*' or 'multi-drug resistan*' or 'drug-resistance' or 'carbapenem-resistant Escherichia coli' or 'carbapenem-resistant Klebsiella pneumoniae' or 'cephalosporin-resistant Escherichia coli' or 'cephalosporin-resistant Klebsiella pneumoniae' or 'carbapenem-resistant Enterobacteral*' or 'carbapenem-resistant Enterobacteriaceae' or 'cephalosporin-resistant Enterobacteral*' or 'cephalosporin-resistant Enterobacteriaceae' or 'Penicillin-resistant Streptococcus pneumoniae' or 'vancomycin-resistant Staphylococcus aureus' or 'methicillin-resistant Staphylococcus aureus' or 'carbapenem-resistant Pseudomonas aeruginosa' or 'carbapenem-resistant Acinetobacter baumanii' or 'vancomycin-resistant Enterococcus' or 'vancomycin-resistant Enterococcus faecium' or 'clarithromycin-resistant Helicobacter pylori' or 'fluoroquinolone-resistant Campylobacter' or 'fluoroquinolone-resistant Salmonella' or 'fluoroquinolone-resistant Neisseria gonorrhoeae' or 'cephalosporin-resistant Neisseria gonorrhoeae' or 'fluoroquinolone-resistant Shigella' or 'ampicillin-resistant Haemophilus influenzae') and ('hospital' or 'inpatient' or 'patient' or 'healthcare' or 'ICU' or 'intensive care unit' or 'ward' or 'clinic' or 'medical' or 'nursing')) not ('HIV' or 'Tuberculosis' or 'TB' or 'virus' or 'fungus' or 'fungal' or 'conference' or 'letter to the editor')).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]

III. Econlit

('Economic Development' OR 'Model' OR 'Economic' OR 'fee' OR 'charge' OR 'Budget' OR 'cost' OR 'cost analysis' OR 'pharmacoeconomic' OR 'pharmaco-economic' OR 'pricing' OR 'economic evaluation' OR 'economic analysis' OR 'economic modelling' OR 'cost utility' OR 'cost minimi*' OR 'cost' OR 'cost saving' OR 'cost allocation' OR 'expenditure' OR 'expense' OR 'finance*' OR 'healthcare cost' OR 'unit cost' OR 'money' OR 'monetary') AND ('Drug resistance' OR 'antimicrobial drug resistan*' OR 'drug resistan*' OR 'antibiotic resistan*' OR 'antimicrobial resistan*' OR 'multi-drug resistan*' OR 'drug-resistance' OR 'carbapenem-resistant Escherichia coli' OR 'carbapenem-resistant Klebsiella pneumoniae' OR 'cephalosporin-resistant Escherichia coli' OR 'cephalosporin-resistant Klebsiella pneumoniae' OR 'carbapenem-resistant Enterobacteral*' OR 'carbapenem-resistant Enterobacteriaceae' OR 'cephalosporin-resistant Enterobacteral*' OR 'cephalosporin-resistant Enterobacteriaceae' OR 'Penicillin-resistant Streptococcus pneumoniae' OR 'vancomycin-resistant Staphylococcus aureus' OR 'methicillin-resistant Staphylococcus aureus' OR 'carbapenem-resistant Pseudomonas aeruginosa' OR 'carbapenem-resistant Acinetobacter baumanii' OR 'vancomycin-resistant Enterococcus' OR 'vancomycin-resistant Enterococcus faecium' OR 'clarithromycin-resistant Helicobacter pylori' OR 'fluoroquinolone-resistant Campylobacter' OR 'fluoroquinolone-resistant Salmonella' OR 'fluoroquinolone-resistant Neisseria gonorrhoeae' OR 'cephalosporin-resistant Neisseria gonorrhoeae' OR 'fluoroquinolone-resistant Shigella' OR 'ampicillin-resistant Haemophilus influenzae') AND ('hospital' OR 'inpatient' OR 'patient' OR 'healthcare' OR 'ICU' OR 'intensive care unit' OR 'ward' OR 'clinic' OR 'medical' OR 'nursing')

Table SM5: Drummond's checklist for assessing economic evaluations

1. Was a well-defined question posed in answerable form?
1.1. Did the study examine both costs and effects of the service(s) or programme(s)? 1.2. Did the study involve a comparison of alternatives? 1.3. Was a viewpoint for the analysis stated, and was the study placed in any particular decision-making context?
2. Was a comprehensive description of the competing alternatives given (i.e., can you tell who did what to whom, where, and how often)?
2.1. Were there any important alternatives omitted? 2.2. Was (should) a do-nothing alternative be considered?
3. Was the effectiveness of the programme or services established?
3.1. Was this done through a randomised, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice? 3.2. Was effectiveness established through an overview of clinical studies? 3.3. Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?
4. Were all the important and relevant costs and consequences for each alternative identified?
4.1. Was the range wide enough for the research question at hand? 4.2. Did it cover all relevant viewpoints? (Possible viewpoints include the community or social viewpoint, and those of patients and third-party payers. Other viewpoints may also be relevant depending upon the particular analysis.) 4.3. Were the capital costs, as well as operating costs, included?
5. Were costs and consequences measured accurately in appropriate physical units (e.g., hours of nursing time, number of physician visits, lost work days, gained life years)?
5.1. Were any of the identified items omitted from measurement? If so, does this mean they carried no weight in the subsequent analysis? 5.2. Were there special circumstances (e.g., joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?
6. Were the cost and consequences valued credibly?
6.1. Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policy-makers views, and health professionals' judgements) 6.2. Were market values employed for changes involving resources gained or depleted? 6.3. Where market values were absent (e.g. ,volunteer labour), or market values did not reflect actual values (such as clinic space donated at a reduced rate), were adjustments made to approximate market values? 6.4. Was the valuation of consequences appropriate for the question posed (i.e., has the appropriate type or types of analysis – cost-effectiveness, cost-benefit, cost-utility – been selected)?
7. Were costs and consequences adjusted for differential timing?

7.1. Were costs and consequences that occur in the future 'discounted' to their present values?
7.2. Was there any justification given for the discount rate used?
8. Was an incremental analysis of costs and consequences of alternatives performed?
8.1. Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits, or utilities generated?
9. Was allowance made for uncertainty in the estimates of costs and consequences?
9.1. If data on costs and consequences were stochastic (randomly determined sequence of observations), were appropriate statistical analyses performed?
9.2. If a sensitivity analysis was employed, was justification provided for the range of values (or key study parameters)?
9.3. Were the study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the confidence interval around the ratio of costs to consequences)?
10. Did the presentation and discussion of study results include all issues of concern to users?
10.1. Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g., cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion?
10.2. Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology?
10.3. Did the study discuss the generalisability of the results to other settings and patient/client groups?
10.4. Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g.,. distribution of costs and consequences, or relevant ethical issues)?
10.5. Did the study discuss implementation issues, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?

Notes: Drummond, et al. 2015 [2].

Table SM6. Reported cost-effectiveness per study (in 2022 USDs) and intervention type (pharmaceutical and non-pharmaceutical, N=59 studies)

First author	Year	Country	Pathogen	Hospital population	Strategy	ICER
I. Pharmaceutical interventions (N= 32 studies)						
Bianchini[3]	2022	USA	CRO	All	New beta-lactam beta-lactamase Inhibitor antibiotics‡ vs. colistin treatment	$3,900/QALY.
Bolaños-Diaz[4]	2022	PER	CRE	BSI and Pneumonia	Ceftazidime avibactam‡ vs. colistin-based treatment.	$6,947/QALY.
Bounthavong[5]	2009	USA	MRSA	cSSSI	Linezolid‡ vs. vancomycin treatment.	Dominant strategy ($/cure).
Bounthavong[6]	2011	USA	MRSA	cSSSI	[a] Linezolid‡ vs. vancomycin treatment.	Dominant strategy ($/treatment success).
					[b] Linezolid‡ vs. daptomycin treatment.	Dominant strategy ($/treatment success).
Cara[7]	2018	KSA	MDR GN	Pneumonia	Low dose of colistin‡ vs. high dose of colistin treatment.	$1,006/nephrotoxicity avoided.
Collins[8]	2015	USA	MRSA	Pneumonia	Linezolid‡ vs. vancomycin treatment.	$7,527/QALY and $84,823/life saved
De Cock[9]	2009	FRA	MRSA	cSSSI	Linezolid‡ vs. vancomycin treatment.	Dominant strategy ($/cure & $/death averted).
De Cock[10]	2009	DEU	MRSA	Pneumonia	Linezolid‡ vs. vancomycin treatment.	$9,223/cure; $6,076/death averted; $345/LY.
Goudarzi[11]	2023	IRN	CRE	All	Ceftazidime avibactam‡ vs. colistin treatment.	$798/QALY.
Gutierrez[12]	2021	CHL	CRE	All	Ceftazidime/avibactam‡ vs. colistin+ meropenem treatment.	$1,340/QALY and $1,342/LY
Kong[13]	2023	CHN	CRE	BSI	[a] Ceftazidime-avibactam‡ vs. polymyxin B (PMB) monotherapy.	Dominant strategy ($/QALY).
					[b] Ceftazidime-avibactam‡ vs. PMB-based therapy.	$639/QALY.
Laohavaleeson[14]	2008	USA	MRSA	cSSSI	Telavancin‡ vs. vancomycin treatment.	Dominant strategy ($/cure).
Lin[15]	2016	TWN	MRSA	Pneumonia	Linezolid‡ vs. vancomycin treatment.	$4,224/cure.
McKinnon[16]	2006	USA	MRSA	cSSSI	Linezolid‡ vs. vancomycin treatment.	Dominant strategy ($/% cure rate).
Mennini[17]	2021	ITA	CRE	All	Vaborem (meropenem-vaborbactam)‡ versus best available treatment.	$9,548/LY and $11,813/QALY.
Mullins[18]	2022	USA	MRSA	Pneumonia	Linezolid‡ vs. vancomycin treatment.	$5,726/life saved.
Niederman[19]	2014	USA	MRSA	Pneumonia	Linezolid‡ vs. vancomycin treatment.	$21,488/treatment success.
Patel[20]	2014	DEU	MRSA	Pneumonia	Linezolid‡ vs. vancomycin treatment.	Dominant strategy ($/treatment success).
Patel[21]	2014	USA	MRSA	Pneumonia	Linezolid‡ vs. vancomycin treatment.	Dominant strategy ($/treatment success).
Prabhu[22]	2017	GBR	ABR GN	IAI	Ceftolozane/tazobactam/ metronidazole‡ vs. piperacillin/tazobactam treatment.	$8,551/QALY.
Rubio-Terres[23]	2012	ESP	MRSA	All	Daptomycin‡ vs. vancomycin treatment.	Dominant strategy ($/cure).

Salas[24]	2016	ESP	MRSA	Post-surgery	Intense mupirocin treatment among MRSA colonised patients‡ vs. conventional mupirocin treatment.	$44,552/infection averted.
Schurmann[25]	2009	DEU	MRSA	cSSSI	Linezolid‡ vs. vancomycin treatment.	Dominant strategy ($/cure).
Simon[26]	2019	USA	CRE	BSI and Pneumonia	Ceftazidime-avibactam‡ vs. colistin-based treatment.	$113,423/QALY.
Tan[27]	2014	CHN	MRSA	Pneumonia	Linezolid‡ vs. vancomycin treatment calibrated to different cities.	Up to $3,312/ treatment success.
Varon[28]	2014	COL	MRSA	Pneumonia	Linezolid‡ vs. vancomycin treatment.	$3,179/cure.
Varon-Vega[29]	2022	COL	CRE	Pneumonia	Ceftazidime-avibactam‡ vs. colistin-meropenem treatment.	$3,797/QALY.
Vlachaki[30]	2022	GBR	CRE	All	Vaborem (meropenem-vaborbactam)‡ versus best available treatment.	$20,486/QALY.
Vu[31]	2021	USA	MRSA	BSI	[a] Linezolid‡ vs. vancomycin 4-weeks treatment.	Dominant strategy ($/treatment failure avoided).
					[b] Daptomycin‡ vs. linezolid 4-weeks treatment.	$14,881/treatment failure avoided.
					[c] Linezolid‡ vs. ceftaroline/daptomycin 4-weeks treatment.	Dominant strategy ($/treatment failure avoided).
Von Dach[32]	2017	CHE	MRSA	All	Trimethoprim-sulfamethoxazole + rifampicin‡ vs. linezolid.	Dominant strategy($/QALY).
Wan[33]	2016	CHN	MRSA	Pneumonia	Linezolid‡ vs. vancomycin treatment calibrated to different cities.	Up to $3,984/ treatment success.
Yang[34, 35]	2022	USA	CR-GN	All	Imipenem/cilastatin/relebactam‡ vs. colistin/imipenem treatment.	Dominant strategy ($/QALY).
II. Non-pharmaceutical interventions (N= 27 studies)						
Brown[36]	2010	EU & USA	MRSA	All	Rapid PCR testing‡ vs. empiric vancomycin treatment.	$55 (EU) and $39 (USA) /LY.
Cho[37]	2019	KOR	CLRHP	All	DPO-based multiplex PCR therapy‡ vs. conventional therapy.	$5/case eradicated.
Dymond[38]	2020	GBR	MRSA	All	Whole genome sequencing‡ vs. standard infection control.	Dominant strategy ($/QALY).
Gidengil[39]	2015	USA	MRSA	ICU	[a] Universal decolonisation‡ vs. standard infection control.	Dominant strategy ($/colonisation or death averted).
					[b] Universal contact precautions + decolonisation‡ vs. universal decolonisation.	$3,102/ colonisation averted and $11,316/ infection averted.
Ho[40]	2016	HKG	CRE	Surgical ICU	Active surveillance (PCR) + isolation of CRE+‡ vs. no surveillance.	$100/QALY.
Hubben[41]	2011	USA	MRSA	All	[a][b] Selective chromogenic-based screening in high and medium prevalence settings‡ vs. do nothing.	$5,787 and $14,538/ case averted, respectively.
					[c][d] Selective PCR-based tests in high and medium prevalence settings‡ vs. selective chromogenic-based screening.	$18,349 and $51,095 per case averted, respectively.
					[e][f] Universal screening with PCR-based tests in high and medium prevalence settings‡ vs. selective PCR-based test	$184,902 and $328,448/ case

						averted, respectively.
Jayaraman[42]	2016	USA	MDR	ICU	Proactive infection control program (enhanced hand hygiene, cleaning wards, increased nurse-to-patient ratio, and replacement of all disposable supplies)‡ vs. standard of care.	$4,949/transmission averted.
Kang[43]	2012	USA	MRSA	All	PCR-universal screening surveillance‡ vs. no surveillance.	$20,401/detected case.
Lapointe-Shaw[44]	2017	USA	CRE	All	Universal screening surveillance (PCR/culture)‡ vs. no surveillance	$32,049/QALY.
Lee[45]	2005	USA	VRE	All	Screening utilising current standards plus those patients with hospitalisations in previous 2-years‡ vs. current standards.	Dominant strategy ($/death averted)
Lee[46]	2009	USA	MRSA	Surgery	[a] Universal preoperative screening (culture of a single anterior nares sample)‡ vs. do nothing at MRSA prevalence of 0.1 in a single location.	$2,452/QALY.
					[b] Universal preoperative screening (culture of a single anterior nares sample)‡ vs. doing nothing at MRSA prevalence >0.1 in a single location.	Dominant strategy ($/QALY).
Lee[47]	2010	USA	MRSA	All	Universal screening surveillance (culture of a single anterior nares sample)‡ vs. no surveillance.	$14,766/QALY.
Lin[48]	2021	USA	CRE	All	Screening surveillance schemes using electronic registry (state-wide and hospital records)‡ vs. doing nothing scenario.	$27,000/ infection averted
Luangasanatip[49]	2018	THA	MRSA	BSI, ICU	[a] Hand hygiene intervention to improve compliance at 20%, 30% and 40%‡ vs. hand hygiene compliance at 10% in paediatric ICU.	$1,160, $806, and $739/QALY.
					[b] Hand hygiene intervention to improve compliance at 20%, 30% and 40%‡ vs. hand hygiene compliance at 10% in adult ICU.	$835, $574, and $524/QALY.
Mac[50]	2019	CAN	VRE	General ward	Screening (swabs and culture) and isolation‡, compared to no screening or isolation.	$9,372/QALY.
Murthy[51]	2010	CHE	MRSA	Surgery	[a] PCR screening at admission‡ vs. no screening.	$38,111/infection avoided.
					[b] PCR screening at admission‡ vs. screening for risk factors + isolation.	Dominant strategy ($/infection avoided).
Nelson[52]	2010	USA	MRSA	All	[a] Active surveillance (PCR screening)+ decolonization‡ vs. active surveillance alone.	Dominant strategy ($/infections or deaths avoided).
					[b] Active surveillance (PCR screening) + decolonization‡ vs. no surveillance.	Dominant strategy ($/infections or deaths avoided).
Nelson[53]	2016	USA	MRSA	HAI	[a][b] 3-year hospital surveillance initiative including screening, contact precautions, improved hand hygiene and infection control‡ vs. no initiative.	Between $34,201 and $64,436/LY, subject to high and low transmission.

Nelson[54]	2021	USA	MRSA and VRE	HAI	[a][b] 3-year hospital surveillance initiative including screening, contact precautions, improved hand hygiene and infection control‡ vs. no initiative.	Between $13,904 and $44,270/LY, subject to high and low transmission
Penno[55]	2015	Africa	PRSP	BSI	Evidence-based antimicrobial surveillance using local data and blood cultures‡ vs. generic antimicrobial management	$3,531/life saved.
Puzniak[56]	2004	USA	VRE	ICU	Use of gown and gloves‡ vs. gloves alone on entry to patient rooms.	$2,939/case averted.
Robotham[57]	2011	GBR	MRSA	ICU	[a] Universal chromogenic agar screening and decolonisation with mupirocin‡ vs. do nothing.	Dominant strategy ($/QALY).
					[b] Universal PCR and decolonisation with mupirocin‡ vs. do nothing.	$11,005/QALY.
					[c] Chromogenic agar screening for high-risk patients and isolation of MRSA+‡ vs. do nothing.	$8,114/QALY
					[d] PCR for high-risk patients and isolation of MRSA+‡ vs do nothing.	$74,114/QALY.
					[e] Universal PCR and isolation of MRSA+‡ vs. do nothing.	$80,159/QALY
					[f] Universal pre-emptive isolation‡ vs. do nothing.	$246,302/QALY.
Robotham[58]	2016	GBR	MRSA	All	Screening strategies using a chromogenic agar test at hospital admission (checklist-activated screening, high-risk specialty-based screening) accompanied by decolonisation and isolation‡ vs. no screening.	Dominated strategy ($/QALY).
Voermans[59]	2019	USA	ABR	Sepsis/LRTI	(PCT)-guided decision algorithm to guide antibiotic prescription‡ vs. standard of care.	Dominant strategy ($/patient diagnosed with ABR bacteria avoided).
You[60]	2012	HKG	MRSA	NICU	Active surveillance (PCR) plus decolonisation‡ vs. active surveillance.	Dominant strategy ($/percentage point reduction in mortality and infection rates).
You[61]	2018	HKG	CRE	ICU	Test-guided selective digestive decontamination‡ vs. no screening.	$688/QALY.
Zboromyrska[62]	2016	ESP	MRSA	BSI	PCR-based assay (GeneXpert) for MRSA detection‡ vs. compared to standard blood culture methods.	$243/LY.

Notes: Costs were calculated in 2022 USDs. ABR=Antibiotic-resistant bacteria. AST=Antimicrobial susceptibility testing. CAN=Canada. CSSSI=complicated skin and skin structure infections. CMS+IMI=Colistin plus imipenem. CNS=Carbapenem-non-susceptible. CPE=Carbapenemase-producing Enterobacteriaceae. CRE=Carbapenem-resistant Enterobacteriaceae. DPO=Dual priming oligonucleotide. FRA=France. DEU=Deutschland or Germany. ICER=Incremental cost-effectiveness ratio. ICU=Intensive Care Unit. IMI/REL=Imipenem/cilastatin/relebactam. IRN= IRAN. KOR= Korea. L= Linezolid. LOS=Length of hospital stay. NLD=The Netherlands. QALYs=Quality-adjusted life years. PCR=Polymerase chain reaction. SD=Standard Deviation. CHE= Switzerland. ESP, Spain. GBR=Great Britain or United Kingdom. KSA= Kingdom of Saudi Arabia. HKG= Hong Kong. TW=Taiwan. USA=United States of America. VRE=Vancomycin-resistant enterococci. IAI=Intrabdominal infections. CR-GN=Carbapenem resistant Gram-negative bacteria. EU= European Union. CRO=Carbapenem-resistant organisms. CLRHP=Clarithromycin-resistant Helicobacter pylori. PRSP= Penicillin-resistant *Streptococcus penumoniae*. MDR=Multidrug resistant bacteria. LRTI= Low respiratory tract infections.

BSI=Bloodstream infections. ‡Mupirocin treatment comparing twice a day during two weeks with no follow-up verification (protocol A) versus all patients who received mupirocin (protocol B) for treating post-surgical infections in cardiac surgery. ICER=Incremental cost-effectiveness ratio. ‡Evaluated strategy (new intervention); ICERs=(cost intervention – cost comparator)/(efficiency intervention – efficiency comparator). A dominant strategy is one in which the incremental cost of the intervention is less than the comparator and the incremental efficacy is greater than the comparator. QALY= Quality adjusted life year. ICU=Intensive care unit. NICU=Neonatal intensive care unit. vs.=versus. HAI= Hospital-acquired infections. LY=Life year.

Table SM7. Characteristics of the included studies (n=59)

First author	Perspective	Type of study	WTP threshold	Discount rate	Time horizon	Source of effectiveness & costs	Year of the EE
I. Pharmaceutical interventions (N= 32 studies)							
Bianchini[3]	Health system	CEA, decision tree	$100,000	3%	Lifetime	Literature and RED BOOK[63]	Not stated
Bolaños-Diaz[4]	Health system	CEA, Markov model	$7,200	3%	5 years	Literature and hospital data on costs	Not stated
Bounthavong[5]	Health system	CEA, decision tree model	WTP range, no specific	Not stated	Not stated	Literature and RED BOOK[63]	Not stated
Bounthavong[6]	Health system	CEA, decision tree model	WTP range, no specific	Not applied	15-16 days	Literature and health economic resource centre and decision support services.	2009
Cara[7]	Hospital	CEA, decision tree	Not stated	Not applied	Days in treatment until failure	Hospital outcomes and costs based on a patient-level study	2016
Collins[8]	Payer	CEA, decision tree	$100,000/ QALY	3%	15 years	The ZEPHyR trial and literature.	2014
De Cock[9]	Health system	CEA, decision tree	$52,200	None	11 days	RCT and drug costs insurance reimbursement price and expert panel.	2006
De Cock[10]	Hospital	CEA, decision tree	Not stated	None	Time to cure	RCT and literature.	2006
Goudarzi[11]	Health system	CEA, decision tree	WTP range, no specific	5.8%	5 years	Literature and tariffs from Iran Health System	2022
Gutierrez[12]	Payer	CEA, decision tree	$15,121	3%	30 days and lifetime	Chilean National Reports, Ministry of Health, and Financial entity entrusted to collect, manage and distribute state funds for health	2020
Kong[13]	Health system	CEA, decision tree	$ 12,528/ QALY	5%	5 years	Literature and Yaozh database that collects successful biding prices of drugs	2021
Laohavaleeson [14]	Hospital	CEA, decision tree	$79,750	None	12 days	ATLAS trial outcomes and DRG-specific hospital costs	2006
Lin[15]	Payer	CEA, decision tree	Not stated	Not stated	7-30 days after end of treatment	The ZEPHyR trial and National Health Insurance database (drug costs)	Not stated
McKinnon[16]	Hospital	CUA, mean comparison	Not stated	None	35 days	RCT and nationally representative hospital costs	2006
Mennini[17]	Health system	CEA, decision tree	$21,322/ QALY	3%	5 years	Clinical inputs from phase 3, RCT TANGO II and costs from the Italian official drug pricing list and legislation	Not stated
Mullins[18]	Health system	CEA, decision tree	Not stated	None	11 days	RCT and health insurance claims data	2003
Niederman[19]	Payer	CEA, piggyback and mean comparison	$130,000	None	30 days	ZEPHyR study and literature.	2011
Patel[20]	Payer	CEA, decision tree	$195,804	None	4 weeks	Literature, expert opinion and DRG data	2012
Patel[21]	Payer	CEA, decision tree	$152,400	None	4 weeks	RCT, expert opinion and literature.	2012
Prabhu[22]	Health system	CEA, decision tree and Montecarlo simulation	$39,430	None	Lifetime	RCT and Healthcare cost and utilisation project (HCUP)	2013
Rubio-Terres[23]	Health system	CEA, decision tree	$21,739	7.5%	14-15 days	Literature, Spanish healthcare costs database and General	2011

						Counsel of Official Colleges of Pharmacists.	
Salas[24]	Health system	CEA, decision tree	Not stated	Not applied	14 days	RCT and hospital accounts	Not stated
Schurmann[25]	Hospital and health system	CEA, decision tree	$179,861	None	29 days	RCT, literature and DRG data	2003
Simon[26]	Health system	CEA, decision tree & Markov	$100,000-$150,000/ QALY	3%	5 years	Literature and U.S. Department of Veterans Affairs Federal Supply Schedule.	2017
Tan[27]	Payer	CEA, decision tree	Not stated	None	4 weeks	Trial literature and clinical expert panel	Not stated
Varon[28]	Health system	CEA, decision tree	$3,522	Not applied	30 days	Literature and ISS 2001 rate manual for procedures and SIS-MED (report January-December 2013)	2013
Varon-Vega[29]	Health system	CEA, decision tree	$2,791	None	7-14 days	Colombian manual tariffs and official databases	2019
Vlachaki[30]	Health system	CEA, decision tree	$29,031 and $43,547	3.5%	5 years	British National Formulary, NHS reference costs and literature.	2020
Vu[31]	Health system	CEA, decision tree	$45,789	None	7 days	Federal Supply Schedule, other government agencies (Medicare reimbursements) and literature	2019
Von Dach[32]	Health system	CEA, decision tree	$67,480	Not applied	Duration of therapy until 6 weeks after	RCTs, literature and wholesale prices of generic drugs.	2016
Wan[33]	Payer	CUA, mean differences and bootstrap simulations	Not stated	Not stated	7–30 days after the end of treatment	The ZEPHyR trial, healthcare resource utilisation and literature	2012
Yang[34, 35]	Payer	CEA, decision tree and Markov model	$113,000–169,500	3%	28 days	Literature and red book online database for drug costs.	2020
II. Non-pharmaceutical interventions (N= 27 studies)							
Brown[36]	Hospital	CEA, decision tree	$4,669 (EU) & $3,264 (USA)	3%	Not stated	Literature and hospital accounts for microbiological samples	2009
Cho[37]	Hospital	CEA, cost comparison and mean differences	Not stated	Not stated	Not stated	Hospital costs and protocol	Not stated
Dymond[38]	Health system	CEA, decision tree	Not stated	None	12 months	Cambridge University Hospitals NHS Foundation and literature	2010
Gidengil[39]	Hospital	CEA, Markov microsimulation model	$3,015 per colonisation averted and $11,306 per death averted	3%	1 year	Literature and expert consensus	2013
Ho[40]	Health system	CEA, Markov model	$49,149	3%	2 and 10 days	Literature and costs from the largest public health care organization (hospital authority)	2014
Hubben[41]	Hospital	CEA, discrete event simulation model	Not stated	3%	15 years	Literature, bureau of labour statistics and hospital costs	2007
Jayaraman[42]	Hospital	CEA, decision analytic model (tree)	$18,215 and $28,623 per transmission averted.	Not applied	6 months	Literature and estimates excess costs from a MDR outbreak in hospitals	2011

Kang[43]	Hospital	CEA, decision tree	Not stated.	None	Hospital stay long	Framework and literature	2009
Lapointe-Shaw[44]	Hospital	CEA, Markov model	$122,000 per QALY	3%	Not stated	WHO-CHOICE and literature	2016
Lee[45]	Hospital	CEA, Markov model	Not stated	Not applied	Not stated	Literature	2001
Lee[46]	Payer	CEA, decision tree with Montecarlo simulations	$63,733 per QALY	Not stated	Not stated	Literature and Healthcare Cost and Utilization Project National Inpatient Sample.	Not stated
Lee[47]	Societal and payer	CEA, decision analytic stochastic model (tree)	$13,600	3%	Not stated	Human mortality dataset and literature	2008
Lin[48]	Health system	CEA, metapopulation transmission model	Not stated	None	Not stated	Maryland health services cost review commission and literature	Not stated
Luangasanatip [49]	Hospital	CUA, metapopulation transmission model	$5,902/QALY	3%	Lifetime	Literature and hospital data	2016
Mac[50]	Hospital	CEA, microsimulation model	Not stated	1.5%	1 year at hospital and lifetime	Literature	2017
Murthy[51]	Hospital	CEA, decision analysis (tree)	Not stated	Not stated	Hospitalisation period	Hospital's cost accounting system and literature	2006
Nelson[52]	Health system	CEA, decision tree	Not stated	Not stated	Inpatient's stay	Literature	Not stated
Nelson[53]	Health system	CEA, decision tree and budget impact model	Not stated	3%	29 years	Literature	2013
Nelson[54]	Health system	CEA, simulation model	WTP range, no specific	3%	8 years	Literature and Nationwide Inpatient Sample database	2019
Penno[55]	Hospital	CEA, decision tree	$6,500 per life saved	Not stated	Not stated	WHO and clinical laboratory data	2011
Puzniak[56]	Hospital	CBA, cost and outcome comparison	Not stated	Not stated	Not stated	Literature and line-item reports from the hospital's microbiology database	Not stated
Robotham[57]	Health system	CEA, mathematical individual-based model of transmission	WTP range, no specific	Not stated	Not stated	Literature, National Health Service data and primary data	Not stated
Robotham[58]	Health system	CEA, mathematical model of transmission	$62,500 per QALY	Not stated	Five years	National health system (NHS) and literature	2011
Voermans[59]	Societal and hospital	CEA, decision tree	Not stated	Not applied	Length of hospital stay (<1 year)	Hospital data and literature	2019
You[60]	Health system	CEA, decision tree	Not stated	Not stated	Not stated	Literature and microbiology laboratory of a public hospital in Hong Kong	Not stated
You[61]	Health system	CEA, Markov model	$50,123	3%	Not stated	Literature and local hospital costs (health authority)	2015
Zboromyrska[62]	Hospital	CEA, decision tree	WTP range, no specific	3%	Length of hospital stay	Literature and hospital data on prevalence	Not stated

Notes: WTP= Willingness to pay. EU= European union. USA= United States of America. QALY= Quality-adjusted life year. EE= Economic evaluation. DRG= Diagnostic-related group. RCT= randomised controlled trial. CEA= Cost-effectiveness analysis. CUA= Cost-utility analysis. Costs are reported in 2022 USD$. CBA= Cost-benefit analysis.

Table SM8. Unit costs per study for pharmacological interventions (in 2022 USDs)

I. Pharmaceutical interventions (A): Patients with MRSA or suspected MRSA investigating Cellulitis or Complicated Skin and Skin Structure Infections (cSSSI) treated with linezolid versus vancomycin												
	Linezolid costs ($)						**Vancomycin costs ($)**					
Article	**ICU ward**	**General ward**	**Tests**	**Drugs**	**Additional**	**Total**	**ICU ward**	**General ward**	**Tests**	**Drugs**	**Additional**	**Total**
Bounthavong, 2009[5]	NS	$1565 Ward per day	NS	$256 (iv) per day $200 (oral) per day	$53 microbiology culture per day $11 platelet monitoring per day	$13938	NS	$1565 Ward per day	NS	$11 (iv) per day	$8 vancomycin labs per day $53 microbiology culture per day $11 platelet monitoring per day	$34076
Bounthavong, 2011[6]	NS	$2687 per day	NS	$303 (iv) per day $232 (oral) per day	$55 Microbiological culture, per day $12 Platelet monitoring, per day	$22752	NS	$2687 per day	NS	$18 (iv) per day	$55 Microbiological culture, per day $12 Platelet monitoring, per day	$29825
De Cock, 2009a[10]	$1095 ICU without ventilator, per day $1594ICU weighted average, per day	$322 Ward per day	$655	$332 (iv), per day. $322 (oral), per day.	$505 Isolation, per day. $27 Infusion (iv) longer than 30 minutes $371 Adverse events	$23,357	$1095 ICU without ventilator, per day $1594ICU weighted average, per day	$322 Ward per day	$803	$89 (iv) per day	$505 Isolation, per day. $27 Infusion (iv) longer than 30 minutes $371 Adverse events	$20722
McKinnon, 2006[16]	$1512 per day	$617 per day	NS	$182 (iv), per day $134 (oral), per day	$68 Intravenous administration/dose $803 Step-down; per day	$6492	$1512 per day	$617 per day	NS	$35 (iv), per day	$68 Intravenous administration/dose $803 Step-down; per day	$7988
Schurmann, 2009[25]	NS	$336 per day	NS	$304 (iv), per day $295 (oral), per day	$530 Isolation, per day $26 Intravenous infusion, per day	$11013	NS	$356 per day	NS	$130 (iv), per day	$530 Isolation, per day $26 Intravenous infusion, per day	$13188

					$68 GP, per home visit. $65 Specialist, per consultation $63 GP, per office visit $489 Other inpatient (test and adverse events) $2490 Post discharge (outpatient antibiotic drugs, test, visit)						$68 GP, per home visit. $65 Specialist, per consultation $63 GP, per office visit $738 Other inpatient (test and Adverse events) $1911 Post discharge (outpatient antibiotic drugs, test, visit)	
I. Pharmaceutical interventions (B): Patients with MRSA or suspected MRSA investigating Cellulitis or Complicated Skin and Skin Structure Infections (cSSSI) Linezolid treated with daptomycin												
Linezolid. Cost ($)							Daptomycin cost ($)					
Article	**ICU ward**	**General ward**	**Tests**	**Drugs**	**Additional**	**Total**	**ICU ward**	**General ward**	**Tests**	**Drugs**	**Additional**	**Total**
Bounthavong, 2011[6]	NS	$2687 per day	**NS**	$303 (iv) per day $232 (oral) per day	$55 Microbiological culture, per day $12 Platelet monitoring, per day	$ 22752	NS	$2687 per day	NS	$344 (iv) per day	$55 Microbiological culture, per day $12 Platelet monitoring, per day	$26079
I. Pharmaceutical interventions (C): Patients with MRSA or suspected MRSA investigating Cellulitis or Complicated Skin and Skin Structure Infections (cSSSI) Telavancin versus Vancomycin												
Telavancin cost ($)							Vancomycin cost ($)					
Article	**ICU ward**	**General ward**	**Tests**	**Drugs**	**Additional**	**Total**	**ICU ward**	**General ward**	**Tests**	**Drugs**	**Additional**	**Total**
Laohavaleeson, 2008[14] (Telavancin versus Vancomycin)	NS	NS	NS	$18	$144 Study drug $528 Additional antibiotic	$11801	NS	NS	NS	$18	$144 Study drug $568 Additional antibiotic $68 Drug monitoring	$10345

I. Pharmaceutical interventions (D): Patients with MRSA or suspected MRSA investigating Nosocomial Pneumonia treated with linezolid versus vancomycin

Article	Linezolid costs ($)						Vancomycin costs ($)					
Collins, 2015[8]	NS	NS	NS	$283 (iv) per day $235 (oral) per day	$16544 Attributable cost, Nephrotoxicity $24047 Attributable cost, Thrombocytopenia $2047 Attributable cost, Pneumonia	$27009	NS	NS	$10	$31	$16544 Attributable cost, Nephrotoxicity $24047 Attributable cost, Thrombocytopenia $2047 Attributable cost, Pneumonia	$2598
De Cock, 2009b[9]	$2401 per day	$391 per day	$171 Biochemistry monitoring test, per unit	$104 (iv or oral)	$255 Monitoring test (biochemical, hemogram, C- reactive protein, other drugs $104 Co-medications $120Treatment Acute Encephalitis Syndrome (AEs) $341 Post-discharge (visit and test)	$12989	$2401 per day	$391 per day	$171 Biochemistry monitoring test, per unit $1079	$7 (iv)	$255 Monitoring test (biochemical, hemogram, C-reactive protein, other drugs $159 Co-medications $149 Treatment Acute Encephalitis Syndrome (AEs) $509 Post-discharge (visit and test)	$14657
Lin, 2016[15]	$474 per day	$87 per day	NS	$1252	$2 Lab work (serum creatinine levels) $	$6900	$474 per day	$87 per day	NS	$263	$2 Lab work (serum creatinine levels) $12 Lab work (serum vancomycin levels)	$6474
Mullins, 2006	NS	NS	NS	$2949, per day	NS	$33331	NS	NS	NS	$3132 per day	NS	$33511 per day
Niederman, 2014[19]	$3520 per day	$1645 per day	$44	$131 (iv)	$2133 Mechanical ventilation $2449 Study drugs	$54905	$3520 per day	$1645 per day	Laboratory test: $47	$7 (iv)	$2086 Mechanical ventilation $306 Study drugs $604 Dialysis	$54774

					$132 Dialysis							
Patel, 2014a [21]	$4078 to adjusted to received therapy. *$4065 per day	$2917 total adjusted to received therapy. *$2349 per day	$78	$25	$205 administration $2344 Physician/attending visit. $1353 Lab work $2573 Serious adverse event $2224 Mechanical ventilation	$54940	$41326 total adjusted to received therapy. *$4065 per day	$4194 total adjusted to received therapy. *$2349 per day	$43	$888	$ 217 administration $2488 Physician/attending visit. $1482 Lab work $3155 Serious adverse event $2171 Mechanical ventilation	$55920
Patel, 2014b[20]	*$1878 ICU +mechanical ventilation, per day	*$1077 Ward + isolation, per day:	NS	$87 (iv)	NS	$23025 Total base case inpatient	*$1878 ICU +mechanical ventilation, per day	*$1077 Ward + isolation, per day:	NS	$14 (iv)	NS	$23212 Total base case inpatient
Tan, 2014[27]	$2093 Beijing $2415 Guangzhou $22157 Nanjing $1530 Xi`an	$277 Beijing $293 Guangzhou $283 Nanjing $223 Xi`an	NS	$143 per vial	NS	$24716 Beijing $28012 Guangzhou $25376 Nanjing $18945 Xi`an	$2093 Beijing $2415 Guangzhou $22157 Nanjing $1530 Xi`an	$277 Beijing $293 Guangzhou $283 Nanjing $223 Xi`an	NS	$46, per vial	NS	$24700 Beijing $28025 Guangzhou $25375 Nanjing $18802 Xi`an
Varon, 2014[28]	$856 Stay (ICU and standard room)		NS	$1097	$4452 Management of kidney failure	1521	$856 Stay (ICU and standard room)		NS	$83	NS	1166

					$83 Management of thrombocytopenia							
Wan, 2016[33]	$1719 Beijing $1176 Xi`an	$287 Beijing $231 Xi`an		$151 (iv) Beijing $151 (iv) Xi`an	$200 Mechanical ventilator Beijing, per day $160 Mechanical ventilator Xi`an, per day  $1066 Continuous renal replacement therapy Beijing, per day $1583 Continuous renal replacement therapy Xi`an, per day	$ 26506 Beijing $30320 Guangzhou $27450 Nanjing $19796 Xi`an	$1719 Beijing $1176 Xi`an	$287 Beijing $231 Xi`an	$32 Beijing and Xi`an	$96 (iv) Beijing $96 (iv) Xi`an	$4452 Management of kidney failure $83 Management of thrombocytopenia $200 Mechanical ventilator Beijing, per day $160 Mechanical ventilator Xi`an, per day  $1066 Continuous renal replacement therapy Beijing, per day $1583 Continuous renal replacement therapy Xi`an, per day	$25852 Beijing $29804 Guangzhou $26922 Nanjing $19260 Xi`an
I. Pharmaceutical interventions (E): Patients with MRSA or suspected MRSA investigating Nosocomial Pneumonia treated with low dose of colistin and high dose of colistin												
Low dose of colistin Cost ($)							High dose of colistin treatment Cost ($)					
Article	**ICU ward**	**General ward**	**Tests**	**Drugs**	**Additional**	**Total**	**ICU ward**	**General ward**	**Tests**	**Drugs**	**Additional**	**Total**
Cara, 2018[7]	$3850 per day	$3908 per day	$836 CBC per day	$932 per day	$1045 GW nurse visits, per day $770 ICU nurse visits, per day $281 Laboratory cultures, per day	$22912	$5587 per day	$3400 per day	$842 CBC, per day	$624, per day	$1052 GW nurse visits, per day $1117 ICU nurse visits, per day $188 Laboratory cultures, per day	$20390
I. Pharmaceutical interventions (F): Patients with MRSA or suspected MRSA investigating Nosocomial Pneumonia treated with Ceftazidime-avibactam vs. colistin-based treatment.												
Ceftazidime-avibactam cost ($)							Colistin-based cost ($)					

Article	ICU ward	General ward	Tests	Drugs	Additional	Total	ICU ward	General ward	Tests	Drugs	Additional	Total
Bolaños-Diaz, 2022[4]	NS	NS	NS	$12240 per day	$267 Hospitalization costs, per day $19999 Long-term care, per year $19094 Nephrotoxicity, Chronic dialysis, per year $2203 Nephrotoxicity, With RRT $12240 Nephrotoxicity, Without RRT	$28764				$163 per day	$267 Hospitalization costs, per day $19999 Long-term care, per year $19094 Nephrotoxicity, Chronic dialysis, per year $2203 Nephrotoxicity, With RRT $12240 Nephrotoxicity, Without RRT	$16322
Simon, 2019[26]	NS	NS	NS	$1028 per day	$100355 chronic dialysis, per year $105113 long-term care, per year $26722 long-term health care for sepsis, first year $8971 long-term health care costs of sepsis, subsequent year	$173493	NS	NS	NS	$29 per day	$100355 chronic dialysis, per year $105113 long-term care, per year $26722 long-term health care for sepsis, first year $8971 long-term health care costs of sepsis, subsequent year	$120768
Varon-Vega, 2022[29]	$332	$37	NS	$43	$452 Adverse event, Renal failure $1269 Adverse event, Dialysis	8781	$332	$13	NS	$13	$452 Adverse event, Renal failure $1269 Adverse event, Dialysis	$5264
I. Pharmaceutical interventions (G): Patients treated with other intervention types for MRSA and gram-negative infections including carbapenem non-susceptible infections												

Intervention 1 cost ($)							Intervention 2 cost ($)					
Article	**ICU ward**	**General ward**	**Tests**	**Drugs**	**Additional**	**Total**	**ICU ward**	**General ward**	**Tests**	**Drugs**	**Additional**	**Total**
Bianchini, 2022[3] (New beta-lactam beta-lactamase Inhibitor antibiotics‡ vs. colistin treatment)	NS	NS	NS	$1259 Meropenem-vaborbactam, per day $870 Ceftolozane-tazobactam, per day $1361 Imipenem-relebactam, per day $40 Polymyxin, per day $207 Meropenem, per day	NS	$17172	NS	NS	NS	$8	NS	$3710
Goudarzi, 2023[11] (Ceftazidime avibactam vs. colistin treatment.)	NS	NS	NS	$649	$598 Long term care $901 nephrotoxicity without renal replacement therapy $9764 Nephrotoxicity with renal replacement therapy	$885	NS	NS	NS	$445	$598 Long term care $901 nephrotoxicity without renal replacement therapy $9764 Nephrotoxicity with renal replacement therapy	$460
Gutierrez, 2021[12] **(**Ceftazidime/ avibactam vs.	$240	$58	NS	$128, per vial	$240 Prevention of kidney failure $1256 Dialysis, per month	$9566	$240	$58	NS	$8 Meropenem $15 Colistin	$240 Prevention of kidney failure $1256 Dialysis, per month	$6423

colistin+ meropenem treatment)					$24 Creatinine $2 Ureic nitrogen $4 Hemogram $0.2 Plasma electrolytes						$24 Creatinine $2 Ureic nitrogen $4 Hemogram $0.2 Plasma electrolytes	
Kong, 2023[13] (Ceftazidime-avibactam vs. polymyxin B (PMB) monotherapy)	NS	NS	NS	$606 per day	$2483 Long-term care $5715 Nephrotoxicity without renal replacement therapy in hospital $11955 Nephrotoxicity with renal replacement therapy in hospital $30746 Hemodialysis, per year	$23726934	NS	NS	NS	$667 per day	$2483 Long-term care $5715 Nephrotoxicity without renal replacement therapy in hospital $11955 Nephrotoxicity with renal replacement therapy in hospital $30746 Haemodialysis, per year	$23514366
Mennini, 2021[17] Vaborem (meropenem-vaborbactam) versus best available treatment	NS	NS	NS	$1141 Carbapenems	$8206 Hospital acquired pneumonia (HAP)/ Ventilation associated pneumonia (VAP) $3856 Complicated urinary tract infections (cUTI)	$3287	NS	NS	NS	$3428 Ceftazidime-Avibactam $642 Colistin $23 Aminoglycosides	$8206 Hospital acquired pneumonia (HAP)/ Ventilation associated pneumonia (VAP) $3856 Complicated urinary tract infections (cUTI) $4975 Complicated intra-abdominal infections (cIAI)	$ 2121

					$4975 Complicated intra-abdominal infections (cIAI) $7844 Bloodstream infections (BSI)						$7844 Bloodstream infections (BSI)	
Rubio-Terres, 2012[23] (Daptomycin vs. vancomycin treatment.)	NS	NS	NS	$160	$2 Sodium chloride 0.9% (1 bag of 50 mL) $1 Sterile water for injection (1 ampoule of 20 mL) $1324 Admission to the Infectious Diseases Service (1 day) $802 Admission to the Internal Medicine Service (1 day) $0.5 IV administrations by a nurse (1 minute of work day)	$ 21359 per patient	NS	NS	NS	$12	$2 Sodium chloride 0.9% (1 bag of 50 mL) $1 Sterile water for injection (1 ampoule of 20 mL) $1324 Admission to the Infectious Diseases Service (1 day) $802 Admission to the Internal Medicine Service (1 day) $0.5 IV administrations by a nurse (1 minute of work day)	$ 21995 per patient
Salas, 2016[24] (Protocol A versus B) [24]	*$4258 per day	*$2063 per day	NS	$1195 Screening and treatment *$10 Mupirocin ointment	*$113 Nurse, per hour *$74 Nursing assistant, per hour *$0.04 Chlorhexidine (sponge)	$49683 per patient	*$4258 per day	*$2063 per day	NS	$2894 Screening and treatment: *$10 Mupirocin ointment	**$113 Nurse, per hour *$74 Nursing assistant, per hour *$0.04 Chlorhexidine (sponge) *$0.35 Syringe 2ml 2 bodies	$47254 per patient

					*$0.35 Syringe 2ml 2 bodies *$0.04 Non-sterile latex glove *$8 Dish culture						*$0.04 Non-sterile latex glove *$8 Dish culture	
Prabhu, 2017[22] (CTM versus PT) [22]	*$659 per day	*$549 per day	NS	$1161 Total cost per patient	NS	$4340 per patient considering hospitalisation and drugs costs	*$659 per day	*$549 per day	NS	$275 Total cost per patient	NS	$3656 per patient considering hospitalisation and drugs costs
Vlachaki, 2021[30] **(**Vaborem (meropenem-vaborbactam) vs. best available treatment)	$2748 per unit	$525 per unit	NS	$ 4222	$96 Adverse events $2793 Clinical failure $143 Nephrotoxicity $61 renal replacement therapy (in hospital) $49 renal replacement therapy $170 Chronic renal replacement therapy	$66338 Total cost for long-term	$2748 per unit	$525 per unit	NS	$1202	$816 Adverse events $5043 Clinical failure $1253 Nephrotoxicity $492 renal replacement therapy (in hospital) $330 renal replacement therapy $1149 Chronic renal replacement therapy	$58656 Total cost for long-term
Yang, 2022[34]	*$4472 per day	*$2618 per day	NS	$12833 Total cost:	$4550 Adverse events	102622	*$4472 per day	*$2618 per day	NS	$2620 Total cost	$16145 Adverse events $95097 Hospital recourse	$114156

(IMI/REL versus CSM+IMI) [34]					$84813 Hospital recourse: $92,153 $426 Long-term monitoring						$294 Long-term monitoring	
I. Pharmaceutical interventions (H): Patients with MRSA tackling interventions with BSI Daptomycin vs. linezolid 4-weeks treatment												
Article	**ICU ward**	**General ward**	**Tests**	**Drugs**	**Additional**	**Total**	**ICU ward**	**General ward**	**Tests**	**Drugs**	**Additional**	**Total**
	Intervention 1 Costs ($)						Intervention 2 Costs ($)					
Vu, 2021[31] Daptomycin vs. linezolid 4-weeks treatment.	NS	$3576	NS	$89 Daptomycin per day	$0.4 Monitoring per Daptomycin: 1Creatinine phosphokinase test per week, per day	$33918	NS	$3576	NS	$35 (iv) per day $3 (oral) per day	NS	$33004
Vu, 2021[31] (Linezolid vs. vancomycin 4-weeks treatment)	NS	$3576	NS	$35 (iv) per day $3 (oral) per day	NS	$33004	NS	$3576	NS	$3 per day	$2 Monitoring per Vancomycin: 1 trough every 3 day, per day	$34414
Vu, 2021[31] (Linezolid vs. ceftaroline/daptomycin 4-weeks treatment)	NS	$3576	NS	$35 (iv) per day $3 (oral) per day	NS	$33004	NS	$3576	NS	$367 Ceftaroline per day $89 Daptomycin per day	$0.4 Monitoring per Daptomycin: 1Creatinine photsphokinese test per week, per day	$33918
I. Pharmaceutical interventions (I): Patients with MRSA tackling interventions Trimethoprim-sulfamethoxazole + rifampicin vs. linezolid												
Trimethoprim-sulfamethoxazole+ rifampicin cost ($)							**Linezolid cost ($)**					
Article	**ICU ward**	**General ward**	**Tests**	**Drugs**	**Additional**	**Total**	**ICU ward**	**General ward**	**Tests**	**Drugs**	**Additional**	**Total**
Von Dach, 2017[32]	NS	NS	NS	$6 (iv) trimethoprim-sulfamethoxazole	$23 adverse drug reaction $2 IV material	$165	NS	NS	NS	$104 (iv) $106 (oral)	$11 adverse drug reaction $2 IV material	$2865

					$1 (iv) trimethoprim-sulfamethoxazole $42 (iv) rifampicin $4 (oral) rifampicin		

Notes: ICU, intensive care unit; tests: included diagnostic tests during inpatient stay; drugs: included drug acquisition cost only; additional: additional costs including monitoring costs, drug administration costs, isolation costs; NS, not stated, i.e., the study did not explicitly state this data. AEs, Acute encephalitis syndrome. CI, Confidence intervals. SD, Standard deviation. LOS, Length of hospital stay. Iv, Intravenous. GP, General practitioner. Where standard deviation or confidence intervals were reported, these have been included. Pd, der diem. Costs were calculated in 2022 USDs. All costs were inflated using the following website (http://eppi.ioe.ac.uk/costconversion/default.aspx). Drug acquisition costs were either found from nationally representative wholesale values or from hospital purchasing departments. Additional costs, whenever reported, ranged from isolation costs for intensive care unit (ICU) wards, monitoring and drug administration and diagnostic costs, as part of moving from empirical therapy to targeted antibiotics. *Generic values used for wards or ICU beds, ventilator, and tests, regardless therapy, or treatment.

Table SM9. Unit costs per study for non-pharmaceutical interventions (in 2022 USDs)

Article	Unit Costs				Total costs
	Staff	Hospital	Test/intervention	Additional costs	
Brown, 2010[36]	Performing the test and specimen collection $32	NS	PCR test USA $79 PCR test UE $89 Total cost PCR. USA $29859 Total cost PCR. UE $22999	The weighted mean treatment. US $41199 The weighted mean treatment. EU $60366	NS
Cho, 2019[37]	Physicians visit $16	Endoscopy without sedation: $67 Endoscopy with sedation: $165	*Helicobacter pylori* diagnosis screening for rapid urease test (RUT): $10 *Helicobacter pylori* diagnosis screening for DPO-PCR testing: $69 *Helicobacter pylori* diagnosis screening biopsy: $9 *Helicobacter pylori* diagnosis screening endoscopy forceps: $21	Urea breath test: $32	Clarithromycin-based triple therapy first -line treatment, per patient: $59820 Clarithromycin-based triple therapy second-line treatment, per patient: $62412 Tailored therapy using DPO-PCR, first-line therapy, per patient: $37468 Tailored therapy using DPO-PCR, second-line therapy, per patient: $37791
Dymond, 2020[38]	NS	NS	Genome sequenced, per unit: $108 Total genome sequences WGS+CP: $77183 Screening positive, per unit: $9 Screening negative, per unit: $5	Symptomatic MRSA, per case: $18617 Asymptomatic MRSA, per case, per case: $418 MRSA-related treatment WGS, annual hospitalized cohort: $2132431 Admission screening cost WGS+CP, annual hospitalized cohort: $296419. Outbreak investigation screening WGS+CP, annual hospitalized cohort: $42237	Total cost WSP+CP, annual hospitalized cohort: $2545423

Article	Unit Costs				Total costs
	Staff	Hospital	Test/intervention	Additional costs	
Gidengil, 2015[39]	NS	NS	Active surveillance cultures test: $15 Contact precautions per day: $146 Chlorhexidine gluconate bath per day: $13 Decolonization (chlorhexidine gluconate + mupirocin) per day: $27	Clinical sampling WGS+CP, annual hospitalized cohort: $554 NS	Active surveillance cultures testing plus selective decolonization, per 10000 patients (millions): $6 Active surveillance cultures testing alone, per 10000 patients (millions): $8 Universal contact precautions alone, per 10000 patients (millions): $10
Ho, 2016[40]	ICU care, per day $3362	NS	PCR : $29	Adequate therapy for CRE infection: $228 Inadequate therapy for CRE infection: $56	Active surveillance CRE-associated, cost per patient: $1436
Hubben, 2011[41]	Take swab by nurse (5 min): $4 Clinical risk assessment by nurse (5 min): $4 PCR test cost lab. Technician time, per sample: $1 Chromogenic clinical lab. technician time, per sample: $7 Contact precaution additional physician time (10 min), per day: $18		PCR- test cost, per sample: $31 Chromogenic screening, per sample: $5	Contact precautions material, per day: $16 Clearing of room (30 min): $62	The investment costs of ‘Selective Chromogenic’ in a high prevalence setting (m): 11 The investment costs of ‘Selective Chromogenic’ in a medium prevalence setting (m): $8 The investment costs of ‘Universal PCR’ in a high prevalence setting (m): 21 The investment costs of ‘Universal PCR’ in a medium prevalence setting (m): $19

Article	Unit Costs				Total costs
	Staff	Hospital	Test/intervention	Additional costs	
Jayaraman, 2016[42]	Total cost nursing, General surgery ICU, per 6 weeks: $ 116813 Staffing Surge pods, per 6 weeks: $2126 Total cost nursing, General surgery ICU, per 1 week:$19469 Staffing Surge pods, per 1 week: $2126	NS	NS	Overall excess costs, per 6 weeks: $41790 Overall excess costs, per 6 weeks $195250 Total Supply renewal, per 6 weeks: $20042 Total Supply renewal, per 1 week: $3218	Model program per year: $83581
Kang, 2012[43]	Registered Nurse, per hour: $40 Physician, per hour: $105	NS	Rapid PCR test: $63	Contact precaution: gown, per unit: $1 Contact precaution: pair of gloves: $0.1	Universal screening strategy: $10248049 Target screening strategy: $8138164 None screening strategy: $8494454
Lapointe-Shaw, 2017[44]	NS	NS	Screening (PCR): $37 Screening (swab and conventional culture plating): $13	Isolation, per day: $40 Attributable cost of pneumonia: $23912 Attributable cost of bloodstream infection: $18400 Attributable cost of urinary tract infection: $3432	NS
Lee, 2005[45]	Physician 'wages, per hour: $270 Healthcare workers' wages, per hour: $38	Hospitalisation, per day: $1610	Screening, per patient admitted-with current screening practice: $3. Screening, per patient admitted-with current screening plus those with a history of renal disease: $3	Isolation cart: $273 Laboratory, per test: $8 Extra laboratory per positive results: $ 11	Total cost per patient admitted with current screening practice: $6816 Total cost per patient with current screening plus those with a history of renal disease: $7770

Article	Unit Costs				Total costs
	Staff	Hospital	Test/intervention	Additional costs	
Lee, 2009[46]	NS	NS	Screening per patient admitted with current screening plus those with a hospitalisation in the previous 2-years: $4. Surveillance: $12 Decolonization: $131	Wound infection (Hospitalization): $5901 Graft infection (Hospitalization): $16327 Amputation (hospitalization): $15022 Infected stump (hospitalization): $9814 Line infection (hospitalization): $30972 Urinary tract infection (hospitalization): $636 Pneumonia (hospitalization): $16439	Total cost per patient admitted with current screening plus those with a hospitalisation in the previous 2-years l: $6096 NS
Lee, 2010[47]	NS	Hospitalisation, per person (range); $5335-$30717	Universal MRSA Surveillance testing (culture): $13	Vancomycin; $11 Extra procedures: blood cultures, cardiac surgery, placing patient in contact isolation.(range): $40-$8,835.	Total cost: $7352
Lin, 2021[48]	Staffing cost for implementing contact precautions, per patient/day: $59	The average cost for implementation electronic registry per CRE infection: $32,923	Total cost per active surveillance screening test (cultured-based screening): $9 Total cost screening (cultured-based screening): $12240	Implementation of the electronic registry, per hospital: $10200 IPC bundle per CRE patient: $652	The net cost of interventions: $222360
Luangasanatip, 2018[49]	NS	Paediatric ICU, per ward, per year: $728 Base case, Adult ICU, per ward, per year: $719	NS	Total cost hand hygiene (paediatric ICU), per year: $763 Total cost hand hygiene (adult ICU), per year: $814	Baseline (hand hygiene compliance 10%) in paediatric ICU: $34302013

Article	Unit Costs				Total costs
	Staff	Hospital	Test/intervention	Additional costs	
					Hand hygiene compliance 20%, in pediatric ICU: $34305035 Hand hygiene compliance 40%, in pediatric ICU: $34306617 Hand hygiene compliance 60%, in pediatric ICU: $34307083 Baseline (hand hygiene compliance 10%) in Adult ICU: $24366979 Hand hygiene compliance 20%, in Adult ICU: $24371521 Hand hygiene compliance 40%, in Adult ICU: $24373669 Hand hygiene compliance 60%, in Adult ICU: $24374285
Mac, 2019[50]	Nurse time, per test: $6	Private room, daily: $264	Rectal swab screen: $3 Culture, positive test: $19 Culture, negative test: $8	Personal protective equipment, per room visit: $2 Antibiotics, bacteraemia, per day: $477 Antibiotics, other infections, per day: $33	NS
Murthy, 2010[51]	NS	Cost per surgical bed-day during the study period: $265	Decolonization treatment, mupirocin 2%: $3 PCR screening: $7 Standard chromogenic agar culture	Cost of standard chromogenic agar culture : $7	No MRSA screening: $1653 Universal rapid PCR screening: $1676
Nelson, 2010[52]	Total cost of extra nurse and physician time attributable to isolation: $105	NS	Screening: $62 Decolonization: $37	Isolation: $594 Chlorhexidine showers: $6	NS

Article	Unit Costs				Total costs
	Staff	Hospital	Test/intervention	Additional costs	
	Physician visit: $93			MRSA infection: $24800 pair of gloves: $9 gown: $1	
Nelson, 2016[53]	NS	NS	NS	NS	Straight line assumption, Total (Overall costs): $88053741 Downward trend assumption Total (Overall costs): $59310260
Nelson, 2021[54]	Workload for nurses, per day: $71 Workload for physicians, per day: $9 workload for other hospital staff, per day: $18 MRSA Prevention Coordinator, per year: $ 28727 Laboratory technician, per year: $ 75179	NS	Screening test, per patient: $29 The total cost of screening on admission (millions): $146	Isolation materials including gowns, gloves, surgical masks, goggles, and isolation laundry double bags, per day: $47 Cleaning materials, per day: $6 educational materials first year: $ 6448 educational materials each subsequent year: $ 1247	NS
Penno, 2015[55]	Laboratory technician performing a human immunodeficiency virus, per hour: $7 Clinical assessment set (10 min), per case: $1	NS	Total Negative blood culture (reagent and supplies, indirect cost, equipment), per test: $14 Total Positive blood culture (reagent and supplies, indirect cost, equipment), per test: $88	Additional cost, per patient: $31	Total cost generic antimicrobials, per case: $16 Total cost evidence-based antimicrobials, per case: $32
Puzniak, 2004[56]	Nursing time to don and doff gowns, per day: $63	NS	Vancomycin-resistant enterococci-negative test, per unit: $17	Gown, per day: $106 Gloves, per day: $10 Hand hygiene, per day: $14	Total cost of policies. Gown period, for patient in ICU: $380312

Article	Unit Costs				Total costs
	Staff	Hospital	Test/intervention	Additional costs	
			Vancomycin-resistant enterococci positive test, per unit: $34		Total cost of policies. Annualized Gown period, for patient in ICU: $ 253541 Total cost of policies. Non gown period, for patient in ICU: $149208
Robotham, 2011[57]	NS	NS	Screening positive result: $16 Screening negative result: $10	Swabbing cost: $8 Contact precaution, general hospital: $30 Decolonisation, general hospital: $103	No screening, per admission: $23326
Robotham, 2016[58]	NS	Hospitalisation Bed (ICU and general ward), per day: $581	Screening positive result: $13 Screening negative result: $7	Swabbing cost: $6 Contact precaution, general hospital: $41. Treatment, 14 days: $925	No screening, per admission: $4552 High risk specialties, per admission: $4618 Checklist activated, per admission: $4686 High risk specialities +checklist activated, per admission: $4719 All admissions: $4807 All admissions + pre-emptive isolation: $4812
Voermans, 2019[59]	NS	Hospitalisation general ward, per day: $1383 Hospitalisation ICU, per day: $2061	PCT test: $102 CDI test: $99	Isolation, per day: $54 Mechanical ventilation, per day: $1143 Antibiotic, per day: $184 Blood culture: $47	NS

Article	Unit Costs				Total costs
	Staff	Hospital	Test/intervention	Additional costs	
You, 2012[60]	NS	Neonatal intensive care unit care, per day: $38	Polymerase chain reaction: $30	NS	Active surveillance plus decolonization in Neonatal Intensive Care Unit: $56280 Active surveillance alone in Neonatal Intensive Care Unit: $57157
You, 2018[61]	NS	ICU-acquired infection: $57 ICU care, per day: $3244	Polymerase chain reaction test: $30	Oral gentamicin and colistin, per day: $109 Empirical treatment for CRE infection, per day:$233	NS
Zboromyrska, 2016[62]	Technical staff (20 min per vial): $12 Microbiologist (10 min per vial): $12 Technical staff (15 min per sample): $9 Microbiologist (10 min per sample): $12		GeneXpert (per sample): $115	Broad-spectrum antibiotic, per day: $119 Narrow-spectrum antibiotic, per day: $84 Central venous catheter (average): $39 blood culture, per vial: $26 PET: $1202 Abdominal ultrasound: $189	GeneXpert and blood culture, per patient: $707

Notes: Costs were calculated in 2022 USDs. NS, Not stated. ARO, Antibiotic-resistant organism. ASTs, Antimicrobial Stewardship Teams. ICU= Intensive care unit. BSI, bloodstream infection. CDI, Clostridium difficile infections. CRE, carbapenem-resistant Enterobacteriaceae. CP, Current practice. DPO, Dual priming oligonucleotide. H. pylori, *Helicobacter pylori*. IPC, infection prevention and control. MRSA, methicillin-resistant Staphylococcus aureus. PCR, polymerase chain reaction. PCT, Procalcitonin. RUT, rapid urease test. UE, Union European. US, United States. WGS, whole-genome sequencing. US, United States. EU, European Union. MRSA= Methicillin-resistant Staphylococcus aureus.

Table SM10: Quality appraisal using Drummond's checklist.

First author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Score	Interpretation compared to studies' average score
I. Pharmaceutical interventions (N= 32 studies)												
Bianchini[3]	1	0	1	0	1	1	1	1	1	1	**8**	Average
Bolaños-Diaz[4]	1	1	1	1	0	1	1	1	1	1	**9**	Above average
Bounthavong[5]	1	1	1	1	0	1	0	1	1	1	**8**	Average
Bounthavong[6]	1	1	1	1	1	0	0	1	1	1	**8**	Average
Cara[7]	1	1	0	1	1	0	0	1	1	0	**6**	Below average
Collins[8]	1	1	1	1	1	1	1	1	1	1	**10**	Above average
De Cock[9]	1	1	0	0	1	1	0	1	1	1	**7**	Below average
De Cock[10]	1	1	1	0	1	0	0	1	1	1	**7**	Below average
Goudarzi[11]	1	1	1	0	1	1	1	1	1	1	**9**	Above average
Gutierrez[12]	1	1	1	1	0	1	1	1	1	0	**8**	Average
Kong[13]	1	1	1	1	1	1	1	1	1	1	**10**	Above average
Laohavaleeson[14]	1	1	1	1	1	1	0	1	1	1	**9**	Above average
Lin[15]	1	1	1	1	0	0	0	1	1	1	**7**	Below average
McKinnon[16]	1	1	1	1	1	1	0	1	0	1	**8**	Average
Mennini[17]	1	1	1	1	0	1	1	1	1	1	**9**	Above average
Mullins[18]	1	1	1	1	0	0	0	1	0	1	**6**	Below average
Niederman[19]	1	1	0	0	1	1	0	1	1	1	**7**	Below average
Patel[20]	1	1	1	1	1	1	0	1	1	0	**8**	Average
Patel[21]	1	1	1	1	1	1	0	1	1	1	**9**	Above average
Prabhu[22]	1	1	1	0	1	1	0	1	1	1	**8**	Average
Rubio-Terres[23]	1	1	1	1	1	1	1	1	1	0	**9**	Above average
Salas[24]	1	1	1	1	0	0	0	1	1	1	**7**	Below average
Schurmann[25]	1	1	1	1	0	1	0	1	1	1	**8**	Average
Simon[26]	1	1	1	1	1	1	1	1	1	1	**10**	Above average
Tan[27]	1	1	1	0	0	0	0	1	1	1	**6**	Below average
Varon[28]	1	1	1	1	1	1	0	1	1	1	**9**	Above average
Varon-Vega[29]	1	1	1	0	0	1	0	1	1	1	**7**	Below average
Vlachaki[30]	1	1	1	1	1	1	1	1	1	1	**10**	Above average
Vu[31]	1	1	1	1	1	1	0	1	1	1	**9**	Above average
Von Dach[32]	1	1	1	1	1	1	0	1	1	1	**9**	Above average
Wan[33]	1	1	1	1	1	0	0	1	1	1	**9**	Above average
Yang[34, 35]	1	1	1	1	1	1	1	1	1	0	**9**	Above average
II. Non-pharmaceutical interventions (N= 27 studies)												
Brown[36]	1	1	1	0	0	1	1	1	1	1	**8**	Average
Cho[37]	1	1	1	1	1	0	0	1	0	0	**6**	Below average
Dymond[38]	1	0	1	0	1	0	0	1	1	1	**6**	Below average
Gidengil[39]	1	1	1	1	1	1	1	1	1	1	**10**	Above average
Ho[40]	1	1	1	1	1	1	1	1	1	1	**10**	Above average
Hubben[41]	1	1	1	1	1	0	1	1	1	1	**9**	Above average
Jayaraman[42]	1	1	1	1	0	1	0	1	1	1	**8**	Average
Kang[43]	1	1	1	1	1	1	0	1	1	1	**9**	Above average
Lapointe-Shaw[44]	1	1	1	1	0	1	1	1	1	0	**8**	Average
Lee[45]	1	0	1	0	1	0	0	1	1	1	**6**	Below average
Lee[46]	1	1	1	0	0	1	0	1	1	1	**6**	Below average
Lee[47]	1	1	1	1	0	1	1	1	1	0	**8**	Average
Lin[48]	1	1	1	0	1	0	0	1	1	1	**7**	Below average
Luangasanatip[49]	1	1	1	1	1	1	1	1	1	1	**10**	Above average

Mac[50]	1	1	1	1	1	0	1	1	1	1	**9**	Above average
Murthy[51]	1	1	1	1	0	0	0	1	1	1	**7**	Below average
Nelson[52]	1	1	1	0	1	0	0	1	1	1	**7**	Below average
Nelson[53]	1	1	1	1	1	0	1	1	1	1	**9**	Above average
Nelson[54]	1	1	1	1	1	1	1	1	1	1	**10**	Above average
Penno[55]	1	0	1	1	0	1	0	1	1	1	**9**	Above average
Puzniak[56]	1	1	1	1	0	0	0	1	1	1	**7**	Below average
Robotham[57]	1	1	1	1	0	1	0	1	1	1	**8**	Average
Robotham[58]	1	1	1	1	1	1	0	1	1	1	**9**	Above average
Voermans[59]	1	1	1	0	1	0	0	1	1	1	**7**	Below average
You[60]	1	1	1	0	0	0	0	1	1	1	**6**	Below average
You[61]	1	1	1	1	0	1	1	1	1	1	**9**	Above average
Zboromyrska[62]	1	1	1	0	0	1	1	1	1	1	**9**	Above average
Average score among all studies					8.1							
Percentage from the total	100	93	95	71	63	66	39	100	95	86		

Notes: See Table SM5 for the full questions detailed. Q stands for question item from Drummond's checklist.[2, 64]

Table SM11: Prisma Checklist[65]

Section and Topic	Item #	Checklist item	Location where the item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title, first page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract, first page
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction, last paragraph
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods, third paragraph
Information sources	6	Specify all databases, registers, websites, organisations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods, third paragraph
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary material, Table SM2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and, if applicable, details of automation tools used in the process.	Methods, paragraphs 3 and 4.
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and, if applicable, details of automation tools used in the process.	Methods, paragraph 5.
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Methods, paragraph 5.
	10b	List and define all other variables for which	Methods, paragraph 5.

Section and Topic	Item #	Checklist item	Location where the item is reported
		data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess the risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Methods, paragraph 6.
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in synthesizing or presenting results.	Methods, paragraph 5.
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Methods, paragraph 4.
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Methods, paragraph 5.
	13c	Describe any methods used to tabulate or visually display the results of individual studies and syntheses.	Methods, paragraph 5.
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Methods, paragraph 5.
	13e	Describe any methods to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	Methods, paragraph 5.
	13f	Describe any sensitivity analyses conducted to assess the robustness of the synthesized results.	Methods, paragraph 5.
Reporting bias assessment	14	Describe any methods used to assess bias risk due to missing synthesis results (arising from reporting biases).	Methods, paragraph 6.
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Methods, paragraph 6.
RESULTS			
Study selection	16a	Describe the search and selection process	Results, first paragraph

Section and Topic	Item #	Checklist item	Location where the item is reported
		results, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria but which were excluded, and explain why they were excluded.	Results, first paragraph, and PRISMA chart
Study characteristics	17	Cite each included study and present its characteristics.	Supplementary Material
Risk of Bias in studies	18	Present assessments of risk of bias for each included study.	Supplementary Material and the last paragraph of the Results section
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and it's precision (e.g., confidence/credible interval), ideally using structured tables or plots.	Results
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Last paragraph of the Results section
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	n/a
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Supplementary material
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	n/a
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Last paragraph of the Results section
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	n/a
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion section
	23b	Discuss any limitations of the evidence included in the review.	Discussion section
	23c	Discuss any limitations of the review processes used.	Discussion section

Section and Topic	Item #	Checklist item	Location where the item is reported
	23d	Discuss the implications of the results for practice, policy, and future research.	Discussion section
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including the register name and registration number, or state that the review was not registered.	Methods section, Prospero registration
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Prospero protocol prepared
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	n/a
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	n/a
Competing interests	26	Declare any competing interests of review authors.	n/a
Availability of data, code, and other materials	27	The report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Data are provided in Excel (https://bit.ly/SR_amrCEingredients).

Notes: n/a= not applicable**.**

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