

## ARTICLE

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# Efficacy and safety of vancomycin compared with those of alternative treatments for methicillin-resistant *Staphylococcus aureus* infections: An umbrella review

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## Abstract

**Objective:** To summarize the evidence on the efficacy and safety of vancomycin compared with those of alternative treatments in adult patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infection.

**Methods:** PubMed, Embase, and Web of Science were searched up to December 15, 2023, for systematic reviews and meta-analyses comparing vancomycin with alternative MRSA treatments. Primary outcomes included clinical cure and microbiological eradication rates. Organ-specific safety outcomes were assessed. Summary estimates were recalculated using a random-effects model. Evidence was graded using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool. This study was registered in PROSPERO (CRD42022340359).

**Results:** This umbrella review included 19 studies and 71 meta-analyses (46 efficacy and 25 safety) comparing vancomycin with 10 alternative treatments across different MRSA infection types and populations. GRADE assessment showed that 29.58% of the meta-analyses were of high quality. Linezolid and daptomycin showed higher efficacy in MRSA-induced skin and soft tissue infections and pneumonia (moderate evidence quality) and bacteremia (very low evidence quality), respectively, compared with that of vancomycin. Cephalosporins had a higher risk of nausea, whereas linezolid had a

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higher risk of nausea, diarrhea, and thrombocytopenia than that of vancomycin. Vancomycin posed a higher risk of rash, pruritus, red man syndrome, and nephrotoxicity than that of alternatives.

**Conclusions:** The quality of evidence supporting the higher efficacy of alternative treatment over vancomycin for MRSA infection was not high. Given varying safety profiles and advancements in therapeutic monitoring, careful consideration of patient-specific factors and pharmacokinetics is crucial when selecting treatment alternatives to vancomycin.

#### KEYWORDS

meta-analysis, MRSA, treatment outcome, umbrella review, vancomycin

## 1 | INTRODUCTION

*Staphylococcus aureus* (*S. aureus*), a Gram-positive bacterium, is a versatile human pathogen that causes various infections ranging from cutaneous infections to pneumonia and bacteremia.<sup>1</sup> Initially, beta-lactamase antibiotics, such as penicillin and methicillin, were effective against *S. aureus*; however, the emergence of methicillin-resistant *S. aureus* (MRSA) in the 1960s posed a significant public health concern owing to the widespread multidrug resistance of MRSA.<sup>2</sup> Several antibiotics have been used to treat MRSA-related infections.

Vancomycin, which inhibits cell-wall synthesis in Gram-positive bacteria, is commonly used to treat MRSA infections. Furthermore, current guidelines recommend vancomycin as a first-line treatment for MRSA,<sup>3</sup> despite concerns regarding its efficacy, resistance, and minimum inhibitory concentration (MIC) creep.<sup>4</sup> Additionally, antimicrobial stewardship programs help monitor and ensure appropriate dosing of vancomycin.<sup>5</sup> Although the widespread use of vancomycin has resulted in a decline in MRSA prevalence since the early 2010s,<sup>6</sup> MRSA infections continue to pose a substantial global health concern,<sup>7</sup> necessitating the development of alternative anti-MRSA antibiotics for treatment selection.

The continuous search for anti-MRSA antibiotics with improved efficacy and safety compared with those of vancomycin, has resulted in the emergence of multiple alternatives, including linezolid, daptomycin, novel lipoglycopeptides, and cephalosporins.<sup>6</sup> Although several systematic reviews and/or meta-analyses (SR-MA) have compared the efficacy and safety of vancomycin with these alternatives, most have focused on newer antibiotics, providing only partial insights into the comparative efficacy and safety of vancomycin.<sup>8,9</sup> Additionally, studies have frequently yielded conflicting results,<sup>10,11</sup> requiring further reassurance of evidence. Moreover, network meta-analysis may not offer a comprehensive evaluation of evidence owing to variations in population characteristics, study designs, and limited data availability, potentially introducing bias into the findings.<sup>12</sup> Thus, there is a need for a comprehensive assessment that considers infection types and analysis populations while accurately evaluating the strength and quality of evidence.

An umbrella review provides a comprehensive summary of the evidence gathered from existing SR-MA.<sup>13</sup> In this study, we conducted an umbrella review to comprehensively evaluate the efficacy and safety of vancomycin against those of alternative treatments for MRSA infections, while also assessing the quality and certainty of evidence across various outcomes.

## 2 | METHODS

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses,<sup>14</sup> and the PROSPERO registration number was CRD42022340359.

### 2.1 | Eligibility criteria

We included SR-MA with full-text availability in English that directly compared vancomycin with other interventional antibiotics in adults for the treatment of confirmed or suspected MRSA infection. For the network meta-analyses, only studies with outcomes of at least one direct comparison were eligible. Adjunctive therapies, such as antibiotics targeting Gram-negative or anaerobic bacteria (including aztreonam), were permitted. Studies involving vancomycin administered in non-intravenous regimens, for non-treatment purposes (including prophylactic antibiotics), pharmacokinetics studies, or cost-effectiveness analyses, as well as those with mixed comparators, were excluded.

### 2.2 | Search strategy and selection criteria

PubMed, Embase, and Web of Science were initially searched until June 16, 2022, to identify eligible SR-MA and were updated until December 15, 2023. The search strategy is presented in Table S1. After reaching an agreement, the two authors independently screened and selected the studies, and any disagreements were resolved by discussion.

## 2.3 | Data extraction

After reaching a consensus on the extracted items, two authors independently extracted the data. Discrepancies were resolved through discussion with a third reviewer, if required. The extracted data included the following: the name of the first author, publication year, location, review type, number of randomized controlled trials (RCTs), funding, infection type, all analysis populations (intention-to-treat (ITT), clinically evaluable (CE), or microbiologically evaluable (ME)), data on MRSA isolates, intervention and comparator, efficacy outcomes (clinical cure rate and/or microbiological eradication rate) and organ-specific adverse events (such as, hepatic dysfunction, renal dysfunction, headache, rash, pruritus), meta-analysis metric, effect size with 95% confidence intervals (CIs) and heterogeneity.

In cases where multiple meta-analyses existed for the same outcome, infection type, and data analysis population, preference was given to the most recent meta-analysis with the largest number of studies. If the largest study count was not obtained from the latest meta-analysis, a comparison of the list of included studies was conducted, and the meta-analysis with the largest number of studies or largest sample size was retained.

## 2.4 | Disease definition

Skin and soft tissue infections (SSTIs) were defined to include complicated SSTIs, complicated skin and soft structure infections, or acute bacterial skin and skin structure infections, including cellulitis/erysipelas, wound infections, and major cutaneous abscesses. Pneumonia included hospital-acquired pneumonia, nosocomial pneumonia, and ventilator-associated pneumonia, whereas bacteremia was defined as patients with or without endocarditis or septicemia.

## 2.5 | Quality assessment and level of evidence

The methodological quality of the SR-MA was evaluated using the "A MeaSurement Tool to Assess Systematic Reviews (AMSTAR2)" tool.<sup>15</sup> Additionally, the level of evidence for the meta-analyses was determined using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework.<sup>16</sup>

## 2.6 | Statistical analysis

For each meta-analysis obtained from the SR-MA, we recalculated the summary effect size (either risk ratio (RR) or odds ratio (OR), depending on the original analysis) and its 95% CIs using random-effects models. To ensure consistency and offer a broader, less model-dependent estimate of effect size, we applied a general method for these recal-

culations, regardless of whether the original analysis used the Mantel-Haenszel or Inverse Variance methods. When a meta-analysis reported summary effect size as a risk difference, it was transformed into an OR. Statistical significance was set at  $p < 0.05$ . Heterogeneity within studies was calculated using  $I^2$  statistics. Egger's method was used to calculate the publication bias in the study, and a  $p$ -value of less than 0.1 was considered significant for small-study effects. All analyses were conducted using Comprehensive Meta-Analysis (version 3, Biostat Inc., Englewood, NJ, USA).

## 3 | RESULTS

### 3.1 | Study selection

We initially identified 604 studies, of which 18 met the inclusion criteria. In the updated search, 102 articles were identified, and two of them met the inclusion criteria. After removing one duplicate, 19 SR-MA were included in the umbrella review (Figure 1). Table S2 provides a list of articles assessed for eligibility but excluded, along with the reasons for their exclusion.

Vancomycin was compared with 10 different treatment alternatives in the included SR-MA: multiple interventions ( $n = 3/19$ , 15.79%),<sup>12,17,18</sup> cephalosporins ( $n = 2/19$ , 10.53%),<sup>19,20</sup> daptomycin ( $n = 1/19$ , 5.26%),<sup>8</sup> linezolid ( $n = 8/19$ , 42.11%),<sup>10,11,21-26</sup> lipoglycopeptides ( $n = 3/19$ , 15.79%),<sup>9,27,28</sup> teicoplanin ( $n = 1/19$ , 5.26%),<sup>29</sup> and tigecycline ( $n = 1/19$ , 5.26%).<sup>30</sup> Table 1 lists the characteristics of the SR-MA. In total, 71 unique meta-analyses were extracted from the 19 SR-MA: 46 for efficacy outcomes (Table S3) and 25 for safety outcomes (Table S4).

### 3.2 | Quality assessment and level of evidence

The AMSTAR 2 ratings of the SR-MA are presented in Table 2. Overall, the quality rating of the SR-MA was critically low ( $n = 17/19$ , 89.47%). The grading evidence of the 71 meta-analyses is shown in Tables S5 (efficacy outcomes) and S6 (safety outcomes). Among the 71 meta-analyses, 11 of 46 efficacy outcomes and 10 of 25 safety outcomes were graded as high quality.

### 3.3 | Efficacy and safety outcomes

Among the 71 unique meta-analyses, 15 of 46 efficacy outcomes and 15 of 25 safety outcomes indicated significant differences between anti-MRSA treatment and vancomycin. The summary results of the umbrella review for efficacy outcomes among the ITT, CE, and ME populations, with or without MRSA isolate data, are illustrated in Figure 2, whereas those for safety outcomes are shown in Figure 3.

**TABLE 1** General characteristics of 19 systematic reviews and/or meta-analysis included in the umbrella review.

| Author, year                   | Study design | Anti-MRSA interventions    | Infection of interest        | Efficacy outcome                              | RCT/total          | Funding      | GRADE evidence | AMSTAR2 Rating |
|--------------------------------|--------------|----------------------------|------------------------------|-----------------------------------------------|--------------------|--------------|----------------|----------------|
| Bounthavong 2010 <sup>22</sup> | MA           | Linezolid                  | SSTIs                        | Clinical cure & microbiological eradication   | 5/5                | None         | No             | Critical low   |
| Cavalcanti 2010 <sup>29</sup>  | MA           | Teicoplanin                | <i>S. aureus</i>             | Clinical & microbiological cure               | 24/24              | None         | Yes            | Low            |
| Liang 2010 <sup>24</sup>       | MA           | Linezolid                  | SSTIs, pneumonia, bacteremia | Treatment success                             | 9/9                | None         | No             | Critical low   |
| Cai 2011 <sup>30</sup>         | SR & MA      | Tigecycline                | SSTIs                        | Clinical & microbiological treatment success  | 8/8                | Not reported | No             | Critical low   |
| Polyzos 2012 <sup>28</sup>     | SR & MA      | Telavancin                 | SSTIs, pneumonia             | Treatment success & microbiologic eradication | 6/6                | None         | No             | Critical low   |
| Vardakas 2012 <sup>17</sup>    | MA           | Multiple                   | MRSA mixed                   | Treatment success                             | 53/53              | Not reported | No             | Critical low   |
| An 2013 <sup>21</sup>          | MA           | Linezolid                  | SSTIs, pneumonia             | Clinical & microbiological treatment success  | 9/9                | None         | No             | Critical low   |
| Wang 2014 <sup>8</sup>         | MA           | Daptomycin                 | SSTIs                        | Clinical & microbiological success            | 6/6                | None         | No             | Critical low   |
| Wang 2015 <sup>25</sup>        | SR-MA        | Linezolid                  | Nosocomial pneumonia         | Clinical & microbiological success            | 9/9                | Non-industry | No             | Critical low   |
| Yue 2016 <sup>26</sup>         | SR-MA        | Linezolid                  | SSTIs and other              | Clinical & microbiological cure               | 9/9                | Non-industry | No             | Low            |
| Ma 2017 <sup>10</sup>          | MA           | Linezolid                  | HAP                          | Clinical cure & pathogen eradication rate     | 7/7                | Not reported | No             | Critical low   |
| Lan 2019 <sup>20</sup>         | SR-MA        | Ceftaroline                | cSSTIs                       | Clinical cure & microbiological eradication   | 5/5                | None         | No             | Critical low   |
| Zhang 2019 <sup>11</sup>       | SR-MA        | Linezolid                  | Pneumonia                    | Clinical & microbiological success            | 8/15               | Non-industry | No             | Critical low   |
| Kato 2021 <sup>23</sup>        | MA           | Linezolid                  | Pneumonia                    | Clinical cure & microbiological evaluation    | 7/7 <sup>a</sup>   | None         | No             | Critical low   |
| Chen 2021 <sup>19</sup>        | SR-MA        | Ceftaroline & Ceftobiprole | ABSSSI                       | Clinical response                             | 8/8                | None         | No             | Critical low   |
| Feng 2021 <sup>12</sup>        | MA (Network) | Linezolid & daptomycin     | SSTIs                        | Clinical & microbiological success            | 17/17 <sup>b</sup> | Non-industry | No             | Critical low   |
| Jame 2021 <sup>27</sup>        | SR-MA        | Lipoglycopeptides          | SSTIs, pneumonia, bacteremia | Clinical & microbiological success            | 11/11              | None         | No             | Critical low   |
| Hsu 2022 <sup>9</sup>          | SR-MA        | Lipoglycopeptides          | ABSSSI                       | Clinical & microbiological response rate      | 8/8                | None         | No             | Critical low   |

(Continues)

TABLE 1 (Continued)

| Author, year             | Study design | Anti-MRSA interventions              | Infection of interest | Efficacy outcome                | RCT/total | Funding      | GRADE evidence | AMSTAR2 Rating |
|--------------------------|--------------|--------------------------------------|-----------------------|---------------------------------|-----------|--------------|----------------|----------------|
| Zhang 2023 <sup>18</sup> | SR-MA        | Daptomycin, Linezolid, & Teicoplanin | Bacteremia            | Clinical & microbiological cure | 15/24     | Non-industry | No             | Critical low   |

Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; AMSTAR, A Measurement Tool to Assess Systematic Reviews; GRADE, grading of recommendations, assessment, development, and evaluation; HAP, hospital acquired pneumonia; MA, meta-analysis; MRSA, methicillin-resistant *Staphylococcus aureus*; RCT, randomized controlled trial; SR, systematic review; SSTI, skin and soft tissue infection.

<sup>a</sup>Data were selected only for RCTs.

<sup>b</sup>Three RCTs compared linezolid with tedizolid, which were not included in our review.

### 3.3.1 | Cephalosporins (ceftaroline and ceftobiprole) versus vancomycin

Ten meta-analyses comparing the efficacy or safety outcomes of cephalosporins and vancomycin among adult patients infected with SSTIs were available. There was no significant difference in the

clinical cure rates of vancomycin and cephalosporins among adult patients with SSTI (Figure 2 and Table S3).<sup>19,20</sup> Patients treated with cephalosporins for SSTI had higher odds of experiencing nausea (OR = 1.392, 95% CI 1.057-1.834,  $p = 0.019$ , supported by high-quality evidence) and lower odds of rash (OR = 0.583, 95% CI 0.394-0.862,  $p = 0.007$ , supported by high-quality evidence) and

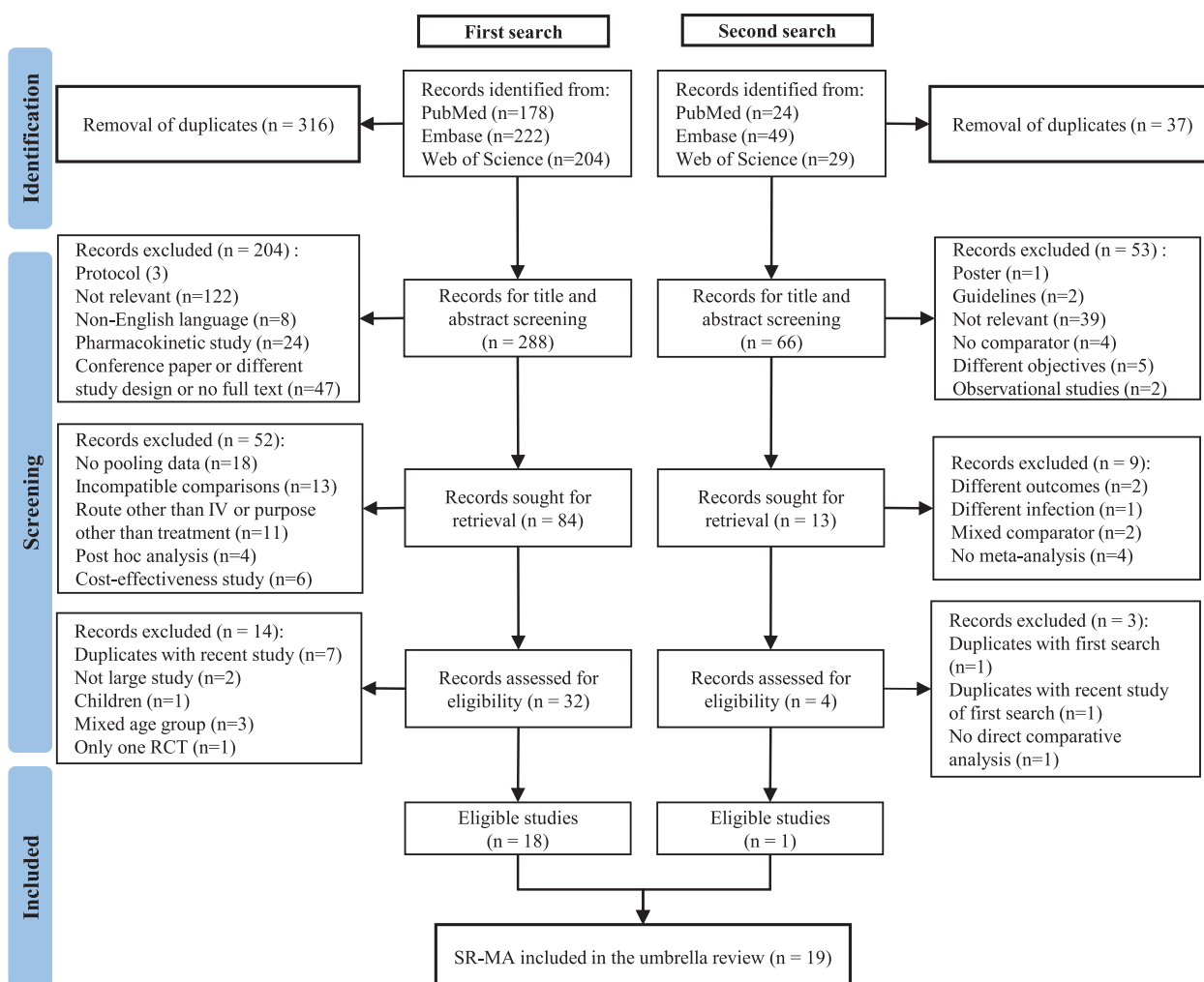


FIGURE 1 PRISMA flowchart.

**TABLE 2** Detailed evaluation of the methodological quality of the included systematic review and/or meta-analysis with AMSTAR2.

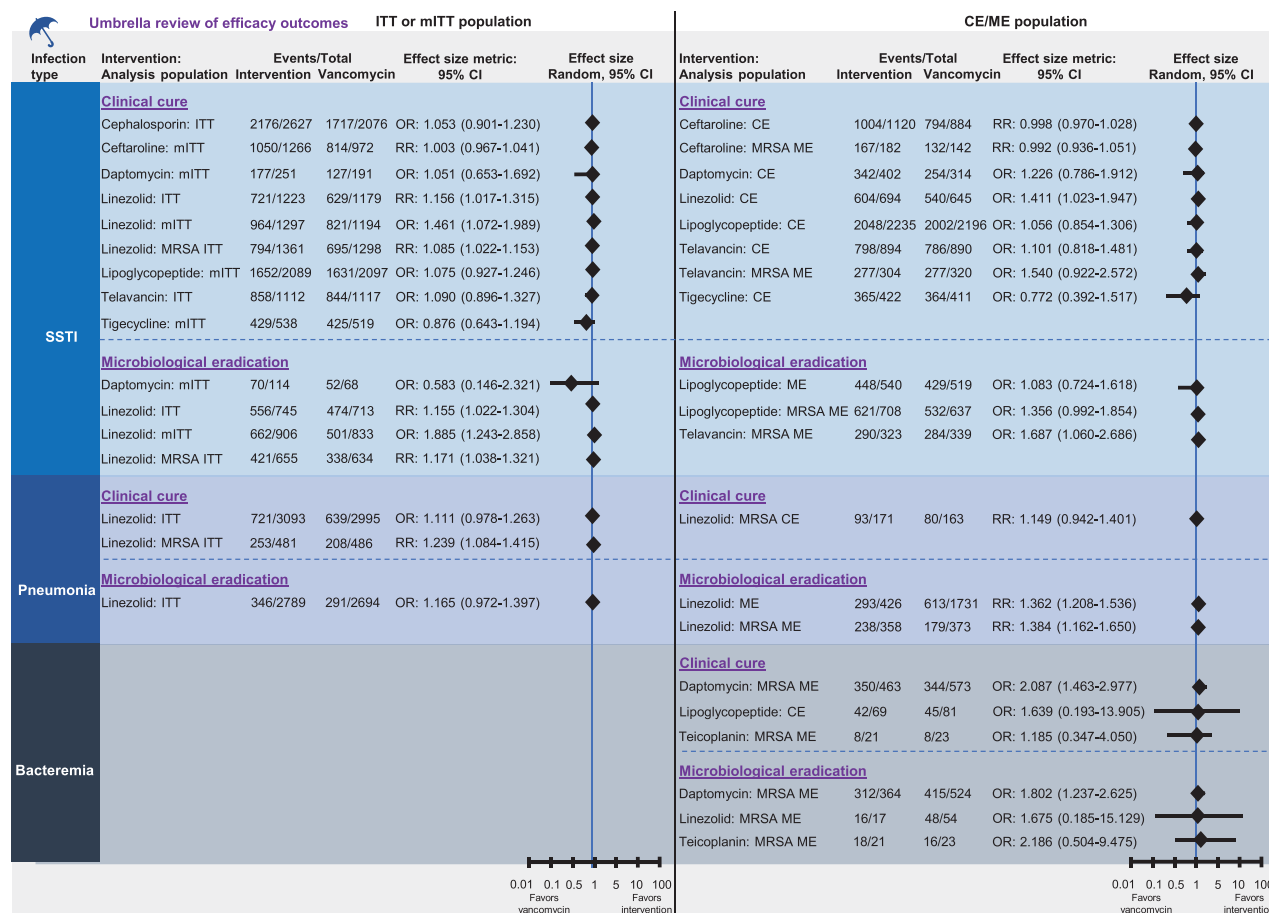
| Author, year                   | Type of review | a | b* | c | d* | e | f | g* | h  | i* | j | k* | l | m* | n | o* | p | AMSTAR2 rating |
|--------------------------------|----------------|---|----|---|----|---|---|----|----|----|---|----|---|----|---|----|---|----------------|
| An 2013 <sup>21</sup>          | MA             | N | N  | Y | PY | Y | Y | N  | PY | Y  | Y | Y  | Y | Y  | N | Y  | Y | Critical low   |
| Bounthavong 2010 <sup>22</sup> | MA             | Y | N  | Y | Y  | N | Y | N  | N  | N  | N | Y  | N | N  | Y | Y  | Y | Critical low   |
| Cai 2011 <sup>30</sup>         | SR & MA        | Y | N  | Y | N  | Y | Y | Y  | PY | PY | Y | Y  | Y | Y  | Y | Y  | Y | Critical low   |
| Cavalcanti 2010 <sup>29</sup>  | MA             | Y | N  | Y | PY | Y | Y | Y  | Y  | PY | N | Y  | N | Y  | Y | Y  | Y | Low            |
| Chen 2021 <sup>19</sup>        | SR & MA        | Y | N  | Y | PY | Y | Y | N  | PY | Y  | N | Y  | N | N  | Y | N  | Y | Critical low   |
| Feng 2021 <sup>12</sup>        | Network MA     | N | N  | Y | PY | Y | Y | N  | PY | Y  | N | Y  | N | N  | Y | Y  | Y | Critical low   |
| Hsu 2022 <sup>9</sup>          | SR & MA        | Y | PY | Y | PY | Y | Y | N  | PY | Y  | N | N  | N | N  | N | N  | Y | Critical low   |
| Kato 2021 <sup>23</sup>        | MA             | Y | N  | Y | N  | N | N | N  | Y  | PY | N | N  | N | N  | Y | Y  | Y | Critical low   |
| Lan 2019 <sup>20</sup>         | SR & MA        | Y | N  | Y | PY | Y | Y | N  | N  | Y  | N | N  | N | N  | N | N  | Y | Critical low   |
| Liang 2010 <sup>24</sup>       | MA             | N | N  | Y | PY | Y | Y | Y  | PY | PY | N | Y  | N | Y  | Y | N  | Y | Critical low   |
| Jame 2021 <sup>27</sup>        | SR & MA        | Y | Y  | Y | PY | Y | Y | N  | PY | Y  | N | N  | N | N  | N | Y  | Y | Critical low   |
| Ma 2017 <sup>10</sup>          | MA             | Y | N  | Y | PY | Y | Y | N  | N  | PY | N | Y  | N | Y  | Y | Y  | N | Critical low   |
| Polyzos 2012 <sup>28</sup>     | SR & MA        | Y | N  | Y | PY | Y | Y | N  | PY | Y  | N | N  | N | N  | N | Y  | Y | Critical low   |
| Vardakas 2012 <sup>17</sup>    | MA             | Y | N  | Y | PY | Y | Y | N  | PY | Y  | N | N  | N | N  | Y | Y  | N | Critical low   |
| Wang 2014 <sup>8</sup>         | MA             | Y | N  | Y | PY | Y | Y | Y  | PY | PY | N | N  | Y | Y  | N | Y  | Y | Critical low   |
| Wang 2015 <sup>25</sup>        | SR & MA        | Y | N  | Y | PY | Y | N | N  | Y  | PY | N | Y  | N | Y  | Y | Y  | Y | Critical low   |
| Yue 2016 <sup>26</sup>         | SR & MA        | Y | N  | Y | Y  | Y | Y | Y  | Y  | Y  | Y | Y  | Y | Y  | Y | Y  | Y | Low            |
| Zhang 2019 <sup>11</sup>       | SR & MA        | Y | N  | Y | PY | Y | Y | N  | Y  | Y  | Y | Y  | Y | N  | Y | Y  | Y | Critical low   |
| Zhang 2023 <sup>18</sup>       | SR & MA        | Y | PY | Y | PY | Y | Y | Y  | PY | Y  | Y | Y  | Y | N  | N | N  | Y | Critical low   |

Abbreviations: Y, yes; PY, denotes partially yes; N, no; AMSTAR, A MeaSurement Tool to Assess Systematic Reviews; SR, systematic review; MA, meta-analysis.

AMSTAR 2 domains:

<sup>a</sup>Did the research questions and inclusion criteria for the review include the components of PICO?<sup>b</sup>Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?<sup>c</sup>Did the review authors explain their selection of the study designs for inclusion in the review?<sup>d</sup>Did the review authors use a comprehensive literature search strategy?<sup>e</sup>Did the review authors perform study selection in duplicate?<sup>f</sup>Did the review authors perform data extraction in duplicate?<sup>g</sup>Did the review authors provide a list of excluded studies and justify the exclusions?<sup>h</sup>Did the review authors describe the included studies in adequate detail?<sup>i</sup>Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?<sup>j</sup>Did the review authors report on the sources of funding for the studies included in the review?<sup>k</sup>If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?<sup>l</sup>If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?<sup>m</sup>Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?<sup>n</sup>Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?<sup>o</sup>If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?<sup>p</sup>Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

\*Critical domains.



**FIGURE 2** Results of the umbrella review of efficacy outcomes. ITT, intention-to-treat; mITT, modified intention-to-treat; ME, microbiologically evaluable; CE, clinically evaluable; MRSA, methicillin-resistant *Staphylococcus aureus*; SSTI, skin and soft tissue infection; CI, confidence interval; OR, odds ratio; RR, risk ratio.

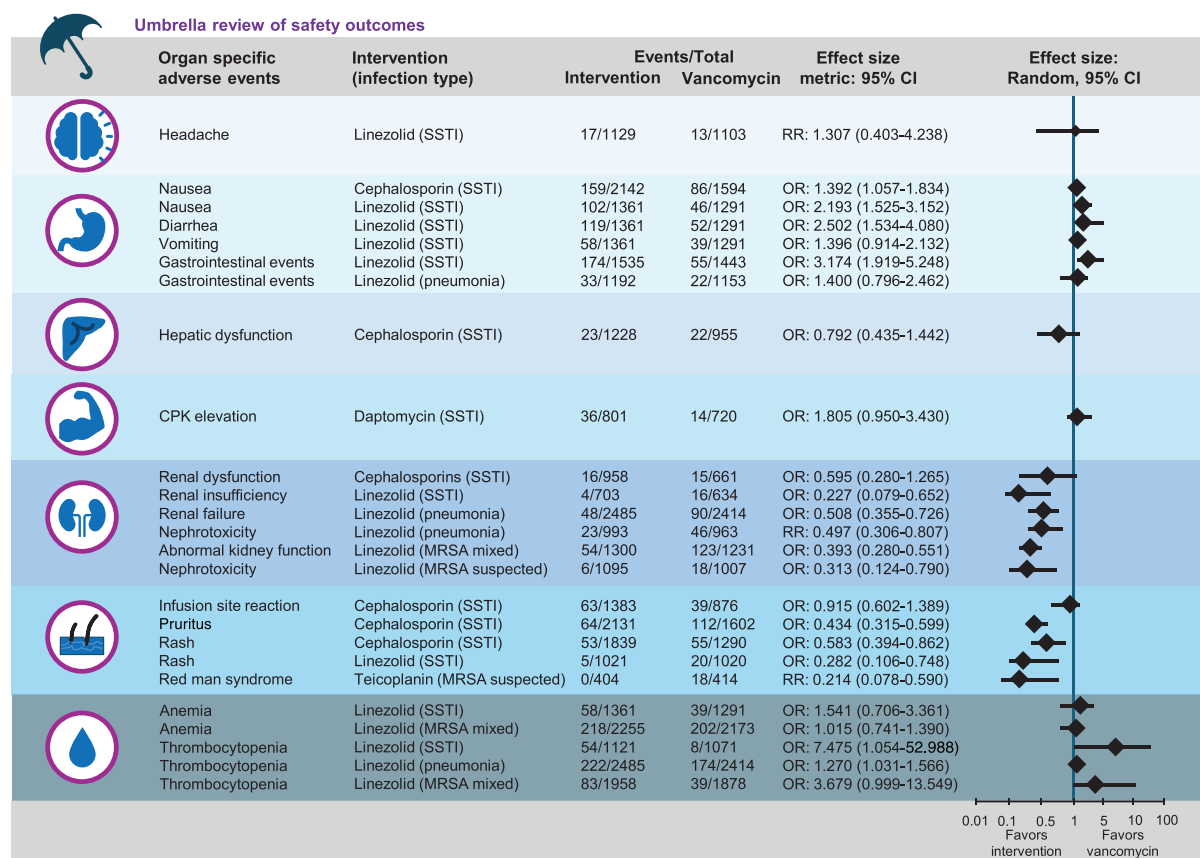
pruritus (OR = 0.434, 95% CI 0.315-0.599,  $p < 0.001$ , supported by high-quality evidence) than those treated with vancomycin (Figure 3 and Table S4).<sup>19</sup>

### 3.3.2 | Daptomycin versus vancomycin

Six meta-analyses were available for adult patients with SSTIs or bacteremia. No significant difference was found between vancomycin and daptomycin in terms of efficacy in adult patients with SSTI (Figure 2 and Table S3).<sup>8,12</sup> However, daptomycin exhibited significantly higher odds of achieving a clinical cure (ME population, OR = 2.087, 95% CI 1.463-2.977,  $p < 0.001$ , supported by very low-quality evidence) and microbiological eradication rate (ME population, OR = 1.802, 95% CI 1.237-2.625,  $p = 0.002$ , supported by very low-quality evidence) than those of vancomycin in patients with MRSA-induced bacteremia (Figure 2 and Table S3).<sup>18</sup> Daptomycin had higher odds of creatinine phosphokinase elevation than those of vancomycin (OR = 1.805, 95% CI 0.950-3.430,  $p = 0.071$ ) (Figure 3 and Table S4).<sup>8</sup>

### 3.3.3 | Linezolid versus vancomycin

A total of 34 meta-analyses compared the efficacy and safety of linezolid and vancomycin. In adult patients infected with MRSA, linezolid demonstrated greater efficacy than that of vancomycin,<sup>21</sup> particularly in cases of SSTIs (clinical cure in the ITT population: RR = 1.085, 95% CI 1.022-1.153,  $p = 0.008$ , supported by moderate-quality evidence; microbiological eradication in the ITT population: RR = 1.171, 95% CI 1.038-1.321,  $p = 0.011$ , supported by moderate-quality evidence)<sup>26</sup> and pneumonia (clinical cure in the ITT population: RR = 1.239, 95% CI 1.084-1.415,  $p = 0.002$ , supported by moderate-quality evidence; microbiological eradication in the ME population: RR = 1.384, 95% CI 1.162-1.650,  $p < 0.001$ , supported by moderate-quality evidence) (Figure 2 and Table S3).<sup>11,23</sup> In patients with SSTIs, linezolid treatment is associated with a lower odds of rash (OR = 0.282, 95% CI 0.106-0.748,  $p = 0.011$ , supported by moderate-quality evidence) and renal insufficiency than that of vancomycin (OR = 0.227, 95% CI 0.079-0.652,  $p = 0.006$ , supported by moderate-quality evidence).<sup>22</sup> However, linezolid-treated patients had higher odds of experiencing gastrointestinal AE (OR = 3.174, 95% CI 1.919-5.248,  $p < 0.001$ ,



**FIGURE 3** Results of the umbrella review of safety outcomes. SSTI, skin and soft tissue infection; MRSA, methicillin-resistant *Staphylococcus aureus*; CPK, creatinine phosphokinase; CI, confidence interval; OR, odds ratio; RR, risk ratio.

supported by moderate-quality evidence),<sup>21</sup> including nausea (OR = 2.193, 95% CI 1.525-3.152,  $p < 0.001$ , supported by moderate-quality evidence) and diarrhea (OR = 2.502, 95% CI 1.534-4.080,  $p < 0.001$ , supported by moderate-quality evidence), and thrombocytopenia (OR = 7.475, 95% CI 1.054-52.988,  $p = 0.044$ ).<sup>22</sup> Similarly, patients with pneumonia treated with linezolid had lower odds of developing renal failure (OR = 0.508, 95% CI 0.355-0.726,  $p < 0.001$ , supported by high-quality evidence)<sup>10</sup> and a lower risk of nephrotoxicity (RR = 0.497, 95% CI 0.306-0.807,  $p = 0.005$ , supported by moderate-quality evidence)<sup>25</sup> but higher odds of experiencing thrombocytopenia than those of patients treated with vancomycin (OR = 1.270, 95% CI 1.031-1.566,  $p = 0.025$ , supported by high-quality evidence).<sup>10</sup> Among MRSA- or Gram-positive-infected adult patients, linezolid was associated with lower odds of abnormal renal function (OR = 0.393, 95% CI 0.280-0.551,  $p < 0.001$ , supported by moderate-quality evidence)<sup>21</sup> or nephrotoxicity than those of vancomycin (OR = 0.313, 95% CI 0.124-0.790,  $p = 0.014$ , supported by moderate-quality evidence) (Figure 3 and Table S4).<sup>24</sup>

### 3.3.4 | Lipoglycopeptides (dalbavancin, oritavancin, and telavancin) versus vancomycin

Twelve meta-analyses were available for adult patients infected with SSTIs, bacteremia, and Gram-positive bacteria. There was no significant

difference in efficacy between lipoglycopeptides and vancomycin (Figure 2 and Table S3)<sup>9,27,28</sup>; however, telavancin exhibited significantly higher odds of achieving microbiological eradication rates than those of vancomycin in treating adult patients (ME population) with confirmed MRSA-induced SSTIs (OR = 1.687, 95% CI 1.060-2.686,  $p = 0.028$ , supported by moderate-quality evidence) (Figure 2 and Table S3).<sup>28</sup> No meta-analyses of organ-specific AEs have been conducted.

### 3.3.5 | Quinupristin/dalfopristin versus vancomycin

Two meta-analyses reported clinical cure rates among adult patients infected with Gram-positive bacteria. No significant difference in efficacy outcomes was observed between quinupristin/dalfopristin and vancomycin in adult patients infected with Gram-positive bacteria (Table S3).<sup>17</sup> No meta-analyses of organ-specific AEs have been conducted.

### 3.3.6 | Teicoplanin versus vancomycin

Four meta-analyses were available for adult patients with bacteremia or *S. aureus* infection. No significant differences were observed between the effects of teicoplanin and vancomycin (Figure 2 and

Table S3).<sup>29</sup> Patients infected with *S. aureus* have lower odds of developing red man syndrome when treated with teicoplanin than when treated with vancomycin (OR = 0.214, 95% CI 0.078-0.590,  $p = 0.003$ , supported by low-quality evidence) (Figure 3 and Table S4).<sup>29</sup>

### 3.3.7 | Tigecycline versus vancomycin

Three meta-analyses were available on the clinical cure rates among adult patients infected with SSTI or MRSA. No significant difference in the clinical cure rate was observed between tigecycline and vancomycin in adult patients with SSTI or MRSA (Figure 2 and Table S3).<sup>30</sup> No meta-analyses of organ-specific AEs have been conducted.

## 4 | DISCUSSION

This umbrella review provides a comprehensive overview of the existing evidence on the current role of vancomycin in MRSA treatment, using 71 unique meta-analyses that compared the efficacy and safety of vancomycin with those of 10 alternative treatments from 19 SR-MA. Our assessment included 71 meta-analyses, 30 of which showed statistically significant results. While a  $p$ -value threshold of  $< 0.05$  is widely used for claiming new evidence in the literature, emerging data frequently show that results based on this criterion typically represent weak evidence.<sup>31</sup> Our umbrella review had similar findings, with 15 efficacy outcomes showing statistical significance, but only one was deemed “high” evidence. Therefore, using the GRADE approach is crucial for assessing the quality of evidence and the strength of recommendations, emphasizing the need to avoid relying solely on statistical significance and  $p$ -values to prevent potential errors in conclusions.<sup>32,33</sup>

Vancomycin is strongly recommended as the first-line treatment for MRSA-induced SSTIs, whereas linezolid and daptomycin are strongly recommended as alternatives.<sup>3</sup> Our umbrella review findings provide moderate-quality evidence that linezolid has a higher clinical cure and microbiological eradication rate than that of vancomycin in the treatment of MRSA-induced SSTIs. No significant difference in efficacy was observed between daptomycin and vancomycin for the treatment of SSTIs. However, the meta-analysis findings were obtained from either ITT MRSA populations<sup>26</sup> or modified ITT populations,<sup>12</sup> necessitating analysis of ME populations confirmed to have MRSA for robust evidence of the efficacy of linezolid and daptomycin in MRSA-induced SSTIs. Additionally, the majority of the RCTs that compared linezolid, daptomycin, and telavancin with vancomycin in the meta-analyses were mostly open-label and industry-funded. Blinding and funding sources in trials could introduce bias into the findings.<sup>34</sup> Therefore, high-quality research is required to identify the most suitable treatment options.

The 2016 Clinical Practice Guidelines of the Infectious Diseases Society of America and the American Thoracic Society strongly recommend the use of either vancomycin or linezolid as the first option

for MRSA-induced pneumonia treatment.<sup>35</sup> This recommendation is based on meta-analyses of RCTs that compared vancomycin and linezolid in patients with suspected or proven MRSA pneumonia and demonstrated similar clinical outcomes for both antibiotics. However, in our umbrella review, a recent meta-analysis conducted in 2021, which included RCTs newer than those referenced in the 2016 guidelines,<sup>23</sup> provided moderate-quality evidence supporting the superiority of linezolid over vancomycin in the treatment of MRSA-induced pneumonia. Consequently, there is a need for robust evidence from recent studies to support the recommendation of the superior efficacy of linezolid in the updated guidelines for the treatment of MRSA-induced pneumonia. Linezolid is also considered an alternative first-line treatment (strongly recommended) for MRSA-induced bacteremia, whereas daptomycin or teicoplanin are weakly recommended as second-line treatments.<sup>3</sup> Consistent with this, in the umbrella review, we found that daptomycin had very low-quality supporting evidence for its higher efficacy over vancomycin in treating MRSA-induced bacteremia. The SR-MA included both RCTs and observational studies in the meta-analysis, lowering the evidence level.<sup>18</sup> However, existing literature provides limited evidence regarding the efficacy of linezolid and teicoplanin relative to that of vancomycin in MRSA-induced bacteremia. Further high-quality studies are required to determine the efficacy and safety of anti-MRSA alternatives to vancomycin for MRSA-induced bacteremia.

Additionally, anti-MRSA treatments exhibited varied safety profiles compared with those of vancomycin, suggesting that treatment selection should be carefully considered based on patient-specific factors and weighted against the benefits of vancomycin. While our findings indicate favorable outcomes for linezolid in MRSA-induced SSTI and pneumonia with moderate-quality supporting evidence, it presents a higher risk of gastrointestinal events, such as diarrhea, nausea, and thrombocytopenia, albeit with a lower risk of other AEs, such as rash, pruritus, red man syndrome, or nephrotoxicity, compared with that of vancomycin. In the case of patients infected with MRSA who suffer from renal insufficiency, vancomycin hypersensitivity, or acquired vancomycin resistance, linezolid may be a preferable option.

Although alternative treatments exist for MRSA infections, vancomycin remains strongly recommended as the first-line treatment for all MRSA infections.<sup>3,35</sup> However, optimizing its administration, particularly through therapeutic drug monitoring, is necessary.<sup>36</sup> Studies show that a higher MIC ( $> 1$  mg/L) is less effective compared to an MIC of  $\leq 1$  mg/L,<sup>37</sup> and monitoring MIC is crucial to maximize clinical efficacy or minimize the risk of nephrotoxicity. The RCTs included in the meta-analysis lacked proper dose monitoring or information on achieving therapeutic drug levels, likely contributing to the lower vancomycin treatment success rates. Additionally, the recent shift in optimizing vancomycin dosing from trough and peak concentrations to population pharmacokinetic modeling, particularly using the area under the concentration–time curve (AUC) as a target index, addresses nephrotoxicity concerns associated with maintaining high trough concentrations.<sup>38</sup> This is further supported by studies demonstrating a reduced risk of nephrotoxicity with AUC-guided dosing.<sup>39</sup> Therefore, the development of user-friendly model-informed precision

dosing tools is crucial for determining the optimal sampling point for AUC estimation<sup>40</sup> and facilitating the widespread implementation of AUC-guided dosing in clinical practice.

Several considerations are crucial for interpreting the results of this study. First, data from the same studies are often used in published SR-MA, resulting in patient data duplication, especially when smaller subsets and larger studies are combined. Moreover, some SR-MA did not include confirmed MRSA cases despite the presence of such cases in the studies, potentially affecting the comprehensiveness of the analysis. Therefore, future meta-analyses should be conducted using RCTs that primarily include MRSA-positive populations. Second, we synthesized evidence from previously published SR-MA, which limited our ability to integrate updated studies or gray literature at the meta-analysis level. Additionally, the lack of RCTs comparing newer antibiotics, such as omadacycline or delafloxacin, with vancomycin has limited the ability to perform direct or indirect meta-analyses of MRSA treatment. Further studies are necessary to compare these drugs with vancomycin because of their clinical importance in treating suspected or confirmed MRSA infections.<sup>3,41</sup> Third, we did not explore community-acquired MRSA or the relation between vancomycin MIC and comparative outcomes, as they were outside the scope of this review. Given the growing concern over community-acquired MRSA infections and MIC creep among healthcare professionals,<sup>7</sup> further umbrella reviews targeting these issues are required. Nonetheless, to the best of our knowledge, this is the first umbrella review to provide a comprehensive assessment of the efficacy and safety of vancomycin and alternative treatments in MRSA management, including an appraisal of the quality of evidence regarding this association.

Our umbrella review findings provide moderate evidence supporting the higher efficacy of linezolid against MRSA infection, particularly SSTI and pneumonia, with very low-quality evidence for the efficacy of daptomycin in MRSA-induced bacteremia. Although alternatives may offer advantages, the varying associated safety profiles necessitate treatment selection based on individual patient-specific factors and pharmacokinetic variability. With the recent implementation of therapeutic monitoring guidelines aimed at optimizing its appropriate use,<sup>36</sup> along with recent advancements in population pharmacokinetic modeling<sup>38</sup> and collaboration with the National Antimicrobial Stewardship Program,<sup>5</sup> clinicians can ensure optimal vancomycin utilization, effectively combating microbial resistance, and prevent the transmission of infections from multidrug-resistant organisms.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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