RAPID RESPONSE REPORT

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Screening, Isolation, and Decolonization Strategies for Vancomycin-Resistant Enterococci or Extended Spectrum Beta-Lactamase Organisms: A Systematic Review of the Clinical Evidence [DRAFT]

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EXECUTIVE SUMMARY

Context and policy issues:

Bacterial resistance to antibiotics is an increasing problem in Canada and worldwide.[1-4] Vancomycin-resistant enterococci (VRE) are strains of *Enterococcus faecium* or *Enterococcus faecalis* that contain genes resistant to vancomycin.[5,6] *Escherichia coli*, (*E. coli*) *Klebsiella pneumonia (K. pneumonia)*, and other gram-negative bacteria may produce the enzyme extended spectrum beta-lactamase (ESBL) that has the ability to inactivate beta lactam antibiotics such as penicillins, ampicillin, and cephalosporins.[7,8]

The presence and growth (colonization) of VRE and ESBL-producing organisms in the gastrointestinal tract is a source of infection for the carrier, and a reservoir for the transmission of VRE and ESBL-producing organisms to other patients.[9,10] Results from the Canadian Nosocomial Infection Surveillance Program showed that from 1999 to 2005, the rate of VRE colonization and VRE infection increased from 0.37 to 1.32 cases, and from 0.02 to 0.05 cases, respectively, per 1,000 patients admitted to hospital.[11] The Canadian Ward Surveillance Study in 2008 found that ESBL-producing *E. coli* were identified in all Canadian geographic regions, and that 4.9% of *E. coli* isolates were ESBL producers.[12]

Prevention and control measures for VRE and ESBL-producing organisms include screening (a process to identify patients colonized with antibiotic-resistant organisms), isolation of the carriers, and decolonization (the use of topical and systemic antimicrobials to eradicate colonization of resistant bacteria). Hospital infection control strategies and guidelines have been developed in Canada for antibiotic-resistant organisms.[13-17]

Antibiotic-resistant pathogens such as VRE and ESBL-producing organisms increase use of hospital resources due to extended hospital stays, laboratory tests, physician consultations, and the need to take costly infection control measures to prevent the further spread of these pathogens.[18]

The objective of this study is to conduct a systematic review of the clinical evidence for the effectiveness of screening, isolation, and decolonization strategies for VRE and ESBL-producing organisms in acute and long-term care facilities. The health services impact of these strategies will be discussed.

Research Questions:

1. What is the clinical evidence on the effectiveness of selective versus universal versus no screening of patients (adult and pediatric) for vancomycin-resistant enterococci (VRE) or extended spectrum beta-lactamase (ESBL)-producing organisms?

2. What is the clinical evidence on the effectiveness of patient isolation for VRE or ESBL-producing organisms?

3. What is the clinical evidence on the impact of isolation on the patient?

4. What is the clinical evidence for the effectiveness of decolonizing patients known to be carrying VRE or ESBL-producing organisms?

5. What is the clinical evidence on the effectiveness of additional precautions in the operating room or post-anesthesia recovery room in patients colonized with VRE or ESBL-producing organisms?

6. What is the health services impact of screening, isolating, and decolonizing patients known to be carrying VRE or ESBL-producing organisms on blocked beds, cancelled or limited surgeries, or the range of services a facility can provide?

Methods:

A peer-reviewed literature search was conducted using the following bibliographic databases: MEDLINE, EMBASE, PubMed, and The Cochrane Library (2012, Issue 3). Grey literature (literature that is not commercially published) was identified by searching relevant sections of the Grey Matters checklist (http://www.cadth.ca/index.php/en/cadth/products/grey-matters). Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2002 and March 26, 2012. Regular alerts were established to update the search until June 8, 2012. For the clinical evidence sections, two independent reviewers screened articles using pre-defined criteria. Trials were eligible for inclusion if they involved adults or pediatric patients in acute or long-term care facilities, with VRE or ESBL-producing organisms; compared the effectiveness of screening, isolation, and decolonization with no screening, no isolation, and no decolonization; and reported outcomes related to VRE or ESBL-producing organisms detection, transmission, and infection.

An additional search on the health services impact of the related main search concepts was conducted with the same time-frame and methodology. Two independent reviewers screened articles using pre-defined criteria. Trials were eligible for inclusion if they involved adults or pediatric patients in acute or long-term care facilities, with VRE or ESBL-producing organisms and discussed the impact of screening, isolation, and decolonization of these patients on hospital resources.

Summary of Findings:

The evidence from a limited number of observational studies (n = 6) showed that active surveillance with weekly rectal swabs in high-risk units may result in lower VRE bacteremia rates compared with no surveillance strategy. Compared to isolates in a hospital without active surveillance, an active surveillance program also helps to induce a population of VRE that is more polyclonal, which, in turn, may cause less horizontal transmission of the organism. In situations where routine infection control measures fail to prevent the transmission of ESBL-producing organisms, an aggressive control strategy may be effective, with daily surveillance cultures, increased contact precautions, and staff reinforcement regarding use of precautionary measures. The implementation of guidelines in hospitals, to ensure strict isolation plus contact precautions, was shown to be important in controlling the spread of VRE. Contact precautions and isolation, however, may have a negative psychological impact on patients, seen in increased rates of depression and anxiety. There was no evidence found on the clinical effectiveness of decolonization compared with no decolonization on VRE and ESBL-producing infection and transmission.

Evidence from retrospective cohort studies suggested that patients infected with hospital-acquired VRE or ESBL-producing organisms have a longer length of hospital stay than matched cohorts of control patients. Prolonged lengths of stay was due to a variety of reasons which included the infection itself, improper administration of initial antibiotic therapy, or infection control measures used to prevent the spread of infection. This increased length of stay contributes to increased use of hospital resources such as blocked beds and rooms, and the need for more health care worker time providing direct patient care.

Conclusions and Implications for Decision or Policy Making:

Evidence from a limited number of observational studies showed that active surveillance, patient isolation, and specific precautionary measures in hospital settings may result in reducing the spread of VRE and ESBL colonization. Implementation of certain precautionary measures needs to take into consideration the psychological effects that isolation may have on hospitalized patients. Stronger evidence, supported by large randomized controlled trials, considering ethics approval difficulty, is needed to confirm the findings.

Since transmission risk was shown to be associated with the number of roommates, design of acute care hospitals is important to minimize the transmission risk. Deployment of staff is important to focus the attention to high risk units. Direct and efficient communication between different teams is also a necessity. With foreign travel identified as an infection transmission risk factor, awareness in medical practitioners of the infection risk in returning travellers is important. Implementation of precautionary measures needs to take into consideration the negative psychological effects that isolation may have on hospitalized patients.

Observational studies showed that patients infected or colonized with VRE or ESBL-producing organisms put a burden on hospital resources due to increased lengths of hospital stays, increased usage of hospital beds, increased health care worker staffing, and the need for precautions to prevent the spread of infection. Though infection control measures may be effective at preventing the spread of these organisms, there is a lack of evidence regarding whether or not these are cost-effective measures, and practice is variable.

ACRONYMS AND ABBREVIATIONS

CI	confidence interval
CVD	cardiovascular disease
E. coli	*Escherichia coli*
ESBL	extended spectrum beta-lactamase
HAM-A	Hamilton Anxiety Rating Scale
HAM-D	Hamilton Depression Rating Scale
HIV	human immunodeficiency virus
ICD-9-CM	International Classification of Disease, ninth revision, Clinical Modification
ICU	intensive care unit
IQR	intraquartile range
K. pneumonia	*Klebsiella pneumonia*
LOS	length of hospital stay
MDR	multi-drug resistant
MRSA	methicillin-resistant *Staphylococcus aureus*
NICU	neonatal intensive care unit
NR	not reported
OD	odds ratio
PIDAC	Provincial Infectious Disease Advisory Committee
RCT	randomized controlled trial
SD	standard deviation
SR	systematic review
VRE	vancomycin-resistant enterococci

CONTEXT AND POLICY ISSUES

Bacterial resistance to antibiotics is an increasing problem in Canada and worldwide.[1-4] Vancomycin-resistant enterococci (VRE) are strains of *Enterococcus faecium* or *Enterococcus faecalis* that contain genes resistant to vancomycin.[5,6] *Escherichia coli (E. coli)*, *Klebsiella pneumonia (K. pneumonia)*, and other gram-negative bacteria may produce the enzyme extended spectrum beta-lactamase (ESBL) that has the ability to inactivate beta lactam antibiotics such as penicillins, ampicillin, and cephalosporins.[7,8] The presence and growth (colonization) of VRE and ESBL organisms in the gastrointestinal tract is a source of infection for the carrier, and a reservoir for the transmission of VRE and ESBL-producing organisms to other patients.[9,10] In a cohort of patients admitted to an acute rehabilitation hospital, who did not have a history of antibacterial-resistant infections, admission swabs were positive for methicillin-resistant *Staphylococcus aureus* (MRSA) or VRE in 16% of the population.[19] Results from the Canadian Nosocomial Infection Surveillance Program showed that from 1999 to 2005, the rate of VRE detection and VRE infection increased from 0.37 to 1.32 cases and from 0.02 to 0.05 cases, respectively, per 1,000 patients admitted to hospital.[11] The Canadian Ward Surveillance Study in 2008 found that ESBL-producing *E. coli* were identified in all Canadian geographic regions, and that 4.9% of *E. coli* isolates were ESBL producers.[12] In one study, the rate of colonization with ESBL-producing organisms among high-risk hospitalized patients doubled from 1.33% in 2000 to 3.21% in 2005.[20] The number of ESBL blood stream infection also increased from nine cases in 2001 to 40 cases in 2005.[20]

Among patients with enterococcal bloodstream infection, bacteria that were resistant to vancomycin were shown to be directly associated with increased mortality compared with bacteria that were susceptible to vancomycin.[21,22] Prevention and control measures for VRE and ESBL-producing organisms include a process to identify patients or health care workers colonized with antibiotic-resistant organisms (screening), isolation of the carriers, and the use of topical and systemic antimicrobials to eradicate colonization of resistant bacteria (decolonization). Hospital infection control strategies and guidelines for antibiotic-resistant organisms have been developed in some Canadian jurisdictions,[13-17] and include restriction of antibiotics such as vancomycin, education of hospital staff concerning procedures such as hand washing with an antiseptic agent, routine screening for VRE and gram negative isolates for ESBL, and contact isolation of patients infected with VRE or ESBL-producing organisms.[23-25]

In Ontario, the Provincial Infectious Diseases Advisory Committee (PIDAC)[16] recommended, among other things, that:

- "Each health care setting should have a prevention and control program for MRSA and VRE" (p.19)
- "Screening for risk factors for MRSA and VRE should include a screening tool that is applied to all clients/patients/residents admitted to the health care facility" (p. 20)
- "Every effort should be made to try to determine the source of new cases of MRSA or VRE. Every new case should warrant an investigation" (p. 21)
- "During an outbreak, all client/patient/resident contacts with common risk factors should be actively screened." (p. 22)
- "Hand hygiene must be performed by all staff before and after each contact with a client/patient/resident or contact with environmental surfaces near the client/patient/resident" (p. 24)
- additional precautions such as contact precautions are required for MRSA and VRE.[16]

These recommendations were based on relevant citations and expert opinions, and were not specific to any particular healthcare setting.

Antibiotic-resistant pathogens such as VRE and ESBL-producing organisms increase use of hospital resources due to extended hospital stays, laboratory tests, physician consultations, and the cost of infection control measures to prevent the further spread of these pathogens.[18] Antibiotic-resistant organisms are commonly detected in the intensive care unit (ICU) where antimicrobial selection pressure is higher and exposure to broad-spectrum antimicrobials is more common.[18] The health care impact of resistance cannot be limited to the hospital perspective, as significant portions of clinical care are provided in other facilities.[26]

The objective of this study is to conduct a systematic review of the clinical evidence for screening, isolation, and decolonization strategies for VRE and ESBL-producing organisms. The health services impact of these strategies will be discussed. In the face of increasing rates of multi-drug resistant infections in Canada, and the lack of a standardized guideline regarding VRE and ESBL-producing organisms, the findings from this report may be used for the development of guidelines in Canadian jurisdictions.

RESEARCH QUESTIONS

1. What is the clinical evidence on the effectiveness of selective versus universal versus no screening of patients (adult and pediatric) for vancomycin-resistant enterococci (VRE) or extended spectrum beta-lactamase (ESBL)-producing organisms?

2. What is the clinical evidence on the effectiveness of patient isolation for VRE or ESBL-producing organisms?

3. What is the clinical evidence on the impact of isolation on the patient?

4. What is the clinical evidence for the effectiveness of decolonizing patients known to be carrying VRE or ESBL-producing organisms?

5. What is the clinical evidence on the effectiveness of additional precautions in the operating room or post-anesthesia recovery room in patients colonized with VRE or ESBL-producing organisms?

6. What is the health services impact of screening, isolating, and decolonizing patients known to be carrying VRE or ESBL-producing organisms on blocked beds, cancelled or limited surgeries, or the range of services a facility can provide?

KEY FINDINGS

Evidence from a limited number of observational studies showed that active surveillance and other precautionary measures in hospital settings may result in reducing the spread of VRE and ESBL infections. Specific infection control strategies to increase the efficacy of and compliance to the precautionary measures are important in the prevention of antibiotic-resistant organisms

infections. Implementation of certain precautionary measures needs to take into consideration the negative psychological effects that isolation may have on hospitalized patients.

Additionally, evidence from a limited number of observational studies showed that patients infected or colonized with VRE or ESBL-producing organisms put an increased burden on hospital resources through increased length of hospital stay, blocking beds and rooms, and increasing the time devoted to direct patient care by health care workers. However, additional studies will be needed to confirm these findings, as uncontrolled studies may be prone to bias.

A. CLINICAL EVIDENCE

METHODS

Literature search strategy

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE with in-process records & daily updates via Ovid; EMBASE via Ovid; The Cochrane Library (2012, Issue 3) via Wiley; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were VRE and ESBL, and screening, isolation, and decolonization.

Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2002 and March 26, 2012. Regular alerts were established to update the search until June 8, 2012. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the Grey Matters checklist (http://www.cadth.ca/resources/grey-matters). Google and other Internet search engines were used to search for additional web-based materials. See Appendix 1 for more information on the grey literature search strategy.

Selection criteria and method

Two reviewers (CH and KC) independently screened citations and selected trials relevant to the research questions regarding VRE and ESBL-producing organisms. The decision to order an article in full text for closer examination was based on screening of the title of each citation and its abstract, when available. Two reviewers (CH and KC) independently selected the final articles for inclusion based on examination of the full-text publications. A study was included for review according to selection criteria established a priori (Table 1). Any disagreement between reviewers was discussed until consensus was reached. The trial selection process is presented in a flowchart according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[27] (Appendix 2)

Table 1: Trial Selection Criteria for Clinical Evidence	
Population	Adults and pediatric patients in acute and long-term care facilities, who are infected with or are carriers of VRE or ESBL-producing organisms
Intervention	• Screening (targeted or universal) for VRE or ESBL-producing organisms • Isolation for VRE or ESBL-producing organisms • Decolonization for VRE or ESBL-producing organisms • Additional precautions taken in the operating room or post-anesthesia recovery room for patients colonized with VRE or ESBL-producing organisms
Comparator	• No screening • No isolation • No decolonization
Outcomes	• Transmission, infections • Intermediate outcomes: VRE or ESBL-producing organisms acquisition and infection. • Health outcomes: morbidity (including complications of VRE or ESBL-producing organisms infection), case-fatality, mortality, quality of care for noninfectious conditions, and medical errors. • Adverse events: adverse effects of screening and treatment, including allergic reactions, non-allergic toxicities, and resistance to antimicrobials. • Duration of hospitalization
Study design	• Randomized controlled trials and non-randomized studies

ESBL=extended spectrum beta-lactamase; VRE=vancomycin-resistant enterococci

Exclusion criteria

Articles were excluded if they did not meet the selection criteria in Table 1, if they were published prior to January 2002, were non-comparative studies, or if they were duplicate publications of the same study. A study inclusion/exclusion form for the clinical effectiveness review was designed a priori, and is shown in Appendix 3.

Data extraction strategy

A data extraction form for the clinical effectiveness review was designed a priori to document and tabulate relevant study characteristics. Data were extracted independently by reviewers (CH and KC), and any disagreements were resolved through discussion until consensus was reached.

Critical appraisal of individual studies

The validated Downs and Black checklist was used to assess the study quality of experimental and observational studies based on quality of reporting, external validity and risk of bias. A copy of the data extraction form for the clinical studies is provided in Appendix 4. Numerical scores for each study were not calculated. Instead, study strengths and limitations were described.

Data analysis methods

Because of the scarcity of the included trials and the clinical heterogeneity of the reported outcomes, a meta-analysis was deemed inappropriate. Instead, a narrative synthesis and summary of study findings were conducted.

RESULTS

Quantity of research available

The literature search yielded 963 citations. Thirty-nine additional studies were identified by searching the grey literature. After screening and review of abstracts, 125 potentially relevant studies were selected for full-text review.

Six observational studies[28-33] were included in the review. The PRISMA flowchart in Appendix 2 details the process of the study selection. Included and excluded trials are listed in Appendices 5 and 6, respectively.

Summary of study characteristics

Study design

Included in the review are six studies, comprising three prospective observational[29-31] and three retrospective trials.[28,32,33] Detailed characteristics of the included studies are summarized in Appendix 7.

Study population

Selected studies included patients with VRE,[28-30] VRE/MRSA,[31] VRE/MRSA/multi-drug resistant gram-negative bacteria[32] or ESBL-producing organisms[33] infections. Detailed characteristics of the patients are summarized in Appendix 8.

Intervention and comparators

Selected studies compared active screening of high-risk patients with no screening,[28] contact isolation with no intervention,[29,31] strict isolation with contact precaution or strict isolation plus modified contact precaution,[30] contact precaution with no contact precaution,[32] routine infection control strategies with reinforced infection control strategies.[33] Details of the interventions and comparators are summarized in Appendix 9.

Outcomes

Main reported outcomes were the incidence of hospital-acquired infection[28-30,33] and rates of depression or anxiety.[31,32]

Summary of critical appraisal

Three studies were prospective designs,[29-31] and the remainder were retrospective. All studies, with the possible exception of the study by Catalano et al.[31] appeared to include patients that were representative of the general population. Compliance with the intervention was considered reliable in three studies.[29,31,33] The main limitations were the lack of randomization and blinding in all studies, small cohort sizes in most studies,[29-31,33] and the inability to determine if confounders were considered in case and control groups in most studies.[29-31,33] Additionally, two studies collected data from the cohorts at different time periods,[28,30] and two studies did not indicate if the same time periods were examined for the patient groups.[31,32] A summary of the critical appraisal can be found in Appendix 10.

Summary of findings

Our review included four studies comparing the effectiveness of different infection control strategies on the detection and transmission rates of VRE or ESBL-producing organisms,[28-30,33] and two studies on their comparative effects on patients' depression or anxiety.[31,32] Main study findings and authors' conclusions can be found in Appendix 11.

1. What is the clinical evidence on the effectiveness of selective versus universal versus no screening of patients (adult and pediatric) for vancomycin-resistant enterococci (VRE) or extended spectrum beta-lactamase (ESBL)-producing organisms?

Two studies found that screening and aggressive infection control strategy were effective in reducing VRE bacteremia rates,[28] and ESBL-producing organisms colonization and infection rates.[33]

A retrospective study published in 2003 compared the effects of active surveillance (screening) versus no active surveillance (no screening) of patients at risk for VRE infection, between two tertiary care hospitals (total 290 patients) during a six-year period.[28] Active surveillance included weekly rectal swabs from all patients for three consecutive weeks in high-risk units such as hematology-oncology, intensive care, and transplant. When VRE were detected, the microbiology department immediately called the nursing unit to indicate that the patient needed contact isolation. VRE isolates were also subjected to molecular typing for strain type identification. The analysis showed that, when corrected for patient-days, the hospital without an active surveillance program had 2.1-fold more cases (17.1 patients per 100,000 versus 8.2 patients per 100,000) of VRE bacteremia than did the hospital with an active surveillance program. The majority of isolates were clonally related in the hospital without active surveillance, while the population of VRE was more polyclonal in the hospital with the active surveillance program. The authors concluded that routine active surveillance of patients in VRE high-risk units may result in lower bacteremia rates and a more polyclonal VRE population, which causes less horizontal transmission.

A prospective study published in 2008 examined the effectiveness of biweekly surveillance cultures and contact precautions compared with a reinforced infection control program including daily surveillance cultures, increased contact precautions, and staff reinforcement regarding use of contact precautions in the reduction of ESBL-producing organisms in an intensive care unit (ICU) setting (31-bed unit).[33] Findings showed that the incidence of ICU-acquired ESBL-producing *K. pneumonia* increased during an outbreak, and the incidence fell dramatically following implementation of reinforced infection control measures. The authors concluded that an aggressive infection control strategy can be efficient in situations in which routine control measures fail to prevent or interrupt the nosocomial transmission of ESBL-producing *K. pneumonia*.

2. What is the clinical evidence on the effectiveness of patient isolation for VRE or ESBL-producing organisms?

Two studies found that strict isolation together with contact precautions helped to reduce the rates of VRE transmission.[29,30]

A prospective study published in 2004 examined the effects of strict contact isolation on control of VRE spread in a 2,000-bed teaching hospital.[29] After identifying that a patient was colonized or infected with VRE, the patient was put on strict contact isolation. Health care workers were asked to wear gowns, gloves, and masks before entering the room of patients infected or colonized with VRE. Devices such as thermometers, stethoscopes, and sphygmomanometers

were dedicated to infected patients only. Upon discharge of an infected patient, bed, bedside equipment, and environment were disinfected. Surveillance cultures of rectal swabs or stool, wounds, or any infected sites of the index patient's roommate were performed to determine colonization status. Screening of patients in neighbouring rooms was also performed. After 2.5 years, VRE precautions were relaxed and no more surveillance was performed. Results showed that hospital-acquired infection rates remained stable during the precaution implementation period, but increased during the no-precaution period. Molecular typing of isolates in the period where strict contact isolation precautions were enforced revealed more types of VRE than in the period during which precautions were relaxed. The authors concluded that precaution guidelines implementation is important in controlling the spread of VRE.

A prospective study published in 2007 examined the effectiveness of different infection control strategies in the reduction of VRE transmission in a 1,250-bed tertiary care hospital.[30] The comparative strategies were: contact precaution (weekly rectal cultures from index patients and roommates, and environmental cultures performed before and after terminal cleaning); strict isolation (patients with positive cultures for VRE isolated in private rooms) plus contact precaution; and strict isolation plus modified contact precaution (rectal cultures from index patients only; environmental cultures performed only after terminal disinfection). Findings showed that the incidence rate for VRE rectal colonization was highest in the contact precaution only period (1.45 cases per 10,000 patient-days). The strict isolation plus modified contact precaution period had a similar incidence rate (0.88 cases per 10,000 patient-days) to the strict isolation plus contact precaution period (0.75 cases per 10,000 patient-days). The authors concluded that strict isolation of affected patients together with contact precautions reduced the transmission of VRE.

3. <u>What is the clinical evidence on the impact of isolation on the patient?</u>

Two studies found that isolation may increase levels of anxiety or depression in hospitalized patients.[31,32]

A prospective study published in 2003 examined the impact of isolation on anxiety and depression in 27 patients hospitalized for colonization or infection with either MSRA or VRE.[31] The control group comprised 24 patients admitted to the hospital for the treatment of infection, but who did not require isolation. The difference of Hamilton Depression Rating Scale (HAM-D) or Hamilton Anxiety Rating Scale (HAM-A) scores at baseline and one- or two-week follow-up in the isolation group was compared to the difference of scores in the control group (time-by-group interaction). Findings showed that after one week of hospitalization, patients in the isolation group experienced an increase in HAM-D and HAM-A scores, while both scores were lower for patients in the control group. Time-by-group interaction analyses showed that differences between the intervention and control groups were statistically significant. The authors suggested that isolation may increase levels of anxiety and depression in hospitalized patients.

A retrospective study published in 2011 examined the effect of contact precautions on depression or anxiety in over 36,000 patients admitted to a tertiary care hospital.[32] Patients were placed on contact precautions when their medical record indicated the presence of multi-drug resistant bacteria or when they were positive upon screening for MRSA, VRE, or ESBL-producing organisms. The incidence of depression, using the International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM), was compared between the contact precaution group and the non-contact precaution group. In the non-ICU population, patients on contact precautions were 40% more likely than those not on contact precautions to be diagnosed with depression (OR 1.5, 95% CI 1.2 to 1.6). There was no association found

between contact precautions and anxiety. In the ICU population, there was no relationship found between contact precautions and depression or anxiety. The authors concluded there was an association between contact precautions and depression in patients hospitalized for multi-drug resistant infections.

4. What is the clinical evidence for the effectiveness of decolonizing patients known to be carrying VRE or ESBL-producing organisms?

There was no evidence found that compared the effectiveness of decolonization to non-decolonization on patients carrying VRE or ESBL-producing organisms.

5. What is the clinical evidence on the effectiveness of additional precautions in the operating room or post-anesthesia recovery room in patients colonized with VRE or ESBL-producing organisms?

There was no comparative clinical evidence found regarding the effectiveness of additional precautions in the operating room or post-anesthesia recovery room, for disease transmission by patients colonized with VRE or ESBL-producing organisms.

B. HEALTH SERVICES IMPACT

6. What is the impact of screening, isolating, and decolonizing patients known to be carrying VRE or ESBL organisms on blocked beds, cancelled or limited surgeries, or the range of services a facility can provide?

METHODS

Literature Search Strategy
See Section A: Clinical Evidence.

Selection Criteria and Methods

Two reviewers (AL and KC) independently screened citations and selected trials relevant to the research question regarding VRE and ESBL-producing organisms. The decision to order an article in full text for closer examination was based on screening of the title of each citation and its abstract, when available. Two reviewers (AL and KC) independently selected the final articles for inclusion based on examination of the full-text publications. A study was included for review according to selection criteria established a priori (Table 2).

Table 2: Trial Selection Criteria for Health Services Impact

Population	Adults and pediatric patients in acute and long-term care facilities with VRE or ESBL organisms
Intervention	• Screening (targeted or universal) for VRE or ESBL-producing organisms • Isolation for VRE or ESBL-producing organisms • Decolonization for VRE or ESBL-producing organisms
Comparator	• No screening • No isolation • No decolonization
Outcomes	• Blocked beds, occupied beds

	• Cancelled or limited surgeries • Duration of hospitalization • Ability to provide services, particularly control programs for MRSA, *C. difficile*, and other antibiotic-resistant organisms
Study design	• Randomized controlled trials and observational studies.

ESBL=extended spectrum beta-lactamase; VRE=vancomycin-resistant enterococci

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 2, if they were published prior to January 2002, or if they were duplicate publications of the same study.

Critical appraisal of individual studies

A formal critical appraisal of the selected health services impact studies was not performed. Instead, limitations of the identified body of literature was narratively described.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 263 citations. After screening and review of abstracts, 260 citations were excluded and three potentially relevant articles were retrieved for full-text review. An additional two potentially relevant reports were identified through grey literature searching. Of the five potentially relevant reports, one did not meet the inclusion criteria. Three retrospective cohort studies and one single-intervention impact study met inclusion criteria. The PRISMA flowchart in Appendix 12 details the process of the study selection.

Summary of Study Characteristics

Details on study characteristics are summarized in Appendix 13.

Country of origin

One retrospective cohort study was conducted in Israel[34] and the two other retrospective cohort studies were from the US.[35,36] The single-intervention impact study was from Canada.[37]

Study setting

All studies were conducted in a hospital setting. Three studies were conducted in urban tertiary-care hospitals[34,36,37] and one study was conducted in the neonatal intensive care unit (NICU) of a freestanding children's hospital.[35]

Patient population

One study[34] included patients infected with VRE, while the remaining three studies[35,36,36] included patients infected with ESBL-producing organisms. Of the ESBL studies, one study[35] looked at an outbreak caused by ESBL-producing *K. pneumonia*, while the two other studies[36,37] looked at patients infected with either ESBL-producing *E. coli* or *Klebsiella* species. In all of the included studies, infection was confirmed by isolation of the organism from a clinical culture.

Interventions and comparators

The single-intervention impact study implemented an infection control intervention to reduce nosocomial ESBL transmission.[37] This intervention involved isolating patients with ESBL-producing organisms as identified from a clinical specimen in a private room for the duration of their hospital stay. Contact precautions involved gown and gloves for any persons entering the patient's room, proper hand hygiene, dedicated patient care equipment and thorough environmental cleaning upon patient discharge.

The three retrospective cohort analyses used various methods to match case patients with appropriate controls.[34-36] One study matched the VRE-infected cohort with other hospital patients on the basis of length of hospital stay at the time of matching, hospital ward location, and calendar date.[34] One study matched ESBL-infected infants in the NICU to other NICU infants with negative surveillance cultures during the outbreak, to neonates discharged during a six-month period before the outbreak, and to infants from a national sample.[35] One study matched patients with non-urinary tract ESBL infections to control patients with infection due to non-ESBL-producing organisms on the basis of initial antibiotic therapy, infecting pathogen, and at least one of either age, site of infection, or date of culture.[36]

Outcomes measured

All included studies reported on length of hospital stay and hospital costs as outcome measures. One study[34] also focused on mortality, admission to an ICU, the need for surgery, and discharge to an institution. One study[37] analyzed the time spent by health care workers giving direct patient care during the ESBL outbreak in addition to surveillance and administrative time related to the outbreak. One study[36] looked at the clinical response to initial antibiotic therapy. The single-intervention impact study[37] evaluated the hospital costs associated with implementing an infection control program.

Summary of Findings

Details on study findings are summarized in Appendix 14.

Length of hospital stay

The three retrospective cohort studies[34-36] found that patients infected with either VRE or ESBL organisms had a longer length of hospital stay (LOS) than a matched cohort of control patients. In one study,[37] this was likely due to the measures taken to isolate patients in private rooms in order to prevent the spread of infection. In the remaining three studies[34-36] the increased LOS was due to the infection or illness of the patient itself[34,35] or to inappropriate administration of initial antibiotic therapy.[36]

In the study by Carmeli et al.,[34] the mean number of days between inclusion and discharge from hospital was 15.1 days (range 1 to107 days) for VRE cases versus 8.5 days (range 1 to116 days) for the control cases. It was estimated that being a VRE case was associated with an average adjusted increase of 6.2 days in LOS. In addition, VRE cases were associated with a significantly higher likelihood for ICU admission after inclusion in the cohort (adjusted RR 3.47, $P < 0.001$) and a higher rate of being discharged to long-term care (RR 2.01, $P = 0.001$), thus increasing the use of resources and extending it beyond the period of hospitalization.

In the study by Stone et al.,[35] a four-month outbreak of ESBL *K. pneumonia* in a NICU was found to result in an increased mean LOS in infected infants that was 48.5 days longer than that of a similarly stratified cohort of infants from a national sample. Colonized infants, or infants from whom *K. pneumonia* was isolated but who manifested no clinical symptoms, had significantly longer LOS than infants admitted to the NICU with negative surveillance cultures and neonates who were discharged during a six-month period before the outbreak.

In the study by Lee et al.,[36] patients infected with ESBL-producing organisms had an increased mean LOS of 9.7 days (95% CI 3.2 to 14.6 days, $P = 0.006$) more than patients who were infected with non-ESBL-producing organisms.

Blocked beds and rooms

The study by Stone et al.[35] found that one third of the total cost of the ESBL outbreak in the NICU was attributable to lost revenue from blocked beds (186 patient-days). Similarly, the study by Lee et al[36] found that bed costs were statistically significantly greater for patients infected with ESBL-producing organisms than for control patients infected with non-ESBL-producing organisms.

In the study by Conterno et al.,[37] the infection control measures that were implemented involved isolating patients infected with ESBL-producing organisms in private rooms. Of the 177 infected patients, 134 were placed in private rooms and the remainder were discharged by the time the culture results were available. The mean LOS in the private rooms by these patients was 21 days (range 1 to142 days) and the use of private rooms was the highest resource use for the hospital.

Health care workers

In the study by Stone et al.,[35] the bulk of hospital resource use was related to health care worker time providing direct patient care. Most health care worker time was attributed to nurse staffing and overtime needed to care for and maintain the infants. In addition, health care worker time was devoted to media preparation, strain identification, antimicrobial susceptibility testing, molecular typing, and interpretation.

In the study be Conterno et al.,[37] additional nursing time accounted for the third highest cost of the infection control measures taken to prevent the spread of ESBL, behind private room and supply costs.

Antibiotic treatments

The study by Lee et al.[36] compared the effectiveness of antibiotic treatment for patients infected with ESBL-producing organisms versus patients infected with non-ESBL-producing organisms. The rate of successful response among patients with ESBL-producing organisms who did not initially receive carbapenem, the appropriate antibiotic, was lower than that of their matched control subjects (39% versus 83%, $P = 0.013$). Treatment was successful for both patient groups who received a carbapenem, regardless of ESBL status of the infecting organism. Due to the poor rate of response to initial therapy, patients with ESBL-producing organisms were more likely to receive subsequent antibiotic therapies, thereby increasing their total infection-related length of stay.

LIMITATIONS

Due to the limited number of studies identified (n = 4), it is difficult to draw definitive conclusions regarding the health services impact of screening, isolating, and decolonizing patients known to be carrying VRE or ESBL-producing organisms. In addition, all of the studies were observational studies and caution must be taken about drawing too many conclusions and generalizing the results. The specific populations in the studies may not be representative of all hospitals. Observational studies may also be prone to bias and confounding, as researcher bias can bias both the design of a study or data collection. These studies appear to show that patients who are infected with VRE or ESBL-producing organisms have a longer hospital length of stay than patients who are not infected with these organisms. However, this may also be evidence that increased length of stay is a risk factor for developing infection in the hospital, or that these patients had underlying conditions that would require longer hospital stays regardless of the infection. This problem was addressed in one study[34] by applying study design and analytic methods to control as much as possible the other factors besides antibiotic resistance that contributed to adverse outcomes. Primary diagnoses and comorbitidies that distinguished VRE cases from their matched controls were accounted for by a propensity score method. Despite adjustments to prevent confounding, these issues may still exist and make data difficult to interpret.

Most of these studies would be applicable in Canada as they were conducted in urban hospitals. However, one study[35] discussed lost revenue when considering costs attributable to blocked beds, which may not be applicable in Canada where health care is publically funded rather than owned by the private sector.

DISCUSSION

Evidence from a limited number of observational studies included in our report showed that active surveillance with weekly rectal swabs in high-risk hospital units may result in lower VRE bacteremia rates compared with no surveillance strategy. Compared to isolates in a hospital without active surveillance, an active surveillance program also helps to induce a population of VRE that is more polyclonal, which in turn causes less horizontal transmission of the infection. In situations where routine infection control measures fail to prevent the transmission of ESBL-producing organisms, an aggressive control strategy may be effective, with daily surveillance cultures, increased contact precautions, and staff reinforcement. The implementation of guidelines to ensure strict isolation plus contact precaution in hospitals was shown to be important in controlling the spread of VRE. Contact precautions and isolation, however, may have a negative psychological impact on patients, with increased rates of depression and anxiety. The isolation process in itself may also inadvertently predispose patients to medical errors and adverse events. In a study at two large North American teaching hospitals, Sunnybrook and Women's College Health Sciences Centre in Toronto, Ontario; and Brigham and Women's Hospital in Boston, Massachusetts,[38] patients isolated due to MRSA colonization or infection were two times more likely to experience adverse events compared with a non-isolated control group ($P < 0.001$).The difference reflected preventable adverse events which were mainly caused by supportive care failures. As well, more isolated patients expressed

dissatisfaction than control patients ($P < 0.001$), particularly regarding treatment, access to staff, and communication.

In order to maximize the efficacy of infection control, in addition to screening, isolation, and decolonization procedures, specific control measures need to be implemented in hospital settings. Surveillance data in an acute tertiary care hospital found that the rates of healthcare-associated infections were highest in the ICUs, and lowest in the wards.[39] A Canadian tertiary care hospital found that the number of roommates a patient was exposed to was directly associated with the risk of acquiring nosocomial MRSA and VRE infections.[40] These findings can have implications for the staff deployment and design of acute care hospitals.

Increased awareness of potential sources of bacteria in hospital settings also helps to reduce the risk of bacterial transmission. Bath basins are found to be a reservoir for VRE, MRSA, and many other bacteria.[41] Mobile phones of patients, companions, and visitors represent a risk for hospital-acquired infections.[42] Despite the belief that white lab coats could be contaminated with antibiotic-resistant organisms,[43] a review of the literature did not support the hypothesis that uniforms or clothing could be a vehicle for the transmission of healthcare-associated infections.[44]

Despite the increased risk of nosocomial infections, compliance of health care workers to hand hygiene was low when working with patients infected with MRSA (47% and 43% in the ICU and intermediate care units, respectively) and ESBL (54% and 51% in the ICU and intermediate care units, respectively).[45] Use of electronic alerts in the form of beeps to prompt health care workers to perform antisepsis was shown to improve hand hygiene compliance.[46] Implementation of a computerized reminder increased the rate of patients appropriately isolated.[47]

The robustness of the evidence on the effects of precaution measures on the detection and transmission of VRE and ESBL-producing organisms is limited, due to the nature of the available evidence. A systematic review (SR) in 2006 of the literature on the use of barrier precautions, patient isolation, and surveillance cultures,[48] showed that the evidence generally supports the use of surveillance culture barrier precautions and patient isolation to prevent the transmission of multi-drug resistant organisms, but the lack of RCTs decreased the robustness of the findings. An SR in 2001 on the efficacy of infection control in the reduction of ESBL transmission in a non-outbreak setting[49] found no conclusion could be made due to the scarcity and the poor-quality of the evidence. A review of guidelines and literature in 2006 on the evidence of infection control strategies for MRSA and VRE[50] concluded that active surveillance and contact precautions have been effective in the reduction of MRSA and VRE transmission in some settings, but infection control measures as currently implemented failed to prevent the spread of MRSA and VRE in most hospitals; the evidence lacked support by RCTs. Long intervals of patient follow-up to determine transmission rates can provide a reliable calculation of the mean rates, but on the other hand, this long time period may allow seasonal effects to influence the results, and care practices may have changed over time. In trials where the transmission rates were compared between different hospitals, the organisms were introduced into each hospital at different times. A direct comparison during the same time would have given a more accurate analysis. Some trials focused on multiple organisms, such as VRE/MRSA, making the conclusion on the effect of precaution measures on a specific type of bacteria difficult. For psychological outcomes such as depression and anxiety, observational studies that identified a predetermined group of high risk patients on isolation tended to be studies of association, not causality.

With regards to the impact of screening, isolating, and decolonizing patients infected or colonized with VRE or ESBL-producing organisms on health services, a limited number of retrospective cohort studies showed that these patients have longer lengths of hospital stays than an appropriately matched cohort of control patients.[34-36] However, one study that compared the effectiveness of antibiotic treatment for patients infected with ESBL-producing organisms versus patients infected with non-ESBL-producing organisms found that poor response rates to initial antibiotic therapy of patients infected with ESBL-producing organisms was likely what resulted in an increased infection-related length of stay.[36] One study that implemented an ESBL infection control program found that the practice of isolating patients in private rooms was the highest resource use for the hospital, followed by additional nursing time.[37] Similarly, a study that retrospectively analyzed an ESBL outbreak in the NICU found that blocked beds contributed to one-third of the total costs of the outbreak due to lost revenue as a result of fewer patients being seen and that health care worker time providing direct patient care contributed to the bulk of hospital resource use.[35] Since there were few studies identified and the majority of the studies were retrospective analyses, the interpretations of the results may be biased.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Evidence from a limited number of observational studies showed that active surveillance, patient isolation, and other precautionary measures such as staff reassignment to high risk units or increased compliance to hand hygiene in hospital settings may result in reducing the spread of VRE and ESBL colonizations and infections. Implementation of precautionary measures needs to take into consideration the negative psychological effects that isolation may have on hospitalized patients. Stronger evidence, supported by large RCTs, is needed to confirm the findings.

Evidence from a limited number of observational studies suggested that patients infected with VRE or ESBL-producing organisms use more hospital resources due to increased lengths of hospital stays, increased usage of hospital beds, increased health care worker staffing, and the need for precautions to prevent the spread of infection.

Infection control measures may be effective at preventing the spread of these organisms, but are costly to implement. There are variable practices among hospitals in implementing infection control measures. Different approaches must be used for all emerging infections instead of following what has been done in regards to MRSA control.

A survey sent to infection control programs in all Canadian acute care hospitals with 80 or more beds[51] found that a significant increase in the number of full-time infection control professionals (ICPs) has not translated into improvement of antibiotic-resistant organisms control (from 1999 to 2005, new nosocomial VRE cases increased 77%). Also, as part of the Canadian Nosocomial Infection Surveillance program, a 2003 survey of Canadian tertiary care hospitals[52] found that greater than 96% and greater than 89% of Canadian teaching hospitals conducted admission screening for MRSA and VRE, respectively, but only one site screened for ESBL/AmpC (organisms that produce AmpC-type beta-lactamase). Revelations from these findings are important for decision makers in infection control policy making. Direct and efficient communication between different teams is also a factor, as shown in another survey of Canadian acute care hospitals,[53] in which VRE infections were found to be less likely to happen

if infection control staff frequently contacted physicians or nurses for reports of new infections. In addition, findings such as the association between a higher rate of infection and a greater number of roommates, and increased risk of infection in certain hospital units as compared to others can have implications for the staff deployment and design of acute care hospitals. Awareness by medical practitioners of the risk of infection in returning travellers is also important.[54-56] Finally, access to staff and communication with isolated patients may help to decrease the rates of preventable medical errors and increase patients' satisfaction.

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APPENDIX 1: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	EMBASE 1974 to 2012 March 23 (oemezd) Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present (pmez) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	March 26, 2012
Alerts:	Monthly search updates began March 26, 2012 and ran until June 11, 2012.
Study Types:	Systematic reviews; meta-analyses; technology assessments; randomized controlled trials; controlled clinical trials; multicenter studies; cohort studies; cross-over studies; case control studies; comparative studies; epidemiologic studies;
Limits:	Publication years 2002-March 2012 Humans Conference abstracts excluded English language only

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.nm	Name of substance word
.jw	Journal word

Multi-database Strategy

Line #	Searches
	VRE/ESBL Concept (MEDLINE)
1	Vancomycin Resistance/
2	(Vancomycin adj5 resistan*).ti,ab.
3	or/1-2
4	exp Gram-Positive Bacterial Infections/
5	exp Enterococcus/
6	Enterococc*.ti,ab.
7	or/4-6
8	3 and 7
9	(VRE or VREs).ti,ab.
10	8 or 9
11	exp beta-Lactam Resistance/
12	exp beta-Lactamases/
13	Beta-lactamas*.nm.
14	or/11-13
15	((extended or expanded) adj5 (spectrum or spectra)).ti,ab.
16	14 and 15
17	((extended or expanded) adj5 (spectrum or spectra) adj5 (lactam* or betalactam*)).ti,ab.
18	(ESBL or ESBLs).ti,ab.
19	or/16-18
20	10 or 19
21	20 use pmez
	VRE/ESBL Concept (EMBASE)
22	vancomycin resistant Enterococcus/
23	(Vancomycin adj5 resistan*).ti,ab.
24	Enterococc*.ti,ab.

25	23 and 24
26	(VRE or VREs).ti,ab.
27	22 or 25 or 26
28	extended spectrum beta lactamase/
29	((extended or expanded) adj5 (spectrum or spectra) adj5 (lactam* or betalactam*)).ti,ab.
30	(ESBL or ESBLs).ti,ab.
31	or/28-30
32	27 or 31
33	32 use oemezd
34	21 or 33
	Screening/Isolation/Decolonization Concept
35	exp Mass Screening/ or exp Screening/
36	(screen or screening or screened).ti,ab.
37	(test or tests or testing or tested).ti,ab.
38	surveillance.ti,ab.
39	(Patient Isolation or Patient Isolators or isolation procedure).sh.
40	((Isolator* or isolation or isolating or isolate or isolated) adj3 (patient* or ward* or unit* or room* or precaution* or pre-caution* or preemptive or pre-emptive or contact)).ti,ab.
41	(cohorting or segregat* or superisolation or quarantine* or containment).ti,ab.
42	(colonization or colonisation or colonize* or colonise* or decolonization or decolonisation or decolonize* or decolonise* or decolonizing or decolonising or de-colonis* or de-coloniz*).ti,ab.
43	(precaution* or pre-caution* or barrier*).ti,ab.
44	or/35-43
45	34 and 44
	Blocked Beds/Cancelled or Limited Surgeries/Range of Services Concept
46	(Health resources or Health care rationing or Resource allocation).sh.
47	*Hospital costs/ or *Hospital cost/
48	Bed occupancy/ or Hospital bed capacity/ or Hospital bed utilization/
49	((block* or capacit* or shortage*) adj5 (room or rooms or bed or beds or ward or wards)).ti,ab.

50	((Limit* or cancel* or postpon* or delay*) adj5 (surgery or surgeries or surgical)).ti,ab.
51	((Additional or opportunity or excess or extra) adj5 (cost or costs)).ti,ab.
52	(hospital* adj2 (cost or costs or utilization or utilisation or facility or facilities)).ti,ab.
53	(economic or cost or costs or expenditure* or budget*).ti.
54	((resource* or service*) adj3 (allocat* or ration* or utilization or utilisation or limit* or range or consumption or constraint*)).ti,ab.
55	or/46-54
56	45 and 55
57	*Infection control/
58	(Hospital adj2 acquired adj2 infection*).ti.
59	(Antibiotic adj2 (resistance or resistant)).ti.
60	(Nosocomial adj2 infection*).ti.
61	or/57-60
62	44 and 55 and 61
63	56 or 62
	Additional Precautions in Operating Room/Post-Anesthesia Recovery Room Concept
64	exp Gloves, Protective/
65	exp Masks/
66	protective clothing/
67	(gown* or glov* or mask*).ti,ab.
68	Handwashing/ or Hand washing/
69	(Hand adj2 (hygiene or wash*)).ti,ab.
70	exp Sterilization/ or instrument sterilization/
71	exp Disinfectants/ or exp disinfectant agent/
72	Equipment Contamination.sh.
73	exp Antisepsis/ or exp asepsis/
74	(clean* or sanitizer* or sanitiser* or sanitization or sanitisation or disinfect* or antiseptic* or anti-septic* or antisepsis or anti-sepsis or decontamina* or scrubbing or steriliz* or sterilis* or soap or soaps).ti,ab.

75	or/64-74
76	exp Surgical Procedures, Operative/ or exp surgery/
77	(surgery or surgeries or surgical or surgeon* or microsurg* or postoperative or postop or post-op or preoperative or perioperative or intraoperative or operation* or operative).ti,ab,hw.
78	surgery.fs.
79	or/76-78
80	75 and 79
81	exp Surgical Attire/
82	Operating Rooms/
83	Recovery Room/ or Anesthesia Recovery Period/ or anesthetic recovery/
84	((Operation* or operating or operative or surger* or surgical) adj5 (room* or unit* or theatre* or theater* or setting* or environment* or ward*)).ti,ab.
85	((Recovery or anesthe* or anaesthe* or postanesthe* or postanaesthe* or postsurg* or postop* or post-op*) adj5 (room* or unit* or setting* or environment* or ward*)).ti,ab.
86	or/81-85
87	80 or 86
88	34 and 87
	Meta-analysis/Systematic Review/Health Technology Assessment Filter
89	meta-analysis.pt.
90	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/
91	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
92	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
93	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
94	(data synthes* or data extraction* or data abstraction*).ti,ab.
95	(handsearch* or hand search*).ti,ab.
96	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.

97	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.
98	(meta regression* or metaregression* or mega regression*).ti,ab.
99	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
100	(medline or Cochrane or pubmed or medlars).ti,ab,hw.
101	(cochrane or (health adj2 technology assessment) or evidence report).jw.
102	or/89-101
	Randomized Controlled Trial/Controlled Clinical Trial Filter
103	(Randomized Controlled Trial or Controlled Clinical Trial).pt.
104	Randomized Controlled Trial/
105	Randomized Controlled Trials as Topic/
106	"Randomized Controlled Trial (topic)"/
107	Controlled Clinical Trial/
108	Controlled Clinical Trials as Topic/
109	"Controlled Clinical Trial (topic)"/
110	Randomization/
111	Random Allocation/
112	Double-Blind Method/
113	Double Blind Procedure/
114	Double-Blind Studies/
115	Single-Blind Method/
116	Single Blind Procedure/
117	Single-Blind Studies/
118	Placebos/
119	Placebo/
120	Control Groups/
121	Control Group/
122	(random* or sham or placebo*).ti,ab,hw.

123	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
124	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
125	(control* adj3 (study or studies or trial*)).ti,ab.
126	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.
127	allocated.ti,ab,hw.
128	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.
129	or/103-128
	Observational Studies Filter
130	epidemiologic methods.sh.
131	epidemiologic studies.sh.
132	cohort studies/
133	cohort analysis/
134	longitudinal studies/
135	longitudinal study/
136	prospective studies/
137	prospective study/
138	follow-up studies/
139	follow up/
140	followup studies/
141	retrospective studies/
142	retrospective study/
143	case-control studies/
144	exp case control study/
145	cross-sectional study/
146	observational study/
147	quasi experimental methods/
148	quasi experimental study/
149	validation studies.pt.

150	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab.
151	(cohort adj7 (study or studies or design or analysis or analyses)).ti,ab.
152	(prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti,ab.
153	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab.
154	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti,ab.
155	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti,ab.
156	((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab.
157	(case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab.
158	(population adj3 (study or studies or analysis or analyses)).ti,ab.
159	(descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab.
160	((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab.
161	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab.
162	((natural adj experiment) or (natural adj experiments)).ti,ab.
163	(quasi adj (experiment or experiments or experimental)).ti,ab.
164	((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab.
165	(prevalence adj3 (study or studies or analysis or analyses)).ti,ab.
166	case series.ti,ab.
167	case reports.pt.
168	case report/
169	case study/
170	(case adj3 (report or reports or study or studies or histories)).ti,ab.
171	organizational case studies.sh.
172	or/130-171
173	45 and (102 or 129 or 172)

174	88 and (102 or 129 or 172)
175	63 or 173 or 174
	Animal Filter
176	exp animals/
177	exp animal experimentation/
178	exp models animal/
179	exp animal experiment/
180	nonhuman/
181	exp vertebrate/
182	or/176-181
183	exp humans/
184	exp human experiment/
185	or/183-184
186	182 not 185
187	175 not 186
188	187 not conference abstract.pt.
189	limit 188 to english language
190	limit 189 to yr="2002 -Current"
191	remove duplicates from 190

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Cochrane Library Issue 3, 2012	Same MeSH, keywords, and date limits used as per Medline search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.

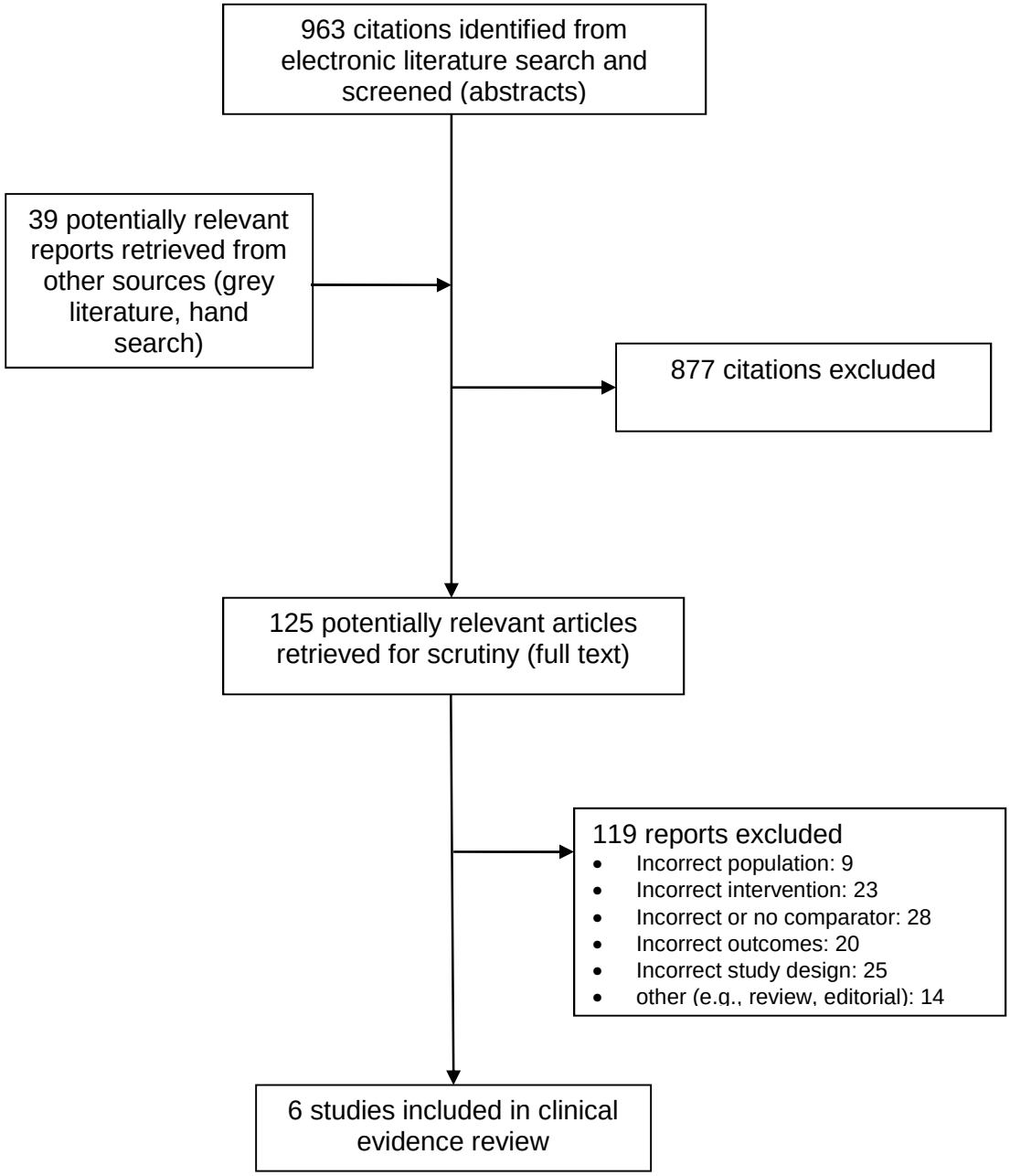
Grey Literature

Dates for Search:	March 27-29, 2012
Keywords:	Included terms for VRE, ESBL, screening, isolation and decolonization
Limits:	Publication years 2002-March 2012 Humans Conference abstracts excluded English language only

The following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/resources/grey-matters) were searched:

- Health Technology Assessment Agencies
- Databases (free)
- Internet Search

APPENDIX 2: Selection of Included Trials for Clinical Evidence



APPENDIX 3: Clinical Study Inclusion/Exclusion Form

Clinical Evidence of Screening, Isolation, and Decolonization Strategies for Vancomycin-Resistant Enterococci or Extended Spectrum Beta-Lactamase Organisms

Title:
First author and year:

Reviewer:

INCLUSION CRITERIA:

1. **Population**: yes_____ no_____ can't tell_____
Adults and pediatric patients in acute and long-term care facilities with VRE or ESBL organisms

2. **Intervention**: yes_____ no_____ can't tell_____
- Screening for VRE or ESBL organisms
- Isolation for VRE or ESBL organisms
- Decolonization for VRE or ESBL organisms

3. **Comparator**: yes_____ no_____ can't tell_____
- No screening
- No isolation
- No decolonization

4**. Outcome Measures** (any of): yes_____ no_____ can't tell_____
- Transmission, infections
- Health outcomes: morbidity (including complications of VRE or ESBL infection), case-fatality, mortality, quality of care for noninfectious conditions, and medical errors.
- Adverse events: adverse effects of screening and treatment, including allergic reactions, no allergic toxicities, and resistance to antimicrobials. Adverse events due to isolation (depression, medical errors)
- Length of hospital stay

5**. Study Design**: yes_____ no_____ can't tell_____
Randomized controlled trials (RCTs), non-randomized studies

- **"yes" (1-5 inclusive): include study and order full paper**_____
- **at least one "can't tell" and others "yes" for 1-5: order full paper for further review**_____
- **"no" (any 1 – 5): exclude study**

APPENDIX 4: Clinical Study Data Extraction Form

Clinical Evidence of Screening, Isolation, and Decolonization Strategies for Vancomycin-Resistant Enterococci or Extended Spectrum Beta-Lactamase Organisms

Reviewer:

Study title:		
Author:		
ID #: Year:		
Methods		
Study design		
Study duration		
Population - Number of patients randomized - Number of patients completing the study		
Diagnosis		
Eligibility criteria		
Country of origin		
Industry sponsorship	☐ Yes ☐No ☐Unknown	
Baseline Characteristics Of Study Participants		
- Age - Diagnosis - Others		
Outcomes	**Intervention**	**Comparator**
SCREENING Detection rate Colonization rate Co-colonization rate (including MRSA) Rate of VRE or ESBL organisms transmission Rate of VRE or ESBL organisms infection **ISOLATION** Rate of compliance with use of transmission-control measures (e.g., alcohol-based hand rubs, gloves, cohorting) Rate of VRE or ESBL organisms transmission		

DECOLONIZATION Rate of VRE or ESBL organisms transmission - Placebo - Drug (different dosages) Rate of VRE or ESBL organisms infection - Placebo - Drug (different dosages) Morbidity - Placebo - Drug (different dosages) Mortality - Placebo - Drug (different dosages) Length of hospital stay - Placebo - Drug (different dosages) Antimicrobial susceptibility and resistance (MIC) Drugs adverse events		
Comments		

ESBL=extended spectrum beta-lactamase; MIC=minimum inhibitory concentration; MRSA=methicillin-resistant *S. aureus*; VRE=vancomycin-resistant enterococci

APPENDIX 5: Included Trials for Clinical Evidence

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

Wang JT, Chen YC, Chang SC, Chen ML, Pan HJ, Chang YY, et al. Control of vancomycin-resistant enterococci in a hospital: a five-year experience in a Taiwanese teaching hospital. J Hosp Infect. 2004;58(2):97-103.

Yoonchang SW, Peck KR, Kim OS, Lee JH, Lee NY, Oh WS, et al. Efficacy of infection control strategies to reduce transmission of vancomycin-resistant enterococci in a tertiary care hospital in Korea: a 4-year follow-up study. Infect Control Hosp Epidemiol. 2007 Apr;28(4):493-5.

Catalano G, Houston SH, Catalano MC, Butera AS, Jennings SM, Hakala SM, et al. Anxiety and depression in hospitalized patients in resistant organism isolation. South Med J. 2003 Feb;96(2):141-5.

Day HR, Perencevich EN, Harris AD, Himelhoch SS, Brown CH, Gruber-Baldini AL, et al. Do contact precautions cause depression? A two-year study at a tertiary care medical centre. J Hosp Infect. 2011;79(2):103-7.

Laurent C, Rodriguez-Villalobos H, Rost F, Strale H, Vincent JL, Deplano A, et al. Intensive care unit outbreak of extended-spectrum beta-lactamase-producing Klebsiella pneumoniae controlled by cohorting patients and reinforcing infection control measures. Infect Control Hosp Epidemiol. 2008 Jun;29(6):517-24.

APPENDIX 6: Excluded Trials for Clinical Evidence

Incorrect population

Goodman ER, Platt R, Bass R, Onderdonk AB, Yokoe DS, Huang SS. Impact of an environmental cleaning intervention on the presence of methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci on surfaces in intensive care unit rooms. Infect Control Hosp Epidemiol. 2008 Jul;29(7):593-9.

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Peirano G, Laupland KB, Gregson DB, Pitout JD. Colonization of returning travelers with CTX-M-producing Escherichia coli. J Travel Med. 2011 Sep;18(5):299-303.

Tekerekoglu MS, Duman Y, Serindag A, Cuglan SS, Kaysadu H, Tunc E, et al. Do mobile phones of patients, companions and visitors carry multidrug-resistant hospital pathogens? Am J Infect Control. 2011 Jun;39(5):379-81.

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Treakle AM, Thom KA, Furuno JP, Strauss SM, Harris AD, Perencevich EN. Bacterial contamination of health care workers' white coats. Am J Infect Control [Internet]. 2009 Mar [cited 2012 Apr 3];37(2):101-5. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2892863/pdf/nihms185144.pdf

Warren DK, Guth RM, Coopersmith CM, Merz LR, Zack JE, Fraser VJ. Impact of a methicillin-resistant Staphylococcus aureus active surveillance program on contact precaution utilization in a surgical intensive care unit. Crit Care Med. 2007 Feb;35(2):430-4.

Waterhouse M, Morton A, Mengersen K, Cook D, Playford G. Role of overcrowding in meticillin-resistant Staphylococcus aureus transmission: Bayesian network analysis for a single public hospital. J Hosp Infect. 2011;78(2):92-6.

Incorrect intervention

The use of gloves for bathing patients with antibiotic-resistant organisms in acute and continuing care: clinical effectiveness, harms, and guidelines [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2011. [cited 2012 Apr 2]. Available from: http://www.cadth.ca/media/pdf/htis/sept-2011/RB0421_Gloves_final.pdf

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infections: results of a quasi-experimental multicenter trial. Crit Care Med. 2009 Jun;37(6):1858-65.

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Harris AD, Kotetishvili M, Shurland S, Johnson JA, Morris JG, Nemoy LL, et al. How important is patient-to-patient transmission in extended-spectrum beta-lactamase Escherichia coli acquisition. Am J Infect Control. 2007 Mar;35(2):97-101.

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Mody L, McNeil SA, Sun R, Bradley SE, Kauffman CA. Introduction of a waterless alcohol-based hand rub in a long-term-care facility. Infect Control Hosp Epidemiol. 2003 Mar;24(3):165-71.

Nseir S, Grailles G, Soury-Lavergne A, Minacori F, Alves I, Durocher A. Accuracy of American Thoracic Society/Infectious Diseases Society of America criteria in predicting infection or colonization with multidrug-resistant bacteria at intensive-care unit admission. Clin Microbiol Infect. 2010 Jul;16(7):902-8.

Paterson DL, Muto CA, Ndirangu M, Linden PK, Potoski BA, Capitano B, et al. Acquisition of rectal colonization by vancomycin-resistant Enterococcus among intensive care unit patients treated with piperacillin-tazobactam versus those receiving cefepime-cbntaining antibiotic regimens. Antimicrob Agents Chemother. 2008 Feb;52(2):465-9.

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Puzniak LA, Leet T, Mayfield J, Kollef M, Mundy LM. To gown or not to gown: the effect on acquisition of vancomycin-resistant enterococci. Clin Infect Dis [Internet]. 2002 Jul 1 [cited 2012 Apr 2];35(1):18-25. Available from: http://cid.oxfordjournals.org/content/35/1/18.full.pdf+html

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Incorrect or no comparator

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APPENDIX 7: Clinical Evidence Study Characteristics

First author, year, country, study design	Objective	Intervention; no. of patients	Comparator; no. of patients	Organism
Price, 2003[28] US Retrospective cohort	To determine if routine screening and contact isolation of high-risk patients would account for differences in VRE bacteremia rates	Hospital B, active screening of high-risk patients; 82 patients	Hospital A, no routine screening; 218 patients	VRE
Wang, 2004[29] Taiwan Prospective cohort	To report the differences in spread of VRE in one hospital, with and without guidelines	Strict contact and cohort isolation; no. of patients NR	No active intervention; no. of patients NR	VRE
YoonChang, 2007[30] Korea Prospective cohort	To evaluate the effectiveness of contact precautions and strict isolation in controlling the transmission of VRE	Period B, strict isolation; 7 patients Period C, follow-up with strict isolation; 95 patients	Period A, contact precautions; 19 patients	VRE
Catalano, 2003[31] US Prospective cohort	To assess the possible association of contact isolation with an increase in the symptoms of anxiety and depression	Contact isolation; 27 patients	Control (did not require isolation); 24 patients	VRE or MRSA
Day, 2011[32] US Retrospective cohort	To assess the impact of contact precautions on symptoms of anxiety and depression	Contact precautions (general hospital); 3,138 patients Contact precautions (ICU); 1,694 patients	No contact precautions (general hospital); 25,426 patients No contact precautions (ICU); 5,854 patients	VRE, MRSA, and MDR gram-negative bacteria
Laurent, 2008[33] Belgium Retrospective cohort	To describe the impact of infection control measures for controlling transmission of ESBL during an outbreak in the ICUs	Reinforced infection control strategies (increased frequency of surveillance cultures to daily; cohort isolation with suspected infection, with increased nurse-to-patient ratio); no. of patients NR	Routine infection control strategies (contact isolation for identified carriers or high-risk patients until confirmed); no. of patients NR	ESBL

ESBL=extended spectrum beta-lactamase; ICU=intensive care unit; no.=number; MDR=multi-drug resistant; MRSA=methicillin-resistant *S. aureus*; NR=not reported; VRE=vancomycin-resistant enterococci

APPENDIX 8: Clinical Studies Patient Characteristics

First author, date	Study arms	No. of patients	Sex (m/f)	Age (years, SD)	Length of hospital stay (mean days)	Prior diagnosis/underlying disease/prior depression
Price, 2003[28]	Hospital A (no routine screening)	218	95/123	58.9 ± 18.5	52.2 ± 25.6 (SD)	Hepatobiliary: 18.6 (% of pts) Cancer: 19.1 CVD: 13.2 Diabetes mellitus: 8.7 HIV infection: 2.2
	Hospital B (routine screening of high-risk patients)	72	42/30	61 ± 71.4	27.3 ± 26.8 (SD)	Hepatobiliary: 20 (% of pts) Cancer: 40 CVD: 28 Diabetes mellitus: 24 HIV infection: 4
Wang, 2004[29]	Patient characteristics not reported					
YoonChang, 2007[30]	Period A (contact precautions)	19	8/11	NR	NR	NR
	Period B (strict isolation)	7	3/4	NR	NR	NR
	Period C (strict isolation follow-up)	95	55/40	NR	NR	NR
Catalano, 2003[31]	Control	24	20/4	59.0 ± 19.7	NR	Prior Axis I psychiatric diagnosis: 8.3%
	Isolation	27	10/15	52.2 ± 15.3	NR	Prior Axis I psychiatric diagnosis: 22.2%
Day, 2011[32]	General hosp: pts on contact precautions	3,138	1,848/ 1,290	51.2 ± 17.5	Median 7.1 (IQR 3.4-18.1)	On antidepressant med: 37 (1.2%)
	General hosp: pts not on contact precautions	25,426	11,776/ 13,650	49.6 ± 19.0	3.2 (2.0-6.0)	On antidepressant med: 54 (0.2%)
	ICU: pts on contact precautions	1,694	1,032/ 662	54.9 ± 17.5	14.8 (7.4-28.8)	On antidepressant med: 333 (19.7%)
	ICU: pts not on contact precautions	5,854	3,494/ 2,360	56.0 ± 17.7	7.0 (3.9-12.5)	On antidepressant med: 573 (9.9%)
Laurent, 2008[33]	Patient characteristics not reported					

CVD=cardiovascular disease; HIV=human immunodeficiency virus; hosp=hospital; ICU=intensive care unit; IQR=intraquartile range; med=medications; No.=number; pts=patients; SD=standard deviation

APPENDIX 9: Interventions and Comparators

First Author, Year	Study arm	Screening methods	Contact precautions
Price, 2003[28]	Hospital with active surveillance	Active surveillance for VRE with weekly rectal swabs for 3 consecutive weeks in high-risk units, then monthly once 3 negative results obtained.	Contact isolation (no further details reported) until rectal swabs negative for VRE.
	Hospital with no active surveillance	No routine screening of patients	Not reported
Wang, 2004[29]	Active surveillance with strict contact and cohort isolation	VRE surveillance cultures of stool or rectal swab, wound, or other infected sites from roommate patients of index patients or patients in neighbouring rooms. Frequency not reported.	Strict contact isolation or cohort isolation (gloves, gowns, handwashing immediately after exiting room; dedicated use of stethoscopes, thermometers, and sphygmomanometers). HCWs were monitored by the head nurse to ensure isolation guidelines were followed. Isolation was discontinued after 3 negative swabs (on 3 different days).
	No active surveillance	No active surveillance	Not reported
YoonChang, 2007[30]	Strict isolation	Weekly rectal swabs from patients with positive VRE results and for patient roommates plus environmental surveillance from rooms and equipment used to treat them.	Strict isolation in private rooms until rectal swabs negative for VRE for 3 consecutive weeks.
	Contact precautions	Weekly rectal swabs from patients with positive VRE results and for patient roommates plus environmental surveillance from rooms and equipment used to treat them.	Contact precautions until rectal swabs negative for VRE for 3 consecutive weeks.
Catalano, 2003[31]	Patients with MRSA or VRE	Not reported	No details provided on type of isolation.
	Patients not requiring isolation	Not reported	No isolation
Day, 2011[32]	Patients with VRE or other drug-resistant organisms	Targeted patients were actively screened for VRE and other drug-resistant organisms (no further details reported).	Contact precautions and private room (if available). Data provided does not distinguish between contact precautions only or combined with private room.

	Patients not requiring contact precautions	Targeted patients were actively screened for VRE and other drug-resistant organisms (no further details reported).	No contact precautions
Laurent, 2008[33]	Reinforced infection control strategies	During outbreak, all ICU patients were tested for ESBL-producing organisms and other drug-resistant organisms by rectal swabs upon admission and daily.	Contact isolation precautions. No information reported on criteria for terminating contact precautions.
	Routine infection control strategies	Surveillance for ESBL-producing organisms and other drug-resistant organisms by rectal swabs upon admission to ICU and biweekly thereafter.	Contact isolation precautions. No information reported on criteria for terminating contact precautions.

ESBL=extended spectrum beta-lactamase; HCWs=healthcare workers; ICU=intensive care unit; MRSA=methicillin-resistant *Staphylococcus* aureus; VRE=vancomycin-resistant enterococci

APPENDIX 10: Critical Appraisal of Included Studies for Clinical Evidence

First author, year	Strengths	Limitations
Price, 2003[28]	• confounders considered • patients and facilities representative of population	• retrospective study • different time periods of data collection for each of the 2 hospitals • no randomization • no blinding indicated • unable to determine if compliance with intervention was reliable
Wang, 2004[29]	• prospective study • patients and facility representative of population • compliance with intervention was reliable	• unable to determine if confounders were considered • no randomization • no blinding indicated • very small number of patients studied
YoonChang, 2007[30]	• prospective study • patients and facility representative of population	• different time periods of data collection for each of the 2 cohorts • no randomization • unable to determine if confounders were considered • no blinding indicated • small number of patients studied
Catalano, 2003[31]	• prospective study • compliance with intervention was reliable	• unable to determine if patients were representative of the population from which they were recruited • no blinding indicated • unable to determine if cases and controls were studied over the same period of time • no randomization • unable to determine if confounders were considered • small number of patients studied
Day, 2011[32]	• patients and facility representative of population • confounders considered • large number of patients studied	• retrospective study • no randomization • no blinding indicated • unable to determine if cases and controls were studied over the same period of time • unable to determine if compliance with intervention was reliable
Laurent, 2008[33]	• patients and facility representative of population • compliance to intervention was reliable	• retrospective study • no randomization • no blinding indicated • unable to determine if confounders were considered • very small number of patients studied

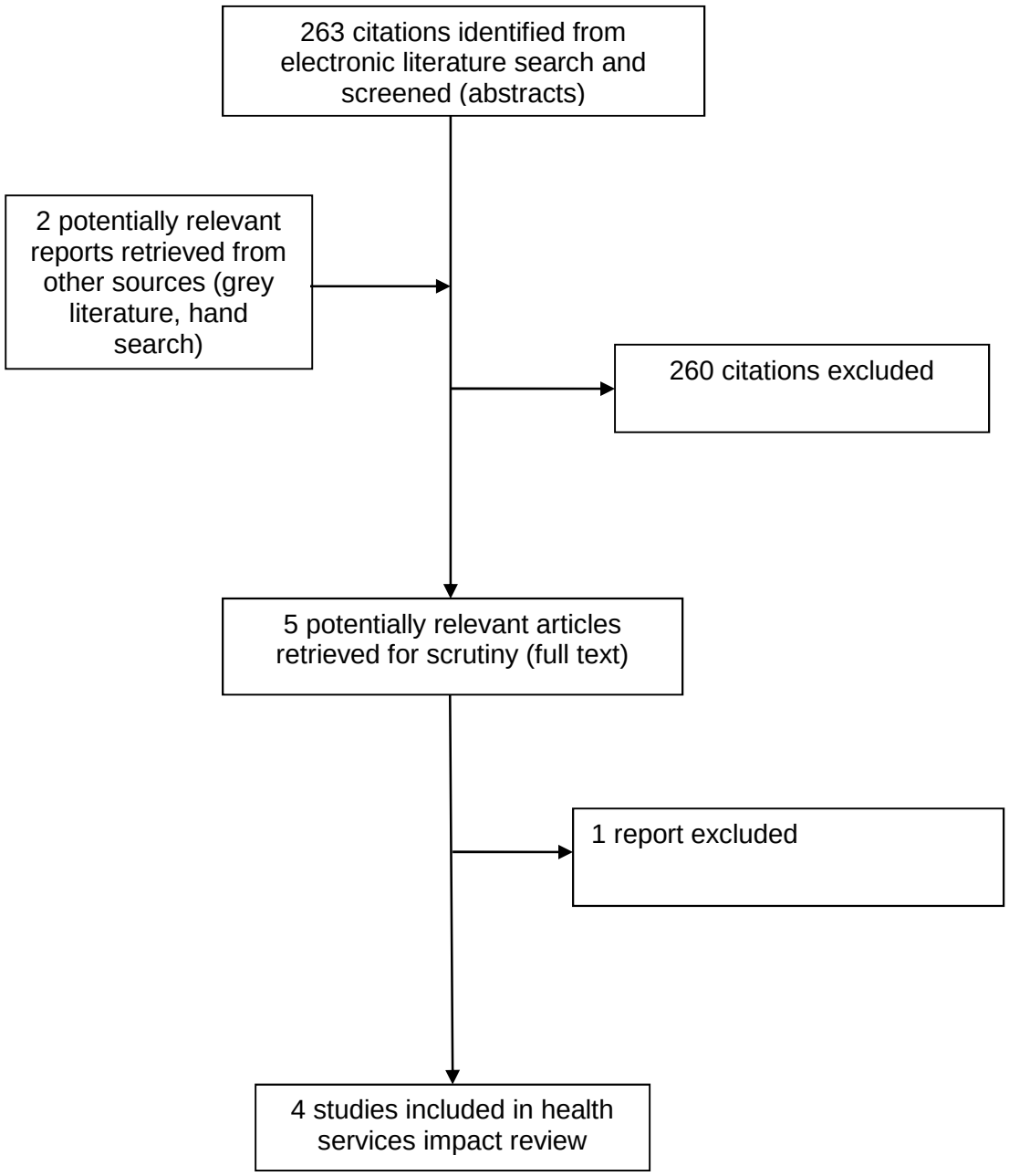
APPENDIX 11: Main Clinical Study Findings and Authors' Conclusions

First author, year	Main study findings	Authors' conclusions
Trials on VRE		
Price, 2003[28]	**Hospital A (no screening):** 17.1 patients with VRE bloodstream isolates per 100,000 patient-days during the 6-year period **Hospital B (with screening):** 8.2 patients with VRE bloodstream isolates per 100,000 patient-days during the 6-year period **Hospital A (no screening):** the majority of isolates were clonally related (4 most predominant clones were responsible for infection in >75% of all patients with VRE bloodstream isolates) **Hospital B (with screening):** the majority of isolates were not clonally related (4 most predominant clones were responsible for infection in 37% of all patients with VRE bloodstream isolates)	"hospital A had 2.1-fold more cases of VRE bacteremia than did hospital B" (p. 923) "Lower VRE bacteremia rates and a more polyclonal population, representing less horizontal transmission, may result from routine screening of patients who are at high risk for VRE…" (p. 921)
Wang, 2004[29]	**Strict contact and cohort isolation period** • hospital-acquired VRE infection rate: 0.03 to 0.09 per 1,000 discharges • molecular typing: 17 different types of VRE **No intervention period** • hospital-acquired VRE infection rate: 0.20 per 1,000 discharges • molecular typing: 8 different types of VRE	"interventions for the control of VRE… are effective for control of VRE spread" (p. 97)
YoonChang, 2007[30]	**Contact precaution period** (weekly rectal cultures from index patients and roommates; environmental cultures performed before and after terminal cleaning) : incidence rate for VRE colonization: 1.45 cases per 10,000 patient-days **Strict isolation** (patients with positive cultures for VRE isolated in private rooms) **plus contact precaution period:** incidence rate for VRE colonization: 0.75 cases per 10,000 patient-days (p = 0.003) **Strict solation plus modified contact precaution** (rectal cultures from index patients only; environmental cultures performed only *after* terminal disinfection) **period** : incidence rate for VRE colonization: 0.88 cases per 10,000 patient-days (p = 0.009)	"Strict isolation of affected patients in private rooms, in addition to use of contact precautions, showed a significantly improved reduction in the transmission of VRE" (p. 493)

First author, year	Main study findings	Authors' conclusions
Catalano, 2003[31]	**Control group (no isolation, patients available at 1 week follow-up):** HAM-D decreased from 8.46 to 6.00 after 1 week of hospitalization HAM-A decreased from 8.37 to 4.71 after 1 week of hospitalization **Intervention group (with isolation, patients available at 1 week follow-up):** HAM-D increased from 8.42 to 10.73 after 1 week of hospitalization. (the difference of change over time between the control and intervention groups was statistically significant; p <0.001) HAM-A increased from 8.00 to 11.11 after 1 week of hospitalization (the difference of change over time between the control and intervention groups was statistically significant; p<0.001) **Control group (no isolation, patients available at 2 weeks follow-up)** HAM-D decreased from 9.78 to 5.44 after 1 week, and to 4.22 after 2 weeks of hospitalization HAM-A decreased from 11.00 to 4.44 after 1 week, then to 2.44 after 2 weeks of hospitalization **Intervention group (with isolation, patients available at 2 weeks follow-up):** HAM-D increased from 7.25 to 8.83 after 1 week, then to 11.50 at 2 weeks of hospitalization (the difference of change over time between the control and intervention groups was statistically significant; p <0.001) HAM-A increased from 5.83 to 8.67 after 1 week, then decreased to 8.33 at 2 weeks of hospitalization (the difference of change over time between the control and intervention groups was statistically significant; p<0.001)	"…suggests that placement in resistant organism isolation may increase hospitalized patients' levels of anxiety and depression" (p. 141)
Day, 2011[32]	**General hospital (contact precautions versus no contact precautions):** Depression OR 1.4 (95% CI: 1.2 – 1.6); p <0.01 Anxiety: OR 0.9 (95% CI: 0.7 – 1.1); p 0.35 **Intensive care Unit (contact precautions versus no contact precautions):** Depression: OR 0.9 (95% CI: 0.7 – 1.2). p 0.44 Anxiety: OR 0.7 (95% CI 0.4 – 1.1)	"…contact precautions were associated with depression but not with anxiety in the non-ICU population" (p. 103) "No relationship was found between contact precautions and depression or anxiety in the ICU population" (p. 104)
Trials on ESBL organisms		
Laurent, 2008[33]	**Routine infection control** (biweekly surveillance cultures and contact precautions): 0.44 cases per 1,000 patient-days (baseline) and 6.86 cases per 1,000 patients-days (during outbreak) . The incidence reached a maximum of 11.57 cases per 1,000 patient-days **Reinforced infection control** (daily surveillance cultures and increased contact precautions and staff reinforcement): 0.08 cases per 1,000 patient-days	"in situations in which routine infection control measures fail to prevent or interrupt the nosocomial transmission of ESBL-producing *K. pneumonia* among critically ill patients, an aggressive control strategy that includes the cohorting of carriers and staff reinforcement can be efficient…" (p. 522)

CI=confidence interval; ESBL=extended spectrum beta-lactamase organisms; HAM-A=Hamilton Anxiety Rating Scale; HAM-D=Hamilton Depression Rating Scale; OR=odds ratio; VRE=vancomycin-resistant enterococci

APPENDIX 12: Selection of Studies for Health Service Impact



APPENDIX 13: Health Services Impact Study Characteristics

First Author, Publication Year, Country, Study Design, Study Period	Study setting	Patient population	Matched comparators	Outcomes Measured
Carmeli, 2002[34] Israel Retrospective cohort study Oct 1993-Dec 1997	Urban tertiary care teaching hospital 320 beds 24 ICU beds 12,000 patient admissions per year	Patients who had VRE isolated from a clinical culture (n=233)	Control patients (n=647) matched based on: - hospital ward - calendar date (±7 days) - duration of hospital stay at the time of matching (±3 days)	- Mortality - LOS - Total hospital costs - Admission to an ICU - Need for surgery or discharge to an institution
Stone, 2003[35] US Retrospective cohort study of a 4-month outbreak Apr 1-July 31, 2001	NICU in a children's hospital 45 beds	Neonates who had ESBL-producing *K. pneumonia* isolated from a sterile body site (infected infants, n=8; colonized infants, n=14)	Control patients matched: - NICU infants with negative surveillance cultures - Neonates discharged during 6-month period before outbreak - Infants from the National Perinatal Information Center	- Hospital costs - Lost revenue - Health care worker time - LOS
Lee, 2006[36] US Retrospective cohort study Oct 2001-May 2004	Urban community hospital 810 beds	Patients infected with non-urinary tract ESBL-producing *E. coli* and *Klebsiella* species isolated from a culture (n=21)	Control patients matched: - Patients with infection due to non-ESBL producing *E. coli* or *Klebsiella* species - Initial antibiotic therapy - Infecting pathogen One of the following: - Age (±5 years) - Site of infection - Stay in ICU - Date of culture (±3 months)	- Hospital costs - Clinical response to initial antibiotic therapy - Mortality - LOS
Conterno, 2007[37] Canada Single intervention impact study Jan 2002-Dec 2005	Tertiary care hospital Three ICUs 1,200 beds	Patients infected with ESBL-producing organisms confirmed by isolation from a clinical culture (n=173)	Infection control measures - All patients with ESBL-producing organisms was placed in a private room - Contact precautions for patients admitted to ICU,	- Costs due to infection control measures - Hospital costs

First Author, Publication Year, Country, Study Design, Study Period	Study setting	Patient population	Matched comparators	Outcomes Measured
			uncontained drainage from culture-positive site, diarrhea or incontinence	

ESBL=extended spectrum beta-lactamase; ICU=intensive care unit; LOS=length of hospital stay; NICU=neonatal intensive care unit; VRE=vancomycin-resistant enterococci

APPENDIX 14: Health Services Impact Study Findings

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Carmeli, 2002[34]	The mean LOS between inclusion in the cohort and discharge from hospital was significantly longer for the VRE cohort than control cases (15.1 days vs 8.5 days; RR 1.73; P<0.001). 25% of the VRE cohort required ICU care for at least 24 hours after being included in the cohort compared with 14% of the control group (RR 3.0; P<0.001). After adjusting for confounding, being a VRE case was associated with a significantly higher likelihood for ICU admission at some time after being included in the cohort (adjusted RR 3.47; P<0.001). 51% of the VRE cohort were discharged to long-term care compared to 35% of the control group (RR 1.98; P<0.001)	"Our major findings were that vancomycin-resistant enterococci culture positivity was associated with the following: (1) 2-fold increased odds of mortality, (2) 2.7-fold increased odds of a major surgical procedure, (3) 3.5 –fold increased odds of admission to the ICU, (4) a 1.7-fold increase in hospital LOS, (5) a 1.4-fold increase in cost of hospitalization, and (6) 2-fold increased odds of discharge to a long-term care facility. The later finding suggests that the impact of vancomycin-resistant enterococci extends beyond the period of hospitalization." (p. 2227)
Stone, 2003[35]	Infants infected with ESBL-producing *K. pneumonia* had a mean LOS that was 48.5 days longer than a national sample. Infants colonized with ESBL-producing *K. pneumonia* did not differ in mean LOS from a national sample. Infants colonized with ESBL-producing *K. pneumonia* had significantly longer LOS than infants admitted to the NICU with negative surveillance cultures than neonates who were discharged during a 6-month period before the outbreak. The largest proportion of costs related to the outbreak was related to health care worker time providing direct patient care (2489 hours). Most health care worker time was attributed to nurse staffing and overtime needed to care for and maintain the infants (1055 hours). Approximately one-third of the total cost was attributable to lost revenue from blocked beds (186 patient-days).	"Lost revenue to the hospital was almost $110,000. Furthermore, infected infants had a 48.5-day longer LOS than did similarly stratified infants from a national sample, wherease infants in the prior and concurrent cohorts had shorter LOS, thus providing evidence that the usual practice patterns of the NICU were altered by the outbreak." (p. 604)
Lee, 2006[36]	Total costs were significantly greater for patients infected with ESBL-producing *E. coli* or *Klebsiella* species (ESBL-EK case patients) than patient infected with non-ESBL-producing organisms (control patients). Only costs associated with bed use were statistically significantly greater among case patients than control patients ($22,441±21,656 vs $12,732±7,583; P=0.032). Mean infection-related length of stay was the main driver of cost, which was prolonged for case patients compared with control patients (21±15 days vs 11±5 days; P=0.006). Patients with ESBL-EK were more likely to receive sequential antibiotic therapy for their	"Similar to other studies, we observed that, among patients who did not receive a carbapenem, infection with ESBL-EK was associated with a rate of antibiotic failure that was higher than that for infection with non-ESBL-producing organisms. Case patients had a higher rate of clinical failure and thus required additional antibiotic regimens that led to prolonged lengths of stay. Therefore, delayed administration of appropriate therapy (ie, carbapenems) for treatment of infections due to ESBL-producing organisms might be correlated with higher hospital costs…" (p. 1230)

	infections (P<0.001) due to poor rate of response, thus increasing their total infection-related LOS.	
Conterno, 2007[37]	During the study period, 77% (134/173) of ESBL cases were placed in private rooms and the remainder were discharged by the time the culture result was available. Of the 134 cases placed in a private room, 69 (51.5%) were placed on contact precautions because of diarrhea/incontinence, uncontained drainage, ICU admission, or other reasons. The mean length of private room stay was 21 days (range 1-142 days), and the mean length of contact precautions was 19 days (range 1-124 days) per patient, after the ESBL-positive result became available. The use of private rooms had the greatest cost impact (85% of total cost), followed by cost of supplies for contact precautions (7.8%) and additional nursing time (6.5%).	"The mean cost of this intervention was $3191.83 per ESBL case. This cost would be higher if active surveillance cultures were used as control measure. Futhermore, if all patients were placed on contact precautions, rather than just patients at higher risk for transmission, the cost would increase by 23% per patient…Overall, 25% of newly detected ESBL cases in this study were imported, and 40% of all ESBL admissions represented re-admissions of known ESBL carriers, challenging containment efforts….We found that the use of private romos for ESBL-colonized or infected patients, along with contact precautions for patients at high risk for transmission, contributed to outbreak prevention but had no impact on the nosocomial ESBL incidence." (p. 359-360)

ESBL=extended spectrum beta-lactamase; ICU=intensive care unit; LOS=length of hospital stay; NICU=neonatal intensive care unit; RR=relative risk; VRE=vancomycin-resistant enterococci