

# A Systemic Literature Review and Meta-Analysis Reporting the Prevalence and Impact of Methicillin-Resistant *Staphylococcus aureus* Infection in India

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## ABSTRACT:

**AIM AND OBJECTIVE:** This systematic review and meta-analysis was conducted to assess the prevalence, burden and epidemiology of methicillin-resistant *S. aureus* (MRSA). This systemic review was also aimed to highlight the challenges in the diagnosis and management of methicillin-resistant *S. aureus* (MRSA) in India (for all age groups). We also examined the published literature on the available treatment options and the role of prevention in the management of MRSA in India. By summarizing the currently available data, our objectives were to highlight the need for the prevention of MRSA infections and also emphasize the role of vaccination in the prevention of MRSA infections in India.

**METHODOLOGY:** Electronic databases such as PubMed and databases of the National Institute of Science Communication and Information Resources and Indian Council of Medical Research Embase were searched for relevant literature published from 2005/01/01 to 2020/05/13 in English language, according to the predefined inclusion and exclusion criteria. A manual search was also conducted using the key term "MRSA 'or' Methicillin Resistant *Staphylococcus aureus* 'and' India." An independent reviewer extracted data from the studies using a structured Microsoft Excel spreadsheet, and a meta-analysis of proportion for MRSA prevalence with a corresponding 95% confidence interval (CI) for all included individual studies were performed.

**RESULT:** A total of 34 studies involving 16237 patients were included in the final meta-analysis. The pooled proportion of patients with MRSA infection was 26.8% (95% CI: 23.2%-30.7%). The MRSA infection was more prevalent among male patients (60.4%; 95% CI: 53.9%-66.5%) as compared to female patients (39.6%; 95% CI: 33.5%-46.1%), while the prevalence of MRSA was higher among adults (18 years and above; 32%; 95% CI: 5%-80%) in comparison to pediatric patients (0-18 years; 68%; 95% CI: 20%-94.8%). The degree of heterogeneity was found to be significant.

**CONCLUSION:** The prevalence of MRSA in India was relatively high at 27% with a higher proportion observed among men aged >18 years. The high prevalence of MRSA infections in India necessitates the implementation of surveillance and preventive measures to combat the spread of MRSA in both hospital and community settings.

**KEYWORDS:** Methicillin resistant *S. aureus*, India, prevalence

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## Introduction

Antimicrobial resistance is a serious global health concern that limits the prevention and treatment of infections, especially in a hospital setting. Antimicrobial resistance develops by the inactivation of the antibiotic, altered drug access to the target, modification of target, and decreased uptake.<sup>1</sup>

As early as 1942, penicillin-resistant *Staphylococcus aureus* strains were recognized, which further paved way to the development of semisynthetic penicillins, including methicillin.<sup>2</sup> Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most tenacious anti-microbial resistant pathogens reported in a range of infections, including the skin and wound infections, pneumonia, and bloodstream infections.<sup>3,4</sup> The emergence of MRSA through the acquisition of *Staphylococcal* cassette chromosome *mec* (SCC*mec*) was first identified in 1960.<sup>2,5</sup> The SCC*mec* carries the *mecA* gene that encodes the penicillin-binding protein (PBP2a), thereby acquiring

resistance to all  $\beta$ -lactam antibiotics.<sup>5</sup> Newer drug-resistant homologues of the *mecA* gene have been reported in the recent years, including *mecB*, *mecC*, and/or *mecD*.<sup>6</sup>

The antimicrobial resistance patterns differ geographically, and the Asia-Pacific region accounts for one-third of the world's population reporting a steadily increasing incidence of MRSA in healthcare settings since the 1980s.<sup>7</sup> Methicillin-resistant *S. aureus* infection is an emerging infection in the Indian subcontinent with incidence rates of 25% to 50% reported in different parts of the country.<sup>8</sup> According to the multicenter report of the Indian Council of Medical Research (ICMR)—Antimicrobial Resistance Surveillance network presented in 2015, the prevalence of MRSA was reported in the range of 21% to 45% across the centres (Jawaharlal Institute of Postgraduate Medical Education and Research [JIPMER], Puducherry; India Institute of Medical Sciences [AIIMS], New Delhi; Postgraduate Institute of Medical Education and



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Research [PGIMER], Chandigarh and Christian Medical College [CMC], Vellore), with an overall prevalence of 37.3%. This study also reported a high prevalence of resistance against commonly prescribed antimicrobials including ciprofloxacin (95%) and erythromycin (91%).<sup>9</sup>

The increasing trend of good clinical practices in hospitals has brought down the incidence of hospital-acquired MRSA infections; however, there is a steady increase in community-acquired MRSA infections, which poses challenges, particularly in densely populated countries like India. Further, the economic burden associated with the cost of treatment, long-term hospitalization, and the psychological stress considerably impact the healthcare systems across all regions.<sup>10</sup>

Over the past few years, several studies have reported the prevalence of MRSA in different clinical settings within the Indian subcontinent, but the results are inconsistent with limited sample sizes.<sup>8,11–13</sup> Furthermore, few studies from the country suggest an impact of age and gender on MRSA carriage.<sup>14,15</sup> It is imperative to understand the prevalence of risk factors, such as age and gender, on MRSA colonization at the country level to facilitate the implementation of appropriate infection control measures. This systematic review and meta-analysis was conducted to assess the prevalence, burden and epidemiology of methicillin-resistant *S. aureus* (MRSA). This systemic review was also aimed to highlight the challenges in the diagnosis and management of methicillin-resistant *S. aureus* (MRSA) in India (for all age groups). We also examined the published literature on the available treatment options and the role of prevention in the management of MRSA in India. By summarizing the currently available data, our objectives were to highlight the need for the prevention of MRSA infections and also emphasize the role of vaccination in the prevention of MRSA infections in India.

## Methodology

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).

### *Eligibility criteria for studies*

All human studies, published from 2005/01/01 to 2020/05/13 in English language that evaluated Indian patients of all age groups with a confirmed diagnosis of MRSA, were eligible for inclusion. We have also considered studies focusing on the Indian subcontinent, in particular or as one of the study sites.

### *Exclusion criteria for studies*

All studies on MRSA patients that were conducted outside India or/and not conducted in the Indian population were excluded from the analysis. In addition, case studies, review articles, or studies for which full text was not available were excluded.

### *Measurements*

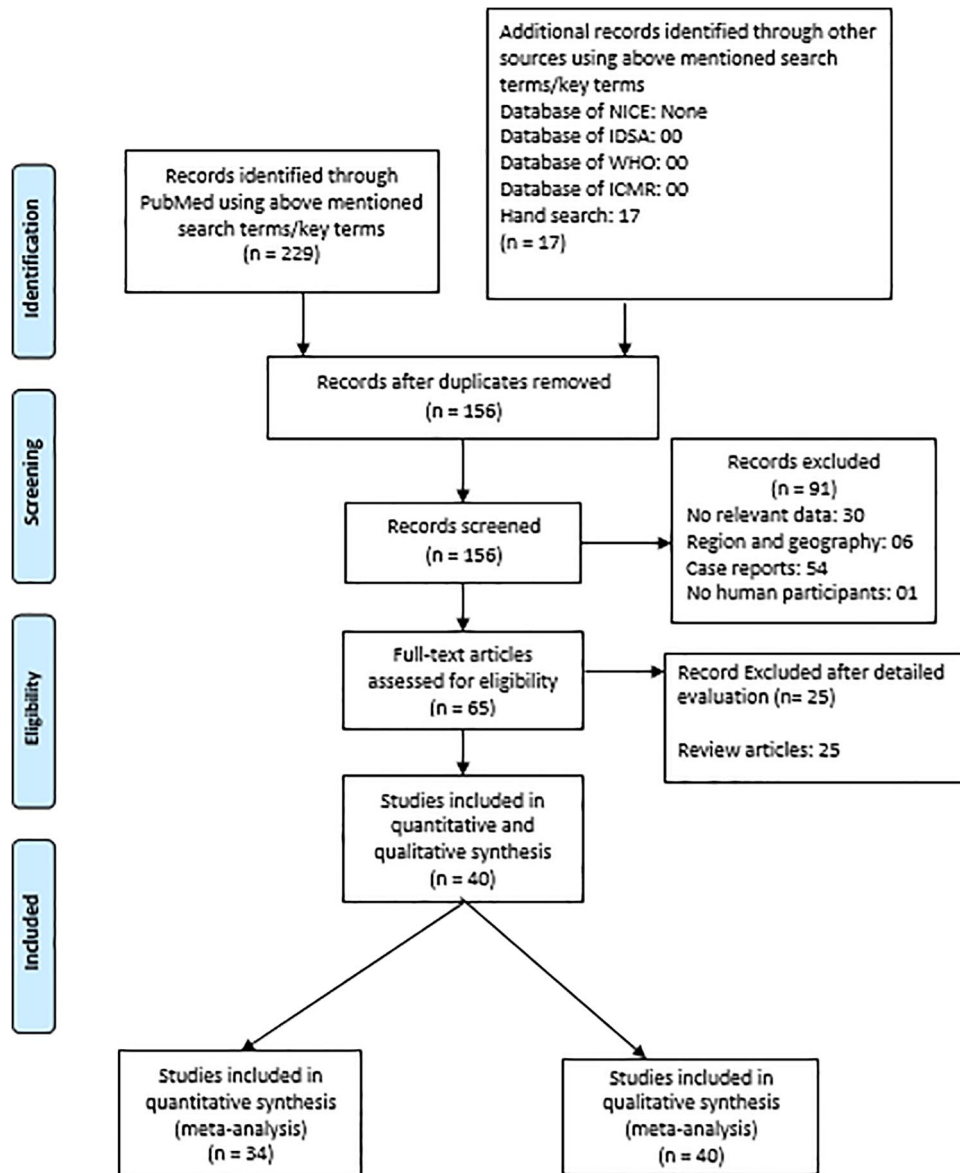
The primary outcome of this study was the proportion of patients with MRSA in India. The secondary outcome was to determine the proportion of patients with MRSA across different age groups and gender from an Indian perspective.

### *Search strategy*

We performed a systematic search on PubMed, using the key terms “(((Methicillin-Resistant *Staphylococcus aureus*) ‘or’ MRSA) ‘and’ Epidemiology) ‘and’ India,” “(((Methicillin-Resistant *Staphylococcus aureus*) ‘or’ MRSA) ‘and’ burden) ‘and’ India,” “((((Methicillin-Resistant *Staphylococcus aureus*) ‘or’ (MRSA)) ‘and’ (Mortality)) ‘and’ (Morbidity)) ‘and’ (India),” “(((Methicillin-Resistant *Staphylococcus aureus*) ‘or’ (MRSA)) ‘and’ (Prevalence)) ‘and’ (india),” “(((Methicillin-Resistant *Staphylococcus aureus*) ‘or’ (MRSA)) ‘and’ (incidences)) ‘and’ (India),” “((((Methicillin-Resistant *Staphylococcus aureus*) ‘or’ (MRSA)) ‘and’ (treatment)) ‘and’ (drug therapy)) ‘and’ (India),” “(((Methicillin-Resistant *Staphylococcus aureus*) ‘or’ (MRSA)) ‘and’ (challenges)) ‘and’ (India),” “(((Methicillin-Resistant *Staphylococcus aureus*) ‘or’ (MRSA)) ‘and’ (clinical Management)) ‘and’ (India),” “(((Methicillin-resistant *Staphylococcus aureus*) ‘or’ (MRSA)) ‘and’ (complications)) ‘and’ (India).” The search was performed after applying constant filters based on these additional search criteria: Article Types—Classical Article, Clinical Study, Clinical Trial, Clinical Trial Protocol, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Consensus Development Conference, Controlled Clinical Trial, Evaluation Study, Government Document, Guideline, Historical Article, Meta-Analysis, Multicenter Study, Observational Study, Overall, Practice Guideline, Pragmatic Clinical Trial, Randomized Controlled Trial; Language—English; Publication Date—2005/01/01 to 2020/05/13; Species—Humans. Additional records were identified through other sources [the National Institute of Science Communication and Information Resources (NISCAIR), Infectious Diseases Society of America (IDSA), World Health Organization (WHO), Indian Council of Medical Research (ICMR)] using the search terms: “Methicillin-Resistant *Staphylococcus aureus*” OR “MRSA” AND “India.” Handsearching was also performed on Google Scholar using the same key terms.

### *Data extraction*

Data was collected from all the primary studies using a structured sheet in Microsoft Excel. Any discrepancies arising while entering the data were sorted out by discussion among all the contributors. The study characteristics extracted included authors details, year of publication, title of study, place of study, and type of study. Patient parameters included the number of study participants and their mean age. Two reviewers were involved in data extraction. Any disagreements among reviewers were resolved by discussion.



**Figure 1.** PRISMA flow diagram.

Abbreviations: ICMR, Indian Council of Medical Research; IDSA, infectious diseases society of America; WHO, World Health Organization; NICE, National Institute for Health and Care Excellence.

### Statistical analysis

To determine the proportion of MRSA, a meta-analysis was performed of 95% confidence interval (CI). Besides, a meta-analysis using a random-effects method (DerSimonian and Laird method), the degree of heterogeneity ( $i$ )<sup>2</sup> among the studies, was planned. The outcomes were presented as pooled estimates with 95% CI. The  $i^2$  test assessed variation in the outcome of all included studies with respect to the primary and secondary objectives. The meta-analyses were carried out using SAS version 9.4 software.

### Results

A total of 229 studies were retrieved via PubMed and Google Scholar search, while 17 studies were obtained by handsearching. No additional studies were retrieved via ICMR, IDSA,

WHO, and NICE database search. Around 40 relevant studies (Figure 1) were identified. The exclusion criteria were: were duplicates (70), case reports (54), does not include relevant data (30), does not match region and geography (06), does not include human participants (1), and reviews (25). All of the 40 studies were considered for qualitative as well as the quantitative synthesis of etiological agents. Ultimately, only 34 of 40 studies were included in the MRSA meta-analysis,<sup>8,9,15-46</sup> as the remaining 6 studies did not include data relevant to MRSA (4 efficacy studies, 1 study that described heteroresistance to vancomycin among methicillin-resistant *S. aureus* isolates, and 1 survey wherein no exact data on prevalence were presented).<sup>47-52</sup> Table 1 represents the characteristics of the studies included in the analysis. The studies included in the systematic literature review did not include randomized controlled trials so risk-bias analysis was not performed.

Table 1. Study characteristics.

AUTHOR	DESIGN OF THE STUDY/TYPE OF LITERATURE	NUMBER OF PATIENTS	RISK FACTOR AND ETIOLOGY	DIAGNOSTIC TEST	MEAN ( $\pm$ SD) / MEDIUM AGE (RANGE) IN YEARS	STUDY OBJECTIVES	GEOGRAPHIC LOCATION/TYPE OF HOSPITAL/ PROVINCE
Bahubali et al <sup>16</sup>	Retrospective study	21 Patients	Postoperative/trauma, otogenic and hematogenous abscess, sinusitis, contiguous spread, immunosuppression (diabetes with pulmonary tuberculosis, malignant tumor, and leprosy)	Cerebral CT scan, MRI, triplex PCR assay	31 (1 month-73 years)	To examine the prevalence, clinical and molecular characteristics, treatment options and outcome of MRSA intracranial abscess over a period of 6 years	India
Kumar et al <sup>17</sup>	Retrospective study	47 <i>S. aureus</i> isolate	VRSA, LRSA, TRSA	PCR amplification	Not available	To evaluate the resistance patterns of <i>S. aureus</i> collected over 2 years (December 2013-November 2015) from blood samples of patients admitted to 1 hospital	Odisha, East India
Kini et al <sup>18</sup>	Retrospective observational study	74 patients	Bone and joint infections, osteomyelitis, septic arthritis, resistance of <i>S. aureus</i> to multiple antibiotics	Laboratory evaluations [including blood hemoglobin and ESR, CRP, WBC, ANC, blood cultures positive for <i>S. aureus</i> , and radiographic studies (plain film, ultrasound evaluation, or MRI)]	8.76 for MRSA and 8.97 for MSSA (8 months to 17 years)	To compare invasive CA-MRSA and CA-MSSA bone and joint infections, characterize the spectrum and incidence of the disease, identify the presence or absence of traditional MRSA risk factors, determine antibiotic susceptibilities of these organisms, and predict a clinical algorithm that will help distinguish an MRSA infection	India
Rajadurai pandi et al <sup>19</sup>	Multicenter study	906 isolates	Resistance of <i>S. aureus</i> to multiple antibiotics, sensitivity to vancomycin and linezolid	Kirby-Bauer disk diffusion method	Not available	To determine the prevalence and antibiotic susceptibility pattern of MRSA	Tamil Nadu
Noguchi et al <sup>20</sup>	Prospective, multicountry study	894 isolates	MRSA	PCR and PFGE typing	Not available	To examine the susceptibilities of MRSA to dyes and antiseptic agents	Asia
Mendem et al <sup>21</sup>	Multicenter study	387 clinical specimens	<i>S. aureus</i> , VRSA, inducible clindamycin resistance	D test, Mueller-Hinton agar plate, Kirby-Bauer disk diffusion method	Not available	To evaluate the prevalence of antibiotic resistance among <i>S. aureus</i> species isolated from clinical samples from different locations in India	Delhi, Bengaluru, Palakkad, Chennai, and Gulbarga

(Continued)

Table 1. (Continued)

AUTHOR	DESIGN OF THE STUDY/TYPE OF LITERATURE	NUMBER OF PATIENTS	RISK FACTOR AND ETIOLOGY	DIAGNOSTIC TEST	MEAN ( $\pm$ SD) / MEDIUM AGE (RANGE) IN YEARS	STUDY OBJECTIVES	GEOGRAPHIC LOCATION/TYPE OF HOSPITAL/ PROVINCE
Sakthirajan et al <sup>22</sup>	Retrospective, observational study	47 patients	Infection-related glomerulonephritis, rheumatic valvular disease, alcohol-related chronic liver disease, HIV infection, urinary tract infection, diarrhea, and pneumonia, ESRD, CKD, requirement of dialysis, hematuria, hypocomplementemia	Not available	42 ( $\pm$ 13.5) years	To analyze the risk factors, etiology, clinical features, and outcome of crescentic infection-related glomerulonephritis.	Tamil Nadu
Kotpal et al <sup>23</sup>	Case-control study	100 patients	Hospitalization, intake of antibiotics, surgical procedure, tuberculosis, diabetes, alcohol intake, malignancy, smoking, corticosteroid intake, candidiasis, dermatitis, HIV infection, immunocompromised	Disk diffusion method, cofoxitin disk diffusion method	33.96 for HIV-infected and 33.78 for HIV-uninfected individuals	To evaluate the prevalence of nasal colonization of <i>S. aureus</i> in individuals with HIV infection attending the Integrated Counselling and Testing Centre in a teaching hospital and compare the prevalence with that of HIV-uninfected individuals	India
Mehndiratta et al <sup>24</sup>	Laboratory perspective study	125 isolates	Not available	Agar screening method, PCR, PCR-RFLP	Not available	To characterize MRSA strains by molecular typing based on PCR-RFLP of <i>spa</i> gene and to assess the utility of <i>spa</i> genotyping over bacteriophage typing in the discrimination of the strains	Delhi
Gupta et al <sup>25</sup>	Laboratory study	200 Non-duplicate <i>S. aureus</i> isolate	Sensitivity to vancomycin and linezolid	Routine Kirby-Bauer disk Diffusion method	Not available	To determine the percentage of <i>S. aureus</i> having inducible clindamycin resistance using Dtest; to ascertain the association between MRSA and inducible clindamycin resistance as well as association of these isolates with community or nosocomial setting; to identify the treatment options for iMLS(B) isolates	Punjab
Batra et al <sup>26</sup>	Retrospective observational study	13 329 cultures	Blood cancer	Kirby-Bauer disk diffusion method, HiCrome MeReSa agar	Not available	To study the epidemiology of microbiologically documented bacterial infection and the resistance pattern, among cancer patients undergoing treatment	Delhi

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Table 1. (Continued)

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Rajkumar et al <sup>9</sup>	ICMR antimicrobial resistance surveillance study	8032 isolates	VRSA, skin and soft tissue infections, <i>S. haemolyticus</i> , <i>S. epidermidis</i> , <i>S. caprae</i> , <i>S. cohnii</i> , <i>S. schleiferi</i> , <i>S. warneri</i> , mupirocin resistance and <i>S. lugdunensis</i>	Kirby–Bauer disk-diffusion method, PCR amplifications	Not available	To study antimicrobial resistance in <i>Staphylococcus</i> species as part of the Indian Council of Medical Research-AMR surveillance network	India
Mahapatra et al <sup>27</sup>	Hospital-based study	1017 specimens	Skin and soft tissue infection, septicemia, pneumonia, meningitis, none and joint space, clindamycin resistance	Not available	Not available	To evaluate antibiotic sensitivity and clinico-epidemiologic profile of <i>Staphylococcal</i> infections	Kolkata
Ravishankar et al <sup>28</sup>	Cross-sectional, observational study	73 patients	Skin and soft tissue infections (SSTIs), hospitalization, surgery, dialysis, diabetes mellitus and HIV infections, resistant to clindamycin	Kirby–Bauer disk-diffusion method, cofoxitin disk diffusion test	34.2 (10-69) years	To study the prevalence of MRSA in CA-SSTIs and to compare the socio-demographic and clinical profile of patients with SSTIs caused by MRSA and MSSA	Delhi
Thacker et al <sup>29</sup>	Retrospective observational study	4198 samples	Gram-negative Bacilli, BSI, coagulase-negative <i>Staphylococci</i>	Kirby–Bauer's disk-diffusion method, cephalosporin–clavulanate combination disks	Not available	To describe the etiology and sensitivity of BSI in the pediatric oncology unit at a tertiary cancer center	Mumbai
Shah et al <sup>30</sup>	Prospective observational study	24355 patients	<i>E. coli</i> , <i>Klebsiella</i> , <i>Pseudomonas</i> , <i>Acinetobacter</i> , <i>Staphylococcus</i> , <i>Enterococcus</i> , <i>Streptococcus</i> , surgeries, SSIs	Not available	51 (2 days-88 years) years	To generate accurate current data on rates, microbial etiology and antimicrobial susceptibility pattern of SSIs	Mumbai, Maharashtra
Mandal et al <sup>31</sup>	Hospital-based observational prospective study	36 cases	Disseminated <i>Staphylococcal</i> disease, neutrophilic leucocytosis, bilateral pyopneumothorax, multiple pyemic abscesses with empyema, meningitis, pyopericardium, trauma, septic arthritis, skin infection	Complete hemogram, LFT, urea, creatinine, blood sugar, Candida skin test, ELISA, catalase test, slide coagulase test and tube coagulase test, Kirby–Bauer disk-diffusion method	6.03 $\pm$ 3.04 (1-12) years	To assess the etiology, precipitating factors, treatment and outcome of DSD in healthy immuno-competent children	West Bengal

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Table 1. (Continued)

AUTHOR	DESIGN OF THE STUDY/TYPE OF LITERATURE	NUMBER OF PATIENTS	RISK FACTOR AND ETIOLOGY	DIAGNOSTIC TEST	MEAN ( $\pm$ SD) / MEDIUM AGE (RANGE) IN YEARS	STUDY OBJECTIVES	GEOGRAPHIC LOCATION/TYPE OF HOSPITAL/ PROVINCE
Mathews et al <sup>32</sup>	Laboratory study	610 isolates	Surgical-site wounds, diabetic foot infections, burns, osteomyelitis/septic arthritis, cellulitis, other skin infections, urinary tract infections, septicemia, pneumonia	Oxacillin disk diffusion, cefoxitin disk diffusion, oxacillin screen agar, PCR, agar diluti on method	Not available	To evaluate the efficacy of cefoxitin disk-diffusion test to detect MRSA and compare it with other phenotypic and molecular methods	Coimbatore, India
Rosenthal et al <sup>33</sup>	Multicenter, prospective cohort surveillance study	21 069 patients	Device-associated infections, VAP, laboratory-confirmed and clinically suspected central venous catheter-associated BSI, catheter-associated UTI, <i>Pseudomonas aeruginosa</i> , <i>S. aureus</i> , <i>Acinetobacter</i> , <i>Enterobacteriaceae</i> , <i>Candida spp.</i>	Not available	Not available	To ascertain the incidence of device-associated infections in the ICUs of developing countries	Argentina, Brazil, Colombia, India, Mexico, Morocco, Peru, and Turkey
Dube et al <sup>47</sup>	Multicenter, open-label, randomized, comparative, parallel -group, active-controlled, phase III clinical trial	162 patients	Postoperative wounds, pneumonia, skin and soft tissue infections such as infected ulcers, and deep abscess, polymicrobial infections, serious infections like meningitis and endocarditis, CAP	Normal Rinne and Weber test	40.80 ( $\pm$ 13.68) in arbekacin group and 40.65 ( $\pm$ 14.69) in vancomycin group	To evaluate the safety and efficacy of arbekacin sulfate injection versus vancomycin injection in patients diagnosed with MRSA infection	9 centres in India
Umashankar et al <sup>48</sup>	Open-label, prospective, placebo-controlled study	372 patients	Pyoderma, <i>Impetigo contagiosa</i> , ecthyma, and folliculitis	Colony morphology, Gram stain, catalase test, slide and tube coagulase test and modified Hugh Leifson's oxidation fermentation test, Kirby-Bauer disk-diffusion method	12.31 in green tea group and 11.01 in placebo group (8 to 16) years	To determine the minimum inhibitory concentration of green tea against <i>S. aureus</i> and MRSA.	Karnataka, India
Corey et al <sup>50</sup>	An international, randomized, double-blind study	968 Patients	Acute wound infection, cellulitis, or major cutaneous abscess, diabetes mellitus, acute bacterial skin and skin-structure infections	Not available	46.2 ( $\pm$ 14.20) in oritavancin group and 44.3 ( $\pm$ 14.50) in vancomycin group (18-93years)	To evaluate the efficacy and safety of a single dose of oritavancin as compared with a regimen of twice daily vancomycin for 7 to 10days	Pune and Lucknow, India

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Table 1. (Continued)

AUTHOR	DESIGN OF THE STUDY/TYPE OF LITERATURE	NUMBER OF PATIENTS	RISK FACTOR AND ETIOLOGY	DIAGNOSTIC TEST	MEAN ( $\pm$ SD) / MEDIUM AGE (RANGE) IN YEARS	STUDY OBJECTIVES	GEOGRAPHIC LOCATION/TYPE OF HOSPITAL/ PROVINCE
Corey et al <sup>49</sup>	Randomized, double-blind, clinical, trial	1019 patients	Acute bacterial SSTIs, lipoglycopeptide, wound infection, cellulitis, abscess, diabetes mellitus	Not available	45.0 (13.40) years in oritavancin group 44.4 (14.29) years in vancomycin group; range: 18-92 years	To evaluate the efficacy and safety of a single dose of oritavancin compared with a regimen of twice-daily vancomycin	One site is from Nagpur, India
Iyer et al <sup>51</sup>	Laboratory study	50 Isolates	Not available	Disk-diffusion method	Not available	To develop, standardize, and compare modified population analysis profile with the existing methodologies to detect hetero-resistance to vancomycin in MRSA isolates	Hyderabad, Andhra Pradesh and Bengaluru, Karnataka
Asati et al <sup>34</sup>	Hospital-based observational study	860 admitted patient	Use of immunosuppressive agents, recent hospitalization, diabetes mellitus, smoking, sepsis, presence of cough, burning micturition, skin infection	Not available	36.56 ( $\pm$ 23.76) years (1-90) years	To study the frequency, etiology, and outcome of sepsis dermatology inpatients	Delhi
Siddaiahgari et al <sup>35</sup>	Prospective study	89 isolates	<i>Escherichia coli</i> , <i>Pseudomonas</i> , <i>Staphylococcus</i> , <i>Acinetobacter</i>	Disk-diffusion method	Not available	To study the likely etiologic agents and their antibiotic sensitivity pattern among systemic infections in children with cancer	Telangana, India
Chatterjee et al <sup>8</sup>	Cohort study <sup>1</sup>	551 subjects	MRSA, MSSA, SSTIs, deep abscess, abdominal sepsis, osteomyelitis, septic arthritis, respiratory tract infection	Kirby-Bauer disk-diffusion method, cefoxitin disk-diffusion method	46.39 $\pm$ 16.08 in MRSA group and 44.77 $\pm$ 14.31 in MSSA group	To determine morbidity and mortality of MRSA and MSSA infections in a tertiary health-care facility	Manipal, South India
Eshwara et al <sup>36</sup>	Prospective observational cohort study	70 cases of <i>S. aureus</i> bacteremia	<i>S. aureus</i> , BSI, MRSA, SSTIs, respiratory infections, MSSA	Kirby-Bauer disk-diffusion method, cefoxitin disk diffusion	44 (0-76) years	To analyze the epidemiology and laboratory characteristics of <i>S. aureus bacteremia</i> in an Indian tertiary care hospital	Southern India
Bouchiat et al <sup>37</sup>	Prospective observational study	92 <i>S. aureus</i> clinical isolates	<i>S. aureus</i> , MRSA, SSTIs, UTI, respiratory infection, bone and joint infection and sepsis, CA <i>S. aureus</i> infection	Disk-diffusion method, PCR	43 years (range, 7 days-91 years)	To determine the antibiotic susceptibility pattern of <i>S. aureus</i> and the circulating clones	Bengaluru, India
Choudhury et al <sup>38</sup>	Retrospective study	724 positive <i>Staphylococcus</i> strains cases	MRSA, MSSA,	Not available	Not available	To determine the prevalence and antimicrobial susceptibility pattern of MRSA	Assam, India

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Table 1. (Continued)

AUTHOR	DESIGN OF THE STUDY/TYPE OF LITERATURE	NUMBER OF PATIENTS	RISK FACTOR AND ETIOLOGY	DIAGNOSTIC TEST	MEAN ( $\pm$ SD) / MEDIUM AGE (RANGE) IN YEARS	STUDY OBJECTIVES	GEOGRAPHIC LOCATION/TYPE OF HOSPITAL/ PROVINCE
Rampal et al <sup>52</sup>	Survey study	264 critical care specialists	MRSA, acute bacterial SSSIs, CAP, VAP, CLABSI, and DFI	Not available	Not available	To determine the burden of Gram-positive infections in critical care settings and to understand the practising behavior among the specialists in the management of MRSA infections	India
Mehta et al <sup>59</sup>	Surveillance study	13610 samples	MRSA, MSSA	Disk-diffusion method	Not available	To determine the incidence of MRSA in Indian hospitals and to compare the antimicrobial activity of currently available antibiotics	Delhi, Mumbai, and Bengaluru
Abimannan et al <sup>40</sup>	A cross-sectional study	769 isolates	CA MRSA, CA MSSA	Kirby-Bauer disk diffusion method, disk approximation test, multiplex PCR; agr typing, spa typing, and multilocus sequence typing	Not available	To evaluate the molecular, epidemiologic, and virulence characteristics of <i>S. aureus</i> in both community and hospital settings	Tamil Nadu, India
Senthilkumar et al <sup>41</sup>	Hospital-based study	98 isolates	Exanthematous illness (fever with rash), history of minor trauma causing skin discontinuity, hospitalization, antibiotic usage, immunosuppressant usage, contact with potential <i>S. aureus</i> -infected patient	PCR, D test,	Not available	To identify the clinical variables that differentiate MRSA from MSSA infection	Pondicherry, India
Chamania et al <sup>42</sup>	Retrospective review study	102 patients	Extended duration of hospitalization, previous procedures, comatose state, and advancing age	Not available	Not available	To analyze the incidence of multi drug-resistant organisms in burn patients and to co-relate sepsis-induced mortality with underlying MDR infection	Indore, India
Nagaraju et al <sup>43</sup>	Prospective study (part of school camp)	372 children	<i>S. aureus</i> carriage, pyoderma caused by <i>S. aureus</i> , ecthyma, immunocompetent patients, lifestyle changes (hygiene) and folliculitis	Kirby-Bauer disk diffusion method	5 to 16 years	To evaluate different types of primary pyoderma in children caused by <i>S. aureus</i> and to determine the incidence of MRSA in community-acquired primary pyoderma in children	Bengaluru, South India

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Table 1. (Continued)

AUTHOR	DESIGN OF THE STUDY/TYPE OF LITERATURE	NUMBER OF PATIENTS	RISK FACTOR AND ETIOLOGY	DIAGNOSTIC TEST	MEAN ( $\pm$ SD) / MEDIUM AGE (RANGE) IN YEARS	STUDY OBJECTIVES	GEOGRAPHIC LOCATION/TYPE OF HOSPITAL/ PROVINCE
Singh et al <sup>15</sup>	Prospective, cross-sectional, and observational study	300 school-going children	Socioeconomic status, frequent medication with antibiotics, hospitalization, chronic disease, and previous infection with MRSA	Cefoxitin 30- $\mu$ g disks and D-zone test, Kirby–Bauer disk diffusion	5 to 15 years	To determine the prevalence of nasal colonization of MRSA, the minimum inhibitory concentration of oxacillin and vancomycin, inducible clindamycin resistance, and antimicrobial resistance pattern of <i>S. aureus</i>	Uttar Pradesh, India
Indian Network for Surveillance of Antimicrobial Resistance Group <sup>44</sup>	Retrospective study	26 310 isolates	Not available	Kirby–Bauer disk diffusion technique	Not available	To determine the prevalence of MRSA and susceptibility pattern of <i>S. aureus</i> isolates in India	15 Indian tertiary care centers across North, South, and West India
Kumar et al <sup>45</sup>	Hospital-based study	133 culture-positive <i>S. aureus</i> samples	Surgical wound infections, intake of antibiotics	Kirby–Bauer disc diffusion method	Not available	To determine the prevalence of MRSA in surgical wound infections and also to define the antimicrobial susceptibility patterns of the strains isolated	North-eastern part of India
Basavaraj et al <sup>46</sup>	Hospital-based study	137 isolates	Excessive antibiotic usage, prolonged hospitalization, intravascular catheterization and hospitalization in an intensive care unit	Oxacillin disk-diffusion method, Kirby–Bauer disk diffusion	Not available	To provide data for empiric selection of appropriate antibiotics for the treatment of diseases caused by <i>S. aureus</i>	Karnataka, South India

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging (MRI); PCR, polymerase chain reaction; MRSA, methicillin-resistant *S. aureus*; VRSA, vancomycin-resistant *S. aureus*; LRSA, linezolid-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; WBC, white blood cell; ANC, absolute neutrophil count; CA, community associated; PFGE, pulsed-field gel electrophoresis; HIV, human immunodeficiency virus; RFLP, restriction fragment length polymorphism; spa, *Staphylococcus aureus* protein A; VRE, vancomycin-resistant enterococci; CA-SSTIs, community-acquired skin and soft tissue infections; BSI, Bloodstream infection; SSI, Surgical-site infections; LFT, liver function tests; ELISA, enzyme-linked immunosorbent assay; DSD, disseminated staphylococcal disease; VAP, ventilator-associated pneumonia; UTI, urinary tract infection; CAP, community-acquired pneumonia; SSSI, skin and skin structure infections; CLABSI: central line-associated bloodstream infection; DFI, diabetic foot infections; TRSA, tigecycline-resistant *S. aureus*.

### Primary outcome

The meta-analysis included 16237 patients aged between 1 month to 93 years. Clinical diagnosis was made by polymerase chain reaction assay, pulsed-field gel electrophoresis typing, radiologic evaluations (computed tomography and magnetic resonance imaging), laboratory evaluations, D test, Mueller–Hinton agar plate, antimicrobial discs methods like Kirby–Bauer disc diffusion method, Candida skin test, enzyme-linked immunosorbent assay, catalase test, slide coagulase test, tube coagulase test, Normal Rinne and Weber test, colony morphology, and Gram's stain. Majority of studies used antimicrobial disc methods such as Kirby–Bauer disc diffusion method for clinical diagnosis of MRSA (Table 1).

The pooled proportion of patients with MRSA infection was 26.8% (95% CI: 23.2%–30.7%;  $I^2=97.69\%$ ;  $P<.001$ ; Table 2, Figure 2). The degree of heterogeneity was significant.<sup>8,9,15–46</sup>

### Secondary outcome

According to the subgroup analysis, the prevalence of MRSA infection was more in males [60.4%; 95% CI 53.9%–66.5%] than in female [39.6%; 95% CI 33.5%–46.1%] (Table 3) while prevalence was more in adult (18 years and above; 68%; 95% CI 20%–94.8%) in comparison with pediatric patients (0–18 years; 32%; 95% CI 5%–80%) (Table 4).

A total of 10 studies<sup>8,16,18,23,28,31,36,38,41,46</sup> identified risk factors and co-morbidities, including diabetes, tuberculosis, malignancy, leprosy, extremes of age, group-house inhabitants, high mean body temperature (101.80°F), history of preceding illness/upper respiratory tract infections/trauma, abnormal laboratory values (hemoglobin [ $<9.5$  g%], erythrocyte sedimentation rate [ $>35$  mm/h], c-reactive protein [ $>32$  mg/dL], leucocytes ( $>14000$  cells/ $10^9$  L), absolute neutrophil count [ $>65\%$ ]), immuno-compromised status, hospitalization in the last 3 months, present intake/history of antibiotics, history of surgical procedures, history of alcohol intake and smoking, history of intravenous drugs, history of corticosteroid intake, history of mucocutaneous candidiasis, history of dermatitis, history of sexually transmitted infections, socio-economic status, chronic kidney disease, heart disease, chronic obstructive pulmonary disease, rheumatoid arthritis, MRSA carriage (nasal or axillary or perineal or hand carriage in patients), prolonged duration of hospital stay, and irrational use/over prescription of antibiotics.

Four studies conducted in India focusing on the treatment of MRSA infections were identified; Arbekacin sulfate (200 mg) has shown 79% cure rate<sup>47</sup> and vancomycin hydrochloride (1000 mg BD) has shown a curate rate of 100% cure rate,<sup>47</sup> 78.90%,<sup>49</sup> and 82.9%<sup>50</sup> in 3 studies, respectively. Besides, 2 studies suggested oritavancin as one of the treatment options for MRSA infections, with a cure rate of 82.30%<sup>49</sup> and 80.1%, respectively.<sup>50</sup>

The survey conducted by Rampal et al, indicated an increasing trend in the prevalence and associated mortality in Gram-positive bacterial infections in critical care settings in India.<sup>52</sup> The limitations of the existing anti-MRSA agents necessitate the development of a newer agent with a broad spectrum antibacterial activity along with an improved safety profile.

### Discussion

In order to reduce the burden of MRSA infections, continuous efforts should be made to prevent the spread and emergence of resistance by early detection of the resistant strains and using proper infection control measures in the hospital setting.<sup>17</sup> As most *S. aureus* strains are resistant to multiple antibiotics, treatment of *S. aureus* infections may have resulting complications. Hence, less interest is shown toward the development of new antibiotics. Other reasons include high cost and limited success rate. In such cases, vaccination might be beneficial to high-risk patients (such as dialysis patients, patients at risk of endocarditis, patients undergoing surgery, sports persons, prison inmates, and health-care workers who are the potential sources of dissemination of hospital-associated MRSA). Therefore, many researchers focus on developing vaccines and therapeutic antibodies, rather than novel antibiotics, as the process is comparatively easy and inexpensive.<sup>17</sup> The IDSA recommended the expansion of National Institute of Allergy and Infectious Diseases funding of both innate and adaptive immune strategies to prevent and treat antimicrobial-resistant infections. The strategies include active vaccination, passive immunization with polyclonal or monoclonal antibodies, and other immune-enhancing therapies.<sup>53</sup>

In recent years, increasing prevalence of hospital-acquired and community-acquired MRSA infections have been reported in Indian population.<sup>40,43</sup> This meta-analysis is the first to report the recent prevalence estimates and burden of MRSA among the Indian population. We also identified the high-risk groups in terms of age and gender so as to improve the disease surveillance and interventions of MRSA.

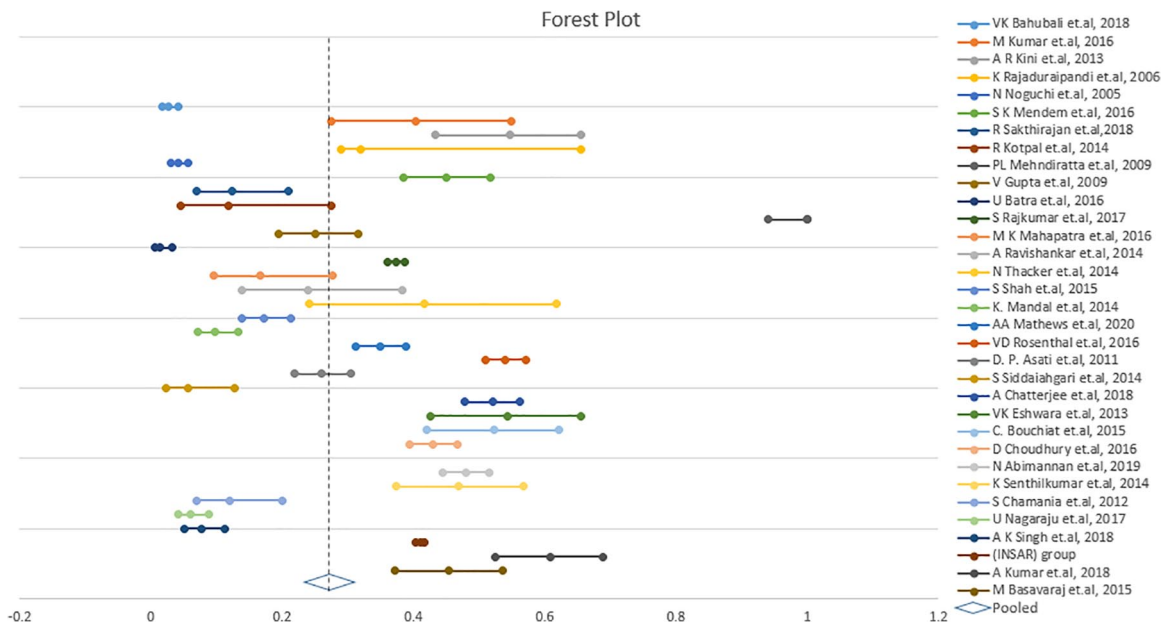
The pooled prevalence of MRSA in our study was 26.8%. These findings are almost similar to the estimates from other regions. The meta-analysis study by Wong et al has reported an MRSA prevalence of 0% to 23% in community settings and 0.7% to 10.4% in hospital settings in the Asia-Pacific region. Further, the study also reported a higher prevalence of community-acquired MRSA in India (16.5%–23.5%), followed by Vietnam (7.9%) and Taiwan (3.5%–3.8%).<sup>54</sup> A meta-analysis conducted by Wu and colleagues had reported an MRSA prevalence rate of 21.2% (95% CI, 18.5%–23.9%) in the healthy Chinese population.<sup>2</sup> Further, the reported prevalence of MRSA in Ethiopia, was 30.90% [95% CI, 21.81%–39.99%], while in Europe and the United States the prevalence rate was only 1.8% (95% CI, 1.34%–2.50%).<sup>55,56</sup>

The subgroup analysis reported a higher prevalence of MRSA among males compared to females in the Indian population (60.4% vs 39.6%), thereby indicating male gender to

**Table 2.** Proportion of MRSA infection in Indian patients.

STUDY	ODDS RATIO/PROPORTION OF PATIENTS WITH MRSA	LOWER CI	UPPER CI	WEIGHT
Bahubali <sup>16</sup>	0.027	0.018	0.041	3.01
Kumar et al <sup>17</sup>	0.404	0.275	0.549	2.68
Kini et al <sup>18</sup>	0.547	0.434	0.655	2.97
Rajaduraipandi et al <sup>19</sup>	0.319	0.289	0.655	3.49
Noguchi et al <sup>20</sup>	0.042	0.031	0.057	3.23
Mendem et al <sup>21</sup>	0.45	0.384	0.518	3.32
Sakthirajan et al <sup>22</sup>	0.124	0.07	0.21	2.57
Kotpal et al <sup>23</sup>	0.118	0.045	0.275	1.73
Mehndiratta et al <sup>24</sup>	1	0.94	1	0.42
Gupta et al <sup>25</sup>	0.25	0.195	0.315	3.24
Batra et al <sup>26</sup>	0.014	0.006	0.033	2.03
Rajkumar et al <sup>9</sup>	0.373	0.36	0.386	3.55
Mahapatra et al <sup>27</sup>	0.167	0.095	0.276	2.53
Ravishankar et al <sup>28</sup>	0.239	0.138	0.382	2.47
Thacker et al <sup>29</sup>	0.417	0.241	0.617	2.18
Shah et al <sup>30</sup>	0.173	0.139	0.214	3.34
Mandal et al <sup>31</sup>	0.098	0.072	0.133	3.19
Mathews et al <sup>32</sup>	0.349	0.312	0.388	3.47
Rosenthal et al <sup>33</sup>	0.54	0.51	0.571	3.51
Asati et al <sup>34</sup>	0.259	0.218	0.305	3.39
Siddaiahgari et al <sup>35</sup>	0.056	0.024	0.128	1.99
Chatterjee et al <sup>8</sup>	0.52	0.478	0.562	3.47
Eshwara et al <sup>36</sup>	0.543	0.426	0.655	2.93
Bouchiat et al <sup>37</sup>	0.522	0.42	0.622	3.06
Choudhury et al <sup>38</sup>	0.43	0.394	0.466	3.49
Mehta et al <sup>39</sup>	0.318	0.285	0.352	3.48
Abimannan et al <sup>40</sup>	0.48	0.445	0.515	3.49
Senthilkumar et al <sup>41</sup>	0.469	0.373	0.568	3.09
Chamania et al <sup>42</sup>	0.12	0.069	0.2	2.63
Nagaraju et al <sup>43</sup>	0.061	0.041	0.089	3.06
Singh et al <sup>15</sup>	0.077	0.051	0.113	3.03
(INSAR) Group <sup>44</sup>	0.41	0.404	0.416	3.56
Kumar et al <sup>45</sup>	0.609	0.524	0.688	3.19
Basavaraj et al <sup>46</sup>	0.453	0.371	0.536	3.21
Pooled proportion	0.268	0.232	0.307	

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; CI, confidence interval.



**Figure 2.** Forest plot displaying meta-analysis of proportion of prevalence in MRSA. Binary random effects model was applied to get pooled proportion and 95% confidence interval (0.268; 95% CI 0.232-0.307;  $P < .001$ ).

**Table 3.** Prevalence of MRSA in males and females.

AUTHOR AND YEAR	NUMBER OF MALE SUBJECTS WITH MRSA	NUMBER OF FEMALE SUBJECTS WITH MRSA	TOTAL NUMBER OF SUBJECTS WITH MRSA	PROPORTION	LOWER CI	UPPER CI
Bahubali et al <sup>16</sup>	18	–	21	0.857	0.637	0.97
Kini et al <sup>18</sup>	27	–	41	0.659	0.494	0.799
Ravishankar et al <sup>28</sup>	4	–	11	0.364	0.109	0.692
Rosenthal et al <sup>33</sup>	312	–	548	0.569	0.527	0.611
Choudhury et al <sup>38</sup>	183	–	311	0.588	0.531	0.643
Singh et al <sup>15</sup>	16	–	23	0.696	0.471	0.868
Summary				0.604	0.539	0.665
Bahubali et al <sup>16</sup>	–	3	21	0.143	0.030	0.363
Kini et al <sup>18</sup>	–	14	41	0.341	0.201	0.506
Ravishankar et al <sup>28</sup>	–	7	11	0.636	0.063	0.891
Rosenthal et al <sup>33</sup>	–	236	548	0.431	0.389	0.473
Choudhury et al <sup>38</sup>	–	128	311	0.412	0.356	0.469
Singh et al <sup>15</sup>	–	7	23	0.304	0.132	0.529
Summary				0.396	0.335	0.461

be a risk factor for MRSA infections. Similar to our findings, multivariate analysis by Harbath and colleagues reported male gender as 1 of the 9 independent risk factors of MRSA with an odds ratio of 1.9 (1.3-2.7).<sup>57</sup> In addition, a long-term study, spanning 7 years, conducted by Kupfer et al suggested male gender as a significant risk factor for

MRSA acquisition.<sup>58</sup> Behavioral and physiological factors contribute to the high occurrence of MRSA in male population. Behavioral practices that may potentially influence MRSA colonization and infection rates in males include personal hygiene issues (including hand hygiene and nose picking and nail-biting habit), profession (those working with



**Table 4.** Prevalence of MRSA in adult and pediatric patients.

AUTHOR	NUMBER OF PEDIATRIC SUBJECTS (0-18YEARS) WITH MRSA	NUMBER OF ADULT SUBJECTS (18YEARS AND ABOVE) WITH MRSA	TOTAL NUMBER OF SUBJECTS WITH MRSA	PROPORTION	LOWER CI	UPPER CI
Kini et al <sup>18</sup>	41	–	41	0.988	0.836	0.999
Sakthirajan et al <sup>22</sup>	0	–	47	0.010	0.001	0.146
Mahapatra et al <sup>27</sup>	11	–	11	0.958	0.575	0.997
Ravishankar et al <sup>28</sup>	0	–	11	0.042	0.003	0.425
Mandal et al <sup>31</sup>	36	–	36	0.986	0.818	0.999
Dube et al <sup>47</sup>	0	–	162	0.003	0.000	0.047
Umashankar et al <sup>48</sup>	24	–	24	0.980	0.749	0.999
Corey et al <sup>49</sup>	0	–	204	0.002	0.000	0.038
Corey et al <sup>50</sup>	0	–	201	0.002	0.000	0.038
Chatterjee et al <sup>8</sup>	0	–	284	0.002	0.000	0.027
Eshwara et al <sup>36</sup>	8	–	38	0.211	0.109	0.368
Nagaraju et al <sup>43</sup>	24	–	24	0.980	0.749	0.999
Singh et al <sup>15</sup>	23	–	23	0.979	0.741	0.999
Summary				0.320	0.052	0.8
Kini et al <sup>18</sup>	–	0	41	0.012	0.001	0.164
Sakthirajan et al <sup>22</sup>	–	47	47	0.990	0.854	0.999
Mahapatra et al <sup>27</sup>	–	0	11	0.042	0.003	0.425
Ravishankar et al <sup>28</sup>	–	11	11	0.958	0.575	0.997
Mandal et al <sup>31</sup>	–	0	36	0.014	0.001	0.182
Dube et al <sup>47</sup>	–	162	162	0.997	0.953	1.000
Umashankar et al <sup>48</sup>	–	0	24	0.020	0.001	0.251
Corey et al <sup>49</sup>	–	204	204	0.998	0.962	1.000
Corey et al <sup>50</sup>	–	201	201	0.998	0.962	1.000
Chatterjee et al <sup>8</sup>	–	284	284	0.998	0.973	1.000
Eshwara et al <sup>36</sup>	–	30	38	0.789	0.632	0.891
Nagaraju et al <sup>43</sup>	–	0	24	0.020	0.001	0.251
Singh et al <sup>15</sup>	–	0	23	0.021	0.001	0.259
Summary				0.680	0.200	0.948

livestock industry), and playing contact sports. The physiological and immunological factors increasing the MRSA prevalence in males include an aggressive inflammatory immune response and higher levels of circulating inflammatory cytokine tumor necrosis factor- $\alpha$ .<sup>14</sup> Limited data on the association of higher gender differences and MRSA necessitate further research on the association between gender dimorphism and higher MRSA carriage in males.

Findings from our analysis indicate a higher prevalence of MRSA among adults (>18years) compared to the pediatric population including adolescents (68% vs 32%).<sup>59</sup> An increased prevalence of MRSA in the adult population is associated with age-related changes including malnutrition and anatomic and physiologic modifications along with immune system dysfunction. Another meta-analysis by Lim et al studying the prevalence of MRSA in the Asia-Pacific region has reported a higher

MRSA carriage prevalence among adults compared to children below 18 years of age. Similarly, a study by Wu et al had reported younger age as an influencing factor for MRSA colonization in healthy Chinese population.<sup>2</sup> The existing literature on the differences in MRSA carriage among different age groups is inconsistent because of the differences in the population included in such studies. Further studies are needed to assess the prevalence of MRSA across different age groups within similar cohorts.

The differences in prevalence across different geographic regions may be attributed to the methodologic variations of isolation and detection of MRSA, study population included for analysis, availability of health-care services, and the economic level of the assessed regions.

In our analysis, we also identified the treatment options for MRSA. Findings from the 4 studies included in our analysis suggest arbekacin sulfate of 200 mg, vancomycin hydrochloride of 100 mg, and oritavancin as the treatment options for MRSA infections in India.<sup>47,49,50</sup> Various clinical studies and systematic reviews have reported beneficial clinical outcomes with these antibiotics in the treatment of MRSA infections.<sup>60-62</sup>

The strengths of our meta-analysis is inclusion of a larger number of studies having a sufficiently large sample size. Further, as MRSA infections are a serious public health concern, this meta-analysis, the first to be conducted in the Indian population, may provide epidemiologic data on MRSA and the associated risk factors.

Our study has a few limitations in terms of inclusion of studies that had heterogeneity in the prevalence of MRSA and wide variation in patient cohorts. Further prospective studies are required to verify these results in order to facilitate preventive measures for mitigating MRSA in the Indian subcontinent.

## Conclusion

This meta-analysis documents the prevalence of MRSA in India, which is considerably higher than that reported in other Asian countries. Further, the increased prevalence of MRSA in male patients of age >18 years highlights the need for further examination in these high-risk cohorts. Appropriate surveillance and preventive measures for reducing the risk of development and transmission of MRSA in the Indian subcontinent are indispensable.

## Author Contributions

CJG was involved in the design of meta-analysis, did the data analyses, and wrote the first draft of this manuscript with input from SW who assisted with the tables and figures and GR who also advised on the statistical analyses. All authors contributed to refining their approved submitted manuscript.

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