RESEARCH
www.commprac.com
ISSN 1462 2815

PREVALENCE AND DISTRIBUTION OF VANCOMYCIN INTERMEDIATE, VANCOMYCIN RESISTANT AND HETEROGENEOUS VANCOMYCIN INTERMEDIATE S. AUREUS IN CLINICAL ISOLATES: A SYSTEMATIC REVIEW

Shane Alam [1]*, Dr. Umar Farooq [2], Dr. Sudhir Singh [3] and Dr. Shweta R. Sharma[4]

[1]Research Scholar, Department of Microbiology, Teerthanker Mahaveer Medical College & Research Centre, Moradabad, Uttar Pradesh, India. *Corresponding Author Email: shanealam5361@gmail.com
[2]Professor & Head, Department of Microbiology, Teerthanker Mahaveer Medical College & Research Centre, Moradabad, Uttar Pradesh, India. Email: farooqzf@yahoo.com.
[3]Professor, Department of Microbiology, Teerthanker Mahaveer Medical College & Research Centre, Moradabad, Uttar Pradesh, India. Email: drsudhir.micro@gmail.com.
[4]Associate Professor, Department of Microbiology, Teerthanker Mahaveer Medical College & Research Centre, Moradabad, Uttar Pradesh, India. Email: drshwetamicro@gmail.com.

DOI: 10.5281/zenodo.10276483

Abstract

Introduction: Methicillin-resistant *Staphylococcus aureus* (MRSA) caused various diseases and created a global crisis to public health. The disease caused by MRSA are treated with vancomycin. Initially vancomycin become a gold standard treatment for the diseases caused by MRSA but after some time prevalence of heterogeneous vancomycin intermediate *S. aureus*, vancomycin intermediate *S. aureus* and vancomycin resistant *S. aureus* (hVISA, VISA and VRSA) has been emerged from different part of the world. **Methods:** A extensive search was conducted with the help of electronic databases, like as PubMed, Scopus and Google Scholar, to identify similar studies to the hVISA, VISA and VRSA. The search strategy employed a combination of keywords and medical terminologies associated with *Staphylococcus aureus* and antibiotic vancomycin. **Result:** This systematic review provide overall prevalence of hVISA was 5.2% in 32180 MRSA strains, the prevalence of VISA 3.8% in 27472 MRSA strains and VRSA prevalence was 6.69% in 4815 MRSA strains. The incidence of hVISA was 1.88% before 2000, 6.89% in 2001-2010, 11% in 2011-2020 and 10.78% in 2021-2023. VISA prevalence was 0.73% before 2000, 2.37% in 2001-2010 and 10.82% in 2011-2020. VRSA was not isolated before 2000, the prevalence of VRSA was 1.8% in 2001-2010 and 7.97% in 2011-2020. **Conclusion:** The incidence of hVISA, VISA and VRSA has been elevated in last few years mainly in Asia continent than Europe/America. This systematic review provide the prevalence of hVISA, VISA and VRSA and suggest to isolate this type of *S. aureus* and control community and hospital associated infections.

Keywords: *Staphylococcus Aureus*, VISA, hVISA, VRSA and MRSA.

INTRODUCTION

Staphylococcus aureus, a gram-positive cocci and cause both community-associated and nosocomial-associated infections.(1) *S. aureus* are colonized around 25–30% of healthy persons on their skins, anterior nares and axilla, at which *S. aureus* present like a commensal and don't cause any illness in immunocompetent individuals.(2) Whereas, *S. aureus* may cause various type of infections through bloodstream or penetrating the internal tissues and causes different types of clinical presentation which range from mild infections to serious and life-effecting pervasive infections like as boils, abscesses, impetigo, cell destruction, infections in hair follicles and sepsis,(3) and these infections become challenging for public health issue because the emergence and dissemination of antibiotics resistant strains, like as, methicillin-resistant *S. aureus* (MRSA).(4) Methicillin resistance in *S. aureus* strains is due to the

alteration of penicillin binding protein to penicillin binding protein 2a and presence of mecA gene in the bacterial chromosome, these proteins and enzymes help to the bacterial cell wall for crosslinking the peptidoglycans. PBP2a and enzymes both showing low affinity to β-lactams antibiotics group and causing resistance to this type of antibiotics category.[5] Vancomycin is the drug of choice for treating the MRSA infections. But unluckily there has been an indiscriminate use of vancomycin for human and as well as in the area of veterinary for other infections resulted in the development of hVISA, VISA and VRSA.[6] However, the first case of VISA was isolated from Japan in 1997[7] and first VRSA strain was isolated from Michigan (USA) in 2002. After some time, VRSA were reported from Oceania, Europe and other Asian countries.[8] Out of these two strains of *S. aureus* there is a strain also present which is called hVISA which has the vancomycin MIC in the susceptible range (< 2µg/ml) but contains some vancomycin intermediate cells like as one vancomycin intermediate cell per 10^5 to 10^6 vancomycin sensitive cells.[9] In last few years, there have been many articles, reports, systematic reviews or meta-analysis published from a hospital or individual countries and shows prevalence of hVISA, VISA and VRSA. The systematic review conducted by Zhang et al. on the epidemiology of hVISA and VISA was published over 7 years ago.[10] A systematic review also conducted by Wu et al. and observe the diagnostic importance and outcomes of VRSA.[11] This review goal to provide the pattern of antibiotics resistance and prevalence of hVISA, VISA and VRSA against *S. aureus* which is carried out by identifying the gene responsible for antibiotics resistance and combat this growing problem. This systematic review give clue to the clinician for empirical therapy and better management of patients and it is beneficial for future research in the field of antibiotics resistance.

METHODOLOGY

Search Criteria

The searching criteria for identifying the appropriate articles related to this systematic review was developed by author. The searching is depend on the characteristics of VISA, hVISA and VRSA infections. These strains causing the infections and isolated from whole world and become a major public health problem in this review the most common type of gene causing vancomycin resistance was reviewed. Electronic database like as Scopus, PubMed and Embase were used to search the appropriate articles. And some other online database such as Google Scholar and PubMed also utilized to identify the appropriate articles. The duration for the search was from 1997 to 2023 set to track maximum of the strains after the first isolation in 1997 of vancomycin intermediate *S. aureus* to till now. Some of the studies and worldwide case reports were reviewed which give a holistic view of the infections. Case reports presented by clinicians, microbiologists, and public health practitioners and published we get original data through it.

Inclusion and exclusion criteria

Studies recognize in the literature search were checked by title and abstract. The articles and reports with relevant title and abstracts were checked carefully. The selection and rejection criteria for the studies were depend on the author criteria. The author provide selection criteria of the studies were given as: 1) Studies which give appropriate original data about the incidence of hVISA, VISA and VRSA, 2) Articles and peer reviewed which included all MRSA strains randomly, 3) Studies employed

publicly accepted methods for the detection of hVISA, VISA and VRSA, 4) Articles included which were published only in English language. The rejection criteria of the studies were given below: 1) Articles that provide wrong data or overlapping, 2) Reviews and conference abstracts, 3) Articles excluded that contain less than 10 cases.

Data extraction

The following part were selected from each included study: Name of the first author, study conducted year, publishing year, name of continent, country name, total number of MRSA strains, source of specimen, isolates number of VRSA, VISA and hVISA, methods used for detection, the MIC of vancomycin data were collected.

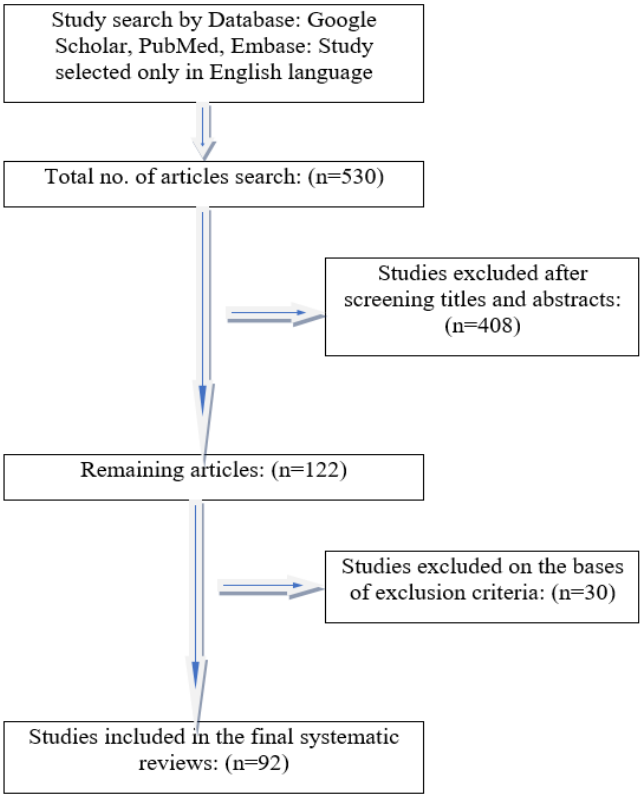

Fig 1: Flowchart showing study selection

DATA ANALYSIS

The information were collected and categorized into groups of hVISA, VISA and VRSA strains. The information were further categorized into subgroups of continents. A differentiation between the genetic causes, Minimum Inhibitory Concentration, and AST was carried out. In this review we also observed, which antibiotics was most effective and common against these type of infections. This study giving a idea about the etiology of these strains, MIC, and vancomycin activity which can help to minimize the prevalence and spread of vancomycin resistant *S. aureus* strains, there are some limitations to this review. There are many cases in developing countries which is not reported due to the lack of resources to identify and treat these infections, limited knowledge, medical infrastructure and economic constraints. Even if the cases were identify and treated but not publish due to the absence of publications so can not track this type of strains.

RESULT

Literature search

Almost, most of the studies were observed from the duration of 1997 to 2023. The number of 530 studies were identified from Google Scholar, PubMed and Embase. Out of these studies, 408 studies were excluded due to title and abstract is not relevant. Remaining 122 studies were further screened on the bases of exclusion and inclusion criteria 30 studies more excluded. Therefore 92 studies were selected on the bases of inclusion and exclusion criteria which is showing in (Fig. 1). These 92 studies were selected from different continent 49 from Asia, 22from Europe, 19 from America and 2 from Oceania.

hVISA, VISA and VRSA prevalence divide into different study periods:

The overall prevalence of hVISA, VISA and VRSA were 5.2% (95% CI 4.96-5.44), 3.8% (95% CI 3.58-4.03) and 6.69% (95% CI 5.98-7.39) respectively. During the different study period observed the variation in hVISA, VISA and VRSA prevalence in last few years, On the basis of study year these strains are categorized into four periods (before 2000, 2001–2010, and 2011–2020 and 2021-2023) were designated. Few articles which was not confirm to the study duration were not included in this analysis.

Table 2, shows the incidence of hVISA increase gradually from 1.88% (95% CI 1.64-2.11) of 12941 MRSA strains in 15 studies before 2000 to 6.89% (95% CI 0.38-7.27) of 16663 strains in 40 studies from 2001-2010, 11.00% (95% CI 9.74-12.26) of 2372 strains in 10 studies from 2011-2020 and reach to 10.78% (95% CI 6.53-15.04) of 204 MRSA strains in 1 study from 2021-2023. The prevalence of VISA was 0.73% (95% CI 0.54-0.92) of 7696 MRSA strains in 7 studies before 2000, 2.37% (95% CI 2.12-2.63) of 13621 MRSA strains in 26 studies from 2001-2010, 10.82% (95% CI 10.04-11.6) of 6155 MRSA strains in 10 studies from 2011-2020. The VRSA strains was not isolated before 2000. The incidence of VRSA was 1.8% (95% CI 0.97-2.62) of 1000 strains in 5 studies from 2001-2010, 7.97% (95% CI 7.97-8.83) of 3815 strains in 10 studies from 2011-2020.

Prevalence of hVISA, VISA and VRSA in various clinical specimens:

The MRSA strains were obtained from the various types of the clinical specimens but here the clinical samples were divided into two category. 1st category was obtained from only blood culture specimens and 2nd category isolates from all diagnostic specimens other than blood culture. All diagnostic specimens, including sputum, ET tip, pus, urine, body fluids etc. The prevalence of hVISA was 7.2% (95% CI 0.64-7.85) in 6312 strains in 20 studies reported from the blood culture sample, prevalence of hVISA is higher in blood culture sample as compare to all clinical samples which shows the prevalence of 4.71% (95% CI 4.45-4.97) in 25868 strains in 46 studies reported from all clinical samples. The prevalence of VISA was 3.04% (95% CI 2.54-3.54) in 4473 strains of MRSA in 7 studies reported from blood culture samples and which is lower than 3.95% (95% CI 3.7-4.2) in 22999 MRSA isolated from all diagnostic specimens in another 36 articles. The VRSA strains were not isolated from blood culture specimens and the prevalence of VRSA in all clinical samples was 6.68% (95% CI 5.99-7.39) in 4815 strains isolated from 15 studies.

Table 1: Characteristics of the eligible studies

Author name, publication year	Country, Continent	Time period of study	Organism isolated from	Methods use for detection	hVISA Prevalence%	VISA Prevalence%	VRSA Prevalence %	References
Keiichi et al. 1997	Japan, Asia	1996-1997	All Diagnostic Specimen	Brain Heart Infusion Agar	34/1149 (3.0)	-	-	(12)
Hideaki et al, 2007	Japan, Asia	1978-2005	All Diagnostic Specimen	Epsilometer-test	-	5/2446 (0.2)	-	(13)
Hui-min et al, 2007	Japan, Asia	1998-2005	Blood culture	PAP-AUC	2/20 (10)	-	-	(14)
Aminaka et al, 2009	Japan, Asia	1999	All Diagnostic Specimen	Brain Heart Infusion Agar	7/138 (5.1)	0/138 (0)	-	(15)
Hideaki et al, 2014	Japan, Asia	2008-2011	Blood culture	Macromethod E-Test	55/830 (6.5)	8/830 (1.0)	-	(16)
Samson et al, 1999	Hong Kong, Asia	1997-1998	All Diagnostic Specimen	Epsilometer-test	3/52 (5.8)	-	-	(17)
Suwanna et al, 2001	Thailand, Asia	1998-1999	All Diagnostic Specimen	Brain Heart Infusion Agar	5/155 (3.2)	-	-	(18)
Aroonlug et al, 2009	Thailand, Asia	2002-2003	All Diagnostic Specimen	Brain Heart Infusion Agar	4/533 (0.8)	-	-	(19)
Aroonlug et al, 2009	Thailand, Asia	2006-2007	All Diagnostic Specimen	Brain Heart Infusion Agar	8/361 (2.2)	3/361 (0.8)	-	(19)
Pawana et al,2014	Thailand, Asia	2010-2011	All Diagnostic Specimen	Brain Heart Infusion Agar	2/68 (2.9)	-	-	(20)
Mi-Na et al, 2000	Korea, Asia	1999/01-1999/08	All Diagnostic Specimen	PAP-AUC	59/3371 (1.8)	-	-	(21)
Mi-Na et al, 2002	Korea, Asia	1998/12-1999/08	All Diagnostic Specimen	Brain Heart Infusion Agar	24/3363 (0.7)	0/3363 (0)	-	(22)
Ki-Ho et al, 2012	Korea, Asia	2008-2010	Blood culture	Epsilometer-test	101/268(37.7)	-	-	(23)
Yong Rae et al, 2016	Korea, Asia	2012/04-2013/04	All Diagnostic Specimen	Macromethod E-Test	79/229 (34.5)	-	-	(24)
Wei-Yao et al, 2009	Taiwan, Asia	2001-2003	All Diagnostic Specimen	Brain Heart Infusion Agar	2/13 (15.3)	8/13 (61.5)	-	(25)
Po-Ren et al, 2010	Taiwan, Asia	2001-2002	All Diagnostic Specimen	MICbased	-	43/1500 (2.9)	-	(26)
C-M et al, 2010	Taiwan, Asia	2003/03-2003/08	All Diagnostic Specimen	Brain Heart Infusion Agar	7/1000 (0.7)	2/1000 (0.2)	-	(27)
Shang-Yi et al, 2012	Taiwan, Asia	2009/03-2009/12	Blood culture	Macromethod E-Test	5/62 (8.1)	-	-	(28)

Yasmeen et al, 2007	Israel, Asia	2003-2004	Blood culture	Macromethod E-Test	16/264 (6.0)	-	-	(29)
Yasmeen et al, 2009	Israel, Asia	2003-2006	Blood culture	Macromethod E-Test	27/223 (12.1)	-	-	(30)
Biswajit et al, 2008	India, Asia	2002-2005	All Diagnostic Specimen	MIC & PCR-based	-	-	1/57 (1.8)	(31)
Floriana et al, 2010	India, Asia	2005-2007	All Diagnostic Specimen	BHI, MET	36/139 (25.9)	0/139 (0)	-	(32)
Rajendra et al, 2011	India, Asia	2003-2007	All Diagnostic Specimen	PCR-based	-	-	4/282 (1.40)	(33)
Venubabu et al, 2011	India, Asia	2008/03-2008/10	All Diagnostic Specimen	MIC based PCR based	-	16/358 (4.5)	7/358 (1.9) 6/358 (1.7)	(34)
Shanmugarajet al, 2013	India, Asia	2009-2010	All Diagnostic Specimen	MHA	-	10/63 (15.9)	-	(35)
Debasmita et al, 2013	India, Asia	2009-2012	All Diagnostic Specimen	Epsilometer-test	-	545/1214 (44.9)	251/1214 (20.6)	(36)
Manu et al, 2013	India, Asia	2013	All Diagnostic Specimen	MHA	8/130 (6.1)	-	-	(37)
Surg et al, 2015	India, Asia	2010-2013	All Diagnostic Specimen	Brain Heart Infusion Agar	4/58 (6.9)	-	-	(38)
Mahadeo et al, 2017	India, Asia	2015-2016	All Diagnostic Specimen	MIC-based	-	11/32 (34.4)	4/32 (12.5)	(39)
Kiranjeet et al, 2019	India, Asia	2016-2017	All Diagnostic Specimen	MIC-based	-	19/162 (11.7)	4/162 (2.5)	(40)
Vinay et al, 2020	India, Asia	2010-2012	All Diagnostic Specimen	MIC- based	-	53/115 (46.08)	7/115 (6.08)	(41)
Sreejisha et al, 2023	India, Asia	2019-2020	All Diagnostic Specimen	PAP-AUC	14/220 (6.4)	-	-	(9)
Nashra et al, 2019	India, Asia	2017-2018	All Diagnostic Specimen	Epsilometer-test	-	8/140 (5.7)	2/140 (1.3)	(42)
Wenjia et al, 2009	China, Asia	2005-2007	Blood culture	Macromethod E-Test	26/200 (13.1)	1/200 (0.5)	-	(43)
Hongbin et al,2011	China, Asia	2005-2008	All Diagnostic Specimen	PAP-AUC	62/559 (11.1)	0/559 (0)	-	(44)
Wang et al,2013	China, Asia	2007-2009	All Diagnostic Specimen	Macromethod E-Test	25/122 (20.5)	-	-	(45)
Guo et al, 2013	China, Asia	2012/06-2012/12	All Diagnostic Specimen	MIC based	-	1/1790 (0.06)	-	(46)

Jin et al,2023	China, Asia	2019-2021	All Diagnostic Specimen	PAP-AUC	22/204 (10.9)	-	-	(5)
Horieh et al, 2008	Iran, Asia	2006-2007	All Diagnostic Specimen	MIC-based	-	3/164 (1.8)	1/164 (0.6)	(47)
Farhad et al, 2016	Iran, Asia	2009-2011	All Diagnostic Specimen	Epsilometer-test	-	-	23/250 (9.2)	(48)
Yousefi et al, 2017	Iran, Asia	2014-2015	All Diagnostic Specimen	MIC & PCR based	-	-	2/30 (6.7)	(49)
Marjan et al, 2017	Iran, Asia	2014-2017	All Diagnostic Specimen	MIC & PCR based	-	2/1789 (0.1)	4/1789 (0.2)	(50)
R.K.C et al, 2009	Singapore, Asia	2005-2006	Blood culture	Macromethod E-Test	3/56 (5.4)	-	-	(51)
Norazah et al, 2012	Malaysia, Asia	2009/01-2009/12	All Diagnostic Specimen	Epsilometer-test	2/43 (4.7)	-	-	(52)
Siti Roszilawati et al, 2012	Malaysia, Asia	2009/02-2009/05	All Diagnostic Specimen	Epsilometer-test	7/320 (2.2)	-	-	(53)
Kaleem et al, 2012	Pakistan, Asia	2012	All Diagnostic Specimen	Epsilometer-test	6/347 (1.7)	-	-	(54)
Jae-Hoon et al, 2004	Asia	1997-2000	All Diagnostic Specimen	Brain Heart Infusion Agar	58/1357 (4.3)	-	-	(55)
Meera et al, 2021	Nepal, Asia	2018/07-2018/12	All Diagnostic Specimen	Epsilometer-test	-	15/45 (33.3)	5/45 (11.1)	(6)
Niranjan et al, 2023	Nepal, Asia	2019/12-2020/06	All Diagnostic Specimen	MIC based	-	4/38 (10.5)	2/38 (5.2)	(56)
Geisel et al, 1999	Germany, Europe	1992-1998	All Diagnostic Specimen	Brain Heart Infusion Agar	7/85 (8.2)	-	-	(57)
Bierbaum et al, 1999	Germany, Europe	1997	All Diagnostic Specimen	Brain Heart Infusion Agar	2/367 (0.5)	-	-	(58)
Canton et al,1999	Spain, Europe	1997-1998	All Diagnostic Specimen	Epsilometer-test	-	12/248 (4.8)	-	(59)
Azzam et al, 2006	Spain, Europe	2002-2004	All Diagnostic Specimen	MHA	-	-	5/139 (3.6)	(60)
Marchese et al, 2000	Italy, Europe	1997-1998	All Diagnostic Specimen	Brain Heart Infusion Agar	2/179 (1.1)	-	-	(61)
Reverdy et al, 2001	French, Europe	1998-1999	All Diagnostic Specimen	Macromethod E-Test	5/171 (2.9)	-	-	(62)
Frederic et al, 2003	France, Europe	1997-2002	All Diagnostic Specimen	Macromethod E-Test	13/48 (27.1	-	-	(63)

Cartolano et al, 2004	France, Europe	2000	All Diagnostic Specimen	MHA	-	31/1070 (2.9)	-	(64)
Jerome et al, 2006	France, Europe	1983-2001	All Diagnostic Specimen	Epsilometer-test	-	1/1445 (0.07)	-	(65)
Arnaud et al, 2006	France, Europe	1999-2000	All Diagnostic Specimen	MHA	11/329 (3.3)	-	-	(66)
Fabien et al, 2006	France, Europe	2001-2002	All Diagnostic Specimen	Macromethod E-Test	255/2300(11.1)	-	-	(67)
Sylvie et al, 2012	France, Europe	2007	All Diagnostic Specimen	MHA	12/20 (60.0)	-	-	(68)
Olivier et al, 2002	Belgium, Europe	1999/01-1999/12	Blood culture	Brain Heart Infusion Agar	4/2145 (0.1)	3/2145 (0.1)	-	(69)
Pierard et al, 2004	Belgium, Europe	2003	All Diagnostic Specimen	Macromethod E-Test	5/1002 (0.5)	1/1002 (0.1)	-	(70)
Nonhoff et al, 2005	Belgium, Europe	2001/01-2001/12	All Diagnostic Specimen	Epsilometer-test	3/455 (0.7)	-	-	(71)
Banu et al, 2005	Turkey, Europe	1998-2002	All Diagnostic Specimen	Macromethod E-Test	46/256 (18.0	0/256 (0)	-	(72)
Banu et al, 2013	Turkey, Europe	2009-2010	Blood culture	Macromethod E-Test	24/175 (13.7)	0/175 (0)	-	(73)
Deniz et al, 2021	Turkey, Europe	2018/04-2019/10	All Diagnostic Specimen	Brain Heart Infusion Agar	43/100 (43)	-	-	(74)
Margaret et al, 2007	Ireland, Europe	1998-2004	All Diagnostic Specimen	Macromethod E-Test	73/3189 (2.3)	-	-	(75)
Ilker et al, 2012	Switzerland, Europe	1995-2003	All Diagnostic Specimen	Brain Heart Infusion Agar	-	55/208 (26.4)	-	(76)
Vaudaux et al, 2012	Switzerland, Europe	2000-2008	All Diagnostic Specimen	MHA	-	13/57 (31.7)	-	(77)
Mlynarczyk et al, 2003	Poland, Europe	2002	All Diagnostic Specimen	PAP-AUC	5/103 (4.8)	0/103 (0)	-	(78)
Ariza et al, 1999	USA, America	1990-1997	All Diagnostic Specimen	Epsilometer-test	14/19 (73.3)	-	-	(79)
Susannah et al, 1999	USA, America	1997	All Diagnostic Specimen	MHA	-	4/630 (0.6)	-	(80)
Fridkin et al, 2003	USA, America	1999-2000	All Diagnostic Specimen	Brain Heart Infusion Agar	-	6/102 (5.8)	-	(81)
Amir et al,2004	USA, America	2002/01-2002/12	Blood culture	Brain Heart Infusion Agar	3/22 (13.6)	-	-	(82)

Michael J et al, 2008	USA, America	1994-2002	All Diagnostic Specimen	Macromethod E-Test	27/356 (7.6)	8/356 (2.3)	-	(83)
Michael J et al, 2008	USA, America	2003-2007	All Diagnostic Specimen	Macromethod E-Test	76/917 (8.3)	3/917 (0.3)	-	(83)
Klaudia et al,2008	USA, America	2006-2007	All Diagnostic Specimen	Macromethod E-Test	2/982 (0.2)	3/982 (0.3)	-	(84)
Adina C et al, 2009	USA, America	1996-1997	Blood culture	MHA	8/61 (13.1)	-	-	(85)
Adina C et al, 2009	USA, America	2000-2001	Blood culture	MHA	5/55 (9.1)	-	-	(85)
Helio S et al, 2009	USA, America	2002-2006	Blood culture	Macromethod E-Test	36/268 (13.4)	-	-	(86)
Pastagia et al, 2009	USA, America	2002-2007	Blood culture	Epsilometer-test	45/699 (6.4)	118/699 (16.9)	-	(87)
Adina C et al, 2009	USA, America	2002-2003	Blood culture	MHA	37/187 (19.8)	-	-	(85)
Adina C et al, 2009	USA, America	2005-2006	Blood culture	MHA	21/186 (11.3)	-	-	(85)
Heather et al, 2010	Canada, America	1995-2006	All Diagnostic Specimen	Epsilometer-test	25/475 (5.3)	-	-	(88)
Adam M et al 2011	USA, America	2000-2008	Blood culture	Epsilometer-test	2/167 (1.2)	-	-	(89)
Riad et al, 2011	USA, America	2002-03, 2005-06	Blood culture	Macromethod E-Test	30/371 (8.1)	6/371 (1.6)	-	(90)
Cory et al, 2012	USA, America	2007-2008	All Diagnostic Specimen	MIC-based	9/77 (11.7)	22/77 (28.6)	-	(91)
Anthony M et al, 2014	USA, America	2002-2013	All Diagnostic Specimen	PAP-AUC	38/266 (18.8)	-	-	(92)
Alessandro Conrado et al, 2014	Brazil, America	2009-2013	All Diagnostic Specimen	Epsilometer-test	12/124 (9.7)	-	-	(93)
Patrick GP et al, 2004	Australia, Oceania	2001-2002	Blood culture	Epsilometer-test	5/53 (9.4)	0/53 (0)	-	(94)
Kylie C et al, 2009	Australia, Oceania	2005/03-2005/12	All Diagnostic Specimen	MIC-based	56/117 (47.9)	2/117 (1.7)	-	(95)

*****PAP-AUC: Population Analysis Profile-Area under the curve, MHA: Mueller Hinton Agar, MIC: Minimum Inhibitory Concentration, PCR: Polymerase Chain Reaction,

Prevalence of hVISA, VISA and VRSA at different geographical regions

hVISA, VISA and VRSA varied prevalence in different geographical regions in this analysis. The incidence of hVISA was 4.83 % (95% CI 0.33-5.16) of 16024 MRSA isolates in 33 studies from Asia/Oceania, and 5.57 % (95% CI 5.22-5.92) of 16156 strains in 33 articles from Europe/America continents. The prevalence of VISA was 4.56 % (95% CI 4.25-4.88) in 16629 strains of MRSA isolates in 25 articles from Asia/Oceania, and 2.64 % (95% CI 0.3-2.94) in 10843 MRSA strains isolated from 18 articles from Europe/America continent. However 6.78 % (95% CI 6.06-7.5) of 4676 MRSA strains were VRSA isolated in14 studies from Asia/Oceania compared with 3.56 % (95% CI 0.5-6.7) of 139 MRSA strains in 1 study from Europe/America.

Table 2: hVISA, VISA and VRSA strains prevalence based on duration of study, origin of study, and selection of isolated organism

Strain	Category	Sub category	No. Studies	Isolated hVISA/ VISA/ VRSA	Total no. of strains	Prevalence(%) (95% CI*)
hVISA	Overall		66	1674	32180	5.2 (4.96-5.44)
	Study period	Before 2000	15	243	12941	1.88 (1.64-2.11)
		2001-2010	40	1148	16663	6.89 (0.38-7.27)
		2011-2020	10	261	2372	11.00 (9.74-12.26)
		2021-2023	1	22	204	10.78 (6.53-15.04)
	Continent	Asia-Oceania	33	774	16024	4.83 (0.33-5.16)
		Europe-America	33	900	16156	5.57 (5.22-5.92)
	Clinical sample	Blood Culture	20	455	6312	7.2 (0.64-7.85)
		All Diagnostic sample	46	1219	25868	4.71 (4.45-4.97)
VISA	Overall		43	1045	27472	3.80 (3.58-4.03)
	Study period	Before 2000	7	56	7696	0.73 (0.54-0.92)
		2001-2010	26	323	13621	2.37 (2.12-2.63)
		2011-2020	10	666	6155	10.82 (10.04-11.6)
		2021-2023	-	-	-	-
	Continent	Asia-Oceania	25	759	16629	4.56 (4.25-4.88)
		Europe-America	18	286	10843	2.64 (0.3-2.94)
	Clinical sample	Blood Culture	7	136	4473	3.04 (2.54-3.54)
		All Diagnostic sample	36	909	22999	3.95 (3.7-4.2)
VRSA	Overall		15	322	4815	6.69 (5.98-7.39)
	Study period	Before 2000	-	-	-	-
		2001-2010	5	18	1000	1.8 (0.97-2.62)
		2011-2020	10	304	3815	7.97 (7.11-8.83)
		2021-2023	-		-	-
	Continent	Asia-Oceania	14	317	4676	6.78 (6.06-7.5)
		Europe-America	1	5	139	3.56 (0.50-6.7)
	Clinical sample	Blood Culture	-	-	-	-
		All Diagnostic sample	15	322	4815	6.68 (5.99-7.39)

*Confidence Interval

DISCUSSION

The elevated prevalence of *S. aureus* strains with resistance to methicillin and reduced sensitivity to vancomycin has making a more dreadful situation and concern for discovery of new antibiotic agents that kill the resistant strains. Emergence of hVISA, VISA and VRSA increase because the indiscriminate use of vancomycin.[42] However, the studies included in this analysis shows that the treatment failure rate of vancomycin had increased. Havaei et al, 2012 studied 171 strains, out of these strains 97.07 % strains shows the MIC within susceptible range (<2µg/ml) and called the VSSA and 5 (2.93%) strains shows the MIC value between 4-8µg/ml and called VISA strains.[96] Amberpet et al, 2019 reported 500 MRSA strains which were isolated from various ward, and they defined the treatment failure of vancomycin and increase mortality of patients. Out of 500 MRSA strains 66 (13.2%) MRSA strains are hVISA which is detected by BHIV4 method. Prevalence of hVISA is higher as compare to this study.[97]

In this systematic review we noted that some of the studies reported the MIC of *S. aureus* strains were higher in Brain Heart Infusion medium as compare to the Mueller hinton medium. This type of MIC results suggest that the vancomycin intermediate level of *S. aureus* is directly depend on the nutritional status of the medium. BHI medium fulfilled of nutrition and give better nutrition to the *S. aureus* which is similar to the medium of human body, but the MH medium does not provide the enough nutrition to the bacterial growth and MH medium act as a external environment due to lack of the nutrient as compare to BHI medium. Therefore, it is the main reason for detection of hVISA strains we used BHI medium and this medium provide better nutrition to the strains and grow easily.[98] Sreejisha et al 2023 studied 220 MRSA strains which is obtained from diabetic and non-diabetic patients, out of these MRSA strains 14 (6.4%) were hVISA. The rate of hVISA among MRSA isolated from diabetic and non-diabetic were 9.0% and 3.1% respectively.[9]

If MRSA or VRSA once established in hospital, then it will become difficult to clear off these strains and environment of the hospital may act as a source of hospital acquired infections in the future. So as soon as possible detection of these strains and genes which is responsible for antibiotic resistance such as van and mec gene would be a useful technique for the identification of these strains and help in the prevention and control of their spread.[6]

CONCLUSION

This systematic review highlights the emergence of hVISA, VISA and VRSA among the different geographical areas. The incidence of these strains has been elevated in last few years specially in Asia/Oceania as compare to Europe/America. The most prevalent of genes which is associated with VRSA and MRSA were vanA and mecA gene respectively. Other than these genes some genes also found in studies like as vanB and mecC genes which is responsible for antibiotics resistance. Prescribed antimicrobial treatments to the patients carefully by the clinicians and do not indiscriminate use of antimicrobial agent, detection of these type of strains are needed for preventing further emergence and dissemination of hVISA, VISA and VRSA strains.

References

1) Rasigade JP, Vandenesch F. *Staphylococcus aureus*: a pathogen with still unresolved issues. Infection, genetics and evolution. 2014 Jan 1;21:510-4.

2) Cong Y, Yang S, Rao X. Vancomycin resistant *Staphylococcus aureus* infections: A review of case updating and clinical features. Journal of advanced research. 2020 Jan 1;21:169-76.

3) Saeed A, Ahsan F, Nawaz M, Iqbal K, Rehman KU, Ijaz T. Incidence of vancomycin resistant phenotype of the methicillin resistant *Staphylococcus aureus* isolated from a tertiary care hospital in Lahore. Antibiotics. 2019 Dec 18;9(1):3.

4) Taylor TA, Unakal CG. *Staphylococcus aureus*. InStatPearls [Internet] 2022 Jul 18. StatPearls Publishing.

5) Liang J, Hu Y, Fu M, Li N, Wang F, Yu X, Ji B. Resistance and Molecular Characteristics of Methicillin-Resistant *Staphylococcus aureus* and Heterogeneous Vancomycin-Intermediate *Staphylococcus aureus*. Infection and Drug Resistance. 2023 Jan 31:379-88.

6) Maharjan M, Sah AK, Pyakurel S, Thapa S, Maharjan S, Adhikari N, Rijal KR, Ghimire P, Thapa Shrestha U. Molecular confirmation of vancomycin-resistant *Staphylococcus aureus* with vanA gene from a hospital in Kathmandu. International Journal of Microbiology. 2021 Dec 2;2021.

7) Hiramatsu K, Hanaki H, Ino T, Yabuta K, Oguri T, Tenover FC. Methicillin-resistant *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility. The Journal of antimicrobial chemotherapy. 1997 Jul 1;40(1):135-6.

8) Howden BP, Davies JK, Johnson PD, Stinear TP, Grayson ML. Reduced vancomycin susceptibility in *Staphylococcus aureus*, including vancomycin-intermediate and heterogeneous vancomycin-intermediate strains: resistance mechanisms, laboratory detection, and clinical implications. Clinical microbiology reviews. 2010 Jan;23(1):99-139.

9) Sreejisha M, Mulki SS, Shenoy S, Dhanashree B, Chakrapani M, Bhat G. Heterogeneous Vancomycin Intermediate *Staphylococcus aureus* Infections in Diabetic and Non-Diabetic Patients–A Hospital-Based Comparative Study. Infection and Drug Resistance. 2023;16:9.

10) Zhang S, Sun X, Chang W, Dai Y, Ma X. Systematic review and meta-analysis of the epidemiology of vancomycin-intermediate and heterogeneous vancomycin-intermediate *Staphylococcus aureus* isolates. PloS one. 2015 Aug 19;10(8):e0136082.

11) Wu Q, Sabokroo N, Wang Y, Hashemian M, Karamollahi S, Kouhsari E. Systematic review and meta-analysis of the epidemiology of vancomycin-resistance *Staphylococcus aureus* isolates. Antimicrobial Resistance & Infection Control. 2021 Dec;10:1-3.

12) Hiramatsu K, Aritaka N, Hanaki H, Kawasaki S, Hosoda Y, Hori S, Fukuchi Y, Kobayashi I. Dissemination in Japanese hospitals of strains of *Staphylococcus aureus* heterogeneously resistant to vancomycin. The Lancet. 1997 Dec 6;350(9092):1670-3.

13) Hanaki H, Hososaka Y, Yanagisawa C, Nakae T, Sunakawa K, Otsuka Y, Nagasawa Z. Occurrence of vancomycin-intermediate-resistant *Staphylococcus aureus* in Japan. Journal of infection and chemotherapy. 2007 Jan 1;13(2):118-21.

14) Neoh HM, Hori S, Komatsu M, Oguri T, Takeuchi F, Cui L, Hiramatsu K. Impact of reduced vancomycin susceptibility on the therapeutic outcome of MRSA bloodstream infections. Annals of Clinical Microbiology and Antimicrobials. 2007 Dec;6:1-6.

15) Aminaka M, Hiramatsu K. Detection of Heterogeneous Vancomycin Intermediate *Staphylococcus aureus* (heteroVISA) in MRSA of Japanese Clinical Isolates. American Journal of Infection Control. 2009; 37(5): E15–E6.

16) Hanaki H, Cui L, Ikeda-Dantsuji Y, Nakae T, Honda J, Yanagihara K, Takesue Y, Matsumoto T, Sunakawa K, Kaku M, Tomono K. Antibiotic susceptibility survey of blood-borne MRSA isolates in Japan from 2008 through 2011. Journal of Infection and Chemotherapy. 2014 Sep 1;20(9):527-34.

17) Wong SS, Ho PL, Woo PC, Yuen KY. Bacteremia caused by staphylococci with inducible vancomycin heteroresistance. Clinical Infectious Diseases. 1999 Aug 15;29(4):760-7.

18) Trakulsomboon S, Danchaivijitr S, Rongrungruang Y, Dhiraputra C, Susaemgrat W, Ito T, Hiramatsu K. First report of methicillin-resistant *Staphylococcus aureus* with reduced susceptibility to vancomycin in Thailand. Journal of clinical microbiology. 2001 Feb 1;39(2):591-5.

19) Lulitanond A, Engchanil C, Chaimanee P, Vorachit M, Ito T, Hiramatsu K. The first vancomycin-intermediate *Staphylococcus aureus* strains isolated from patients in Thailand. Journal of clinical microbiology. 2009 Jul;47(7):2311-6.

20) Panomket P, Thirat S, Wanram S, Sranujit RP. Methicillin-resistant *Staphylococcus aureus* with reduced susceptibility to vancomycin in Sanprasitthiprasong Hospital. Journal of the Medical Association of Thailand Chotmaihet thangphaet. 2014 Apr 1;97:S7-11.

21) Kim MN, Pai CH, Woo JH, Ryu JS, Hiramatsu K. Vancomycin-intermediate *Staphylococcus aureus* in Korea. Journal of clinical microbiology. 2000 Oct 1;38(10):3879-81.

22) Kim MN, Hwang SH, Pyo YJ, Mun HM, Pai CH. Clonal spread of *Staphylococcus aureus* heterogeneously resistant to vancomycin in a university hospital in Korea. Journal of clinical microbiology. 2002 Apr;40(4):1376-80.

23) Park KH, Kim ES, Kim HS, Park SJ, Bang KM, Park HJ, Park SY, Moon SM, Chong YP, Kim SH, Lee SO. Comparison of the clinical features, bacterial genotypes and outcomes of patients with bacteraemia due to heteroresistant vancomycin-intermediate *Staphylococcus aureus* and vancomycin-susceptible *S. aureus*. Journal of antimicrobial chemotherapy. 2012 Aug 1;67(8):1843-9.

24) Koh YR, Kim KH, Chang CL, Yi J. Prevalence and clinical impact of heterogeneous vancomycin-intermediate *Staphylococcus aureus* isolated from hospitalized patients. Annals of Laboratory Medicine. 2016 May;36(3):235.

25) Wang WY, Lee SY, Chiueh TS, Lu JJ. Molecular and phenotypic characteristics of methicillin-resistant and vancomycin-intermediate *Staphylococcus aureus* isolates from patients with septic arthritis. Journal of clinical microbiology. 2009 Nov;47(11):3617-23.

26) Hsueh PR, Lee SY, Perng CL, Chang TY, Lu JJ. Clonal dissemination of meticillin-resistant and vancomycin-intermediate *Staphylococcus aureus* in a Taiwanese hospital. International journal of antimicrobial agents. 2010 Oct 1;36(4):307-12.

27) Ho CM, Hsueh PR, Liu CY, Lee SY, Chiueh TS, Shyr JM, Tsao SM, Chuang YC, Yan JJ, Wang LS, Wang JH. Prevalence and accessory gene regulator (agr) analysis of vancomycin-intermediate *Staphylococcus aureus* among methicillin-resistant isolates in Taiwan—SMART program, 2003. European journal of clinical microbiology & infectious diseases. 2010 Apr;29:383-9.

28) Lin SY, Chen TC, Chen FJ, Chen YH, Lin YI, Siu LK, Lu PL. Molecular epidemiology and clinical characteristics of hetero-resistant vancomycin intermediate *Staphylococcus aureus* bacteremia in a Taiwan Medical Center. Journal of Microbiology, Immunology and Infection. 2012 Dec 1;45(6):435-41.

29) Maor Y, Rahav G, Belausov N, Ben-David D, Smollan G, Keller N. Prevalence and characteristics of heteroresistant vancomycin-intermediate *Staphylococcus aureus* bacteremia in a tertiary care center. Journal of clinical microbiology. 2007 May;45(5):1511-4.

30) Maor Y, Hagin M, Belausov N, Keller N, Ben-David D, Rahav G. Clinical features of heteroresistant vancomycin-intermediate *Staphylococcus aureus* bacteremia versus those of methicillin-resistant *S. aureus* bacteremia. The Journal of infectious diseases. 2009 Mar 1;199(5):619-24.

31) Saha B, Singh AK, Ghosh A, Bal M. Identification and characterization of a vancomycin-resistant *Staphylococcus aureus* isolated from Kolkata (South Asia). Journal of medical microbiology. 2008 Jan;57(1):72-9.

32) Campanile F, Borbone S, Perez M, Bongiorno D, Cafiso V, Bertuccio T, Purrello S, Nicolosi D, Scuderi C, Stefani S. Heteroresistance to glycopeptides in Italian meticillin-resistant *Staphylococcus aureus* (MRSA) isolates. International journal of antimicrobial agents. 2010 Nov 1;36(5):415-9.

33) Goud R, Gupta S, Neogi U, Agarwal D, Naidu K, Chalannavar R, Subhaschandra G. Community prevalence of methicillin and vancomycin resistant *Staphylococcus aureus* in and around Bangalore, southern India. Revista da Sociedade Brasileira de Medicina Tropical. 2011;44:309-12.

34) Thati V, Shivannavar CT, Gaddad SM. Vancomycin resistance among methicillin resistant *Staphylococcus aureus* isolates from intensive care units of tertiary care hospitals in Hyderabad. The Indian journal of medical research. 2011 Nov;134(5):704.

35) Gowrishankar S, Thenmozhi R, Balaji K, Pandian SK. Emergence of methicillin-resistant, vancomycin-intermediate *Staphylococcus aureus* among patients associated with group A Streptococcal pharyngitis infection in southern India. Infection, Genetics and Evolution. 2013 Mar 1;14:383-9.

36) Dubey D, Rath S, Sahu MC, Pattnaik L, Debata NK, Padhy RN. Surveillance of infection status of drug resistant *Staphylococcus aureus* in an Indian teaching hospital. Asian Pacific journal of tropical disease. 2013 Apr 1;3(2):133-42.

37) Chaudhary M, Payasi A. Prevalence of heterogeneous glycopeptide intermediate resistance in Methicillin-Resistant *Staphylococcus aureus*. American Journal of Infectious Diseases. 2013 Jul 1;9(3):63.

38) Chaudhari CN, Tandel K, Grover N, Sen S, Bhatt P, Sahni AK, Praharaj AK. Heterogeneous vancomycin-intermediate among methicillin resistant *Staphylococcus aureus*. medical journal armed forces india. 2015 Jan 1;71(1):15-8.

39) Mandal M, Dey S, Kumar D, Biswas PP, Nandan K, Sen A. Determination of vancomycin and linezolid resistance in *Staphylococcus aureus* isolated from Katihar district of Bihar, India. JEMDS. 2017 Feb 23;6(16):1244-7.

40) Kaur K, Gill A K, Kaur M. Methicillin resistance, vancomycin intermediate and vancomycin resistance *Staphylococcus aureus* prevalence in a tertiary care hospital of Punjab, India. Blood. 2019;21:12-9.

41) Moses VK, Kandi V, Rao SK. Minimum inhibitory concentrations of vancomycin and daptomycin against methicillin-resistant *Staphylococcus Aureus* isolated from various clinical specimens: A study from south india. Cureus. 2020 Jan 23;12(1).

42) Nashra A, Sujatha R, Sameer D, Kumar A, Bagoliwal. Screening and molecular characterization of VISA and VRSA among the MRSA isolates at a tertiary care centre kanpur. International Journal of Health Sciences and Research. 2019 may;9(5).

43) Sun W, Chen H, Liu Y, Zhao C, Nichols WW, Chen M, Zhang J, Ma Y, Wang H. Prevalence and characterization of heterogeneous vancomycin-intermediate *Staphylococcus aureus* isolates from 14 cities in China. Antimicrobial agents and chemotherapy. 2009 Sep;53(9):3642-9.

44) Chen H, Liu Y, Sun W, Chen M, Wang H. The incidence of heterogeneous vancomycin-intermediate *Staphylococcus aureus* correlated with increase of vancomycin MIC. Diagnostic microbiology and infectious disease. 2011 Nov 1;71(3):301-3.

45) Wang Y, Hu YJ, Ai XM, Xu HT, Sun TY. Prevalence and clinical prognosis of heteroresistant vancomycin-intermediate *Staphylococcus aureus* in a tertiary care center in China. Chinese medical journal. 2013 Feb 5;126(03):505-9.

46) Guo Y, Wang H, Zhao CJ, Wang ZW, Cao B, Xu YC, et al. A surveillance study of antimicrobial resistance of gram-positive cocci strains isolated from 16 teaching hospitals in China in 2012. Chinese Journal of Microbiology and Immunology (China). 2013; 33(6):401–9.

47) Saderi H, Owlia P, Maleki Z, Habibi M, RAHMATI N. Susceptibility to vancomycin in Staphylococcus aureus isolated from patients of four university-affiliated hospitals in Tehran.

48) Sarrafzadeh F, Mirzabiegi Z, Torabi-Nami M. Vancomycin-resistant *Staphylococcus aureus* isolates among hospitalized patients; a tertiary medical care center experience from Southern Iran. Cogent Medicine. 2016 Dec 31;3(1):1163768.

49) Yousefi M, Fallah F, Arshadi M, Pourmand MR, Hashemi A, Pourmand G. Identification of tigecycline-and vancomycin-resistant *Staphylococcus aureus* strains among patients with urinary tract infection in Iran. New Microbes and New Infections. 2017 Sep 1;19:8-12.

50) Shekarabi M, Hajikhani B, Salimi Chirani A, Fazeli M, Goudarzi M. Molecular characterization of vancomycin-resistant *Staphylococcus aureus* strains isolated from clinical samples: A three year study in Tehran, Iran. PloS one. 2017 Aug 30;12(8):e0183607.

51) Fong RK, Low J, Koh TH, Kurup A. Clinical features and treatment outcomes of vancomycin-intermediate *Staphylococcus aureus* (VISA) and heteroresistant vancomycin-intermediate *Staphylococcus aureus* (hVISA) in a tertiary care institution in Singapore. European journal of clinical microbiology & infectious diseases. 2009 Aug;28:983-7.

52) Ahmad N, Ling LN, Ghani MK, Nawi S. The presence of heterogeneous vancomycin-intermediate *Staphylococcus aureus* (heteroVISA) in a major Malaysian hospital. Med J Malaysia. 2012 Jun;67(3):269.

53) Ramli SR, Neoh HM, Aziz MN, Hussin S. Screening and detection of heterogenous vancomycin intermediate *Staphylococcus aureus* in Hospital Kuala Lumpur Malaysia, using the glycopeptide resistance detection Etest and population analysis profiling. Infectious disease reports. 2012 Jan;4(1):e20.

54) Kaleem F, Usman J, Amanat S. Current status of Glycopeptide intermediate and heterogenous Glycopeptide intermediate *Staphylococcus aureus* and their prevailing susceptibility pattern at two tertiary care hospitals of Pakistan. International Journal of Infectious Diseases. 2012 Jun 1;16:e420-1.

55) Song JH, Hiramatsu K, Suh JY, Ko KS, Ito T, Kapi M, Kiem S, Kim YS, Oh WS, Peck KR, Lee NY. Emergence in Asian countries of *Staphylococcus aureus* with reduced susceptibility to vancomycin. Antimicrobial agents and chemotherapy. 2004 Dec;48(12):4926-8.

56) Nepal N, Mahara P, Subedi S, Rijal KR, Ghimire P, Banjara MR, Shrestha UT. Genotypically Confirmed Vancomycin-Resistant *Staphylococcus aureus* With vanB Gene Among Clinical Isolates in Kathmandu. Microbiology Insights. 2023 Jul;16:11786361231183675.

57) Geisel R, Schmitz FJ, Thomas L, Berns G, Zetsche O, Ulrich B, Fluit AC, Labischinsky H, Witte W. Emergence of heterogeneous intermediate vancomycin resistance in *Staphylococcus aureus* isolates in the Düsseldorf area. Journal of Antimicrobial Chemotherapy. 1999 Jun 1;43(6):846-8.

58) Bierbaum G, Fuchs K, Lenz W, Szekat C, Sahl HG. Presence of *Staphylococcus aureus* with reduced susceptibility to vancomycin in Germany. European Journal of Clinical Microbiology and Infectious Diseases. 1999 Nov;18:691-6.

59) Canton R, Mir N, Martinez-Ferrer M, Sanchez del Saz B, Soler I, Baquero F. Prospective study of *Staphylococcus aureus* with reduced susceptibility to glycopeptides. Rev esp quimioter. 1999; 12(1):48–53.

60) Bataineh HA. Resistance of *Staphyiococcus aureus* to vancomycin in Zarqa, Jordan. Pakistan Journal of Medical Sciences. 2006;22(2):144.

61) Marchese A, Balistreri G, Tonoli E, Debbia EA, Schito GC. Heterogeneous vancomycin resistance in methicillin-resistant *Staphylococcus aureus* strains isolated in a large Italian hospital. Journal of clinical microbiology. 2000 Feb 1;38(2):866-9.

62) Reverdy M, Jarraud S, Bohin-Duhreux S, Buret E, Girardo P, Lina G, Vandenesch F, Etienne J. Incidence of *Staphylococcus aureus* with reduced susceptibility to glycopeptides in two French hospitals. Clinical microbiology and infection. 2001 May 1;7(5):267-72.

63) Bert F, Clarissou J, Durand F, Delefosse D, Chauvet C, Lefebvre P, Lambert N, Branger C. Prevalence, molecular epidemiology, and clinical significance of heterogeneous glycopeptide-intermediate *Staphylococcus aureus* in liver transplant recipients. Journal of clinical microbiology. 2003 Nov;41(11):5147-52.

64) Cartolano GL, Cheron M, Benabid D, Leneveu M, Boisivon A. Methicillin-resistant *Staphylococcus aureus* (MRSA) with reduced susceptibility to glycopeptides (GISA) in 63 French general hospitals. Clinical microbiology and infection. 2004 May 1;10(5):448-51.

65) Robert J, Bismuth R, Jarlier V. Decreased susceptibility to glycopeptides in methicillin-resistant *Staphylococcus aureus*: a 20 year study in a large French teaching hospital, 1983–2002. Journal of Antimicrobial Chemotherapy. 2006 Mar 1;57(3):506-10.

66) de Lassence A, Hidri N, Timsit JF, Joly-Guillou ML, Thiery G, Boyer A, Lable P, Blivet A, Kalinowski H, Martin Y, Lajonchere JP. Control and outcome of a large outbreak of colonization and infection with glycopeptide-intermediate *Staphylococcus aureus* in an intensive care unit. Clinical infectious diseases. 2006 Jan 15;42(2):170-8.

67) Garnier F, Chainier D, Walsh T, Karlsson A, Bolmström A, Grelaud C, Mounier M, Denis F, Ploy MC. A 1 year surveillance study of glycopeptide-intermediate *Staphylococcus aureus* strains in a French hospital. Journal of Antimicrobial Chemotherapy. 2006 Jan 1;57(1):146-9.

68) Parer S, Lotthé A, Chardon P, Poncet R, Jean-Pierre H, Jumas-Bilak E. An outbreak of heterogeneous glycopeptide-intermediate *Staphylococcus aureus* related to a device source in an intensive care unit. Infection Control & Hospital Epidemiology. 2012 Feb;33(2):167-74.

69) Denis O. Emergence of vancomycin-intermediate *Staphylococcus aureus* in a Belgian hospital: microbiological and clinical features. Journal of Antimicrobial Chemotherapy. 2002; 50(3):383–91.

70) Pierard D, Vandenbussche H, Verschraegen I, Lauwers S. Screening for *Staphylococcus aureus* with a reduced susceptibility to vancomycin in: a Belgian hospital. Pathologie Biologie. 2004 Oct 1;52(8):486-8.

71) Nonhoff C, Denis O, Struelens MJ. Low prevalence of methicillin-resistant *Staphylococcus aureus* with reduced susceptibility to glycopeptides in Belgian hospitals. Clinical microbiology and infection. 2005 Mar 1;11(3):214-20.

72) Sancak B, Ercis S, Menemenlioğlu D, Çolakoğlu Ş, Hasçelik G. Methicillin-resistant *Staphylococcus aureus* heterogeneously resistant to vancomycin in a Turkish university hospital. Journal of Antimicrobial Chemotherapy. 2005 Sep 1;56(3):519-23.

73) Sancak B, Yagci S, Gür D, Gülay Z, Ogunc D, Söyletir G, Yalcin AN, Dündar DÖ, Topçu AW, Aksit F, Usluer G. Vancomycin and daptomycin minimum inhibitory concentration distribution and occurrence of heteroresistance among methicillin-resistant *Staphylococcus aureus* blood isolates in Turkey. BMC infectious diseases. 2013 Dec;13:1-6.

74) Gazel D, Erinmez M, Manay AB, Zer Y. Investigation of heteroresistant vancomycin intermediate *Staphylococcus aureus* among MRSA isolates. The Journal of Infection in Developing Countries. 2021 Jan 31;15(01):89-94.

75) Fitzgibbon MM, Rossney AS, O'Connell B. Investigation of reduced susceptibility to glycopeptides among methicillin-resistant *Staphylococcus aureus* isolates from patients in Ireland and evaluation of agar screening methods for detection of heterogeneously glycopeptide-intermediate *S. aureus*. Journal of clinical microbiology. 2007 Oct;45(10):3263-9.

76) Uçkay I, Bernard L, Buzzi M, Harbarth S, François P, Huggler E, Ferry T, Schrenzel J, Renzoni A, Vaudaux P, Lew DP. High prevalence of isolates with reduced glycopeptide susceptibility in persistent or recurrent bloodstream infections due to methicillin-resistant *Staphylococcus aureus*. Antimicrobial agents and chemotherapy. 2012 Mar;56(3):1258-64.

77) Vaudaux P, Ferry T, Uçkay I, Francois P, Schrenzel J, Harbarth S, Renzoni A. Prevalence of isolates with reduced glycopeptide susceptibility in orthopedic device-related infections due to methicillin-resistant *Staphylococcus aureus*. European journal of clinical microbiology & infectious diseases. 2012 Dec;31:3367-74.

78) Młynarczyk A, Młynarczyk G, Łuczak M. Searching for *Staphylococcus aureus* strains with reduced susceptibility to glycopeptides among clinical isolates obtained during the year of 2002. Medycyna Doświadczalna. 2003;55(3):216.

79) Ariza J, Pujol M, Cabo J, Pena C, Fernandez N, Linares J, Ayats J, Gudiol F. Vancomycin in surgical infections due to meticillin-resistant *Staphylococcus aureus* with heterogeneous resistance to vancomycin. The Lancet. 1999 May 8;353(9164):1587-8.

80) Hubert SK, Mohammed JM, Fridkin SK, Gaynes RP, McGowan Jr JE, Tenover FC. Glycopeptide-intermediate *Staphylococcus aureus*: evaluation of a novel screening method and results of a survey of selected US hospitals. Journal of Clinical Microbiology. 1999 Nov 1;37(11):3590-3.

81) Fridkin SK, Hageman J, McDougal LK, Mohammed J, Jarvis WR, Perl TM, Tenover FC, Vancomycin-Intermediate *Staphylococcus aureus* Epidemiology Study Group. Epidemiological and microbiological characterization of infections caused by *Staphylococcus aureus* with reduced susceptibility to vancomycin, United States, 1997–2001. Clinical Infectious Diseases. 2003 Feb 15;36(4):429-39.

82) Khosrovaneh A, Riederer K, Saeed S, Tabriz MS, Shah AR, Hanna MM, Sharma M, Johnson LB, Fakih MG, Khatib R. Frequency of reduced vancomycin susceptibility and heterogeneous subpopulation in persistent or recurrent methicillin-resistant *Staphylococcus aureus* bacteremia. Clinical infectious diseases. 2004 May 1;38(9):1328-30.

83) Rybak MJ, Leonard SN, Rossi KL, Cheung CM, Sadar HS, Jones RN. Characterization of vancomycin-heteroresistant *Staphylococcus aureus* from the metropolitan area of Detroit, Michigan, over a 22-year period (1986 to 2007). Journal of clinical microbiology. 2008 Sep;46(9):2950-4.

84) Kosowska-Shick K, Ednie LM, McGhee P, Smith K, Todd CD, Wehler A, Appelbaum PC. Incidence and characteristics of vancomycin nonsusceptible strains of methicillin-resistant *Staphylococcus aureus* at Hershey Medical Center. Antimicrobial agents and chemotherapy. 2008 Dec;52(12):4510-3.

85) Musta AC, Riederer K, Shemes S, Chase P, Jose J, Johnson LB, Khatib R. Vancomycin MIC plus heteroresistance and outcome of methicillin-resistant *Staphylococcus aureus* bacteremia: trends over 11 years. Journal of clinical microbiology. 2009 Jun;47(6):1640-4.

86) Sader HS, Jones RN, Rossi KL, Rybak MJ. Occurrence of vancomycin-tolerant and heterogeneous vancomycin-intermediate strains (hVISA) among *Staphylococcus aureus* causing bloodstream infections in nine USA hospitals. Journal of antimicrobial chemotherapy. 2009 Nov 1;64(5):1024-8.

87) Pastagia M, Kleinman L, Huprikar S, Jenkins S. Clinical and bacteriologic characteristics of a 5-year cohort of MRSA patients at a large U.S. metropolitan hospital. Clinical Microbiology and Infection. 2009; 15:S20–S1.

88) Adam HJ, Louie L, Watt C, Gravel D, Bryce E, Loeb M, Matlow A, McGeer A, Mulvey MR, Simor AE. Detection and characterization of heterogeneous vancomycin-intermediate *Staphylococcus aureus* isolates in Canada: results from the Canadian Nosocomial Infection Surveillance Program, 1995-2006. Antimicrobial agents and chemotherapy. 2010 Feb;54(2):945-9.

89) Pitz AM, Yu F, Hermsen ED, Rupp ME, Fey PD, Olsen KM. Vancomycin susceptibility trends and prevalence of heterogeneous vancomycin-intermediate *Staphylococcus aureus* in clinical methicillin-resistant *S. aureus* isolates. Journal of clinical microbiology. 2011 Jan;49(1):269-74.

90) Khatib R, Jose J, Musta A, Sharma M, Fakih MG, Johnson LB, Riederer K, Shemes S. Relevance of vancomycin-intermediate susceptibility and heteroresistance in methicillin-resistant *Staphylococcus aureus* bacteraemia. Journal of antimicrobial chemotherapy. 2011 Jul 1;66(7):1594-9.

91) Hafer C, Lin Y, Kornblum J, Lowy FD, Uhlemann AC. Contribution of selected gene mutations to resistance in clinical isolates of vancomycin-intermediate *Staphylococcus aureus*. Antimicrobial agents and chemotherapy. 2012 Nov;56(11):5845-51.

92) Casapao AM, Davis SL, McRoberts JP, Lagnf AM, Patel S, Kullar R, Levine DP, Rybak MJ. Evaluation of vancomycin population susceptibility analysis profile as a predictor of outcomes for patients with infective endocarditis due to methicillin-resistant *Staphylococcus aureus*. Antimicrobial agents and chemotherapy. 2014 Aug;58(8):4636-41.

93) de Oliveira Silveira AC, Sambrano GE, da Silva Paim TG, Caierão J, de Cordova CM, d'Azevedo PA. Is prediffusion test an alternative to improve accuracy in screening hVISA strains and to detect susceptibility to glycopeptides/lipopeptides?. Diagnostic microbiology and infectious disease. 2014 Aug 1;79(4):401-4.

94) Charles PG, Ward PB, Johnson PD, Howden BP, Grayson ML. Clinical features associated with bacteremia due to heterogeneous vancomycin-intermediate *Staphylococcus aureus*. Clinical infectious diseases. 2004 Feb 1;38(3):448-51.

95) Horne KC, Howden BP, Grabsch EA, Graham M, Ward PB, Xie S, Mayall BC, Johnson PD, Grayson ML. Prospective comparison of the clinical impacts of heterogeneous vancomycin-intermediate methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-susceptible MRSA. Antimicrobial agents and chemotherapy. 2009 Aug;53(8):3447-52.

96) Havaei SA, Azimian A, Fazeli H, Naderi M, Ghazvini K, Samiee SM, Masoumi Z, Akbari M. Genetic characterization of methicillin resistant and sensitive, vancomycin intermediate *Staphylococcus aureus* strains isolated from different Iranian Hospitals. International Scholarly Research Notices. 2012.

97) Amberpet R, Sistla S, Sugumar M, Nagasundaram N, Manoharan M, Parija SC. Detection of heterogeneous vancomycin-intermediate *Staphylococcus aureus*: a preliminary report from south India. The Indian journal of medical research. 2019 Aug;150(2):194.

98) Xu J, Pang L, Ma XX, Hu J, Tian Y, Yang YL, Sun DD. Phenotypic and molecular characterisation of *Staphylococcus aureus* with reduced vancomycin susceptibility derivated in vitro. Open Medicine. 2018 Oct 22;13(1):475-86.