Economic Analysis of VRE: Assessing Attributable Cost and Length of Stay
Dr. Marc Romney, Providence Health, Vancouver
A Webber Training Teleclass

Economic Analysis of VRE: Assessing Attributable Cost and Length of Stay

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Hosted by
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INFECTION PREVENTION AND CONTROL
PROVIDENCE HEALTH CARE
Vancouver, BC, Canada

Disclosures

- Participated in a Medical Advisory Board meetings for Pfizer (Canada)
- Participated in a lunch meeting sponsored by Sunovion Pharmaceuticals Canada

Objectives

1. To review the published evidence supporting (or refuting) the de-escalation of VRE control programs
2. To appreciate the attributable impact of VRE on hospitalization costs
3. To appreciate the attributable impact of VRE on length of stay

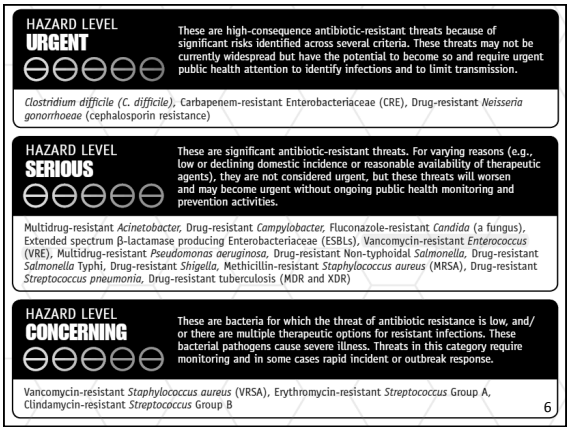
Background

- Enterococci cause a range of illnesses, including:
  - bloodstream infections
  - urinary tract infections
  - other infections
- Infections due to Vancomycin Resistant Enterococci (VRE) are usually healthcare-associated
- VRE outbreaks in hospitals have been reported
- Treatment options are limited
- *Enterococcus faecium > Enterococcus faecalis*

Background (2)

- In 2013, US Centers for Disease Control and Prevention (CDC) released a report entitled:

  "Antibiotic Resistance Threats in the United States"
- Raise awareness regarding the threat of antibiotic resistance
- Immediate action to address this threat
- For the first time, CDC prioritized antibiotic resistant bacteria into 3 categories



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Background (3)

- In Canada, there is considerable controversy over the value of VRE control programs in hospitals
- Some hospitals in British Columbia, Ontario and other provinces have abandoned VRE prevention and control programs
  - VRE are not very virulent
  - New antibiotics exist to treat VRE infections
  - Serious VRE infections are uncommon (mostly colonization)
  - VRE control programs are very expensive

7

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

Provincial Infectious Diseases Advisory Committee (PIDAC)

Published: August 2012
Revised: December 2012

Public Health Ontario | Santé publique Ontario

8

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.[8] 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[8] identified one study in nursing home patients in which none of 86 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.[9]
- 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.[7]
- 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 (20% were primary bacteremia). One patient death was attributable to VRE infection.[10]

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.[12]

Ontario data for the past seven years have shown that as VRE colonizations increase, infections - including bacteremias - have also increased[13-17] (Appendix B)

2. VRE in High-risk Patients

The risk of developing VRE infection after colonization is much higher in certain patient populations.[18-20] Some studies of patients with haematological malignancies have shown rates higher than 23% for developing VRE bacteremia after colonization.[21-23]

Patients with VRE infections died earlier and consumed more resources.[24-27] In allogeneic hematopoietic stem cell transplant recipients, VRE bacteremia was associated with a significant reduction in survival, despite treatment with linezolid and/or daptomycin.[27-29][30]

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.[31,32] 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.[27,33,34]

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

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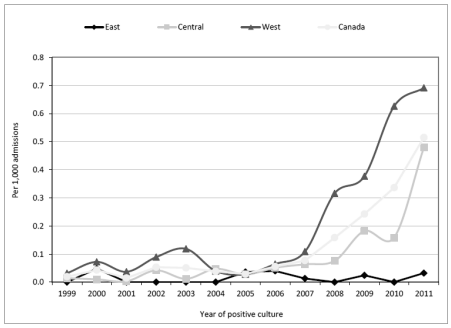
9

Regional VRE infection incidence rates per 1,000 patient admissions, 1999-2011 (n=1,241)
(NOTE: Central Canada includes Ontario and Quebec)



10

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

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11

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.

12

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Background (4)

- Canadian data on the *effectiveness* of hospital-based VRE control programs are somewhat lacking
- Some hospitals in which VRE control programs had been discontinued did not perform (or publish) cost-effectiveness studies prior to discontinuation

13

Background (4)

- Canadian data on the *effectiveness* of hospital-based VRE control programs are somewhat lacking
- Some hospitals in which VRE control programs had been discontinued did not perform (or publish) cost-effectiveness studies prior to discontinuation
- What is the relative value of a VRE control program?

14

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journal homepage: www.elsevierhealth.com/journals/jhin

Economic analysis of vancomycin-resistant enterococci at a Canadian hospital: assessing attributable cost and length of stay

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[d] Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, British Columbia, Canada

15

The Study – Introduction

- Limited number of reports from US hospitals describing attributable costs and length of stay (LOS) due to VRE
- Mostly estimates and are highly variable
  - Small samples sizes
  - Inherent differences in the settings
  - Different study design

16

The Study – Introduction

- Limited number of reports from US hospitals describing attributable costs and length of stay (LOS) due to VRE
- Mostly estimates and are highly variable
  - Small samples sizes
  - Inherent differences in the settings
  - Different study design
- Each study reported an increased cost and LOS for patients with VRE

17

Providence Health Care

- Largest Catholic health care organization in Canada
- Six facilities in Vancouver
  - 3 hospitals
  - 3 residential care facilities
  - 1 hospice
- ~1500 beds
- St. Paul's Hospital
  - HIV/AIDS Program
  - Cardiac Program
  - Renal Program

18

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The Study – Methods (Data Source)

- Fiscal year 2008-2009
- All VRE positive patients (colonization or infection) from IPAC database
  - Incident cases only
- Cases required laboratory confirmation, N=217
- Controls were randomly identified, N=1075
- Acknowledged by the PHC / University of BC REB as quality improvement project

19

The Study – Methods (Variables and Outcomes)

- Variables chosen for investigation:
  - Surveillance database
  - Finance database
  - Those variables previously reported in the published literature
- Patient characteristics were stratified by the presence or absence of VRE colonization or infection
- Two outcomes for the analysis:
  - ATTRIBUTABLE COST
  - ATTRIBUTABLE LENGTH OF STAY (LOS)

20

The Study – Methods (Statistics 1)

- An attributable cost analysis determines patient costs had the infection (or colonization) never occurred
- Hospitalization costs attributable to VRE
- *Attributable cost is NOT the money spent on controlling VRE*
- Determined by "comparative attribution"
- Construction of a statistical model
- Relationship between cost and infection status
- Simultaneously controlling for other variables affecting patient cost

21

The Study – Methods (Statistics 2)

- Generalized Linear Modeling (GLM) approach was chosen for both cost and LOS analyses
- Non-normal distribution of data
- Cost variables were highly skewed
- GLM showed the best fit for the data
- GLM is a very flexible and robust statistical model

22

The Study – Results

Table I
Patient characteristics stratified by presence or absence of vancomycin-resistant enterococcus (VRE)

Variable	Controls ($N = 1075$)	VRE patients ($N = 217$)	*P*-value
Age (years, mean ± SD)	69.1 ± 17.5	63.3 ± 17.5	<0.0001
Male sex	596 (55.4)	129 (59.5)	0.2601
Died	84 (7.8)	42 (19.4)	<0.0001
Operating room visit	364 (33.8)	72 (33.2)	0.8675
ICU visit	101 (9.4)	75 (34.6)	<0.0001
Human immunodeficiency virus*	30 (2.8)	21 (9.7)	<0.0001
ICD-10 codes (number codes, mean ± SD)	5.1 ± 3.5	9.8 ± 5.2	<0.0001
Cost (Canadian $, mean ± SD)	13,069 ± 17,783	46,924 ± 55,881	<0.0001
Length of hospital stay (days, mean ± SD)	10.9 ± 14.3	34.0 ± 33.2	<0.0001

→ VRE patients had higher mean total cost and LOS

23

The Study – Results

Table III
Attributable costs and length of stay of vancomycin-resistant enterococcus (VRE) using the generalized linear model

	Relative (%)[a]		Absolute (dollars/days)[b]	
	Mean	95% CI	Mean	95% CI
Attributable cost (Canadian $)	61.9	42.3–84.3	17,949	13,949–21,464
Length of stay (days)	68.0	41.9–98.9	13.8	10.0–16.9

CI, confidence interval.
[a] The estimated relative costs remain constant for each VRE case.
[b] The estimated absolute costs will be different for each VRE case, depending on the reference costs. The numbers reported in this table are estimated at the average costs of a VRE patient.

24

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The Study – Results

- Attributable cost: 61.9% greater than the total hospital cost of a patient without VRE
- Absolute cost: $17,949 CAD greater than the total hospital cost of a patient without VRE
- The presence of VRE increases LOS by 68.0% in relative terms
- This translates to an additional 13.8 additional days of hospitalization

25

The Study – Results

- A smaller secondary analysis investigated attributable costs between VRE colonizations (N=200) and VRE infections (N=17)
- There was no statistically significant difference in the attributable cost or VRE between patients who were infected versus those who were colonized

26

The Study – Discussion

- GLM showed that VRE had a positive and highly significant impact on both cost and LOS
- These cost estimates are within the range of attributable costs reported in the US literature
  → albeit at the lower end of the range
- VRE sample contained 90% colonizations (lower costs)
- Of those patients infected with VRE, 60% had urinary tract infections (lower costs)

27

The Study – Discussion

- Secondary analysis was unable to discern a difference in attributable cost due to VRE infection versus VRE colonization
- Could be due to relatively small number of infections
- This suggests that VRE colonizations alone could carry significant cost and may prolong LOS
- VRE colonization may not be a totally benign event

28

The Study – Limitations

- Potential bias arising from the relationship between VRE and LOS
  → A longer LOS puts patients at higher risk for VRE
  → VRE positivity increases patients' LOS

"ENDOGENOUS VARIABLE BIAS"

29

The Study – Limitations

- Secondary analysis was conducted on a small sample size
  - Additional analyses with a larger number of VRE infections may help overcome this limitation
- Societal costs were not investigated as part of the study (e.g., lost productivity, excess mortality)
- These costs may triple attributable hospital costs
- The data from our study are conservative estimates

30

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The Study – Conclusions

- At St. Paul's Hospital, VRE positivity is associated with:
  - Attributable cost of approximately $18,000 CAD
  - Attributable LOS of approximately 14 days
- VRE colonizations alone may account for significant cost and LOS implications
- These data can be used for future cost-effectiveness studies and broader rigorous economic evaluations of VRE control programs
- A cost-effectiveness study at St. Paul's Hospital is currently underway

31

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY JULY 2014, VOL. 35, NO. 7

ORIGINAL ARTICLE

Evaluation of Vancomycin-Resistant Enterococci (VRE)–Associated Morbidity Following Relaxation of VRE Screening and Isolation Precautions in a Tertiary Care Hospital

Kristin Y. Popiel, MD;[1] Mark A. Miller, MD, FRCPC[2]

OBJECTIVE. To determine whether relaxing vancomycin-resistant enterococci (VRE) precautions results in an increase in the incidence of invasive VRE infections over time.

DESIGN. Retrospective analysis of a microbiology database before and after relaxation of VRE screening and isolation precautions.

SETTING. Urban tertiary care teaching hospital in Montreal, Canada.

PARTICIPANTS. All hospitalized and emergency room patients over a 13-year period from January 1, 2000, to March 31, 2013.

METHODS. We assessed the results of all microbiology cultures for the presence of VRE as well as the results of all polymerase chain reaction assays for *vanA* and *vanB* during the study period. Applying criteria for 4 clinical situations (bacteremia, definite infection, possible infection, and colonization with VRE), we analyzed the effects of relaxed VRE screening and isolation precautions on the incidence of each of these outcomes over the time preceding and following this change.

RESULTS. When VRE screening and isolation precautions were relaxed, a marked rise in VRE colonization was observed, with a lesser but definite rise in the 3 other outcomes. Despite this initial rise in all measures, all incidences other than colonization plateaued during the 34 months of follow-up.

CONCLUSIONS. Relaxation of VRE screening and isolation precautions was associated with an immediate increase in colonization and infection incidence. Despite increasing colonization, infection outcomes remained infrequent and stable, suggesting a finite number of susceptible hosts at risk. Relaxation of VRE protocols may not lead to increasing infection incidence in a hospital setting, advocating that cost effectiveness exercises, with targeted screening and isolation precautions, are crucial.

Infect Control Hosp Epidemiol 2014;35(7):818-825

32

Relaxation of VRE Screening and Isolation Precautions

- Large, urban tertiary-care hospital in Montreal
- Retrospective, observational study performed over 13 years
- Analysis of microbiological data comparing two intervention periods:
  - "Pre-relaxation period" (2000 to May 2010)
    - Intensive VRE prevention and control program
  - "Post-relaxation period" (May 2010 to April 2013)
    - Intended to protect high-risk patients from VRE

33

TABLE 1. Comparison of Pre- and Postrelaxation Vancomycin-Resistant Enterococcus (VRE) Screening Policies[a]

	Prerelaxation, 2000 to May 2010	Postrelaxation, May 2010 to present
Admissions screening	All admissions	Only admissions from endemic[a] hospitals or admitted to high-risk[b] wards
Contact tracing after positive case	Roommates: twice, 5–7 days apart; all patients on ward every week	Roommates only, 1 time only
Destination of VRE+ patients	VRE cohort unit	Anywhere (with VRE contact precautions); avoid admissions to high-risk[b] wards if medically possible
Regular VRE surveillance	Every 2 weeks for all patients on any ward with a recent case	None
Discharge screening	All transfers to long-term care or rehabilitation facilities	All transfers to long-term care or rehabilitation facilities

[a] Endemic refers to any hospital with a public health notification disclosing the presence of VRE.
[b] High-risk wards refer to the hematology/oncology ward, intensive care unit, and neonatal intensive care unit.

Popiel KY and M Miller. ICHE 2014;35(7):818-825

34

Relaxation of VRE Screening and Isolation Precautions (2)

- Pre-relaxation interventions included:
  - Dedicated nursing staff for VRE positive patients (starting 2005/2006)
  - Temporary closure of wards with ongoing VRE transmission (starting 2005/2006)
  - PCR testing for rectal screening (starting 2005/2006)
  - Creation of a dedicated VRE cohort unit (2007 to May 2010)
  - Placement of security guard to enforce hand washing and compliance with personal protective equipment (2007 to May 2010)

35

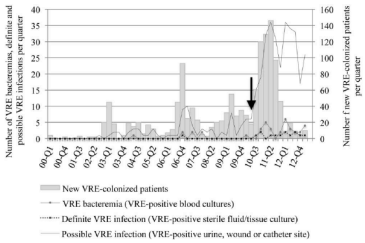

FIGURE 1. Number of cases of vancomycin-resistant enterococcal (VRE) bacteremia, definite infection, and possible infection in relation to the number of newly VRE-colonized patients per quarter, from January 2000 through April 2013. Arrow indicates the start of relaxation of the VRE screening and isolation precautions relaxation.

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Relaxation of VRE Screening and Isolation Precautions (3)

- Post-relaxation period:
  - "Dramatic" rise in VRE colonization observed
  - Concurrent increase in VRE bacteremias and other VRE infections (definite and possible)
  - Subsequent incidence of VRE bacteremias and definite VRE infections eventually reached a plateau
  - Possible VRE infections remained elevated

37

Relaxation of VRE Screening and Isolation Precautions (4)

- Conclusions:
  - "Guarded" support for relaxation and de-escalation of VRE control programs
  - Focus on preventing VRE in patients who are at high risk
    - immunocompromised patients
    - severely ill patients
  - Not complete discontinuation of VRE control
  - Re-allocate infection control resources to other interventions
- Study is limited by observational design and potential confounders spanning the 13 year study period

38

***Proportionality* in Infection Prevention and Control**

- Many different infectious "threats" or "hazards"
- Response (interventions) should be proportionate to the threat
- Usually not an "all or none" approach
- Response should be based on:
  - An assessment of risk (including patient population)
  - Local epidemiology
  - Local resources (including financial resources)
- Responses should be coordinated and not implemented unilaterally

39

**Economic Analysis of VRE:
Assessing Attributable Cost and Length of Stay**

- In a hospital with a large number of immunocompromised and medically complicated patients, VRE positivity was associated with:
  - Attributable cost of approximately $18,000 CAD
  - Attributable LOS of approximately 14 days
- Local data should guide the intensity of a VRE prevention and control program
- Response should be proportionate to the threat

40

Acknowledgements

- Dr. Patrick Lloyd-Smith
- Jaime Younger
- Dr. Elisa Lloyd-Smith
- Howard Green
- Dr. Victor Leung
- PHC Infection Prevention and Control Team

41

**Economic Analysis of VRE:
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42

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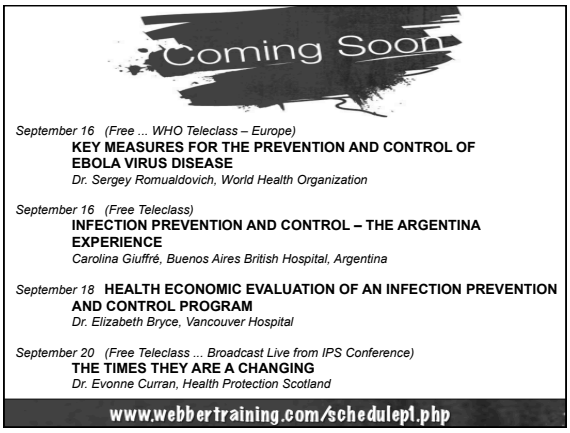

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