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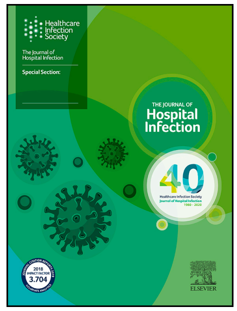

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Economic analysis of healthcare-associated infection prevention and control interventions in medical and surgical units: Systematic review using a discounting approach

Running Title: Review of HCAI economic analysis

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SUMMARY

Background: Nosocomial or healthcare-associated infections (HCAIs) are associated with a financial burden that affects both patients and healthcare institutions worldwide. The clinical best care practices (CBPs) of hand hygiene, hygiene and sanitation, screening, and basic and additional precautions aim to reduce this burden. The COVID-19 pandemic has confirmed these four CBPs are critically important prevention practices that limit the spread of HCAIs.

Aim: This paper conducted a systematic review of economic evaluations related to these four CBPs using a discounting approach.

Methods: We searched for articles published between 2000 and 2019. We included economic evaluations of infection prevention and control of *Clostridioides difficile*-associated diarrhoea, meticillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, and carbapenem-resistant Gram-negative bacilli. Results were analyzed with: cost-minimization, cost-effectiveness, cost-utility, cost-benefit and cost-consequence analyses. Articles were assessed for quality.

Results: A total of 11 898 articles were screened and seven were included. Most studies (4/7) were of overall moderate quality. All studies demonstrated cost effectiveness of CBPs. The average yearly net cost savings from the CBPs ranged from $252 847 (2019 $CAD) to $1 691 823 depending on the rate of discount (3% and 8%). The average incremental benefit cost ratio of CBPs varied from 2.48 to 7.66.

Conclusion: In order to make efficient use of resources and maximize health benefits, ongoing research in the economic evaluation of infection control should be carried out to support evidence-based healthcare policy decisions.

KEYWORDS: Systematic review, nosocomial infections, healthcare-associated infections, prevention and control, clinical best practices, economic evaluation, rate of discount, cost, cost savings, incremental benefit cost ratio.

INTRODUCTION

Nosocomial infections (NIs) or healthcare-associated infections (HCAIs) have been defined as “localized or systemic conditions resulting from an adverse reaction to the presence of an infectious agent(s) or its toxin(s) (1). In addition, the condition should develop 48 hours after admission to a healthcare setting, and there must be no previous evidence of the infection. HCAIs are a serious public health problem experienced around the world. They are associated with extra treatment costs, complications, reduction of quality of life, and mortality (2-4). In 2013, The Public Health Agency of Canada reported that each year more than 200 000 patients contract a HCAI, which resulted in over 8000 deaths (5). The same agency estimated that one in every 41 hospitalizations results in a HCAI, incurring costs of approximately 281 million dollars, a sum representing 41% of the total cost of adverse events(6). Since 2004, in Canada, there have been mandatory monitoring programmes for the prevention and control of four pathogens: *Clostridioides difficile* associated diarrhoea (CDAD), meticillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and carbapenem-resistant Gram-negative bacilli (CR-GNB)(7-10). These programmes are generally based on four clinical best practices (CBPs) related to HCAI prevention and control interventions: hand hygiene, hygiene and sanitation, admission screening, and basic and additional precautions(11). The COVID-19 pandemic has confirmed these four CBPs are critically important prevention practices to limit the spread of HCAIs in hospitals and to protect patients and healthcare providers (12).

There are some literature reviews related to the economic impacts of HCAI prevention and control interventions. Most of them generally focus on the economic burden of HCAIs (13-15). The systematic review conducted by Arefian and colleagues provided an economic analysis of the prevention and control of HCAIs in hospitals around the world (2). It dealt with the prevention and control of falls, urinary tract infections, surgical site infections, blood infections, and pneumonia in medical, surgical, paediatric and intensive care units. However, this systematic review did not focus directly on the prevention and control of the four multi-drug resistant organisms mentioned above (CDAD, MRSA, VRE, and CR-GNB). Furthermore, among the interventions analyzed, additional precautions (e.g. isolation of patients) and hygiene and sanitation were not considered. Other systematic and audit reviews of the literature have focused on the effectiveness of the prevention and control of a single HCAI (16-18) . Stone et al. undertook a systematic review of economic analyses of healthcare associated infections (19). However, their review was limited to research papers published between January 2001 and June 2004, and focused on interventions aimed at controlling surgical site infection, bloodstream infection, ventilator-associated pneumonia, and urinary tract infections. Prior to this, in 2002, Stone and colleagues performed an information audit of HAI prevention and control programmes(20). This audit highlighted their efficiency by considering different economic analyses: cost-minimization analysis (CMA); cost-effectiveness analysis (CEA); cost-utility analysis (CUA); and cost-benefit analysis (CBA)(21-25). Unfortunately, this audit review was not a systematic review, and did not assess the quality or risk of bias of the included articles. It also did not assess the effectiveness of the four CBPs (hand hygiene, hygiene and sanitation of surfaces and equipment, admission screening, and additional precautions) simultaneously. Finally, few systematic reviews have used discounting approaches to report their findings, for example see MacDougall (18), which would facilitate comparisons between studies, the year of investigation, currencies and economic evaluation methods.

Faced with these gaps in the literature, a systematic review was needed to consolidate the evidence on economic evaluation of the four CBPs related to HCAI prevention and control interventions using a discounting approach. This review allowed our team to measure the return on investment or net cost savings of the CBPs for the prevention and control of the four most monitored HCAIs in medical and surgical units in Canadian hospitals. Furthermore, this review analyzed the effectiveness of the interventions through five economic analysis approaches: CMA, CEA, CUA, CBA, and cost-consequences analysis (CCA). This systematic review answers the following question: what is the cost-effectiveness of the four CBPs related to HCAI prevention and control interventions in medical and surgical units in 2019 Canadian dollars using a discounting approach.

METHODS

Theoretical Framework

This study is based on the infection control intervention framework developed by Resar et al. (2012)(11) at the Institute for Healthcare Improvement in the United States, which defines a set of CBPs, or ‘bundles’, each of which consists of three to five evidence-based practices. These practices ensure that all healthcare professionals can provide safe care to their patients. This intervention framework supported the implementation, in Canadian healthcare institutions, of infection prevention and control strategies as well as the creation of Canadian (10) safe care campaigns. According to the Public Health Agency of Canada, best practices focusing on HCAI prevention and control would reduce the risk of contracting some HCAI to nearly zero (26).The four actions that will be considered in this study across all bundles are: 1) hand hygiene; 2) hygiene and sanitation of surfaces and equipment; 3) at admission, screening of patients with, or who are at-risk of infection in accordance with the healthcare facility’s protocols; and 4) the application of basic and additional precautions. This HCAI theoretical framework highlighting the four CBPs associated with reduction of rates of infection is presented in supplementary file 1.

1. Hand hygiene. Hand hygiene refers to the washing and disinfection of hands, wrists, and forearms using water, soap, hydro-alcoholic solutions, or alcoholic antiseptic solutions. This action begins with wetting the hands and continues until they are completely dry. The World Health Organization (WHO) estimates that hand hygiene could help reduce healthcare-associated infections by 30-70% (27).

2. Hygiene and sanitation of surfaces and equipment. In 2005, the Aucoin report, entitled *D'abord, ne pas nuire* (*First, do no harm*), stressed the importance of cleanliness and sanitation as a basic measure for infection prevention and control(28). Neglecting the regular preventive cleaning and disinfection of surfaces and equipment results in a reservoir for the proliferation of microorganisms. Hygiene and sanitation must be carried out with appropriate frequency (one or more times per day) depending on the prevalence of infection at the site(29, 30) .

3. Screening, upon admission, of patients who are carriers or who are at-risk. Screening is the systematic testing of persons for a previously undetected HCAI or who may be a potential carrier. Screening techniques differ depending on the type of organisms of concern which have the potential to cause a HCAI in the patient or others. In general, it consists of making a clinical diagnosis and performing laboratory analyses. Any patient who is currently in triage or has been previously hospitalized is considered at-risk if he or she presents with signs and symptoms related to an infection. Those patients who present without any signs or symptoms are considered colonized or potential carriers. Analyses of faeces and blood, nasal smears, laboratory tests, and blood cultures are used to detect pathogens, according to predefined surveillance protocols (31-33). A bacterial strain is considered resistant if it meets certain clinical diagnostic criteria in conjunction with minimum inhibitory concentration tests used to determine the most appropriate antibiotics (31, 34).

4. Basic and additional precautions. In addition to the three above-mentioned basic practices, additional precautions must be taken when a HCAI is reported. While these depend on the infection detected, they include, but are not limited to, the use of personal protective equipment, isolation measures and the application of contact precautions with patients who are carriers or infected (26). In the event that a major outbreak is declared, CBPs must be intensively applied, and additional meetings and resources are added over the course of its duration (35)

Economic Analysis and Research Questions

Before embarking on an economic analysis, it is important to clarify that the interpretation of economic studies must consider three elements: the analytical perspective, the time horizon, and the factors influencing cost, all the while considering the patient's prior condition (36). The analytical perspective—patient, hospital, or societal—determines the choice of costs to include in the calculations. For example, from a hospital perspective, medical costs would not include patient-related costs after discharge, or costs related to lost productivity due to hospitalization. The time horizon sets the time frame within which medical costs are measured. Other factors influencing the costs of care are the stage and severity of disease, comorbidities, risk factors, admitting diagnosis, and length of stay (25, 36).

We included several approaches in our economic analysis of intervention efficiency: CMA; CEA; CUA; CBA; and CCA (21-25). The first three are based on comparing interventions. A CMA compares the costs of two similar processes or interventions to determine which one is the least expensive; it assumes identical outcomes and compares only intervention costs. A CEA measures both the costs (in monetary units) and health benefits (years of life gained) of an intervention in relation to another intervention, or in relation to the status quo. A CEA provides the differential cost-effectiveness ratio represented as: the incremental cost, divided by number of life-years gained. A CUA calculates the differential cost-utility ratio. Here costs are measured in monetary units; however, gains are adjusted to more accurately represent the value of the years of life that the intervention provides. A CUA is reported as the additional cost required for health-related quality of life (quality-adjusted life-year: QALY) improvements. In a CBA, costs and benefits are measured in monetary units. The difference between economic benefits and costs in terms of net gains or losses is estimated. In this approach, an examined intervention will be compared against the status quo to determine its return on investment or profitability. Finally, a CCA is based on a tabular presentation of costs and consequences, leaving benefits (outcomes) in their natural units. Once the cost valuation has been completed, a list is drawn up of all possible intervention outcomes and the choice can be made to value certain potential outcomes.

Conducting an economic analysis of HCAI prevention and control therefore involves examining issues of quality management, prevention, and care safety. Thus, as Finkler (1993, 1996) stated, the cost of quality management takes into account both the cost of investing in preventive measures and the cost of disease or problems experienced(37, 38). The author suggests a certain level of quality can be achieved by investing in prevention. As such, there is a threshold, called the optimum, beyond which prevention could increase quality. Therefore, according to Finkler's model, the economic analysis of a HCAI prevention and control programme using CBPs requires that the following questions be asked:

i) What are the costs of HCAIs?

ii) What is the cost of investing in prevention through CBPs in HCAI prevention and control?

iii) What is the optimal break-even point to measure return on investment or cost savings when comparing prevention intervention costs against potential benefits?

Eligibility Criteria

The inclusion and exclusion criteria were based on the Population, Interventions, Comparators and designs, Outcomes (PICO) framework, summarized in Table I.

Type of population (P)

This review included studies related to the prevention and control of the most commonly monitored pathogens in Quebec hospitals since 2004: CDAD and the three multi-drug resistant organisms or MDROs: MRSA, VRE and CR-GNB. We considered only the care of adult patients in acute-care wards (medicine and surgery) as these wards handle the highest numbers of hospitalized patients. Finally, countries belonging to the Organization for Economic Co-operation and Development (OECD) were targeted because in general they hold comparable health systems (39). Paediatric as well as long-term care settings were excluded.

Type of interventions (I)

The interventions targeted by this review were based on the study's theoretical framework (Supplementary File I). The four major types of intervention (hand hygiene, hygiene and sanitation, screening, and additional precautions) related to CBPs in HCAI prevention and control programmes were analyzed. Studies that investigated any practice other than the four CBPs were excluded.

Type of comparators or designs

In regard to Comparators and Designs, this review included: randomized clinical trials (RCTs), quasi-experimental, case-control, cohort, retrospective, prospective, longitudinal, and cross-sectional studies. Any review or study that was purely clinical, or a technological assessment, or based solely on mathematical and statistical modelling was excluded. We also excluded pharmacoeconomic studies (i.e., those that compared the value of therapeutic or preventative drug interventions).

Type of Outcomes (O)

Outcomes included all quantitative studies using CMA, CEA, CUA, CBA, and CCA, as well as those combining any of these types of analyses. We considered healthcare facilities for the analytical frame and one year as the time horizon. Only studies that assessed the cost-effectiveness analysis of the four CBPs were included. Measurements of cost-effectiveness were reported as: net cost savings (savings - costs); incremental cost-effectiveness ratio (ICER = effectiveness / costs); incremental cost per quality-adjusted life year (QALY); incremental cost per disability-adjusted life year (DALY); and incremental benefit-cost ratio (IBCR = savings / costs).

Data Sources and Research Strategy

This systematic review was registered with the Research Registry (unique identifying number 5355) (40)and conducted in accordance with the recommendations of PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-analysis)(41). All specifications for elements related to the construction of the flow diagram were explicitly presented. Articles were selected from the scientific literature and only those written in English or French and published between 2000 and 2019 were included. The following six electronic bibliographical databases were considered, using iterative exploratory searches: MEDLINE via Ovid, CINAHL, EMBASE, Cochrane, Web of Science, and JSTOR. Grey literature, namely Cordis and OpenGrey, in the same period, were also added. Two nursing HCAI prevention and control programme officers (SB and NP) and co-authors (ET, IB, DS, KK, MJ, AB, CS) contributed to the definition of the keywords. The databases were queried using descriptors or thesauri with the logical operators "AND" and "OR". We developed the search strategy in collaboration with an experienced librarian (CS) at the Saint-Jérôme campus of the Université du Québec en Outaouais and the research strategies to be tested were defined during the working meetings of the co-investigators. All query terms can be found in supplementary file 2. In order to improve reliability, before the full screening of all of the articles, the authors (SB, NP, ET, IB, DS, KK, MJ, AB, CS) screened the same 10% of the titles and abstracts.

Selection Process

A research librarian (CS) implemented the research strategy for article selection and assisted with the preparation of Endnote bibliographic database. Duplicates were identified and removed. Citations were exported into Rayyan system(42) by two reviewers working independently. Two independent reviewers (ET, IB) screened all of the titles and abstracts of the articles. Duplicates were again identified and removed. An algorithm with predefined eligibility criteria was used to select articles (Figure 1).

An article was retained if both independent reviewers considered it eligible after the first screening. If one of the reviewers rejected an article, a third reviewer (other co-authors) analyzed the article title and abstract and made a final decision. An article was rejected if at least two of the three reviewers consider it ineligible. After screening, all the records with a conflict were reviewed (by ET and IB), and an agreement on rejection or acceptance was made. The full text of the selected articles was reviewed for this purpose. Finally, two PCI programme specialists (SB and NP) assessed the content to ascertain whether the final selected studies were technically sound and fell into HCAI prevention and control programs as defined by our four pathogens and CBPs.

Data Extraction

For data extraction, an Excel spreadsheet built by the research team and based on Consolidated Health Economic Evaluation Reporting Standards (CHEERS)(43) was used to extract the following information: authors, year of publication, title and abstract, objective of the study, country, type of clinical unit, design, type of economic evaluation, sample size, population size, currency and adjustment year, time horizon, outcomes related to incremental cost, and funding sources. The extraction was made by one reviewer (IB) and the principal investigator (ET) validated all data.

Assessment of quality

The quality of included articles was assessed using three tools commonly used in economic evaluations. We used these tools because each assesses the economic evaluation components that may differ within, and between, articles. By using them simultaneously we ensured the robustness of our assessment of quality analysis. We first used the audit guidelines for economic evaluation studies recommended by the Scottish Intercollegiate Guidelines (SIGN)(44). Second, the Economic Evaluation criteria developed by Drummond et al. (2015) assessed the quality of the articles(25). These criteria are commonly used in health economic evaluations and were used in previous research we conducted(23). Third, the Cochrane criteria (45) for economic evaluation was used to ensure compliance with the standards of the *Cochrane Handbook for Systematic Reviews of Interventions*.

As with the extraction of articles, two reviewers (ET and IB) independently assessed the quality of the articles. If a consensus was not reached, a third reviewer (SD) arbitrated. Studies were classified as “high quality” if the average score across quality assessment tools was at least 80 %; “moderate quality” if the average score was between 60% and 79.9% and “low quality” if below 60% .

Data Analysis and Aggregation of Results

For each type of intervention, net cost savings, cost-effectiveness ratios, cost-utility ratios, and cost-benefit ratios were tabulated. The year of calculation and the currency used were also indicated. Based on the exchange rate, all currencies were converted to Canadian dollars ($CAD) of the same benchmark year. Using the discount rates of 3%, 5%, and 8% recommended by Montmarquette and Scott in 2007 (46) the values were converted to $CAD for 2019. The net cost savings and incremental ratios (cost-effectiveness, cost-utility, and cost-benefit) were estimated for each discount rate. Sensitivity analyses were carried out on the median values, indicating the maximum and minimum values of the outcomes. This approach was used in a study conducted by Tchouaket et al (2017) (47).

RESULTS

Results of searches and screening

The searches of MEDLINE, CINAHL, Embase, Cochrane, Web of Science, JSTOR, Cordis and OpenGrey databases produced 11 898 records of which 3885 were duplicates. Screening titles and abstracts of 8013 lead to the exclusion of 7979 records based on the eligibility criteria. We had to settle 834 disagreements (10.6% of screened records). Ultimately 34 records met the eligibility criteria for full-text assessment. We read and then excluded 27 manuscripts based on the following reasons: (1) the purpose of the study related to economic burden of HCAIs; (2) studies had the wrong methodological approach or only reported costs of CBPs with no analysis of effectiveness; (3) studies were editorials or poster publications; (4) studies were conducted either hospital wide, or not in the target units (medical and surgical unit); (5) studies did not target at least one HCAI or CBP and finally (6) one study was not in English or French. Seven studies were included in our review (Figure 1).

Study characteristics

Table II summarizes the characteristics of all included studies.

All the manuscripts were published in English from 2001 to 2016. Two studies (28.6%) were conducted in the United States (48, 49), two (28.6%) in the

Netherlands(50, 51)' and the remaining three in the Republic of South Korea(52), Israel (53) and the United Kingdom(54).

Clinical best practices included

One study (14.3%) referred exclusively to the effectiveness of a hand hygiene campaign(52). One (14.3%) focused only on the effectiveness of a screening procedure using a polymerase chain reaction (PCR) assay(54), and one (14.3%) compared two additional contact precautions (48). Four studies (57.1%) combined at least two CBPs: three (42.8%) referred to the effectiveness of screening with basic and additional isolation contact precautions (50, 51, 53) ' , while one (14.3%) focused on the effectiveness of screening, cleaning and sanitation, and basic and additional contact isolation precautions (49).

Nosocomial infections targeted

All the included papers focused on a single HCAI. Six (85.7%) targeted MRSA (48, 49, 51-54) and one (14.3%) VRE (50). None of the included studies focused on CDAD or CR-GNB infections.

Study design used and population

Three (42.8%) studies used a non-experimental retrospective design(50, 52, 54)using historical data. Chun et al. (2016) collected data from January 2008 to December 2014, and included 245 episodes of hospital-onset MRSA. Hassan et al. (2007) screened 686 patients, of which 10 had a MRSA infection, over a period of three months in 2005. Montecalvo et al. (2001) assessed screening and basic and additional contact isolation precautions for VRE in 520 admissions over a period of one year.

Three (42.8%) focused on non-experimental prospective designs (48, 49, 51). Bessesen et al. (2013) compared, in 2006, the MRSA colonization bundle for contact precautions (contact precautions of CDC and contact precautions defined as the use of gloves only) for 159 and 145 colonized patients respectively. From 2001 to 2006, van Rijen et al. (2009) assessed yearly costs of MRSA screening, cleaning and sanitation, basic and additional contact isolation precautions of 38 943 admitted patients representing 282 585 patient days per year. Wassenberg et al. (2011) measured screening from December 2005 to June 2008 in 1764 patients at risk for MRSA; 59 were MRSA infected. Only one study (14.3%) used a matched case control historical prospective design from 2005 to 2011(53). In this study, 53 patients with MRSA were matched with 101 control patients without MRSA. Finally, none of the seven included studies used an experimental or quasi experimental design.

Settings

Three studies (42.8%) were conducted in a single university or teaching hospital (50, 52, 53),one study (14.3%) in a teaching hospital (49) and one study (14.3%) in a general hospital (54). Moreover, one study (14.3%) made the comparison of two tertiary care hospitals (48), and one study (14.3%) conducted comparisons of 14 hospitals (five university hospitals, nine teaching hospitals) (51).

Economic evaluation characteristics

An overview of the reviewed studies using the CHEERS checklist is provided in Table IIIa and Table IIIb.

Economic evaluation design

Table IV summarizes the economic evaluation characteristics of all included studies. We found five studies (71.4%) reporting a cost benefit/cost savings analysis (49, 50, 52-54), one study (14.3%) presented a cost minimization analysis (48), and one study (14.3%) conduced a cost efficacy analysis (51). None of the seven included studies used cost utility analysis or cost consequence analysis approaches.

Data included in the economic evaluations

Six studies (85.7%) used a hospital perspective and only one (14.3%) used a broader perspective (patient and caregiver) (52). The time horizon was explicitly stated in three studies (42.8%) (49, 51, 53). No study reported discounting of costs and effects, and only three studies (42.8%) performed sensitivity analyse s for the calculation of costs and effects (49, 52, 53).

Cost-effectiveness of clinical best practices

Chun et al. (2016) showed that the annual cost of hand hygiene for an MRSA prevention campaign was 167 495 $US. The annual savings, due to a 33% reduction of MRSA incidence, was 851 565 $US. Therefore, the incremental benefit-cost ratio (IBCR) using a 95% confidence interval (CI) with Bayesian model was 5.08 [0.94 - 8.76].

Chowers et al. (2015) found that the annual cost of a prevention and control programme (screening with nasal swabs, additional contact isolation precautions, basic precautions with gloves and gowns, eradication treatment, nasal mupirocin and chlorhexidine body wash) was 208 100 $US per year. When the annual cost of prevention was compared to the annual cost of the reduction of MRSA bacteaemia cases per year (70% as assumed by the authors), the annual net cost savings of this programme was calculated to be 199 600 $US.

Bessessen et al. (2013) showed no difference in the reduction of the incidence of MRSA surgical site infections between MRSA contact precautions as defined by Centers for Diseases Control and Prevention (CDC) or when using only gloves (1.58 versus 1.56 MRSA transmissions per 1,000 patient-days respectively). The annual cost of MRSA contact precautions as defined by CDC was 183 609 $US whereas costs from only the use of gloves was 25 812 $US.

Hassan et al. (2007) found that the annual cost savings of MRSA screening using PCR was 301 000 £ in the first year of implementation and 261 000 £ in the second year; the annual average cost of MRSA infections was 384,000 £.

In the Montecalvo et al. (2001) study, the annual cost of a VRE prevention and control programmr including screening, basic precautions with gloves and gowns, patient education by nurses, and antimicrobial control using nurse monitoring was between 97 939 $US and 148 883 $US. The annual savings of this programme due to the reduction of 6 patients, from a total of 9 per year with VRE, varied between 271 531 $US and 412 461 $US. The average net cost savings associated with enhanced infection control strategies was 189 318 $US for one year.

In the van Rijen et al. (2009) study, the annual cost of the MRSA intervention search and destroy policy based on screening, additional isolation precautions, basic precautions with gowns, gloves and masks, cleaning and sanitation, contact tracing, treatment of carriers, closure of wards, and outbreak situation was estimated at 251 559 € a year, which equals 5.54 € per admission. This policy brought about savings of 427 356 € for the hospital due to a 30% of reduction of MRSA incidence and ten lives saved per year.

Finally, Wassenberg et al. (2011) showed that, because of MRSA screening using Chromogenic agar, IDI and GeneXpert in “nare only”, the cost per isolation day avoided was 15.19 €, 30.83 €, and 45.37 € respectively. The cost per isolation day avoided when all body sites were screened was 19.95 €, 95.77 € and 125.43 € respectively.

Quality assessment

An overview of the quality assessment using SIGN, Drummond and Cochrane grids are provided in Table V. Tables VI-VIII summarize the quality for all studies as assessed by the SIGN, Drummond and Cochrane grids respectively.

Only three studies (42.8%) met at least 80% of the criteria in the SIGN guidelines. These were the studies by Chun et al. (2016), Chowers et al. (2015), and Bessesen et al. (2013). The same three met at least 80% of the criteria in the Drummond grid. In regards to the Cochrane grid, none of seven studies reached 80% of the criteria. Two of them, Chun et al. (2016) and Chowers et al. (2015), met more than 70% of criteria. Overall, only two studies (28.6%) met a minimum average 80% of criteria for the three assessment guidelines and were considered "high quality": Chun et al. (2016) and Chowers et al. (2015). Four studies (57.1%) were considered "moderate quality": Bessesen et al. (2013), van Rijen et al. (2009), Montecalvo et al. (2001) and Wassenberg et al. (2011). Finally, one study (14.3%) Hassan et al. (2007) was considered "low quality".

Synthesis of review results

Net cost savings of included studies in 2019 Canadian dollars

Table IX presents the net cost-savings and incremental cost-benefit ratios for every dollar invested in each CBP as it related to its target in a HCAI prevention and control programme. Values are estimated and presented in 2019 Canadian dollars ($CAD), using discount rates of 3%, 5% and 8%.

The annual net cost savings of hand hygiene for MRSA prevention would be between 1 288 068 and 2 501 211 $CAD based on the discount rates of 3% and 8% respectively.

The annual net cost savings of a prevention and control programme (screening with nasal swabs, additional contact isolation precautions, basic precautions with gloves and gowns, eradication treatment, nasal mupirocin and chlorhexidine body wash) would be between 252 847 and 369 445 $CAD based on the discount rates.

The annual net cost savings of MRSA contact precautions as defined by the CDC would be between 304 688 and 564 262 $CAD. Comparatively, the annual net cost savings of MRSA contact precautions, using only gloves, would be between 42 833 and 79 324 $CAD. Furthermore, the annual net cost savings of MRSA screening using PCR would be between 871 251 and 1 691 823 $CAD.

For the VRE prevention and control programme using screening, basic precautions with gloves and gowns, patient education by nurses, and antimicrobial control using nurse monitoring, the annual net cost savings would be between 527 237 $CAD and 1 644 684 $CAD, based on discount rates of 3% and 8% respectively.

The annual net cost savings of the search and destroy MRSA intervention, based on screening, additional precautions isolation, basic precautions with gowns, gloves and masks, cleaning and sanitation, contact tracing, treatment of carriers, closure of wards, and outbreak status would between 891 173 and 1 650 391 $CAD, based on discount rates of 3% and 8% respectively.

When screening for MRSA, the cost for each isolation day avoided using Chromogenic agar, IDI and GeneXpert in “nare only” would be between 71.3 and 120.1 $CAD. The cost for each isolation day avoided using Chromogenic agar, IDI and GeneXpert in all body sites would between $290.0 and $372.9 $CAD. These are based on the discount rates of 3% and 8% respectively.

Incremental cost-benefit ratios of included studies in 2019 Canadian dollars

For every dollar invested in the hand hygiene campaign, we would save between 9.3 and 18.1 $CAD based on the discount rates of 3% and 8% respectively.

For every dollar invested in the prevention and control programme based on screening with nasal swabs, additional contact isolation precautions, basic precautions with gloves and gowns, eradication treatment, nasal mupirocin and chlorhexidine body wash we would save between 2.5 and 3.6 $CAD.

For every dollar invested in the VRE prevention and control programme using screening, basic precautions with gloves and gowns, patient education by nurses, and antimicrobial control using nurse monitoring, we would save between 6.7 and 20.9 $CAD based on the discount rates of 3% and 8% respectively.

Finally, for every dollar invested in the MRSA search and destroy intervention using screening, additional precautions isolation, basic precautions with gowns, gloves, masks, cleaning and sanitation, contact tracing, treatment of carriers, closure of wards and outbreak situation, we had savings between 4.1 and 7.7 $CAD based on the discount rates of 3% and 8% respectively.

DISCUSSION

Summary of evidence

The objective of this study was to conduct a systematic review of the literature to consolidate the evidence, using a discounting approach, of the economic evaluation of any of the four CBPs (hand hygiene, hygiene and sanitation of surfaces and equipment, admission screening, and additional precautions) related to HCAI prevention and control interventions. This review allowed our team to measure the net cost savings or incremental cost benefit ratio of these practices for the prevention and control of the four most monitored pathogens (CDAD, MRSA, VRE, and CR-GNB), in medical and surgical units in Canadian hospitals.

To the best of our knowledge, this is the first systematic review that focuses on economic evaluations using a discounting approach of these four CBPs simultaneously as they relate to the four pathogens investigated, within the context of HCAI prevention and control interventions in medical and surgical units.

Our systematic review searched scientific and grey literature with a large number (eight) of databases. It identified seven studies that evaluated the net cost savings or incremental cost benefit ratios associated with at least one of the CBPs related to two (MSRA and VRE) prevention and control interventions. Hand hygiene, contact isolation precautions, screening, and combinations of hand hygiene, cleaning and sanitation, contact isolation precautions, basic precautions with gloves, gowns, marks and screening were cost-effective.

To summarize, first, a hand hygiene MRSA prevention campaign could save more than 1.2 million $CAD annually, and up to 2.5 million $CAD depending to the proportion of the reduction of MRSA. Also, for every one dollar invested in the hand hygiene campaign, we would save more than 9.3 $CAD, and that translates into more than 18 $CAD based on the discount rates in medical and surgical hospital units.

Second, MRSA screening using PCR would provide an annual net cost savings of more than 870 000 $CAD, and could reach 1.7 million $CAD. For every dollar invested in the MRSA screening using PCR, two studies show we could save more than 2.9 $CAD and possibly more than 6.5 $CAD in medical and surgical hospital units. Moreover, the MRSA screening intervention could permit healthcare facilities/systems to save more than 290 $CAD per isolation day and could surpass 372 $CAD per isolation day depending on the type of test and the sampling site (e.g. “nare only” testing versus whole body screening).

Third, MRSA contact precautions could provide minimum savings of 42 000 $CAD. This could reach more than 564 000 $CAD if the MRSA contact precautions intervention is that of using only gloves.

Fourth, an MRSA prevention and control programme using a combination of screening with a nasal swab, additional contact isolation precautions, basic precautions with gloves and gowns, eradication treatment, nasal mupirocin and chlorhexidine body wash would provide an annual net cost savings more than 252 000 $CAD, and could reach 369 000 $CAD. Also, for every dollar invested in this programme, we could save more than 2.5 $CAD.

Fifth, a MRSA search and destroy intervention based on the combination of screening, additional isolation precautions, basic precautions with gowns, gloves and masks, and cleaning and sanitation could allow for annual savings of more than 891 000 $CAD. This amount could surpass 1.6 million $CAD depending on the reduction of MRSA. Finally, for every dollar invested in this MRSA search and destroy program, the savings exceed 4.1 $CAD.

Finally, VRE prevention and control programmes using a combination of screening, basic precautions with gloves and gowns, patient education by nurses, and antimicrobial control using nurse monitoring, could help to save more than 527 000 $CAD annually and potentially more than 1.6 million $CAD, depending on the reduction of VRE. Also, for every dollar invested in this VRE prevention and control programme, we could realize savings surpassing 6.7 $CAD.

Our systematic review revealed a lack of studies that made use of cost utility and cost consequence analyses of CBPs. Furthermore, none of the included studies used experimental or quasi experimental designs comparing healthcare facilities with or without the implementation of the CBPs. From this extensive review (2000 to 2019), we noted that, since 2016, no relevant empirical research has been conducted on the economic evaluation of the four CBPs to prevent and control the four targeted pathogens that cause problematic and costly healthcare associated infections.

Rigorous quality assessment using three tools (SIGN, Drummond, and Cochrane) highlighted some limitations of the included studies. First, not all studies reported discounting of costs and effects. Only one study used an analysis from a perspective other than that of a hospital, such as the patient perspective (Chun et al., 2016). Second, as also found by MacDougall et al. (18) none of the included studies estimated the societal costs of the four CBPs including: the infection prevention and control actions of the family, loved ones, caregivers and visitors. Third, in terms of the estimation, only three of the included studies clearly reported the date or the year of valuation of costs (50, 52, 54) . This is a fundamental parameter in economic evaluation (55, 56)because it helps to know the year of the value of costs and savings in order to discount to the actual year for the comparisons in different jurisdictions. Similarly, only three of seven studies clearly reported the sensitivity analysis re: the estimate of costs and effects of the interventions (49, 52, 53). Due to the variation in the effect of the reduction in HCAIs and also the variation in the salary of professional staff according to their experience, it would be useful to present a sensitivity analysis for the real valuation of costs and savings.

Limitations

Our study has some limitations. First, in focusing only on English and French published studies, our research strategy may have missed publications in other languages. Second, we conducted our review of studies that exclusively took place in medical and surgical hospital units. Considering other types of care units (e.g. intensive care or emergency department) could change the estimation of net cost savings / incremental benefit cost ratios of the CBPs. Finally, estimating costs of infection in a fixed period of time does not consider the costs of future infection (or prevention of disease) as evidence suggests an initial infection predisposes patients to future infections(57, 58).

Implications of findings

This systematic review evaluated the cost-effectiveness of implementing CBPs related to HCAI prevention and control. Studies related to MSRA and VRE found these practices provide an important cost-saving/cost-benefit. These financial benefits could be used by public authorities to strengthen the quality of the four CBPs in medical and surgical units of hospitals (47, 59). Savings could be used to strengthen medical human resources (physicians, nurses, nursing assistants, patient attendants, and hygiene and sanitation workers), material resources (gloves, gowns, masks), equipment and products (hydro-alcoholic solutions, hydrogen peroxide), as well as information resources (web/mobile applications for case detection) dedicated to infection prevention and control programmes.

Care providers should take better precautions before, during and after every care intervention by practicing good hand hygiene, thorough hygiene and sanitation, taking precautionary measures and respecting any required additional precautions. Health administrators must reinforce prevention and control procedures in their organization as these processes ultimately lead to cost savings. They could systematically assess the cost-effectiveness of CBPs to better administer HCAI prevention and control, and encourage the effective application of infection control guidelines (47, 60) .

Research results should be shared with patients and their families so that they can be made aware of the financial and human repercussions and benefits associated with infection prevention. They could thus better collaborate in infection prevention actions to ensure their own or their loved one's health and safety during hospitalization.

Finally, as seen with the COVID-19 pandemic, hand hygiene, cleaning and sanitation, screening, and basic precautions with gloves, gowns, masks, and additional isolation precautions are critically important prevention strategies to limit the spread of disease and protect patients and healthcare providers. Our study highlights its importance from an economic perspective. These results would be useful for comparison between OECD countries in terms of CBPs related to HCAI prevention and control. Future research should improve the quantity and quality of economic evaluations of CBPs related to HCAI prevention and control to provide relevant and timely information to healthcare policy makers. This investment in the assessment of cost-effectiveness would empower healthcare policy makers to make the most efficient use of valuable, shared and limited health resources in order to achieve the best health outcomes.

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ABBREVIATIONS

AB: Aurélie Baillot

CBP: Clinical Best Practice

CDAD: *Clostridioides difficile* associated diarrhoea

CISSS: Centre intégré de santé et des services sociaux

CIUSSS: Centre intégré universitaire de santé et des services sociaux

CPE or CP-GNB: Carbapenemase-producing *Enterobacterales*

CS: Catherine Séguin

DS: Drissa Sia

ET: Eric Tchouaket Nguemeleu

INSPQ: Institut national de santé publique du Québec

IB: Idrissa Beogo

KK: Kelley Kilpatrick

MRSA : Meticillin-resistant *Staphylococcus aureus*

MSSS: Ministère de la Santé et des Services sociaux

NI: Nosocomial infection

NIPC: Nosocomial infection prevention and control

NP: Natasha Parisien

OECD: Organization for Economic Co-operation and Development

SB: Sandra Boivin

SPIN: Surveillance provinciale des infections nosocomiales

SR: Stephanie Robins

VRE: Vancomycin-resistant enterococcus

WHO: World Health Organization

DECLARATIONS

1. Ethics approval and consent to participate: Not applicable. However, this systematic review is included in the protocol of the research programme entitled “Analyse économique de la prévention et contrôle des infections nosocomiales”. This programme has been accepted by the Research Ethics Committee of the Université du Québec en Outaouais.

2. Consent for Publication: Not applicable

3. Availability of Data and Material: Yes, upon request from the corresponding author.

4. Competing Interests: The authors declare that they have no competing interests.

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<u>Figures, Supplementary Files and Captions</u>

Supplementary File 1. Proposed framework based on clinical best practices

Supplementary File 2. Query terms used in search

Figure 1. Flow diagram of studies selected for inclusion in systematic review