Author's response to reviews

Title: Does vancomycin prescribing intervention affect vancomycin-resistant enterococcus infection and colonization in hospitals? A systematic review

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Author's response to reviews: see over
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RE: MS 4270622221087913, “Does vancomycin prescribing intervention affect vancomycin-resistant enterococcus infection and colonization in hospitals? A systematic review”

Dear Editors:

Please find enclosed point-by-point responses to the concerns of the two reviewers. We have also uploaded the revised manuscript, and have ensured that it conforms to the journal’s style and formatting standards.

We wish to apologize for postponing the deadline in responding to the reviewer’s comments, and wish to extend our appreciation to the reviewers for their critiques and helpful suggestions. We feel that their suggestions have contributed to make the manuscript more understandable and more helpful to readers of the journal. We have highlighted in blue our answers to the reviewers and all changes in the body of the manuscript for easy identification. Each of our responses corresponds to the order of the questions and comments of the reviewers. To attempt to more clearly present our answers to each of the reviewer’s concerns, we have numbered them in the order in which they originally appeared. References cited within the following text correspond to the references of the revised manuscript.
Below are our responses to the questions raised by the reviewers:

**Reviewer #1**

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1.1 Why was Medline not included as one of the search engines?

The electronic databases that were searched included PubMed, Web of Science, ClinicalTrials.gov and the Cochrane Library. PubMed provides coverage of Medline and OldMedline ([http://www.ncbi.nlm.nih.gov/entrez/query/static/overview.html](http://www.ncbi.nlm.nih.gov/entrez/query/static/overview.html)). To clarify the issue raised by Referee #1, we should change the phrasing to, “PubMed including Medline, as well as Web of Science and the Cochrane Library” (page 5, ¶ 3, line 1 of the revised manuscript).

1.2 Which conferences were included when abstracts from conference proceedings were reviewed?

Only published studies were eligible for inclusion into our review, as stated on page 5, ¶ 1, line 5 of the original manuscript. Therefore, we should delete the mention of searching meeting abstracts from our description of our search methods (page 4, ¶ 3, line 3 from bottom of the original manuscript). Similarly, the statement on searching ClinicalTrials.gov has been removed, as the trials on this website are also unpublished (page 4, ¶ 3, line 3 from bottom of the original manuscript).

1.3 Did only one reviewer assess all the possible abstracts?

The initial screening of all abstracts was performed by the first author (MAD), who excluded studies that irrefutably did not meet inclusion criteria. As a second step, both authors (MAD and LWR) critically reviewed the full text of each of the remaining eligible studies. The decision to include the final 13 studies was reached by consensus (MAD and LWR).
1.4 The simple comparison of composite data from the pre-intervention period and post-intervention period may provide a misleading assessment of the impact of the intervention. Segmented regression analysis (which assesses both the change in the rate over time in the outcome of interest, as well as the immediate change concurrent with the intervention) provides a more robust estimate of the impact of the intervention. It is unlikely that the authors could conduct these analyses for each paper based on the data available in each of the primary papers. However, did the authors assess whether specific included papers conducted segmented regression analysis? Two references which might be considered for inclusion in the manuscript (at the authorsâ€™ discretion) are: 1) Ramsay et al, J Antimicrob Chemother, 2003; 52: 764-71; and 2) 86. Wagner AK, Soumerai SB, Zhang F and Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther 2002;27:299-309

We agree with referee #1. Segmented regression analysis enhances the internal validity of results and provides a more robust analysis for the impact of an intervention, as compared with a simple comparison of composite data from pre- and post-intervention periods.

As per Ramsay et al. (Ramsay, Brown et al. 2003) among the current literature on antibiotic prescribing, often there are an inadequate number of pre-and post-intervention time points. A minority of the studies in their review used the recommended segmented regression analysis.

The following paragraphs have been inserted to the Discussion section under “Limitations of this review” (page 14, ¶ 2, line 1 of the revised manuscript).

“None of the 13 studies reviewed in this report used experimental designs that would have allowed a definitive answer to our main question. Each of these studies used a quasi-experimental approach of lower hierarchy. In fact, all the studies fell below category A3 of the classification proposed by Harris et al. (Harris, Lautenbach et al. 2005; reference #36). Quasi-experimental studies possess significant limitations.
including 1) difficulty in controlling for important confounding variables (due to lack of randomization), 2) results that are explained by the statistical principle of regression to the mean (the principle that elevated rates will tend to return to baseline, even without an intervention) and 3) maturation effects (natural changes over time) (Harris, Bradham et al. 2004, reference #39).

None of these studies used segmented regression analysis nor were they randomized clinical trials. To evaluate the efficacy of a single intervention (e.g. reduction in vancomycin usage), randomized clinical trials may be ethically unacceptable given that commonly there is urgency in controlling an infectious agent or disease (e.g. VRE colonization and infection) in a timely manner and in including other interventions (e.g. infection control, reduction in the usage of other antibiotics). An alternative to randomized clinical trials may be the use of segmented regression analysis. This experimental approach is considered superior in design to other types of quasi-experimental studies by several investigators (Shaikh, Osting et al. 2002, reference #32). Segmented regression analysis enhances the internal validity of results, as compared with a simple comparison of composite data from pre- and post-intervention periods. None of the 13 studies obtained or provided sufficient data for us to perform a segmented regression analysis. To perform such analysis would have required collection of pre- and post-intervention data at equally spaced time intervals that span enough periods to detect pre-existing trends and cyclical patterns. Specifically, according to Wagner et al. (Wagner, Soumerai et al. 2002, reference #40), “A general recommendation is for 12 data points both before and after the intervention.”

1.5 The authors review papers which all describe quasi-experimental (pre-post) studies. They allude in the results section to various characteristics of the quality of the quasi-experimental studies (e.g., confounding) but never comment on the fact that there are several well defined aspects of quasi-experimental study design which should be considered in assessing the validity of a given study. Two recent papers which focus on quasi-experimental study design in studies of antimicrobial resistance might be useful as references in better formalizing this discussion in the paper. The references are: 1) Harris

Please see answer to comment 1.4.

1.6 The papers reviewed by the authors are clearly not in agreement in their conclusions. I believe the main strength of this systematic review is in highlighting the heterogeneity and limitations of the work done thus far. This is very useful in demonstrating how future work could improve on what has been done. As such, I think it would be useful for the authors to expand in the discussion on possible future areas for improvement in research in this area.

Agree with referee’s comment. We have now added a new heading and paragraph to the Discussion section (page 16, ¶ 3 of the revised manuscript).

“Suggestions for the design of future studies

Several of the methodological shortcomings observed in the studies reviewed here could be improved upon in future research. Ideally, randomized clinical trials should be performed. However, this design is often considered impractical by infection control personnel and may be unethical in outbreak settings. Alternatively, implementing higher quality quasi-experimental study designs (e.g. Category B) or using segmented regression analysis may allow for more causal interpretation of observed associations than using quasi-experimental designs of lower quality (e.g. < A3) (Harris, Nemoy et al. 2004, reference #39; Harris, Lautenbach et al. 2005, reference #36). When possible, distinct control groups should be used. Collection of additional data points before and after implementation of an intervention may shed further light on baseline trends, the immediate and sustained impacts of the intervention, maturation effect, and cyclical / seasonal patterns. By having sufficient data points to perform segmented regression analysis, the internal validity of studies would be improved.

In order to clearly answer the question of whether reduction in vancomycin usage results in a decrease of VRE colonization and disease, a significant decrease in vancomycin
prescriptions should be the only variable introduced. This approach would not be possible in outbreak settings. However, it would be feasible in endemic settings where there is less of a need for concurrent implementation of infection control measures. Additionally, collection of adequate pre-intervention data points would be more possible because of relatively less urgency. More discussion of why authors chose their particular study design, as well as its strengths and limitations would be helpful to readers and in the design of future studies. Standardized nomenclature regarding study designs should be implemented to enhance the clarity of research designs and methodology.”

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1.7 The summary of articles is valuable in nicely summarizing the available data. I’m not sure the conclusion should be that VRE interventions have a potential role in VRE reduction. Only about half of the papers reported a decrease in rates. I think the main take home message here is that this issue remains controversial. The most valuable message is that more research needs to be conducted in this area.

We agree with referee 1. As such, we have revised our conclusion to state that it is not possible to determine, from the available data whether the intervention is helpful, and that more research is needed (page 17, ¶ 2 of the revised manuscript).

“In summary, based on this systematic review of the literature, it was not possible to conclusively determine a potential role for vancomycin usage reductions in controlling VRE colonization and infection in hospitals in the Untied States, as is recommended by current guidelines (1995). The effectiveness of such interventions and their sustainability remain poorly defined because of heterogeneity in study design and results, as well as insufficient study quality to enable adequate causal inference. In general, studies implementing vancomycin reduction as the sole intervention to control VRE were less successful than those implementing additional VRE control strategies, although numbers were too small to detect a significant difference between groups. Future research using
experimental designs of higher quality and implementing vancomycin use reduction as
the sole intervention is needed to answer this question.”

1.8 In the background, it is stated that VRE is associated with greater morbidity,
mortality, and length of stay. While several studies have certainly shown this, others
have not. It might be reasonable, to at least acknowledge that this remains an area of
some controversy.

Agree. The following sentence has been added to the Background section, “Of note, this
topic remains controversial as some investigators have reported a lack of association
between VRE infections and increased morbidity and mortality (Shay, Maloney et al.
1998, reference #10; Lautenbach, Bilker et al. 1999, reference #36; Garbutt,
Ventrupragada et al. 2000, reference #8; Peset, Tallon et al. 2000, reference #11) (page 4,
¶ 2, line 2 from bottom of the revised manuscript). Additionally, in the Abstract section,
we have changed the phrasing of our first sentence from “…VRE…leads to greater
morbidity, mortality and healthcare costs…” to “…may be associated with…” (page 2, ¶
1, line 1 of the revised manuscript).

Reviewer #2

• Major Compulsory Revisions

2.1. First, the authors state that they reviewed/extracted information on the study design,
but little comment on the design followed. The authors need to review work by Harris et
This article and perhaps another important article should be reviewed and referenced
include mention that none of the reviewed studies were randomized controlled trials and
all were quasi-experimental designs. General limitations of quasi-experiments must be
mentioned including regression to the mean, which is an important problem in
interventions initiated in outbreak situations. The standard text concerning quasi-
experiments is: Shadish WR, Cook,T.D., Campbell,D.T. Experimental and quasi-
experimental designs for generalized causal inference. Boston: Houghton Mifflin Company; 2002. I suggest a quick glance at this important text. Additionally, since the Gold-Standard is a randomized trial (in this case it would be a cluster-randomized trial), the authors could reference this paper that discusses whether experiments and quasi-experiments yield the same answer. (Shadish WR, Heinsman DT. Experiments versus quasi-experiments: do they yield the same answer? NIDA Res Monogr.1997;170:147-164)

We agree with the suggestion regarding analyzing our findings further from the perspective of the type of design utilized by the 13 published studies. We have now mentioned in our Discussion and Abstract sections that none of the studies were randomized-controlled trials, and have detailed the key limitations of quasi-experimental study designs (page 14, ¶ 2, line 1, and page 2, ¶ 3, line 1 of the revised manuscript). Please see our response to referee #1 (1.4 under responses to referee #1).

We have also added into our Selection criteria section of the Methods section the following comment in parentheses; “eligible studies were experimental in design (randomized controlled trials or quasi-experimental studies)” (page 5, ¶ 4, line 1 of the revised manuscript).

In addition, we have added the quasi-experimental study design covariate to the Methods section, “… 5) type of quasi-experimental design and 6) duration of intervention” (page 8, ¶ 2, line 1 from bottom of the revised manuscript). To the results section, we have added the outcome of a stratified analysis based on type of quasi-experimental design (page 12, ¶ 3 of the revised manuscript). We have now added a column to table 1 describing the study design of each article (see below response to referee comment 2.2).

2.2 I suggest adding another column to Table 1 called "Study Design" and review each paper and list which type of quasi-experiment was employed (e.g. before-after without control, before-after with non-equivalent control group). Again, review papers by Harris above. If all of the studies had low-level designs, this needs to be mentioned and interpreted in the results and discussion sections respectively.
The following statements have been added to the Methods section: “Studies were categorized according to the hierarchy of quasi-experimental study designs [36]. According to this classification scheme, category A studies do not use control groups, while category B studies do. A1 studies use a 1-group pretest-posttest design and A2 studies use a 1-group pretest-posttest design with a double pretest. We have chosen to denote A1 studies which use multiple posttest measurements as “A1*” and A2 studies using multiple posttest measurements as “A2†.” In general, studies using a control group are of higher quality than those without controls, and studies with multiple pretest and posttest measurements are preferable to those without such repeated measurements. For a more complete review on the subject, see bibliographical reference 36 (page 7, ¶ 3 of the revised manuscript). We have also added, “…5) type of quasi-experimental design…” (page 8, paragraph 2, line 2 from bottom of the revised manuscript).

A “Study design” column and corresponding footnotes have been added to Table 1.

The following text has been added to the Results section to elaborate on the association between study design and results: “They were clustered around the lowest ranking designs of the classification of quasi-experimental studies proposed by Harris et al. [1] (Table 1). All studies lacked a control group and none removed and reintroduced interventions” (Results, page 8, ¶ 5, line 2 of the revised manuscript).

The following text has also been added to the Results section, “To assess for an association between study design and results, studies were stratified according to the hierarchy of quasi-experimental study designs scheme [1]. Five studies were of 1-group pretest-posttest design (A1), four were of this same design but with multiple posttests (A1*), and five performed a double pretest with multiple posttests (A2†). No significant difference in outcomes based on the present small variations in design could be detected, in part due to the small number of studies in each category. For A1 classification, the proportion of studies finding a significant reduction in VRE was 3/5 (60%), for A1* studies, 4/4 or 100%, and for A.2† studies, 2/5 or 40% (see footnote of Table 1)” (page 12, ¶ 3 of the revised manuscript).
2.3. In addition, quasi-experiments are typically poor at ruling out alternative "causes" for what has been found. An important, but discouraging trend in infection control research is to "bundle" interventions. This is nice for patients in the short run since we don't know how best to control outbreaks, but in the long run it makes it much harder to determine what exactly works, which is what the authors have discovered. Therefore, the primary finding of this systematic review should only describe the findings of the 6 studies that implemented vancomycin reduction alone. For completeness, it is important to include and discuss the other papers, but the primary focus must be on the papers that actually had some potential (internal validity) to actually measure an association between exposure (vanco restriction) and outcome (VRE levels) without being confounded by other interventions. The abstract, results and discussion should all focus on the 6 studies identified by the authors that only implemented vancomycin reduction efforts.

We appreciate the input of referee #2 and acknowledge the drawbacks of “bundle” interventions in terms of isolating the impact of a particular intervention. We agree with highlighting the results of the six studies that did implement vancomycin reduction measures without concurrent interventions.

To the Abstract, we have added, “Among the six studies that implemented vancomycin reduction strategies as the sole intervention, two of six (33%) found a significant reduction in VRE colonization and/or infection. In contrast, among studies implementing additional VRE control measures, five of seven (71%) reported a significant reduction” (page 2, ¶3, line 3 from bottom of the revised manuscript).

In the Results section, we perform a separate stratified analysis to look at these studies alone and cite the importance of this particular subgroup. We have expanded on our comments in this section to include the following, “Six studies (46%) implemented vancomycin reduction measures as the sole type of VRE control intervention [2-6]. The remaining seven studies also implemented infection control and/or restriction of additional antimicrobial agents [7-13]. Although it was not statistically significant,
studies that used vancomycin alone revealed a trend towards lower efficacy in reducing VRE colonization and infection (33%) when compared to those that used additional measures (71%). Additionally, both studies (100%) restricting multiple classes of antimicrobial agents reported improvements [12, 13]”(page 11, ¶ 4, line 1 of the revised manuscript).

See also table 3 of the original and revised manuscript, where we have included a comparison of studies implementing vancomycin reduction efforts alone vs. those implementing additional measures to reduce VRE. In our Discussion, we further highlight this subgroup of six studies (page 13, ¶ 3, line 3 from bottom of the revised manuscript).

We believe that discussing in detail the studies that implemented vancomycin reduction measures with other interventions, to control VRE colonization and infection, enhances the utility of the manuscript. Although the primary question of interest is whether vancomycin restriction alone is effective, we were also interested in investigating whether vancomycin reduction may need other measures to facilitate its effectiveness (synergism) or whether the impact of this intervention is less pronounced when coupled with certain other interventions (antagonism). In other words, we wished to examine the impact of vancomycin usage reductions, with or without other interventions.

Including studies that evaluate additional VRE control measures is representative of much of the current literature. In actual clinical practice settings, vancomycin reduction efforts are often implemented along with other interventions as it is often not feasible to implement vancomycin reduction strategies alone. We believe that including this broader spectrum of studies adds to the comprehensiveness and generalizeability of this review.

We have attempted to address the serious limitations of “bundling” interventions, including the impact on causal inference (page 16, ¶ 4 of the revised manuscript), as well as the heterogeneity created in our review by including both groups (page 15, ¶ 2 of the revised manuscript).
2.4. In the discussion when discussing limitations and also when discussing the duration of the studies (where longer duration studies found less benefit), it should be noted that the "background of VRE epidemiology" in the US is one of persistent increase, so that even if quasi-experiments reduced VRE to a "slower" increase in a ward or hospital than would be expected, this would be missed in an uncontrolled quasi-experimental study. This would be more likely to occur in studies of longer duration since larger population effects would have more time to impact the hospital/ward. Thus, because none of the studies where randomized trials there may be a bias against finding a benefit (slower rise of VRE) in the quasi-experimental studies.

We acknowledge the importance of noting the “background of VRE epidemiology.” To the Results section, we have added, “Furthermore, the background VRE epidemiology in the US is one of persistent increase, so studies looking over a longer time period may have greater difficulty in achieving reductions in VRE” (page 13, ¶ 1, line 3 of the revised manuscript).

Additionally, we have added into the Discussion section, “Studies with longer durations of interventions often reported less successful results. As an example, Lautenbach et al. [5] report that after the fourth year of vancomycin reduction efforts, vancomycin usage had increased to baseline, while VRE acquisition continued to increase throughout the study period. Such findings may relate to challenges with sustaining interventions, as well as possible increases in the overall prevalence and incidence of VRE within the United States, whereby a slowing in the rise of the organism may still signify improvement” (page 15, ¶ 3, line 4 of the revised manuscript).

2.5. The conclusion must be changed to focus on the 6 studies that looked at vanco-restriction alone. Should state that only 2 of 6 showed significant reduction in VRE. We agree with highlighting studies that looked at vanco-restriction alone. We have revised our conclusion paragraph to state the following:
“In summary, based on this systematic review of the literature, it was not possible to conclusively determine a potential role for vancomycin usage reductions in controlling VRE colonization and infection in hospitals in the United States, as is recommended by current guidelines [14]. The effectiveness of such interventions and their sustainability remain poorly defined because of heterogeneity in study design and results, as well as insufficient study quality to enable adequate causal inference. In general, studies implementing vancomycin reduction as the sole intervention to control VRE were less successful than those implementing additional VRE control strategies, although numbers were too small to detect a significant difference between groups. Future research using experimental designs of higher quality and implementing vancomycin use reduction as the sole intervention is needed to answer this question” (page 17, ¶ 2 of the revised manuscript).

• Minor Essential Revision

2.1. The authors should confirm that the paper by Fridkin et al (Emerg Infect Dis 2002) actually ruled out alternative interventions. If it did not, then the above 6 studies should be reduced to 5.

Fridkin et al. [4] used vancomycin reduction as the sole intervention; therefore, we have included this study among the six studies implementing vancomycin reduction measures alone.

2.2. In the background section, paragraph 2, sentence 2, I suggest that you add reference to Diaz-Granados, Clin Infect Dis 2005 (Aug 1) 41(3):327-33, since it is an important meta-analysis on the impact of vancomycin resistance.

We thank referee #2 for suggesting reference to the important meta-analysis by DiazGranados et al., comparing mortality associated with VRE vs. VSE infections. We have referenced this article as suggested in our Background section (page 4, ¶ 2, line 2 from bottom of the revised manuscript).
2.3. In background paragraph 3, would change the reported OR of the Carmeli paper to 2.7 and mention 15 studies (not 20). The OR=4.5 in the 20 studies is the over-inflated OR due to the fact that 5 of the studies used a suboptimal control group.

We agree with referee #2, and have now changed the statement regarding the meta-analysis by Carmeli et al. The OR for the 20 patients (4.5) has now been changed to the OR for the 15 studies that used controls who had no VRE isolated (OR=2.7) (page 4, ¶ 4, line 2 from bottom of the revised manuscript).

2.4. In the methods section (Selection criteria), after saying "…experimental in design…” would add in (randomized-controlled trial or quasi-experimental study) in brackets. The suggestion of referee #2 has now been incorporated into the text of the revised manuscript (page 5, ¶ 4, line 2 of the revised manuscript).

2.5. In the Selection criteria last paragraph would change the word "ecological" to "population-level"

We have substituted the word “ecological” for “population level” (page 2, ¶ 1, line 4, page 5, ¶ 2, line 2, page 6, ¶ 2, line 5, and page 13, ¶ 2, line 2 from bottom, all of the revised manuscript).

Additionally, minor changes were made to the wording of the original manuscript when clarity could be enhanced. These changes are also highlighted in blue on the revised manuscript.

Again, thank you for your consideration of our manuscript. We hope that it is now acceptable for publication in your journal. Should you have any questions, please contact me at (415)846-5389, or via email at monique.debruin@stanford.edu

Sincerely,
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