Review of Literature for Evidence-based Best Practices for VRE Control

Provincial Infectious Diseases Advisory Committee (PIDAC)

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Public Health Ontario
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The Provincial Infectious Diseases Advisory Committee on Infection Prevention and Control (PIDAC-IPC) is a multidisciplinary committee of health care professionals with expertise and experience in Infection Prevention and Control. The committee advises Public Health Ontario on the prevention and control of health care-associated infections, considering the entire health care system for protection of both clients/patients/residents and health care providers. PIDAC-IPC produces knowledge products that are evidence-based, to the largest extent possible, to assist health care organizations in improving quality of care and client/patient/resident safety.

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NOTES

This document is intended to provide best practices only. Health care settings are encouraged to work towards these best practices in an effort to improve quality of care.

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This document is current to December 2012. New material in this revision is highlighted in grey in the text.

Summary of major revisions from December, 2012 version:

Page	Revision
2	Information regarding search metholodology
3	Inclusion of information about Ontario VRE data
7	PIDAC Response: Risk of VRE to immunocompromised patients
7	PIDAC Response: Inclusion of Ontario VRE data
7	PIDAC Response: Relationship between length of stay and infections
9	Inclusion of evaluation of practice change and interim recommendations
10	New Appendix A, showing search methodology
11	New Appendix B, showing provincial and national VRE epidemiological data

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Executive Summary

The Provincial Infectious Diseases Advisory Committee on Infection Prevention and Control (PIDAC-IPC) undertook an update of the scientific review of published literature on the control of vancomycin-resistant enterococci (VRE) up to July 2012. A detailed summary of this review is provided in this document.

Based on the evidence reviewed, PIDAC-IPC continues to recommend VRE admission screening, surveillance and control measures as outlined in PIDAC's *Routine Practices and Additional Precautions in All Health Care Settings, Annex A: Screening, Testing and Surveillance for Antibiotic-Resistant Organisms (AROs)*.

- PIDAC's Annex A is available at: http://www.oahpp.ca/resources/pidac-knowledge/best-practice-manuals/screening-testing-and-surveillance-for-antibiotic-resistant-organisms-aros.html.

The major recommended components of VRE control programs are:

a) control of vancomycin use;
b) early detection of VRE colonization and infection in patients;
c) surveillance cultures (stool, rectal swabs) to detect patients colonized with VRE; and
d) single room accommodation, gloves, and gown (if needed) for contact with the VRE patient or the patient's environment.

I. Background

Vancomycin-resistant enterococci (VRE) are strains of *Enterococcus faecium* and *Enterococcus faecalis* that are resistant to the antibiotic vancomycin. Infection prevention and control (IPAC) measures have been shown to be effective in interrupting VRE transmission, thereby reducing a patient's risk of developing VRE infections, including bacteremia.[1-5]

Ontario and many other health care jurisdictions currently recommend surveillance and control measures for VRE (e.g., Public Health Agency of Canada (PHAC),[6] the Centers for Disease Control and Prevention (CDC),[7] British Columbia's Provincial Infection Control Network (PICNet)[8]). Best practices for VRE surveillance and control may be found in PIDAC's *Routine Practices and Additional Precautions: Annex A: Screening, Testing and Surveillance for Antibiotic-Resistant Organisms (AROs)*,[9] available at: http://www.oahpp.ca/resources/pidac-knowledge/best-practice-manuals/screening-testing-and-surveillance-for-antibiotic-resistant-organisms-aros.html.

On June 25, 2012, three Ontario tertiary-care, teaching hospitals implemented a change in IPAC practices relating to VRE surveillance in their facilities, followed by a fourth hospital on July 5, 2012. The local experience of each of the four centres was similar in that they experienced increasing rates of VRE colonization of patients despite intensive VRE control measures.
The practice changes included cessation of:

a) screening patients for VRE;
b) Additional Precautions (AP) for patients with VRE; and
c) declaring VRE outbreaks.

On July 5, 2012 representatives from these centres met with PIDAC - IPC to present their rationale for making these changes in VRE practice. The four centres cited the following arguments for changing practice:

1. There had been few clinical infections and no known significant adverse outcomes related to VRE at their centres, despite increasing rates of colonization.

2. There are adverse events associated with the use of AP.
3. Patient flow and access to care were compromised in their facilities by the use of AP for the control of VRE.
4. The cost associated with surveillance and containment of VRE was significant in their facilities.
5. Concerns that vancomycin resistance would be transferred to other pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA), and would become clinically significant, have not been realized.
6. There are antibiotics currently available to treat VRE infection, which was not the case in the past.
7. While current VRE control measures are effective in controlling transmission of VRE, the costs and resources required for VRE control measures were not sustainable in their facilities. Furthermore, it was felt that there is no evidence that patient safety and outcomes are improved through implementation of these measures, and that they detract resources from other IPAC activities.
8. The standard of routine IPAC practice (such as hand hygiene, environmental cleaning, practice bundles for central line-associated bloodstream infections) is higher in Ontario today than it was in the past, when VRE first appeared.

One of the centres will be collecting data prospectively on VRE infections and adverse outcomes. One centre mentioned that they will specifically follow patient access data to monitor the effect of these changes.

A cost-benefit analysis was not carried out by any of the four hospitals prior to cessation of control efforts. The centres recommended that other hospitals continue to follow current PIDAC recommendations pending results of ongoing data collection.

To assist health care facilities that are reviewing their VRE control programs, PIDAC-IPC has formally updated our literature review regarding such programs to July 2012, and provides herein a summary of the evidence.

A summary of the search methodology used may be found in Appendix A. The detailed search strategy may be found at: http://www.oahpp.ca/resources/documents/pidac/PIDAC%20IPC_VRE%20search%20strategy_2013_02_07.pdf.

II. Review of Scientific Evidence on VRE (to July 2012)

A. CLINICAL IMPACT OF VRE

1. Risk of Infection in Colonized Patients

The majority of people who acquire VRE are colonized with the organism in their large bowel and do not develop infection.[10] However, patients who become colonized with VRE are at higher risk of developing VRE infection:

- In a 2008 review of published studies of the incidence of VRE bacteremia among VRE-colonized patients, Salgado[11] identified one study in nursing home patients in which none of 36 patients developed bacteremia; four studies in cancer patients in which 15.7% of VRE colonized patients developed bacteremia; and three studies in transplant patients in which 23% of colonized patients developed bacteremia.
- In a 4-year study in a tertiary medical centre with an active screening program, 15% of all patients initially identified as being colonized with VRE subsequently had a clinical specimen that grew VRE.[12]
- In a second 4-year study in another tertiary medical centre with an active screening program of all medical and surgical wards , 4.1% of patients identified as VRE colonized developed VRE bacteremia during the hospitalization in which they became colonized.[3]
- In a 15-month study in a 750-bed academic medical centre with active VRE surveillance only in ICUs, 8% of patients developed a subsequent VRE infection (26% were primary bacteremia). One patient death was attributable to VRE infection. [13]

More than one-third (37%) of VRE infections occur after discharge and these post-discharge infections are often severe, with 20% involving bacteremia and 30% resulting in readmission.[13]

Ontario data for the past seven years have shown that as VRE colonizations increase, infections - including bacteremias - have also increased[14, 15] (Appendix B).

2. VRE in High-risk Patients

The risk of developing VRE infection after colonization is much higher in certain patient populations.[16-20] Some studies of patients with haematological malignancies have shown rates higher than 29% for developing VRE bacteremia after colonization.[18, 19]

Patients with VRE infections died earlier and consumed more resources.[21, 22] In allogeneic hematopoietic stem cell transplant recipients, VRE bacteremia was associated with a significant reduction in survival, despite treatment with linezolid and/or daptomycin.[17, 20, 23]

3. Morbidity and Mortality Associated with VRE Infections

There have been two meta-analyses (2003, 2005) comparing outcomes of VRE and vancomycin-sensitive enterococcal (VSE) bacteremia.[24, 25] Both meta-analyses found higher mortality associated with VRE bacteremia compared to VSE bacteremia, independent of other risk factors. The studies in these meta-analyses were performed before the availability of newer agents to treat VRE. However, three more recent studies in bone marrow transplant patients treated with newer antimicrobials continue to show poor outcomes in treating VRE.[17, 20, 23]

One recent paper suggests that VRE infections may occur in addition to, rather than as a replacement for, VSE infections. The paper found that VRE bacteremia was associated with central venous catheter use, neutropenia, and allogenic bone marrow

transplantation, while VSE bacteremia was associated with age, exposure to metronidazole and gastrointestinal disease (OR 6.4, 95% CI 1.2-34.5). The authors concluded that the absence of substantial overlap of risk factors for VRE and VSE argued in favour of differences in pathogenesis, and suggested that environmental sources are more important in VRE bacteremia, while endogenous sources, particularly the gastrointestinal tract, play a pivotal role in VSE bacteremia.[26] If these findings are confirmed, the impact of VRE infections should be measured independently, rather than by comparison to VSE infections.

4. Impact of VRE Infections on Hospital Length of Stay (LOS)

Multiple studies have found that duration of hospitalization is increased with VRE bacteremia.[27-30] In one study, bacteremia with VRE was shown to increase length of stay by 18 days compared to VSE bacteremia.[28] In another study It was demonstrated that nosocomial VRE bacteremia prolonged patient hospitalization by 17 days and intensive care stay by 12 days.[29] A 2003 meta-analysis[24] also found increased LOS and excess ICU days. In a retrospective, case-controlled study done in 2008, the mean LOS among VRE-colonized patients who developed VRE bloodstream infection (BSI) was significantly longer (44.2 days) than that among VRE-colonized patients who did not develop BSI (19.4 days).[3]

B. SURVEILLANCE AND CONTROL MEASURES

1. Effectiveness and Sustainability of VRE Control Measures

Multiple studies have shown that VRE control measures are effective in endemic settings.[1, 4, 12, 31-35] Early implementation of VRE control measures may lead to a reduction in overall control measures needed over time. In a study involving two hospitals in the same city over a period of six years, it was demonstrated that the hospital that did not perform routine surveillance for VRE had 2.1-fold more cases of VRE bacteremia than the hospital that routinely screened high-risk patients for VRE, and VRE isolates tended to be monoclonal in nature, indicating horizontal or common-source spread within the facility.[32]

In a 2007 study, the implementation of effective infection control strategies resulted in a significant reduction in the transmission of VRE, despite an initial VRE colonization rate of 43%.[36] In a study that analysed surveillance data over a 7-year period in a centre where VRE was endemic, it was shown that routine surveillance for VRE together with other measures can control VRE BSI and colonization, even where VRE is endemic and where resources are constrained.[31]

2. Issues with Patient Flow

VRE precautions may result in admission delays[37, 38] within the hospital but may equally be an impediment to external transfers from centres with high endemic rates of VRE. The extended length of stay due to higher numbers of VRE infections (*see above, Section A4*) also impacts patient flow.[3, 24, 27-30]

3. Costs Associated with VRE

Costs associated with VRE bacteremia are significantly greater than with VSE bacteremia.[24, 27-29]

While infection control practices for VRE (screening, surveillance, Contact Precautions) may initially increase the cost of health services delivery, studies evaluating the cost of treatment of additional VRE BSIs and increased LOS in the absence of control measures have found that VRE control programs are cost-effective and justify the costs of preventive measures.[39, 40] In a two-hospital comparison, the cost for VRE cultures and isolation in the hospital with an active VRE control program

($253,099 USD) was exceeded by the costs of treatment of excess VRE bacteremias ($761,320 USD) in the comparator hospital without a VRE control program.[39]

Control of VRE in a non-endemic setting is cost-effective to the hospital due to reductions in LOS and avoidance of costs associated with VRE BSIs. Costs of control measures are significantly less than treatment costs and increased costs associated with increased LOS.[39, 41]

4. Regional Impact of VRE

A major impediment to VRE control in endemic settings is the large, unrecognized population of patients who are colonized with VRE and who thus serve as a reservoir for transmission.[33] Colonization pressure has been reported as an independent risk factor for VRE acquisition and VRE infection,[16, 42] i.e., as the number of colonized patients increases, the risk of further transmission and colonization also increases with a corresponding increase in risk of infection. If VRE is not contained in a small number of centres but disseminates to other patients in a region, the costs associated with treatment of serious VRE infections and associated increased LOS may be borne by facilities other than the facility where VRE was acquired.[13]

VRE can rapidly disseminate throughout a region, facilitated by multiple inter-facility admissions, transfers and clinic visits,[1, 43] which is common practice in the Ontario health system. Active IPAC interventions, which include obtaining surveillance cultures and isolation of infected patients, [33] as well as good communication between health care settings with regard to IPAC precautions,[1] can reduce or eliminate the transmission of VRE in the health care facilities of a region. Screening of high-risk hospital patients (e.g., those with prolonged lengths of stay, increased severity of illness, or antimicrobial use) at the time of inter-facility transfer may prevent the unknown dissemination of VRE-colonized patients to other health care facilities.[43]

However, limitations and turnaround time for current VRE testing methods may delay results for three to four days, leading to transmission and possible outbreaks in the receiving facilities.

5. Impact on the Patient of Additional Precautions, Including Contact Precautions for VRE Control

Numerous studies on the use of AP have highlighted the potential for a negative effect on quality of patient care and quality of life, such as depression, anxiety, loneliness, and other psychological problems related to isolation.[44-51] However, recent studies have noted that patients on Contact Precautions did not perceive a negative impact on their care[52, 53] and often perceived AP as an improvement in their care.[53] Some patients valued the privacy and solitude afforded by Contact Precautions[49] and the quietness and privacy of single rooms.[50]

In addition, two recent studies in paediatric hospitals reported no difference in health care worker behaviour between patients on AP and those not on AP.[54, 55]

There is also evidence that single-room accommodation is associated with a reduced risk of infection and other improved outcomes.[56]

The decision to institute AP for any infectious disease balances the risks/ benefits to the individual patient with the risk/ benefit to the entire patient population. It is important that AP not be used any longer than necessary and that frequent assessment of the risks of transmission are carried out by IPAC professionals, with the goal being the removal of precautions as soon as it is safe to do so. It is also important to put appropriate supports in place and to provide patient and patient family education to minimize the impact of AP.[45, 50, 53, 57-60]

C. FUTURE ISSUES WITH RESISTANCE

1. Transfer of Resistance Genes

The possibility that VRE may transfer the vancomycin resistance gene, *vanA,* to strains of MRSA when present at the same time in patients colonized with VRE, creating vancomycin-resistant strains of *Staphylococcus aureus* (VRSA) has contributed to the impetus for VRE control measures. Although 12 cases of VRSA have been reported in the United States, eight of which occurred in southeast Michigan,[61-67] initial fears of widespread dissemination of VRSA have not been realized despite years of co-circulation of MRSA and VRE in some jurisdictions. The risk continues to exist, but is apparently small, and is thus now a secondary consideration regarding VRE control programs.

2. Availability of Antibiotics to Treat VRE Infection

There are three available antibiotics with activity against VRE – daptomycin, linezolid and tigecycline.

Tigecycline is not as effective as linezolid for treating life-threatening infections[68] and carries a "black box" warning from the US Food and Drug administration because, in the phase 3 and 4 licensing trials for tigecycline, patients randomized to tigecycline were more likely to die than those randomized to comparator antibiotics.[69]

Daptomycin has also been shown to result in reduced efficacy and increased rates of recurrence of VRE bacteremia compared to linezolid, making linezolid the preferred agent for treating serious VRE infection (e.g., bacteremia).[70-72] While daptomycin resistance remains uncommon in enterococci, it has been described.[73, 74] Although the mechanisms of resistance are not well understood, the evidence that daptomycin resistance has emerged in patients being treated with daptomcyin[75] and that single step mutations confer resistance[76] suggests that daptomycin resistance is likely to increase as this antibiotic is used more frequently. In one study of VRE bacteremia, daptomycin resistance emerged in 11% of patients treated with daptomycin.[77]

Linezolid is thus the only antibiotic available that is adequate for the treatment of life-threatening infections due to enterococci, including enterococcal bacteremia. Resistance to linezolid remains uncommon, but may arise either due to single step mutations[78] or to the horizontal acquisition of resistance genes.[79] Most clinical infections with linezolid-resistant VRE appear to arise when resistance emerges during therapy for VRE infections.[80-84] Numerous outbreaks of linezolid-resistant VRE have been reported,[78, 82, 85-91] and inter-institutional transmission of linezolid-resistant VRE has been described in Germany and Greece.[78, 89, 90] Eleven linezolid-resistant isolates of VRE from multiple regions of Ontario were identified in the Public Health Ontario Laboratory between January, 2010 and December 2011.[92]

The emergence of VRE will inevitably lead to increasing use of daptomycin and linezolid for the treatment of VRE infections. This use has implications beyond enterococci: daptomycin and linezolid are the only two currently available antibiotics effective against MRSA and coagulase-negative staphylococci with reduced susceptibility to vancomycin. Increasing use of daptomycin and linezolid will select for resistance in staphylococci, and may compromise our ability to treat staphylococcal infections.[93-97]

III. PIDAC Response to Arguments for Discontinuing VRE Control Based on Review of Evidence

ARGUMENT #1:

There have been few clinical infections and no known significant adverse outcomes related to VRE, despite increasing rates of colonization.

PIDAC RESPONSE:

Although VRE colonization rates exceed VRE infection rates, VRE infections are associated with significant morbidity, mortality and cost, particularly in certain high-risk patient groups. The highest risk for VRE infection is in immunocompromised patients.

As the size of the VRE reservoir increases in hospitals, it becomes increasingly difficult to protect high-risk patients from exposure to VRE.

Centres discontinuing VRE control measures may be expected to experience significant increases in VRE infection rates, including VRE BSI, over the next two to five years. A significant proportion of infections may occur after discharge and result in readmission, sometimes to another facility. Dissemination across the province, with higher overall VRE rates, may also be expected. [Section A3]

ARGUMENT #2:

There are adverse events associated with the use of AP.

PIDAC RESPONSE:

There is literature documenting negative consequences associated with AP. 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 LOS, 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. [Section B5]

ARGUMENT #3:

Patient flow and access to care are compromised by the use of AP for the control of VRE.

PIDAC RESPONSE:

Although initial placement of patients requiring single room accommodation may delay admission, VRE infections have clearly been shown to significantly increase length of stay. Data, including data from Ontario, show that as colonizations increase, infections have also increased.

Published data show that as infections increase, there is increased length of stay (e.g., compared to infection with vancomycin-sensitive enterococci). Further, the impact of increased colonization rates on inter-facility transfer to facilities that continue VRE containment programs are unknown, but could lead to an overall worsening of patient flow across the overall health care system. [Section B2]

ARGUMENT #4:

The costs associated with surveillance and containment of VRE are significant.

PIDAC RESPONSE:

Although there are significant direct costs associated with surveillance cultures and isolation of VRE-colonized patients, the indirect costs (e.g., treatment of serious VRE infections, including VRE bacteremia, increased length of stay) of allowing VRE spread within hospitals are higher than the costs associated with containment. Published evidence demonstrates that VRE control programs are cost-effective

when compared to the costs of increased VRE infections (e.g., treatment, ICU care, length of stay). The absence of a regional approach may lead to a short term shifting of costs from facilities that have discontinued VRE containment to those facilities that continue to follow the Best Practices recommendations. In the longer term, it may be expected that overall health care system costs related to VRE will increase due to the lack of a regional containment strategy. [Section B3]

ARGUMENT #5:

Concerns that vancomycin resistance would be transferred to other pathogens, such as MRSA, and would become clinically significant, have not been realized.

PIDAC RESPONSE:

Transfer of vancomycin resistance from VRE to MRSA to create VRSA has occurred in a small number of cases in the United States, but this has not become widespread and remains a secondary consideration to the increased morbidity and mortality, LOS and costs associated with clinical VRE infections. [Section C1]

ARGUMENT #6:

There are antibiotics currently available to treat VRE infection, which was not the case in the past.

PIDAC RESPONSE:

There are three agents available for treating VRE infections, only one of which is adequate for the treatment of bacteremia and life-threatening infections (i.e., linezolid). Resistance to linezolid occurs by single-step mutation, and emerging resistance is clearly linked to increasing linezolid use. Linezolid resistance has been seen in multiple jurisdictions, including Ontario. There are no new drugs currently available to replace them should resistance become widespread. [Section C2]

ARGUMENT #7:

While current VRE control measures are effective in controlling transmission of VRE, the costs and resources required for VRE control measures are not sustainable. There is no evidence that patient safety and outcomes are improved through implementation of these measures and they detract resources from other IPAC activities.

PIDAC RESPONSE:

VRE control has been attained in a number of jurisdictions through surveillance, Contact Precautions and Environmental Services efforts. VRE containment strategies have achieved success in both endemic and non-endemic settings, and have been demonstrated to be cost-effective and sustainable over many years in numerous jurisdictions. [Section B1]

ARGUMENT #8:

The standard of routine infection prevention and control (IPAC) practice is higher in Ontario today than it was in the past, when VRE first appeared.

PIDAC RESPONSE:

While Ontario has implemented several successful strategies to improve IPAC practices in health care settings, VRE transmission is still occurring and the rate of new VRE colonizations is increasing, which reinforces the need to continue VRE surveillance and containment.

IV. Conclusions

Based on the foregoing evidence, PIDAC concludes that, for both patient safety and cost-effectiveness reasons, Ontario health care facilities should continue to carry out screening, surveillance and containment measures for cases of VRE colonization and infection until the results of an evaluation by PHO of the change of VRE control measures at four hospitals in Ontario are available.

V. Recommendations

PIDAC recommends the following:

1. Continue VRE control measures as recommended in *Annex A*:
    a) active surveillance screening for VRE;
    b) containment of identified VRE cases through use of Additional Precautions; and
    c) enhanced environmental cleaning for rooms of, and equipment used by, patients with VRE.

2. Management of patients transferred from a hospital that has discontinued VRE containment practices:
    a) Receiving hospitals should monitor VRE colonization/ infection rates in patients returning from these hospitals. Expect colonization levels to increase with time, with subsequent increases in rates of VRE infections, including bacteremia. With most current screening methods, results may not be available for 3-4 days depending on local laboratory turnaround time, delaying detection of colonization.
    b) Consideration might be given to managing these patients in the same manner as patients who have been in a hospital in another country where VRE rates are high, i.e., pre-emptive isolation pending screening.
    c) If routine pre-emptive isolation is not feasible (e.g., insufficient numbers of single rooms) then pre-emptive isolation should be considered for patients at higher risk of having acquired VRE in the referral facility (e.g., those who have received care in an ICU setting; have been in a transplant unit; have had a longer LOS overall and/or in an ICU setting). Medical patients are at more risk than surgical patients; obstetrical and psychiatric patients are at lowest risk for VRE.
    d) If the transferring hospital is aware that a patient has VRE, the receiving facility should be notified. **Close collaboration by regional centres and clear communication with receiving facilities is crucial.**

3. Health care facilities should await the results of evaluation before changing current practice.

4. Four hospitals in Ontario have discontinued VRE control measures. The impact of this change of infection control practice will be evaluated in real-time. PHO will work with these and other hospitals in Ontario to measure VRE infection rates and patient outcomes. The results of this study will be reported back to the field when data becomes available.

Appendix A: Search Methodology

The following is a summary of the search methodology used for this report. The full search methodology may be found at: http://www.oahpp.ca/resources/documents/pidac/PIDAC%20IPC_VRE%20search%20strategy_2013_02_07.pdf.

BIBLIOGRAPHIC RESEARCH DATABASES SEARCHED

Literature searches were conducted in MEDLINE (Ovid) and CINAHL. Additional searches conducted via the Ovid platform in Embase and BIOSIS Previews for selected topics. Only English language articles from 2005 to the current time were retrieved. The search concepts were expressed in combination of databases specific controlled vocabularies (MeSH, Emtree, CINAHL SH) and keywords. Boolean logic was applied as was proximity searching. Searches were designed to retrieve information on eight topics:

- Adverse effects of patient isolation
- Cost effectiveness of health care acquired infection control measures
- Cost effectiveness of vancomycin-resistant enterococcus control measures
- Epidemiology of vancomycin-resistant *Staphylococcus aureus*
- Vancomycin-resistant enterococcus control measures
- Vancomycin-resistant enterococcus screening, cost and other measures
- Vancomycin-resistant enterococcus and vancomycin-sensitive entercococcus: virulence, epidemiology and patient outcomes

GREY LITERATURE SEARCHED

A web search was conducted to identify grey literature. Several custom search engines were used to conduct jurisdiction-specific searches. Keywords used to identify relevant items mirrored search terms employed in bibliographic databases and their related synonyms. Conceptually, the grey literature search was framed as:

> (VRE or vancomycin-resistant)/ screening OR control/ (cost OR economic OR expense OR expenditure OR investment)

The following custom search engines were used to conduct jurisdiction-specific searches (first 100 results reviewed):

- Canadian Federal and Provincial Health Departments and Public Health Agencies
- US State Government
- US Federal Government
- UK Government
- Australia & NZ Federal & State Government

References and linked document in highly relevant results were also examined. The following topical web resources were also searched:

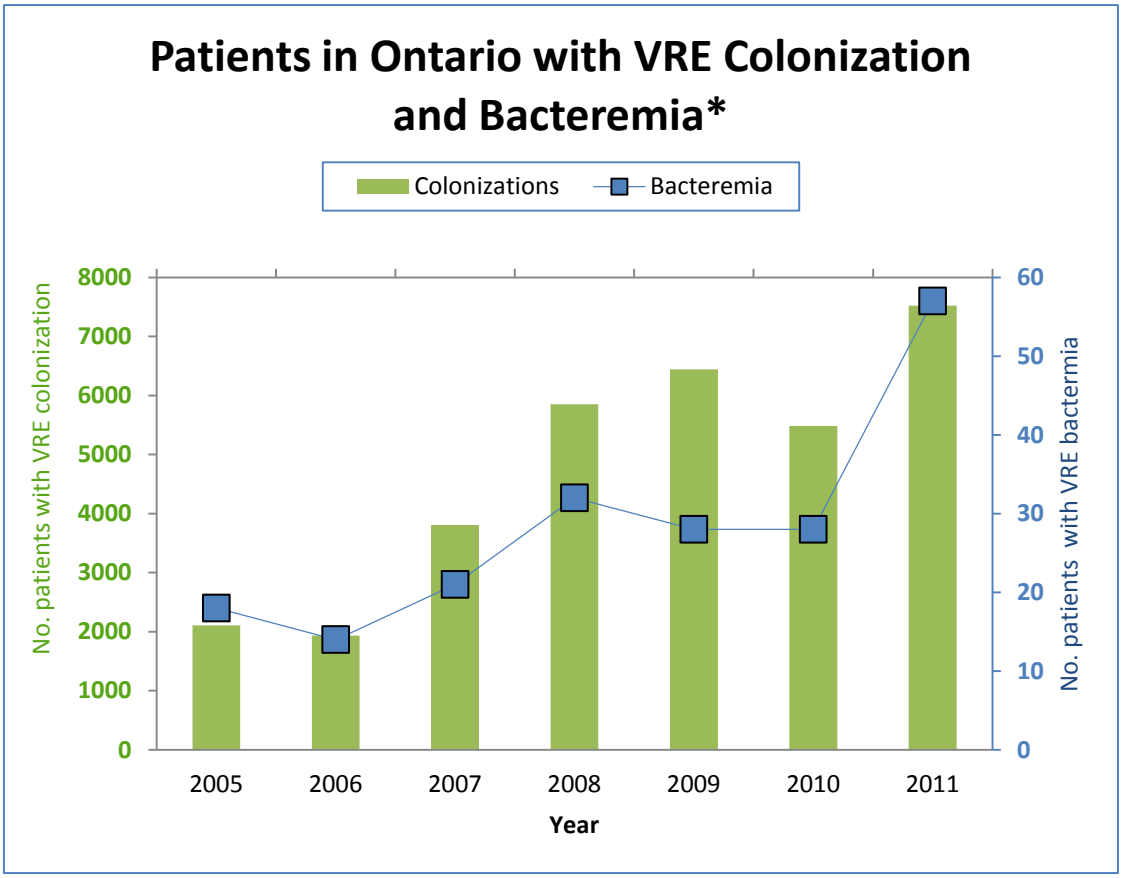
.who.int/	*.shea-online.org/*
.cdc.gov/	*.apic.org/*
*.ecdc.europa.eu/ *	*.picnet.bc.ca/*
.idsociety.org/	*.isid.org/*

Appendix B: Epidemiological Data

While there are more people colonized with VRE than infected with VRE, both have increased over the past seven years at a similar rate. Data from the Ontario Medical Association's Quality Management Program—Laboratory Services (QMP-LS) are shown below.

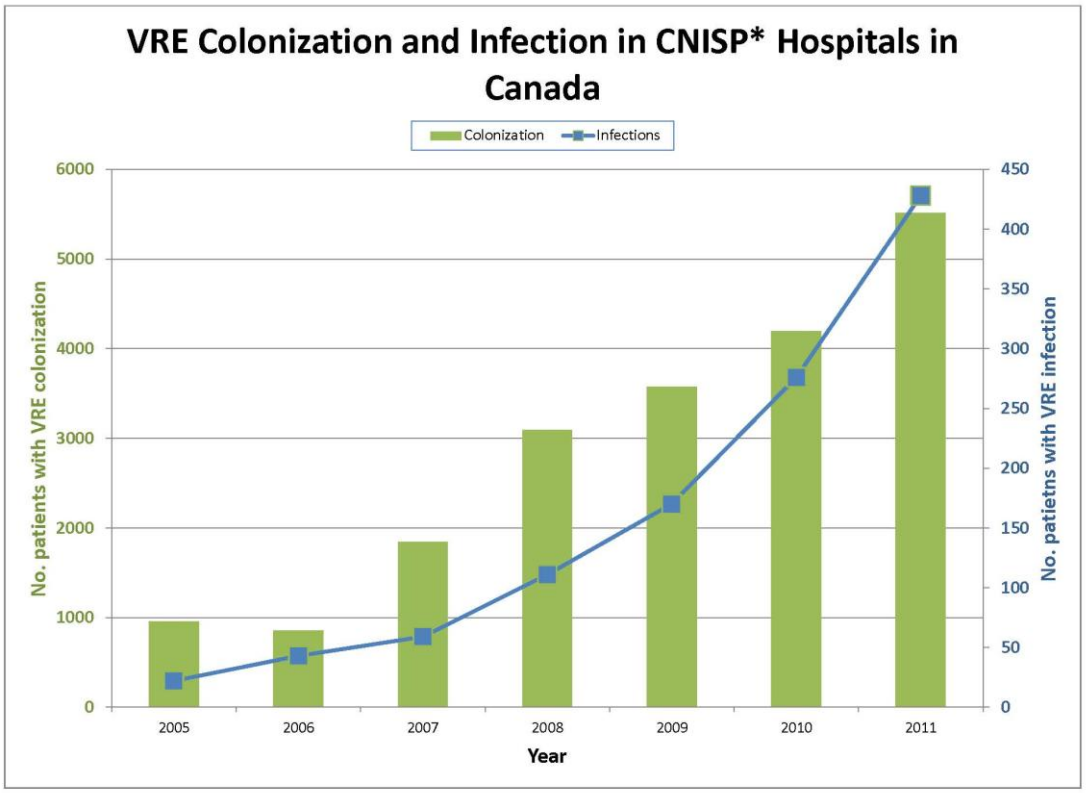
QMP–LS Data for VRE: 2005–2011

Year	Total New Patients with VRE Colonization	No. New Patients with VRE Bacteremia
2005	2161	18
2006	1984	14
2007	3900	21
2008	5964	32
2009	6541	28
2010	5567	28
2011	7643	57



* Based on QMP-LS Data

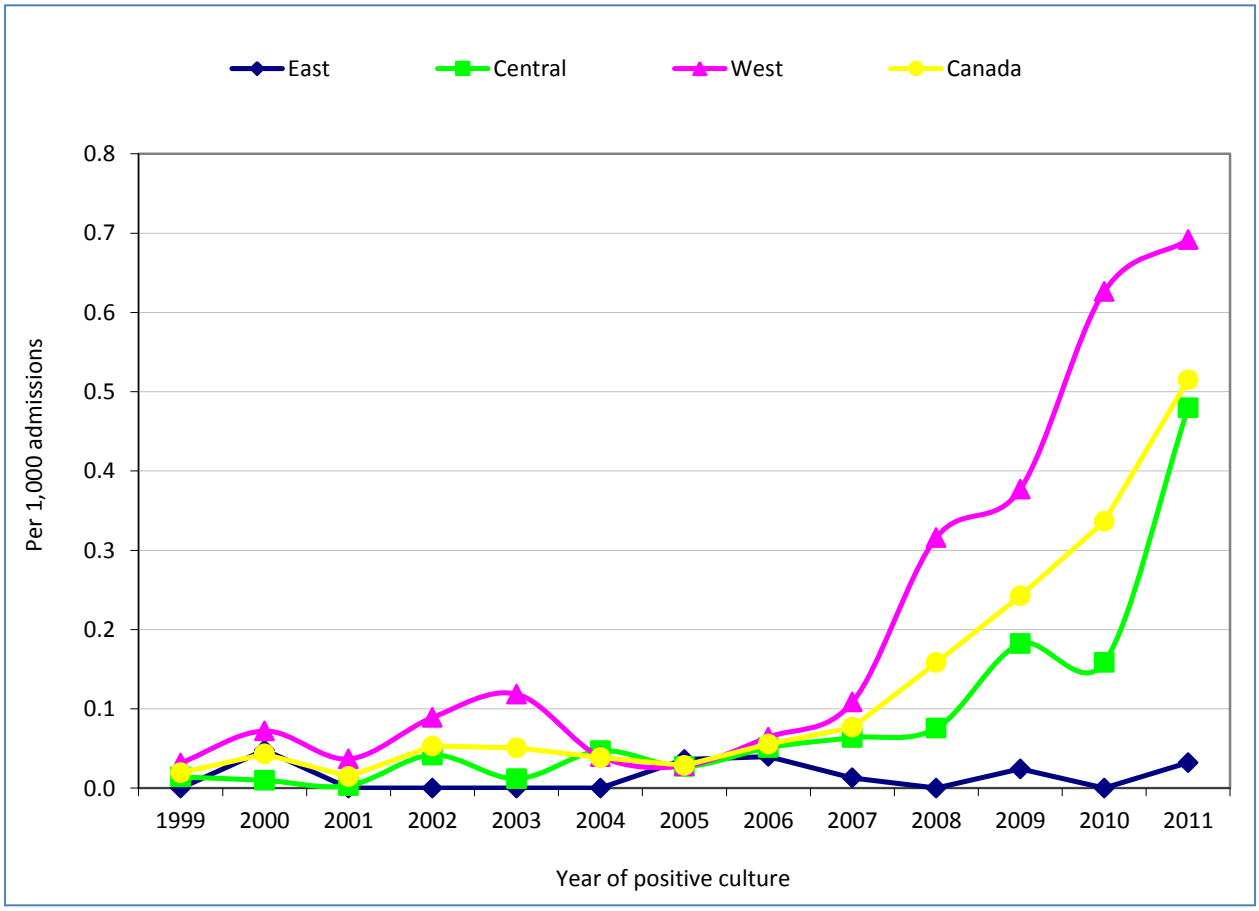
National data from the Canadian Nosocomial Infections Surveillance Program (CNISP) also show that the incidence of VRE infection is increasing. It should be noted that, in 2011, bacteremias accounted for 30% of all infections [unpublished data from the Public Health Agency of Canada, *Vancomycin-resistant Enterococci Infections in Canadian Acute-care Hospitals. Surveillance Report January 1, 1999 to December 31, 2011*].



* CNISP: Canadian Nosocomial Infections Surveillance Program

Regional VRE infection incidence rates per 1,000 patient admissions, 1999-2011 (n=1,241)

(NOTE: Central Canada includes Ontario and Quebec)



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