

**EPIDEMIOLOGICAL STATUS OF METHICILLIN RESISTANCE
STAPHYLOCOCCUS AUREUS (MRSA) IN INDIA****Vinod H. Jadhav^{*1}, Gunjan P. Malode², Chanchal M. Rathod³**¹Doctor of Philosophy, Pharmaceutical Sciences, Parul University, Vadodara, Gujrat, India,
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Attribution 4.0 International license.**ABSTRACT**

Staphylococcus aureus (S. aureus) persists as specifically prominent causes of mortality and morbidity globally. The antibiotic-resistant strains in specific methicillin-resistance S. aureus (MSRA) is the root cause to develop resistance against antibiotics. Methicillin-resistance in *Staphylococcus aureus* (MRSA) appeared within two years of initial use of methicillin. To find relevant scientific publications linked with wise epidemiological burden of MRSA (CA-MRSA, HA-MRSA) in different regions of India, the literature search was conducted using PubMed, Pubmed central and Google Scholar. Search terms involved worldwide prevalence of MRSA, Risk Factors for MRSA, Resistance of MRSA and Clinical outcome, Epidemiology of MRSA in India, Incidence of HA-MRSA in Indian Settings, Incidence of CA-MRSA in Indian Settings. The literature search included evidence on incidence of HA –

MRSA from 11 studies and incidence of CA-MRSA from 12 studies. The present review collectively developed a data of epidemiological burden of MRSA (HA-MRSA and CA-MRSA) in different years from different regions. Additionally, in present article we exposed the threat of MRSA in Indian settings. There is strong need to investigate the current epidemiological burden from all the regions of India and to develop strategies to overcome the threat of MRSA in future.

KEYWORDS: Staphylococcus aureus, MRSA, Epidemiology, CA-MRSA, HA-MRSA.

INTRODUCTION

Globally, Staphylococcus aureus (*S. aureus*) continues to be one of the leading causes of morbidity and mortality. The primary reason for the spread of antibiotic resistance is the presence of antibiotic-resistant bacteria in particular methicillin-resistant *S. aureus* (MRSA).^[1] Methicillin-resistant Staphylococcus aureus (MRSA) first emerged two years after methicillin was first used.^[2] In many hospitals throughout the world, MRSA is the antimicrobial-resistant infection with the highest prevalence. The reported prevalence in Europe was 17%.^[3] It is predicted that 150,000 individuals from the European Union contract MRSA infections each year +4. According to reports, resistance is most prevalent in Europe's north to south region. According to epidemiological data from the European Antimicrobial Resistance Survey, roughly 25% of MRSA infections were found in Croatia, Israel, Spain, Italy, Israel, Croatia, and Greece.^[5]

2011 Data suggests 11,285 documented fatalities among an estimated 80,461 populations infected with invasive MRSA in the United States.^[6] Incidences of MRSA bloodstream infections that started in hospitals and communities between 2005 and 2016 decreased by 74% and 40%, correspondingly.^[7] In a hospital context, the Epidemiology of MRSA may change depending on the particular clinical scenario. According to an investigation from north India, orthopaedic patients (46.67 percent) and general surgery (35.42 percent) wards had the highest MRSA prevalence rates. 81.34 percent of patients had multi-drug resistant MRSA, which is defined as resistance to more than three drugs.^[8] The Incidence of MRSA among *S. aureus* isolates in India varies across community and hospital settings, ranging from 40% to 70%. India estimates a frequency of MRSA around 40 and 70 percent between hospitals and populations.^[9]

In a hospital setting, prevalence of MRSA may vary in different clinical situations. A study from north India reported highest MRSA prevalence in the orthopaedics patients (46.67%) followed by general surgery (35.42%) wards. Multi-drug-resistant MRSA defined as resistance to >3 antibiotics was reported in 81.34% patients.^[8] The prevalence of MRSA in India ranges from 40% to 70% among *S. aureus* isolates, with variations observed between hospital and community settings India reports 40%-70% of prevalence of MRSA observed between hospitals and populations.^[9] The major MRSA infection is community acquired type

MRSA and it is increasing in India.^[10] Region-wise, the prevalence of MRSA was reported to be 41% in the North, 43% in the East, 33% in the West, 34% in the South, 36% in the Central, and in 40% in the North-East region.^[11] Even though widespread data were suggestive of antibiotic resistance were majorly reported in Europe, America, and Australia, MSRA prevalence recounted in all continents. Majority of nations were accounted for surpassing 20% and, sporadically, up to 80%.^[12]

MRSA infections are one of the major triggers of hospital-acquired infections and is most frequent cause of morbidity, mortality, long term hospitalization, and cost Burden. Additionally, MRSA infections are considered of two different types one is hospital associated (HA-MRSA) infections and another is community-associated (CA-MRSA).^[13]

In nursing home patients, it can spread to skin, vascular catheters and wound area as well as to the nasopharyngeal region. Among colonizing strains of *Staphylococcus aureus*, methicillin-resistant strains involved in subsequent hospital infections. Recent antibiotic therapy, an ICU stay, Intravenous catheterization, soft tissue wounds, and a prior contact with MRSA are the major risk factors for infection after colonization.^[14] Majority of MRSA cases found in hospitals, relevant health care environments, and patients under these healthcare facilities. However, cases involving MRSA not associated with such healthcare environment are also increasingly reported.^[15] The other form of MRSA is Community-acquired methicillin-resistant *S. aureus* (CA-MRSA) which is recognised for speedy community transmission and producing hostile skin infection, soft tissue infections and community acquired pneumonia.^[16]

The present review aims to discuss the year-wise epidemiological burden of MRSA (CA-MRSA and HA-MRSA) in different regions of India. The secondary aim was to identify the year and the region in which incidence of MRSA was highest.

METHOD

To find relevant scientific publications linked with wise epidemiological burden of MRSA (CA-MRSA and HA-MRSA) in different regions of India, the literature search was conducted using PubMed, Pubmed central and Google Scholar. Search terms involved worldwide prevalence of MRSA, Risk Factors for MRSA, Resistance of MRSA and Clinical outcome, Epidemiology of MRSA in India, Incidence of HA-MRSA in Indian Settings,

Incidence of CA-MRSA in Indian Settings. The literature search included evidence on incidence of HA-MRSA from 11 studies and incidence of CA-MRSA from 12 studies.

OVERVIEW OF MRSA AND EPIDEMIOLOGICAL BURDEN

Risk Factors for MRSA

HIV infection, admission to nursing homes, haemodialysis, ICU admission, recent hospitalisation, open wounds, Long-term hospitalisation, recent antimicrobials use, broad-spectrum antimicrobial, MRSA colonisation, medical interventions, and central venous access for longer time or lengthy implantable catheterization are the most commonly identified possible threats for MRSA infection. Healthcare professionals that have contact with the patient who suffers from MRSA infections these risk factors are responsible for high prevalence of MRSA infections. Additionally, people with age more than 65 are more prone to MRSA infection. A potential threat for MRSA colonisation includes living in an area with high incidence of CA-MRSA or being hospitalised with an increased number of HA-MRSA. MRSA faces significant risks from past hospitalisation and related infections, soft tissue infections, including bacteraemia and pneumonia.^[17,18]

Resistance of MRSA- Clinical outcome

Methicillin resistance develops due a penicillin-binding protein (PBP-2a) which is encoded by *mecA* gene that supports organism to flourish and multiply in the existence of methicillin and other beta-lactam antibiotics.^[19] Staphylococcus develops resistance to β -lactam structure which are not hydrolysed by β -lactamase (methicillin, oxacillin, nafcillin, dicloxacillin and cloxacillin) is considered as pure methicillin resistance.^[20] Population with MRSA colonized presents MRSA in their noses, on the skin, and probably on other parts of body. However, they may not affect these parts much but may transfer the germs to others. Additionally in hospital MRSA can continue from patients to patients and or from patients to health workers. Likewise, it can spread through objects, skin to skin contacts, close contact with an infected individual.^[21]

CA-MRSA is leading cause of SSTI (cellulitis, necrotizing fasciitis and diabetic foot ulcers). Moreover, these infections are multidrug resistant leading to reappearance, long term hospitalization and mortalities.^[22,23] Evidence shows MRSA associated morbidity and mortalities are seen widely in elder, hospitalized patients, and those who live with organ dysfunction. The MRSA associated deaths are majorly seen in patients with end stage liver disease, renal insufficiency and those admitted to the ICU. Staphylococci are the most

frequent cause of bone and joint infections. However, several evidence revealed Oxacillin resistance in those patients. MRSA infection can result in osteomyelitis of spine, hematogenous infection to longer bones of upper and lower extremities. Additionally septic arthritis of native and prosthetic joints may occur due to MRSA. MRSA is a prominent cause behind hospital-acquired and ventilator-associated pneumonia.^[13] Several CA-MRSA isolates hold Panton-Valentine leucocidin (PVL) gene which is linked with breakdown of white blood cells and tissue necrosis resulting skin and soft tissue infections in children's and young adults. Additionally, it causes dangerous multilobed, necrotizing pneumonia develops with or followed by CA-MRSA infection.^[24] A data from National hospitalization number when analysed in 1999 to 2005 were revealed MRSA associated hospitalization were increased (n=278,2023).^[25] Additionally, a study from veterans' health administration (VHA) uncovered MRSA is responsible for pneumonia to develop frequently, nearly 20-40% of pneumonia case that presents after 48 hours are considered due to MRSA infection.^[26]

Epidemiology of MRSA in INDIA

In India, MRSA has become prevalent. MRSA prevalence ranges from 25% in the western portion of India to 50% in the southern part. In India, community-acquired MRSA (CA-MRSA) is becoming more common. Data from a retrospective study that was done in 15 Indian tertiary care Hospitals from January 2008 to December 2009, to find out the incidence of MRSA. The study comprised 26310 isolates in all. During the period of study, MRSA incidence was present in 41% of cases overall, OPD, (28%) inpatient settings (42%) and the ICU (43%) respectively, in 2008 and 27, 49, and 47%, in 2009.^[27] In Bombay, Delhi, and Bangalore, a surveillance study showed a sizable proportion of MRSA-infected people. 13,610 test specimens in aggregate were collected from various locations. Of the total 739 *S. aureus* samples, 235 (32%) were discovered to be MRSA-infected people, with the percentages in each city being 27 percent (Bombay), 42.5 percent (Delhi), and 47 percent (Bangalore).^[28]

At a tertiary care centre in Central India, Mallick S. et al. discovered that MRSA had affected half of the population which were observed in the prevalence study. 145 (51.8%) of the 280 Isolates examined were MRSA strains, and 51 (35.2 percent).^[29]

Incidence of HA-MRSA in Indian Settings

Previous year, Preeja P, et al conducted a cross-sectional study in a tertiary care hospital in Mangalore to investigate the incidence of HA-MRSA and CA-MRSA. Of total 520 *S. aureus*

isolates 362 samples were obtained from Inpatients (IP) and 158 samples were obtained from outpatients, Further, only 132 MRSA isolates acquired from 94 inpatients and 38 outpatients. Of these, HA-MRSA incidence revealed in 52.1 % of Inpatients and 5.3 % in outpatients.^[30] Ganapuram A, et al investigated 30 samples of MRSA in a tertiary care hospital, Hyderabad, India. Of total MRSA infections 40% were HA-MRSA, of these total MRSA infections, 44.4% were induced by SCCmec type IV and type V.^[31] Bouchiat C, et al studied prevalence of *S. aureus* in Bangalore, India. From this one-year retrospective data it was observed that of total 92 collected strains 52% were MRSA infected, out of these MRSA strains 39.6% were HA-MRSA.^[32] Jana H, et al conducted prospective study in a tertiary care hospital of West Bengal to identify the incidence of HA-MRSA and CA-MRSA. Over the three months 940 clinical samples were acquired from the hospitals and assessed using orthodox microbiological methods. Of total 940 samples 122 were *S. aureus* positive and 23 were MRSA positive. The study exposed 65.21% HA-MRSA infections.^[33] Uria G, et al reported 82 HA-MRSA infections out of 201 in one-year prospective study from private district healthcare centre of a rural region of Andhra Pradesh. HA- MRSA were revealed in more than half of the infections (67%) from SSTI (pus or exudes), blood cultures indicated 23% infection, 5% isolates were from sputum, 2% from urine and rest of another specimen indicated 3%.^[34]

A cohort study from southern India conducted in tertiary care hospitals in the year 2011-2012 revealed significant incidence and mortalities for MRSA infections. 284 (52%) of the 551 total participants tested positive for MRSA. A total of 184 individuals (65%) had HA-MRSA. Hospitalizations for longer period, more complications, and mortality are more common among patients suffering MRSA infections.^[35] From 2010 to 2011, Eshwara V, et al. recorded a retrospective data (prevalence, clinical and analytical data) on every case of *S. aureus*. A total of 70 instances of *S. aureus* were reported, of these, 54 percent were MRSA, and 69 percent of these patients had HA-MRSA infection.^[36] Dhawan B, et al conducted descriptive type of investigation in the year between 2009 to 2011 at a tertiary care centre (All India Institute of Medical Sciences-AIMS), New Delhi, India. Total 200 isolates of MRSA from hospital-based source HA-MRSA. Out of total HA-MRSA samples 37.5% were of genotype SCCmec IV/V type which was responsible for comorbid conditions like malignancies and bone fractures.^[37] Additionally, A cross-sectional study aimed to assess MRSA incidence and antibiotic sensitivity patterns by Arora S, et al. in the GMC (Government Medical College)-affiliated hospitals in Amritsar, Punjab. Around 6743

clinical samples (such as vaginal swabs, pus, sputum, blood, urine, etc.) collected from individuals hospitalised to in GMC-affiliated hospitals in Amritsar between 2008-2009. Investigation revealed 250 coagulase-positive staphylococci (COPS). Around 115 cases (46%) were discovered to be MRSA.^[38] Tiwari H, et al assessed at the prevalence of HA-MRSA in several hospital wards between 2002-2006. At a 972-bed tertiary care hospital of Banaras, India. Among 783 strains of *S. aureus* had been isolated from a variety sample of various patients who visited and hospitalised. Of the 783 Strains isolated, 301 (38.44 percent) were MRSA, including 187 from OPD and 114 (14.55 percent) from hospitals. Investigation from MRSA specimens indicated Pus and wound specimens 42.2%, Respiratory specimens 34.6%, stream 26.7%, Catheterized 63.1%, Bone aspirate 12.5%, CSF, ascetic fluid, EPF, HVS 10%.^[39]

Dar J, et al evaluated 750 individuals between the year 2000 to 2003 to detect incidence, procurement and spreading of resistance gene. All the subjects revealed 850 strains of *S. aureus* notably, 575 strains were observed from clinical specimens, 100 strains from nasal isolates and 50 strains from eye and 125 strains from nasal cavity of hospital workers. Clinical samples were targeted to isolate the organism, after isolation isolates were cultures and evaluated following standard measures. *S. aureus* comprised 60.3% of the 850 clinical specimens of staphylococci examined. MRSA prevalence was 35.1% of these were MRSA.^[40] A total of 450 sufferers from the orthopedics and burns departments of the LN Hospital in New Delhi were included in the study by Vidhani S., et al. It lasted 10 months, from March 1998 to December 1998. 407 patients (90.4 percent) of these high-risk patients had bacterial growth visible in their wounds samples. *S. aureus* was recovered from 188 patients (41.8%), of whom 51.6 percent had MRSA.^[41]

Table No. 1: Region/state-wise prevalence of HA-MRSA.

Sr. No.	MRSA type	State/region	Type of study	Year	Incidence (%)	Author
1	HA-MRSA	Mangalore, Karnataka, Southern India	Cross-sectional study	2021	52.1 % (Inpatients) 5.3 % (outpatients).	Preeja P, et al
2	HA-MRSA	Hydrabad, Southern India	Prospective	2020	40%	Ganapuram A, et al
3	HA-MRSA	Bangalore, Southern India	Retrospective	2015	52%	Bouchiat C, et al
3	HA-MRSA	West Bengal, East India.	Prospective	2015	65.21%	Jana H, et al.
4	HA-MRSA	Andhra Pradesh,	Prospective	2011-2012	70.7%	Uria G, et al

		Southern India				
5	HA-MRSA	Southern India	Cohort	2011-2012	65%	Chatterjee A, et al
6	HA-MRSA	Karnataka, Southern India	Observational, Retrospective	2010-2011	69%	Eshwara V, et al.
7	HA-MRSA	New Delhi, North India.	Descriptive/ Prospective	2009-2011	37.5%	Dhawan B, et al
8	HA-MRSA	Amritsar, Punjab, North India.	Cross-sectional	2008-2009	46%	Arora S, et al.
9	HA-MRSA	Banaras, South-eastern, India	Cross-sectional	2002-2006	14.55	Tiwari H, et al
10	HA-MRSA	Aligarh (North India)	Prospective	2000 to 2003	35.1%	Dar, J.A etal
11	HA-MRSA	New Delhi, North India	Prospective	1998	41.8%	Vidhani S, et al.

Incidence of CA-MRSA in Indian Settings

Preeja P, et al conducted a cross-sectional study in a tertiary care hospital in Mangalore to investigate the incidence of CA-MRSA and HA-MRSA. Of total 520 *S. aureus* isolates 362 Inpatients and 158 outpatients were infected with MRSA. Further, only 132 MRSA isolates acquired from 94 inpatients and 38 outpatients. Of these, CA-MRSA incidence revealed in 47.9% of Inpatients and 94.7% in outpatients.^[30] Ganapuram A, et al examined 30 samples of MRSA in a tertiary care hospital, Hyderabad, India. Of total MRSA infections 60% were CA-MRSA, of these total MRSA infections, 33.3 % were induced by SCCmec type I and type III.^[31] In order to determine the prevalence of CA-MRSA and HA-MRSA, Jana H, et al. undertook a prospective investigation in a tertiary care hospital in West Bengal. 940 clinical samples were obtained from the hospitals over the course of three months, and they were examined using conventional microbiological techniques. 122 of the 940 samples overall were *S. aureus* whereas 23 people tested positive for MRSA. Incidence of 34.78 percent of CA-MRSA infections were shown by the study.^[33]

Uria G, et al reported 119 CA-MRSA infections out of 201 in one-year retrospective study from private district hospital of a rural region of Andhra Pradesh. The median age of infected population was 29 years. CA-MRSA were revealed in more than half of the infections (70%) from SSTI (pus or exudes), blood cultures indicated 12% infection, 9% isolates were from sputum, 2% from urine and rest of another specimen indicated 7%.^[34] Chatterjee A, et al conducted a cohort study from in tertiary care hospitals, southern India in the year 2011-

2012. The outcome from the study revealed significant prevalence and mortalities for MRSA infections. 284 (52%) of the 551 total participants tested positive for MRSA. A total of 100 (35%) had CA-MRSA. Hospitalizations for longer period, more complications, and mortality are more common among patients suffering MRSA infections.^[35]

Similarly, Goud R, et al studied epidemiological status of MRSA in one of the communities of Bangalore, south India. Total 1000 healthy peoples were included and Palms of hand, forearms and anterior nares were targeted to collect the samples. The final outcome revealed 16.6 % population indicated MRSA positive samples. Furthermore, 58.8% of childrens (1-5 years of age) were positive for MRSA. The highly affected age groups (4.4%) were <1 year, the age between 5-20 year indicated 21.7% MRSA infection, however >40 age group population presented 11% incidence, and young adults between 20-40 year presented 9.9% if overall MRSA infection.^[42] Eshwara V. et al. recorded a retrospective data (prevalence, clinical and analytical data) on every case of *S. aureus* from 2010 to 2011. A total of 70 occurrences of *S. aureus* were reported, of these, 54 % were MRSA, and 74 % of these patients had CA-MRSA infection.^[36] In the years 2009 to 2011, Dhawan B. et al. carried out a descriptive type of investigation at a tertiary care facility (All India Institute of Medical Sciences-AIMS), New Delhi, India. 100 MRSA isolates total from the community (CA-MRSA). Eighty-three percent of all CA-MRSA samples belonged to the genotype SCCmec IV/V, which was in charge of comorbid diseases like cancer and bone fractures.^[37]

Nadig S, et al studied the incidence of epidemic MRSA-15 (EMRSA-15) in Bangalore, southern India. Rural and tribal populations in the radius area of 350km around Bengaluru were targeted and other outpatients who went to Bangalore government-run Victoria Hospital., Nasal swabs were collected from these around 1500 resident people. *S. aureus* incidence in the rural areas was extremely low (3%), and of MRSA incidence (0.8%).^[43] A community-based cross-sectional analysis was carried out in a few schools in Karnataka, India. Between July 2009 and December 2010, 1503 children between the ages of 5 and 16 were approached. Out of 1503 patients examined, *s. aureus* was isolated among 441 children, and the incidence of *s. aureus* colonisation was calculated to be 29.3 percent (95 percent CI 27, 31.6). 17 (1.1%) children were found to have MRSA colonisation, with a 95% CI of 6, 17.^[44]

CA-MRSA and HA-MRSA incidence in Mumbai, India, totalling 412 in number, were assessed between years 2006-2009. D' Souza et al. discovered that 54% of them were genuine

CA-MRSA carrying the SCCmec IV and SCCmec V genes. Most were identified from SSTIs.^[45] Furthermore, a study from clinical labs in Kanchipuram, Tamil Nadu, Southern India, found that MRSA was prevalent in various demographics. The age category of 21–30 yrs yielded the most specimens (18), followed by the age category of 31–40 yrs (15 specimens). Specimens each from the 61–70 years old age category and the 1–10-year-old age category were collected. MRSA isolate incidence among ages ranging of specimen donors was 21%. The age range of 21–30 years acquired the highest proportion of 38.1 isolates, followed by the age group of 31–40 years. MRSA isolates were not discovered in the age groups of 1 to 10 or 61 to 70.^[46]

Table 2: State/region –wise Prevalence of CA-MRSA in Indian Settings.

Sr. No.	MRSA type	State/region	Type of study	Year	Incidence (%)	Author
1	CA-MRSA	Mangalore, Karnataka, Southern India	Cross-sectional study	2021	47.9% (Inpatients) 94.7% (OPD).	Preeja P, et al
2	CA-MRSA	Hydrabad, Southern India	Prospective	2020	60%	Ganapuram A, et al
3	CA-MRSA	West Bengal, East India.	Prospective	2015	34.78%	Jana H, et al.
4	CA-MRSA	Andhra Pradesh, Southern India	Prospective	2011-2012	64.7%	Uria G, et al
5	CA-MRSA	Southern India	Cohort	2011-2012	35%	Chatterjee A, et al
6	CA-MRSA	Bangalore, South India	Prospective	2011	16.6 %	Goud R, et al
7	CA-MRSA	Karnataka, Southern India	Observational, Retrospective	2010-2011	74%	Eshwara V, et al.
8	CA-MRSA	New Delhi, North India.	Descriptive/ Prospective	2009-2011	83%	Dhawan B, et al
9	CA-MRSA	Bangalore, Southern India	Prospective	2010	0.8%	Nadig S, et al
10	CA-MRSA	Karnataka, Southern India	Cross-sectional	2009-2010	1.1%	Govindan S, et al
11	CA-MRSA	Mumbai, West India	Prospective	2006-2009	54%	D'Souza N, et al
12	CA-MRSA	Kanchipuram, Tamil Nadu, Southern India	Retrospective	2007	14.55%	Prakash M, et al

DISCUSSION

The present review on epidemiological burden of HA-MRSA in India revealed Southern zone of India had highest epidemiological burden compared to other zones of India. From 2011-2012 (being highest-70.7%), 2020 (40%) and 2021 (52.1%) and was lowest burden in 2009-

2011 was 37% in north India. From 1998 to 2010, the burden was high in north India (41.8% - New delhi, 46% - Amritsar, Punjab). HA-MRSA prevalence in south zone indicated 69% (Karnataka), in 2009-2011, 70.7% (AP) in 2011-2012, 52% (Bangalore) in 2015, 40% (Hyderabad) in 2020, 52.1% (Karnataka) in 2021 and in west Bengal (east India) incidence was 65.21% in 2015.

CONCLUSION

The present review collectively developed a data of epidemiological burden of MRSA (HA-MRSA and CA-MRSA) in different years from different regions. Additionally, in present article we exposed the threat of MRSA in Indian settings. There is strong need to investigate the current epidemiological burden from all the regions of India and to develop strategies to overcome the threat of MRSA in future.

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