RESEARCH ARTICLE

Systematic Review and Meta-Analysis of the Epidemiology of Vancomycin-Intermediate and Heterogeneous Vancomycin-Intermediate Staphylococcus aureus Isolates

Shanshan Zhang¹, Xiaoxi Sun², Wenjiao Chang², Yuanyuan Dai², Xiaoling Ma²*

¹ School of Medicine, Shandong University, Ji'nan, 250061, PR China, ² Department of Clinical Laboratory, Affiliated Provincial Hospital of Anhui Medical University, Hefei, 230001, PR China

* xiaolingma@126.com

Abstract

Background
Vancomycin-intermediate Staphylococcus aureus (VISA) and heterogeneous VISA (hVISA) are associated with vancomycin treatment failure, and are becoming an increasing public health problem. Therefore, we undertook this study of 91 published studies and made subgroup comparisons of hVISA/VISA incidence in different study years, locations, and types of clinical samples. We also analyzed the genetic backgrounds of these strains.

Methods
A systematic literature review of relevant articles published in PubMed and EMBASE from January 1997 to August 2014 was conducted. We selected and assessed journal articles reporting the prevalence rates of hVISA/VISA.

Results
The pooled prevalence of hVISA was 6.05% in 99,042 methicillin-resistant S. aureus (MRSA) strains and that of VISA was 3.01% in 68,792 MRSA strains. The prevalence of hVISA was 4.68% before 2006, 5.38% in 2006–2009, and 7.01% in 2010–2014. VISA prevalence was 2.05%, 2.63%, and 7.93%, respectively. In a subgroup analysis of different isolation locations, the prevalence of hVISA strains was 6.81% in Asia and 5.60% in Europe/America, and that of VISA was 3.42% and 2.75%, respectively. The frequencies of hVISA isolated from blood culture samples and from all clinical samples were 9.81% and 4.68%, respectively, and those of VISA were 2.00% and 3.07%, respectively. The most prevalent genotype was staphylococcal cassette chromosome mec (SCC mec) II, which accounted for 48.16% and 37.74% of hVISA and VISA, respectively. Sequence Type (ST) 239 was most prevalent.
Conclusion
The prevalence of hVISA/VISA has been increasing in recent years, but has been grossly underestimated. Its incidence is higher in Asia than in Europe/America. hVISA is isolated from blood culture samples more often than from other samples. These strains are highly prevalent in epidemic MRSA strains. This study clarifies the epidemiology of hVISA/VISA and indicates that the detection of these strains and the control of nosocomial infections must be strengthened.

Introduction

*Staphylococcus aureus*, one of the major nosocomial and community-acquired pathogens, causes a variety of clinical problems, including infections of the skin and soft tissues [1]. Since the 1960s, the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) has increased at a dramatic rate [2, 3], and is associated with higher rates of morbidity and mortality than methicillin-susceptible *S. aureus* (MSSA) [4].

Glycopeptides, such as vancomycin, are popular and effective antimicrobial drugs for treating MRSA. Unfortunately, vancomycin-intermediate *S. aureus* (VISA) and heterogeneous VISA (hVISA) have been reported since 1997. hVISA is an *S. aureus* isolate with a minimum inhibitory concentration (MIC) for vancomycin within the susceptible range when tested with routine methods, but in which a proportion of the cell population is within the vancomycin-intermediate range [5]. hVISA/VISA infections are commonly associated with persistent infections, prolonged bacteremia, and/or prolonged hospitalization [6–9]. Today, there is growing concern that hVISA and VISA are becoming prevalent worldwide [10–12].

In recent years, there have been many reports from single medical centers or individual countries of the incidence of hVISA/VISA, but few systematic reviews or meta-analyses on their prevalence. The review by Liu et al. on the epidemiology of hVISA/VISA was published over 10 years ago [13]. Another meta-analysis, by Van Hal et al., selectively analyzed the clinical significance and outcomes of hVISA [9]. In this systematic review and meta-analysis, we pooled the published studies that have reported the prevalence of hVISA/VISA, and made sub-group comparisons of the incidence of hVISA/VISA in different years, locations, and types of clinical samples. We also analyzed the genetic backgrounds of these strains. The results of this study will help to clarify the epidemiology of hVISA/VISA and will advance the control and management of these drug-resistant isolates.

Methods

Search strategy

Two independent examiners (S.S.Z. and X.X.S.) performed a systematic literature review of potentially relevant studies pertaining to VISA and hVISA. The studies were identified in the PubMed and EMBASE databases from articles published between January 1997 and August 2014. The following terms and connectors were used in the search strategy: (1) ‘vancomycin-intermediate *Staphylococcus aureus*’, VISA; (2) ‘heterogeneous vancomycin-intermediate *Staphylococcus aureus*’, hVISA; (3) ‘*Staphylococcus aureus* with reduced vancomycin susceptibility’, SA-RVS; (4) ‘glycopeptide-intermediate *Staphylococcus aureus*’, GISA; and (5) ‘heterogeneous glycopeptide-intermediate *Staphylococcus aureus*’, hGISA. The search was restricted to human studies.
Selection of studies

Studies identified in the literature search were checked by title and abstract. The papers with relevant abstracts were examined in full. The criteria for the inclusion and exclusion of the studies were established by the investigators before the literature was reviewed. The inclusion criteria were as follows: (1) studies that were original articles, short communications, correspondence, or letters that provided sufficient original data about the prevalence of hVISA/VISA; (2) studies in which all MRSA strains were randomly selected; (3) studies that used normative and publicly accepted detection methods for hVISA/VISA; and (4) studies that were published in English. The exclusion criteria were: (1) studies that contained duplicate data or were overlapping articles; (2) reviews and conference abstracts; and (3) articles that included fewer than 10 cases.

Data extraction

Two authors independently ascertained the characteristics of each study, including the first author’s surname, year of publication, continent, country, study years, isolate source, detection method, hVISA frequency, VISA frequency, and genotypes. When there was disagreement, the relevant paper was reviewed and the differences were resolved by consensus.

Assessment of study quality

The studies were assessed for quality, and only high-quality studies were included in the analysis. The criteria for high-quality studies were (1) that they provided basic data that included the study period and area, total number of isolates tested, and number of hVISA/VISA isolated; and (2) that they used dilution methods or E-test to detect VISA, and population analysis profile–area under the curve (PAP-AUC), macromethod Etest (MET), or screening agar to detect hVISA. When two studies overlapped, the more recent and larger study was included in the analysis. If one article included more than one study period, it was divided into several independent studies.

Statistical analysis

Statistical analyses were performed with STATA version 12.0. The data were pooled using the fixed-effects model (FEM) [14] and the random-effects model (REM) [15]. Statistical heterogeneity was assessed using the Cochran Q and I² statistical methods [16]. P < 0.1 was considered statistically significant. For all analyses, the results of FEM are presented only when there was no heterogeneity between the studies. Otherwise, the results of REM are presented. Freeman–Tukey arcsine transformations were performed to stabilize the variances, and after the meta-analysis, we transformed the summary estimates and the confidence interval (CI) boundaries back to proportions using the sine function [17].

Results

Results of the systematic literature search

In total, 1258 citations were identified in the initial electronic database search. Ultimately, 91 studies were included, based on the inclusion and exclusion criteria (Fig 1). These 91 studies that reported the prevalence of hVISA/VISA included 39 from Asia, 28 from Europe, 21 from America, and 3 from Australia (Table 1) [18–108]. In the pooled analysis, hVISA was reported in 76 studies, with an overall prevalence of 6.05% among 99,042 MRSA strains (95% CI 4.78–7.48), and VISA was reported in 38 studies, with a prevalence of 3.01% among 68,792 MRSA strains (95% CI 1.62–4.83) (Table 2).
Prevalence of hVISA/VISA in different study periods

To analyze the trends in the changes in hVISA/VISA prevalence in recent years, we performed a subgroup analysis of the prevalence of these two types of strains according to the study year. Three periods (before 2006, 2006–2009, and 2010–2014) were designated. Some studies that did not conform to the periods (e.g., reported for 2003–2007) were not included in this analysis.

It can be seen from Table 2 that the prevalence of the hVISA isolates increased gradually from 4.68% (95% CI 3.19–6.41) of 40,119 MRSA strains before 2006 to 5.38% (95% CI 2.40–9.48) of 6485 strains in 2006–2009, reaching 7.01% (95% CI 2.12–14.42) of 680 strains in 2010–2014. The incidence of VISA was 2.05% (95% CI 0.95–3.55) of 13,394 strains before 2006, 2.63% (95% CI 0.29–7.22) of 5,630 strains in 2006–2009, and 7.93% (95% CI 0.06–26.67) of 2090 strains in 2010–2014. Thus, the frequency of VISA during the years 2010–2014 represents a 3.87-fold increase over the years before 2006.

Prevalence of hVISA/VISA at different locations

The prevalence of hVISA/VISA differed among geographic regions in the subgroup analysis, as shown in Table 2. The prevalence of hVISA was 6.81% (95% CI 4.76–9.16) of 64,692 MRSA strains in 35 studies from Asia, and 5.60% (95% CI 3.85–7.64) of 34,350 strains in 41 studies
| Study, Year Published | Country, Continent | Study Year | Isolate Source | Detection Method | hVISA Frequency (%) and Genotype (%) | VISA Frequency (%) and Genotype (%) |
|-----------------------|-------------------|------------|----------------|-----------------|---------------------------------------|-------------------------------------|
| Hanaki et al, 2007[76] | Japan, Asia       | 1978–2005  | All clinical samples | E-test          | 5/2446 (0.2) 5/5 (100) SCCmec II     |                                     |
| Hiramatsu et al, 1997[36] | Japan, Asia     | 1996/01–1997/03 | All clinical samples | BHI            | 34/1149 (3.0)     |                                     |
| Song et al, 2004[38] | Asia              | 1997/01–2000/03 | All clinical samples | BHI            | 58/1357 (4.3)     |                                     |
| Wong et al, 1999[20] | Hong Kong, Asia   | 1997/07–1998/06 | All clinical samples | E-test          | 3/5 (5.8)        |                                     |
| Ike et al, 2001[75] | Japan, Asia       | 1997/09–1997/12 | All clinical samples | BHI            | 0/6625 (0)        |                                     |
| Trakulsomboon et al, 2001[45] | Thailand, Asia | 1998–1999  | All clinical samples | BHI            | 5/155 (3.2)       |                                     |
| Neoh et al, 2007[56] | Japan, Asia       | 1998/01–2005/10 | Blood samples | PAP-AUC          | 2/20 (10.0)       |                                     |
| Kim et al, 2002[27]  | Korea, Asia       | 1998/12–1999/08 | All clinical samples | BHI            | 24/3363 (0.7)     | 0/3363 (0)                          |
| Aminaka et al, 2009[34] | Japan, Asia     | 1999        | All clinical samples | BHI            | 7/138 (5.1)       | 0/138 (0)                           |
| Kim et al, 2000[108] | Korea, Asia       | 1999/01–1999/08 | All clinical samples | BHI            | 59/3371 (1.8)     |                                     |
| Kim et al, 2003[73]  | Korea, Asia       | 1999/06–2001/01 | All clinical samples | BHI            | 0/439 (0)         |                                     |
| Hsueh et al, 2010[26] | Taiwan, Asia     | 2001/09–2002/08 | All clinical samples | MIC based      | 43/1500 (2.9)     | 43/1500 (100) SCCmec III            |
| Wang et al, 2009[70] | Taiwan, Asia     | 2001–2003   | All clinical samples | BHI            | 2/13 (15.3)       | 8/13 (61.5)                        |
| Ghung et al, 2010[74] | Korea, Asia       | 2001–2006   | All clinical samples | MIC based      | 18/41639 (0.04)  | 15/41639 (0.04)                    |
| Lulitanond et al, 2009[46] | Thailand, Asia | 2002/08–2003/04 | All clinical samples | BHI            | 4/533 (0.8)       |                                     |

(Continued)
Table 1. (Continued)

| Study, Year Published | Country, Continent | Study Year | Isolate Source | Detection Method* | hVISA Frequency (%) and Genotype (%) | VISA Frequency (%) and Genotype (%) |
|-----------------------|--------------------|------------|----------------|------------------|--------------------------------------|-------------------------------------|
| Maor et al, 2009[25]  | Israel, Asia       | 2003–2006  | Blood samples  | PAP              | 4/4 (100) SCCmec III-ST239            |                                     |
| Maor et al, 2007[82]  | Israel, Asia       | 2003/01–2004/12 | Blood samples | MET              | 27/223 (12.1)                        |                                     |
| Ho et al, 2010[81]    | Taiwan, Asia       | 2003/03–2003/08 | All clinical samples | MET            | 16/264 (6.0)                          |                                     |
| Aminaka et al, 2009[34]| Japan, Asia        | 2005–2006  | All clinical samples | PAP             | 3/477 (0.6)                          | 0/477 (0)                           |
| Sun et al, 2009[83]   | China, Asia        | 2005–2007  | Blood samples  | PAP-AUC          | 20/26 (77.0) SCCmec III-ST239        | 1/1 (100) SCCmec II-ST5            |
| El Ayoubi et al, 2014[48]| Lebanon, Asia      | 2006/02–2013/03 | All clinical samples | MIC based      | 5/113 (3.8)                          |                                     |
| Lulitanond et al, 2009[46]| Thailand, Asia    | 2006/09–2007/12 | All clinical samples | PAP             | 8/8 (100) SCCmec III-ST239           | 2/3 (66.7) SCCmec III-ST239       |
| Wang et al, 2013[84]  | China, Asia        | 2007/07-2009/03 | All clinical samples | MET             | 25/122 (20.5)                        | 23/25 (92.0) SCCmec III           |
| Hanaki et al, 2014[19]| Japan, Asia        | 2008/01–2011/05 | Blood samples | MET              | 55/830 (6.5)                         | 8/830 (1.0)                        |
| Study, Year Published | Country, Continent | Study Year | Isolate Source | Detection Method\(^a\) | hVISA Frequency (%) and Genotype (%) | VISA Frequency (%) and Genotype (%) |
|-----------------------|-------------------|------------|----------------|-----------------|------------------------------------|-----------------------------------|
| Park et al, 2012\(^{[28]}\) | Korea, Asia | 2008/08–2010/09 | Blood samples | E-test | 101/268 (37.7) |  |
|                       |                   |            |                | PAP-AUC | 73/268 (72.3) SCC\(^{mec}\) II-ST5 |  |
|                       |                   |            |                |       | 17/268 (6.4) SCC\(^{mec}\) IV-ST72 |  |
|                       |                   |            |                |       | 9/268 (8.9) SCC\(^{mec}\) III-ST239 |  |
|                       |                   |            |                |       | 2/268 (3.0) others |  |
| Gowrishankar et al, 2013\(^{[40]}\) | India, Asia | 2009–2010 | All clinical samples | MHA | 10/63 (15.9) |  |
| Norazah et al, 2012\(^{[79]}\) | Malaysia, Asia | 2009/01–2009/12 | All clinical samples | E-test | 2/43 (4.7) |  |
| Ramli et al, 2012\(^{[94]}\) | Malaysia, Asia | 2009/02–2009/05 | All clinical samples | E-test | 7/320 (2.2) |  |
| Lin et al, 2012\(^{[72]}\) | Taiwan, Asia | 2009/03–2009/12 | Blood samples | MET | 5/62 (8.1) |  |
|                       |                   |            |                | PAP-AUC | 3/5 (60.0) SCC\(^{mec}\) III-ST239 |  |
|                       |                   |            |                |       | 1/5 (20.0) SCC\(^{mec}\) III-ST900 |  |
|                       |                   |            |                |       | 1/5 (20.0) SCC\(^{mec}\) II-ST1301 |  |
| Dubey et al, 2013\(^{[99]}\) | India, Asia | 2009/09–2012/04 | All clinical samples | E-test | 545/1214 (44.9) |  |
| Khanal et al, 2010\(^{[87]}\) | Nepal, Asia | 2010 | All clinical sample | Arg screening |  |  |
|                       |                   |            |                | 80/300 (26.8) |  |  |
| Chaudhari et al, 2015\(^{[51]}\) | India, Asia | 2010/09–2013/03 | All clinical samples | BHI | 4/58 (6.9) |  |
| Panomket et al, 2014\(^{[68]}\) | Thailand, Asia | 2010/11–2011/11 | All clinical samples | BHI | 2/68 (2.9) |  |
| Liu et al, 2014\(^{[71]}\) | China, Asia | 2011/06–2012/05 | All clinical samples | PAP-AUC | 17/77 (22.1) |  |
|                       |                   |            |                |       | 15/17 (88.2) SCC\(^{mec}\) III-ST239 |  |
|                       |                   |            |                |       | 1/17 (5.9) SCC\(^{mec}\) III-ST5 |  |
|                       |                   |            |                |       | 1/17 (5.9) SCC\(^{mec}\) II-ST1301 |  |
| Kaleem et al, 2012\(^{[31]}\) | Pakistan, Asia | 2012 | All clinical samples | E-test | 6/347 (1.7) |  |
| Guo et al, 2013\(^{[100]}\) | China, Asia | 2012/06–2012/12 | All clinical samples | MIC based | 1/1790 (0.06) |  |
| Chaudhary et al, 2013\(^{[85]}\) | India, Asia | 2013 | All clinical samples | MHA | 8/130 (6.1) |  |

(Continued)
| Study, Year Published | Country, Continent | Study Year | Isolate Source | Detection Method | hVISA Frequency (%) | VISA Frequency (%) |
|----------------------|--------------------|------------|----------------|------------------|---------------------|-------------------|
| Wootton et al, 2001 [69] | UK, Europe | 1983–1999 | All clinical samples | E-test | 0/100 (0) | |
| Robert et al, 2006 [32] | France, Europe | 1983–2001 | All clinical samples | E-test | 1/1445 (0.07) | |
| Geisel et al, 1999 [39] | Germany, Europe | 1992–1998 | All clinical samples | BHI | 7/85 (8.2) | |
| Kantzanou et al, 1999 [91] | Greece, Europe | 1994–1997 | All clinical samples | E-test | 1/72 (1.5) | |
| Uçkay et al, 2012 [54] | Switzerland, Europe | 1995/01–2003/08 | All clinical samples | BHI | 55/208 (26.4) | |
| Bert et al, 2003 [88] | France, Europe | 1997/01–2002/01 | All clinical samples | MET | 13/48 (27.1) | |
| Schmitz et al, 1999 [101] | Europe | 1997/04–1998/04 | All clinical samples | E-test | 0/302 (0) | |
| Marchese et al, 2000 [50] | Italy, Europe | 1997/08–1998/12 | All clinical samples | BHI | 2/367 (0.5) | |
| Sancak et al, 2005 [67] | Turkey, Europe | 1998/01–2002/01 | All clinical samples | MET | 46/256 (18.0) | 0/256 (0) |
| Aucken et al, 2000 [102] | UK, Europe | 1998/05–1999/04 | All clinical samples | MIC | 0/11242 (0) | |
| Reverdy et al, 2001 [59] | France, Europe | 1998/11–1999/04 | All clinical samples | BHI | 5/171 (2.9) | |
| Lassence et al, 2006 [30] | France, Europe | 1999–2000 | All clinical samples | MHA | 11/329 (3.3) | |
| Denis et al, 2002 [41] | Belgium, Europe | 1999/01–1999/12 | Blood samples | BHI | 4/2145 (0.1) | 3/2145 (0.1) |
| Vaudaux et al, 2012 [86] | Switzerland, Europe | 2000–2008 | All clinical samples | MHA | 13/57 (31.7) | 13/13 (100) SCCmec I-ST228 |
| Nonhoff et al, 2005 [65] | Belgium, Europe | 2001/01–2001/12 | All clinical samples | E-test | 3/455 (0.7) | 2/3 (66.7) SCCmec I |

(Continued)
| Study, Year Published | Country, Continent | Study Year | Isolate Source | Detection Method* | hVISA Frequency (%) and Genotype (%) | VISA Frequency (%) and Genotype (%) |
|-----------------------|-------------------|------------|----------------|-------------------|--------------------------------------|--------------------------------------|
| Cartolano et al, 2004[66] | France, Europe | 2000/06 | All clinical samples | MHA | 1/3 (33.3) SCCmec IV | 31/1070 (2.9) |
| Garnier et al, 2006[18] | France, Europe | 2001/07–2002/06 | All clinical samples | MET | 255/2300 (11.1) |  |
| Nakipoglu et al, 2005[61] | Turkey, Europe | 2001/09–2002/04 | All clinical samples | BHI | 7/135 (5.1) |  |
| Mlynarczyk et al, 2003[96] | Poland, Europe | 2002 | All clinical samples | PAP-AUC | 5/103 (4.8) | 0/103 (0) |
| Bataineh et al, 2006[93] | Spain, Europe | 2002/04–2004/08 | All clinical samples | MHA | 5/139 (3.6) |  |
| Piérard et al, 2004[95] | Belgium, Europe | 2003 | All clinical samples | E-test | 5/1002 (0.5) | 1/1002 (0.1) |
| Kirby et al, 2010[99] | UK, Europe | 2004–2006 | All clinical samples | MET | 86/2550 (3.4) |  |
| Lewis et al, 2009[43] | UK, Europe | 2005–2007 | Blood samples | MET | 35/195 (18.0) |  |
| Parer et al, 2012[78] | France, Europe | 2007 | All clinical samples | MHA | 12/20 (60.0) |  |
| Sancak et al, 2013[103] | Turkey, Europe | 2009–2010 | Blood samples | MET | 24/175 (13.7) | 0/175 (0) |
| Rybak et al, 2008[21] | USA, America | 1986–1993 | All clinical samples | MET | 5/225 (2.2) | 1/225 (0.4) |
| Ariza et al, 1999[104] | USA, America | 1990/01–1997/12 | All clinical samples | E-test | 14/19 (73.7) |  |
| Rybak et al, 2008[21] | USA, America | 1994–2002 | All clinical samples | MET | 27/356 (7.6) | 8/356 (2.3) |
| Adam et al, 2010[33] | Canada, America | 1995–2006 | All clinical samples | E-test GRD | 25/475 (5.3) |  |
| Musta et al, 2009[105] | USA, America | 1996–1997 | Blood samples | MHA | 8/61 (13.1) |  |
Table 1. (Continued)

| Study, Year Published | Country, Continent | Study Year | Isolate Source | Detection Method* | hVISA Frequency (%) and Genotype (%) | VISA Frequency (%) and Genotype (%) |
|-----------------------|---------------------|------------|----------------|-------------------|--------------------------------------|-------------------------------------|
| Hubert et al, 1999[49]| USA, America        | 1997       | All clinical samples | E-test 7/8 (93.0) SCC mec II | 4/630 (0.6) |
| Tallent et al, 2002[106]| USA, America        | 1997/01–2000/12 | Blood samples | PAP-AUC | 1/619 (0.2) |
| Franchi et al, 1999[97]| USA, America        | 1997/03–1997/05 | All clinical samples | E-test PAP | 0/30 (0) |
| Fridkin et al, 2003[42]| USA, America        | 1999/03–2000/12 | All clinical samples | BHI | 6/102 (5.8) |
| Eguia et al, 2005[63]| USA, America        | 1999/12–2000/08 | All clinical samples | BHI | 0/211 (0) |
| Musta et al, 2009[105]| USA, America        | 2000–2001 | Blood samples | PAP-AUC | 5/55 (9.1) |
| Pitz et al, 2011[107]| USA, America        | 2000–2008 | Blood samples | E-test GRD 2/167 (1.2) | 5/ (100) SCC mec II |
| Musta et al, 2009[105]| USA, America        | 2002–2003 | Blood samples | PAP-AUC | 37/187 (19.8) |
| Sader et al, 2009[77]| USA, America        | 2002–2006 | Blood samples | PAP-AUC | 36/268 (13.4) |
| Pastagia et al, 2009[22]| USA, America        | 2002–2007 | Blood samples | E-test 45/699 (6.4) | 118/699 (16.9) |
| Khosrovaneh et al, 2004[47]| USA, America        | 2002/01–2002/12 | Blood samples | BHI | 3/22 (13.6) |
| Casapao et al, 2014[44]| USA, America        | 2002/01–2013/06 | All clinical samples | PAP-AUC | 38/266 (18.8) |
| Khatib et al, 2011[92]| USA, America        | 2002–03 and 2005–06 | Blood samples | MET | 30/371 (8.1) |
| Rybak et al, 2008[21]| USA, America        | 2003–2007 | All clinical samples | PAP-AUC | 76/917 (8.3) |
| Delgado et al, 2007[53]| Mexico, America     | 2003/09–2004/08 | All clinical samples | PAP | 1/152 (0.7) |
| Musta et al, 2009[105]| USA, America        | 2005–2006 | Blood samples | MHA | 21/186 (11.3) |

(Continued)
from Europe/America. Moreover, 3.42% (95% CI 1.10–6.99) of 55,362 MRSA strains were VISA in 18 studies from Asia compared with 2.75% (95% CI 1.19–4.91) of 13,430 strains in 20 studies from Europe/America.

Prevalence of hVISA/VISA in different clinical samples

In this subgroup analysis, we divided the MRSA strains into two groups. One group was isolated from only blood culture samples and the other from all clinical samples, including blood, sputum, pus, urine, and so forth (the authors of the original studies did not classify the prevalence rates in the different types of samples). In total, the frequency of hVISA was 9.81% (95% CI 6.71–13.42) in 5944 MRSA strains isolated from blood culture samples reported in 21 studies, significantly higher than in the group of all clinical samples (4.68% [95% CI 3.51–6.00] in 93,098 strains in 55 studies) (P = 0.023). The prevalence rates for VISA were 2.00% (95% CI 0.03–6.88) in 2542 blood-borne MRSA strains in seven studies, and 3.07% (95% CI 1.58–5.02) in 66,250 strains isolated from all clinical samples in another 32 studies (Table 2).
Genetic backgrounds of hVISA/VISA

As shown in Table 3, 25 studies presented information on the genotypes of the hVISA/VISA strains. Sixteen studies that included 685 MRSA strains reported the staphylococcal cassette chromosome mec (SCCmec) types for hVISA. The predominant type was SCCmec II, which accounted for 48.16% (95% CI 32.82–63.68), followed by SCCmec IV (18.07%; 95% CI 7.50–31.98) and SCCmec III (17.99%; 95% CI 7.69–31.42). SCCmec I accounted for only 2.12% (95% CI 0.70–4.30). Among the 454 strains from 10 studies that reported multilocus sequence typing (MLST), 11 ST types were identified. ST239 was found in 58.62% (95% CI 22.98–89.73) of hVISA, followed by ST5 in 14.45% (95% CI 4.59–28.53) and ST72 in 3.28% (95% CI 0.98–6.88). SCCmec types in VISA strains were reported in nine studies, which included 97 strains. SCCmec II was predominant (37.74%, 95% CI 10.01–70.94), followed by SCCmec III (32.72%, 95% CI 3.35–73.85). SCCmec I and SCCmec IV accounted for 11.79% (95% CI 0.01–40.76) and 10.08% (95% CI 1.77–24.05) of isolates, respectively. Six ST types were reported among the VISA strains in 62 strains in six studies. The most prevalent ST types were ST239 (27.05%, 95% CI 2.34–65.22) and ST5 (22.77%, 95% CI 4.66–49.26) (Table 3).

Discussion

The infections caused by MRSA are problematic because they entail high mortality and only limited antimicrobial drugs are available for their treatment [109]. Vancomycin has generally been the first drug of choice for the treatment of MRSA infections [110]. However, studies have reported that the treatment failure rate for vancomycin is increasing. Takesue et al. studied 128 strains of MRSA causing bacteremia and reported that the efficacy of vancomycin in patients infected with strains with a vancomycin MIC of ≤ 1 μg/ml was 78.8%, whereas it was only 30.0% for patients infected with strains with an MIC of 2 μg/ml [111]. Moore et al. also investigated MRSA bacteremia, and defined treatment failure as a composite of mortality,
microbiological failure, and/or the recurrence of infection. The treatment failure rate was 31% in patients infected with 118 MRSA strains with vancomycin MIC > 1 μg/ml [112]. Casapao et al. defined treatment failure as bacteremia for > 7 days or death attributable to MRSA, and observed 64.4% treatment failure in 266 patients with MRSA endocarditis [44]. hVISA and VISA are thought to be among the primary causes of treatment failure. However, in 76 studies (including 99,042 strains) chosen for our analysis, the prevalence of hVISA was only 6.05%, and the prevalence of VISA was only 3.01% in 68,792 strains in 38 studies. Therefore, we speculate that the incidence of hVISA/VISA was underestimated, possibly because of the resistance mechanisms and biological characteristics of these strains. Unlike MRSA and vancomycin-resistant S. aureus (VRSA), the genetic backgrounds associated with hVISA/VISA remain unclear, and a molecular biological method to detect these strains is not yet available. The growth rates of hVISA/VISA are also slow [113, 114]; hence, conventional methods, such as the Kirby–Bauer and instrument-based methods, do not produce accurate results. The PAP-AUC method is considered the gold standard technique for detecting hVISA. However, this method is time-consuming, cumbersome, and unsuitable for clinical laboratories [69], so a significant number of strains may have been missed. Therefore, there is an urgent need for a convenient and effective method with which to detect these strains.

To analyze the trends in the prevalence of hVISA/VISA in recent years, we divided the study period into three periods: before 2006, 2006–2009, and 2010–2014. The first period used

| Table 3. Genetic prevalence of hVISA and VISA. a |
| --- |
| **Category** | **Subcategory** | **No. Studies** | **No. Strains** | **Prevalence (%) (95% CI)** |
| hVISA | SCCmec | 16 | 685 | 2.12 (0.70–4.30) |
| | SCCmec I | | | |
| | SCCmec II | | | 48.16 (32.82–63.68) |
| | SCCmec III | | | 17.99 (7.69–31.42) |
| | SCCmec IV | | | 18.07 (7.50–31.98) |
| MLST | | 10 | 454 | 58.62 (22.98–89.73) |
| | ST239 | | | 14.45 (4.59–28.53) |
| | ST72 | | | 3.28 (0.98–6.88) |
| | ST59 | | | 1.64 (0.28–4.10) |
| | ST900 | | | 0.95 (0.13–2.49) |
| | Others (ST1, ST247, ST228, ST398, ST45, ST1301) | | | 9.51 (0.48–27.95) |
| VISA | SCCmec | 9 | 97 | 11.79 (0.01–40.76) |
| | SCCmec I | | | 37.74 (10.01–70.94) |
| | SCCmec II | | | 32.72 (3.35–73.85) |
| | SCCmec III | | | 10.08 (1.77–24.05) |
| MLST | | 6 | 62 | 27.05 (2.34–65.22) |
| | ST239 | | | 22.77 (4.66–49.26) |
| | ST5 | | | 42.44 (10.44–78.65) |
| | Others (ST59, ST72, ST228, ST8) | | | 42.44 (10.44–78.65) |

CI, confidence interval

References: [21, 26, 28, 29, 33, 44, 46, 52, 55, 59, 65, 70–72, 74, 76, 83, 84, 86, 92, 105]

doi:10.1371/journal.pone.0136082.t003
the initial resistance breakpoint (vancomycin MIC of 8–16 μg/ml) and the two later periods used the present resistance breakpoint (vancomycin MIC of 4–8 μg/ml). Our study suggests that the prevalence of hVISA/VISA has been increasing in recent years. We consider that the more frequent use of vancomycin for MRSA infections is responsible for this situation because the high prevalence of hVISA/VISA reflects the level of vancomycin use [115, 116]. The inappropriate management of drug-resistant strains has accelerated the spread of hVISA/VISA, and the change in the vancomycin-resistance breakpoint has also contributed to the increase in the prevalence rate.

Since the first reports of hVISA/VISA, the occurrence rates of these strains have varied throughout the world: the incidence of hVISA was 6.81% in Asia and 5.60% in Europe/America, and that of VISA was 3.42% and 2.75%, respectively. Current evidence supports the proposition that hVISA/VISA is more endemic in Asian countries than in Europe/America. Several factors may account for this situation. First, most countries in Europe and America are developed, with high public hygiene standards and scrupulous antimicrobial treatments [69, 101, 102]. Second, the control of nosocomial infections is more successful in European and American countries [41, 95]. Third, Asia is the most populous region of the world, which can create an environment amenable to microbial transmission. The pooled prevalence rate for hVISA in mainland China was 15.78% [58, 71, 83, 84], and in India, the pooled prevalence rates for of hVISA and VISA were 12.41% and 15.09%, respectively [40, 51, 52, 85, 99]. Fourth, because far more MRSA infections occur in Asian countries [117], vancomycin has been used more frequently for their treatment. Therefore, it is not surprising that hVISA and VISA are more common in Asia than elsewhere.

Previous studies have demonstrated that hVISA/VISA are prevalent among bacteremic specimens, and that these strains can persist in the bloodstream for a long time [19]. Our analysis confirms that hVISA is more common in blood-borne MRSA, consistent with previous opinion. However, the prevalence of VISA was not obviously higher among isolates from blood culture samples than other samples. The reason for this is unclear, but this result suggests that not only blood culture samples but all clinical samples should be given attention.

The mecA gene, which is located within the SCCmec element, is the specific genetic mechanism of methicillin resistance [118]. Many epidemiological studies have demonstrated that community-associated MRSA (CA-MRSA) can be distinguished from hospital-acquired MRSA (HA-MRSA) by the type of the SCCmec element present. The most common SCCmec types in CA-MRSA strains are SCCmec IV and V, whereas SCCmec I, II, and III predominate in HA-MRSA strains [119]. The results of our pooled analysis show that SCCmec II and III were the most prevalent molecular types among the VISA strains. Previous studies have demonstrated limited vancomycin-resistance potential in SCCmec IV MRSA clones [120]. However, we found that the prevalence of SCCmec IV in hVISA was similar to that of SCCmec III. This phenomenon suggests that hVISA is not limited to typical “hospital” clones of S. aureus.

MLST is a powerful and highly discriminatory method for analyzing the population structures and epidemiology of S. aureus [121]. Our study demonstrates that ST239 and ST5 are the most epidemic genotypes of hVISA/VISA. ST239 and ST5 are two international HA-MRSA lineages prevalent in Asia, South America, and Eastern Europe [122, 123]. ST239 MRSA strains are typically resistant to many classes of antibiotics, including β-lactams, fluoroquinolones, aminoglycosides, and macrolide antibiotics. Our results strongly suggest that hVISA and VISA are highly prevalent among international epidemic MRSA strains. Moreover, the genetic backgrounds of these strains are complex, and many ST types are dispersed among hVISA/VISA isolates, including ST59, ST72, and ST900 [70, 72, 74].

The present study had several limitations. Genetic information was available in only 27% (25/91) of the studies we reviewed, which could have led to publication bias and influenced our
results. There was also considerable heterogeneity between studies because they differed in various study variables, such as the patient populations examined, testing methodologies used, study durations, previous vancomycin therapy, and concomitant illnesses. These confounding factors could not be circumvented with subgroup analyses. As in previous meta-analyses in which unexplained heterogeneity was identified, we accommodated this condition by using REM, in which the effects underlying the results of different studies are assumed to be drawn from a normal distribution [124]. However, this heterogeneity could not be balanced out by REM alone, so that the stability of the final results must have been affected by the heterogeneity of the sample.

In summary, the results of our study suggest that the prevalence rates of hVISA/VISA have increased in recent years. Our data also supports the view that hVISA/VISA are more prevalent in Asian countries than in Europe/America. Our study confirms that hVISA strains are more common in blood-borne MRSA than in other MRSA. Finally, the most epidemic genotypes of hVISA/VISA are SCCmec II and SCCmec III on SCCmec typing, and ST239 and ST5 on MLST typing, which are predominant among the HA-MRSA strains. However, the incidence of hVISA/VISA is grossly underestimated. Therefore, the detection of hVISA/VISA must be strengthened, especially in samples from patients with bacteremic HA-MRSA infections, and the use of vancomycin and nosocomial infections must be urgently and strictly controlled, particularly in Asian hospitals.

Supporting Information
S1 PRISMA Checklist. PRISMA 2009 checklist.
(DOC)

Author Contributions
Conceived and designed the experiments: SSZ XXS XLM. Performed the experiments: SSZ XXS. Analyzed the data: SSZ XXS. Contributed reagents/materials/analysis tools: SSZ XXS WJC YYD. Wrote the paper: SSZ XLM.

References
1. Lowy FD. Staphylococcus aureus infections. The New England journal of medicine. 1998; 339(8):520–32. Epub 1998/08/26. doi:10.1056/nejm199808203390806 PMID: 9709046.
2. M CL, D RS, B-V S, M K, M LG.. Community-associated methicillin-resistant Staphylococcus aureus isolates causing healthcare-associated infections. Emerg Infect Dis. 2007; 13(2):236–42. PMID: 17479885
3. LC M. Trends in Antimicrobial Resistance in Health Care-Associated Pathogens and Effect on Treatment. Clinical Infectious Diseases. 2006; 42(2).
4. Kaye KS, Engemann JJ, Mozaffari E, Carmeli Y. Reference group choice and antibiotic resistance outcomes. Emerging infectious diseases. 2004; 10(6):1125–8. PMID: 15207068
5. H K.. Vancomycin-resistant Staphylococcus aureus: a new model of antibiotic resistance outcomes. Emerging infectious diseases. 2001; 1(3):147–55. PMID: 11871491
6. Fridkin SK. Vancomycin-intermediate and -resistant Staphylococcus aureus: what the infectious disease specialist needs to know. Clin Infect Dis. 2001; 32(1):108–15. Epub 2000/12/19. doi: 10.1086/317542 PMID: 11118389.
7. Hal SJv, Paterson DL. Systematic review and meta-analysis of the significance of heterogeneous vancomycin-intermediate Staphylococcus aureus isolates. Antimicrob Agents Chemother. 2011; 55(1):405–10. doi: 10.1128/AAC.01139-10 PMID: 21079399
10. Ariza J, Pujol M, Cabo J, Pena C, Fernandez N, Linares J, et al. Vancomycin in surgical infections due to methicillin-resistant Staphylococcus aureus with heterogeneous resistance to vancomycin. Lancet. 1999; 353(9164):1587–8. Epub 1999/05/20. PMID: 10334262.

11. Kim MN, Pai CH, Woo JH, Ryu JS, Hiramatsu K. Vancomycin-intermediate Staphylococcus aureus in Korea. Journal of clinical microbiology. 2000; 38(10):3879–81. Epub 2000/10/04. PMID: 11015427; PubMed Central PMCID: PMC87500.

12. Sng LH, Koh TH, Wang GC, Hsu LY, Kapi M, Hiramatsu K. Heterogeneous vancomycin-resistant Staphylococcus aureus (hetero-VISA) in Singapore. International journal of antimicrobial agents. 2005; 25(2):177–9. Epub 2005/01/25. PMID: 15664490.

13. Liu C, Chambers HF. Staphylococcus aureus with heterogeneous resistance to vancomycin: epidemiology, clinical significance, and critical assessment of diagnostic methods. Antimicrob Agents Chemother. 2003; 47(10): 3040–5. PMID: 14506006

14. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. Journal of the National Cancer Institute. 1959; 15(4):639–40.

15. Dersimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials. 1986.

16. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002; 21(11):1539–58. Epub 2002/07/12. doi: 10.1002/sim.1186 PMID: 12111919.

17. Freeman MF, Tukey JW. Transformations Related to the Angular and the Square Root. ANNALS OF MATHEMATICAL STATISTICS. 1950; 6(2):180–9.

18. Gamier F, Chainier D, Walsh T, Karlsson A, Bolmstrom A, Groelaud C, et al. A 1 year surveillance study of glycopeptide-intermediate Staphylococcus aureus strains in a French hospital. The Journal of antimicrobial chemotherapy. 2006; 57(1):146–9. doi: 10.1093/jac/dki413 PMID: 16286482.

19. Hanaki H, Cui L, Ikeda-Dantsuji Y, Nakae T, Honda J, Yanagihara K, et al. Antibiotic susceptibility survey of blood-borne MRSA isolates in Japan from 2008 through 2011. Journal of infection and chemotherapy: official journal of the Japan Society of Chemotherapy. 2014; 20(9):527–34. PMID: 25066429.

20. W SS, H PL, W PC, Y KY. Bacteremia caused by staphylococci with inducible vancomycin heteroresistance. Clinical Infectious Diseases. 1999; 29(4):760–7. PMID: 10589883.

21. Rybak MJ, Leonard SN, Rossi KL, Cheung CM, Sader HS, Jones RN. Characterization of vancomycin-intermediate Staphylococcus aureus from the metropolitan area of Detroit, Michigan, over a 22-year period (1986 to 2007). Journal of clinical microbiology. 2008; 46(9):2950–4. doi: 10.1128/JCM.00582-08 PMID: 18632899; PubMed Central PMCID: PMC2546725.

22. 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.

23. Fong RK, Low J, Koh TH, Kurup A. Clinical features and treatment outcomes of vancomycin-intermediate Staphylococcus aureus (VISA) and heterogeneous resistant vancomycin-intermediate Staphylococcus aureus (hVISA) in a tertiary care institution in Singapore. European journal of clinical microbiology & infectious diseases: official publication of the European Society of Clinical Microbiology. 2009; 28(8):983–7. Epub 2009/04/24. doi: 10.1007/s10096-009-0741-5 PMID: 19387707.

24. C PG, W PB, J PD, H BP, G ML. Clinical Features Associated with Bacteremia Due to Heterogeneous Vancomycin-Intermediate Staphylococcus aureus. Clinical Infectious Diseases. 2004; 38(3):448–51. PMID: 14727222

25. Maor Y, Hagan M, Belausov N, Keller N, Ben-David D, Rahav G. Clinical features of heterogeneous vancomycin-intermediate Staphylococcus aureus bacteremia versus those of methillin-resistant S. aureus bacteremia. The Journal of infectious diseases. 2009; 199(5):619–24. doi: 10.1086/596629 PMID: 19199552.

26. Hseueh PR, Lee SY, Perng CL, Chang TY, Lu JJ. Clonal dissemination of methillin-resistant and vancomycin-intermediate Staphylococcus aureus in a Taiwanese hospital. International journal of antimicrobial agents. 2010; 36(4):307–12. PMID: 20685086.

27. 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; 40(4):1376–80. doi: 10.1128/JCM.40.4.1376-1380.2002 PMID: 11923359

28. Park KH, Kim ES, Kim HS, Park SJ, Bang KM, Park HJ, et al. Comparison of the clinical features, bacteriologic genotypes and outcomes of patients with bacteraemia due to heterogeneous vancomycin-intermediate Staphylococcus aureus and vancomycin-resistant S. aureus. The Journal of antimicrobial chemotherapy. 2012; 67(8):1843–9. doi: 10.1093/jac/dks131 PMID: 22539621.

29. Hafer C, Lin Y, Komblum J, Lowy FD, Uhlmann AC. Contribution of selected gene mutations to resistance in clinical isolates of vancomycin-intermediate Staphylococcus aureus. Antimicrobial agents
Systematic Review and Meta-Analysis of Epidemiology of VISA/hVISA

and chemotherapy. 2012; 56(11):5845–51. doi: 10.1128/AAC.01139-12 PMID: 22948864; PubMed Central PMCID: PMC3486570.

30. dl A, H N, T JF, J-G ML, T G, B A, et al. 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; 42(2):170–8. PMID: 16355325

31. Kaleem F, Usman J, Amanat S. Current status of Glycopeptide intermediate and heterogeneous Glycopeptide intermediate Staphylococcus aureus and their prevailing susceptibility pattern at two tertiary care hospitals of Pakistan. International Journal of Infectious Diseases. 2012; 16:e420–e1. doi: 10.1016/j.ijid.2012.05.582

32. 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. The Journal of antimicrobial chemotherapy. 2006; 57(3):506–10. doi: 10.1093/jac/dkl486 PMID: 16410265.

33. Adam HJ, Louie L, Watt C, Gravel D, Bryce E, Loeb M, et al. 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; 54(2):945–9. doi: 10.1128/AAC.01316-09 PMID: 19949062; PubMed Central PMCID: PMC2812162.

34. Takata T. Detection of Heterogeneous Vancomycin Intermediate Staphylococcus aureus (hetero-VISA) in MRSA of Japanese Clinical Isolates. American Journal of Infection Control. 2009; 37(5):E15–E6.

35. Richter SS, Satola SW, Crispell EK, Heilmann KP, Dohrn CL, Riahi F, et al. Detection of Staphylococcus aureus isolates with heterogeneous intermediate-level resistance to vancomycin in the United States. Journal of clinical microbiology. 2011; 49(12):4203–7. doi: 10.1128/JCM.01152-11 PMID: 21976789; PubMed Central PMCID: PMC3232863.

36. Hiramatsu K, Antaka N, Hanaki H, Kawasaki S, Hosoda Y, Hori S, et al. Dissemination in Japanese hospitals of strains of Staphylococcus aureus heterogeneously resistant to vancomycin. The Lancet. 1997; 350(9092):1670–3.

37. Van Hal SJ, Barbagnanos T, Mercer J, Chen D, Gosbell IB, Paterson DL. Emergence and evolution of heteroreistant vancomycin intermediate Staphylococcus aureus in a single hospital over a 12-year period. Clinical Microbiology and Infection. 2011; 17:558.

38. Song JH, Hiramatsu K, Suh JY, Ko KS, Ito T, Kapi M, et al. Emergence in Asian countries of Staphylococcus aureus isolates with reduced susceptibility to vancomycin. Antimicrobial agents and chemotherapy. 2004; 48(12):4926–8. doi: 10.1128/AAC.48.12.4926-4928.2004 PMID: 15561894; PubMed Central PMCID: PMC529235.

39. Geisel R, Schmitz FJ, Thomas L, Berns G, Zetsche O, Ulrich B, et al. Emergence of heterogeneous intermediate vancomycin resistance in Staphylococcus aureus isolates in the Dusseldorf area. The Journal of antimicrobial chemotherapy. 1999; 43(6):846–8. Epub 1999/07/15. PMID: 10404328.

40. 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: journal of molecular epidemiology and evolutionary genetics in infectious diseases. 2013; 14:383–9. doi: 10.1016/j.meegid.2013.01.002 PMID: 23337611.

41. Denis O. Emergence of vancocyn-intermediate Staphylococcus aureus in a Belgian hospital: microbiological and clinical features. Journal of Antimicrobial Chemotherapy. 2002; 50(3):383–91. doi: 10.1093/jac/dkf142 PMID: 12205063

42. SK F. Epidemiological and Microbiological Characterization of Infections Caused by Staphylococcus aureus with Reduced Susceptibility to Vancomycin, United States, 1997–2001. Clinical Infectious Diseases: an Official Publication of the Infectious Diseases Society of America. 2003; 36(4):429–39.

43. Lewis T, Chaudry R, Das I, Lambert P. Epidemiology of MRSA bacteremia and clinical relevance of reduced susceptibility to vancomycin. Clinical Microbiology and Infection. 2009; 15:S544–S5.

44. Casapao AM, Davis SL, McRoberts JP, Lagnf AM, Patel S, Kullar R, et al. 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; 58(8):4636–41. doi: 10.1128/AAC.02820-13 PMID: 24890596; PubMed Central PMCID: PMC4136033.

45. Trakulsomboon S, Danchaiyijit S, Rongrupruang Y, Dhirapatra C, Susaemgrat W, Ito T, et al. First report of methicillin-resistant Staphylococcus aureus with reduced susceptibility to vancomycin in Thailand. Journal of clinical microbiology. 2001; 39(2):591–5. doi: 10.1128/JCM.39.2.591-595.2001 PMID: 11158112; PubMed Central PMCID: PMC87781.
46. Lakitanond A, Engchanil C, Chairanee P, Vorachit M, Ito T, Hiramatsu K. The first vancomycin-intermediate Staphylococcus aureus strains isolated from patients in Thailand. Journal of clinical microbiology. 2009; 47(7):2311–6. doi: 10.1128/JCM.01749-08 PMID: 19403764; PubMed Central PMCID:PMC2708526.

47. K A, R K, S S, T MS, S AR, H MM, et al. Frequency of Reduced Vancomycin Susceptibility and Heterogeneous Subpopulation in Persistent or Recurrent Methicillin-Resistant Staphylococcus aureus Bacteremia. Clin Infect Dis. 2004; 38(9):1328–30. PMID: 15127350.

48. El Ayoubi MD, Hamze M, Mallat A, Achkar M, Dabboussi F. Glycopeptide intermediate Staphylococcus aureus and prevalence of the luk-PV gene in clinical isolates, in Northern Lebanon. Medecine et maladies infectieuses. 2014; 44(5):223–8. doi: 10.1016/j.medmal.2014.03.004 PMID: 24835167.

49. H SK, M JM, F SK, G RP, J M Jr, T FC. Glycopeptide-intermediate Staphylococcus aureus: evaluation of a novel screening method and results of a survey of selected U.S. hospitals. Journal of clinical microbiology. 1999; 37: 3590–3. PMID: 10523558.

50. M A, B G, T E, D EA, S GC. Heterogeneous vancomycin resistance in methicillin-resistant Staphylococcus aureus strains isolated in a large Italian hospital. Journal of clinical microbiology. 2000; 38(2):866–9.

51. Chaudhari CN, Tandel K, Grover N, Sen S, Bhatt P, Sahni AK, et al. Heterogeneous vancomycin-intermediate among methicillin resistant Staphylococcus aureus. Medical journal, Armed Forces India. 2015; 71(1):15–8. PMID: 25609857; PubMed Central PMCID: PMC4297820.

52. Campanile F, Bortone S, Perez M, Bongiorno D, Calcio V, Bertuccio T, et al. Heteroresistance to glycopeptides in Italian meticillin-resistant Staphylococcus aureus (MRSA) isolates. International journal of antimicrobial agents. 2010; 36(5):415–9. PMID: 20727722.

53. Delgado A, Riordan JT, Lamichhane-Khadka R, Winnett DC, Jimenez J, Robinson K, et al. Heterovancoycin-intermediate methicillin-resistant Staphylococcus aureus isolate from a medical center in Las Cruces, New Mexico. Journal of clinical microbiology. 2007; 45(4):1325–9. doi: 10.1128/JCM.02437-06 PMID: 17267639; PubMed Central PMCID: PMC1685829.

54. Uckay I, Bernard L, Buzzi M, Harbarth S, Francois P, Huggler E, et al. 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; 56(3):1258–64. doi: 10.1128/AAC.00808-11 PMID: 22155824; PubMed Central PMCID: PMC3294919.

55. Wang JL, Lai CH, Lin HH, Chen WF, Shih YC, Hung CH. High vancomycin minimum inhibitory concentrations with heteroresistant vancomycin-intermediate Staphylococcus aureus in meticillin-resistant S. aureus bacteraemia patients. International journal of antimicrobial agents. 2013; 42(5):390–4. PMID: 24041465.

56. Neoh H-m, Hori S, Komatsu M, Oguri T, Takeuchi F, Cui L, et al. Impact of reduced vancomycin susceptibility on the therapeutic outcome of MRSA bloodstream infections. Annals of Clinical Microbiology and Antimicrobials. 6:13: 13.

57. Kosowska-Shick K, Ednie LM, McGhee P, Smith K, Todd CD, Wehler A, et al. Incidence and characteristics of vancomycin nonsusceptible strains of methicillin-resistant Staphylococcus aureus at Hershey Medical Center. Antimicrobial agents and chemotherapy. 2008; 52(12):4510–3. doi: 10.1128/AAC.00808-11 PMID: 17267639; PubMed Central PMCID: PMC2592881.

58. 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; 71(3):301–3. PMID: 21856109.

59. Reverdy ME, Jarraud S, Bobin-Dubreux S, Burel E, Girardo P, Lina G, et al. Incidence of Staphylococcus aureus with reduced susceptibility to glycopeptides in two French hospitals. Clinical Microbiology and Infection: the Official Publication of the European Society of Clinical Microbiology and Infectious Diseases. 2001; 7(5):267–72.

60. Fitzgibbon MM, Rossney AS, O’Connell B. Investigation of reduced susceptibility to glycopeptides among meticillin-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; 45(10):3263–9. doi: 10.1128/JCM.00836-07 PMID: 17687008; PubMed Central PMCID: PMC2045355.

61. Nakipoglu Y, Derbentli S, Cagatay AA, Katranci H. Investigation of Staphylococcus strains with heterogeneous resistance to glycopeptides in a Turkish university hospital. BMC infectious diseases. 2005; 5:31. doi: 10.1186/1471-2334-5-31 PMID: 15871748; PubMed Central PMCID: PMC1156892.

62. Silveira AC, Sambrano GE, Paim TG, Caierao J, Cordova CM, d’Azvedo 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; 79(4):401–4. PMID: 24906792.
73. Kim HB, Park WB, Lee KD, Choi YJ, Park SW, Oh Md, et al. Nationwide Surveillance for Staphylococcus aureus with Reduced Susceptibility to Vancomycin in Korea. Journal of clinical microbiology. 2003; 41(6):2279–81. doi: 10.1128/jcm.41.6.2279-2281.2003 PMID: 12791836

74. Chung G, Cha J, Han S, Jang H, Lee K, Yoo J, et al. Nationwide surveillance study of vancomycin intermediate Staphylococcus aureus strains in Korean hospitals from 2001 to 2006. Journal of microbiology and biotechnology. 2010; 20(3):637–42. Epub 2010/04/08. PMID: 20372039.

75. Ike Y, Arakawa Y, Ma X, Tatewaki K, Nagasawa M, Tomita H, et al. Nationwide survey shows that methicillin-resistant Staphylococcus aureus strains heterogeneously and intermittently resistant to vancomycin are not disseminated throughout Japanese hospitals. Journal of clinical microbiology. 2001; 39(12):4445–51. doi: 10.1128/JCM.39.12.4445-4451.2001 PMID: 11724859; PubMed Central PMCID: PMC88563.

76. Hanaki H, Hososaka Y, Yanagisawa C, Otsuka Y, Nagasawa Z, Nakae T, et al. Occurrence of vancomycin-intermediate-resistant Staphylococcus aureus in Japan. Journal of infection and chemotherapy: official journal of the Japan Society of Chemotherapy. 2007; 13(2):118–21. PMID: 17458681.

77. 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. The Journal of antimicrobial chemotherapy. 2009; 64(5):1024–8. doi: 10.1093/jac/dkp319 PMID: 20264529; PubMed Central PMCID: PMC3256079.

78. Parer S, Lother 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 and hospital epidemiology. 2012; 33(2):167–74. doi: 10.1086/663703 PMID: 22279896.

79. N A, L NL, K AG, S N.. The presence of heterogeneous vancomycin-Intermediate Staphylococcus aureus (heteroVISA) in a major Malaysian hospital. The Medical journal of Malaysia. 2012;. (3 ).
80. B G, F K, L W, S C, S HG.. Presence of Staphylococcus aureus with Reduced Susceptibility to Vancomycin in Germany. European Journal of Clinical Microbiology and Infectious Diseases. 1999; 18 (10):691–6. PMID: 10584894

81. Ho CM, Hsueh PR, Liu CY, Lee SY, Chiuheh TS, Shyr JM, et al. 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: official publication of the European Society of Clinical Microbiology. 2010; 29(4):383–9. doi: 10.1007/s10096-009-0868-4 PMID: 20155296.

82. 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; 45(5):1511–4. doi: 10.1128/JCM.01262-06 PMID: 17344363; PubMed Central PMCID: PMC1865872.

83. Sun W, Chen H, Liu Y, Zhao C, Nichols WW, Chen M, et al. 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: official publication of the European Society of Clinical Microbiology. 2010; 29(4):383–9. doi: 10.1007/s10096-009-0868-4 PMID: 20155296.

84. W Y, H YJ, A XM, X HT, S TY.. Prevalence and clinical prognosis of heteroresistant vancomycin-intermediate Staphylococcus aureus in a tertiary care center in China. Chin Med J (Engl). 2013; 126 (3):505–9.

85. Chaudhary M, Payasi A. Prevalence of heterogeneous glycopeptide intermediate resistance in Methicillin-Resistant Staphylococcus aureus. American Journal of Infectious Diseases. 2013; 9(3):63–70.

86. Vaudaux P, Ferry T, Uckay I, Francois P, Schrenzel J, Harbarth S, et al. 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: official publication of the European Society of Clinical Microbiology. 2012; 31(12):3367–74. doi: 10.1007/s10096-012-1705-8 PMID: 22833247.

87. Khanal B, Baral R, Acharya A. Prevalence of Vancomycin Intermediate Staphylococcus aureus (VISA) in a tertiary care hospital in Eastern Nepal. International Journal of Infectious Diseases. 2010; 14: e342–e3.

88. Bert F, Clarissou J, Durand F, Delefosse D, Chauvet C, Lefebvre P, et al. Prevalence, Molecular Epidemiology, and Clinical Significance of Heterogeneous Glycopeptide-Intermediate Staphylococcus aureus in Liver Transplant Recipients. Journal of clinical microbiology. 2003; 41(11):5147–52. doi: 10.1128/jcm.41.11.5147-5152.2003 PMID: 14605151

89. Horne KC, Howden BP, Grabsch EA, Graham M, Ward PB, Xie S, et al. Prospective comparison of the clinical impacts of heterogeneous vancomycin-intermediate methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-susceptible MRSA. Antimicrobial agents and chemotherapy. 2009; 53(8):3447–52. doi: 10.1128/AAC.01365-08 PMID: 19506056; PubMed Central PMCID: PMC2715624.

90. Khatib R, Jose J, Musta A, Sharma M, Fakih MG, Johnson LB, et al. Relevance of vancomycin-intermediate susceptibility and heteroresistance in methicillin-resistant Staphylococcus aureus bacteraemia. The Journal of antimicrobial chemotherapy. 2011; 66(7):1594–9. doi: 10.1093/jac/dkr169 PMID: 21525024.

91. K M, T PT, T-K A, L NJ, V AC.. Reduced susceptibility to vancomycin of nosocomial isolates of methicillin-resistant Staphylococcus aureus. The Journal of antimicrobial chemotherapy. 1999; 43(5):729–31. PMID: 10382899.

92. Khatib R, Jose J, Musta A, Sharma M, Fakih MG, Johnson LB, et al. Relevance of vancomycin-intermediate susceptibility and heteroresistance in methicillin-resistant Staphylococcus aureus bacteremia. The Journal of antimicrobial chemotherapy. 2011; 66(7):1594–9. doi: 10.1093/jac/dkr169 PMID: 21525024.

93. Bataineh HA. Resistance of Staphylococcus aureus to vancomycin in Zarqa, Jordan. Pakistan Journal of Medical Sciences. 2006; 22(2):144–8.

94. 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; 4(1):e20. PMID: 24470927; PubMed Central PMCID: PMC3892648.

95. 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; 52 (8):486–8. doi: 10.1016/j.patbio.2004.07.016 PMID: 15465269.
100. 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.

101. Schmitz F-J, Krey A, Geisel R, Verhoef J, Heinz H-P, Fluit AC. Susceptibility of 302 methicillin-resistant Staphylococcus aureus isolates from 20 European university hospitals to vancomycin and alternative antistaphylococcal compounds. European Journal of Clinical Microbiology and Infectious Diseases. 1999; 18(7):528–30. doi:10.1007/s10096944; PMID:10482037.

102. A HM, W M, G M, J AP, R JF, C BD, et al. Twenty months of screening for glycopeptide-intermediate Staphylococcus aureus. The Journal of antimicrobial chemotherapy. 2000; 46(4):639–40.

103. S B, Y S, G D, G Z, O D, S G, et al. Vancomycin and daptomycin minimum inhibitory concentration distribution and occurrence of heteroresistance among methicillin-resistant Staphylococcus aureus blood isolates in Turkey. BMC infectious diseases. 2013; 13(50):46–54.

104. Ariza J, Pujol M, Cabo J, Peña C, Fernández N, Liñares J, et al. Vancomycin in surgical infections due to meticillin-resistant Staphylococcus aureus with heterogeneous resistance to vancomycin. The Lancet. 1999; 353(9164):1587–8.

105. Musta AC, Riederer K, Shemes S, Chase P, Jose J, Johnson LB, et al. Vancomycin MIC plus heteroresistance and outcome of methicillin-resistant Staphylococcus aureus bacteremia: trends over 11 years. Journal of clinical microbiology. 2009; 47(6):1640–4. doi:10.1128/JCM.02135-08 PMID:19369444; PubMed Central PMCID:PMC2691078.

106. Tallent SM, Bischoff T, Climo M, Ostrowsky B, Wenzel RP, Edmond MB. Vancomycin Susceptibility of Oxacillin-Resistant Staphylococcus aureus Isolates Causing Nosocomial Bloodstream Infections. Journal of clinical microbiology. 2002; 40(6):2249–50. doi:10.1128/JCM.40.6.2249-2250.2002 PMID:12037100.

107. Pitz AM, Yu F, Hermson 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; 49(1):269–74. doi:10.1128/JCM.00914-10 PMID:20962147; PubMed Central PMCID:PMC3020454.

108. Kim MN, Pai CH, Woo JH, Ryu JS, Hiramatsu K. Vancomycin-intermediate Staphylococcus aureus in Korea. Journal of clinical microbiology. 2000; 38(10):3879–81. PMID:11015427.

109. Pastagia M, Kleinman LC, Cruz EGdl, Jenkins SG. Predicting risk for death from MRSA bacteremia. Emerging Infectious Diseases. 2012; 18(7):1072–80. doi:10.3201/eid1807.101371 PMID:22709865.

110. CG G. Glycopeptide resistance in Staphylococcus aureus: is it a real threat? Journal of infection and chemotherapy: official journal of the Japan Society of Chemotherapy. 2004; 10(2):69–75.

111. T Y, N K, T Y, I K, I M, W Y, et al. Clinical characteristics of vancomycin minimum inhibitory concentration of 2 μg/ml methicillin-resistant Staphylococcus aureus strains isolated from patients with bacteremia. Journal of Infection and Chemotherapy. 2011; 17(1):52–7. PMID:20625789.

112. Moore CL, Osaki-Kiyan P, Haque NZ, Perri MB, Donabedian S, Zervos MJ. Daptomycin versus vancomycin for bloodstream infections due to methicillin-resistant Staphylococcus aureus with a high vancomycin minimum inhibitory concentration: a case-control study. Clin Infect Dis. 2012; 54(1):51–8. Epub 2011/11/24. doi:10.1093/cid/cir764 PMID:22108947.

113. Tenover FC, Biddle JW, Lancaster MV. Increasing resistance to vancomycin and other glycopeptides in Staphylococcus aureus. Emerg Infect Dis. 2001; 7(2):327–32. Epub 2001/04/11. PMID:11294734; PubMed Central PMCID:PMC2631729.

114. Saito M, Katayama Y, Hishimura T, Iwamoto A, Alba Y, Kuwahara-Arai K, et al. "Slow VISA," a novel phenotype of vancomycin resistance, found in vitro in heterogeneous vancomycin-intermediate Staphylococcus aureus strain Mu3. Antimicrobial agents and chemotherapy. 2014; 58(9):5024–35. Epub 2014/05/21. doi:10.1128/aac.02470-13 PMID:24841271; PubMed Central PMCID:PMCPmc4135821.
115. Ho PL, Lo PY, Chow KH, Lau EH, Lai EL, Cheng VC, et al. Vancomycin MIC creep in MRSA isolates from 1997 to 2008 in a healthcare region in Hong Kong. The Journal of infection. 2010; 60(2):140–5. Epub 2009/12/08. PMID: 19961873.

116. Chang W, Ma X, Gao P, Lv X, Lu H, Chen F. Vancomycin MIC creep in methicillin-resistant Staphylococcus aureus (MRSA) isolates from 2006 to 2010 in a hospital in China. Indian journal of medical microbiology. 2015; 33(2):262–6. Epub 2015/04/14. doi: 10.4103/0255-0857.148837 PMID: 25865979.

117. Chen CJ, Huang YC. New epidemiology of Staphylococcus aureus infection in Asia. Clin Microbiol Infect. 2014; 20(7):605–23. Epub 2014/06/04. doi: 10.1111/1469-0691.12705 PMID: 24888414.

118. K Y, I T, H K.. A new class of genetic element, staphylococcus cassette chromosome mec, encodes methicillin resistance in Staphylococcus aureus. Antimicrobial agents and chemotherapy. 2000; 44 (6): 1549–55. PMID: 10817707

119. N TS, L KH, C-S K, B SM, B DJ, E J, et al. Comparison of community- and health care-associated methicillin-resistant Staphylococcus aureus infection. JAMA. 2003; 290(22):2976–84. PMID: 14665659

120. K SL, M WJ, N GR.. In vitro exposure of community-associated methicillin-resistant Staphylococcus aureus (MRSA) strains to vancomycin: does vancomycin resistance occur? International journal of antimicrobial agents. 2006; 27(2):168–70. PMID: 16420976

121. E J, E-G C, S I, L AR, G L.. Carriage frequency, diversity and methicillin resistance of Staphylococcus aureus in Danish small ruminants. Veterinary Microbiology. 2013; 163:110–5. doi: 10.1016/j.vetmic.2012.12.006 PMID: 23290574

122. Aires de Sousa M, Concejiao T, Simas C, de Lencastre H. Comparison of genetic backgrounds of methicillin-resistant and -susceptible Staphylococcus aureus isolates from Portuguese hospitals and the community. Journal of clinical microbiology. 2005; 43(10):5150–7. Epub 2005/10/07. doi: 10.1128/jcm.43.10.5150-5157.2005 PMID: 16207977; PubMed Central PMCID: PMCPmc1248511.

123. L M, D X, V AE, D BA, W D, S Y, et al. MRSA epidemic linked to a quickly spreading colonization and virulence determinant. Nature Medicine. 2012; 18(5):816–9. doi: 10.1038/nm.2692 PMID: 22522561

124. JP H. A re-evaluation of random-effects meta-analysis. J R Stat Soc Ser A Stat Soc. 2009; 172 (1):137–59. PMID: 19381330