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Antimicrobial Resistance and Infection Control

REVIEW

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Systematic review and meta-analysis of the epidemiology of vancomycin-resistance *Staphylococcus aureus* isolates

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Abstract

Background: Vancomycin-resistant *Staphylococcus aureus* (VRSA) is a serious public health challenging concern worldwide.

Objectives: Therefore, the objective of present study of 62 published studies was to evaluate the prevalence of VRSA based on different years, areas, isolate source, antimicrobial susceptibility testing, and the genetic determinants.

Methods: We searched the relevant articles that focused on the prevalence rates of VRSA in PubMed, Scopus, Embase, and Web of Science from 2000 to 2019. Statistical analyses were conducted using STATA software (version 14.0).

Results: The prevalence of VRSA was 2% before 2006, 3% in 2006–2014, and 7% in 2015–2020 that showed a 3.5-fold increase in the frequency of VRSA between before 2006 and 2020 years. The prevalence of VRSA was 5% in Asia, 1% in Europe, 4% in America, 3% in South America, and 5% in Africa. The frequencies of VRSA isolated from clinical, non-clinical, and mixed samples were 6%, 7%, and 14%, respectively. The prevalence of VRSA was 12% using disk diffusion agar method, 7% using MIC-base methods, and 4% using mixed-methods. The prevalence of *vanA, vanB*, and *vanC1* positive were 71%, 26%, and 4% among VRSA strains. The most prevalent genotype was staphylococcal cassette chromosomemec (SCC*mec*) II, which accounted for 57% of VRSA. The most prevalent staphylococcal protein A (*spa*) types were t002, t030, and t037.

Conclusion: The prevalence of VRSA has been increasing in recent years particularly in Africa/Asia than Europe/America. The most prevalent of genetic determinants associated with VRSA were *vanA* and SCC*mec* II. This study clarifies that the rigorous monitoring of definite antibiotic policy, regular surveillance/control of nosocomial-associated infections and intensive surveillance of vancomycin-resistance are required for preventing emergence and further spreading of VRSA.

Keywords: Antimicrobial resistance, Vancomycin-resistant *Staphylococcus aureus*, Systematic review and meta-analysis

Introduction

Staphylococcus aureus is a major human nosocomial and community-acquired pathogen that causes infections of the skin and soft tissues, and life-threatening systemic diseases and is associated with the high rate of morbidity and mortality worldwide [1–3]. It remains a challenging,

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global public health crisis due to the emergence and spread of methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *S. aureus* (VRSA) [1, 4]. Currently, MRSA and VRSA are categorized as agents of high significance with potential to cause considerably devastating worldwide mortality in the absence of effective containment and treatment options [1, 5, 6]. In addition, VRSA tends to be multi-drug resistant (MDR) against a diversity of currently available antimicrobial agents.

The glycopeptide vancomycin has been regarded as the last therapeutic agent for the treatment of infections due to severe MRSA and other resistant Gram-positive strains [7]. In 2002, the first case of VRSA was recovered in a 40-year-old Michigan woman with diabetes [8]. Hitherto, the previous in vitro literature proposed two mechanism underlying vancomycin resistance of VRSA: (1) Decreased permeability and thickened and poorly cross-linked cell wall, whereby many vancomycin molecules are trapped within the cell wall [1, 9], (2) Another type of vancomycin resistance in bacteria is mediated by several *van* gene clusters (plasmid-mediated) that are found in some Gram-positive pathogens specially, enterococcal species [1]. A recent published systematic review and meta-analysis, by Shariati et al. [10], analyzed the prevalence VRSA, vancomycin intermediate *S. aureus* (VISA) and heterogeneous VISA (hVISA) variability depending on different years and locations.

In current comprehensive systematic review and meta-analysis, we pooled the published studies that have reported the prevalence of VRSA, and made sub-group variability of the prevalence of VRSA in different years, areas, isolate source, and antimicrobial susceptibility testing. We also analyzed the genetic backgrounds of VRSA strains. The results of present study will help to more completely elucidate the current epidemiology of VRSA and will promote the more proper antimicrobial stewardship programs to combat, control, management and limit the development of these drug-resistant organisms.

Methods

Guidelines

This review is reported accordant with the Preferred Reporting Items for Systematic Reviews and Meta Analyses guidelines (PRISMA) [11].

Search strategy

Four bibliographic databases, including international databases (MEDLINE [PubMed], Scopus, Embase, and Web of Science) for relevant articles were searched (Until January 8, 2020) by using the following keywords: ("*Staphylococcus aureus*" OR "*S. aureus*" OR "Vancomycin Resistant *Staphylococcus aureus*" OR "Vancomycin Resistant *S. aureus*" OR "VRSA") in the Title/Abstract/Keywords fields. No limitations were used while searching the databases. But inclusion in the study for full analysis required at least the abstract to be available in English. The search strategy was designed and conducted by study investigators (E.K, S.K and M.SH). The detailed search strategy and complete list of studies included in the study are shown in Additional file 1: Table. References lists of all related studies were also reviewed for any other related publication. The records found through database searching were merged and the duplicates were removed using EndNote X7 (Thomson Reuters, New York, NY, USA). One of the team researchers randomly evaluated the search results and confirmed that no relevant study had been ignored. All these steps were done by the three authors (M.SH and any disagreements about article selection were resolved through discussion, and a fourth author (E.K) acted as arbiter.

Inclusion and exclusion criteria

Three reviewers (YW, E.K, and QW) screened all titles and abstracts independently and excluded irrelevant and duplicate articles first. Three reviewers then independently assessed the remaining articles for inclusion. Discrepancies were resolved by discussion. Identified studies, met the criteria of being original articles published in English, and concerning the prevalence of VRSA based on different years, areas, isolate source, antimicrobial susceptibility testing, and the genetic determinants. The exclusion criteria were as follows: (1) studies that contained duplicate data or were overlapping articles; (2) reviews, meta-analysis and/or systematic review, and conference abstracts or article without full text; and (3) VRSA rate was not presented or clearly reported; (4) articles that included fewer than 10 *S. aureus* isolates.

Data extraction

The following items were extracted from each included study: the last name of the first author, year of study, year published, continent, country, number of tested *S. aureus*, sample source, isolates number of VRSA, phenotypic and genotypic methods used, and the genetic determinants associated with VRSA isolates. Data were collected by two independent examiners and verified by another researcher (Additional file 1: Table).

Assessment of study quality

The quality of the included studies was assessed by 2 reviewers (N.S and M.H) independently using an adapted version of the tool proposed by the Newcastle–Ottawa assessment scale adapted for cross-sectional studies [12]. A score ranging from 0 to 7 points was attributed to each study (≥ 6 points: high quality, ≤ 5 points: low quality). A higher score indicated a higher study quality. A third

reviewer (E.K) adjudicated in any cases where there was disagreement.

Study outcomes

The main outcome of interest was the weighted pooled resistance rate (WPR) of strains resistant to vancomycin. A subgroup analysis was performed; (1) subgroup analyses were then employed by publication date (< 2006, 2006–2014, and 2015–2020), (2) geographic areas (continent/countries), (3) antimicrobial susceptibility testing, (4) quality of studies, (5) isolate source, and (6) the genetic determinants associated with VRSA.

Risk of bias within studies

Publication bias was analysed using Egger's linear regression test.

Statistical analysis

Cross-sectional studies presenting raw data on VRSA were included in the meta-analysis that was performed by computing the pooled using a random- effects model with Stata/SE software, v.14.1 (StataCorp, College Station, TX). The inconsistency across studies was examined by the forest plot as well as the I^2 statistic. Values of I^2 (25%, 50% and 75%) were interpreted as the presence of low, medium, or high heterogeneity, respectively. So, the DerSimonian and Laird random effects models were used [13]. Subgroup analyses were then employed by publication year, geographic area (continent/countries), antimicrobial susceptibility testing, quality of studies, isolate source and the genetic determinants associated with VRSA. Publication bias was assessed using Egger's test. All statistical interpretations were reported on a 95% confidence interval (CI) basis.

Results

Study selection

A total of 2751 records were identified in the initial search. From these, 2565 articles were excluded after an initial screening of the title and abstract due to their irrelevance and duplication. The full texts of the remaining 185 articles were reviewed (Fig. 1).

Study characteristics

From the 185 articles, 102 were excluded for the following reasons: meta-analysis, review, conference abstract and article without full text (n = 66), and non-relevant data or no data for VRSA (n = 36). Eighty-three studies included in qualitative synthesis (62 cross-sectional studies and 21 case reports) (Additional file 1: Table; Additional file 2: Figure S1). Finally, 62 cross-sectional studies [14–75] were included in this meta-analysis.

Risk of bias within studies

Publication bias was assessed for 62 studies (Additional file 2: Figure S1). The analysis displayed visual asymmetry of the funnel plot and a significant Egger's test ($P < 0.05$).

Characteristics of included studies

The 62 studies included [14–75] in the analysis investigated 807 VRSA isolates from 12,816 *S. aureus* isolates. Among the 62 studies included, 15 cross-sectional studies also investigated 367 VRSA isolates from 3925 MRSA isolates (Table 1). All 62 studies had a cross-sectional design. The quality of data was high in 43 (69.3%) studies and low in 19 (30.7%) studies. The forest plots that show the analyses for overall VRSA and subgroups are displayed in the Additional file 3: Figure S2. In addition, twenty-one case-reports [76–96] included in qualitative synthesis which were not taken into account during the meta-analysis, have reported 29 VRSA isolates between 1999 to 2019 among different continents (Additional file 1: Table). However, most case reports have been from America (n = 14 isolates) and Asia (n = 11 isolates) continent. There has been no report of VRSA isolates in Oceania.

The prevalence of VRSA in three study periods

To analyze the trends for changes in the prevalence of VRSA in more recent years, we performed a subgroup analysis for three periods (< 2006, 2006–2014, and 2015–2020) (Table 2, Fig. 2). As shown in the Table 2, the prevalence of VRSA gradually increased from 2% (95% CI 0–4) of 466 strains before 2006 to 6% (95% CI 3–9) of 6692 strains in 2006–2014, reaching 7% (95% CI 4–11) of 5798 strains in 2015–2020. Thus, the frequency of VRSA during the years 2006–2014 represents a threefold increase over the years before 2006. Additionally, the frequency of VRSA during the years 2015–2020 represents a ~ 1.2-fold increase over the years before 2015. The changes in VRSA and VRSA from MRSA prevalence between periods are showed in Fig. 2. The prevalence of VRSA from MRSA gradually increased from 1% (95% CI 0–5) before 2006 to 5% (95% CI 0–14) in 2006–2014, reaching 6% (95% CI 0–10) in 2015–2020.

Prevalence of VRSA at different locations

The prevalence of VRSA differed among geographic regions in the subgroup analysis, as shown in Table 1 and Figs. 3, 4, 5. The prevalence of VRSA was 5% (95% CI 3–8) among 11,074 *S. aureus* isolates in Asia, 1% (95% CI 0–5) among 456 *S. aureus* isolates in Europe, 4% (95% CI 2–7) among 395 isolates in America, 3% (95% CI 0–17) among 171 isolates in South America and 16 (95% CI 3–35) among 720 isolates in Africa. There has been no

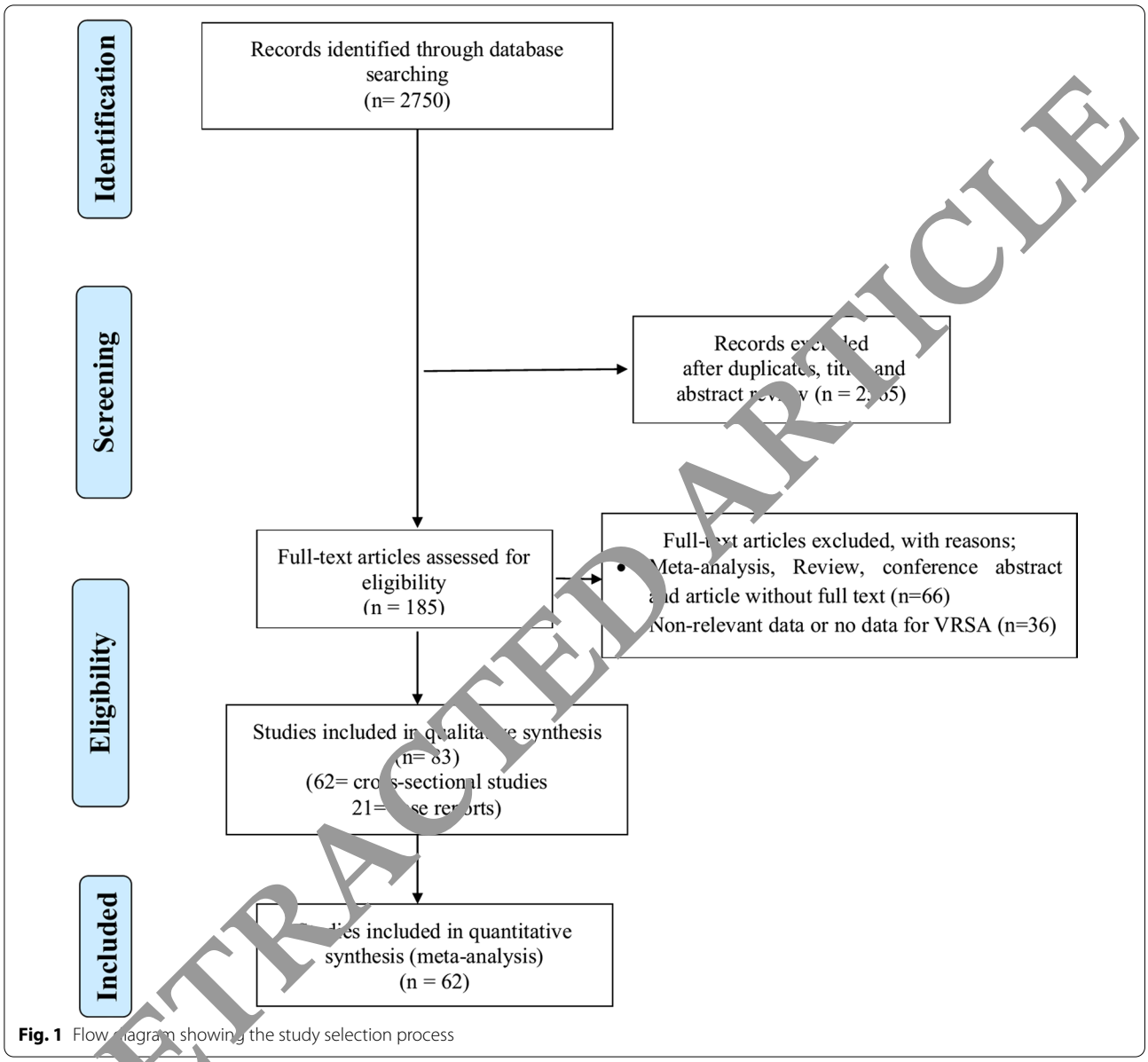

Fig. 1 Flow diagram showing the study selection process

reported VRSA from Oceania. The most frequent VRSA prevalence was 29% (95% CI 24–35) in Nigeria, followed by 18% (95% CI 12–26) in Saudi Arabia (Table 1 and Figs. 4, 5).

Prevalence of VRSA based on different clinical samples

In this subgroup analysis, we divided the VRSA strains into three groups (clinical, non-clinical, and both of them). In total, the frequency of VRSA was 14% (95% CI 0–44) in 501 *S. aureus* strains isolated from mixed (clinical, non-clinical) samples in four studies, higher than in the clinical samples in (6% [95% CI 4–8] in 11,891 *S. aureus* strains in 53 studies) (Table 1). The prevalence rate for VRSA was 7% (95% CI 1–15) in 424 non-clinical *S. aureus* strains in six studies.

Prevalence of VRSA based on AST methods

Disk diffusion agar and Mixed-methods were the most frequent antimicrobial susceptibility testing method (n = 33), followed by MIC-base methods (n = 25). The prevalence of VRSA was 12% (95% CI 2–27) among 6736 *S. aureus* isolates using disk diffusion agar method, 7% (95% CI 4–12) among 5671 isolates using MIC-base methods, and 4 (95% CI 2–7) among 6596 isolates using mixed-methods (Table 1).

Table 1 Prevalence of VRSA in *S. aureus* and VRSA in MRSA based on quality, continent, countries, isolate source, and AST method

Subject	Sub group	No. studies	No. strains	Proportion (95% CI)	%Weight	P	I^2	P sig
Overall	VRSA	62	12,816	0.06 (0.04, 0.09)	100	0	0.9574	0
	VRSA from MRSA	25	3925	0.06 (0.03, 0.09)	100	0	0.930	0
Quality								
High quality	VRSA	43	10,990	0.05 (0.03, 0.07)	70.83	0	0.959	0
	VRSA from MRSA	19	3390	0.07 (0.03, 0.12)	68.85	0	0.931	0
Low quality	VRSA	19	1826	0.1 (0.04, 0.17)	28.68	0	0.9460	0
	VRSA from MRSA	9	675	0.02 (0.01, 0.05)	31.15	0.03	0.5328	0
Continent								
Asia	VRSA	46	11,074	0.05 (0.03, 0.08)	5.03	0	0.9555	0
	VRSA from MRSA	22	3416	0.06 (0.03, 0.11)	82.	0	0.9443	0
South America	VRSA	2	171	0.03 (0.00, 0.17)	1.39			0.16
	VRSA from MRSA		–					
Africa	VRSA	7	720	0.16 (0.03, 0.35)	11.20	0	0.9706	0
	VRSA from MRSA	1	50	0.00 (0.0 ,)	3.06			0
America	VRSA	3	395	0.04 (0.02, 0.07)	6.48	0.23	0.3054	0
	VRSA from MRSA	2	272	5(0.03, 0.08)	8.08			1
Europe	VRSA	4	456	0. (0, 0.05)	5.90	0.03	0.6616	0.14
	VRSA from MRSA	2	187	0 (0 .02)	6.19			0.87
Countries								
Pakistan	VRSA	5	9	0.1 (0.01, 0.24)	8.40	0	0.9693	0.01
	VRSA from MRSA	3	301	0.07 (0, 0.25)	11.61			0.06
India	VRSA	14	5647	0.07 (0.03, 0.13)	23.42	0	0.9778	0
	VRSA from MRSA	6	29	0.06 (0, 0.18)	23.50	0.01	0.98	0.03
Brazil	VRSA	3	203	0.03 (0.01, 0.07)	4.48	0.00	0	0
	VRSA from MRSA	1	140	0.04 (0.01, 0.08)	4.08			0
Nigeria	VRSA	2	273	0.29 (0.24, 0.35)	3.30			0
	VRSA from MRSA							
Iran	VRSA	16	3464	0.02 (0.01, 0.04)	26.28	0	0.7848	0
	VRSA from MRSA	6	875	0.04(0.01, 0.08)	23.20	0.01	67.03	
Algeria	VRSA	3	583	0.01 (0, 0.04)	1.72			0.01
	VRSA from MRSA	1	220	0.02 (0, 0.05)	4.08			0.01
USA	VRSA	2	363	0.04 (0.02, 0.07)	3.39			0
	VRSA from MRSA	1	132	0.08 (0.04, 0.13)	3.66			0
Italy	VRSA	3	448	0.02 (0, 0.05)	5.03			0.02
	VRSA from MRSA	1	179	0.01 (0, 0.04)	4.10			0.03
Saudi Arabia	VRSA	2	128	0.18 (0.12, 0.26)	3.02			0
	VRSA from MRSA	1	98	0.15 (0.09, 0.24)	3.95			0
Tanzania	VRSA	1	53	0.11 (0.04, 0.23)	1.53			0
	VRSA from MRSA	–	–	. (.,.)				
Egypt	VRSA	4	394	0.16 (0.01, 0.45)	6.36	0	0.9719	0.02
	VRSA from MRSA	1	50	0 (0, 0.07)	3.66			1
Turkey	VRSA	5	469	0.05 (0, 0.14)	7.65	0	0.8895	0.02
	VRSA from MRSA	3	245	0.04 (0, 0.13)	9.56			0.1
Bangladesh	VRSA	2	73	0.12 (0.05, 0.21)	2.86			0
	VRSA from MRSA	2	73	0.27 (0.13, 0.43)	5.76			0
Germany	VRSA	1	8	0.13 (0, 0.53)	0.87			0.15
	VRSA from MRSA	1	8	0.13 (0, 0.53)	2.09			0.15
Jordan	VRSA	1	139	0.04 (0.01, 0.08)	1.68			0
	VRSA from MRSA	–	–	. (.,.)				

Table 1 (continued)

Subject	Sub group	No. studies	No. strains	Proportion (95% CI)	%Weight	P	I^2	P sig
Isolate source								
Clinical	VRSA	53	11,891	0.06 (0.04, 0.08)	84.56	0	0.9[illegible]	0
	VRSA from MRSA	23	5779	0.06 (0.03, 0.10)	85.92	0	0.9420	0
Clinical, non-clinic	VRSA	4	501	0.14 (0.00, 0.44)	06.54	0	0.981[illegible]	0.04
	VRSA from MRSA	1	179	0.01 (0.00, 0.04)	04.10			0.03
Non-clinical	VRSA	6	424	0.07 (0.01, 0.15)	8.91	0	0.[illegible]615	0
	VRSA from MRSA	3	245	0.04 (0.00, 0.13)	9.98			0.10
AST method(s)								
MIC-base	VRSA	25	5671	0.07 (0.04, 0.12)	[illegible]9.87	0	0.9599	0
	VRSA from MRSA	9	1223	0.09 (0.03, 0.17)	30.[illegible]	0	0.874	0
Mixed-methods	VRSA	32	6596	0.04 (0.02, 0.07)	51.95	0	0.9527	0
	VRSA from MRSA	17	4995	0.04 (0.01, 0.09)	64.48	0	0.9538	0
Disk diffusion	VRSA	33	6736	0.12 (0.02, 0.27)	[illegible].18	0	0.9532	0
	VRSA from MRSA	1	85	0.05 (0.0[illegible].17)	3.52			0.03

I^2: the percentage of variance in a meta-analysis that shows study heterogeneity. VRSA: Vancomycin-[illegible]*aphylococcus aureus*. MRSA: Methicillin-resistant *Staphylococcus aureus*. AST: Antimicrobial Susceptibility Testing. MIC: minimum inhibitory concentrati[illegible]n

Table 2 Prevalence of VRSA in *S. aureus* and VRSA in MRSA bas[illegible]d on [illegible]ar published

Subject	Sub group	No. studies	No. st[illegible]ns	Pro[illegible]portion (95% CI)	%Weight	P	I^2	P sig
2015–2020	VRSA	31	[illegible]98	0.07 (0.04, 0.11)	54.71	0	0.9579	0
	VRSA from MRSA	16	16[illegible]	0.06 (0.03, 0.10)	61.54	0	0.8246	0
2006–2014	VRSA	28	6692	0.06 (0.03, 0.09)	39.35	0	0.9620	0
	VRSA from MRSA	9	4408	0.05 (0.00, 0.14)	28.22	0	0.9771	0.01
< 2006	VRSA	4	[illegible]66	0.02 (0, 0.04)	5.93	0.17	0.3949	0.01
	VRSA from MRSA		327	0.01 (0, 0.05)	10.24	–	–	0.15

I^2: the percentage of variance in a meta-analysis [illegible]h[illegible]s study heterogeneity. *VRSA* Vancomycin-resistant *Staphylococcus aureus*, *MRSA* Methicillin-resistant *Staphylococcus aureus*

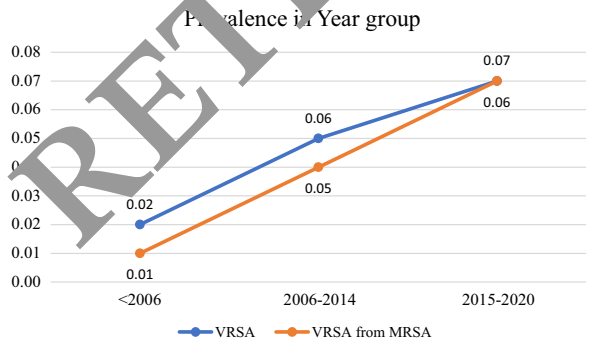

Fig. 2 The prevalence of VRSA in *S. aureus* and VRSA in MRSA based on published year

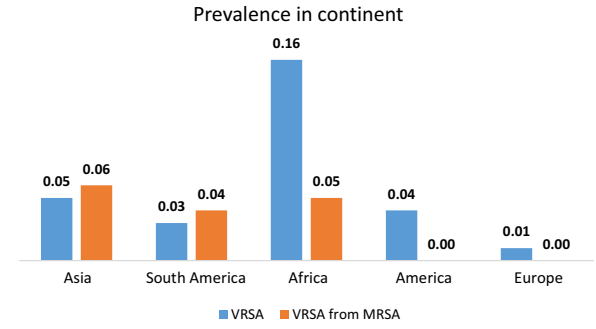

Fig. 3 Prevalence of VRSA in continent

Prevalence of genetic determinants associated with VRSA

The prevalence of *vanA*, *vanB*, and *vanC1* positive were %71 (95% CI 48–89), 26% (95% CI 5–52), and 4% (95% CI 0–55) among 250, 75, and 9 of the *S. aureus* strains, respectively (Table 3). The prevalence of SCC*mec* II, SCC*mec* III, and SCC*mec* IV were 57% (95% CI 33–8), 17% (95% CI 1–43), and 39% (95% CI 14–67) among the *S. aureus* strains, respectively (Table 3).

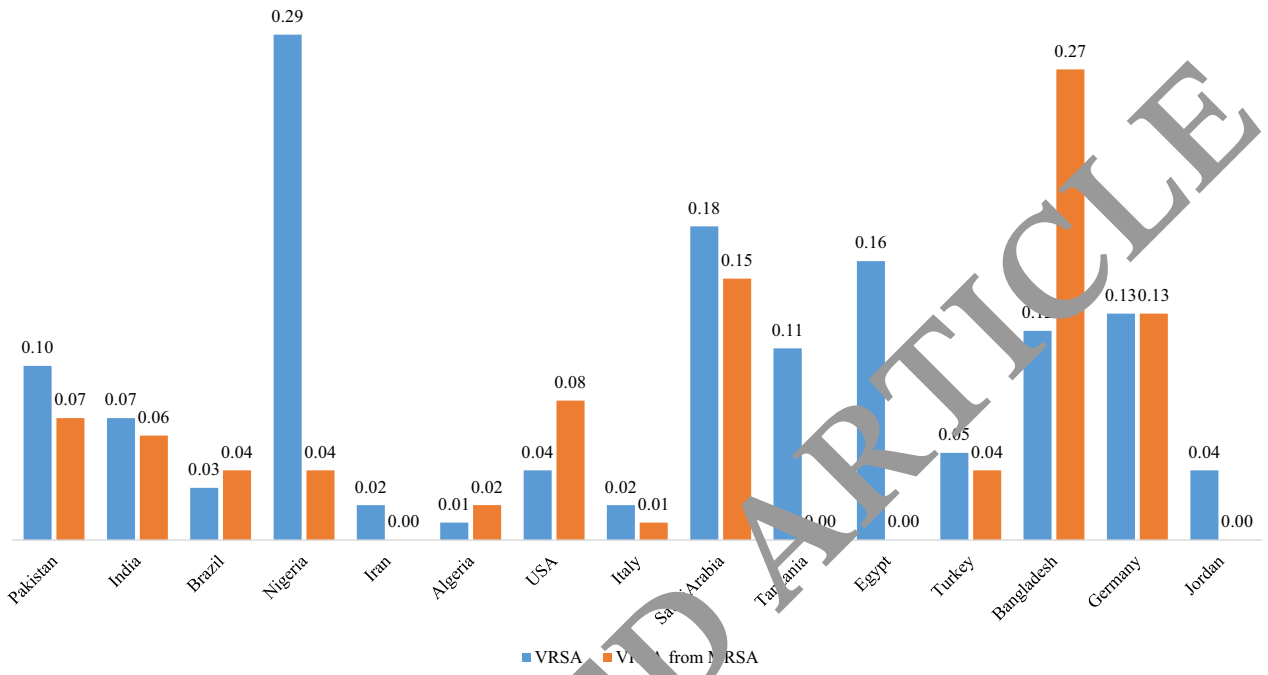

Fig. 4 The prevalence of VRSA in *S. aureus* and VRSA in MRSA based on countries

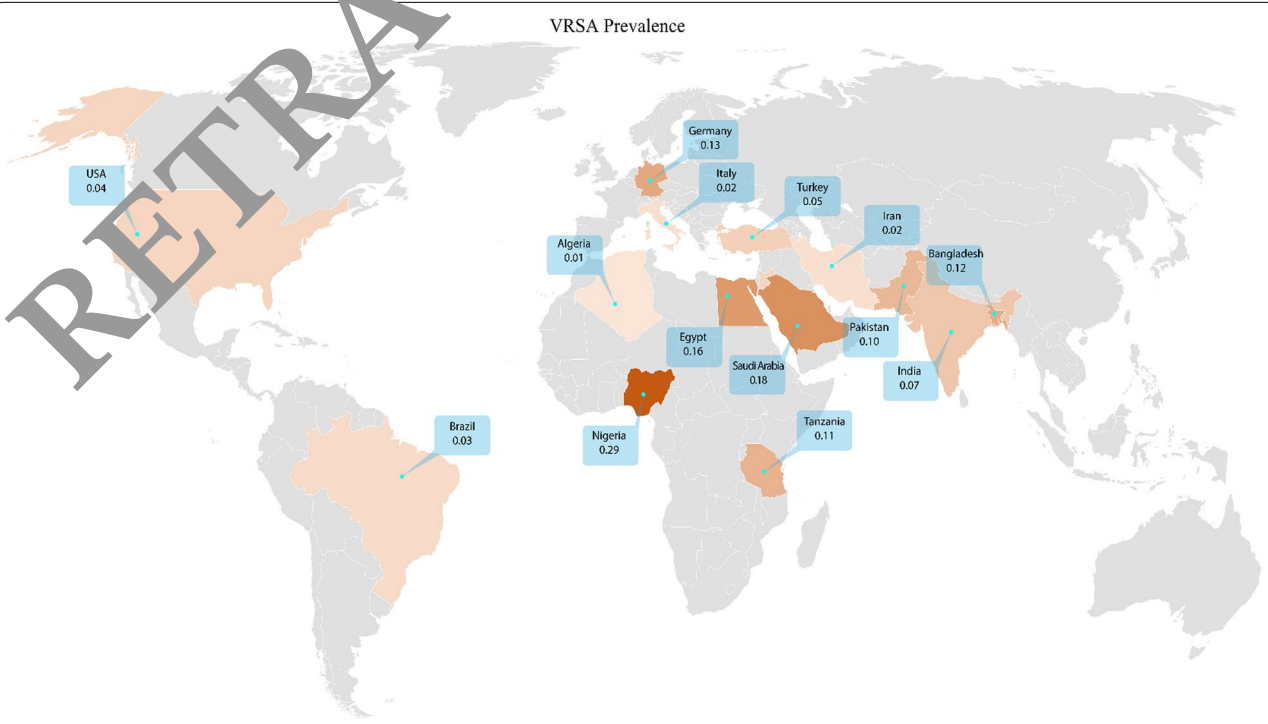

Fig. 5 Distribution of VRSA, among different countries based on meta-analysis of published original articles

Table 3 Prevalence of genetic determinants associated with VRSA

Subject	Sub group	No. studies	No. strains	Proportion (95% CI)	%Weight	P	I^2	P sig
*van*A	VRSA	34	181	0.71 (0.48, 0.89)	100	0	0.8515	0
*van*B	VRSA	16	20	0.26 (0.05, 0.52)	100	0	0.6002	0
*van*C1	VRSA	4	1	0.04 (0, 0.55)	100	0.21	0.3341	0.63
SCC*mec* II	VRSA	4	13	0.57 (0.33, 0.8)	100	0.58	–	0
SCC*mec* III	VRSA	2	3	0.17 (0.01, 0.43)	100	–	–	0.02
SCC*mec* IV	VRSA	6	14	0.39 (0.14, 0.67)	100	0.1	0.4635	0

I^2: the percentage of variance in a meta-analysis that shows study heterogeneity. VRSA: Vancomycin-resistant *Staphylococcus aureus*. MRSA: Methicillin-resistant *Staphylococcus aureus*

Discussion

The MRSA infections are the major clinical, public health, and economic challenges and also because concerns associated to inadequate dosing, poor tissue penetration of the drug and antimicrobial resistance is dramatically associated with the limited number of antimicrobials that can be used for the treatment of MRSA infections since they remain a significant cause of mortality [97, 98]. The vancomycin has been considered as the last resort for the treatment of MRSA infections [7]. Increasingly literature have reported the vancomycin treatment failure [99–101]. Our meta-analysis reports the prevalence of VRSA worldwide. In 62 studies (including 1,810 strains) chosen for our analysis, the global prevalence of VRSA was only 6%. Thus, we think that the incidence of VRSA was underestimated, probably because of the resistance mechanisms and biological features of VRSA strains. By the way, VRSA tends to be MDR against a diversity of currently available antibiotics including β-lactams, have been found from livestock farming that emphasizes the over-use and misuse of antibiotics in animals [102–104].

To analyze the trends in the prevalence of VRSA in more recent years, we allotted the study published into three periods: before 2006, 2006–2014, and 2015–2020. Our study suggests that the prevalence of VRSA has been increasing in recent years. A threefold increase was found in the frequency of VRSA between before 2006 to 2006–2014 and ~ 1.2-fold increase between 2006–2014 and 2015–2020. In recent years, the possible purposes for the emergence or detecting more VRSA strains include: most frequent administration of vancomycin for treatment of MRSA infections, improved diagnostics, inadequate monitoring of definite antibiotic policy, insufficient surveillance for vancomycin-resistance and the change in the vancomycin-resistance breakpoints since 2006 [105–107].

The incidence rates of VRSA strains have diverse all over the world: the occurrence of VRSA was 16% in Africa, 5% in Asia and 1% in Europe, 4% in North America, and 3% in South America.

Furthermore, 773 strains of VRSA were found in Africa/Asia versus 24 VRSA in Europe/America. The proposition that VRSA is more prevalent in African/Asian countries than in Europe/America. There are numerous reasons including; the high public hygiene standards, careful consideration of current antimicrobial treatments and the more successful monitoring of nosocomial associated infections in most of developed countries [108, 109] may account in the lower prevalence of VRSA in developed, in comparison to developing countries. However, the lack of testing in many situations in developing countries due to limited resources, may lead to the false impression of higher VRSA prevalence as the total number tested is not the true number of *S. aureus* infections.

The most reports (46 reports) of VRSA were from Asia (particularly from Iran [16 reports] and India [14 reports]) was higher than on the other continents. On the other hand, it should be mentioned that 56.8% (459/807) of VRSA strains were reported from Iran and India. Thus, our meta-analysis displays that the Asian data are biased towards Iran and India. Current evidence of VRSA in India and Iran supports rigorous monitoring of definite antibiotic policy, and active surveillance of nosocomial-associated infections. Furthermore, there is an alarm for the high prevalence of VRSA strains in Nigeria (29%) and Saudi Arabia (18%).

The clinical laboratories have the important role in the diagnosis of VRSA cases to warrant rapid recognition, isolation, and monitoring by infection control personnel [110]. Several methods can be used to determine the susceptibility of *S. aureus* isolates to vancomycin. The vancomycin resistance rates differ significantly when comparing the disk diffusion and MIC tests (threefold; 12%/4%). Disk diffusion is unreliable and does not differentiate between wild type isolates and those with non-*vanA*-mediated glycopeptide resistance [111, 112]. The MIC tests method is considered the gold standard technique for determining the susceptibility of *S. aureus* isolates to vancomycin [111, 112]. However, these tests are

time-consuming, laborious, and inappropriate for clinical laboratories specially in developing countries, so it may be some number of VRSA strains may have been missed.

Up to now, the genetic backgrounds associated with VRSA is clear, and also a molecular biological method to detect VRSA strains is available. In cross-sectional studies indicated in Table 3, the occurrence of mobile vancomycin-resistance genes; *vanA* and *vanB* in VRSA strains by PCR showed that 71% and 26% of the VRSA strains were *vanA* and *vanB* positive. This relative high rate of *vanA* and *vanB* in VRSA strains suggests the high potential of horizontal gene transfer of resistance determinants associated with VRSA from a vancomycin-resistant *Enterococcus* species or from one of the other *vanA* positive bacteria [113, 114]. In the other VRSA isolates did not detect *vanA* and *vanB* suggests that possibly decreased permeability, thickened and poorly cross-linked cell wall may be responsible for the increase of vancomycin resistance in VRSA isolates. Additionally, numerous studies did not detect *vanC1* gene. It has been demonstrated that SCC*mec* IV and V are prevalent in community-associated MRSA strains while SCC*mec* I, II, and III are the most common in hospital-acquired MRSA strains [115, 116]. The results of our analysis display that SCC*mec* II and V were the most frequent molecular types associated with VRSA strains. It has been showed a partial vancomycin resistance potential in SCC*mec* IV MRSA clones [117, 118]. However, we found that the high prevalence of SCC*mec* IV in VRSA strains suggesting that VRSA is not considered to classic hospital clones of *S. aureus*. Han et al. [119] displayed that the reduced vancomycin susceptibility was lower in SCC*mec* IV MRSA than SCC*mec* II MRSA isolates in concordance with our meta-analysis. The Centers for Disease Control and Prevention (CDC) [110] has listed the risk factors that may involve to VRSA emergence including: prior MRSA and enterococcal infections or colonization, underlying conditions (such as chronic skin ulcers and diabetes), and previous treatment with vancomycin. Infection control precautions should remain in place until a defined endpoint has been determined in consultation with public health authorities. The current study had some limitations were including genetic determinants associated with VRSA was presented in 54.8% (34/62) of the studied articles. In addition, more than half (56.8%; 459/807) of VRSA strains were described from Iran and India. Therefore, our meta-analysis shows that the Asian data are biased towards Iran and India.

Conclusions

The prevalence of VRSA has been increasing in recent years particularly in Africa/Asia than Europe/America. The most prevalent of genetic determinants associated with VRSA were *vanA* and SCC*mec* II. We found that VRSA is not considered only to classic hospital clones of *S. aureus*. Carful antimicrobial treatments by healthcare providers, adherence to recommended infection control recommendations, and, finally, the control of both MRSA and VRE are needed for preventing further emergence and dissemination of VRSA strains.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13756-021-00967-y.

Additional file 1: Table. Characteristics of the eligible cross-sectional studies.

Additional file 2: Fig. S1. Funnel plot of the meta-analysis on overall vancomycin-resistant *S. aureus* in 62 studies included.

Additional file 3: Fig. S2. Detailed forrest plots of the meta-analysis.

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