

Methicillin-Resistant *Staphylococcus aureus* among Clinical Isolates in Indonesia: A Systematic Review

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The high infection of methicillin-resistant *Staphylococcus aureus* (MRSA) accompanied by increased resistance to many groups of antibiotics is a major concern in the field of infection. This study aims to evaluate the prevalence of MRSA isolates and antimicrobial susceptibility to MRSA isolates in Indonesia. We did searches in Pubmed, Proquest, DOAJ, GARUDA, and google scholar for studies published in 2006-2020. Study in Indonesian (Bahasa) and English with the keywords "methicillin-resistant *Staphylococcus aureus*", "MRSA" and "Indonesia". More than 30 *S. aureus* isolates derived from human samples were included. A total of 738 articles based on the search results, 13 studies were included in this systematic review. The prevalence of MRSA reported from all studies is 0.3%-52%. The study with the largest prevalence of MRSA was found in Jakarta. The susceptibility of vancomycin antibiotics to MRSA isolates is known to range from 87%-100%. Based on all studies, Linezolid, Tigecycline, Nitrofurantoin, and quinupristin/dalfopristin were reported to have 100% susceptibility. The prevalence of MRSA is still found high in one of the cities in Indonesia. Surveillance of antibiotic use, monitoring of antimicrobial susceptibility patterns, and antibiotic resistance control programs need to be optimized. MRSA screening is based on a rapid diagnosis when an inpatient admission is also necessary.

Keywords: Methicillin-resistant *Staphylococcus aureus*, Indonesia, Systematic review.

Methicillin-Resistant *S. aureus* (MRSA) infections are a tenacious problem in many healthcare settings around the world¹. MRSA infections can range from mild, such as skin infections to bacteremia or sepsis. These infections include endocarditis, pneumonia, osteomyelitis, device-related, cellulitis, and impetigo in health and community care for people²⁻⁴.

In 2017, WHO included *S. aureus* as a pathogenic bacterium in the list of "high priority" pathogenic bacteria that required a new generation of antibiotics⁵. Since the 1960s, the prevalence of MRSA has increased at a dramatic rate and is associated with higher rates of morbidity and mortality⁶. MRSA was reported to reach 20% in all regions of the World Health Organization (WHO)

and more than 80% in some regions⁷. Resistant to methicillin confers resistance to all β -lactamase-resistant penicillins and cephalosporins⁸. Vancomycin has been an approved and effective option for treating *S. aureus* infections, especially MRSA. It has been successfully used worldwide for over 50 years. However, its effectiveness is questioned by the emergence of *S. aureus* strains that show intermediates to total resistance to this antibiotic⁴. Current therapeutic options approved by the Food and Drug Administration (FDA) for MRSA are limited like linezolid, teicoplanin, daptomycin, tedizolid, and streptogramins^{9,10}. In contrast, least resistance was observed to vancomycin⁹.

A hospital-acquired infection caused by *S. aureus* is widely reported throughout the world, mainly in Asia¹¹. The problem of antibiotic resistance in developing countries such as Indonesia, where infectious disease is rampant, is highly pronounced. *S. aureus* infections cause long hospital stays and increase health care costs⁹. *S. aureus* has gained resistance to most of the antibiotics shown by antimicrobial chemotherapy and once it is resistant, it will be difficult to control and eradicate⁹. To control the increase in antimicrobial resistance, it is necessary to collect data about the sensitivity and resistance of each antibiotic. Therefore, this systematic review aims to evaluate the prevalence and antimicrobial susceptibility patterns of MRSA from each study in Indonesia.

MATERIALS AND METHODS

Search strategy

This study refers to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method¹². A search was conducted in April 2020 on PubMed, Proquest, Directory of Open Access Journal (DOAJ), Garuda (<http://garuda.ristekbrin.go.id/>), and Google Scholar. We use search terms (“methicillin-resistant *Staphylococcus aureus*” OR “MRSA”) AND “Indonesia”. We also identified a list of references to search for additional studies.

Study selection and eligibility criteria

All studies reviewed are based on inclusion criteria: (1) Report the prevalence of MRSA; (2) *S. aureus* isolate samples are human

clinical specimens; (3) Publication of articles from January 2006 to March 2020; (4) Articles in English and Indonesian (Bahasa); (5) Isolates amount more than 30; (6) The study is an original journal article include cross-sectional, case-control and cohort. Studies that have less than 30 isolate bacteria do not accurately represent resistant bacteria¹³. Excluded studies, include: (1) review studies; (2) repetitive isolates; (3) does not explain the number of isolates and sensitivity test methods.

Two authors (RS, R) screened the titles and abstracts of the articles obtained from the initial search. To complete the selected articles, two authors (RS, R) read the full text and were assessed and selected based on inclusion criteria. The disagreement between the two authors was decided by discussion.

Data Extraction and Synthesis

All articles provide the following information: first author, year of publication, study location, study period, data type, sample source, a total of isolates, prevalence of MRSA, and antimicrobial susceptibility results. The data is presented in description and synthesized with a narrative.

RESULTS

Selection and characteristics of studies

Database search results on Pubmed, Proquest, GARUDA, and DOAJ get 733 articles. Additional articles were identified from Google Scholar and cross-referenced articles were obtained 5 articles. After eliminating duplication, a total of 656 articles are screened for title and abstract. After screening, a total of 43 full-text articles are carried out eligibility assessments. A total of 30 studies were excluded because they did not match with inclusion criteria and duplication of isolates in some studies. The majority of studies are excluded due to the number of *S. aureus* isolates that do not reach 30. The total articles to be included in 13 studies (Fig. 1).

The most studies for sample collection came from Jakarta^{14,15,16,17,18}. One multicenter study collected isolates from Padang, Denpasar, Malang, Semarang¹⁹. Besides, one study collected isolates from 2 cities is Surabaya and Semarang²⁰. Each of the other studies from Makasar, Pekanbaru, Sanglah, Bandung, Malang, Surabaya, Lampung^{14,21,22,23,24,25}.

Five studies are retrospective based on patient medical record data^{17,18,21,22,24}. A total of 8 studies are prospective studies^{14,15,16,19,20,23,25,26}. Seven studies used phenotypic sensitivity tests, two using genotypic, and five using both combinations. Based on all phenotypic tests showing that the most used are disk diffusions. MRSA isolates were taken from various clinical samples, including nose, wound, pus, blood, sputum, etc.

Prevalence of MRSA and Antibiotic Susceptibility

The prevalence of MRSA reported from each study was 0.3%-52%. The study with the largest prevalence of MRSA was conducted in Jakarta¹⁷. The lowest prevalence of MRSA was reported in multicenter studies in Surabaya and Semarang²⁰. Studies with the largest prevalence of MRSA did not perform sensitivity tests on other antibiotics. A total of 5 studies conducted antibiotic sensitivity tests on MRSA isolates (Table 2)^{14-16,23}.

The sensitivity of vancomycin antibiotics to MRSA isolates is known to be 87%-100%(14),(21),(22). Based on all studies, Linezolid, Tigecycline, Nitrofurantoin, and quinupristin/dalfopristin have 100% sensitivity.

DISCUSSION

Overall, the highest prevalence of MRSA reached 52%. This result was higher than the survey conducted through the SENTRY Antimicrobial Surveillance Program in 1997-2016 involving North America, Europe, Latin America, and the Asia-Pacific region of 40.3%. In the Asia-Pacific region, the SENTRY program reported MRSA amounting to 39.6%²⁷. In 2017-2018, Indonesia is not included in the Global Antimicrobial Resistance Surveillance System as reported by WHO, so there is no available prevalence of *S. aureus* resistance⁵.

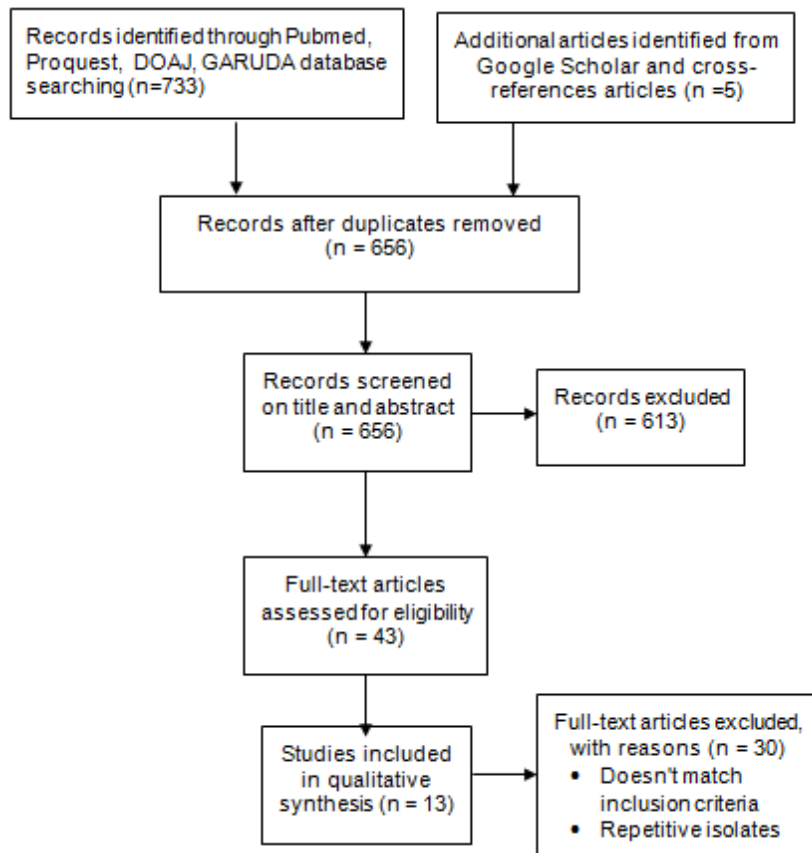


Fig. 1. Flow chart of the study selection process in this systematic review

Table 1. Summary of studies

Study	Study period, Location	Data type	Isolate Source	Total Isolate S.aureus	Isolate MRSA	Prevalence of MRSA (%)	Antimicrobial resistance test method
Wildana et al., 2010 (21)	July 2008 to June 2009, Makassar	Secondary	Clinical specimens	56	27	48.2	Not reported
Anggraini et al., 2020 (22)	1 Januari 2015 hingga 31 Desember 2018, Pekanbaru	Secondary	Pus and wound swabs	36	9	24	VITEK-2
Santika et al., 2014 (14)	August 2013 to October 2013, Sanglah	Primary	Clinical specimens	41	6	14.6	Compact Vitek 2 and disk diffusion
Suryatenggara et al., 2018(26)	August to October 2013, Jakarta	Primary	sputum, swabs (corneal, nasal, pustule, throat, ulcer, vaginal, wound), blood, pus/abscess, urine, and other sources	133	37	28	disk diffusion and PCR
Santosaningih et al., 2016(19)	January 2008 to January 2009 (Padang, Denpasar); October 2009 to January 2010 (Malang); April 2008 to October 2009 (Semarang)	Primary	Blood, pus, sputum, sterl sites	259	17	6.6	Vitek2 system and PCR
Severin et al., 2008(20)	July to October 2001 in Surabaya and January to May 2002 in Semarang.	Primary	Nasal swabs	329	1	0.3	PCR
Safari et al., 2015(15)	June to September 2011, Jakarta	Primary	Nasopharyngeal swabs	42	9	6	disk diffusion and PCR
Nelwan et al., 2018(16)	April and September 2015, Jakarta	Primary	Nasal swabs	60	3	0.8	disk diffusion and PCR
Lestari et al., 2017(17)	2011 and 2014, Jakarta	Secondary	Clinical specimens	46	24	52	Vitek 2 System and PCR
Erikawati et al., 2016(24)	2010-2014, Malang	Secondary	Blood, pus, sputum, urine	772	295	38.2	Vitek 2 System and PCR
Dahesihdew A et al., 2017(23)	January-December 2015, Bandung	Primary	Nasal, axilla and groin swabs	442	183	9.7	cefoxitin disk diffusion and chromogenic media
Putra et al., 2014(18)	January 2009 to April 2013, Jakarta	Secondary	Clinical specimens	381	179	47	disk diffusion
Setiawan et al., 2014(25)	Lampung	Primary	Hand swab	46	15	32.6	disk diffusion

Table 2. Prevalence of MRSA (%) and Antibiotic Susceptibility Patterns Reported in Each Study

Study	CLI	ERY	GEN	CIP	SXT	SUL	LZD	OFX	TET	TZP	CFZ	CRO	CAZ	FEP	NEO	NOR
Wildana et al.,2010(21)			37	38.5		47.4	100	48	22	76	46	15	8.3	76	44.5	37.5
Anggraini et al., 2020(22)	81	87	88	64			100				76	76	76			
Santika et.al, 2014(14)	83	67			83		100									
Suryatenggara et.al.2018(26)		41	30		81				41							
Safari et.al.2015(15)		56	67		67				56							

Abbreviations: clindamycin (CLI), erythromycin (ERY), gentamicin (GEN), ciprofloxacin (CIP), trimethoprim-sulfamethoxazole (SXT), sulbactam (SUL), linezolid (LZD), ofloxacin (OFX), tetracycline (TET), piperacillin-tazobactam (TZP), ceftazidime (CAZ), ceftioxone (CRO), ceftazidime (CAZ), cefepime (FEP), penicillin (PEN), tobramycin (TOB), levofloxacin (LVX)

Table 3. Prevalence of MRSA (%) and Antibiotic Susceptibility Patterns Reported in Each Study

Study	FOX	ETP	MEM	TGC	COT	AZM	VAN	NIT	QUD	OXA	CHL	AMX	ATM	CTX	CXM	DOX
Wildana et al.,2010(21)					40		96				38.5	12	0	20	36	32
Anggraini et al, 2020(22)	28	76	76	100	86	87	87									
Santika et.al, 2014(14)				100			100	100	100							
Suryatenggara et.al.,2018(26)									0	0	59					
Safari et.al, 2015(15)									0	0	67					

Abbreviations: ceftioxin (FOX), ertapenem (ETP), meropenem (MEM), tigecycline (TGC), cotrimoxazole (COT), azithromycin (AZM), vancomycin (VAN), nitrofurantoin (NIT), quinupristin/dalfopristin (QUD), oxacillin (OXA), chloramphenicol (CHL), amoxicillin (AMX), aztreonam (ATM), cefotaxime (CTX), cefturoxime (CXM), doxycycline (DOX), neomycin (NEO), norfloxacin (NOR)

Once the isolate *S. aureus* is identified as MRSA, it is immediately classified as MDR, because resistance to ceftazidime or oxacillin causes an inability to all categories of antimicrobial β -lactam (i.e. all categories of penicillin, cephalosporins, β -lactamase inhibitors, and carbapenem)²⁸. MRSA resistance to beta-lactam antibiotics is due to the order of the *mecA* gene, which is known to produce PB2a transpeptidase thereby lowering the affinity of organisms to bind to beta-lactam antibiotics. *S. aureus* resistant to penicillin can produce a penicillinase, which can hydrolyze the β -lactam penicillin ring, causing resistance to penicillin²⁹. Penicillin-resistant *S. aureus* has long been known since 1942. After being known for penicillin resistance, scientists developed a new semisynthetic penicillin-resistant penicillinase, called Methicillin, which is more resistant to the hydrolysis of β -lactamase^{30,31}.

The treatment option for MRSA is the Glycopeptide group such as Vancomycin and Teicoplanin, which can only be administered by injection³². Resistance to vancomycin has been reported since the year 2002³³. The results of this study show vancomycin are still sensitive to *S. aureus* and can be used in invasive MRSA infections^{14,21,22}. Other antibacterial agents to defy MRSA, include quinupristin/dalfopristin, linezolid, daptomycin, and tigecycline²⁸. In this review, quinupristin/dalfopristin, linezolid, and tigecycline were reported to be 100% sensitive.

The choice of empiric antibiotic for the treatment of MRSA infection depends on the type of disease, the local pattern of *S. aureus* resistance, drug availability, side effect profile, and individual patient profile. Empiric treatment of uncomplicated skin and soft tissue infections with suspected MRSA infection can be given oral antibiotics such as trimethoprim / sulfamethoxazole, tetracyclines (such as doxycycline or minocycline) and clindamycin³⁴. There were three studies in this review, tetracycline reported to be less sensitive to MRSA isolate^{15,21,26}. Excessive empirical antibiotic therapy can also be one of the contributing factors to resistance.

Risk factors in someone infected with MRSA consist of many things. Increased risk with activities or places involving crowding, skin-to-skin contact, and the use of shared equipment.

Some people who carry MRSA may continue to having MRSA infection. Intact skin, such as if there are blisters or incisions, is often the location of MRSA infection. Those who have surgery or receive inpatient medical care or have medical devices inserted into their bodies are at a higher risk of developing MRSA infections³⁵. Over-use and misuse of antibiotics can lead to resistance such as MRSA³⁶.

Based on all the studies reviewed, the location of the most isolated retrieval and the largest prevalence of MRSA came from Jakarta^{15,16,17,18,26}. This can be due to major cities such as Jakarta more microbiology examination laboratories with PCR for MRSA detection. Checks using PCR are quite sensitive, so it detects MRSA more. Multicenter research involving many locations including Jakarta and other cities is still needed to see the spread of MRSA in Indonesia.

In Indonesia, many large hospitals, especially vertical hospitals have performed the best standard of microbiology laboratory services following the Guidelines International (latest CLSI) and National (Ministry of Health). Based on PMK 8, 2015 national regulations on Hospitals Anti-Microbial Resistance Control Program (PPRA), antibiograms in hospitals are regularly developed and standardized at least once a year. Antibiograms must be prepared as one of the measurements elements in the ASP (National Standards Program Group) Standard³⁷. This antibiogram is considered local Empirical Antibiotics guidelines. Most of these antibiograms are not published, although there are also those in the publication. Also, based on our search for local articles published, some did not meet the inclusion criteria, so we were excluded. There are some limitations to this study such as other systematic reviews, potential publication biases may exist.

CONCLUSIONS

MRSA infections are still reported quite high in some studies. Vancomycin, linezolid, and Tigecycline are reportedly still quite sensitive to MRSA isolates. Existing antimicrobial control programs need to be maximized and evaluated in line with the MRSA report found.

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Conflict of interest

All authors declare no conflicts of interest in this paper.

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