ZANCO Journal of Pure and Applied Sciences

TYPE: Original article
DOI http://dx.doi.org/10.21271/ZJPAS.36.6.4

Epidemiology of S. *aureus* Non-Susceptible to Vancomycin in Western Asia

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RECEIVED :10 /06/ 2024
ACCEPTED :09/11/ 2024
PUBLISHED :31/ 12/ 2024

KEYWORDS:

Vancomycin-resistant S. aureus, methicillin-resistant S. aureus, Vancomycin non-susceptible S. aureus, Asia.

Abstract

Staphylococcus aureus is considered among the most severe hazardous bacteria, especially, after the emergence of methicillin-resistant *Staphylococcus aureus,* that associated with significant levels of pathogenicity along with mortality. Vancomycin is the treatment of choice for methicillin-resistant *Staphylococcus aureus* infections worldwide. Unfortunately, Vancomycin non-susceptible *Staphylococcus aureus* strains have also emerged, making controlling *Staphylococcus aureus* infections an international health challenge. The availability of accurate epidemiological information from all over the world aids in developing the best surveillance and control programs, limiting the spread and evolution of infections. In this paper, we review the mechanism of vancomycin non-susceptibility among *Staphylococcus aureus* and focus on the emergence, epidemiological characteristics, and the latest progress in Western Asia.

1.Introduction

Staphylococcus aureus (s. aureus) is among the highest-frequency pathogens in hospitals and communities. This bacterium has the characteristic of good adaption to varied environments (Rasigade and Vandenesch, 2014). Around a quarter of healthy individuals have *S. aureus* colonization on the skin and nasopharyngeal membrane (Hemmadi and Biswas, 2020; Zefenkey, 2022). However, *S. aureus* is involved in many infections, ranging from simple infections such as folliculitis to more serious cases such as Toxic Shock Syndrome as well as bacteremia (Cheung et al., 2021).

The treatment of *S. aureus* infection is getting increasingly more complicated due to the development of various antibacterial-resistant strains. Nowadays, *S. aureus* is a member of the ESKAPE group (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* species), which includes the most significant pathogen that has multidrug resistance (Oliveira et al., 2020). The most important type of multidrug-resistant *S. aureus* is methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant *Staphylococcus aureus* (VRSA). MRSA can lead to various infectious diseases with high mortality, CDC estimates that MRSA is responsible for more than 70,000 severe infections and 9,000 deaths per year. (CDC, 2024). It is noticed that the incidence of MRSA rose significantly and became a global challenge (Sharma et al., 2024). When it comes to treating MRSA, vancomycin is the therapy of choice, but unfortunately, *S. aureus* has gained resistance to this antibacterial, announcing the emergence of VRSA and thus raising the concern of public health worldwide (Cong et al., 2020).

Our epidemiological information on MRSA and VRSA is significantly limited by the shortage of information or even its complete absence, which poses a threat to the continued spread and development (Xu et al., 2020). There are several cases of VRSA in different countries in Western Asia, so it could be an important source of the development of VRSA isolates, and the frequency with which they are found may be growing. In light of this, the current review investigates the latest prevalence and molecular characterization of Vancomycin non-susceptible *S. aureus* in Western Asia. This article will define more accurately the present epidemiology of VRSA, vancomycin-intermediate *S. aureus* (VISA), and heterogeneous vancomycin-intermediate *S. aureus* (hVISA) in Western Asia, additionally, it may aid in the development of other effective antibiotic stewardship programs to address vancomycin resistance.

2.S. aureus resistance to antibacterials

S. aureus has resistance to a lot of antibacterials due to changes in their genetic structure, in addition to the important role of the plasmid, bacteriophage, and other mobile genetic components such as transposons which has a crucial role in the development and dissemination of antibiotic resistance in bacteria by the horizontal transmission (Mlynarczyk-Bonikowska et al, 2022).

2.1- Resistance to Beta-Lactam Antibiotics

Almost immediately after the introduction of penicillin for the management of bacterial infections, strains of Penicillin-resistant *S. aureus* came out (McNeil, 2024). Later, over 80% of *S. aureus* had developed penicillin resistance in less than two decades due to acquiring the *blaZ* gene that encodes beta-lactamase enzymes that hydrolyze crucial beta-lactam ring resulting in inactive penicillin (Bondi, 1945). Finding alternative antibacterials became an urgent issue, so semisynthetic penicillinase-resistant beta-lactam antibacterials were introduced in the treatment to overcome the world dissemination of penicillin-resistant *S. aureus* such as methicillin and oxacillin. The first methicillin usage was in 1961, and as with penicillin, resistance to this antibiotic rapidly emerged in the same year in the UK (Jevons, 1961). The resistant strains to this antibacterial were detected and named methicillin-resistant *S. aureus* (MRSA). MRSA is characterized by resistance to β-lactams antibacterials because of the horizontal acquiring of *mecA*, a gene responsible for the synthesis of penicillin-binding protein (PBP2a) has a poor affinity for most β-lactams antibacterials. Although this issue has a broad spectrum, and

methicillin is not used anymore in clinical practice, MRSA has continued to be the preferred classification of *mecA*-positive *S. aureus* (Vestergaard et al., 2019).

MRSA infection cases have increased and expanded worldwide in the last five decades, and a new strain named healthcare-associated MRSA (HA-MRSA) has emerged around the globe to be one of the main reasons for potentially fatal illnesses like sepsis and pneumonia (Shoaib et al., 2023). Around the end of 1990, another new strain of MRSA developed in the community, then it was called community-acquired MRSA (CA-MRSA). This strain has a severe degree of pathogenicity in addition to, the high ability to spread, putting healthy people at an increased chance of infection (DeLeo et al., 2010). Both CA-MRSA and HA-MRSA spread globally, with increasing morbidity and mortality. Many researchers have reported that the death rate because of MRSA (Klein et al., 2007; Tang et al., 2015; Baede et al., 2022), for instance, around 19,000 patients die annually due to HA-MRSA in the US (Klevens et al., 2007; Tsuzuki et al., 2020), and in Japan, mortality due to MRSA pneumonia infection is more than the mortality due to non-MRSA pneumonia infection (OR: 1.94; 95% CI: 1.72–2.18; $p < 0.001$)(Sakamoto et al., 2021).

The primary issue is the elevated prevalence of MRSA worldwide. According to studies published in 2022, the incidence of this infection was 26% in Italy (Vecchia, et al., 2022), 79% in Japan (Ogura et al., 2022), 84.9% in Australia (Coombs et al., 2022), 61% in Norway (Enger et al., 2022), and 44.3% in Iran (Tabandeh et al., 2022). This makes the control of this infection at the top of health sector priorities through the early detection of cases with rapid treatment and following the best measures to limit its spread.

2.2- Resistance to Vancomycin

Vancomycin has been the preferred treatment for significant diseases brought on by MRSA since the 1980s (Rehm and Tice, 2010). Vancomycin targets the cell wall of gram-positive bacteria, for interacting with high affinity to dipeptide D-alanyl-D-alanine which is an important structure of peptidoglycan, leading to disruption of cell wall assembly (Barna and Williams, 1984). In 1997, Japan was the location where the first documented instance of *S. aureus* that was resistant to vancomycin was presented, The minimum inhibitory concentration (MIC) was = 8 µg/mL, and it was called vancomycin-intermediate resistant *S. aureus* (VISA) (Werner, 2008), then two more cases emerged in America. In 2002, the United States of America was the location where the first case of vancomycin-resistant *S. aureus* (VRSA) was described (Weigel et al., 2003). Later several strains of VRSA emerged worldwide. The causes of the evolution of VISA and VRSA strains are highly different. VISA strains result from the accumulation of mutations that lead to multiple characteristic phenotypes such as increasing cell wall thickness, cell wall modifications that cause vancomycin to diffuse through abnormally, decreasing in the negative charges of *S. aureus* surface, and decreasing in the autolysis (Zakaria et al., 2023), In comparison, VRSA strains emerge because of different van operons acquired by plasmids from gram-positive cocci, especially enterococci. These operons hydrolyze D-alanyl-D-alanine precursors to be substituted by D-ala-D-lactate precursor preventing vancomycin binding (Jain et al., 2024). The new precursor still works as a substrate for the biosynthesis of cell wall enzymes which allows the functional peptidoglycan formation. The mechanism of vancomycin resistance has been best clarified in *Enterococci* which are the prime reservoir of this resistance. Till now, eleven operons have been identified in the vancomycin resistance (Lebreton et al., 2019), and the ligases they encode are what divide them into two groups. The operons vanA, vanB, vanD, vanF, vanI, and vanM, which encode for D-Ala-D-Lac ligase, make up the first group and often have high vancomycin resistance (MIC > 256 µg/ml). The operons vanC, vanE, vanG, vanL, and vanN make up the second group, which encode D-Ala-D-Ser ligase, and usually have low vancomycin resistance (MIC ranges between 8–16 µg/ml). Five essential proteins are encoded by the vanA operon to express vancomycin resistance, namely, VanS, VanR, VanH, VanA and VanX, deletion of any one of them results in the restoration of vancomycin action, making

these van components interesting goals for antibacterial development research (Hamza et al., 2024).

Clinical Laboratory Standards Institute (CLSI) has determined minimum inhibitory concentration breakpoints for vancomycin-susceptible *S. aureus* (VSSA), VISA, and VRSA are 2 µg / mL, 4–8 µg / mL, and >16 µg / mL respectively. The rise in the number of prescriptions for vancomycin is known to increase the MIC of this antibacterial agent. In 2006, the MIC breakpoint of vancomycin was decreased by CLSI for VSSA from 4 µg/ mL to 2 µg/ mL (CLSI, 2017).

Heterogeneous VISA (hVISA) has MIC ≤2 µg/mL, with a subset of resistant phenotype (MIC = 4–8 µg/mL), making this strain considered as *S. aureus* with decreased vancomycin susceptibility (Chen et al., 2011). The hVISA strains have a thick cell wall with the absence of the accumulation of mutations. Contact with non-glycopeptide antibacterials such as beta-lactam can trigger this special phenotype (Roch et al., 2014). VISA and hVISA infections lead to an increase in the failure of vancomycin treatment, and thus an increase in hospitalization and an increase in costs. SlowVISA (sVISA), is a VISA phenotype that is characterized by extremely slow growth, colony formation taking 72 hours or longer, and somewhat high MICs (>8 µg/ml) of vancomycin. Resistance phenotype of sVISA is unsteady (Saito *et al*., 2014). The fact that conventional susceptibility testing cannot detect the hVISA and sVISA strains poses a serious problem. Both variants are brought on by exposure to vancomycin, although hVISA can develop when exposed to beta-lactam antibacterials, sVISA stabilizes when a stringent response is established. None of these mechanisms are present during the susceptibility test. Haaber *et al*. (2015) made an analogous discovery when they found that *S. aureus* showed reversible and decreased sensitivity to vancomycin in lack of genetic alteration after exposure to colistin. As a whole, these results show that VISA derivatives can arise through mutations and/ or unrelated phenotypic pathways (McGuinness et al., 2017).

Tolerance to glycopeptides is another feature found in *S. aureus* (MBC/MIC ratio of ≥32). In this case, the strains are susceptible to glycopeptides, but they survive after applying this antibacterial in the treatment. For the purpose of providing an explanation for this occurrence, a number of theories have been developed, the most prominent of which is the capacity of biofilm to form (Jansen *et al*., 2007).

3.Vancomycin-resistant S. aureus in Western Asia

3.1- Iraq

The research on VRSA started in Iraq by Mahmood and Flayyih (2014) in Baghdad, the capital of Iraq, there was a 3.6% VRSA of *S. aureus* isolates, and *vanA* was positive with half of VRSA isolates. Ten years later, Neamah et al., (2024) conducted another study in Baghdad, they found the prevalence of VRSA increased to 10%.

In Erbil, the capital of the Kurdistan Region, no case of VRSA appeared in 2014 (Taha and Al-Salihi, 2014), but in 2021 there was 10.3% VRSA with positive *vanA* (Mahmood and Anwer , 2021).

Looking at the status of VRSA and VISA in the rest of the Iraqi cities, we found the rate of VRSA and VISA were in Al-Qadisiya 7.1% and 0% (Yassen, 2016), Basrah at 2.5% and 7.6% (Mohammed et al., 2021), and Kufa at 13.4% and 1.5% (Reyad and Saaid, 2021) respectively. All VRSA isolates in Basrah (Mohammed et al., 2021) and Wasit (Raheema et al., 2021) were *vanA* negative, but in Kufa (Reyad and Saaid, 2021), *vanA* and *vanB* were found in 30% and 15% of strains respectively.

According to these findings, the presence of VRSA in Iraq is a matter for concern, and most strains do not have vanA operon. This means the main cause of VRSA in Iraq is not to acquire the *vanA* gene from *Enterococcus*, making recognizing the potential source, responsible genes, and transmission route by further studies an urgent for better control and surveillance.

By studying the resistance of VRSA to antibacterials, no statistically significant difference was found in Abdul-Hameed's study in Baghdad between VRSA and VISA in the resistance rates to all antibacterials. Still, differences in these resistance rates between VRSA and VSSA, as well as between VRSA and MRSA were statistically significant (Abdul-

Hameed, 2015). The results of Mohammed et al. (2021) in Basrah confirmed the previous finding.

It is worrisome in Iraq that there is not rare to find carriers of VRSA among apparently healthy and young people. In a screening study conducted in Thi-Qar in 2019, 576 nasal samples were collected from restaurant workers to detect infectious agents. 6% of the workers were carriers of VRSA with positive *vanA* gene (Salih and Salih, 2019). In another study in Al-Muthanna in 2022 which included secondary students in rural and urban areas, 4% of the students had VRSA in the nasal swap samples (Hantoosh, 2022).

Nasal carriers of VRSA constitute a source of infection threat, especially for patients who need surgery or intensive care, so carrier cases must be dealt with seriously.

3.2- Iran

Iranian literature documented the first two cases of VRSA in 2008 in Tehran, MICs were 64 µg/ml and 512 µg/ml, and both isolates were *vanA* gene positive (Aligholi et al., 2008). In 2012 two other cases were documented. The first one was detected in a diabetic foot ulcer in Tehran, with MIC of vancomycin 512 µg/ml, and positive *vanA* gene. The history of the patient indicated that this case is a community-acquired VRSA (CA-VRSA), this would be the first document of (CA-VRSA) in Iran (Dezfulian et al., 2012). The second case was detected in the bronchial aspirate of a young patient with Crohn's disease. He did 3 abdominal surgeries during three months of hospitalization to manage the ileal perforation and peritonitis which he had as consequences of his disease. The MIC of the isolate for vancomycin and oxacillin was 512 µg/ml and 128 µg/ml respectively indicating a resistance to both antibiotics, PCR was positive for *mecA* and *vanA* genes. This case is considered hospital-acquired VRSA according to the history of the patient (Azimian et al., 2012). Also in 2012, five cases of VISA were documented in the hospitals of Isfahan, Mashhad, and Tehran. All these isolates were *vanA* negative (Havaei et al., 2012).

Noting that the resistance of vancomycin has high levels of MICs (512 µg/ml) in Iran is important, this could be due to the continuous prescription of vancomycin in Iranian hospitals for most serious *S. aureus* infections (Dezfulian et al., 2012).

In general, cases of VRSA are relatively few in Iran. Shekarabi et al. (2017) found by analyzing 1798 *S. aureus* isolates from various samples in different university hospitals in Tehran that there were four strains of VRSA (MIC was 512µg/ml and 64 µg/ml) and two isolates of VISA (MIC was 8 µg/ml), all the six strains were MRSA. The four VRSA cases had the *vanA* gene and belong to patients who had vancomycin treatment during the previous 11 months. According to antimicrobial susceptibility testing (AST) findings, linezolid was the antibacterial agent that delivered the best outcomes. Other studies documented a low rate of vancomycin non-susceptible *S. aureus*. Asadpour and Ghazanfari (2019) detected 3 (2.73%) VRSA strains and 8 (7.27%) VISA strains out of 110 strains of *S. aureus* in a study conducted in Rasht. Another low prevalence of VRSA was documented by Moghaddam et al. (2021), where four strains were identified as VRSA (1.29%) out of 308 S. aureus strains from Bojnurd, and all the strains were positive for *vanA* gene. Shahabinejad et al. (2024) detected only one VRSA case by analyzing 34 MRSA samples (2.9%) with positive *vanA* gene from different sources. Aslanimehr et al. (2024) collected 270 *S. aureus* isolates and identified only two isolates as VRSA (0.7%) with MIC > 256 µg/ml and positive *vanA* gene, and four isolates as VISA (1.4%) with negative *vanA* gene. Interestingly, this rate increased in cases of serious infections such as bacteremia to reach 5.9% (Navidinia et al., 2023) and ICU patients at 6.7% (Karamolahi et al., 2024). These findings highlight the importance of strict ICU environment control and the monitoring of antibiotics policies in the prevalence of vancomycin-resistant bacteria.

Iranian studies analyzed the genetic characteristics of the isolated VRSA strains, and a diversity of genetic clones was found (Dezfulian et al., 2012; Azimian et al., 2012; Havaei et al., 2012; Shekarabi et al., 2017; Asadpour and Ghazanfari, 2019; Moghaddam et al., 2021). This may indicate independent sources of acquiring resistance which is a concerning issue since it may predict a higher

prevalence and more possibility of mutations. This diversity could be due to the holy value of some Iranian cities making them destinations for many visitors from Islamic countries and allowing different clones to enter the area. As a result of the appearance of VRSA in Iran, it is necessary to maintain ongoing surveillance programs and carefully monitor the administration of vancomycin in order to minimize the spread of VRSA strains.

3.3- Turkey

Based on Turkish literature no VRSA cases were reported, but many hVISA strains emerged to be a source of concern in Turkey (Sancak et al., 2005; Sancak et al., 2013; Ozmen Capin et al., 2020; Gazel et al., 2021; Gümüş, 2023). The outcome of hVISA infection in most cases is poor, the mortality rate is around 75% (Appelbaum, 2007). The routine AST shows hVISA strains are susceptible to vancomycin (MIC ≤2 µg/mL) although they contain a subset of resistant phenotype (MIC = 4–8 µg/mL) that led to a raise in the failure of vancomycin treatment (Chen et al., 2011). Several studies have detected the prevalence of hVISA in Ankara and Gaziantep, and the rates varied greatly between them. The prevalence rates were 17.97%, 13.7%, 0%, and 43% (Sancak *et al*., 2005; Sancak *et al*., 2013; Ozmen Capin *et al*., 2020; Gazel *et al*., 2021). We can attribute the main cause of the high difference between the prevalence rates in Turkish studies to the difference in the detection method. The population analysis profile-area under the curve (PAP-AUC) method is the gold standard technique for hVISA identification, but because it requires a lot of labor and is expensive, this method is not appropriate for screening purposes (Wootton *et al*., 2007). All the results of previous studies were confirmed by PAP-AUC except Gazel's study in Gaziantep in 2021 which used Satola's test (Gazel *et al*., 2021). Sancak et al. (2013) observed that the prevalence of hVISA was higher in instances with MIC >1 µg/ml compared to isolates with MIC ≤1 µg/ml, regardless of the diagnostic method employed. So this study recommended monitoring the efficacy of vancomycin therapy, particularly when the MIC > 1 µg/ml.

3.4- Saudi Arabia

In Saudi Arabia, the first instance of decreased susceptibility to vancomycin was reported in 2010 according to the published literature. It was isolated from a Saudi man 68 years old, who was admitted to the hospital and at once developed severe sepsis. Although the level of vancomycin in the blood was so high, the laboratory isolated the same strain five times in one week. The strain was confirmed as hVISA according to population analysis. However, this hVISA case emerged because of vancomycin treatment failure (Al-Obeid *et al*., 2010).

The subsequent research revealed that the rate of VRSA has skyrocketed in Arabia Saudi. A study carried out in 2012 at Qassim University–affiliated hospitals, included 80 children with atrophic dermatitis found that 30% of *S. aureus* were vancomycin-resistant (Alzolibani *et al.,* 2012). Later, a cross-sectional research was conducted in 2022 and included urinary tract infection patients. A total of 103 *S. aureus* were identified, and there were 23 vancomycin-resistant samples (22.3%) (Selim *et al*., 2022).

A study conducted at King Saud University, Riyadh in 2017 should be referenced. The main goal was to investigate the presence of VRSA in the oral cavity of patients with dental caries. A total of 150 samples were analyzed; 59 patients were hospitalized for a minimum of 10 days, and 42 patients had a history of postoperative oral infection. The results revealed 27 vancomycin-resistant isolates (18%). PCR detected 13 (8.6%) positive *vanA* and 2 (2.13%) positive *vanB,* the antimicrobial susceptibility testing in this work revealed the majority of VRSA strains are susceptible to linezolid and daptomycin (Vellappally *et al*., 2017).

By the large, the rate of VRSA in Saudi Arabia is higher than in other countries in Western Asia. Al-Mustafa *et al*. (2002) determined that twenty-nine antibacterials were in use for poultry, and most of them are essential for human infection treatment. The antibacterial residue in poultry products can cause many complications to human health, foremost of them is the resistance to antibacterials (Sajid *et al*., 2016).

Notably, studies published in 2023 and 2024 showed very low and even non-existent levels of

VRSA (Ahmed *et al.,* 2024; Almutairi *et al*. 2024; Almuhayawi *et al*., 2023; Al-Said *et al*., 2023), which contradicts all previous studies, requiring further research and investigation to determine the mechanism of this sudden decrease and explain its causes.

3.5- The Other Countries

Western Asia has an area of 5,994,935 km2, and a population of 298,386,199 based on the United Nations estimation, with the highest populations in Iran, Turkey, Iraq, Saudi Arabia, and Yemen (UN, 2022). Fortunately, most of the studies concerning the VRSA issue in Western Asia involved the most populated countries **(Table 1)**. Also, there was one study conducted in Jordan (Hussein Azzam and Bataineh, 2006), and three studies mentioned the resistance of *S. aureus* to vancomycin in a secondary manner during an MRSA study in Lebanon (El Ayoubi *et al*., 2014), Oman (Al Rahmany *et al*., 2019), and Bahrain (AlSaleh *et al*., 2023). This means the studies of VRSA involved eight countries out of 18 countries in Western Asia despite the importance of this issue **(Figure 1).** It is worth noting that several studies were excluded from this review due to using the disc diffusion method for vancomycin susceptibility detection, and this method is not approved by CLSI.

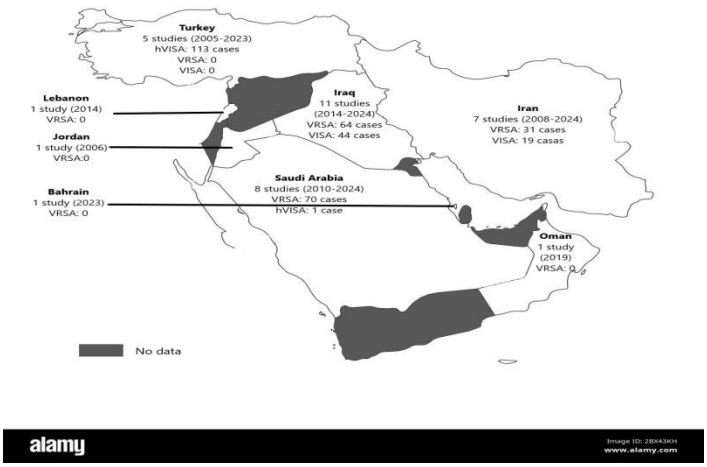

Figure 1. Number of VRSA, VISA, and hVISA cases in Western Asia

The prevalence of VRSA in Jordan was 3.6%, this study included 139 *S. aureus* isolates from different clinical samples of patients from Prince Hashem Hospital in Zarqa (Hussein Azzam and Bataineh, 2006). All isolated VRSA were classified as MRSA according to the results of AST. The high value of MICs demands a national surveillance program to monitor antibacterial resistance in Jordan.

The prevalence of vancomycin non-susceptible *S. aureus* was in Lebanon 0% (El Ayoubi *et al*., 2014), Oman 0% (Al Rahmany *et al*., 2019), and Bahrain 0% (AlSaleh *et al*., 2023). One study in each country is not sufficient to deny the existence of VRSA, many studies should be conducted to confirm this result. Moreover, the use of molecular methods that were lacking in the mentioned studies, can support the findings and give a more comprehensive profile.

4.Conclusion

Based on the findings of this review, the prevalence of VRSA, VISA, and hVISA in Western Asia countries was shown to be varied by geographic location. The most prevalent genes associated with VRSA were vanA followed by vanB, although these genes were absent in many cases. Interestingly, there is a trend of increasing the MIC of vancomycin in the area, which is considered an alarm to aggravate the situation in the future, and makes developing surveillance and control programs an urgent need. Healthcare providers should prescribe antimicrobials (especially vancomycin) with caution, and adhere to the local guidelines of the infection control program to prevent further increase in vancomycin non-susceptible *S. aureus*.

A general lack of epidemiological information was present throughout the entire study. in terms of genetic characteristics, potential sources, and antibacterial susceptibility trends. There was also a complete lack of studies in some countries, making a precise estimation more difficult. More studies are required to investigate the resistance mechanisms and epidemiological trends.

Table 1. Characteristics of reported VRSA, VISA, and hVISA isolates in Western Asian countries

Country/ City	Study period	Specimens	No of strains	No of VRSA (%)	No of VISA (%)	No of hVISA (%)	Positive Genes	Reference
Iraq/ Baghdad	2014	Various samples	32 *S. aureus*	1 (3.6%)	-	-	van A (+)	(Mahmooda nd Flayyih, 2014)
Iraq/ Erbil	from June 2011 to Novembe r 2012	Various specimens	453 *S. aureus*	0 (0%)	32 (7%)	-	NA	(Taha and Salihi, 2014)
Iraq/ Al-Qadisiya	2016	Wound swabs	42 *S. aureus*	3 (7.1 %)	-	-	NA	(Yassen, 2016)
Iraq/ Baghdad	from January to April 2015	Various samples	40 *S. aureus*	2 (5%)	4 (10%)	-	NA	(Mahmooda nd Flayyih, 2017)
Iraq/ Thi-Qar	2019	Nasal swabs	25 *S. aureus*	3(6%)	-	-	van A (+)	(Salih and Salih, 2019)
Iraq/ Erbil	from April to Decembe r 2020.	Various specimens	175 *S. aureus*	18 (10.3%)	-	-	van A (+)	(Mahmood and Anwer, 2021)
Iraq/ Basrah	from October 2018 to Decembe r 2020	Various specimens	79 MRSA	2 (2.5%)	6 (7.6%)	-	van A (-) van B (-)	(Mohammed et al., 2021)
Iraq/ Kufa	from May to Novembe r 2019.	Urine and burn wound swabs	134 *S. aureus*	18 (13.4%)	2 (1.5%)	-	van A (+) van B (+)	(Reyad and Saaid, 2021)
Iraq/ Wasit	from October 2020 to January 2021	Diabetic foot ulcer swabs	25 *S. aureus*	-	-	-	van A (-)	(Raheema et al., 2021)
Iraq/ Al-Muthanna	from Novembe r 2020 to May 2021	Nasal swabs	72 MRSA	15(4%)	-	-	NA	(Hantoosh, 2022)
Iraq/ Baghdad	2021 to 2022	Various samples	50 *S. aureus*	5 (10%)	-	-	van A (+)	Neamah et al., 2024)
Iran/ Tehran	2008	NM	356 *S. aureus*	2	-	-	van A (+)	(Aligholi et al., 2008)
Iran/ Tehran	2012	Diabetic foot ulcer swab	1 case study	1			van A (+)	(Dezfulian et al., 2012)
Iran/ Tehran	from Septembe r 2011 to Decembe r 2011	Respiratory tract sample	1 case study	1			van A (+)	(Azimian et al., 2012)
Iran/ Isfahan,	From Septembe	Various samples	171 *S. aureus*	-	5 (2.9%)	-	vanA (-)	(Havaei et al., 2012)

Mashhad, and Tehran	r 2011 to Decembe r 2011							
Iran/ Tehran	From March 2014 to February 2017	Various samples	1789 *S. aureus*	4 (0.2%)	2 (0.1%)	-	van A (+)	(Shekarabi et al., 2017)
Iran/ Rasht	2019	Various samples	110 *S. aureus*	3 (2.73%)	8 (7.27%)	-	NA	(Asadpour and Ghazanfari, 2019)
Iran/ Bojnurd	From 2013 to 2018.	Various samples	308 *S. aureus*	4 (1.29%)	-	-	van A (+) van B (-)	(Moghadda m et al., 2021)
Iran/ Tehran	2023	Blood	85 *S. aureus*	5 (5.9%)	-	-	NA	(Navidinia et al., 2023)
Iran/ Kerman	2024	Various samples	34 MRSA	1 (2.9%)	-	-	van A (+)	(Shahabinej ad et al., 2024)
Iran/ Qazvin and Tehran	2014-2018	Various samples	270 *S. aureus*	2 (0.7%)	4 (1.4%)	-	van A (+)	(Aslanimehr et al., 2024)
Iran/ Ilam	2024	Various samples	123 *S. aureus*	8 (6.7%)	-	-	NA	(Karamolahi et al., 2024)
Turkey/ Ankara	From January 1998 to January 2002	Various samples	256 MRSA	-	-	46 (18%)	NA	(Sancak et al., 2005)
Turkey/ Ankara	From 2009 to 2010	Blood	175 MRSA	-	-	24 (13.7%)	NA	(Sancak et al., 2013)
Turkey/ Ankara	From 2001 to 2014	Blood	127 MRSA	0%	0%	0%	NA	(Ozmen Capin et al., 2020)
Gaziantep , Turkey	From 2018 to 2019	Various samples	100 MRSA	-	-	43 (43%)	NA	(Gazel et al., 2021)
Turkey/ Adana	From 2021 to 2023	Blood	488 *S. aureus*	0%	0%	-	NA	(Gümüş, 2023)
Saudi Arabia/ Riyadh	2010	Blood	1 case study			1	NA	(Al-Obeid et al., 2010)
Saudi Arabia/ Qassim	March 2009 to February 2010	Swap from atopic dermatitis lesions	30 *S. aureus*	9 (30%)	-	-	NA	(Alzolibani et al., 2012)
Saudi Arabia/ Riyadh	2017	Dental caries	150 *S. aureus*	27 (18%)	-	-	van A (+) van B (+)	(Vellappally et al., 2017)
Saudi Arabia/ Sakaka	from October 2020 to February	Urine	103 *S. aureus*	23 (22.3%)	-	-	NA	(Selim et al., 2022)

	2022.							
Saudi Arabia/ Jeddah	2022	Wound swabs	188 *S. aureus*	5 (2.7%)	-	-	van A (+) van B (-)	(Almuhayawi et al., 2023)
Saudi Arabia/ Makkah	2017-2021	Wound swabs	188 *S. aureus*	6 (3.1%)	-	-	-	(Al-Said et al., 2023)
Saudi Arabia/ Makkah	2019-2020	Various samples	187 MRSA	0 (0%)	-	-	NA	(Ahmed et al., 2024)
Saudi Arabia/ Al-Qassim	2020-2022	Various samples	69 MRSA	0 (0%)	-	-	NA	(Almutairi et al. 2024)
Jordan/ Zarqa	From April 2002 to August 2004	Various samples	139 *S. aureus*	5 (3.6%)	-	-	NA	(Hussein Azzam, 2006)
Lebanon/ Tripoli	From February 2006 to March 2013	Various samples	113 MRSA	0 (0%)	-	-	NA	(El Ayoubi et al., 2014)
Oman/ Sohar	From January 2016 to Decembe r 2017	Various samples	15733 MRSA	0 (0%)	-	-	NA	(Al Rahmany et al., 2019)
Bahrain / Manama	from Decembe r 2020 to Decembe r 2021	Various samples	161 *S. aureus*	0 (0%)	-	-	NA	(AlSaleh et al., 2023)

NA: Not Available
NM: Not Mentioned

Acknowledgments: Not applicable
Conflicts of Interest: Authors declare no conflict of interest.

List of abbreviations

Abbreviation	Full name
s. aureus	*Staphylococcus aureus*
VRSA	Vancomycin-resistant *Staphylococcus aureus*
MRSA	Methicillin-resistant *Staphylococcus aureus*
CDC	Centers for Disease Control and Prevention
VISA	Vancomycin-intermediate *S. aureus*
hVISA	Heterogeneous vancomycin-intermediate *S. aureus*
MIC	Minimum inhibitory concentration
CLSI	Clinical Laboratory Standards Institute
VSSA	Vancomycin-susceptible *S. aureus*
sVISA	Slow vancomycin-intermediate *S. aureus*
AST	Antimicrobial susceptibility testing
PCR	polymerase chain reaction

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