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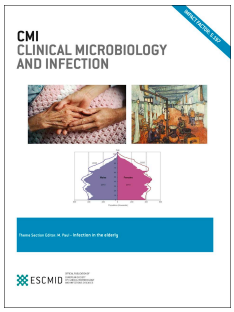

Evaluation of vancomycin MIC Creep in Methicillin resistant *Staphylococcus aureus* infections – a systematic review and meta-analysis

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Abstract

Objectives: Vancomycin is currently the primary option treatment for methicillin-resistant *Staphylococcus aureus* (MRSA). However, an increasing number of MRSA isolates with high minimum inhibitory concentrations (MICs), within the susceptible range (vancomycin MIC creep), are being reported worldwide.

Resorting to a meta-analysis approach, this study aims to assess the evidence of vancomycin MIC creep.

Methods: We searched for studies in the Pubmed database. The inclusion criteria for study eligibility included the possibility of retrieving from the reported data values of vancomycin MIC and information concerning the applied MIC methodology.

Results: The mean values of vancomycin MICs, of all 29.234 *S. aureus* isolates reported in the 55 studies included in the meta-analysis, were 1.23 mg/L (CI (95%) 1.13 – 1.33) and 1.20 mg/L (CI (95%) 1.13 – 1.28) determined by Etest and BMD method, respectively. No significant differences were observed between these two methodologies. We found negative correlation between pooled mean/pooled proportion and time strata.

Conclusions: We have found no evidence of the MIC creep phenomenon.

Key words

Staphylococcus aureus; vancomycin; MIC creep, meta-analysis, MIC methodologies

1. Introduction

Nowadays, *Staphylococcus aureus* (*S. aureus*) is one of the most common pathogen causing severe infections (1). Infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) are associated with increased morbidity, longer antibiotic therapy, higher healthcare costs, prolonged hospitalization and increased risk of death (2).

The first option for the treatment of invasive MRSA infections is the glycopeptide vancomycin, which continues to be the gold standard approach in this context (3). The utilization of vancomycin has been increasing continuously since mid 1980's, resulting in the emergence of MRSA with reduced susceptibility to vancomycin (2). Recently, a phenomenon of gradual increase in the value of glycopeptides MIC (Minimal Inhibitory Concentration) for *S. aureus* was observed and reported in the literature as MIC creep (4). The publications related to MIC creep included studies that report increase in the mean vancomycin MIC as well as studies that did not confirm these findings in MSRA (3, 5, 6). In this context, and as a result of the reported vancomycin therapy failure in patients with *S. aureus* infections with a MIC ≥ 4 mg/L, the Clinical and Laboratory Standards Institute (CLSI) reduced vancomycin breakpoints from ≤ 4mg/L to ≤ 2mg/L, for susceptible *S. aureus,* and from ≥ 32 mg/L to ≥ 16mg/L for resistant *S. aureus*. These changes aimed to increase the sensitivity of the detection of non-susceptible isolates (3, 7). The apparent increase in vancomycin MIC amongst MRSA, observed in recent years, can represent the first step towards the appearance of fully resistant isolates. Patients with MRSA isolates that exhibit MIC creep might experience poorer clinical outcomes, including delayed treatment response, increased mortality, increased rate of relapse, extended hospitalization or overall increased cost of hospitalization (2, 7, 8).

Soriano, *et al*. showed that mortality associated with MRSA bacteremia was significantly higher when the empirical antibiotic was inappropriate and when vancomycin was empirically used for treatment of infection with strains with high vancomycin MIC (>1 mg/L) (9).

The MIC creep phenomenon may be influenced by the type of microbiological susceptibility test used (Etest, broth microdilution (BMD) or automated system) (2, 10), type of *S. aureus* strain or type of patient population evaluated (2). The gold standard for measuring MIC remains BMD (11).

In the literature it is possible to find studies that show vancomycin MIC creep by using BMD (12) and Etest methods (13), and studies that found no vancomycin MIC creep when using the same methods (12-14). This demonstrate inconsistent information about MIC creep phenomenon and conflicting results have been noted in cases in which MIC creep could not be detected. Thus, in an attempt to clarify these inconsistencies and conflicting results, this study aims to assess the evidence of MIC creep, using a meta-analysis, highlighting the type of applied MIC methodologies.

2. Methods

2.1. Search Strategy and Selection Criteria

The studies to be included in the meta-analysis approach were retrieved from Pubmed database. Search query was “methicillin-resistant *staphylococcus aureus*” OR "Methicillin-Resistant Staphylococcus aureus"[Mesh]"" OR “MRSA” AND “vancomycin” OR "vancomycin"[Mesh]"" AND “minimal inhibitory concentration” OR “MIC” OR “MIC creep” OR “reduced vancomycin susceptibility” OR “vancomycin susceptibility trends”.

The abstracts of the collected articles were reviewed and a study was considerable to be eligible for inclusion if included values of vancomycin MIC and details of the applied MIC methodologies. Selected MIC methodologies were: microdilution (BMD), Etest, agar diffusion and automated systems.

2.2. Data Analysis

2.2.1. Data Extraction

After the analysis of both titles and abstracts, the selected studies were independently assessed and analyzed by three authors (R. Diaz, V. Afreixo and C. Rodrigues).

Data extracted from the identified studies included MIC vancomycin information applied methodology, number of studied isolates, source of isolate, year of study completion and country (supplementary material).

2.2.2. Data Uniformization

In the cases of the studies that only reported median, minimum (min) and maximum (max) values, it was assumed the symmetry and mean values were estimated from the median. To estimate the standard deviation (std), the authors assumed the uniform with a variable distribution and the std=(max-min)/√12. In order to complete the table of statistics (mean, std, min), all MIC values ≤0.5 were converted to 0.5.

In studies in which the results were grouped by periods of two years or more, the count were divided in a uniform manner by periods under review.

To create groups with similar numbers of effects, the following stratification of study years under analysis was selected, resulting in seven time strata:

<2000; 2000-2001; 2002-2003; 2004-2005; 2006-2007; 2008-2009 and ≥2010. The time strata <2000 and ≥2010 are created to reach a more uniform number of studies in each stratum. To aggregate results from different years, from the same study, weighted averages, combined variances and/or accumulated frequencies were used.

Some criteria were defined before starting the meta-analysis on the 53 included studies: 1) in studies that presented data of frozen isolates and data of "at time" isolates, data of "frozen isolates" was used because most of the studies determined MICs in "frozen isolates" (6); 2) in the case of studies with data of automated methods, only data of VITEK method was considered since it is the only common to all studies (15); 3) studies of the same author and year were identified with A and B (15-18); 4) studies which included different cities were identified with A and B (3); 5) data presented in more than one study of the same author were excluded (17, 18).

2.2.3. Statistical analysis

Homogeneity among studies was computed using the Cochran's Q statistic and the I^2 statistic. A significant Q statistic suggests that the distribution of effect sizes around the mean is greater than it would be predicted from sampling error alone. On the other hand, I^2 provides an estimate of the proportion of the variance in the aggregate effect size that is attributable to studies heterogeneity, with values of 0.25, 0.50, and 0.75 indicating low, moderate, and high degrees of heterogeneity.

In order to perform a secondary study, a subgroup analysis was carried out with the mean of vancomycin MIC and the proportion of *S. aureus* isolates with vancomycin MIC ≥ 2 mg/L in four subgroups of regions: (i) Europe, (ii) USA, (iii) Asia and (iv) others. Due to the significant heterogeneity between the studies, the pooled prevalence for each group was estimated using the random-effects model.

To compare the pooled effect size in different groups (subgroups) the Z-test was used and for simultaneous statistical tests the Sidak correction was applied (19).

MetaXL 1.0, a tool for meta-analysis in Microsoft Excel, was used to pool individual prevalence from each study.

1

2

3. Results

Literature search, based on the keywords described in methods, identified 980 studies (figure 1). After title and abstract analysis, 880 were excluded and 100 full-text articles were reviewed, (1, 3-6, 8, 9, 11-18, 20-104). Of these, 55 studies were included in the meta-analysis (table 1 in online - only appendix), 45 were excluded for the following reasons: data was included in other study of the same author (2 studies) (87), no MIC data was available (35 studies) (21, 26, 27, 30, 31, 33, 35, 37, 38, 41, 44, 47, 48, 53, 54, 59, 64, 69, 70, 78, 80, 82, 83, 89, 90, 92, 94, 95, 97, 101, 102, 104), full-text versions unavailable (2 studies) (75, 77), different guidelines used (2 studies) (47, 103) and meta-analysis and review articles (4 studies) (8, 46, 57, 93).

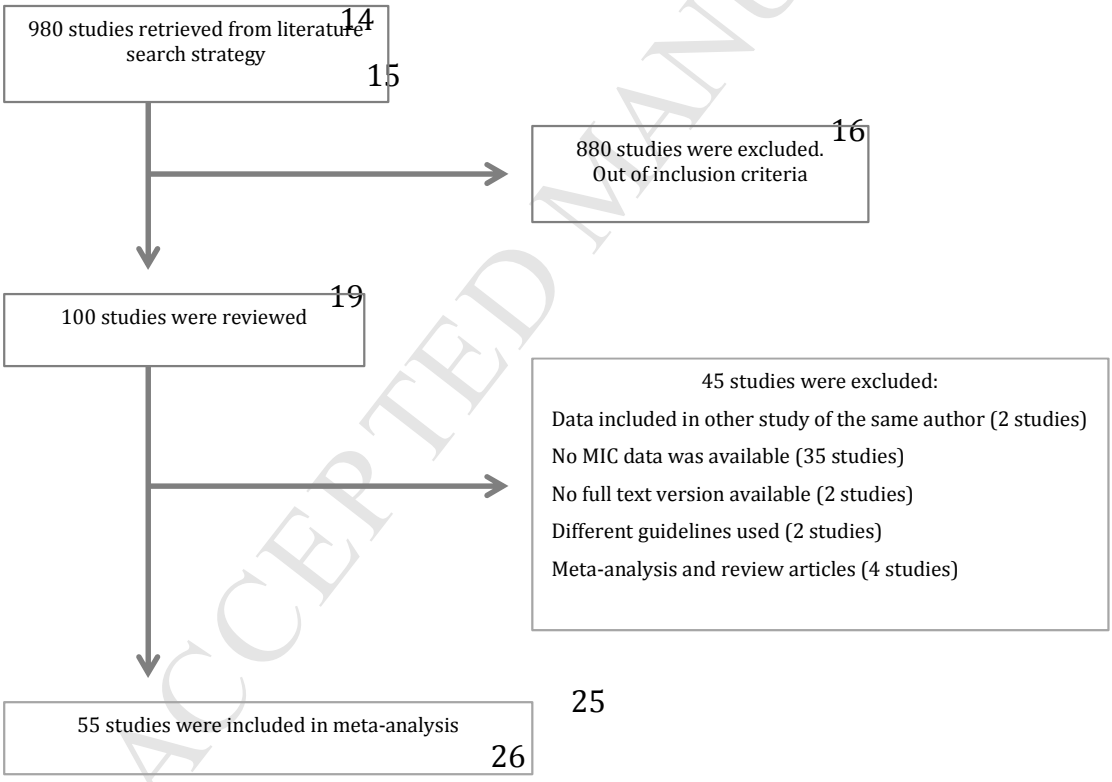

Figure 1: Results of literature search.

Considering all studies included in the pool (n=55), the mean vancomycin MIC was 1.20 mg/L (CI (95%) 1.13 – 1.28), 1.23 mg/L (CI (95%) 1.13 – 1.33) and 1.19 mg/L (CI (95%) 1.07 – 1.30), when determined by the BMD method, Etest method and by the agar method, respectively. The pooled mean of vancomycin MIC determined resorting to the automated method was lower comparing with values obtained with the other methods (1.10 mg/L) (table II). The differences between studied MIC methodologies were not statistically significant (p values > 0.05, Z-test with Sidak correction for multiple comparisons).

To evaluate the robustness of our uniformization, sensitivity analysis was conducted. In four studies the mean value was inferred through the median (Zhuo2013 (40), Kehrmann2011 (3), Cojutti2015 (24), Patel2009 (79)), excluding this studies the overall results do not present significant differences, the overall results are similar with negative correlation values, -0.68 and -0.64 for Etest and BMD, respectively.

Table II: Statistical results of pooled mean vancomycin MICs determined resorting to different MIC testing methodologies.

	MIC testing methodologies	Pooled mean	Confidence Interval (95%)		Spearman correlation [1]	I^2	Number of independent studies	Number of samples
			Lower bound	Upper bound				
MRSA	BMD	1.20	1.13	1.28	-0.82	98.69	16	8328
	Etest	1.23	1.13	1.33	-0.57	99.61	27	7426
	Agar	1.19	1.07	1.30	-	97.64	6	1626
	Automated system	1.10	0.83	1.38	-	99.24	7	1555

[1] Spearman correlation: correlation between time strata and pooled mean.

Considering the pooled mean of vancomycin MIC over each time strata represented in figure 2 and 3, studies before the year 2000 showed the highest vancomycin MICs pooled values. After the year 2007 vancomycin MIC showed a slight decreased (negative Spearman correlation between time

strata and pooled mean) (table II). In general, the results were similar with BMD (figure 2) and Etest (figure 3) methods.

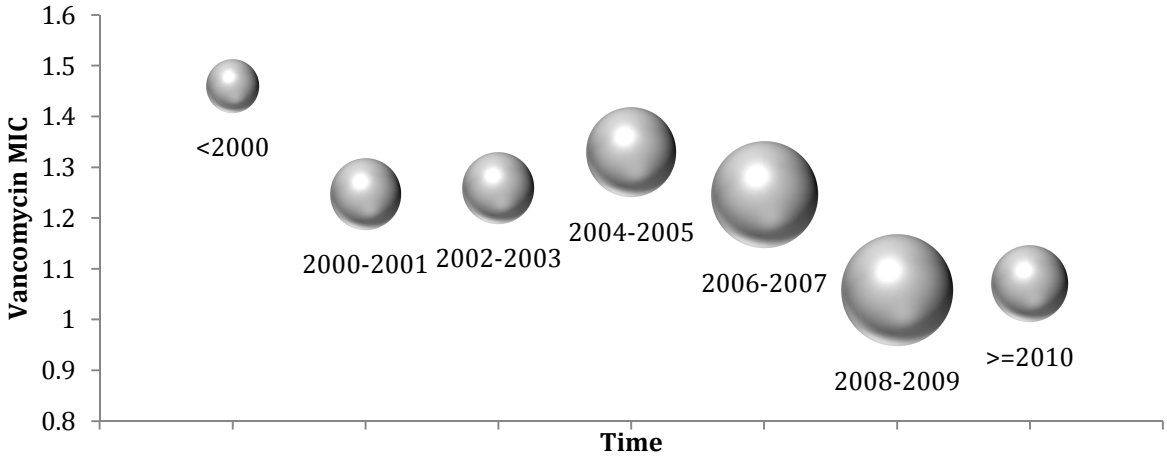

Figure 2: Pooled mean of vancomycin MIC determined by the BMD method over time. The bubble size represents the meta-analysis sub-group weight.

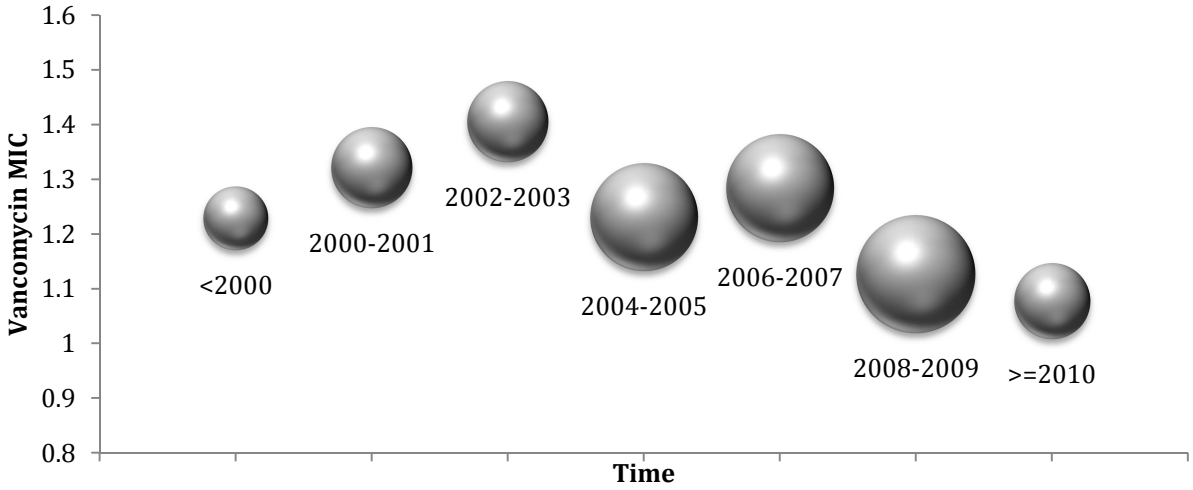

Figure 3: Pooled mean vancomycin MIC determined by the Etest method over time. The bubble size represents the meta-analysis sub-group weight.

Clinical and Laboratory Standards Institute (CLSI) guidelines consider that *S. aureus* is susceptible to vancomycin for MICs lower then 2 mg/L (105). Considering this guideline, the pooled proportion of MRSA isolates with

vancomycin MIC ≥ 2 mg/L was evaluated and showed to be low, between 14% and 18%, for all the applied testing methods (table III).

Table III: Pooled proportion the *S. aureus* isolates with vancomycin MIC ≥ 2 mg/L determined resorting to different MIC testing methodologies.

	MIC testing methodologies	Pooled proportion	Confidence Interval (95%)		Spearman correlation [(1)]	I^2	Number of independent studies	Number of samples
			Lower bound	Upper bound				
MRSA	BMD	0.18	0.12	0.25	-0.89	98.48	17	10350
	Etest	0.14	0.10	0.19	-0.64	96.86	27	7389
	Agar	0.15	0.04	0.30	-	98.32	7	2016
	Automated system	0.18	0.05	0.36	-	97.99	6	1406

[(1)] Spearman correlation: correlation between time strata and pooled proportion.

The analysis of the distribution of MRSA isolates with vancomycin MIC ≥ 2 mg/L showed a decrease over time, either with BMD (figure 4) or Etest (figure 5) methods. For the Etest method, a slight oscillation was observed between 2000 and 2007, followed by a tendency to decrease after 2007 (negative Spearman correlation) (table III).

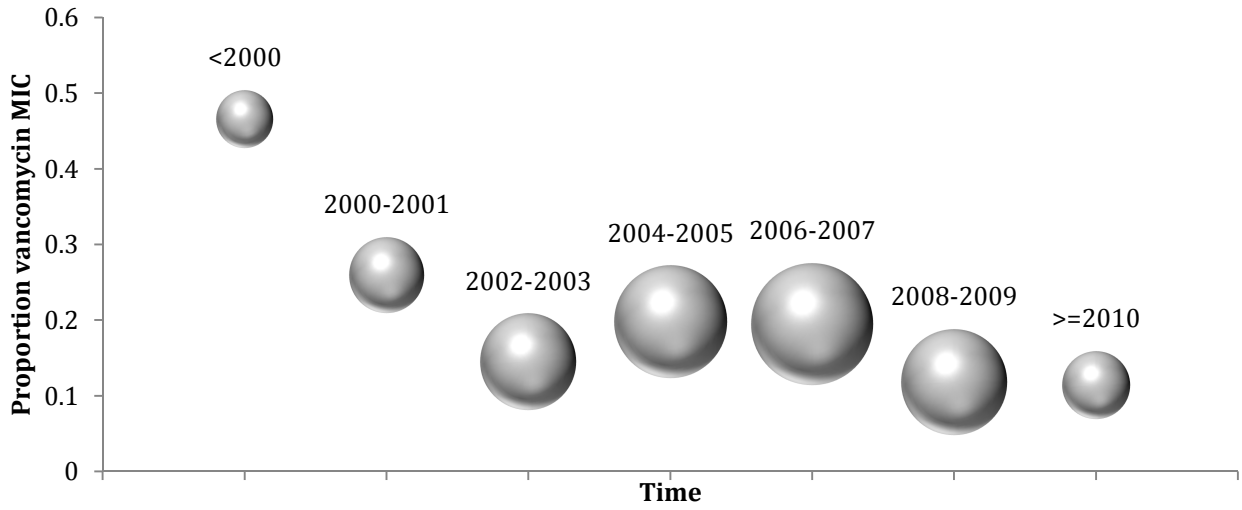

Figure 4: Pooled proportion of MRSA isolates with vancomycin MIC ≥ 2 mg/L determined with the BMD method. The bubble size represents the meta-analysis sub-group weight.

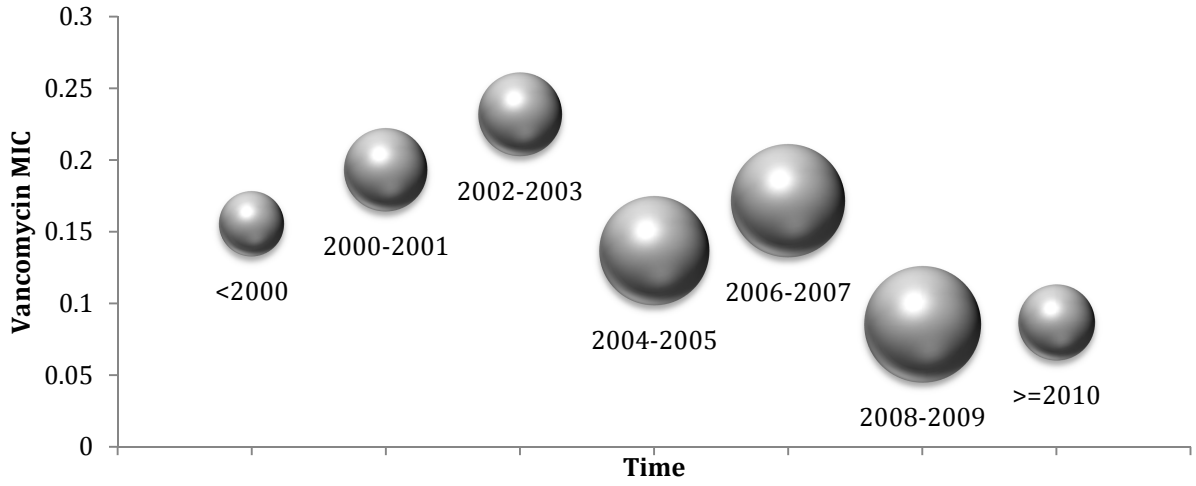

Figure 5: Pooled proportion of MRSA isolates with vancomycin MIC ≥ 2 mg/L determined with the Etest method. The bubble size represents the meta-analysis sub-group weight.

Regarding the analysis of the pooled mean of vancomycin MIC by region, (Europe, USA, Asia and other countries), in Europe the pooled mean of vancomycin MIC determined with the BMD method was 1.12 mg/L (figure 6

online-only appendix) and with the Etest method was 1.13 mg/L (figure 7 online-only appendix). In Asia, the pooled mean of vancomycin determined with the BMD method was 1.17 mg/L (figure 6 online-only appendix) and with the Etest method was 0.98 mg/L (figure 7 online-only appendix). Regarding the USA, these values were slightly increased, with values of 1.37mg/L and 1.53 mg/L for the BMD method (figure 6 online-only appendix) and Etest method (figure 7 online-only appendix), respectively.

By region, the proportion of MRSA isolates with vancomycin MIC ≥ 2 mg/L was 17% in Europe, 26% in USA and 18% in Asia, for BMD method. For Etest method the proportion of MRSA isolates was 11% in Europe, 27% in USA and 3% in Asia (table IV).

Table IV: Pooled proportion the MRSA isolates with vancomycin MIC ≥ 2 mg/L, by region.

MIC testing methodologies	Region	Pooled	Confidence Interval (95%)		I^2	Number of independent studies	Number of samples
			Lower bound	Upper bound			
BMD	Europe	0.17	0.06	0.31	99.58	5	1585
	USA	0.26	0.00	0.71		4	4518
	Asia	0.18	0.00	0.44		4	3235
	Other	0.10	0.00	0.42		2	435
Etest	Europe	0.11	0.04	0.20	98.92	10	1730
	USA	0.27	0.11	0.46		11	4578
	Asia	0.03	0.00	0.09		5	987
	Other	0.23	0.00	0.65		2	435

4. Discussion

This study is the first meta-analysis with a worldwide perspective that evaluates the trends of vancomycin MIC over time, determined by different MIC methodologies, and no statistically significant evidence of the MIC creep phenomenon was detected.

The standard for measuring MIC remains BMD; but this is a labour intensive technique and many laboratories use the Etest method as an alternative. These two methods were selected for evaluation in more detail in this work.

The results of the pooled mean of vancomycin MICs for all MRSA isolates reported with BMD and Etest methods were 1.20mg/L and 1.23mg/L, respectively and no significant differences were observed between these two methods. The number of strains studied with agar method was very low when compared with others methodologies, however the pooled mean of vancomycin MIC for this method (1.19mg/L) was not significantly different from the others. Based on clinical laboratory practice, as expected, the pooled mean of vancomycin MIC determined with an automated method (1.10mg/L) was lower than the ones determined with other methodologies studied. This result is consistent with the study of Tomczak, *et al*., that reports differences between vancomycin MIC assayed with automated method and Etest method (4).

When considering pooled mean of vancomycin MIC over time, studies published before the year 2000 exhibited the highest vancomycin MICs and after 2007 vancomycin MICs showed a slight decrease. Results were similar for BMD and Etest methods. These findings are consistent with the results reported previously by other authors that did not found trends in vancomycin MIC. Some examples are the SENTRY Antimicrobial Surveillance Program database, where, between 1998 and 2003, 35,458 *S. aureus* isolates where studied (106), a multi-center study of nine US medical centers where 1800 MRSA samples where studied, between 1999 and 2006, (107) and a survey from Spain that, between 2002 and 2006, evaluated 3141 *S. aureus* isolates (12).

Considering the upper vancomycin breakpoint for susceptible *S. aureus* a subgroup analysis was carried with the proportion of *S. aureus* isolates with

vancomycin MIC ≥ 2 mg/L and comparing the two main testing methods under analysis the MRSA pooled proportion was very low (11% to 27%). Additionally, over time strata, both BMD and Etest methods showed a decrease in vancomycin MIC, strengthening the observation of no evidence of MIC creep, as supported by the Spearman´s correlation coefficient (table III). The decrease trends observed in both analysis for the last time-strata, can suggest a positive impact of implementation of more rigorous clinical strategies for the management of MRSA infection.

This study also enabled the evaluation of the pooled mean of vancomycin MIC by region (figure 6 and 7 online-only appendix). The results showed a lower pooled mean of vancomycin MIC in Europe and a slightly higher pooled mean of vancomycin MIC in USA. It is expected that an increased value of vancomycin MIC is related to the overall prevalence of MRSA, with higher value of vancomycin MIC linked to higher MRSA prevalence. When correlating our results with the overall prevalence of countries included in the meta-analysis, this can be found in USA and China where the overall prevalence of MRSA in USA is 55,9% (56) with a pooled mean of vancomycin 1.12mg/L and 1.13mg/L, determined with BMD and Etest, respectively and in China with an overall prevalence of MRSA of 46.8% (56) and with a pooled mean of vancomycin 1.17mg/L for BMD and 0,98 for Etest.

One of the problems of combining data from multiple centres, is that it can obscure trends that may exist within a given institution(s) or country, because of differences in patient populations and drug usage patterns. One possible limitation of our study is the inclusion of large multicenter studies, but the negative values obtained with Spearman´s correlation coefficient even with inclusion of these studies, substantiate no evidences of vancomycin MIC creep over time.

The present study did not detect an increase in vancomycin MIC suggesting that vancomycin continues to be the standard option in treatment of MRSA infections when MIC is determined with Etest or BMD methods and in institutions that continuously evaluate their local susceptibility profiles. Future studies must focus on the analysis of vancomycin MIC creep on a regional basis, tested at the same locations and using the same methodologies.

Supplementary material

It includes an Excel file with two data sheet. The first sheet contains the data sets of all studies under detailed analysis with the information obtained directly from each study and the second sheet contains each study results after the data uniformization procedure.

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Transparency declarations

None to declare.

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