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Title	Vancomycin resistant enterococcus-positive blood culture rates in Ontario: a quasi-experimental study
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Reviewer 1	Dr. Todd Lee MD
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General comments (author response in bold)	Thank you for the chance to review this manuscript. To be transparent, I have been waiting for papers to start being published based on this quasi-experiment which has befallen Ontario. I believe screening and isolation for VRE is a very important issue with national and international implications. I am not a zealot or believer. I just want good information to inform practice – if VRE precautions don't work, I'll be glad when they are gone. If they do work, then the Ontario experiment must come to an end! I am really impressed with what you have done. I think this could be a VERY important paper. I've tried to make some helpful observations/suggestions: 1. Overall, I wonder if some of the "intervention" hospitals have been grouped incorrectly. For example, in your 26 quarter study, do the 3 hospitals who changed in quarter 26 really belong to the "intervention group"? Or should they be included in the control since really that's where they belonged for most of the time you have studied? What about quarter 25? I'm not sure enough "after time" has passed for a meaningful time series interpretation in both cases. But for the 9 sites who changed in 2012 – enough time probably has passed. You could include the sites who changed in 25 and 26 in the control group up until 25/26. **We appreciate this thoughtful comment and we agree on retrospect, it's unclear which cohort they best belonged to. However, we defined the ceased screening group (any hospital that ceased screening at some point within the study period) a priori, when the protocol was developed. We are therefore reluctant to change the definition post-hoc.** However, we believe the following will help address this concern: i. The three hospitals that changed in quarter 25 and 26 were not acute teaching hospitals, thus they were excluded from the sensitivity analysis that was restricted to acute teaching hospitals. We have also made this clearer by adding the following sentence to the results (line 9, page 9): "In total, 13 of the 63 hospitals discontinued vancomycin resistant enterococcus screening and isolation at some point during the study period; 9 acute teaching hospitals stopped in June 2012 (reporting quarter 15), 1 large community hospital in February 2015 (reporting quarter 25) and 3 (2 large community and 1 small community hospital) in April 2015 (reporting quarter 26). Fifty hospitals continued to screen and isolate patients colonized or infected with vancomycin resistant enterococcus and included the following hospital types: 10 acute teaching, 35 large community and 5 small community." **The results from the sensitivity analysis restricting the analyses to acute teaching hospitals can be found in Table 2 and Figure 3.** ii. These hospitals will not have contributed data post discontinuation in the lagged (3 month and 6 month) sensitivity analyses (Table 2). **Thus in summary, we have left these hospitals in the ceased-screening hospital group, but the sensitivity analysis allows for assessment without their data.** 2. I am therefore most interested in you comparing the 9 sites who changed in 2012 with the best possible matching hospitals (size, acuity, university/teaching vs. community) who did not. I wonder if that is the cleanest comparison which could be made. I worry a bit that by combining all of the smaller hospitals and comparing them to centres like the UHN if there isn't a little bit of an apples/oranges problem. Now, maybe because most of these 9 sites are the big teaching hospitals you will have some problem finding the "apples" – that can be acknowledged in the limitations if you feel it is important to do so. But the "cleanest comparison" might be the people who stopped vs. as many matched by size/teaching status hospitals as you can find as an analysis which either replaces as the primary analysis or complements as a secondary analysis to what you have already presented. **We agree that the ideal approach would have been matching, and indeed this was our first approach. Unfortunately, we were unable to find matches for many of the centers. We instead chose to adjust for hospital type, and include a comparison group.** **As the Reviewer may know, the 9 hospitals that discontinued screening in 2012 were all acute teaching hospitals. In this revised version, we have made this fact clearer (as described in the response to Reviewer #1 comment #1) and we have included a sensitivity analysis that restricted the analyses to only acute teaching hospitals in both the ceased screening cohort (n=9 hospitals) and screening cohort (n=10 hospitals). The results can be found in Table 2 and Figure 3; the results were essentially unchanged from the main analysis.** 3. Put another way, I worry a bit that your "control" rates are diluted by the small Ontario hospitals who have had 1 VRE bacteremia and who are very very different than UHN, Ottawa, St. Joseph's, London and Kingston General. **We agree with the Reviewer and have made the types of hospitals included in the ceased screening cohort and screening cohort more transparent (as described in the response to Reviewer #1 comment #1). In addition, we have included a sensitivity analysis that only includes data from the acute teaching hospitals, as described in the response to Reviewer #1 comment #1 and #2.** 4. Show me the likes of Mount Sinai, Sunnybrook, St. Michael's (and maybe Trillium) vs. these centres and I think you are on to something. Try to be sure you attribute, for example, UHN bacteremia who shows up at Sinai ICU (like all princess Margaret patients do) and you'll get a result which not only convinces me (as you pretty much have with your existing paper) but also, importantly, convinces all the people who will methodologically pick apart your paper and explain all the reasons why they should not change back to control programs. As described in the response to Reviewer #1, comments #1, 2 and 3, we have now included a sensitivity analysis that restricts the analyses in the ceased screening and screening cohorts to only acute teaching hospitals; the results were essentially unchanged from the main analysis, enhancing our confidence in these results. **We agree that understanding transfer patterns between hospitals would enhance our ability to better understand antibiotic resistant organism transmission patterns, but we were unable to obtain these data from the public reporting dataset. However, the facility attribution for the vancomycin resistant enterococcus bacteremia is reportable and we have now included a sensitivity analysis restricting the analyses in the ceased screening cohort and the screening cohort to vancomycin resistant enterococcus blood cultures attributable to the reporting facility, in an effort to mitigate this potential misclassification bias. The results were essentially unchanged from the main analysis, and the results can be found in Table 2.** **However, the attribution is only for the bacteremia itself, and not necessarily for the acquisition of vancomycin resistant enterococcus. Thus patients may have acquired their vancomycin resistant enterococcus in a ceased screening hospital, but developed their bacteremia in a screening hospital. This misclassification is a limitation of our study and has now been explicitly outlined in the Discussion as follows (line 21, page 12):** **"Last, misclassification bias may have occurred as we did not have knowledge of patient's prior hospitalizations; thus a patient could have acquired vancomycin resistant enterococcus in a ceased screening hospital, but developed the positive blood culture in a screening hospital and vice versa. We included a sensitivity analysis, which restricted the analyses to only positive blood cultures attributable to the reporting facility to mitigate this potential bias as these cases were more likely to have been acquired locally. However, the attribution is only for the bacteremia**

itself, and not necessarily for the acquisition of vancomycin resistant enterococcus and the possibility of misclassification remains."

5. Page 5 line 41 – Where would a reader find this data (citation) so we could judge its completeness or accuracy?
The data from the Institute for Quality Management in Healthcare (IQMH) are not publically reportable. However, should the Editor have concerns regarding these data, we would be happy to connect you with the co-author and our IQMH collaborator, Elaine Kerr to view the data if needed.

6. Line 56 – I assume you mean that you grouped them based on the CIHI criteria cited but this could be more clear.
The Reviewer is correct, the hospital sites were grouped as specified by both the Ontario Hospital Association and Canadian Institutes for Health Information definitions. We have more clearly stated this in the revised manuscript as follows (line 6, page 5):
"Hospitals were classified as acute teaching, large community, small community and complex continuing care and rehabilitation hospitals using Ontario Hospital Association and Canadian Institutes for Health Information definitions [32-33]."

7. Page 8 line 8 – is this overall bacteremias? What about VRE bacteremia attributable to another institution? For example, the Mount Sinai Hospital isolates patients. UHN does not. They are 200 meters apart and patients from UHN are frequently admitted to Sinai. If Sinai VRE bacteremia rates go up (control group) due to VREs from UHN (intervention group) there is misclassification introduced. This data seems to exist (Page 6 line 30). Was this analysis done? If not, why not?
Please see response to Reviewer #1 Question #4.

8. Line 48 – Were not the majority of those who stopped academic teaching hospitals (UHN, London, Ottawa, McMaster)? How will this influence your results?
Indeed, the majority who stopped screening were acute teaching hospitals. Please see responses to Reviewer #1 comments #1, 2 and 3.

9. Page 9 line 3 – I concur that a lagged model makes the most sense since there would be a delay between giving up on VRE control and the adverse effects (bacteremia increase). I don't believe contact precautions do anything to prevent a patient with VRE from getting bacteremia; rather, when you give up on VRE control, VRE colonization rates go up, and statistically VRE bacteremias follow. It is an issue of colonization pressure whereby the greater the colonization, the greater the transmission and the bacteremias and infections follow. A self-fulfilling prophecy.
We completely agree with the Reviewer and this was our rationale for presenting the 3 month and 6 month lagged effects. We have more clearly explained our rationale in the Methods section as follows (line 1, page 8):
"Last, the main analyses and two sensitivity analyses were examined for lagged intervention effects; follow-up time 3 and 6 months post-intervention were excluded. We hypothesized that the 3 and 6 month post intervention exclusion should magnify any differences seen in the ceased-screening cohort analysis, as the impact of discontinuing screening and isolation practice, if present, would become more apparent over time (e.g. as colonization spread) but should have no effect in the screening cohort analysis."

10. Page 9 line 30 – Wow. I can't believe 25% were not correctly reported (and that 63% of that was rectal swab reported as bacteremia).
We agree. Please see our response to the Editor's comment #8.

11. Line 46 – Even if 80% were attributable to source facility, that leaves up to 1 in 5 attributable elsewhere or unknown (and potentially crossing from intervention to control and vice-versa). Table 1 is helpful but I wonder if you know whether or not you have details on attributable elsewhere which could correspond to intervention vs. control sites (and reassign them for the analysis).
Unfortunately we do not have information on source facility. We have now performed the sensitivity analysis restricting the analyses to the attributable facility, but as mentioned in our response to Reviewer #1 comment #4, potential misclassification remains a limitation of our study.

12. Page 10 Line 46 – Herein we see a bit of the problem. The ceased screening hospitals are quite different from the continued screening hospitals even at baseline when they were performing control. I suspect this is because most are some of the largest tertiary care university hospitals in the province. There will be confounding by the type of patients they see and are referred. Using each as an internal control as you have done is good, but I'm not sure this totally eliminates the problem (limitation).
To help mitigate this concern, we have performed the sensitivity analysis restricting analyses in the ceased screening (n=9 hospitals) and screening cohort (n=10 hospitals) to acute teaching hospitals only, as described in responses to Reviewer #1 comments #1, 2 and 3.

13. Page 11 Line 39 – I think this paragraph could be rewritten to make it more clear what you are saying. I needed to read it a few times to understand what you were trying to say. If I may paraphrase: "In Ontario hospitals, overall rates of VRE-positive blood cultures have almost doubled since 2009. This increase has occurred in hospitals which have maintained VRE screening and those who have ceased; however, the increases seen in hospitals which have ceased screening are substantially greater in both rate of increase and in overall numbers." Or something like that.
Thank you for the suggestion. We have changed the first paragraph of the Discussion to read as follows (line 1, page 11):
"In Ontario hospitals, overall rates of vancomycin resistant enterococcus-positive blood cultures have almost doubled since 2009. In hospitals that ceased screening and isolation programs, there was a significant increase in the rate of rise of vancomycin resistant enterococcus-positive blood cultures and this was not seen in hospitals that continued to screen and isolate."

14. I would also highlight the strength of your study in comparison to the observational and interventional pieces you cite. You have years of data, an objective outcome (bacteremia), and a very large number of patient days. Maybe the largest ever published. And you have the perfect quasi-experimental design due to the natural experiment of some hospitals just unilaterally deciding to stop and good data for years before that to establish a baseline. Don't sell yourselves short.
Thank you. We have added the following sentence to the Discussion (line 6, page 12),
"Our study has many strengths including comprehensive data collection from multiple hospitals over a 6-year time period encompassing approximately 38,000,000 patient days, a quasi-experimental study design using an interrupted time series Poisson regression model with an objective outcome."

15. I would also spend more time discussing the RCTs than the observational pieces. What did they show for VRE? What did they compare? Were they adequately powered? (Looking at the NEJM trial, they powered to show difference in colonization rates of 40%! So they didn't show that. That doesn't mean they couldn't show 20% if they had a larger sample size or a more accurate initial estimate of colonization (they were 64% higher than anticipated).
We have considerably shortened the sections discussing the observational studies and added to the discussion of randomized controlled trials and changed the Discussion from:
"There have also been two cluster randomized controlled trials investigating the efficacy of screening and isolating patients for antimicrobial resistant organisms in the intensive care unit setting [22, 23]. Results of these trials question the use of contact precautions for the prevention of antibiotic resistant organism transmission in the intensive care unit setting; however whether these results are generalizable outside the

	intensive care unit setting [22, 23] is unknown." **To the following in the revised manuscript (line 21, page 11):** **"There have been two cluster randomized controlled trials investigating the efficacy of screening and isolating patients for antimicrobial resistant organisms in the intensive care unit setting [22, 23] and the results of these trials question the use of contact precautions for the prevention of antibiotic resistant organism transmission; however, neither trial reported on the results of vancomycin resistant enterococcus bacteremia, and neither were powered to detect this difference [22, 23]. Thus, no randomized controlled trial data are available which definitively answers whether discontinuing screening and isolation for vancomycin resistant enterococcus is associated with increased rates of vancomycin resistant enterococcus bacteremia."** 16. The single centre 125 bed observational study which "showed no difference" is not even in the same ballpark. That study was, frankly, underpowered to say anything meaningful re: VRE bacteremia unless it showed a difference. P>0.05 does not mean anything for rare events like bacteremia (you only had ~400 in the entire province of Ontario (Pop >10 million) for 6 years). **We agree. We have limited the discussion of the observational studies in the revised manuscript.** 17. I would suggest you spend some time revisiting the messaging of this section. **Thank you for the opportunity. Please see responses to Reviewer #1 comments #15 and #16** 18. I would actually say that a lagged analysis makes more sense to begin with. Just because tomorrow I stop screening and isolating in my hospital doesn't mean tomorrow VRE rates will go up. There will be some delay until the critical mass of VRE increases to the point that my VRE rates go up. I would expect a several month delay for this to occur. **We agree. Please see response to Reviewer #1 comment #9.** 19. Page 14 line 15 – You may wish to comment on the emergence of Daptomycin and Linezolid resistant VRE in the era of effective VRE-bacteremia therapy may be short lived. **We agree with the reviewer. We have added the following sentence to the Discussion (line 17, page 13):** **"Furthermore, the emergence of daptomycin and linezolid resistance is also of concern [37, 38]."** 20. Line 41-46. Ends with a bit of a whimper? This can probably be stronger, something like: "In summary, rates of VRE-positive blood cultures are increasing in all Ontario hospitals; however, this increase has been greatest amongst the hospitals who have ceased VRE control programs. Hospitals who aim to minimize the rising rate of VRE-positive blood cultures should consider maintaining an active screening and isolation program" **We have revised the final sentence of the Discussion to read as follows (line 3, page 14):** **"In summary, rates of vancomycin resistant enterococcus-positive blood cultures are increasing in Ontario. Hospitals aiming to minimize the rising rate of vancomycin resistant enterococcus-positive blood cultures should consider maintaining an active screening and isolation program."** 21. Figure 1: Can you put a vertical line at the time when the natural experiment began in most sites? **This has been added to Figure 1.** 22. Figure 2: The line of best fit certainly looks better for the control group than the intervention. There is a lot of variation in the intervention group both before and after the natural experiment. I wonder, looking at the data, if a lagged model isn't a better fit overall. **We agree there is an argument for performing a lagged model. However, to be the most transparent we a priori decided to perform the main analysis using all the data, and perform the 3 and 6 month lag as a sensitivity analysis. The results can be found in Table 2. Indeed, the results became amplified in the ceased screening cohort as the lagged effects were incorporated, however no significant was observed in the screening cohort.** 23. You have 9 changing in quarter 15 and then to the right another 1 in quarter 15 and 3 in quarter 26. Do you mean 25 and 26? I think you do because that is what is shown and written in the legend, but not what it says in the figure. **Thank you for noting this. This error in Figure 2 has been fixed in the revised manuscript.** 24. I'm not sure that these 3 sites who changed in the last quarter of data you have really should be counted amongst those in the "intervention" group. They really didn't contribute enough "after time", did they? In fact, if the lag hypothesis is correct, they contributed zero after time. To me, it would make more sense to keep them in the "control" group for the first 25 periods and exclude period 26 because there was inadequate follow up. If the 1 hospital called period 15 really was period 25, you may need to exclude that too (but still count its control time). **Please see response to Reviewer #1 comment #1.**
Reviewer 2	Dr. Esther van Kleef PhD
Institution	Mahidol Oxford Tropical Medicine Research Unit, Department of Mathematical Modelling and Economics, Mahidol University, Bangkok, Thailand
General comments (author response in bold)	This study uses routinely collected VRE data from Canada to assess the impact of the discontinuation of screening and isolation practices since 2012 in a fraction of hospitals in Ontario taking an interrupted time series approach. The study provides a detailed description of the data used and it should be applauded that the authors provide an example of how to make use of routinely collected data. Nevertheless, I have some questions regarding the methods used and the inferences made outlined below. 1. From baseline onwards (reporting quartier 1), the group that ceased screening around 2012 appears to have been different from the non-ceased group, i.e. the baseline of the ceased group was much higher, whereas it was low and remained almost stable for the non-ceased group. This does make me wonder whether the impact of screening and isolation on VRE incidence rates is mediated by a (potentially unmeasured) factor. Could it be that the hospitals that ceased screening and isolation had a shared common factor (e.g. poorer hand hygiene adherence, no deep cleaning, rural vs urban hospital, case-mix), which could explain the difference in baseline reporting rates and whether/why screening and isolation might indeed provide added value to existing practice in these circumstances? **We believe the main difference between the ceased screening cohort and the screening cohort were differences in hospital types; the ceased screening cohort was comprised of mainly acute teaching hospital and the screening cohort was comprised of mainly large community hospitals. In this revised manuscript, we have more transparently described the hospital types, and included a sensitivity analysis restricting the analyses to acute teaching hospitals only in the ceased screening cohort (n=9 hospitals) and screening cohort (n=10 hospitals) . The results are presented in Table 2 and Figure 3. Please see response to Reviewer #1 comment #1 for more detail.** 2. The authors point out that they do not have data on potential confounders. More general hospital characteristics as listed above could be collected I expect. Have the authors considered these? Trying to further understand what other differences might exist between the ceased and non-ceased group could potentially help generate hypothesis on why contradictions are found in existing literature on the effect of screening and isolation for VRE. **Please see response to the Editor's comment #1.**

3. For reasons listed above, I don't necessarily agree that the change in potential confounders might apply for the non-ceased group as well as listed in the discussion. I think these groups are likely to be very different and non-comparable as a whole.
We agree with you and have qualified our comment in, our Discussion from:
"However, we included a comparison cohort and would have expected changes in these potential confounders to apply to this group as well."
And it now reads as follows (line 11, page 12):
"We included a comparison cohort and would have expected changes in these potential confounders to apply to this group as well, particularly when comparing acute teaching hospitals."

4. I am not entirely convinced by the fitted trends per segmented time period. In the non-ceased group, the rate of reported cases appears to be quite stochastic whilst fluctuating a lot. Pre- and post-intervention, some quartiers reach similar levels (e.g. quartier 9 and 17-21 (it seems that the fitted increases are also barely significant, see next point for further follow up). I think it would be good to show the individual reporting rates over time of each of the hospitals in the non-ceased group (e.g. as supplementary material), to see to what extend these claimed continuous de- and increase are seen among the individual hospitals as well.
We have appended the results at the end of this cover letter, however, we do not believe it offers additional meaningful information due to the small numbers from each hospital. If the Editors feel strongly, we can include this as supplemental information. Please note, that the manuscript published by Lemieux et al (Reference #31 of our manuscript), the trend lines for the 4 hospital corporations (n=9 hospitals) are presented, thus the data are now available, if transparency is the primary concern.

5. As a follow up to the above, the use of a Poisson model for count data is appropriate, at least as a starting point, but when autocorrelated count data are aggregated (as is the case here) the result is overdispersion. I would be surprised if there was no overdispersion, as this is the norm rather than the exception with biological count data. Overdispersion can be accounted for with a quasipoisson or negative binomial distribution (and failure to account of overdispersion can lead to underestimation of SEs and hence overestimation of statistical significance). Was this considered?
We agree with the Reviewer and we were concerned about the possibility of overdispersion in our model. When exploring model fit, we first used a negative binomial distribution; however the model fit was better using Poisson regression. In addition, we used the generalized estimating equation to help account for overdispersion.

6. Also, considering the reported percentage in- and decreases in table 2 and after visually expected figure 2, I think the authors have fitted a quadratic time trend. Could the authors please clarify, and justify their choice?
Thank you for the opportunity to clarify. All presented models were Poisson models with linear time trends and used the log link. Thus, the reason for apparent curvilinear trend is because we plotted the results on a linear scale rather a log scale for ease of interpretation.

7. The ceased-screening group was defined by two factors, i.e. stop of screening and/or stop of isolation. How comparable are hospitals that stopped screening only, to those that stopped isolation only to those that stopped both? Have the authors looking at these separate groups and did they find any differences?
All hospitals stopped screening and isolating, and none stopped screening only and none stopped isolation only. This can be found in our Results section on line 9, page 9:
"In total, 13 of the 63 hospitals discontinued vancomycin resistant enterococcus screening and isolation at some point during the study period."

8. The authors report that a vast majority of the VRE bacteremias was reported by acute teaching hospitals. The percentage reported does not provide insight in how hospital types compare when accounting for the difference in size (table 1). The rate of cases per e.g. 100 000 bed days per hospital type would provide an interesting and more meaningful statistic, in particular as this is also the outcome of the statistical analysis. Could the authors add these to table 1?
Thank you. The rate of cases 100,000 per hospital type in the table

9. Also, how was the number of patient days established? Was this a rough estimate based on the total number of hospital beds of all included 63 Ontarian hospitals multiplied by the study period included? Please clarify, as this would provide transparency of the accuracy of the number of bed days (often bed occupancy is not 100%).
The data were not rough estimates but quarterly patient safety data provided to us from the Ministry of Health and Long-term Care. The Ministry of Health and Long-term Care calculates patient days from the daily bed census. This information is sent by the hospitals on a quarterly basis to the Ministry of Health and Long Term Care as part of the requirements to report patient safety indicators. We have now added this detail to the Methods section as follows (line 13, page 6):
"Patient days were provided by the Ministry of Health and Long-term Care."