

October 22, 2012

Response to the Provincial Infectious Diseases Advisory Committee *Review of literature for evidence-based best practices for VRE control*

In August 2012, the Provincial Infectious Diseases Advisory Committee (PIDAC) released a review of evidence-based best practices for control of vancomycin-resistant enterococci (VRE), in response to the decision of a number of Ontario academic hospitals to discontinue VRE control measures (PIDAC 2012a). This statement reflects the collective response of these four academic centres.

We wish to open by referring to the vision statement of Public Health Ontario:

We are accountable to support health care providers, the public health system and partner ministries in making *informed decisions and taking informed action* to improve the health and security of all Ontarians, through the *transparent* and timely provision of *credible scientific advice* and practical tools (emphasis added).

In keeping with this vision, Ontarians should expect that any document released by PIDAC will be fair, balanced, and based on an unbiased appraisal of the existing literature. In addition, that in grey areas where the path forward is less clear or where a number of alternative opinions exist, that PIDAC acknowledge these and fairly consider the evidence that supports different approaches. This is particularly important in a field like infection prevention and control (IPAC), where practice is frequently based on observational literature and where expert opinion is relied upon heavily in the absence of definitive studies. Our four academic centres are not the first in Canada to discontinue VRE-specific control measures and the debate about VRE control has been an active one for some time within the IPAC community: VRE control is clearly a grey area.

We have found the PIDAC review to contain a number of significant omissions and to include some dated and poorer quality literature. One important omission is consideration of Ontario and Canadian VRE data. Further, studies conducted in highly select patient subpopulations and in the United States have been extrapolated to the larger context of overall hospital care in Canada. Finally, no search strategy has been provided to rationalize why certain studies were included and others excluded. Accordingly, we do not believe the existing PIDAC statement aligns with the vision of PHO.

Argument 1[Section A3 of PIDAC review]

The PIDAC review states “VRE infections are associated with significant morbidity, mortality and cost, particularly in certain high-risk patient groups”. Patients with significant health conditions and those who are highly immunocompromised are certainly at higher risk of all-

cause mortality; however, it is impossible to draw conclusions as to the causal role of VRE from these papers. Many confounders exist, such as intercurrent illness, antibiotic exposure and varying patient care practices, which given the observational nature of the cited studies, cannot be adequately controlled for.

PIDAC extrapolates findings from small, single centre U.S observational studies in immunocompromised patients (almost exclusively bone marrow transplants) to the Ontario hospital patient population as a whole. As such, the literature cited fails to demonstrate an association between VRE infections and morbidity and mortality in the vast majority of patients who are not bone marrow transplants. Further, U.S. IPAC and clinical practice are poorly comparable to that in Canada, including that of our own hospitals. We collectively care for the majority of seriously immunocompromised patients in Ontario, yet we have never experienced VRE outcomes equivalent to those reported in these studies.

The two meta-analyses included in the review as evidence that VRE infection is associated with increased mortality were, as conceded by PIDAC, completed prior to the availability of effective VRE therapies. The authors of each of these papers comment on the large degree of heterogeneity between the exclusively observational studies included, which diminishes the strength of the final conclusions (Salgado, 2003; DiazGrandos, 2005). Further, both meta-analyses considered several papers that did not find an association between VRE infection and increased morbidity and mortality, yet none of these papers were referred to in the PIDAC statement.

PIDAC has not provided evidence that discontinuation of VRE control measures will lead to a significant increase in the rate of VRE infections: the statement “Centres discontinuing VRE control measures may be expected to experience significant increases in VRE infection rates, including VRE (blood stream infection) BSI (*sic*), over the next two to five years” is not supported by the literature and is speculative. We note that PIDAC did not cite the robust data of the Canadian Nosocomial Infection Surveillance Program (CNISP), which has recently reported an 8-fold increase in VRE colonization rates for member hospitals over a 5-year period with only a very modest increase in the number of positive clinical isolates (see Appendix A). Further, many of these reported clinical isolates likely represent colonization or non-clinically significant infections, as the majority are urine or wound specimens (Appendix B).

PIDAC posted a companion document to the literature review, which unfortunately contains the original preamble from a current PIDAC best practices document: Screening, Testing and Surveillance for Antibiotic-Resistant Organisms (AROs) in All Health Care Settings (PIDAC 2012b). Readers will likely find this part of the companion document confusing as it directly contradicts PIDAC’s current claim of VRE associated morbidity and mortality stating “There is no evidence that infection with VRE is associated with greater mortality than infection with vancomycin-sensitive enterococci”.

Additionally, the review also did not cite the Ontario VRE colonization or bacteremia data found in the companion document, which demonstrate that VRE infection rates have remained stable in Ontario from 2009 to 2012 despite a large overall increase in VRE colonizations with existing VRE control measures (MoHLTC, 2012; McGeer, 2012).

Argument 2[Section B5 of PIDAC review]

The PIDAC review states:

There is literature documenting negative consequences associated with (Additional Precautions) AP (*sic*). There is also literature that has not identified negative consequences, and literature that the use of single rooms benefits patients. Given the reduction in morbidity and mortality, costs and (length of stay) LOS (*sic*), the benefit of VRE control programs to the overall patient population (including AP for colonized/infected patients) outweighs the potential adverse effects of AP on individual patients. Care plans should provide supports and education to minimize any potential negative consequences of AP.

The preponderance of literature demonstrates that isolation harms patients. Two of the studies cited by PIDAC as evidence of a lack of negative consequence associated with isolating patients are dated and their relevancy is questionable. Both the 1989 article by Klein et al. and the 1977 study by Kellerman et al. do not consider changes in patient awareness, standards of hospital care, surveillance methods, hand hygiene and isolation practices that have occurred since publication of these articles several decades ago. Further, PIDAC has chosen to highlight patients' enjoyment of quietness and privacy provided by isolation rooms noted in the Barratt paper; this is misleading as the majority of the article was dedicated to describing the stigma, loss of freedom, social isolation and loneliness patients associated with implementation of contact precautions and isolation. Similarly, we feel it misleading to cite the Wassenberg paper as evidence that patients are not affected by isolation, as this paper deals with short-term isolation only; most VRE patients require long term isolation, often spanning different hospital inpatient stays.

A recent literature review that included 15 studies investigating the adverse effects of isolation on patients concluded that the majority of available studies demonstrate a negative impact on patient mental health and patient safety, as well as a decrease in time spent with healthcare providers when patients are isolated (Abad, 2010). Notably, the PIDAC review failed to include the prominent paper by Stelfox et al. on the adverse impacts of patient isolation: less documented care, increased dissatisfaction, and more preventable adverse events (Stelfox, 2003).

Finally, the argument made for patient preference for single rooms cannot be made in the context of isolating patients for the purposes of infection control. Single room accommodation is not the same as an isolation room.

Argument 3 [Section B2 of PIDAC Review]

PIDAC argues that patient flow will be affected in the long term by an increase in VRE infections and the associated increase in length of patient hospitalization: “As colonizations increase, infections will also increase, leading to further increases in length of stay which will compromise patient flow”. PIDAC is again speculating that clinically relevant VRE infections will significantly increase LOS. PIDAC is also clearly implying that VRE infections *cause* an increased length of stay, presumably through increased morbidity. While clinically significant infections caused by any organism do contribute to length of stay, most VRE infected patients have severe comorbid illness and other significant infections in addition to VRE; it is therefore difficult, if not impossible to determine the degree to which VRE infections *per se* contribute to length of stay.

Importantly and as noted above, PIDAC has not referenced our own Canadian experience, which is remarkably different from the American studies cited. Central Canada has seen a huge increase in VRE colonization over the past 5 years, yet true serious infections have remained quite rare in Ontario (CNISP, unpublished data; MoHLTC, 2012; McGeer, 2012). In our experience VRE does indeed impact upon patient flow; however it is the IPAC measures requiring isolation in single rooms for colonized patients that is by far the major contributor to hampering patient flow. Flow is also hampered during patient transfers as many receiving institutions block transfer of a VRE colonized patient until a single room is available. The situation of increasing colonization leading to delayed inter-facility transfers is already a very real issue in 2012 Ontario.

One of our major arguments for stopping VRE-specific control measures is the large impact these measures have upon the availability of isolation rooms. For the past year, three of our institutions cared for a combined 1 282 VRE colonized patients who required 31 929 isolation days, tying up a huge amount of isolation resources. All Ontario hospitals live with a limited number of isolation rooms, and further limitation of isolation capacity means that newly admitted patients requiring isolation will often necessitate multiple bed moves; multiple patient transfers are well known to have the potential to lead to further nosocomial transmission. Nowhere in its statement does PIDAC consider the substantial impact of VRE control measures on the ability to control other antibiotic resistant organisms and nosocomial infections.

Argument 4 [Section B3 of PIDAC Review]

PIDAC acknowledges the significant direct hospital costs associated with VRE surveillance and patient isolation; however, the general statement that “...VRE control programs are cost-effective when compared to the costs of increased VRE infections...” is not supported by published evidence and does not account for the opportunity cost associated with diverting time and resources away from other patient care into VRE control. VRE control programs cannot be assessed in isolation from other hospital efforts as hospitals have fixed budgets. VRE screening

and isolation shifts resources such as personal protective equipment, isolation rooms, laboratory resources and nursing time away from general patient care and other significant hospital infections, including methicillin-resistant *Staphylococcus aureus* (MRSA) and *C. difficile*. The only mention of opportunity cost in any of the evidence cited by the PIDAC report was in Puzniak et al., which focused only on the direct workload associated with gowning prior to entering VRE isolation rooms and did not address more significant costs, such as removing finite resources from other infection control programs.

The PIDAC review exclusively cites American costing studies, where the for-profit structure of hospitals inflates costs and healthcare facilities function within separate and non-comparable economic structures. The U.S. cost-benefit analyses are hospital-specific and not directly comparable to other healthcare systems. The cited Puzniak et al. study concedes that it is difficult to compare costs attributed to excess length of stay and VRE due to variations in methodologies across sites.

We once again refer to Canadian and Ontario data. Despite skyrocketing VRE colonization rates in CNISP and Ontario hospitals, the rate of VRE bacteremias reported through the mandatory Ontario Ministry of Health and Long-Term Care (MoHLTC) patient safety public reporting system has not increased (CNISP; MoHLTC, 2012b). In our experience, a large proportion of VRE clinical isolates do not represent true infection, but rather colonization. CNISP data indicates that only 20% of reported clinical isolates are bacteremias, the remainder being urine, wound, and skin/soft tissue isolates which are frequently colonizations (see Appendix B). Ontario spends a significant amount of healthcare dollars controlling VRE and the benefit of this expense is questionable given the very low rate of serious VRE infections such as bacteremia despite escalating colonization rates. No formal cost-benefit analysis has yet been done with respect to VRE control measures in Ontario; however, the low and steady bacteremia rates in the setting of rapidly increasing VRE colonization rates strongly suggest that VRE control is not cost-effective in this province.

Argument 5 [Section C1 of PIDAC Review]

PIDAC's position regarding the transfer of clinically significant vancomycin resistance from VRE to MRSA is consistent with the available evidence. Concerns of widespread transfer of resistance have not been realized. This effectively neutralizes a major concern that prompted Ontario hospitals to attempt to control VRE transmission some twenty years ago (Noble, 1992).

Argument 6 [Section C2 of PIDAC Review]

PIDAC asserts that cessation of VRE control measures may drive increasing resistance to linezolid and daptomycin. Like all infection prevention and control programs, we strongly support the judicious use of antibiotics and are concerned about increasing drug resistance, not just for VRE but also for all pathogens.

PIDAC acknowledges that linezolid resistance development is an uncommon event, with only eleven resistant VRE isolates in Ontario over a recent 2-year period. Again, CNISP and Ontario mandatory reporting data do not support the contention that clinically significant infections will escalate to the point that driving linezolid resistance will become a concern.

Argument 7 [Section B1 of PIDAC Review]

PIDAC's position is that VRE control measures are effective and sustainable; however, as pointed out previously, Canadian and Ontario data quite dramatically reveal that VRE control measures have failed (MoHLTC, 2012a; CNISP). Until very recently, all CNISP member hospitals followed PIDAC-recommended practices for control of VRE yet the rate of VRE colonization has increased 8-fold between 2006 and 2011. Ontario data further supports this trend and demonstrate stable VRE bacteremia rates despite a 4-fold increase in VRE colonization among Ontario hospitals following PIDAC's VRE control practices over a similar time frame (MoHLTC, 2012a).

PIDAC cites an inter-institutional study of infection control practices comparing cases of VRE bacteremia between two hospitals, only one of which was performing routine VRE surveillance (Price, 2003). We assert this study has significant methodologic flaws. It was conducted from 1992 to 1998, before the introduction of antimicrobials effective against VRE, which might have an influence upon secondary patient spread. Also, data were collected from patient chart reviews carried out at the hospital conducting VRE screening, then reviewed against patient data from the non-VRE screening comparison hospital based on a previously released study (Kim, 1999).

The authors of the study conducted by Morris-Downes et al., which was cited by PIDAC as evidence that VRE infection control measures result in a decrease in VRE colonization and VRE bacteremias actually concluded that it was impossible to determine the precise contribution of any one of multiple interventions, (such as surveillance, hand hygiene, an electronic alert system and antibiotic stewardship) in lowering rates of VRE.

Importantly, PIDAC's review omitted a cluster-randomized controlled trial published in 2011 (Huskins et al), one of the very few such trials assessing infection control measures. This study assessed the effect of active surveillance, barrier precautions and isolation on rates of VRE and MRSA colonization and infection. In this study 2132 intervention patients and 1356 control patients were included. No difference was found in incident colonization or infection between control and intervention groups for both VRE and MRSA.

Argument 8

PIDAC concedes that despite implementation of infection control strategies and practices in health care settings, there is ongoing VRE transmission. We fully agree with this statement, which appears to contradict the previous PIDAC argument that VRE control strategies have been

successful in controlling VRE through “...surveillance, Contact Precautions and Environmental Services efforts”.

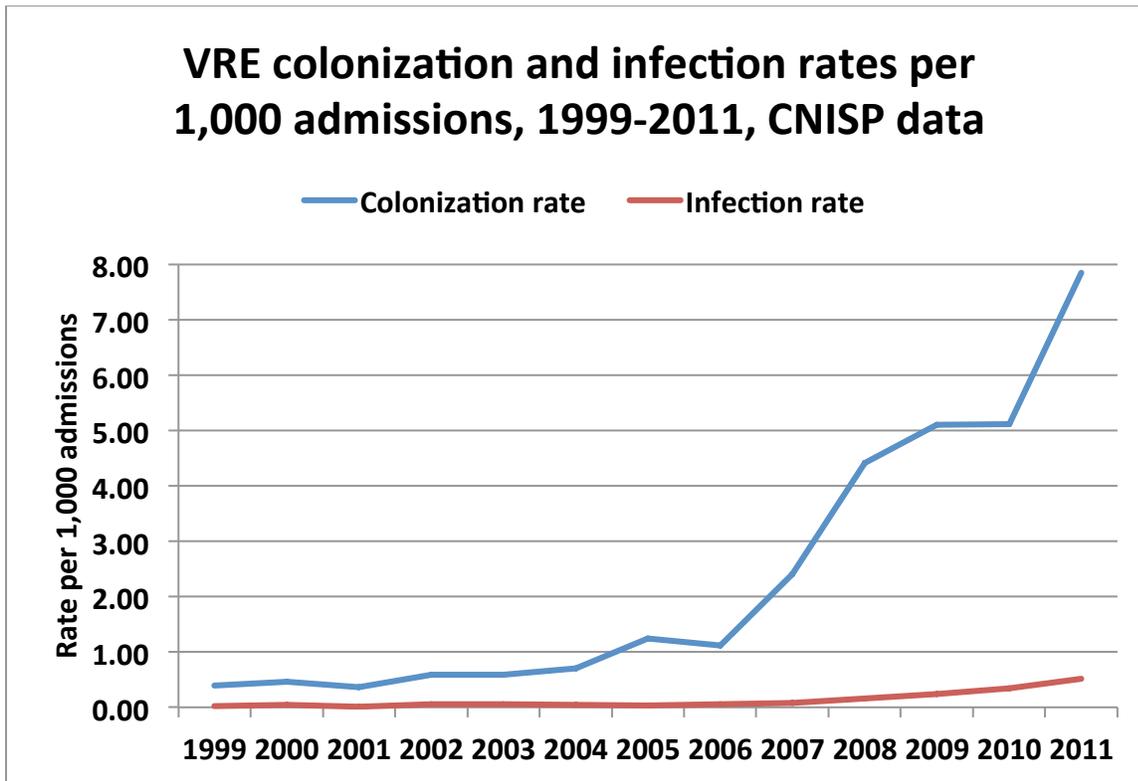
Conclusion:

Our position remains that VRE control is a grey area, and that no definitive data or literature exist to prove either side of the argument for control versus no control. After long and measured consideration, our own experiences with VRE have led us to the conclusion that there is more risk inherent in VRE control measures, in terms of patient safety, than there is benefit. We feel this is a highly complex issue that requires open and transparent debate and discussion, as well as study. We have chosen to take the initial step in questioning VRE control measures and to centrally collect robust prospective data so that we can rigorously evaluate the impacts of our decision. As stated previously, there are key Canadian opinion leaders on both sides of this argument, so we are not alone or irresponsible in our opinions.

Respectfully, we feel that the PIDAC review has not been sufficiently robust, inclusive and open to substantiate its position on the issue of VRE control. The literature supports our position as equally as PIDAC argues it supports theirs and the debate remains an active one.

University Health Network	Dr. Michael Gardam Dr. Camille Lemieux
Kingston General Hospital	Dr. Gerald Evans
The Ottawa Hospital	Dr. Virginia Roth
London Health Sciences Centre & St. Joseph’s Health Care London	Dr. Michael John

Appendix A



Unpublished data, Canadian Nosocomial Infection Surveillance Program, Public Health Agency of Canada

Appendix B

CNISP VRE RESULTS 2006 to 2010: Site of positive culture												
Site of positive culture	2006		2007		2008		2009		2010		Total (2006-2010)	
	#	%	#	%	#	%	#	%	#	%	#	%
Blood	8	20	17	27	22	18	48	27	50	17	145	21
Surgical wound	7	17	5	8	24	20	32	18	43	14	111	16
Skin, soft tissue	1	2	4	6	12	10	17	10	26	9	60	9
Urine	18	44	24	39	46	38	71	40	130	44	289	41
Other site	7	17	12	19	16	13	8	5	49	16	92	13
Total	41	100	62	100	120	100	176	100	298	100	697	100

Unpublished data, Canadian Nosocomial Infection Surveillance Program, Public Health Agency of Canada

References

Abad C, Fearday A, Safdar N. Adverse effects of isolation in hospitalised patients: a systematic review. *J Hosp Infect.* 2010 Oct;76(2):97-102.

Barratt RL, Shaban R, Moyle W. Patient experience of source isolation: lessons for clinical practice. *Contemp Nurse.* 2011 Oct;39(2):180-93.

Canadian Nosocomial Infection Surveillance Program (CNISP). Public Health Agency of Canada. 2012; unpublished data.

DiazGranados CA, Zimmer SM, Klein M, Jernigan JA. Comparison of mortality associated with vancomycin-resistant and vancomycin-susceptible enterococcal bloodstream infections: a meta-analysis. *Clin Infect Dis.* 2005 Aug 1;41(3):327-33.

Huskins WC, Huckabee CM, O'Grady NP, Murry P, Kopetskie H, Zimmer L, Walker, ME, Sinkowitz-Cochran RL, Jernigan J, Samore M, Wallace D, Goldmann DA. Intervention to reduce transmission of resistant bacteria in intensive care. *N Engl J Med.* 2011 April;364(15):1407-18.

Kellerman J, Rigler D, Siegel SE. The psychological effects of isolation in protected environments. *Am J Psychiatry.* 1977 May;134(5):563-5.

Kim W, Weinstein RA, Hayden MK. The changing molecular epidemiology and establishment of endemicity of vancomycin resistances in enterococci at one hospital over a 6-year period. *J Infect Diseases.* 1999 Jan;179:163-71.

Klein BS, Perloff WH, Maki DG. Reduction of nosocomial infection during pediatric intensive care by protective isolation. *N Engl J Med.* 1989 Jun 29;320(26):1714-21.

McGeer A, Fleming CA. Antimicrobial resistance in common hospital pathogens in Ontario: 2011 report. Toronto, ON: Ontario Medical Association, Quality Management Program – Laboratory Services; 2012.

Morris-Downes M, Smyth EG, Moore J, Thomas T, Fitzpatrick F, Walsh J, et al. Surveillance and endemic vancomycin-resistant enterococci: some success in control is possible. *J Hosp Infect.* 2010 Jul;75(3):228-33.

Noble WC, Virani Z, Cree RG. Co-transfer of vancomycin and other resistance genes from *Enterococcus faecalis* NTC12201 to *Staphylococcus aureus*. *FEMS Microbiol Lett* 1992;72:495-8.

Ontario Ministry of Health and Long-Term Care (MoHLTCa). Patient Safety Indicator Reporting: Ontario Trends. 2012; Available from:

http://patientsafetyontario.net/Reporting/en/PSIR_ProvincialTrends.aspx?IndicatorId=3&view=1&hosptid=4265&seltype=3&lhin=0&city=toronto&pc=&dist=0.

Ontario Ministry of Health and Long-Term Care (MoHLTCa), Web-Enabled Reporting System, extracted by Health Analytics Branch [2012/07/20].

Price CS, Paule S, Noskin GA, Peterson LR. Active surveillance reduces the incidence of vancomycin-resistant enterococcal bacteremia. *Clin Infect Dis*. 2003 Oct 1;37(7):921-8.

Provincial Infectious Diseases Advisory Committee (PIDAC). PIDAC Evidence-based Review on Best Practices for VRE Control . 2012. Available from:

http://www.oahpp.ca/resources/documents/pidac/PIDAC-IPC_VRE%20-%20Evidence-based%20review_ENGLISH_2012-09-03.pdf.

Provincial Infectious Diseases Advisory Committee (PIDAC). Companion Document to: Evidence-based Review on Best Practices for VRE Control . 2012. Available from:

http://www.oahpp.ca/resources/documents/pidac/Companion%20Document%20to%20VRE%20Control_ENGLISH_September%2011,2012.pdf

Puzniak LA, Gillespie KN, Leet T, Kollef M, Mundy LM. A cost-benefit analysis of gown use in controlling vancomycin-resistant *Enterococcus* transmission: is it worth the price? *Infect Control Hosp Epidemiol*. 2004 May;25(5):418-24.

Salgado CD, Farr BM. Outcomes associated with vancomycin-resistant enterococci: a meta-analysis. *Infect Control Hosp Epidemiol*. 2003 Sep;24(9):690-8.

Stelfox HT, Bates DW, Redelmeier DA. Safety of patients isolated for infection control. *J. Am Medical Assoc*. 2003 Oct;290(14):1899-1905.

Wassenberg MW, Severs D, Bonten MJ. Psychological impact of short-term isolation measures in hospitalised patients. *J Hosp Infect*. 2010 Jun;75(2):124-7.