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Research

Rates of blood cultures positive for vancomycin-resistant *Enterococcus* in Ontario: a quasi-experimental study

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Abstract

Background: Some Ontario hospitals have discontinued active screening and isolation programs for vancomycin-resistant *Enterococcus* (VRE). The aim of this study was to determine whether this practice change is associated with a change in the rate of rise of VRE-positive blood cultures.

Methods: All Ontario hospitals are mandated to report VRE bacteremia. Using this publicly reported data set, we included all validated results between January 2009 and June 2015. Beginning in June 2012, some hospitals discontinued active VRE screening and isolation programs (intervention). We used an interrupted time series Poisson regression to assess the slope change in the incidence rate of VRE-positive blood cultures (primary outcome) after versus before the intervention. Hospitals that continued to screen were the comparison group. Incidence rates were adjusted for hospital type and clustering within hospital site; slope changes are presented as incidence rate ratios (IRRs) with 95% confidence intervals (CIs).

Results: In hospitals that had ceased screening (n = 13), there was an increase in slope after screening and isolation were discontinued compared with before screening and isolation were discontinued (slope change IRR 1.25 [95% CI 1.01–1.54]). In hospitals that continued screening (n = 50), the slope was not significantly different after June 2012 compared with before June 2012 (slope change IRR 0.81 [95% CI 0.56–1.15]).

Interpretation: There was a significant increase in the rate of rise of VRE-positive blood cultures in hospitals that discontinued active VRE screening and isolation programs but not in hospitals that continued to screen and isolate. Hospitals aiming to minimize rising rates should consider maintaining active screening and isolation programs.

Vancomycin-resistant *Enterococcus* (VRE) is an important nosocomial pathogen.[1] Since its emergence in the 1980s,[2,3] rates of colonization and infection with this microorganism have risen dramatically in hospitals worldwide.[4–8] Patients with bacteremia due to VRE are thought to have worse outcomes than patients with vancomycin-susceptible enterococcal bacteremia, including increased mortality and length of hospital stay.[9] Preventing nosocomial VRE infections is therefore a patient safety priority in many jurisdictions.[10–13]

In an effort to minimize the spread of antimicrobial resistance within hospitals, it is widely recommended to emphasize hand hygiene, environmental cleaning and antimicrobial stewardship (including control of vancomycin use).[14–18] Additional infection control interventions such as an active screening program for patients at increased risk for colonization with VRE and placing patients colonized or infected with the organism on contact precautions have generated controversy owing to the lack of robust evidence.[19,20] Active screening programs increase the identification of patients colonized with

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VRE and reduce the time before contact precautions are implemented.[21] However, the efficacy of contact precautions to prevent the spread of antimicrobial-resistant organisms including VRE has been questioned in 2 randomized controlled trials,[22,23] and studies investigating the impact of discontinuation of VRE screening and isolation practices have given conflicting results.[24–27]

Infection control practices for VRE in Canadian institutions are increasingly heterogeneous, and there is no clear consensus on the best approach.[28–30] In Ontario, before June 2012, all inpatient hospitals maintained active VRE screening and isolation programs;[14] in June 2012, some hospitals discontinued this practice, citing concern over the effectiveness of the programs and potential adverse effects of isolating patients.[31] The objective of this study was to examine the rates of VRE-positive blood cultures in Ontario between January 2009 and June 2015, and to determine whether discontinuation of active screening and isolation programs for this organism was associated with a change in the rate of rise of VRE-positive blood cultures.

Methods

Setting

All 219 inpatient hospitals in Ontario publicly report their cases of VRE-positive blood cultures. Hospital facilities that reported at least 1 such validated case between Jan. 1, 2009 and June 30, 2015 were included for analysis as the final sample in our study. We classified hospitals as acute teaching, large community, small community, and complex continuing care and rehabilitation hospitals using Canadian Institute for Health Information[32] definitions.

Definition of VRE bacteremia

We used the Ontario Ministry of Health and Long-Term Care's case definition for bacteremia due to VRE.[33] Briefly, a case is defined as a patient identified with a laboratory-confirmed bloodstream infection with VRE. A bloodstream infection is a single blood culture positive for strains of *E. faecium* or *E. faecalis* that have a minimum inhibitory concentration to vancomycin of 32 μg/mL or greater.

Data sources

Since January 2009, Ontario hospitals have been mandated to report cases of VRE bacteremia to the Ontario Ministry of Health and Long-Term Care via the Self-Reporting Initiative. Cases are reported publicly on the Health Quality Ontario website.[10] We used these Health Quality Ontario data as the data source for this study. To minimize any potential false-positive cases in the data set, we validated the data by contacting infection control practitioners at each hospital site after each reporting quarter to confirm whether the reported cases met the case definition. To quantify the accuracy of the validated case count, we compared the hospital-verified count of cases of VRE-positive blood cultures with the number of VRE-positive blood cultures reported by hospital laboratories on quarterly surveys issued by the Institute for Quality Management in Healthcare, during the same study period.

Hospital VRE screening and isolation practices

To identify whether an Ontario hospital ceased or continued VRE screening and isolation practices, we conducted a short survey in 2013, 2014 and 2015. The survey was sent to the infection control practitioners at each hospital site across the province (Appendix 1, www.cmajopen.ca/content/5/2/E273/suppl/DC1). Follow-up reminder emails were sent to nonresponders at 3-week intervals. We contacted any remaining nonresponding sites by telephone until we achieved a 100% response rate.[28]

Statistical analysis

The study period consisted of 26 time-variable reporting quarters between Jan. 1, 2009 and June 30, 2015. The primary outcome was the slope change in the incidence rate of VRE-positive blood cultures before versus after the intervention. All data were reported as the number of VRE-positive blood cultures divided by patient-days per quarter. Patient-days were provided by the Ontario Ministry of Health and Long-Term Care.

First, we used a slope term within a time series Poisson regression to assess the annual change in the incidence rate of VRE-positive blood cultures during the study period, as an incidence rate ratio (IRR). As such, a slope of 1.1 would represent a 10% multiplicative growth in the incidence rate per year, and a slope of 0.9 would represent a 10% reduction in incidence per year. Next, we stratified the cohort into 2 groups: a ceased-screening cohort, defined as hospitals that discontinued VRE screening and isolation practices at some point within the study period, and a screening cohort (used as a comparison group), which included hospitals that continued to screen and isolate patients throughout the study period. For the ceased-screening cohort, we defined the intervention date as the calendar quarter in which the hospital stopped screening and isolating for VRE. For the screening cohort, the intervention date was defined as beginning after June 2012 (quarter 15). We used an interrupted time series Poisson regression stratified by VRE control strategy (i.e., ceased or continued screening) to determine whether the slope of VRE-positive blood culture incidence rates was different after versus before the change in screening practice (slope change). For both cohorts, we examined the slope change by fitting an interaction between the intervention and time in the Poisson model (level and slope change model[34]). As with the slope, the slope change was reported as an IRR. The number of cases was used as the outcome, and the log of the number of patient-days was used as the offset. We adjusted the model for hospital type (acute teaching v. community), and we accounted for clustering within hospital site using a generalized estimating equation with the independence covariance structure. The unadjusted and adjusted slope change annual IRRs are presented alongside their associated 95% confidence intervals (CIs). We checked for the

presence of residual autocorrelation within hospitals using a plot of the autocorrelation function.

We performed 3 additional sensitivity analyses. The first restricted the interrupted time series Poisson regression in the ceased-screening and screening cohorts to acute teaching hospitals, to better compare hospitals with similar patient acuity and case-mix. We defined acute teaching hospitals as acute and pediatric hospitals that provide highly complex patient care, are affiliated with a medical or health sciences school and have substantial research activity and postgraduate training.[32] Second, to help maximize confidence in our analyses, we restricted the analyses to cases attributable to the reporting facility, given that these cases were more likely to have been acquired locally (when reporting a case of VRE-positive blood culture, hospital facilities are required to indicate whether the case is attributable to the reporting facility itself [i.e., symptom onset arising > 72 hr after admission to the facility] or to another health care facility[33]). Last, we examined the main analyses and 2 sensitivity analyses for lagged intervention effects; follow-up times of 3 and 6 months following the intervention were excluded. We hypothesized that this exclusion should magnify any differences seen in the ceased-screening cohort analysis, as the impact of discontinuing screening and isolation practices, if present, would become more apparent over time (e.g., as colonization spread) but should have no effect in the screening cohort analysis.

For all analyses, a 2-tailed p value of < 0.05 was deemed as significant. We used SAS version 9.3 (SAS Institute) and R version 3.3.1 to analyze the data.

Ethics approval

The study received Research Ethics Board approval at Public Health Ontario before its commencement.

Results

In total, 525 VRE-positive blood cultures were reported publicly by hospitals during the study period (Figure 1). Contact with the hospitals showed that 130 cases (24.8%) had been erroneously reported, resulting in 395 VRE-positive blood cultures as our final study sample. Reasons for erroneous reporting included reporting of a VRE-positive screening rectal swab rather than blood culture (82 cases) and missing records or data entry error (28); in 20 cases the reason was unknown. The final study sample was comparable to the number of cases reported to the Institute for Quality Management in Healthcare during the same period (n = 362).

Most VRE-positive blood cultures occurred in acute teaching hospitals (288 [72.9%]), and over three-quarters (309 [78.0%]) were attributable to the reporting facility About half of the cases (195 [49.4%]) occurred in the ceased-screening cohort.

Hospital screening and isolation practices

The 395 VRE-positive blood cultures were reported by 63/219 (28.8%) hospitals. All 63 hospitals responded to the VRE survey each year. Thirteen of the 63 hospitals discontinued VRE 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

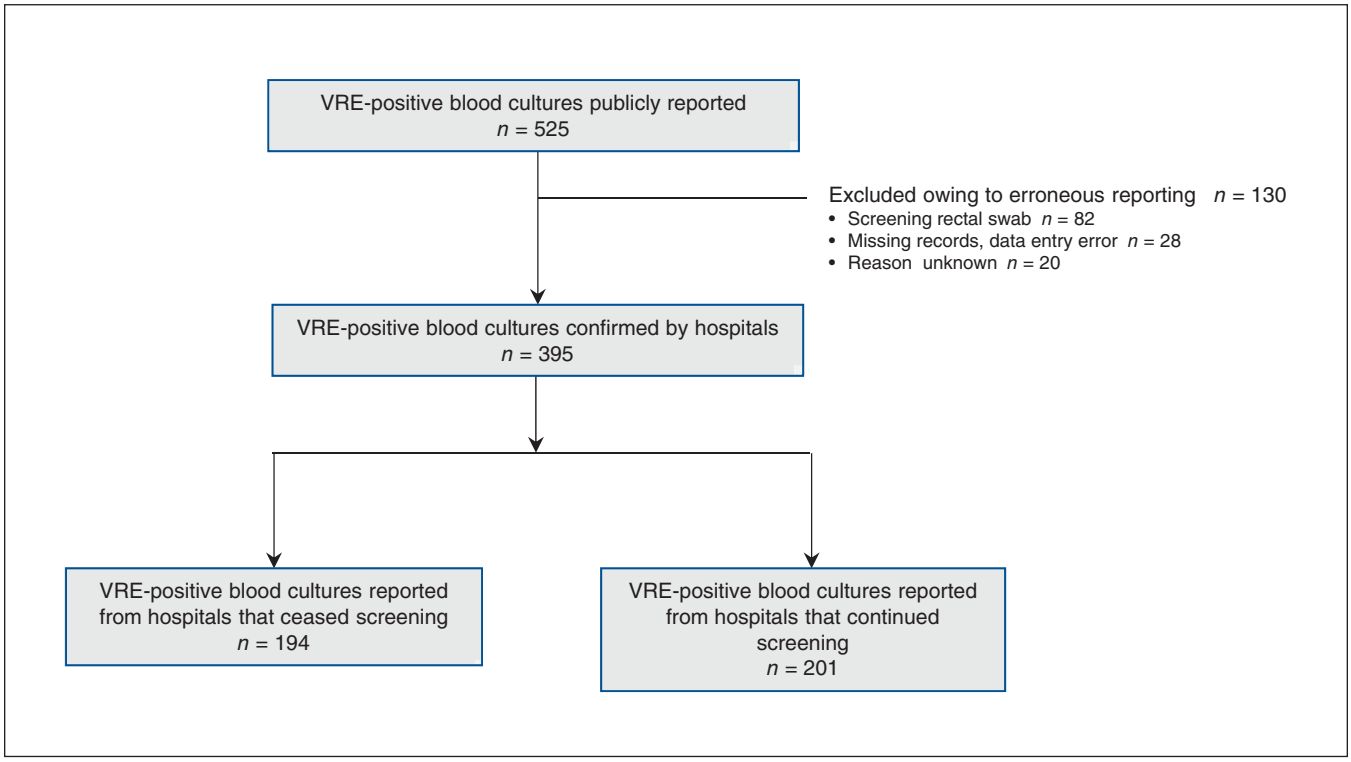

Figure 1: Flow diagram of blood cultures positive for vancomycin-resistant *Enterococcus* (VRE) occurring between January 2009 and June 2015 in Ontario.

Table 1: Incidence rate of VRE-positive blood cultures per 100 000 patient-days in Ontario between January 2009 and June 2015, overall and by whether VRE screening and isolation practices were ceased or continued

Variable	Incidence rate per 100 000 patient-days		
	Total *n* = 395	Screening ceased *n* = 194	Screening continued *n* = 201
Hospital type			
Acute teaching	1.74	2.50	1.11
Large community	0.47	0.41	0.48
Small community	1.81	0.88	2.13
Case attribution			
Reporting facility	0.81	1.70	0.54
Other facility	0.07	0.07	0.06
Unknown	0.16	0.36	0.09
Year			
2009	0.94	2.54	0.43
2010	0.55	1.38	0.30
2011	0.82	1.67	0.56
2012	1.13	1.75	0.94
2013	1.21	2.74	0.74
2014	1.36	2.48	1.00
2015	1.37	2.60	0.97

Note: VRE = vancomycin-resistant *Enterococcus*.

2015 (reporting quarter 25), and 3 (2 large community hospitals and 1 small community hospital) in April 2015 (reporting quarter 26). The 50 remaining hospitals (10 acute teaching, 35 large community and 5 small community) continued to screen and isolate patients colonized or infected with VRE.

Rates of VRE-positive blood culture

When all blood cultures in the data set validated to be VRE-positive were included (*n* = 395 cases), the overall rate during the study period was 1.04 per 100 000 patient-days. The overall incidence rates of VRE-positive blood cultures per 100 000 patient-days, overall and by cessation/continuation of VRE screening and isolation, are shown in Table 1. The rate increased from 0.93 per 100 000 patient-days in the first reporting quarter to 1.48 per 100 000 patient-days in the last reporting quarter. The slope was statistically significant, with rates increasing by 12.5% per year (95% CI 6.1–18.3) ($p < 0.001$) (Figure 2).

Interrupted time series Poisson regression analysis

In the ceased-screening cohort, in unadjusted analysis, there was a change in the slope after screening and isolation practices were discontinued compared to before the practices were discontinued (slope change IRR 1.37 [95%CI 1.04–1.80]) (p = 0.03); adjusted analysis was similar (slope change IRR 1.25 (95% CI 1.01–1.54]) (p = 0.04) (Table 2, Figure 3). In the screening group, in unadjusted analysis comparing rates after versus before June 2012, the slope change was not significantly different (IRR 0.80 [95% CI 0.59–1.09]) (p = 0.16). In adjusted analysis, the results were essentially the same (slope change IRR 0.81 [95% CI 0.56–1.15]) (p = 0.24) (Table 2, Figure 3). The

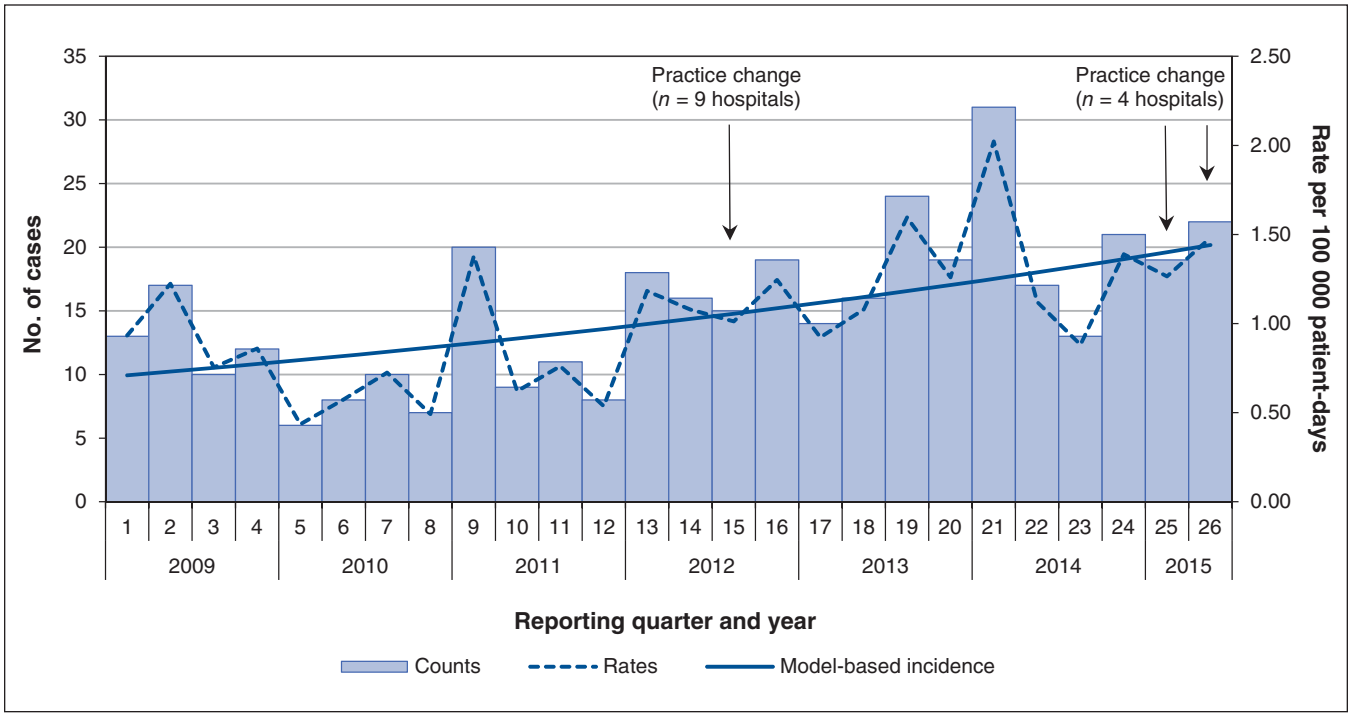

Figure 2: Numbers of cases and rates per 100 000 patient-days of blood cultures positive for vancomycin-resistant *Enterococcus*, January 2009–June 2015.

results of the sensitivity analyses restricting the analyses to acute teaching hospitals (9 in the ceased-screening cohort and 10 in the screening cohort) were essentially identical to the main analysis (Table 2, Figure 4), as were the results when the analyses were restricted to cases attributable to the reporting facility (Table 2). When lagged effects were incorporated into the model, the results were magnified for the ceased-screening cohort but remained unchanged for the screening cohort (Table 2). For both the screening and ceased-screening models, residual autocorrelation within each facility was low ($\rho < 0.2$).

Interpretation

In Ontario hospitals, overall rates of VRE-positive blood cultures almost doubled between January 2009 and June 2015. In hospitals that ceased screening and isolation programs, there was a significant increase in the rate of rise of VRE-positive blood cultures, and this was not seen in hospitals that continued to screen and isolate.

Our finding that discontinuation of active VRE screening and isolation of patients with VRE colonization or infection

Table 2: Annual change in the incidence rate (slope*) of VRE-positive blood cultures before, after and slope change† after versus before discontinuation of VRE screening and isolation (in ceased-screening cohort) and June 2012 (in screening cohort) in unadjusted and adjusted analysis and sensitivity analyses restricting analyses to 1) acute teaching hospitals, 2) cases attributable to the reporting facility and 3) lagged-effect models incorporating a 3-month lag and 6-month lag

	Unadjusted incidence rate ratio				Adjusted incidence rate ratio			
Variable	Slope before	Slope after	Slope change (95% CI)	Slope change *p* value	Slope before	Slope after	Slope change (95% CI)	Slope change *p* value
Main analysis (*n* = 395 cases)								
Ceased-screening cohort								
No lag	0.80	1.09	1.37 (1.04–1.80)	0.03	0.90	1.12	1.25 (1.01–1.54)	0.04
3-mo lag	0.80	1.20	1.51 (1.14–2.00)	0.004	0.90	1.24	1.38 (1.07–1.79)	0.01
6-mo lag	0.80	1.35	1.70 (1.27–2.27)	0.0004	0.90	1.39	1.56 (1.19–2.03)	0.001
Screening cohort								
No lag	1.32	1.06	0.80 (0.59–1.09)	0.2	1.31	1.06	0.81 (0.56–1.15)	0.2
3-mo lag	1.32	1.23	0.93 (0.68–1.28)	0.7	1.31	1.23	0.94 (0.66–1.33)	0.7
6-mo lag	1.32	1.52	1.15 (0.83–1.60)	0.4	1.31	1.52	1.16 (0.81–1.66)	0.4
Acute teaching hospitals (*n* = 287 cases)								
Ceased-screening cohort								
No lag	0.84	1.12	1.34 (0.99–1.83)	0.06	0.84	1.13	1.35 (1.13–1.60)	< 0.01
3-mo lag	0.84	1.25	1.49 (1.09–2.05)	0.01	0.84	1.25	1.49 (1.19–1.88)	< 0.01
6-mo lag	0.84	1.41	1.68 (1.22–2.32)	0.002	0.84	1.41	1.68 (1.32–2.14)	< 0.001
Screening cohort								
No lag	1.23	0.88	0.72 (0.46–1.13)	0.2	1.23	0.88	0.72 (0.45–1.15)	0.2
3-mo lag	1.23	1.01	0.82 (0.52–1.30)	0.4	1.23	1.01	0.82 (0.53–1.27)	0.4
6-mo lag	1.23	1.40	1.13 (0.70–1.83)	0.6	1.23	1.40	1.13 (0.98–1.88)	0.6
Cases attributable to reporting facility (*n* = 309 cases)								
Ceased-screening cohort								
No lag	0.86	1.16	1.35 (0.99–1.85)	0.06	0.93	1.18	1.27 (0.95–1.70)	0.1
3-mo lag	0.86	1.30	1.51 (1.09–2.08)	0.01	0.93	1.32	1.42 (0.96–2.10)	0.08
6-mo lag	0.86	1.40	1.62 (1.17–2.26)	0.004	0.93	1.42	1.53 (1.05–2.23)	0.03
Screening cohort								
No lag	1.47	1.00	0.68 (0.48–0.97)	0.03	1.46	1.00	0.69 (0.48–0.98)	0.04
3-mo lag	1.47	1.14	0.77 (0.54–1.11)	0.2	1.46	1.14	0.78 (0.55–1.11)	0.2
6-mo lag	1.47	1.41	0.96 (0.66–1.39)	0.8	1.46	1.41	0.96 (0.67–1.39)	0.8

Note: CI = confidence interval, VRE = vancomycin-resistant *Enterococcus*.
*Defined as the year-over-year ratio change in incidence. For example, a slope of 1.1 would represent a 10% multiplicative growth in the incidence rate per year, and a slope of 0.9 would represent a 10% reduction in incidence per year.
†Defined as the ratio of the slope after the cessation of screening divided by the slope before the cessation of screening in the ceased-screening cohort (and after June 2012 v. before June 2012 in the screening cohort).

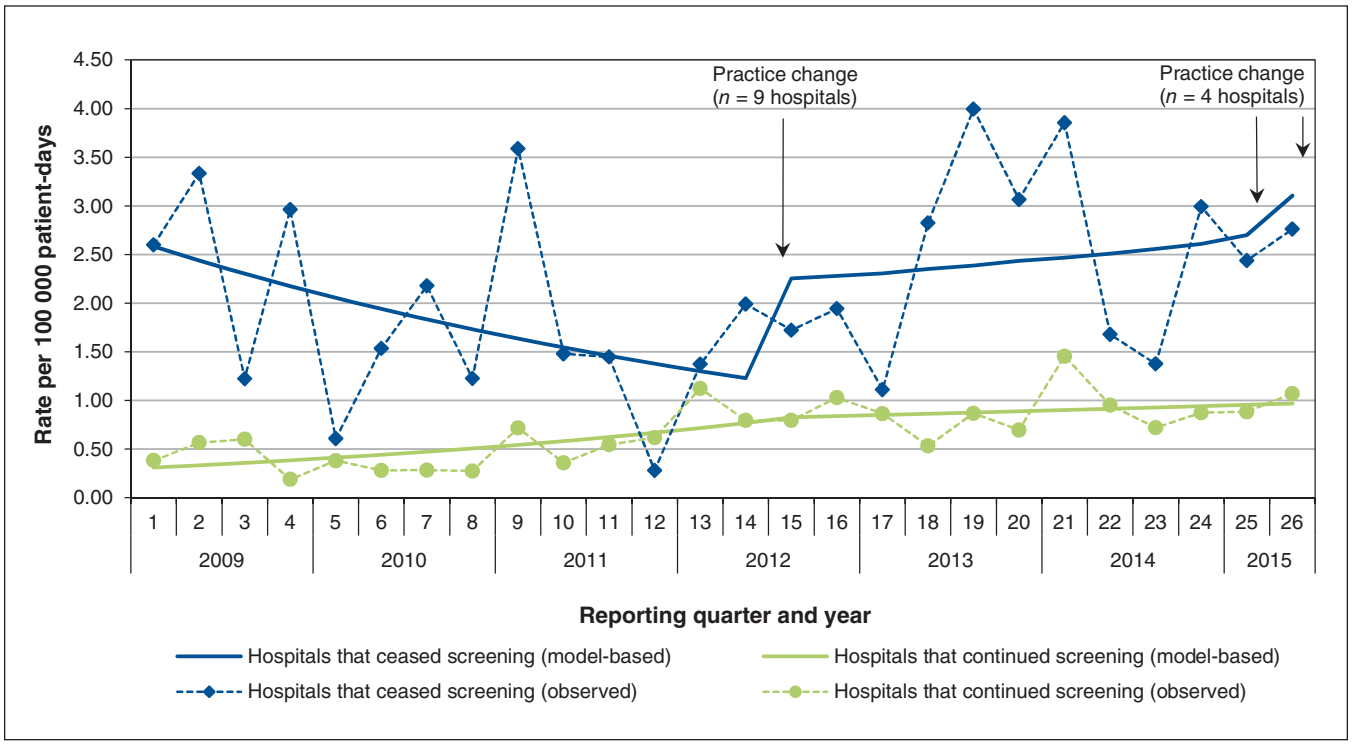

Figure 3: Rates of blood cultures positive for vancomycin-resistant *Enterococcus* (VRE), January 2009–June 2015, stratified by hospitals that ceased VRE screening and isolation practices within the study period versus hospitals that continued screening and isolation practices within the study period.

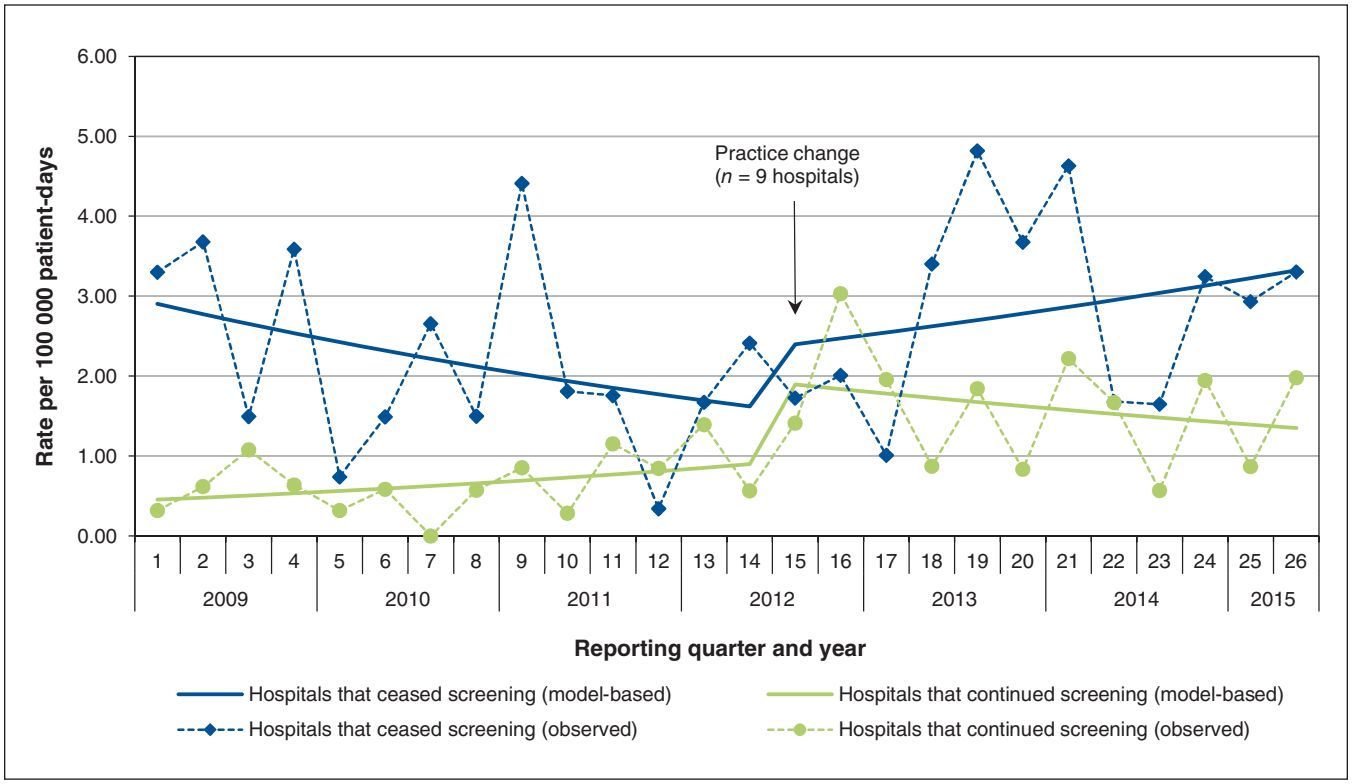

Figure 4: Rates of blood cultures positive for vancomycin-resistant *Enterococcus* (VRE) in acute teaching hospitals, January 2009–June 2015, stratified by hospitals that ceased VRE screening and isolation practices within the study period (n = 9) versus hospitals that continued screening and isolation practices within the study period (n = 10).

was associated with an increased rate of rise of VRE-positive blood cultures is consistent with several prior observational studies, which similarly suggest that active screening for VRE colonization and isolation of those affected is associated with reduced rates of bacteremia due to VRE.[24,26,35] In contrast, our results are not consistent with 2 recent studies.[27,31] However, one study[27] was conducted in an immunocompromised patient population at a single centre where all patients were admitted to single-bed rooms with private bathroom. Thus, the results may not be generalizable to less specialized hospital settings where patients are admitted to multipatient rooms and share bathrooms. A second observational study[31] included some of the data from the ceased-screening hospital cohort in our study and showed a trend toward increased VRE-positive blood cultures, but the trend did not reach statistical significance. The difference in findings might be explained by the shorter duration of follow-up in that study (18 mo v. 36 mo in our study) and, consequently, fewer data points.

There have been 2 cluster randomized controlled trials investigating the efficacy of screening for antimicrobial-resistant organisms and isolating affected patients in the intensive care unit setting.[22,23] The results of those trials raise questions about the use of contact precautions for preventing transmission of antibiotic-resistant organisms; however, neither trial reported on the results of VRE bacteremia, and neither was powered to detect this difference.[22,23] Thus, no randomized controlled trial data are available that definitively answer whether discontinuing screening and isolation for VRE is associated with increased rates of bacteremia due to this organism.

Strengths and limitations

Our study has many strengths, including comprehensive data collection from multiple hospitals over a 6-year period encompassing approximately 38 000 000 patient-days and a quasi-experimental study design using an interrupted time series Poisson regression model with an objective outcome. However, several limitations require consideration. First, we did not have data on potential confounders such as changes over time in adherence to hand hygiene guidelines, environmental services activities and antibiotic use within each hospital. 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. Second, this study had a quasi-experimental design and was not a randomized controlled trial and was therefore susceptible to biases inherent to this type of design, including regression to the mean as a potential explanation for the results. To help mitigate this potential bias, our sensitivity analyses incorporated lag effects, which amplified the results in the ceased-screening cohort, thus increasing the level of confidence in our results. Third, we did not have patient-level clinical data, and the clinical consequences of having a VRE-positive blood culture were unknown; we chose to use the term "VRE-positive blood culture" rather than "VRE bacteremia" because of this limitation. Last, misclassification bias may have occurred as we did not have knowledge of patients' prior hospital stays; thus, a patient might have been colonized with VRE in a ceased-screening hospital but had the positive blood culture in a screening hospital and vice versa. We included a sensitivity analysis that restricted the analyses to positive blood cultures attributable only 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 positive blood culture and not necessarily for the acquisition of VRE colonization, and the possibility of misclassification remains. Additional misclassification may have occurred owing to false-positive and false-negative culture results in the data set. We sought to minimize this bias by validating each reported positive case with the individual hospital and verifying case count accuracy with a separate data set. The large number of false-positive results in the original data set (25%) was unexpected and highlights the importance of validation when using publicly reported data as well as the need for enhanced education for those imputing data at the local level.

Conclusion

Whether there is still a need to prevent transmission of VRE, given the availability of effective anti-VRE therapy, has been debated; however, the best available evidence suggests that patients with VRE-positive blood cultures have an associated increased risk of death and longer duration of hospital stay compared to patients with vancomycin-susceptible blood cultures, and the emergence of daptomycin and linezolid resistance remains a concern. Future research should better characterize the costs and benefits of screening and isolation programs. In summary, rates of VRE-positive blood cultures have increased in Ontario. Hospitals aiming to minimize the rising rate of VRE-positive blood cultures should consider maintaining active screening and isolation programs.

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