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Prevalence Of Methicillin-Resistant Staphylococcus Aureus (MRSA) In India: A Systematic Review and Meta-Analysis

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KEYWORDS:

MRSA, India, Staphylococcus aureus, prevalence

ABSTRACT:

Background

Methicillin is a therapeutic agent developed for the management of infections caused by penicillin-resistant S. aureus. Later, MRSA emerged as the most important nosocomial pathogens worldwide. According to various research, the incidence of MRSA ranges from 21% to 45% among the Indian population. The prevalence of CA-MRSA keeps increasing gradually, whereas there is a reduction in the prevalence of HA-MRSA because of regular practice of GCP in hospital settings. This systematic review was directed to assess the prevalence of methicillin-resistant S. aureus (MRSA) in India and analyze the challenges in diagnosis and management of MRSA in India.

Methods

The present systematic review was conducted in accordance with the PRISMA-P statement 2015. Several databases such as PubMed, Embase and Cochrane Library were searched for studies published from January 2008 to December 2018 in the English language, confer to the predefined inclusion and exclusion criteria. The quality of included studies was assessed in accordance with MOOSE guidelines for assessing the risk of bias. Statistical analysis was analyzed using the 1.3.1073 version of RStudio software package. The results were presented as OR and 95% CI to measure the association between PPI and NON-PPI.

Results

Epidemiological studies of MRSA assessed in different geographical locations of India were included. A total of 17 studies involving 30618 patients were included in the study. The prevalence of MRSA infection was 37.34%. MRSA prevalence was higher in northern India when compared to other parts of India. The degree of significance was found to be high.

Conclusion

Our meta-analysis reports that there is an increase in the prevalence of MRSA in India (37.34%) when compared to other Asian countries. A futuristic approach towards the development of rapid diagnostic tests for MRSA screening will be beneficial for its early management.

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INTRODUCTION:

Antimicrobial resistance has emerged as one of the leading public health challenges worldwide, which restricts the prevention and management of nosocomial infections. The development of antimicrobial resistance inactivates the antibiotics by altering the drug target resulting in therapeutic failure [1]. Earlier in the 1960s, Methicillin was first developed as a therapeutic agent for the management of infections caused by penicillin's resistant S. aureus. But in later, Methicillin-resistant Staphylococcus aureus (MRSA) emerged as a serious threat to public health worldwide [2].

The usage of antimicrobial agents for the management of MRSA infections is limited due to the acquisition of SCCmec that results in intrinsic resistance to all beta-lactam antibiotics [3]. Thus, it leads to prolonged hospitalization, high cost of care and mortality. The geographical variations among the antimicrobial resistance patterns led to the gradual increase in the incidence of MRSA infections [4]. The rise in the incidence of Methicillin-resistant Staphylococcus aureus infections ranges from 25% to 50% in the different parts of India [5]. The Antimicrobial Resistance Surveillance network – ICMR has reported that the incidence of MRSA ranges from 21% to 45% in the Indian population [6]. Recent studies have suggested that many characteristics of CA-MRSA are different from strains of HA-MRSA. Isolates of CA-MRSA tend to be susceptible to various non β-lactam antibiotics, whereas HA-MRSA isolates are generally resistant to multiple antibiotics [7].

The regular practice of GCP in hospital settings has reduced the prevalence of HA-MRSA infections. However, the prevalence of CA-MRSA infections is gradually increasing, which causes a burden to healthcare workers, especially in India. Furthermore, the factors which impact the healthcare system includes the high cost of treatment, prolonged hospitalization across the different parts of India [8]. In the past few years, many epidemiological studies on MRSA prevalence being reported from different regions of India. But the frequency of studies reporting is inconsistent as well as variation among the results. Hence, the present systematic review and meta-analysis aimed to assess the prevalence of MRSA infections in the Indian population. Furthermore, we aimed to analyze the quality of literature published as well as to summarize the characteristics of studies available on the prevalence of MRSA.

METHODOLOGY:

Data source

The present systematic review was conducted in accordance with preferred reporting items for systematic review and meta-analysis protocols (PRISMA) statement 2015. All the pertinent studies reporting the prevalence of MRSA were initially screened. Two independent reviewers (KKR and JME) conducted a coherent search in Cochrane Library, Google Scholar, PubMed, and Embase. The keywords used for the literature search include the prevalence of MRSA, Staphylococcus aureus, resistance, MRSA in India. Any disagreements between two reviewers were resolved by a discussion with another reviewer (JM).

Eligibility criteria

Observational studies investigating the prevalence of MRSA in India are included in the present study. After the initial screening, studies following the guidelines of Clinical and Laboratory Standard Institute for diagnosis of MRSA were selected for inclusion. The exclusion criteria's of the present review were

- Case study
- Review articles
- Studies with Non-Standard methods
- Animal studies

Study Design

Study population, timing, and setting

Studies reporting the prevalence of MRSA among the Indian population in the health care settings of India were included. The studies included were published between January 2008 and December 2018.

Languages

The studies reported only in the English language were included in this study.

Publication status

The studies included in the present systematic review were published in scientific journals.

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Data extraction

Two independent reviewers (KKR and JME) conducted a review using the predefined inclusion criteria. The selection process of studies was mentioned using a PRISMA flow chart. The information was extracted from the included studies: year of publication, first author name, study period, provinces, number of staphylococcus aureus, number of MRSA, Diagnostic methods, source of samples, and prevalence of MRSA.

Quality assessment

Quality assessments of the included studies were conducted in accordance with the Meta-analysis of observational studies in epidemiology (MOOSE) guidelines for evaluating the risk of bias. Two independent reviewers (KKR and JME) assessed the quality of included studies. Disagreement was resolved by concerning the predefined criteria by considering the risk of bias.

Statistical analysis

All the statistical analysis analyzed using the 1.3.1073 version of RStudio software package. The results were presented as OR and 95% CI to assess the association between PPI and NON-PPI. The assumption of heterogeneity was assessed by a Chi-square test based on a Q-test. Usually, the levels of heterogeneity were classified into low, moderate, and high based on I^2 statistics. If $p < 0.05$ and/or $I^2 > 50\%$, pooled data with the 95% confidence interval (CI) was calculated using random-effect model.

RESULTS:

Characteristics of included studies

A total of 292 studies were initially screened. Among 292 studies, 219 were included after the exclusion of duplicate articles. 145 out of 219 studies were selected based on the title review by excluding studies irrelevant to the topic. After screening the abstracts of selected studies, 17 studies were included for meta-analysis [9-25]. Figure 1 represents the reason for study exclusion based on the full text of the articles. The summary of the characteristics of the included studies was mentioned in Table 1.

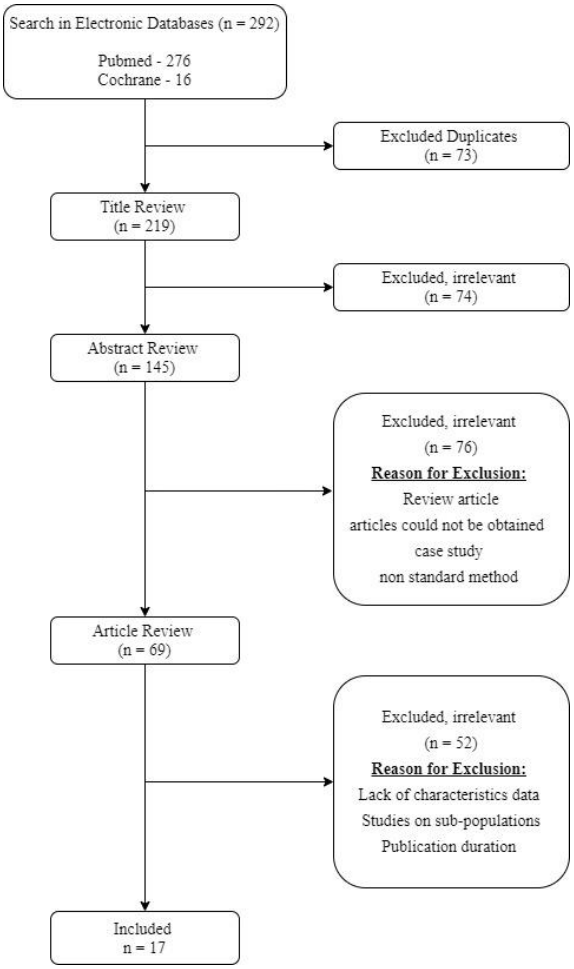

Figure: 1 Study Selection Process

S.no	Study	Study period	Province	No. of S.aureus	No. of MRSA	Diagnostic method	Source of sample	Prevalence of MRSA (%)	Result
1	Hare Krishna Tiwari et.al 2008 [9]	August 2002- June 2006	Northern India	783	301	disc diffusion and MIC tests and were	All specimens, except urine	38.44%	Resistance to penicillin (97%), cotrimoxazole (95.68%),

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						confirmed as MRSA by the mecA gene PCR			chloramphenicol (92.36%), and norfloxacin (90.7%).
2	AM Ciraj et.al 2009 [10]		Karnataka	150	26	Kirby Bauer method D-test	Urine, pus, throat swab	38.40%	Resistance to Erythromycin-32% Clindamycin-13.1%
3	V Gupta et.al 2009 [11]	January 2008-June 2008	Chandigarh	200	50	Kirby Bauer method D-test	pus/wound swab, respiratory tract, high vaginal swab and body fluids	25%	MRSA isolates showed both higher inducible resistance (20%) and constitutive resistance (46%) to clindamycin
4	Uma.A et.al 2009 [12]	October 2007-november 2007	Tamilnadu	13	2	Kirby Bauer method gram staining, O-F testing, mannitol fermentation, tube coagulase test	Nasal swab	15.40%	Resistance to Cloxacillin-44.4%, Ampicillin, cotrimoxazole-33.3%, Cephalexin-30.1%, Ceftriaxone-25.4%, Gentamycin-23.8%, Ciprofloxacin-22.2%, Erythromycin-20.6%, Doxycycline-14.3%
5	Lahari Saikia et.al 2009 [13]	January 2007-February 2008	Assam	276	96	Kirby Bauer disc diffusion method	pus/wound swabs, sputum/throat swab	34.78%	50% had constitutive resistance (resistance to both

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									erythromycin and clindamycin), 9.38% had the inducible MLSB resistance.
6	Lakshmana swamy parasa et.al 2010 [14]		Andhra Pradesh	41	5	BHI broth sub cultured onto blood agar plates.		33.30%	Resistance to From community, (Penicillin-76 Cotrimazole-62) From hospital (Penicillin-86 Oxacillin-33 Cotrimazole-53)
7	Ashish Pathak et.al 2010 [15]	November 2007-February 2009	Ujjain	98	16	MRSA-cefoxitin disk screen test . Kirby Bauer's disc diffusion method	Nose swab	16.30%	prevalence of nasal carriage of S.aureus was 6.3% out of which 16.3% were methicillin-resistant S. aureus (MRSA) isolated S. aureus showed resistance to oral antibiotics.

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8	Habeeb Khadri et.al 2010 [16]	June 2007-december 2007	Anantapur	235	117	antibiotic susceptibility pattern - Kirby Bauer disc diffusion method MRSA-Oxoid PBP2' latex agglutination test	Pus, urine, wound swabs, nasal and ear swabs, blood	54.90%	MRSA isolates were significantly more resistant to different classes of antibiotics. Resistance to Penicillin-100% Erthyromycin-83% Co-trimoxazole-82%
9	Vidya Pai et.al 2010 [17]	June 2007-june 2008	Mangalore	237	69	oxacillin disc by disc diffusion method and confirmed by agar screen test	pus, sputum, urine, blood, and body fluids	29.10%	Resistance to Inducible clindamycin-18.8% erythromycin, gentamicin, and 11.chloramphenicol – 40-50% ciprofloxacin and amikacin-less than 30%
10			North india	COps-250	115		pus, blood,	46%	Resistance to

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	Pushpa Devi et.al 2010 [18]	January 2008−February 2009				disc diffusion method	urine, high vaginal swab, sputum, etc.	In various parts of the country ranging from 40.6% to 54.85% to 59.3%	multidrug-resistant -73% 100% sensitivity of MRSA to vancomycin
11	Sangeeta Joshi et.al 2013 [19]	Jan 2008-december 2009	India	In 2008-13975 In 2009-12335	In 2008 - 5864 In 2009 - 5133	Kirby Bauer's' disc diffusion, minimum inhibitory concentration (MIC) testing.	Pus, blood, respiratory samples,urine, tissue,ear swab, nasal swab, skin swab and fluids.	2008-42% 2009-40%	Resistance to antibiotics amongst the MRSA isolates was more than that in methicillin sensitive S. aureus (MSSA).
12	C. Bouvchait et.al 2015 [20]	November 2011-February 2012	Bangalore	92	48	Cefotoxin disc diffusion method	SSTI, UTI, Respiratory infection.	72.70%	MRSA-52.2% For CA-47.5% For HA-61.3% Resistance to Erythromycin-54.3% ciprofloxacin-85.4%
13	Neerja Jindal, Rubina Malhotra	2012-2013	Punjab	248	161	Antibiotic susceptibility test.	pus, blood, urine, body	64.90%	Resistance to Erythromycin-63.3%

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	et.al 2016 [21]						fluids, catheter tips etc.		Clindamycin - 29.8% Gentamicin-18% Ciprofloxacin-69.6% Ampicillin-82% Co-trimoxazole-57.1
14	Devarsi Choudhury et.al 2016 [22]	January 2014 - June 2015	Assam	724	311	Kirby-Bauer disc diffusion method	blood, urine, pus and ear swab.	42.96%	Resistance to Cefuroxime-59.50% Amoxicillin and Clavulanic acid-34.40% Gentamicin-24.73% Levofloxacin-20.43% Ciprofloxacin-20.07% Ceftriaxone-9.68% Nitrofurantoin-8.22% Amikacin-4.66%
15	Rojaleen Das et.al 2017 [23]	January 2016 - December 2016	India (AIIMS)	479	107	standard biochemical tests and susceptibility to oxacillin was determined using the cefoxitin (30 µg)	Soft tissue	22.30%	Resistance to Amikacin-68.2% ciprofloxacin-80.3% Erythromycin-44.8% rifampicin-1.8% significant

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						disc diffusion method.			decline in nosocomial MRSA SSTIs- 38.5% in 2002 41.3% in 2005-2007 22.3% in 2016
16	Chandrima Bhattacharyya et.al 2017 [24]	December 2014 - June 2015	Eastern India	122	20	cefoxitin disk on Mueller-Hinton agar and phenotypic testing.	Clinical specimen	17%	20 isolates were found to be positive for mecA gene. isolates in this study were predominantly of SCCmecA Type IV
17	T.P. Rajesh et.al 2018 [25]	January 2016 - June 2018	Kerala	403 In 2016-125 In 2017-205 In 2018-73	173 In 2016-54 In 2017-90 In 2018 29	30 µg cefoxitin disc on Mueller–Hinton agar.	30 µg cefoxitin disc on Mueller–Hinton agar. Blood, pus, urine, sputum Blood, pus, urine, sputum	2016-43.2% 2017-43.9% 2018-39.7%	Resistance to Amikacin-13.9% Azithromycin-83.3% Ciprofloxacin-74.8% Clindamycin-35.7% Co-trimoxazole-32.2% Erythromycin-65.2%

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									Gentamycin-37.0% Levofloxacin-72.60% Norfloxacin-94.2% Ofloxacin-64.1% Penicillin-100% Tetracycline-64.1%

Epidemiological studies of MRSA assessed in different geographical locations of India were included. The maximum number of patients were from all over India. The clinical diagnosis of MRSA was performed by standard methods in all included studies. The isolates of MRSA were obtained from a variety of clinical samples such as sputum, nasal swabs, urine, respiratory tract specimen and blood.

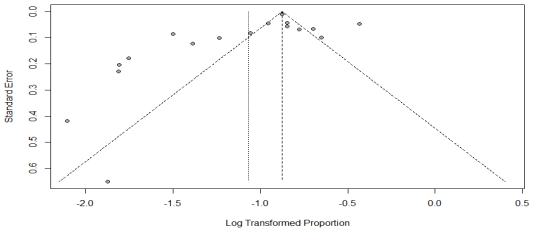
Risk of bias assessment

The included studies were analyzed for risk of bias before meta-analysis. The majority of studies included in the present meta-analysis were determined as low risk of bias. However, few studies were found with a moderate risk of bias due to undetermined data.

Prevalence of methicillin-resistant Staphylococcus aureus (MRSA) strains

The prevalence of MRSA infection among confirmed S.aureus isolates was found to be 37.34% (Table 2). Table 2 shows stratified analyses according to the different geographic locations of India among the included studies. The prevalence of MRSA infection among confirmed S.aureus isolates was higher in northern India when compared to other parts of India. Figure 2 represents the forest plot of the meta-analysis of MRSA prevalence. The forest plot represents the 95% CI of all the included studies except three studies overlap mid-value. The 95% CI of the overall effect estimate also overlaps mid-value. So, there is a statistical significance at the study level except for three studies ($p<0.01$). However, there is no statistical significance at the meta-analysis level. Figure 3 shows the funnel plot of the meta-analysis of MRSA prevalence. The funnel plot reveals the effect estimates from independent studies against the measure of sample size. In Figure 3, the outer dashed lines specify the triangular area within which 95% of included studies are anticipated to lie in the absence of both heterogeneity and biases (fixed effect summary log-prevalence rate ± 1.96 x standard error of summary log odds ratio). The solid vertical line agrees to no intervention effect.

Figure 3: Funnel plot of the meta-analysis on the prevalence of methicillin-resistant Staphylococcus aureus (MRSA) infections



Funnel plot of Standard Error by Log Transformed proportion

Table 2: Prevalence of MRSA infection in different parts of India

SUBGROUP	NUMBER OF STUDIES	PREVALENCE OF MRSA	n/N

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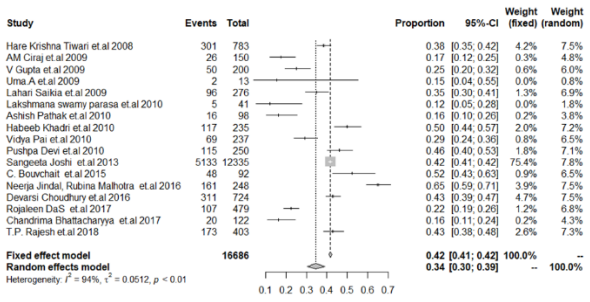
Overall	17	37.34 %	12701/30618
North India	4	41.41 %	593/1379
South India	7	40.87 %	440/1171
East India	3	31.58 %	514/1479
West India	1	25 %	50/200
Entire India	2	31.65 %	11104/26389

N – Total number of Staphylococcus aureus

n – Number of MRSA isolates

Figure: 2 Forest plot of the meta-analysis on the prevalence of methicillin-resistant Staphylococcus aureus infections.



CI - confidence interval.

DISCUSSION:

Early identification of resistant strains of S. aureus and proper implementation of infection control measures could benefit in reducing the burden of MRSA infection. In the present scenario, the occurrence of MRSA is in a worrisome state, as the fact that most S. aureus strains are resistant to various antibiotics and treatments currently provided for MRSA infection have low success rate [26]. Hence, the research interest shown towards the development of newer antibiotics is less. Thus, vaccination might be favorable to the high-risk population such as patients undergoing dialysis, patients with endocarditis, prisoners and health care workers who are significant sources of spreading hospital-associated MRSA infection. Therefore, many scientists are focusing on the development of vaccines and monoclonal antibodies instead of new antibiotics, since the procedure for developing vaccines is comparatively inexpensive and easy [26].

The prevalence of MRSA keeps changing since its emergence. The percentage of MRSA isolates among the American and European populations ranges from 29% to 35%. Recently, a rise in the prevalence of HA-MRSA and CA-MRSA infections has been reported in the Indian population [4]. However, the epidemiological studies of MRSA in India are not frequently reported due to the non-uniformity among the prevalence of MRSA among the Indian population. So, the present meta-analysis reports the prevalence estimates of MRSA infection in different geographic locations of India. According to the meta-analysis performed, the pooled prevalence of MRSA infection was found to be 37.34% (Table 2). A meta-analysis conducted by Wong et al reported that the prevalence of MRSA among hospital settings ranges from 0.7% to 10.4% and MRSA among community settings ranges from 0% to 23% in the Asia-pacific region [27]. Further, a meta-analysis performed by Wu et.al reported that the prevalence of MRSA was found to be 21.2% in the Chinese population [28]. Further, a meta-analysis performed by Reta et.al has reported that the rate of MRSA prevalence was 30.90% [29]. The overall prevalence of MRSA in our study was found to be 37.34%, which is almost similar to Rajkumar et.al. 2017 study [30]. However, the findings of the present study are not similar to Ghia CJ et.al 2020 study since there is a variation among the inclusion criteria of the study [31].

The variation in the prevalence of MRSA across various geographic regions of India may be attributed to a difference in the ethnicity of study participants included, changes in the methods of isolation and detection of MRSA, the economical status of study regions and lack of health care service availability [7]. Additionally, there is an unselective, irrational use of antibiotics and improper implementation of prophylactic sanitization are the main reason for a drastic increase in MRSA prevalence in India. The findings of the studies included in the present meta-analysis have suggested that vancomycin hydrochloride, oritavancin and arbekacin sulfate as

therapeutic options for the management of MRSA in India [32, 33]. The clinical outcomes after administration of these antibiotics are reported to be beneficial in the management of MRSA infection.

The present meta-analysis has included a large number of studies with a sufficient sample size. Furthermore, our meta-analysis was conducted to provide prevalence data on MRSA in the Indian population and identifies that MRSA should be considered as a serious public health issue in India. However, we need to discuss further certain limitations of the present study. Firstly, heterogeneity in the prevalence of MRSA was observed among the included studies. Data available for CA-MRSA and HA-MRSA among included studies were undetermined. The current study cannot represent the entire prevalence of MRSA in India since the epidemiology of MRSA has not been studied extensively in many regions of India. Thus, future epidemiological studies are required to estimate the frequency of MRSA across different regions of India to facilitate its mitigation.

CONCLUSION:

Our meta-analysis reports that there is an increase in the prevalence of MRSA in India when compared to other Asian countries, which necessities systematic surveillance of nosocomial infections. Being a public health concern, implementation of standard infection control measures is required to reduce the risk of MRSA transmission among the Indian population. A Futuristic approach towards the development of rapid diagnostic tests for MRSA screening will be beneficial for its early management.

Abbreviations:

CA-MRSA - Community-Associated Methicillin-Resistant Staphylococcus aureus

CI – Confidence Interval

GCP - Good Clinical Practice

HA-MRSA - Hospital-Associated Methicillin-Resistant Staphylococcus aureus

ICMR - Indian Council of Medical Research

MOOSE - Meta-Analysis of Observational Studies in Epidemiology

MRSA - Methicillin-resistant Staphylococcus aureus

PRISMA - Preferred Reporting Items for Systematic review and Meta-analysis

SCCmec - Staphylococcal cassette chromosome mec

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Conflict of interest:

The authors declare no competing interests.

Ethical approval:

Not applicable

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