Reviewer's report

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

Version: 1 Date: 2 November 2006

Reviewer: Eli N Perencevich

The authors have completed an important systematic review of the literature regarding the population-level (ward or hospital) impact of vancomycin restriction on the level of vancomycin-resistant enterococcus (VRE). VRE is an increasingly important nosocomial pathogen, which has increased greatly over the past 2 decades. Over-all this project has required a great amount of work and the authors should be commended for their efforts, however, I offer several important suggestions that may improve their analysis and interpretation.

The authors spend a good deal of time talking about statistical validity (i.e. p-values) and little attention to another important factor that should be considered when deciding if an intervention CAUSED a specific outcome, namely internal validity. In this case, the authors need to spend more time focusing on the study designs utilized in the 13 studies and also need to place more weight on the fact that few of the studies ruled out the impact of other interventions. That is, what did the authors do about potential confounding factors. It is not enough to say they were all pre-post studies, because not all pre-post studies are considered the same.

• Major Compulsory Revisions

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 al. (Clin Infect Dis. 2004 Jun 1;38(11):1586-91.) regarding quasi-experimental designs. This article and perhaps another important article should be reviewed and referenced (Harris et al. Clin Infect Dis. 2005 Jul 1;41(1):77-82). A paragraph in the discussion must 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)

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.

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.

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.

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.

• Minor Essential Revision

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

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.

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.

4. In the methods section (Selection criteria), after saying "...experimental in design..." would add in (randomized-controlled trial or quasi-experimental study) in brackets.

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

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

I declare that I have no competing interests