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September 2012

Screening, Isolation, and Decolonization Strategies for Vancomycin-Resistant Enterococci or Extended Spectrum Beta-Lactamase Producing Organisms: A Systematic Review of the Clinical Evidence and Health Services Impact

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Screening, Isolation, and Decolonization Strategies for Vancomycin-Resistant Enterococci or Extended Spectrum Beta-Lactamase Producing Organisms: A Systematic Review of the Clinical Evidence and Health Services Impact

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Health technology assessment agencies face the challenge of providing quality assessments of medical technologies in a timely manner to support decision-making. Ideally, all important deliberations would be supported by comprehensive health technology assessment reports, but the urgency of some decisions often requires a more immediate response.

The Rapid Response Service provides Canadian health care decision-makers with health technology assessment information, based on the best available evidence, in a quick and efficient manner. Inquiries related to the assessment of health care technologies (drugs, devices, diagnostic tests, and surgical procedures) are accepted by the service. Information provided by the Rapid Response Service is tailored to meet the needs of decision-makers, taking into account the urgency, importance, and potential impact of the request.

Consultations with the requestor of this Rapid Response assessment indicated that a review of the literature would be beneficial. The research question and selection criteria were developed in consultation with the requestor. The literature search was carried out by an information specialist using a standardized search strategy. The review of evidence was conducted by one internal reviewer. The draft report was internally reviewed and externally peer-reviewed by two or more peer reviewers. All comments were reviewed internally to ensure that they were addressed appropriately.

This report is a review of existing public literature, studies, materials, and other information and documentation (collectively the "source documentation") that are available to CADTH. The accuracy of the contents of the source documentation on which this report is based is not warranted, assured, or represented in any way by CADTH, and CADTH does not assume responsibility for the quality, propriety, inaccuracies, or reasonableness of any statements, information, or conclusions contained in the source documentation.

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ACRONYMS AND ABBREVIATIONS

ARO	antibiotic-resistant organism
CI	confidence interval
CRE	carbapenem-resistant *Enterobacteriaceae*
E. coli	*Escherichia coli*
ESBL	extended spectrum beta-lactamase
HAM-A	Hamilton Anxiety Rating Scale
HAM-D	Hamilton Depression Rating Scale
ICU	intensive care unit
K. pneumonia	*Klebsiella pneumonia*
LOS	length of hospital stay
MDR	multidrug resistant
MRSA	methicillin-resistant *Staphylococcus aureus*
NICU	neonatal intensive care unit
OR	odds ratio
RCT	randomized controlled trial
SR	systematic review
VRE	vancomycin-resistant enterococci

TABLE OF CONTENTS

TITLE: Screening, Isolation, and Decolonization Strategies for Vancomycin-Resistant Enterococci or Extended Spectrum Beta-Lactamase Producing Organisms: A Systematic Review of the Clinical Evidence and Health Services Impact

DATE: September 2012

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 conferring resistance to vancomycin.[5,6] *Escherichia coli (E. coli)*, *Klebsiella pneumonia (K. pneumonia)*, and other gram-negative bacteria may produce the enzymes known as extended spectrum beta-lactamases (ESBL). These have the ability to inactivate beta lactam antibiotics such as penicillin, ampicillin, and the cephalosporins.[7,8]

The presence and growth (colonization) of VRE and ESBL-producing micro-organisms in the gastrointestinal tract is usually of no consequence for the host, but under certain circumstances, such as immunosuppression, gastrointestinal surgery, or physical debilitation, they may serve as a source of infection for the carrier. These hosts may also serve as a reservoir for the transmission of VRE and ESBL-producing organisms to other persons.[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 laboratory-based *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]

Specific prevention and control measures for antibiotic-resistant organisms (AROs) include screening (a process to identify persons colonized with AROs) and isolation of the carriers. Hospital infection prevention and control strategies have been developed in some Canadian jurisdictions,[13-16] and these are compatible with other national and international documents.[17,18] Non-specific strategies for controlling ARO transmission and infection include hand hygiene; environmental cleaning; antimicrobial stewardship; and bundled practices, such as those to prevent central line-associated blood stream infections.

Antibiotic-resistant organisms, such as VRE and ESBL-producers, lead to the increased use of hospital resources due to extended hospital stays, laboratory tests, physician consultations, costly medications if therapy for a VRE or ESBL-related infection were to arise, and the need to adhere to infection prevention and control measures to prevent the further spread of these pathogens.[19] Some of the increased resource usage results from the morbidity caused by VRE or ESBL-producing organism infections, while some is a consequence of control strategies. For example, it may be harder to transfer a patient to a rehabilitation facility if they are currently in isolation, which will in and of itself, prolong the length of stay.

The objective of this systematic review is to evaluate the clinical evidence for the effectiveness of screening, isolation, and decolonization strategies for persons colonized or infected with 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 VRE or 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?
   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?
5. 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://cadth.ca/resources/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 the publication of the final report. 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 showed that active surveillance with weekly rectal swabs in high-risk units was associated with lower VRE bacteremia rates compared with no surveillance strategy. Compared to isolates in a hospital without active surveillance, an active surveillance program was associated with a population of VRE that is more polyclonal (i.e., having genetically different origins), which may be evidence of less person-to-person transmission of the organism. In situations where routine infection prevention and control measures fail to prevent the transmission of ESBL-producing organisms, that is, during a clonal

outbreak, an aggressive control strategy may be effective, with daily surveillance cultures, increased contact precautions, and staff reinforcement regarding the 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 colonization. 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 were due to a variety of reasons, which included the infection itself, improper administration of initial antibiotic therapy, or infection prevention and control measures used to prevent the spread of infection to other patients. 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

There are few reports upon which to formulate evidence-based conclusions; however, evidence from a limited number of observational studies with methodological concerns showed that active surveillance (screening of all high-risk patients), patient isolation, and specific precautionary measures in hospital settings may result in reducing the spread and colonization of, and infection with VRE and ESBL-producing organisms. Increased rates of depression and anxiety were seen in patients under strict isolation and contact precautions. Stronger evidence, supported by adequately powered, multicentre cohort studies with robust analyses to minimize the potential biases are needed to confirm these findings. There was no evidence found that compared the effectiveness of decolonization to non-decolonization of patients carrying VRE or ESBL-producing organisms. Decolonization is not typically performed for patients with VRE or ESBL colonization.

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 on 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 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. Though infection prevention and 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.

1 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 conferring resistance to vancomycin.[5,6] *Escherichia coli (E. coli)*, *Klebsiella pneumonia (K. pneumonia)*, and other gram-negative bacteria may produce enzymes known as extended spectrum beta-lactamases (ESBLs). These have the ability to break down beta lactam antibiotics such as penicillin, 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 persons.[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.[20] 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 laboratory-based 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 increased from 1.33% in 2000 to 3.21% in 2005.[21] The number of blood stream infections caused by ESBL-producing organisms also increased from nine cases in 2001 to 40 cases in 2005.[21]

Among patients with enterococcal bloodstream infections, bacteria that were resistant to vancomycin were shown in two meta-analyses to be directly associated with increased mortality compared with bacteria that were susceptible to vancomycin.[22,23] It is noteworthy that the meta-analyses were systematic reviews (SRs) of cohort studies, most of them with inadequate sample size, and most studies were conducted before the availability of newer antimicrobials against VRE.

Prevention and control measures for VRE and ESBL-producing organisms include a screening process to identify patients colonized with antibiotic-resistant organisms (AROs), and isolation of the carriers. Decolonization is not typically performed for patients with VRE or ESBL colonization.

Hospital infection prevention and control strategies and guidelines for AROs have been developed in some Canadian jurisdictions,[13-16] and these include non-specific control measures such as the appropriate use of antimicrobials like vancomycin, and implementing an antimicrobial stewardship program that promotes the appropriate selection, dose, route and duration of antimicrobial therapy. The non-specific guidelines also include performing environmental cleaning, implementing bundled practices to prevent procedure-associated infections such as central line-associated blood stream infections, and education of hospital staff concerning procedures such as hand washing with an antiseptic agent. Organism-specific guidance includes routine screening for VRE and gram-negative isolates for ESBL production, and contact isolation of

patients infected with VRE or ESBL-producing organisms.[24-26] The relative contribution of specific versus non-specific measures is unknown, especially as compliance with non-specific measures would be expected to vary between institutions.

In one example of organism-specific guidance, the Ontario Provincial Infectious Diseases Advisory Committee (PIDAC)[16] recommended, among other things, that:

- "Each health care setting should have a prevention and control program for AROs." (p. 27)
- "Screening for risk factors for MRSA, VRE, and CRE should include a screening tool that is applied to all clients/patients/residents admitted to the health care facility." (p. 27)
- "Every effort should be made to try to determine the source of new cases of MRSA, VRE, and CRE. Every new case should warrant an investigation." (p. 27)
- "During an outbreak, all client/patient/resident contacts with common risk factors should be actively screened." (p. 27)
- "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)
- "VRE, CRE or ESBL decolonization is not effective and is not recommended." (p. 27)
- 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 health care setting. However, some of these specific recommendations remain controversial, with some Canadian hospitals discontinuing screening for VRE colonization or isolating patients with VRE, arguing that the increased resources required for containment are not commensurate with the increased patient risk from VRE.[27]

AROs such as VRE and ESBL-producing organisms increase the use of hospital resources due to extended hospital stays, laboratory tests, physician consultations, and the cost of infection prevention and control measures to prevent the further spread of these pathogens.[19] However, both morbidity caused by infection and screening and control strategies contribute to this increased resource use. Additionally, AROs are commonly detected in the intensive care unit (ICU) where antimicrobial selection pressure is higher and exposure to broad-spectrum antimicrobials is more common.[19] The health care impact of antimicrobial resistance cannot be limited to the hospital perspective, as significant portions of clinical care are provided in other facilities.[28]

The objective of this study is to conduct an SR 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 multidrug resistant (MDR) infections in Canada, the findings from this report may be used to update guidelines in Canadian jurisdictions.

2 RESEARCH QUESTIONS

1. What is the clinical evidence on the effectiveness of selective versus universal versus no screening of patients

(adult and pediatric) for VRE or 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?
   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?
5. 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?

3 KEY MESSAGE

Evidence from three observational studies with significant methodological concerns showed that active surveillance (screening of all high-risk patients) and other precautionary measures in hospital settings may result in reducing the spread of VRE; thus, decreasing colonization and infections. Findings on the effectiveness of surveillance and contact precautions for ESBL-producing organisms were identified in one outbreak study, which is insufficient to draw firm conclusions. Specific infection prevention and control strategies to increase the effectiveness of and compliance to the precautionary measures may be important in the prevention of ARO colonization and possibly infections, depending on the organism and setting. With the implementation of certain precautionary measures, such as isolation, negative psychological effects that isolation may have on hospitalized patients need to be considered. Patients who are infected or colonized with VRE or ESBL-producing organisms and the use of patient isolation increase use of hospital resources through increased length of hospital stay (LOS), blocking of beds and rooms, and increasing the time devoted to direct patient care by health care workers. There was no evidence found that compared the effectiveness of decolonization with non-decolonization for patients carrying VRE or ESBL-producing organisms.

A. CLINICAL EVIDENCE

4 METHODS

4.1 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 and daily updates through Ovid; Embase through Ovid; The Cochrane Library (2012, Issue 3) through 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, SRs, meta-analyses, randomized controlled trials (RCTs), 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 the publication of the final report. 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.

4.2 Selection Criteria and Methods

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 further evaluation was based on the 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.

Table 1: Trial Selection Criteria for Clinical Evidence

Population	Adult and pediatric patients in acute and long-term care facilities, who are infected with or are potential carriers of VRE or ESBL-producing organisms.
Intervention	• Screening (selective 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 organism acquisition and infection. • Health outcomes: morbidity (including complications of VRE or ESBL-producing organism infection), case-fatality, mortality, quality of care for non-infectious conditions, and medical errors. • Adverse events: adverse effects of screening and treatment, including allergic reactions, non-allergic toxicities, and resistance to antimicrobials
Study design	• Randomized controlled trials and non-randomized studies

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

4.3 Exclusion criteria

Articles were excluded if they did not meet the selection criteria in Table 1, if they were published before 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.

4.4 Data Extraction Strategy

A data extraction form for the clinical effectiveness review was designed a priori to document creation and tabulates relevant study characteristics (Appendix 4). Data were extracted independently by reviewers (CH and KC), and any disagreements were resolved through discussion until consensus was reached.

4.5 Critical Appraisal of Individual Studies

The validated Downs and Black checklist[29] was used to assess the study quality of experimental and observational studies based on quality of reporting, external validity, and risk of bias. Numerical scores for each study were not calculated. Instead, study strengths and limitations were described.

4.6 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.

5 RESULTS

5.1 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[30-35] were included in the review. The trial selection process is presented in a flowchart according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Appendix 2).[36] Included and excluded trials are listed in Appendices 5 and 6 respectively.

5.2 Summary of Study Characteristics

5.2.1 Study design

Included in the review are six studies, comprising three prospective cohort[31-33] and three retrospective cohort trials.[30,34,35] Three included studies are on VRE,[30-32] one study on a ESBL-producing organism outbreak,[35] and two studies on anxiety and depression in isolated patients.[33,34] Three studies were conducted in the US (two in 2003 and one in 2011),[30,33,34] one in Taiwan (2004),[31] one in Korea (2007),[32] and one in Belgium (2008).[35] Four studies[30-33] included patients throughout the hospital, one study[34] compared patients in the ICU with patients not in the ICU, and one study[35] included only patients in the ICU. Detailed characteristics of the included studies are summarized in Appendix 7.

5.2.2 Study population

Selected studies included patients with infections or colonization caused by VRE,[30-32] VRE/MRSA,[33] VRE/MRSA/MDR gram-negative bacteria,[34] or ESBL-producing organisms.[35] None of the studies indicated that pediatric patients were included. Except for the study by Price et al.,[30] little detail was provided by most studies regarding patient comorbidities. Detailed characteristics of the patients are summarized in Appendix 8.

5.2.3 Intervention and comparators

Selected studies compared active screening of patients in high-risk units (hematology-oncology, transplant, and ICU) with no screening of patients in non–high-risk units,[30] contact isolation with no intervention,[31,33] strict isolation with contact precautions or strict isolation plus modified contact precautions,[32] contact precautions with no contact precautions,[34] and routine infection prevention and control strategies with reinforced infection prevention and control strategies.[35] Details of the interventions and comparators are summarized in Appendix 9.

5.2.4 Outcomes

Main reported outcomes were the incidence of hospital-acquired infection[30-32,35] and rates of depression or anxiety.[33,34]

5.3 Summary of Critical Appraisal

Three included studies were prospective designs (two on VRE and one on depression),[31-33] and the remainder (one on VRE, one on ESBL-producing organisms, and one on anxiety and depression) were retrospective. All studies, with one possible exception,[33] appeared to include patients that were representative of the general population. Compliance with the intervention was considered reliable in three studies (one on VRE, one on ESBL-producing organisms, and one on depression).[31,33,35] The main limitations were the lack of randomization and blinding in all studies, which increase the potential for bias; size of the included populations; and the inability to determine if confounders were considered in case and control groups in most studies (two on VRE, one on ESBL-producing organisms, and one on depression).[31-33,35] Additionally, two studies on VRE collected data from the cohorts at different time periods,[30,32] and two studies on anxiety and depression did not indicate if the same time periods were examined for the patient groups.[33,34] A summary of the critical appraisal of individual studies can be found in Appendix 10.

5.4 Summary of Findings

Our review included four studies comparing the effectiveness of different infection prevention and control strategies on the detection and transmission rates of VRE or ESBL-producing organisms,[30-32,35] and two studies on their comparative effects on patients' depression or anxiety.[33,34] Main study findings and authors' conclusions can be found in Appendix 11.

What is the clinical evidence on the effectiveness of selective versus universal versus no screening of patients (adult and pediatric) for VRE or ESBL-producing organisms?

Overall, two studies found that screening and aggressive infection prevention and control strategies were associated with reduced ESBL-producing organisms colonization and infection rates,[35] and VRE bacteremia rates.[30]

A prospective cohort study published in 2008 examined the effectiveness of

biweekly surveillance cultures and contact precautions (type of contact precautions not specified) compared with a reinforced infection prevention and control program including daily surveillance cultures, increased contact precautions, and staff reinforcement regarding use of contact precautions, in the control of an ESBL-producing organism outbreak in an ICU setting (31-bed unit).[35] Findings showed that the incidence of ICU-acquired ESBL-producing *K. pneumonia* increased during an outbreak, and the incidence fell significantly (P = 0.001) following implementation of reinforced infection prevention and control measures. The authors concluded that an aggressive infection prevention and control strategy can be efficient in situations in which routine control measures fail to prevent or interrupt the nosocomial transmission of an ESBL-producing *K. pneumonia* outbreak; however, this study examined precautions taken during an outbreak, which limits its generalizability to routine screening on a day-to-day basis.

A retrospective cohort 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.[30] Active surveillance included weekly rectal swabs from all patients for three consecutive weeks in high-risk units such as the hematology-oncology, transplant, and ICU wards. When VRE were detected, staff from 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 presence of polyclonal strains of VRE suggests less horizontal spread throughout the hospital or less patient-to-patient transmission. 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, though differences between the two settings, such as housekeeping practices, hand hygiene, or skill of staff, may contribute to observed effects.

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

Overall, two studies found that strict isolation together with contact precautions helped to reduce the rates of VRE transmission.[31,32]

A prospective cohort study published in 2007 examined the effectiveness of different infection prevention and control strategies in the reduction of VRE transmission in a 1,250-bed tertiary care hospital.[32] The comparative strategies were: contact precautions (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 were isolated in private rooms) plus contact precautions; and strict isolation plus modified contact precautions (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 precautions only

period (1.45 cases per 10,000 patient-days). The strict isolation plus modified contact precautions period had a similar incidence rate (0.88 cases per 10,000 patient-days) to the strict isolation plus contact precautions 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. Infection rates associated with VRE rectal colonization in these populations were not described.

A prospective cohort study published in 2004 examined the effects of strict contact isolation on control of VRE spread in a 2,000-bed teaching hospital.[31] 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 or colonized patients. Upon discharge of an infected or colonized patient, the 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 (no detail provided in study as to how precautions were relaxed) and no more surveillance was performed. Results showed that hospital-acquired infection rates remained stable during the precautions implementation period, but increased during the no-precautions period. Molecular typing of isolates in the period where strict contact isolation precautions were enforced revealed more types of VRE (i.e., VRE isolates were more polyclonal) than in the period during which precautions were relaxed. The authors concluded that implementation of precautions guidelines is important in controlling the spread of VRE. The findings of this study need to be interpreted with caution. While the authors state that the definition of infection was based on the Centers for Disease Control criteria, the type or severity of the described infections was not provided.

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

Overall, two studies found that isolation may increase levels of anxiety or depression in hospitalized patients.[33,34]

A retrospective cohort study published in 2011 examined the effect of contact precautions on depression or anxiety in more than 36,000 patients admitted to a tertiary care hospital.[34] Patients were placed on contact precautions (no detail provided on specific contact precautions, but patients were given a private room when available) when their medical record indicated the presence of MDR 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, 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 (odds ratio [OR] 1.5, 95% confidence interval [CI], 1.2 to 1.6). In the ICU population, there was no relationship found between contact precautions and depression or anxiety. The authors concluded that there was an association between contact precautions and depression in patients hospitalized with MDR infections, except for ICU patients.

A prospective cohort 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.[33] 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 with the difference of scores in the control group (time-by-group interaction or changeover time between groups). 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.

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. Decolonization is not typically performed for patients with VRE or ESBL colonization.

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

What is the 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?

6 METHODS

6.1 Literature Search Strategy

See Section A: Clinical Evidence

6.2 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-producing organisms.
Intervention	• Screening (selective 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, *Clostridium difficile (C. difficile)*, and other AROs
Study design	• Randomized controlled trials and observational studies

ARO = antibiotic-resistant organism; ESBL = extended spectrum beta-lactamase; MRSA = methicillin-resistant *Staphylococcus aureus*; VRE = vancomycin-resistant enterococci.

6.3 Exclusion Criteria

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

6.4 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 are narratively described.

7 RESULTS

7.1 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. Four retrospective studies met the inclusion criteria. The PRISMA flowchart in Appendix 12 details the process of the study selection.

7.2 Summary of Study Characteristics

Details on study characteristics are summarized in Appendix 13.

7.2.1 Study design

Three retrospective cohort studies[37,38,39] and one cost analysis[40] were included in this review. One retrospective study was conducted in Israel[37] and the two other retrospective studies were from the US.[38,39] The cost-analysis study was from Canada.[40] All studies were conducted in in-patient hospital settings. Three studies were conducted in urban tertiary care hospitals[37,39,40] and one study was conducted

in the neonatal intensive care unit (NICU) of a freestanding children's hospital.[38]

7.2.2 Study population

One study[37] included patients colonized with VRE, while the remaining three studies[38-40] included patients infected or colonized with ESBL-producing organisms. Of the ESBL studies, one study[38] examined an outbreak caused by ESBL-producing *K. pneumonia*, while the two other studies[39,40] assessed 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.

7.2.3 Interventions and comparators

One cost-analysis study implemented an infection prevention and control intervention to reduce nosocomial transmission of ESBL-producing organisms.[40] 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 gowns 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 analyses used various methods to match case patients with appropriate controls.[37-39] One study matched the VRE-colonized cohort with other hospital patients on the basis of LOS at the time of matching, hospital ward location, and calendar date.[37] One study matched ESBL-infected infants in the NICU to ESBL colonized infants, 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.[38] 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.[39]

7.2.4 Outcomes measured

All included studies reported on LOS and hospital costs as outcome measures. One study[37] also focused on mortality, admission to an ICU, the need for surgery, and discharge to an institution. One study[40] analyzed the time spent by health care workers giving direct patient care during an outbreak caused by an ESBL-producing organism, in addition to surveillance and administrative time related to the outbreak. One study[39] looked at the clinical response to initial antibiotic therapy. The Canadian cost-analysis study[40] evaluated the hospital costs associated with implementing an infection prevention and control program.

7.3 Summary of Findings

Details on study findings are summarized in Appendix 14.

7.3.1 Length of hospital stay

The three retrospective cohort studies[37-39] and one cost-analysis study[40] found that patients infected with either VRE or ESBL-producing organisms had a longer LOS than a matched cohort of control patients. In three studies,[37,38,40] a contributing factor was the implementation of infection prevention and control measures, including isolating patients in private rooms to prevent the spread of infection. In one study, the increased LOS was due to the infection or illness of the patient or to inappropriate administration of initial antibiotic therapy.[39] It is uncertain how much of the increased LOS was attributed to the infection itself or

to the precautionary measures taken to control the spread of infection.

In one retrospective cohort study,[37] the mean number of days between inclusion into the cohort and discharge from hospital was 15.1 (range 1 to 107 days) for VRE cases (patients colonized with VRE) versus 8.5 days (range 1 to 116 days) for the control cases. It was estimated that being colonized with VRE 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 this study, no isolation practices were reported for colonized or infected patients.

In a second retrospective cohort study,[38] a four-month outbreak of an ESBL-producing strain of *K. pneumonia* in a NICU was found to result in an increased mean LOS for 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 from a sterile body site and neonates who were discharged during a six-month period before the outbreak. Infection control measures to prevent bacterial spread to others were likely a contributing factor to the increased LOS.

In one retrospective cohort,[39] patients infected with ESBL-producing *E. coli or Klebsiella* organisms, at a site other than the urinary tract, 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 *E. coli or Klebsiella* organisms.

7.3.2 Blocked beds and rooms

One retrospective cohort study[38] found that one third of the total cost of the ESBL outbreak in the NICU was attributable to lost revenue from blocked beds for infection control purposes (186 patient-days). Similarly, a second cohort study[39] found that bed use costs were statistically significantly greater for patients infected with ESBL-producing organisms than for control patients infected with non-ESBL-producing organisms.

One cost-analysis study[40] evaluated the infection prevention and control measures that were implemented involving 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 to 142 days), likely attributable to infection prevention and control measures, and the use of private rooms was the highest resource use for the hospital.

7.3.3 Health care workers

In one cohort study,[38] 38% of the total cost 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 Canadian cost-analysis study,[40] additional nursing time accounted for the third highest cost of the infection prevention and control measures taken to prevent the spread of ESBL, this after private room and supply costs.

7.3.4 Antibiotic treatments

One retrospective cohort study[39] 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-resistant *Enterobacteriaceae*, the appropriate antibiotic, was lower than that of their matched control patients (39% versus 83%, P = 0.013). Treatment was successful for both patient groups who received a carbapenem-resistant *Enterobacteriaceae*, regardless of the 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 LOS.

7.4 Limitations of Health Services Impact

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 from single institutions, which may limit the generalizability of the results. The specific population 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. The retrospective nature of these studies may also be prone to bias and confounding as both outcomes and exposures have already been established at the time of participant selection. These studies appear to show that patients who are infected or colonized with VRE or ESBL-producing organisms have a longer LOS than patients who are not infected or colonized with these organisms. However, this may also be evidence that increased LOS is a risk factor for being colonized or developing infection in the hospital, and that these patients had underlying conditions that would require longer hospital stays regardless of the infection, or that increased LOS resulted at least partially from the control measures that were implemented to prevent spread of the organisms to other patients. This issue was addressed in one study[37] 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 comorbidities 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.

8 DISCUSSION

Evidence from a limited number of observational studies (one ESBL outbreak study, three VRE studies) included in our report showed that active surveillance with weekly rectal swabs from all patients in high-risk hospital units may be associated with lower VRE bacteremia rates compared with no surveillance strategy. Isolates in a hospital with an active surveillance program

showed a population of VRE that was more polyclonal, suggesting that active surveillance and infection prevention and control measures help to prevent horizontal transmission of the infection. In outbreak situations where routine infection prevention and control measures fail to prevent the transmission of ESBL-producing organisms, an aggressive control strategy consisting of daily surveillance cultures, increased contact precautions, environmental cleaning, and staff reinforcement, may be effective. The implementation of guidelines to ensure strict isolation and contact precautions in hospitals was shown to be important in controlling the spread of VRE colonization. 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 Health Sciences Centre and Women's College Hospital, both in Toronto; and Brigham and Women's Hospital in Boston ,[41] 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 that 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.

To maximize the effectiveness of infection prevention and control, in addition to specific control measures, such as patient screening and isolation procedures, non-specific measures such as antimicrobial stewardship programs, hand hygiene programs, practice bundles, and environmental cleaning need to be implemented in hospital settings. Surveillance data in an acute tertiary care hospital found that the rates of health care-associated infections were highest in the ICUs and lowest in the wards.[42] A Canadian tertiary care hospital found that the number of roommates to which a patient was exposed was directly associated with the risk of acquiring nosocomial MRSA and VRE infections.[43] These findings can have implications for the staff deployment and design of acute care hospitals. Decision-makers in several hospitals are choosing to discontinue screening and isolation for VRE infections because they find that: VRE infections are relatively rare compared to infections with sensitive enterococci or other AROs; new drugs are available to treat infections; and there is a need to free up organizational capacity to address more pathogenic organisms.[27]

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.[44] Mobile phones of patients, companions, and visitors represent a risk for hospital-acquired infections.[45] Despite the belief that white lab coats could be contaminated with AROs,[46] a review of the literature did not support the hypothesis that uniforms or clothing could be a vehicle for the transmission of health care-associated infections.[47]

Despite the increased risk of nosocomial infections, health care worker compliance with hand hygiene was low when working with patients infected with MRSA (47% and 43% in the ICU and intermediate care units respectively) and ESBL-producing organisms (54% and 51% in the ICU and intermediate care units respectively).[48] Use of electronic alerts in the form of beeps, to prompt health care workers to perform

antisepsis, was shown to improve hand hygiene compliance.[49] Implementation of a computerized reminder increased the rate of patients appropriately isolated.[50]

The robustness of the evidence on the effects of precaution measures on the detection and transmission of VRE and ESBL-producing organisms is limited. An SR in 2006 of the literature on the use of barrier precautions, patient isolation, and surveillance cultures,[51] showed that the evidence generally supports the use of these measures to prevent the transmission of MDR organisms, but the lack of RCTs decreased the robustness of the findings. High-quality evidence, supported by adequately powered multicentre cohort studies with robust analyses to minimize potential biases, is needed to confirm the findings. An SR in 2001 on the efficacy of infection prevention and control in the reduction of ESBL-producing organisms transmission in a non-outbreak setting[52] found that 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 prevention and control strategies for MRSA and VRE[53] (not including ESBL) concluded that active surveillance and contact precautions have been effective in the reduction of MRSA and VRE transmission in some settings, but infection prevention and 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. In trials where the transmission rates were compared between different hospitals, the organisms were detected in 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 the inclusion of populations carrying either VRE or MRSA, making the conclusion on the effect of precautionary 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 regard to the impact of screening and isolating 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 LOS than an appropriately matched cohort of control patients.[37-39] However, one study that compared the effectiveness of antibiotic treatment for patients infected with ESBL-producing organisms with 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 LOS.[39] One study that implemented an ESBL-producing organism infection prevention and 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.[40] Similarly, a study that retrospectively analyzed an ESBL-producing organism 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.[38] Since there were few

studies identified and the majority of the studies were retrospective analyses, the interpretations of the results may be subject to bias.

9 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 with hand hygiene in hospital settings may result in reducing the spread of VRE. Implementation of precautionary measures needs to take into consideration the negative psychological effects that isolation may have on hospitalized patients and the impact on patient flow and the unavailability of single rooms for other types of isolation. One study of an ESBL-producing organism outbreak showed reinforced infection prevention and control measures reduced the incidence of ICU-acquired ESBL-producing *K. pneumonia*, though it is unclear how this finding might translate to routine, day-to-day infection control policies. These findings on the effectiveness of infection prevention strategies for VRE and ESBL-producing organisms should be interpreted with caution given the scarcity of evidence, and the noted limitations of the included studies. There was no evidence identified that compared the effectiveness of decolonization with non-decolonization for patients carrying VRE or ESBL-producing organisms. Decolonization is not typically performed for patients with VRE or ESBL colonization.

Evidence from a limited number of observational studies suggested that both infection prevention and control measures and patients infected or colonized with VRE or ESBL-producing organisms use more hospital resources due to increased LOS, increased usage of hospital beds, increased health care worker staffing, and the need for precautions to prevent the spread of infection. The relative contributions of infection control measures versus the effect of infection or illness itself to resource use were not clear. A balance between a potential reduction in infection risk and increased resource use is an important consideration when implementing control strategies. The cost-effectiveness of infection prevention and control measures was not considered in this review.

In Canada, there are variable practices among hospitals in implementing infection prevention and control measures for both VRE and ESBL-producing organisms. Different approaches for infection control must be used for all emerging infections. Infection prevention and control measures should take into consideration the setting, epidemiology, virulence factors, mode of transmission, and degree of transmissibility of various pathogens as well as the robustness of non-specific control measures such as hand hygiene. Treatment options and strategies for prevention and control may differ among pathogenic organisms and depend on the availability of local resources.

A survey sent to infection prevention and control programs in all Canadian acute care hospitals with 80 or more beds[54] found that a significant increase in the number of full-time infection prevention and control professionals (ICPs) has not translated into improvement of AROs 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[55] 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). These findings suggest that appropriate strategies, not just an increase in resources, are important factors in the success of infection prevention and control policies. Direct and efficient communication between different teams is also a factor, as shown in another survey of Canadian acute care hospitals,[56] in which VRE infections were found to be less likely to occur if infection prevention and 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 with others can have implications for staff deployment and design of acute care hospitals. Awareness by medical practitioners of the risk of infection of ESBL-producing organisms in returning travellers is also important.[57-59] 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 the publication of the final report.
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-

Multi-Database Strategy	
Line #	**Searches**
	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/

Multi-Database Strategy	
Line #	**Searches**
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/

Multi-Database Strategy	
Line #	**Searches**
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

Multi-Database Strategy	
Line #	**Searches**
	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.

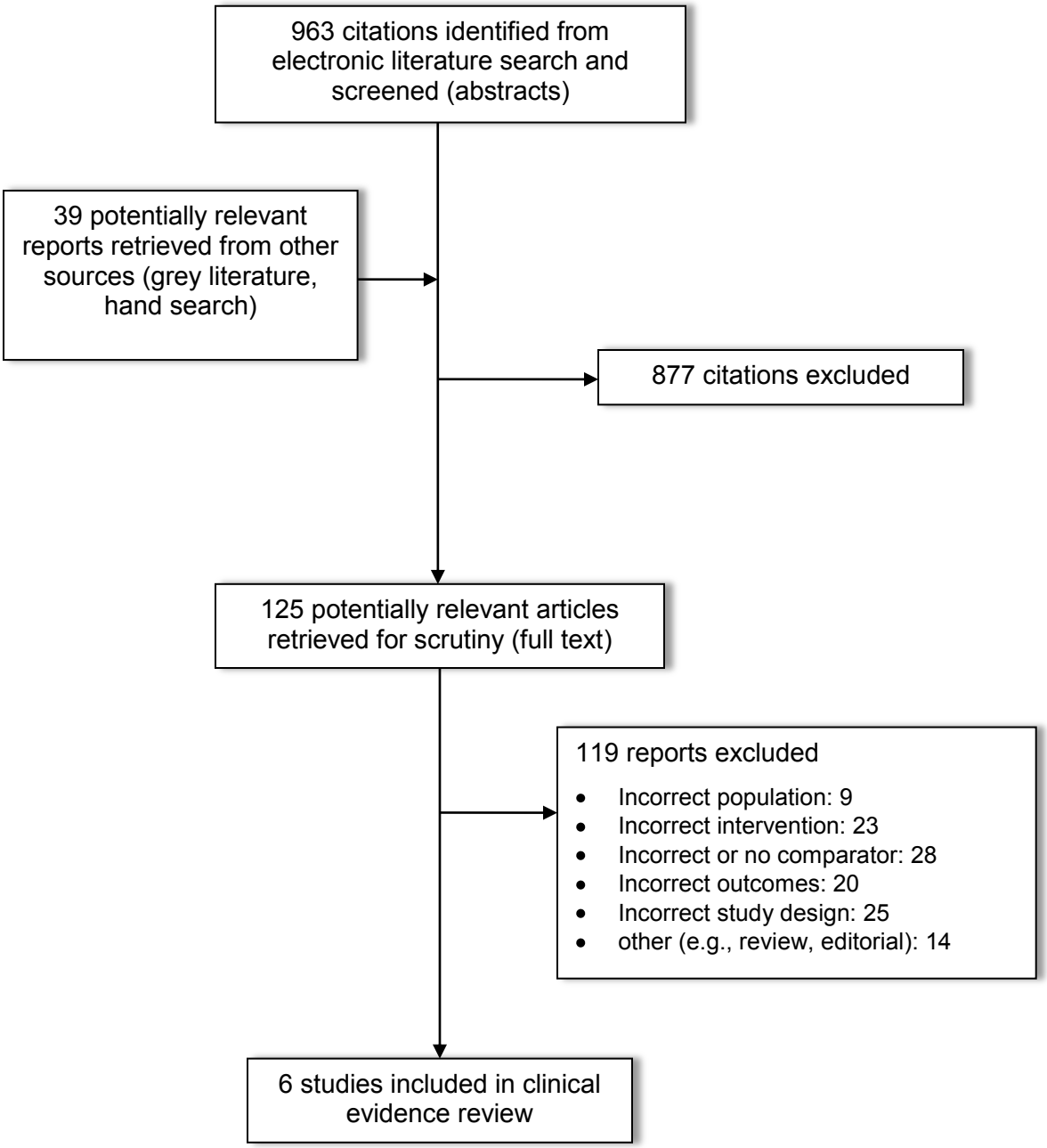
Grey Literature

Dates for Search:	March 27-29, 2012
Keywords:	Included terms for VRE, ESBL, screening, isolation, and decolonization
Limits:	Publication years 2002 to 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 Producing 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-producing organisms

2. Intervention: yes _____ no _____ can't tell _____
- Screening for VRE or ESBL-producing organisms
- Isolation for VRE or ESBL-producing organisms
- Decolonization for VRE or ESBL-producing 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)
- LOS

5. Study Design: yes_____ no_____ can't tell_____

RCTs, non-randomized studies

- **"yes" (1 to 5 inclusive): include study and order full paper_____**
- **at least one "can't tell" and others "yes" for 1 to 5: order full paper for further review_____**
- **"no" (any 1 to 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 Producing 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-producing organisms transmission Rate of VRE or ESBL-producing 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-producing organisms transmission **DECOLONIZATION** Rate of VRE or ESBL-producing		

organisms transmission • Placebo • Drug (different dosages) Rate of VRE or ESBL-producing organisms infection • Placebo • Drug (different dosages) Morbidity • Placebo • Drug (different dosages) Mortality • Placebo • Drug (different dosages) LOS • 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 *Staphylococcus 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.

Hamel M, Zoutman D, O'Callaghan C. Exposure to hospital roommates as a risk factor for health care-associated infection. Am J Infect Control. 2010 Apr;38(3):173-81.

Kotilainen P, Routamaa M, Peltonen R, Oksi J, Rintala E, Meurman O, et al. Elimination of epidemic methicillin-resistant Staphylococcus aureus from a university hospital and district institutions, Finland. Emerg Infect Dis [Internet]. 2003 Feb [cited 2012 Mar 2];9(2):169-75. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2901945/pdf/02-0233.pdf

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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APPENDIX 7: CLINICAL EVIDENCE STUDY CHARACTERISTICS

First Author, Year, Country, Study Design	Objective, Clinical Setting, Length of Study	Intervention; No. of Patients	Comparator; No. of Patients	Outcomes
Day 2011[34] US Retrospective cohort	To assess the impact of contact precautions on symptoms of anxiety and depression Tertiary care teaching hospital 2 years	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	Depression and anxiety, stratified by admission to the ICU
Laurent 2008[35] Belgium Retrospective cohort	To describe the impact of infection prevention and control measures for controlling transmission of ESBL during an outbreak in the ICUs 4 ICUs of a university hospital 4 months	Reinforced infection prevention and 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 prevention and control strategies (contact isolation for identified carriers or high-risk patients until confirmed); no. of patients NR	Rates of nosocomial acquisition of ESBL-producing *K. pneumonia*
Yoonchang 2007[32] Korea Prospective cohort	To evaluate the effectiveness of contact precautions and strict isolation in controlling the transmission of VRE Tertiary care university hospital Approximately 3 years	Period B, strict isolation; 7 patients Period C, follow-up with strict isolation; 95 patients	Period A, contact precautions; 19 patients	Rates of nosocomial acquisition of VRE
Wang 2004[31] Taiwan Prospective cohort	To report the differences in spread of VRE in one hospital, with	Strict contact and cohort isolation; no. of patients NR	No active intervention; no. of patients NR	Rates of nosocomial acquisition of VRE

First Author, Year, Country, Study Design	Objective, Clinical Setting, Length of Study	Intervention; No. of Patients	Comparator; No. of Patients	Outcomes
	and without guidelines University hospital 3.5 years			Molecular type of VRE isolates
Catalano 2003[33] US Prospective cohort	To assess the possible association of contact isolation with an increase in the symptoms of anxiety and depression University hospital 1 to 2 weeks of individual patient follow-up	Contact isolation; 27 patients	Control (did not require isolation); 24 patients	Symptoms of anxiety or depression
Price 2003[30] US Retrospective cohort	To determine if routine screening and contact isolation of high-risk patients would account for differences in VRE bacteremia rates 2 hospitals 6 years	Hospital B, active screening of high-risk patients; 82 patients	Hospital A, no routine screening; 218 patients	Rates of VRE bacteremia, by assessing number of VRE bloodstream isolates per 100,000 patient-days and the degree of clonality.

ESBL = extended spectrum beta-lactamase; ICU = intensive care unit; no. = number; NR = not reported; VRE = vancomycin-resistant enterococci.

APPENDIX 8: CLINICAL EVIDENCE PATIENT CHARACTERISTICS

First Author, Date	Study Groups	No. of Patients	Gender (m/f)	Age (years, SD)	LOS (mean days)	Prior Diagnosis/Underlying Disease/Prior Depression
Day 2011[34]	General hospital: patients on contact precautions	3,138	1,848/ 1,290	51.2 ± 17.5	Median 7.1 (IQR 3.4 to 18.1)	On antidepressant med: 37 (1.2%)
	General hospital: patients not on contact precautions	25,426	11,776/ 13,650	49.6 ± 19.0	3.2 (2.0 to 6.0)	On antidepressant med: 54 (0.2%)
	ICU: patients on contact precautions	1,694	1,032/ 662	54.9 ± 17.5	14.8 (7.4 to 28.8)	On antidepressant med: 333 (19.7%)
	ICU: patients not on contact precautions	5,854	3,494/ 2,360	56.0 ± 17.7	7.0 (3.9 to 12.5)	On antidepressant med: 573 (9.9%)
Laurent 2008[35]	Patient characteristics not reported					
Yoonchang 2007[32]	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
Wang 2004[31]	Patient characteristics not reported					
Catalano 2003[33]	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%
Price 2003[30]	Hospital A (no routine screening)	218	95/123	58.9 ± 18.5	52.2 ± 25.6 (SD)	Hepatobiliary: 18.6 (% of patients) Cancer: 19.1 CVD: 13.2 Diabetes mellitus: 8.7 HIV infection: 2.2
	Hospital B (routine	72	42/30	61 ± 71.4	27.3 ± 26.8 (SD)	Hepatobiliary: 20 (% of patients)

First Author, Date	Study Groups	No. of Patients	Gender (m/f)	Age (years, SD)	LOS (mean days)	Prior Diagnosis/Underlying Disease/Prior Depression
	screening of high-risk patients)					Cancer: 40 CVD: 28 Diabetes mellitus: 24 HIV infection: 4

CVD = cardiovascular disease; HIV = human immunodeficiency virus; ICU = intensive care unit; IQR = intraquartile range; med = medications; No. = number; NR = not reported; SD = standard deviation.

APPENDIX 9: CLINICAL EVIDENCE INTERVENTIONS AND COMPARATORS

First Author, Year	Study Group	Screening Methods	Contact Precautions
Day 2011[34]	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[35]	Reinforced infection prevention and 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 prevention and 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.
Yoonchang 2007[32]	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 three 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 three consecutive weeks.
Wang 2004[31]	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.	Strict contact isolation or cohort isolation (gloves, gowns, hand washing immediately after exiting room; dedicated use of stethoscopes, thermometers,

First Author, Year	Study Group	Screening Methods	Contact Precautions
		Frequency not reported.	and sphygmomanometers). HCWs were monitored by the head nurse to ensure isolation guidelines were followed. Isolation was discontinued after three negative swabs (on three different days).
	No active surveillance	No active surveillance	NR
Catalano 2003[33]	Patients with MRSA or VRE	NR	No details provided on type of isolation.
	Patients not requiring isolation	NR	No isolation
Price 2003[30]	Hospital with active surveillance	Active surveillance for VRE with weekly rectal swabs for three consecutive weeks in high-risk units, then monthly once three negative results are obtained.	Contact isolation (no further details reported) until rectal swabs negative for VRE.
	Hospital with no active surveillance	No routine screening of patients.	NR

ESBL = extended spectrum beta-lactamase; HCWs = health care workers; ICU = intensive care unit; MRSA = methicillin-resistant *Staphylococcus* aureus; NR = not reported; VRE = vancomycin-resistant enterococci.

APPENDIX 10: CRITICAL APPRAISAL OF INCLUDED STUDIES FOR CLINICAL EVIDENCE

First Author, Year	Strengths	Limitations
Day 2011[34]	• 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[35]	• 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 • number of patients studied difficult to determine; approximately 61
Yoonchang 2007[32]	• prospective study • patients and facility representative of population	• different time periods of data collection for each of the two cohorts • no randomization • unable to determine if confounders were considered • no blinding indicated • number of patients studied = 121
Wang 2004[31]	• 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 • number of patients studied not specifically reported
Catalano 2003[33]	• 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 • number of patients studied = 51
Price 2003[30]	• confounders considered • patients and facilities representative of population	• retrospective study • different time periods of data collection for each of the two hospitals • no randomization • no blinding indicated • unable to determine if compliance with intervention was reliable

APPENDIX 11: MAIN CLINICAL STUDY FINDINGS AND AUTHORS' CONCLUSIONS

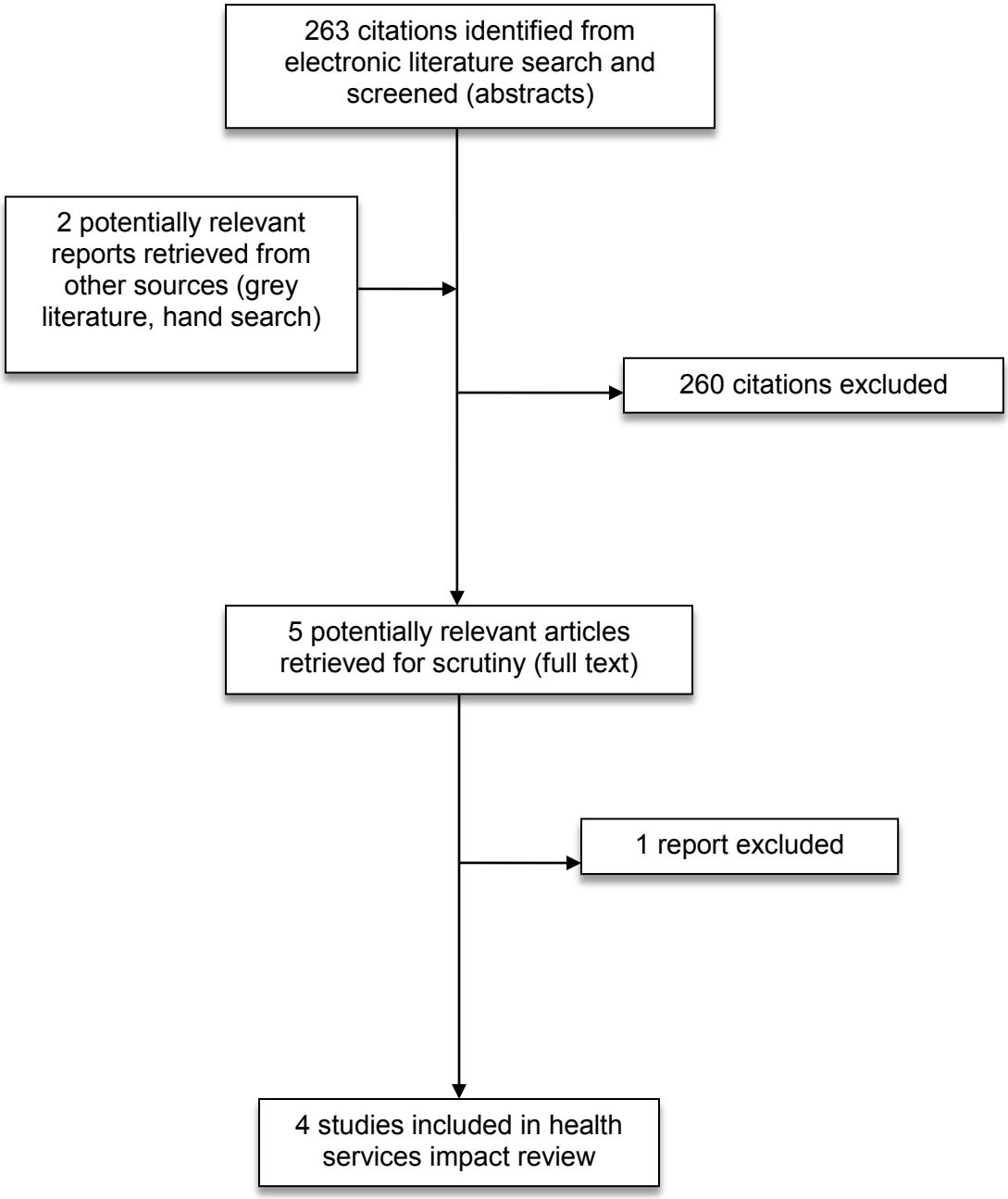
First Author, Year	Main Study Findings	Authors' Conclusions
Trials on VRE		
Day 2011[34]	**General hospital (contact precautions versus no contact precautions):** Depression OR 1.4 (95% CI, 1.2 to 1.6); p < 0.01. Anxiety: OR 0.9 (95% CI, 0.7 to 1.1); P = 0.35. **Intensive care Unit (contact precautions versus no contact precautions):** Depression: OR 0.9 (95% CI, 0.7 to 1.2). P = 0.44. Anxiety: OR 0.7 (95% CI, 0.4 to 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)
Yoonchang 2007[32]	**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)
Wang 2004[31]	**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:	"interventions for the control of VRE … are effective for control of VRE spread." (p. 97)

First Author, Year	Main Study Findings	Authors' Conclusions
	0.20 per 1,000 discharges • molecular typing: 8 different types of VRE.	
Catalano 2003[33]	**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)

First Author, Year	Main Study Findings	Authors' Conclusions
Price 2003[30]	**Hospital A (no screening):** 17.1 patients with VRE bloodstream isolates per 100,000 patient-days during the six-year period. **Hospital B (with screening):** 8.2 patients with VRE bloodstream isolates per 100,000 patient-days during the six-year period. **Hospital A (no screening):** the majority of isolates were clonally related (four 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 (four 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)
Trials on ESBL-Producing Organisms		
Laurent 2008[35]	**Routine infection prevention and 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 prevention and control** (daily surveillance cultures and increased contact precautions and staff reinforcement): 0.08 cases per 1,000 patient-days (P = 0.001).	"… in situations in which routine infection prevention and control measures fail to prevent or interrupt the nosocomial transmission of ESBL-producing *K. pneumoniae* 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[37] 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[38] 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[39] 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:	• Hospital costs • Clinical response to initial antibiotic therapy • Mortality • LOS

First Author, Publication Year, Country, Study Design, Study Period	Study Setting	Patient Population	Matched Comparators	Outcomes Measured
			• Age (± 5 years) • Site of infection • Stay in ICU • Date of culture (± 3 months)	
Conterno 2007[40] Canada Cost-analysis 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 prevention and control measures • All patients with ESBL-producing organisms were placed in a private room. • Contact precautions used for patients admitted to ICU, uncontained drainage from culture-positive site, diarrhea, or incontinence.	• Costs due to infection prevention and control measures • Hospital costs

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[37]	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 versus 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 was discharged to long-term care compared with 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. 2,227)
Stone 2003[38]	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, and neonates who were discharged during a six-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 (2,489 hours). Most health care worker time was attributed to nurse staffing and overtime needed to care for and maintain the infants (1,055 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, whereas 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[39]	Total costs were significantly greater for	"Similar to other studies, we observed

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	patients infected with ESBL-producing *E. coli* or *Klebsiella* species (ESBL-EK case patients) than patients 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 versus $12,732 ± 7,583; P = 0.032). Mean infection-related LOS was the main driver of cost, which was prolonged for case patients compared with control patients (21 ± 15 days versus 11 ± 5 days; P = 0.006). Patients with ESBL-producing *E. coli* or *Klebsiella* species were more likely to receive sequential antibiotic therapy for their infections (P < 0.001) due to poor rate of response; thus, increasing their total infection-related LOS.	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 (i.e., carbapenems) for treatment of infections due to ESBL-producing organisms might be correlated with higher hospital costs …" (p. 1,230)
Conterno 2007[40]	During the study period, 77% (134/173) of patients with ESBL were placed in private rooms and the remainder were discharged by the time the culture result was available. Of the 134 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 to 142 days), and the mean length of contact precautions was 19 days (range 1 to 124 days) per patient, after the ESBL-positive result was 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. Furthermore, 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 rooms 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-p.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.