Author's response to reviews

Title: Natural history of colonization with methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus (VRE): a systematic review

Authors:

Erica S Shenoy (eshenoy@partners.org)
Molly L Paras (mparas@partners.org)
Farzad Noubary (fnoubary@tuftsmedicalcenter.org)
Rochelle P Walensky (rwalensky@partners.org)
David C Hooper (dhooper@partners.org)

Version: 3 Date: 7 March 2014

Author's response to reviews: see over
Author’s response to reviews

Title: Natural history of colonization with methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus (VRE): a systematic review

Authors:
Erica S. Shenoy, MD, PhD, eshenoy@partners.org
Molly L. Paras, MD, mparas@partners.org
Farzad Noubary, PhD, fnoubary@tuftsmedicalcenter.org
Rochelle P. Walensky, MD, MPH, rwalensky@partners.org
David C. Hooper, MD, dhooper@partners.org

Version: 2 Date: 7 March 2014
Author’s response to reviews: see over
Reviewer’s report

Title: Natural history of colonization with methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus (VRE): a systematic review

Version: 1 Date: 10 December 2013

Reviewer: Editor

Reviewer's report:

1. This systematic review and meta-analysis may contribute a valuable overview of the current literature of VRE and MRSA colonisation. However, the reviewers have brought up some issues that need to be addressed before publication. Of importance, Dr McKinnell has pointed to the need to revisit the study selection process and add certain studies that may have been missed. Furthermore, I agree with Dr den Heijer comments about the clinical heterogeneity issues. This needs to be discussed further in the manuscript. Although there is an interest in performing a meta-analysis on the duration of colonisation the authors may have to consider focusing more on the systematic review and downgrade any conclusions and comments that are based on the pooled analysis.

Update in email communication from Dr. Philippa Harris dated 1/27/2014:

We have now discussed your manuscript and the reviewers’ comments further with our editorial board. In light of the additional advice we received we do not feel that you need to broaden your search strategy and this revision can be ignored (though please include this clarification in your accompanying point-by-point response). However they requested that you address the rest of the comments of the reviewers and include the information provided about the exclusion of the two papers referenced by the reviewer (Donskey and Almyroudis) also within this response.

We have addressed the concerns described above throughout the text in the revised manuscript. The specific comments and revisions are discussed in detail throughout this Response to Review. Here, we enumerate the overall changes to the manuscript in response the Editor’s request that we focus more on the systematic review and less on the pooled results.

We have modified the abstract in the results and conclusion sections to emphasize the heterogeneity of the studies included, and place less emphasis on the pooled results.

Abstract Section
[Page 3, Lines 69-72]
“The heterogeneity of study characteristics limits interpretation of pooled estimates of time to clearance, however, studies included in this review suggest an increase in documented clearance over time, a result which is sensitive to duration of follow-up.”
Results Section
[Pages 12-13, Lines 234-243]
“However, three studies (Lucet, 2009; Manzur, 2010 and Scanvic, 2001) did provide these data, and in general the demographic characteristics of the subjects in the colonized and cleared groups from each cohort were similar, with some notable exceptions. Lucet found assistance with ADLs to be significantly different between the groups (57.5% versus 49.3%, respectively). Manzur reported the presence of decubitus ulcers to be a risk factor for persistent colonization (27.5% versus 13.7%, respectively). Scanvic reported residence at another healthcare institution and break in the skin to be significantly associated with persistent carriage (32% vs 11% and 67.7% vs 28%, respectively).”

[Page 15, Lines 298-306]
“Only two of the studies included, Park (2011) and Yoon (2011) provided sufficient demographic data to formally evaluate variables associated with either persistence or clearance of colonization. Park (2011) found three variables, age (odds ratio [OR]: 0.99; P=0.05), duration of glycopeptide use prior to VRE positivity (OR: 2.16; P=0.003), and length of hospital stay (OR 1.01; P=0.001) associated with subjects having three consecutive negative rectal cultures. Mean duration of glycopeptide use was reported with respect to hemodialysis; patients on chronic HD were observed to be exposed to 12.7 days while patients on non-chronic HD were observed to be exposed to 4.5 days (P=0.001).”

We have modified the Introduction Section to emphasize the systematic review.

[Page 5, Lines 83-88]
“We performed a systematic review of randomized controlled trials and observational studies that followed patients with a history of MRSA and VRE colonization and assessed study characteristics and study quality. In the absence of individual data, we pooled study-level data to calculate estimates of time to clearance of colonization.”

We added substantial detail to study-level characteristics for both MRSA and VRE in response to Reviewer 1, Question 12 (see Page 12 of this Response to Review).

We added additional detail throughout the discussion and conclusion to emphasize the systematic review, the heterogeneity of studies included and limitations of the pooled results. These additional details include:

Discussion Section

[Page 18, Lines 346-348]
“There is substantial heterogeneity among the included studies. This heterogeneity both identifies a clear need for further investigation and tempers our interpretation of the pooled estimates of time to clearance of colonization.”
Lack of a consistent definition of clearance, uncertainty regarding the time of initial colonization, variation in frequency of sampling for persistent colonization, and variation in duration of follow-up and loss to follow-up all impose substantial constraints on our interpretation of the median time to clearance.

The diversity of results that were considered evidence of clearance across the studies is a reflection of the lack of consensus on this point, and limits our interpretation of the pooled estimates. The frequency of re-sampling and duration of follow up varied as well. These factors would be expected to affect reported time to clearance and thus add reasons to be cautious in the interpretation of the systematic review.

Conclusion Section

Our review highlights a substantial degree of heterogeneity across the studies, beyond those common in such analyses. The fundamental differences across studies, including definition of clearance of colonization, frequency of sampling, assays implemented and duration of follow up, highlight the gaps in the available data and caution the interpretation of estimates of clearance derived from pooling the studies included. Despite the strengths and weaknesses of the existing literature and the methodological challenges of interpreting pooled results across a heterogeneous group of studies, the data suggest a decline in colonization over time.

Prospective studies of the natural history of colonization, based on consensus definitions of colonization and clearance, are needed. Such studies will be critical for informing screening policies for identifying those patients no longer colonized with MRSA or VRE and to support guidelines on duration of contact precautions.

2. EDITORIAL REQUIREMENTS:
   a. Competing Interests: Please be advised that manuscripts must include a Competing interests section. This should be placed after the Conclusions/Abbreviations. If there are none to declare, please include the statement “The authors declare that they have no competing interests.”

   We have reviewed the financial and non-financial competing interests description provided by the editor and concluded that there are none to declare. Accordingly, we have included the following statement as requested in the revised manuscript.

   “The authors declare that they have no competing interests.”
b. Authors’ Contributions: For manuscripts with more than one author, all BMC Series journals require an Authors’ Contributions section to be placed after the Competing Interests section.

We have created an Author’s Contributions section which now appears after the new Competing Interests Section. The Author’s Contributions appear using the format suggested.

[Page 27, Lines 502-506]
“ESS and DCH conceived of the study. ESS, MLP, FN, RPW and DCH participated in the design of the study. ESS, MLP and FN performed the analysis. ESS, MLP, FN, RPW and DCH analyzed the data. ESS and MLP wrote the first draft of the manuscript and ESS, MLP, FN, RPW and DCH contributed to the writing of the manuscript and approved the final manuscript.”

c. In addition, could you also move your role of funding sources section from your methods to the end of your manuscript (near to where your competing interest section should be) and move your figure legends to after your references and just before your figures.

We have moved the role of funding sources section from the methods section to the end of the manuscript near the new competing interest section as requested and it now appears on Page 24, Lines 489-497. We have moved the figure legends to after the references and just before the figures, and they now appear on Page 34, Lines 732-760.
Reviewer's report

Title: Natural history of colonization with methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus (VRE): a systematic review

Version: 1 Date: 6 November 2013

Reviewer: James McKinnell

Major Compulsory Revisions:

1. First, I think the systematic review could have been improved. Why was the medline search not complimented with EMBASE or other search engines? Also, why did the authors not review the bibliographies of full-text manuscripts to help identify additional manuscripts. Lastly, why did the authors of the current investigation not contact authors of primary data manuscripts that did not meet criteria or did not present the correct data in the primary manuscript to see if they had additional data that could be included. In a review of a recent publication related to MRSA/VRE colonization, I found multiple references that could have possibly met their inclusion criteria.

   For example, why was the recent report by Almyroudis et al not included in the review? PMID 21515980. Or the sentinel paper by Donskey et al on antibiotics and recurrent VRE colonization? PMID: 12186208. Or, similar work by Donskey in VRE colonization dynamics.

   The authors should pursue: 1) the above multiple recommendation to expand their search. Further, I would suggest a broader initial search strategy. A Pubmed search including "((enterococcus) OR VRE) AND ((((((screening) OR testing) OR screen) OR test) OR swab) OR surveillance)" limited to English, Adults, and Humans resulted in over 1400 results; far more than the 284 records found in the authors search.

Please refer to updated Editor's comments on Pages 1-3 of this Response to Review regarding expansion of the search to identify additional manuscripts.

Here, we take the opportunity to discuss the reasons why Almyroudis et al (PMID 21515980) and Donskey et al (PMID 12186208) were excluded from the systematic review and meta-analysis. Both citations were captured in the initial search strategy and reviewed based on the criteria established for the study.

Almyroudis et al (2011) conducted weekly surveillance for VRE using perianal swabs among patients with hematologic malignancies and HSCT recipients admitted to the hospital. The authors did not report on any patients who, after documentation of VRE
colonization, were later found to be swab-negative. Because of this limitation, the study did not meet criteria for inclusion in our study.

Donskey et al (2002) reported on a year-long prospective cohort study to determine the impact of concurrent antimicrobial therapy on recurrence of colonization in patients who had previously cleared VRE colonization. The study was excluded because patients were followed for recurrence, not clearance of colonization. The impact of antibiotics on ability to recover VRE, however, is an important point, and one which, while beyond the scope of this review, has been further elaborated upon in the revised manuscript in response to question 2, below.

2. Second, the Almyroudis and Donskey articles also raise some conceptual limitations of the paper, principally related to colonization dynamics. The loss of colonization typically represents “clearance” of the original colonizing strain, which as the authors comment may only represent reduction of colonization below detectable levels of routine culture, i.e. culture versus PCR. The concept of test sensitivity may be particularly relevant to VRE as there is specific research by Donskey et al on the impact of antibiotics on VRE density in stool. The authors comment on antibiotic exposure and duration of VRE carriage, but do not provide any statistical analysis. The authors should i) pursue the large and growing literature on antibiotic impacts on VRE colonization and ii) provide formal calculations or describe this more completely.

We agree with the reviewer that a major conceptual limitation of the paper relates to colonization dynamics and specifically clearance of the colonizing strain (or apparent clearance given sensitivity of assays available) or re-colonization with a new strain. The issue of sensitivity is particularly relevant in the setting of selective antibiotic pressure, as has been demonstrated in the case of VRE in Donskey et al (2002). Others, including Karki (2012) and Isoifidis (2013), have reported on the association between antibiotic use and detection of VRE. Drees (2008) demonstrated a protective effect of non-use of antibiotics on ICU room contamination with VRE. While the impact of antibiotics on colonization dynamics was not directly within the scope of the study, we agree of the importance of this issue as raised by the reviewer and have revised the Discussion Section of the manuscript to address this and reference the publications mentioned above.

[Pages 20-21, Lines 407-417]
“A conceptual limitation of our review relates to colonization dynamics and specifically the clearance of the colonizing strain or re-colonization with a new strain, which may be particularly relevant in the setting of selective antibiotic pressure. In the VRE analysis, one clinical variable, prior antibiotic use, was associated with a trend toward early clearance of colonization, supporting the observation that concurrent antibiotic therapy affects the sensitivity of surveillance cultures for VRE. The issue of test sensitivity is particularly relevant in the setting of selective antibiotic pressure, as has been demonstrated in the case of VRE. A detailed analysis of the impact of antibiotics on
colonization dynamics was not directly within the scope of the study, however, is an important area for further investigation, especially with respect to VRE.”

3. The authors do not comment on the underlying dynamics of failure to clear as being the result of sustained colonization with the individual strain, versus acquisition of a second isolate. Although they may not be appropriate for inclusion in the current review, there is a literature on strain typing of MRSA colonizing isolate and VRE colonizing isolate, including the idea of multi-strain colonization that should be commented on in the discussion.

We agree that the dynamics of clearance or persistence of colonization either with the endogenous strain or the acquisition of additional strain (s) is an important concept. Although, as the reviewer states, not appropriate for inclusion in the current review, we have modified the manuscript to raise this point in the Discussion Section.

[Page 20, Lines 395-403]
“Beyond the concepts of transient, intermittent or persistent colonization, isolates identified in the screening studies may represent an initial colonizing strain or a second (or third) isolate. Some studies performed additional analysis to identify strain types. In the absence of strain-typing, it is not possible to conclude that a patient who remains persistently colonized is in fact colonized with the endogenous strain, or intermittently colonized with different strains. From the perspective of infection control implementation, such distinctions may not be meaningful in terms of the practical implementation of CP measures, and those cases in which cohorting is permitted.”

Additionally, we have revised Tables 1A (Column 8) and 1B (Column 9) to identify the studies that employed strain typing.

Minor Essential Revisions:
1. Did the authors make a distinction between VRE. faecalis and VRE.faecium? see Ruiz-Garbarjosa J Clin Micro 2009.

We appreciate this question, which focuses attention on differences reported in the dynamics of intestinal colonization of different enterococci. Ruiz-Garbarjosa (2009) reported that *E. faecalis* had longer persistence than *E. faecium*.

In the manuscript under review, seven of the 13 studies reported on *E. faecium* alone, while six of 13 made no distinction between *E. faecalis* and *E. faecium*. This additional information has been added to Table 1B (Column 2). We have also included the following in the revised manuscript:

Methods Section

[Page 8, Lines 135-136]
“For VRE, it was noted if studies made distinction between *E. faecalis* and *E. faecium*.
faecium.”

Results Section

[Page 14, Lines 279-281]
“Seven of the 13 studies reported on *E. faecium* alone, while six of 13 made no distinction between *E. faecalis* and *E. faecium*.”

2. Figures 3, 4, and 5 are referred to Figures 2A, 2B, and 2C respectively in the text. Consider “Percentage of patients with documented clearance of MRSA colonization” on y-axis of Figure 3.

In the revised manuscript, and Figures 2A, 2B and 2C are now referred to as Figures 3, 4 and 5 so that all references to the figures are consistent throughout and conform to BMC ID requirements.

We have modified the y-axis of Figure 3 (previously numbered as 2A) as requested.

[Figure 3]
“Percentage of patients with documented clearance of MRSA colonization”

We have modified the y-axis of Figure 5 (previously numbered as 2C) as well and it now appears as requested.

[Figure 5]
“Percentage of patients with documented clearance of MRSA colonization”
3. References 8, 14, and 15 were excluded from the time-restricted analysis for MRSA clearance, but it is unclear whether three other studies that had duration to clearance times in excess of 43 week (References 9, 19, and 20) were excluded as well.

References 9 (Mulhausen; B in Fig 3, B1 in Fig 5) and 22 (Manzur, O in Figure 3 and O1 in Fig 5) were included in the time-restricted analysis because time points earlier than 43 weeks were reported. References 8 (Sanford, A in Fig 3), 14 (Vriens, G in Fig 3), 15 (Marschall, H in Fig 3), 19 (Lucet, L in Fig 3) and 20 (Robicsek, M in Fig 3) were excluded from the time-restricted analyses because they did not report on time points earlier than 43 weeks and thus do not appear at all in Figure 5. To clarify this difference, we have included the Study IDs B1 and O1 in Table 1A. Additionally, we have modified the Results Section of the manuscript to address this point.

[Page 17, Lines 339-342]
“Figure 5 shows that with this restriction, which results in the exclusion of five studies (A, G, H, L, M) and the inclusion of earlier-reported time intervals from two studies (Manzur, 2010, “O1” and Mulhausen, “B1”), the model-fitted median time to documented clearance would occur at 41 weeks.”

4. Citation needed in Introduction, 3rd sentence: “…the growing pools of colonized and therefore isolated patients affect patient care and burden the healthcare system”

We have included three additional citations which support the impact of CP on patient care and resource utilization. These references include Stelfox et al., 2003 (reports on patient care and safety for isolated patients), Conterno et al., 2007 (reports on cost of CP implementation) and Shenoy et al., 2012 (reports on additional resource burden imposed by implementation of CP in hospital administration) [Page 5, Lines 78-80].

Additions of these references have affected the numbering of all references in the manuscript, which have been adjusted accordingly.

5. Space needed between “time” and “period” in Methods, 5th sentence.
We have included this modification in the revised manuscript [Page 6, Line 102].

6. Study Selection: Clarification needed whether screening methods and locations were consistent within individual studies.
We have clarified the issue raised by the reviewer in the revised manuscript; our modifications to address this issue appear in the Methods Section.

[Page 7, Lines 117-118]:
“Studies were required to report on screening from at least one anatomical site; any anatomical site for screening was permitted for inclusion.”
7. Comparison of MRSA and VRE Pooled Clearance Rates: References 8, 14, and 15 were excluded from the time-restricted analysis for MRSA clearance, but it is unclear whether three other studies that had duration to clearance times in excess of 43 week (References 9, 19, and 20) were excluded as well.

Please see our response to Reviewer 1, Question 3, above, Page 10 of this Response to Review.
Discretionary Revisions:

8. Consider “Percentage of patients with documented clearance of VRE colonization” on y-axis of Figure 4

We agree and have modified the y-axis of Figure 4 (previously 2B) as follows: “Percentage of patients with documented clearance of VRE colonization”

9. Data on cohorts of MRSA colonized versus cleared cohorts could be presented and compared using simple descriptive statistics or multiple logistic regression, if appropriate. These data could be interesting in light of recent publications relating to risk factors for MRSA colonization.

A minority of studies included reported detailed characteristics of colonized versus cleared cohorts (MRSA: Lucet, 2009; Manzur, 2010; and Scanvic, 2001; VRE: Park, 2011 and Yoon, 2011), beyond patient-type (hospitalized, long-term care, or ambulatory), a point which is illustrated in Figures 3 and 4.

Due to the sparsely reported data, multiple logistic regression was not feasible. We agree with the reviewer’s comment on the additional interest in such risk factors for persistence of colonization and have modified the manuscript in the Results Section.

[Pages 12-13, Lines 234-243]

“However, three studies (Lucet, 2009; Manzur, 2010 and Scanvic, 2001) did provide these data, and in general the demographic characteristics of the subjects in the colonized and cleared groups from each cohort were similar, with some notable exceptions. Lucet found assistance with ADLs to be significantly different between the groups (57.5% versus 49.3%, respectively). Manzur reported the presence of decubitus ulcers to be a risk factor for persistent colonization (27.5% versus 13.7%, respectively). Scanvic reported residence at another healthcare institution and break in the skin to be significantly associated with persistent carriage (32% vs 11% and 67.7% vs 28%, respectively).”

[Pages 15-16, Lines 298-317]

“Only two of the studies included, Park (2011) and Yoon (2011), provided sufficient demographic data to formally evaluate variables associated with either persistence or clearance of colonization. Park (2011) found three variables, age (odds ratio [OR]: 0.99; P=0.05), duration of glycopeptide use prior to VRE positivity (OR: 2.16; P=0.003), and length of hospital stay (OR 1.01; P=0.001) associated with subjects having three consecutive negative rectal cultures. Mean duration of glycopeptide use was reported with respect to hemodialysis; patients on chronic HD were observed exposed to 12.7 days while patients on non-chronic HD observed exposed to 4.5 days (p=0.001)…In multivariable logistic regression analysis, they found that vancomycin use after VREF colonization was significantly associated with prolonged carriage (OR 4.1; P=0.02).”
Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Needs some language corrections before being published
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: None
Reviewer’s report

Title: Natural history of colonization with methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus (VRE): a systematic review

Version: 1 Date: 2 December 2013

Reviewer: Casper den Heijer

Reviewer’s report:

Major Compulsory Revisions:

1. There appears to be a lot of heterogeneity between the studies included in the meta analysis (type of design, setting, definition of clearance, variation in frequency of sampling and variation in duration of follow-up). With this heterogeneity, I wonder whether it is justified to perform a pooled analysis. At this moment, isn’t it better to show your results of the systematic review, point out the limitations (eg heterogeneity) of the present literature and conclude that consensus is needed regarding the definition of clearance, sampling frequency and follow-up in order to allow a meta analysis in the future?

We agree that a major limitation of the study (and of the existing literature) is the heterogeneity of the studies on many different levels, including study design, setting, definition of clearance, variation in frequency of sampling, assays used for sampling and duration of follow up. Because of these differences, we have decreased the emphasis on the pooled analysis and included additional discussion with respect to the need for consensus on definition of clearance, sampling frequency and follow up.

The greatest limitation of the present literature is that we do not know patients’ timing of colonization. Estimating timing of colonization would require a study design whereby patients who are not colonized though perhaps at high risk of at the start of the study are recruited and tested for colonization at regular visits. Given an estimate of timing of colonization, such patients could then be followed longitudinally until clearance in order to estimate time from colonization to clearance, the true parameter of interest. Because current studies report on MRSA- and VRE-prevalent cohorts, we have instead estimated time from documented colonization to documented clearance.

Our modifications to address this issue appear in the revised manuscript as described in detail in our response to the editor on Pages 1-3 of this Response to Review.
Minor Essential Revisions:

2. I wonder whether it was possible to find a decrease of documented clearance over time, because all included patients at baseline needed to be colonized. The conclusion that the documented clearance decreased over time doesn't seem surprising to me.

We agree that it is not surprising that colonization decreases over time when starting with a population that is colonized at baseline. We believe that a better understanding of the timing or pace of clearance has practical implications for both patient care and policy. We have clarified the goal of the study to emphasize this point. Our modifications to address this issue appear in the revised manuscript Introduction Section.

[Page 5, Lines 81-83]
“Thus, pooling of these data might provide a better understanding of the natural history of colonization and the timing of clearance and thereby inform clinical care and public policy.”

3. Could the authors comment on why the quality of the studies was assessed separately and not included (as a weight) in the main analyses, i.e. assessment of the median time to clearance?

We assessed the quality of the subset of cohort studies included in the systematic review. For the MRSA studies, while a total of 16 studies were included in the review, three of these were RCTs and thus only 13 were included in the quality assessment. For the VRE studies, while a total of 13 studies were included in the review, one was an RCT and thus 12 of the studies were included in the quality assessment. In the revised manuscript, we have modified Figures 1A and 1B to end with the box of included studies, and in the Results Section of the manuscript describe the subset for which the quality analyses were performed.

[Page 13, Line 259]
“The 13 cohort studies were assessed using the modified NOS.”

[Page 16, Line 330]:
“The 12 cohort studies were assessed using the modified NOS.”

The quality assessment applied an adapted version of the Newcastle Ottawa Scale (NOS) tool. While the tool allowed us to compare the cohort studies based on a series of six criteria as described in the Methods Section [Pages 9-10, Lines 166-193]. These scores were not included as a weight in the main analyses because of the clustering of quality scores (MRSA range 4-6, mean 4.8; VRE range 3-5, mean 4.6) and the lack of applicability of the assessment for non-cohort studies.

We have highlighted this approach in the revised manuscript in Results Section for the MRSA and VRE results, respectively.
[Pages 13-14, Lines 260-265]
“The remainder of the studies were missing quality criteria in either comparability, appropriate time to follow-up or loss of follow-up; overall, these studies were of moderate quality, with the mean score of 4.8/6 (range 3-6). As the NOS results lacked variation and were applicable only to cohort studies, they were not used as weights in the pooled analyses.”

[Pages 16-17, Lines 330-334]
“No study fulfilled all quality criteria for the modified NOS; the majority were of moderate quality with the mean score of 4.6/6 (range 3-5). As was the case for the MRSA analysis, the NOS results were not used as weights in the pooled analyses.”

4. On page 11, different categories are given on the proportion of loss to follow-up reported and a category of studies that did not report loss to follow-up. The number of studies given add up to 10 (3+3+4). Was it not possible to classify the other (six) included studies?

We appreciate the opportunity to correct this error; our modifications appear in the revised in the Results Section of the manuscript.

[Page 11, Lines 213-214]
“For loss to follow-up, seven studies had less than 30%, four had more than 30%, and five provided no information.”

5. Why was logistic regression analysis performed on these data? It seems to me that survival analyses are more suitable to analyze the median time to clearance.

The reviewer raises an important limitation of the data available to us. If we had access to patient-level data from each study (i.e., time of clearance for each patient), we would have pursued a survival analysis approach. However, as we had access to summary statistics at the study level (e.g., 23% of patients had cleared at 13 weeks after documented colonization), we instead chose to model the probability of clearance over time. We have modified the manuscript to reflect the study-level as compared to patient-level approach as follows:

Introduction Section
[Page 5, Lines 86-88]
“In the absence of individual data, we pooled study-level data to calculate estimates of time to clearance of colonization.”
Discussion Section

[Page 22, Lines 436-437]
“Our analysis was also limited by the use of aggregate data rather than patient-level data, which would have permitted a survival analysis approach.”

6. On page 13, it is stated that the median time to clearance exceeded 208 weeks by excluding the Robicsek study. However, the Robicsek study was the only study that had a follow-up time of 208 weeks. Isn't it better to state that the median time to clearance exceeded 172 weeks (Sanford study: study with most weeks to clearance in this sensitivity analysis)?

We agree and have modified the manuscript in the Results Section to reflect this change.

[Page 13, Lines 248-250]:
“The exclusion of Manzur (2010) resulted in a model-fitted median time to clearance of 68 weeks. Separately, the exclusion of Robicsek (2009) resulted in a model-fitted median clearance time >172 weeks after documented colonization.”

7. On page 14, how was the duration of glycopeptide use defined by Park (2011)? Was it categorized or measured in days/hours? This will help to interpret the given ORs.

The duration of glycopeptide use was defined in days (Park, 2011). The authors provide a comparison of mean duration for both the chronic HD patients and non-chronic HD patients (12.7d ± 8.3; 4.5±8.2; P=0.001). Our modifications to address this issue appear in the revised manuscript Results Section.

[Page 15, Lines 303-306]
“Mean duration of glycopeptide use was reported with respect to hemodialysis; patients on chronic HD were observed to be exposed to 12.7 days while patients on non-chronic HD were observed to be exposed to 4.5 days (P=0.001).”

8. On page 16, it is stated that three studies were excluded in the sensitivity analysis restricting the time to follow-up for MRSA studies to 43 weeks. However, in table 1A more than three studies have follow-up times longer than 43 weeks (eg Robicsek)? Can the authors explain this discrepancy?

Table 1A includes the latest time point provided for follow-up. In the sensitivity analysis restricting to inclusion of MRSA studies with follow up at ≤43 weeks (to be able to compare to the VRE studies which reported shorter follow up), we included studies that reported clearance at ≤ 43 weeks. In the case of studies that report the latest time point > 43 weeks but which were included in this analysis, interim time points ≤ 43 weeks were reported. Please see our response to Reviewer 1, Question 6, above, which addresses our modifications to how the time-restricted analysis has been modified in the revised manuscript.
We have additionally modified the presentation of these data in Tables 1A and 1B by changing the heading of the column from “Follow up (weeks)” to “Latest documented follow up (weeks)” in the revised manuscript.

9. Figures 2A-C are given as Figures 3-5 in my documents

Please see Reviewer 1, Page 9 of this Response to Review, above.

Discretionary:

10. In the Introduction, the sentences "... the prevalence of colonization is increasing. It is estimated that these infections..." implies, to me, that colonization is equal to infection, which is actually not the case. Perhaps the authors could rewrite one of the sentences.

We agree that this is confusing and have revised the manuscript to address this concern in the Introduction Section.

[Page 5, Lines 76-80]
“Methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus (VRE) are endemic in hospital settings and long-term care facilities (LTCF), and the prevalence of colonization is increasing. The growing pools of colonized and therefore isolated patients affect patient care and burden the healthcare system.”

11. On page 13 it is stated "... again resulted in 13 studies included..." I wonder why "again" is used? In the MRSA meta analysis I believe that 16 studies were included.

We agree that this is confusing—our aim was to describe how we arrived at the 13 VRE studies. In the revised manuscript, we have modified Figures 1A and 1B to end with the box of included studies, and in the text describe the subset for which the quality analyses were performed. We have further revised the manuscript to address this concern in the Results Section.

[Page 14, Lines 271-273]
“This procedure resulted in 13 studies included in the review, and 12 cohort studies included in the quality assessment (Figure1B).”

12. On page 17/18 it is mentioned that the colonization time could be underestimated due to the lag time between initial colonization and identification. However, I think that the colonization time could also be overestimated, because of infrequent sampling in the follow-up period.

We appreciate this important point and have addressed it in the revised manuscript in
the Discussion Section.

[Page 19, Lines 368-372] “Under these inevitable circumstances, calculations of duration of colonization may underestimate the true duration of colonization and the pattern of clearance. On the other hand, if the time interval between initial documentation of colonization and re-screening is prolonged, duration of colonization may also be overestimated.”

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests: I declare that I have no competing interests.