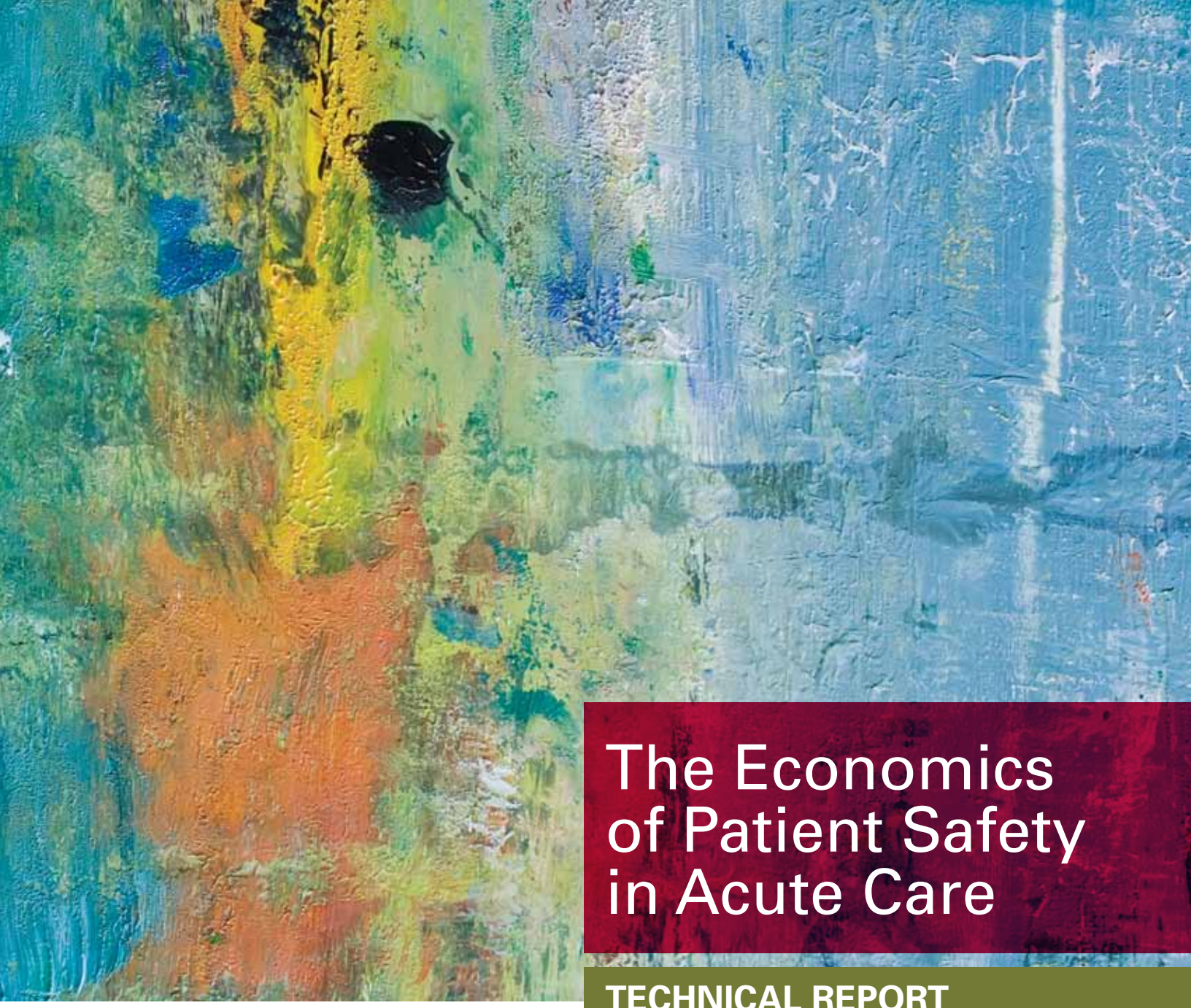

The Economics of Patient Safety in Acute Care

TECHNICAL REPORT

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Safe care... accepting no less

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EXECUTIVE SUMMARY

Patient safety has received considerable public, professional, political, and scientific attention over the past 12 years. Adverse events are injuries caused by healthcare, rather than the patient's underlying condition, leading to disability (prolonged length of stay, morbidity at the time of discharge, or death) (1). Although the human burden associated with adverse events is well established, the economic burden has received less attention. A fuller understanding of the economic burden of unsafe care may inform Canadian health policy, health services research priorities, patient safety research programs, and patient safety improvement priorities for healthcare organizations.

Our objectives were to:

1. Summarize the scope and quality of published studies on the economic burden of adverse events in the acute care setting.
2. Summarize the scope and quality of published comparative economic evaluations (cost effectiveness analyses) of patient safety improvement strategies in the acute care setting.
3. Estimate the economic burden of adverse events on the Canadian acute care system.
4. Provide a framework and guidelines for performing economic burden studies and comparative economic evaluations (cost effectiveness analyses) in patient safety.

METHODS

We searched the published literature from the year 2000 to 2011, linking eight patient safety targets and six patient safety improvement strategies with the following search terms for costs: "costs and cost analysis," "cost-effectiveness," "cost," and "financial management, hospital."

We searched eight patient safety targets:

1. Adverse events (including adverse drug events)
2. Nosocomial colonization and infections
3. Nosocomial pressure ulcers
4. Wrong-site surgery
5. Retained surgical foreign body
6. Contrast nephropathy
7. Nosocomial venous thromboembolism
8. Fall-related injuries.

We also searched six patient safety improvement strategies

1. Hand hygiene
2. Rapid response teams
3. Bundles
4. Checklists
5. Automatic stop orders
6. Bar-coded medication administration.

Potentially relevant abstracts were obtained and reviewed in duplicate using standard economic evaluation methods. For cost effectiveness evaluations, we expected evidence of effectiveness based on the rules of evidence described by the Cochrane Effective Practice and Organisation of Care Group.

We estimated the economic burden of adverse events for the Canadian acute care hospital system based on the results of our systematic review, the results of the Canadian Adverse Events Study (1) and data from the Canadian Institute for Health Information (2).

RESULTS

We identified 158 potentially eligible studies of economic burden, of which only 61 (39 per cent) reported any costing methodology. We found wide estimates of economic burden from these 61 studies, due to variations in case definitions, patient populations, costing methodology, and study setting. The majority of studies reported the economic burden of adverse events and nosocomial infections. We found that the reported attributable costs of adverse events ranged from US$2,162 (CAN$4,028) to AUS$11,846 (CAN$12,648). In general hospital populations, the cost per case of hospital-acquired infection ranged from US$2,027 (CAN$2,265) to US$12,197 (CAN$22,400). Nosocomial bloodstream infection was associated with costs ranging from €1,814 (CAN$3,268) to €16,706 (CAN$29,950).

We found five cost effectiveness analyses that reported a total of seven comparisons based on at least one study with adequate evidence of effectiveness. Based on these limited studies, pharmacist-led medication reconciliation, the Keystone Michigan ICU Intervention for central line associated blood stream infections, chlorhexidine for vascular catheter site care, and standard surgical sponge counts were economically attractive patient safety improvement strategies.

We calculated a preliminary estimate of the economic burden of adverse events in Canada in 2009–2010 was $1,071,983,610 ($1.1 billion), including $396,633,936 ($397 million) for preventable adverse events. This estimate does not include the direct costs of care after hospital discharge, or societal costs of illness, such as loss of functional status or occupational productivity.

We developed a guideline for future economic evaluations in patient safety (see page 24 and *Appendix 2*).

CONCLUSIONS

1. The majority of published studies on the economic burden of patient safety in acute care describes no costing methodology.
2. For studies that report a costing methodology, there is variability in methods for measuring and attributing costs.
3. Most studies report on the economic burden of adverse events and nosocomial infections.
4. The reported attributable costs of adverse events ranged from US$2,162 (CAN$4,028) to AUS$11,846 (CAN$12,648).
5. The cost per case of hospital-acquired infection ranged from US$2,027 (CAN$2,265) to US$12,197 (CAN$22,400). Nosocomial bloodstream infection was associated with costs ranging from €1,814 (CAN$3,268) to €16,706 (CAN$29,950).
6. We found only five comparative economic analyses of patient safety improvement strategies in the acute care setting based on adequate evidence of effectiveness based on guidelines from the Cochrane Effective Practice and Organisation of Care Group.
7. Based on these limited analyses, the following patient safety improvement strategies are economically attractive:
    - Pharmacist-led medication reconciliation to prevent potential adverse drug events was the dominant strategy (improved safety and lower cost) when compared to no reconciliation.
    - The Keystone ICU Patient Safety Program to prevent central line associated bloodstream infections was the dominant strategy compared to usual care. The Keystone ICU Patient Safety Program included two key components: (*a*) a Comprehensive Unit-Based Safety Program, which included interventions to improve safety culture, teamwork, and communication; a daily goals sheet; and other communication tools; and (*b*) specific interventions to improve compliance with evidence-based care to reduce CLABSI.
    - Chlorhexidine for catheter site care to prevent catheter-related bloodstream infections was the dominant strategy when compared to povidone-iodine.
    - Standard counting was associated with a cost of US$1,500 (CAN$1,676) for each surgical foreign body detected, when compared to a strategy of no counting.
8. We estimate that the economic burden of preventable adverse events in the Canadian acute care system was approximately $397 million in 2009-2010.
9. Safety improvement programs should consider the EPOC standards when planning their program evaluations.
10. Cost effectiveness analyses should explicitly consider the impact of patient safety on economically important parameters such as staff retention, staff absenteeism, and patient (market) retention.
11. Cost effectiveness analyses should explicitly consider the societal value of improving safety over improving care of primary clinical conditions.
12. Studies of the health-related quality of life associated with patient safety targets are needed.
13. Guidelines for performing or assessing economic research in patient safety could be based on the Drummond Checklist (3) (*Appendix 2*).

INTRODUCTION

Patient safety (PS) has received considerable public, professional, political, and scientific attention over the past 12 years. Adverse events are injuries caused by healthcare, rather than the patient's underlying condition, leading to disability such as prolonged length of acute care stay, morbidity at the time of discharge or death (1).

Although the human burden associated with adverse events is well established, the economic costs have received less attention. Despite the substantial effort that has been expended to develop and implement safety improvements, there is uncertainty about both the economic impact of unsafe care and the improvement strategies that offer the best value.

A fuller understanding of the economic burden of unsafe care may inform Canadian health policy, health services research priorities, PS research programs and PS improvement priorities for healthcare organizations.

Economic evaluations should be based on rigorous analytical methods, be impartial and credible in the use of data, and be transparent for and accessible by the reader (4).

The purpose of an economic evaluation is to "identify, measure, value and compare the costs and consequences of alternatives being considered" to inform "value for money" judgments about an intervention or program (5). In Canada, national guidance on the conduct of resource costing and economic evaluations has been available through the Canadian Agency for Drugs and Technologies in Health (CADTH) since 1994 (4;6;7).

There are two common types of economic evaluations in healthcare: the economic burden study and the comparative economic analysis.

ECONOMIC BURDEN STUDIES

The objective of an economic burden study is to describe the economic impact of a PS target. We highlight three important methodologic considerations in economic burden studies: economic perspective, time horizon and attribution of healthcare resources to the care of the PS target, rather than the care of the patient's underlying condition.

The choice of economic **perspective** will determine the type of resources and costs measured and attributed to the PS target. For example, a study with an acute care hospital perspective will focus on the direct medical costs of providing hospital care. In this perspective, costs of care after hospital discharge or societal costs of illness, such as loss of functional status or occupational productivity, are not measured.

The choice of **time horizon** will influence the amount and types of resources measured. The optimal time horizon for many PS target conditions is not known, but a significant proportion of the cost of severe PS events is accrued after acute care hospital discharge (8).

The **attribution of healthcare resources** to the management of a PS target, rather than the patient's underlying condition, is particularly important. Patients with more comorbidity, and longer hospital

stays, are more likely to consume healthcare resources for the management of their underlying condition, and these resources are therefore not attributable to PS. However, these individuals are also more likely to experience an adverse event.

There are several methodologic approaches to the attribution of healthcare resources. In the case review method, a clinical expert explicitly attributes resources to the care of the PS target or the underlying condition. For example, a specialist could review the chart of a patient admitted with congestive heart failure who develops a nosocomial infection on day four. The expert would determine which resources, and which hospital days, were directed primarily for the treatment of the infection, rather than the congestive heart failure. This method was used in the Canadian Adverse Events Study (1). Major limitations of this study design are its resource-intensive effort, and the potential unreliability of retrospective judgments.

A second burden of illness approach compares groups of patients with (cases) and without (controls) the PS target. In this approach, the resource use for patients who develop post-operative infections is compared to the resource use for similar patients who do not develop infections. A limitation of this study design is that there may be resource and cost differences between cases and controls that are unrelated to the PS target (confounders). Several analytic techniques are used to reduce the effect of these confounders. Matched case-control studies can reduce the confounding effect of a small number of known variables, but matching is usually performed on a limited number of variables. Propensity score methods can accommodate many more potential confounding variables than case-control methods. Traditional multivariable statistics can also be used to estimate the impact of known confounders on differences between cases and controls (9). Differential timing of the occurrence of adverse events can lead to wide estimates of attributable costs (10-12).

COMPARATIVE ECONOMIC ANALYSIS (COST EFFECTIVENESS ANALYSIS)

The second type of economic evaluation is the comparative economic analysis. Comparative economic analyses in PS should compare the costs and outcomes of one or more safety improvement strategies aimed at a PS target. The goal is to identify interventions that provide the best value for money. Many people are familiar with the term cost effectiveness analysis, which is a common type of comparative economic analysis. For ease of reading of this report, we will use the term cost effectiveness analysis throughout. Cost effectiveness analyses are conducted using widely accepted frameworks, which can be modified for specific target conditions (3;13-15).

An ideal improvement strategy will be associated with lower costs and greater safety; such an intervention is considered economically *dominant*. In some cases, a strategy can be associated with greater costs and less safety; such strategies are considered economically *dominated* and should not be adopted. Other improvement strategies can be associated with increased cost and greater safety. In these situations, the additional dollars spent for the gain in PS can be calculated. The relative value must be weighed against other available interventions, which could be implemented within our resource-constrained healthcare systems.

There are several key considerations in cost effectiveness analyses. First, **evidence of effectiveness** is a prerequisite for any meaningful cost effectiveness analysis. The rules of evidence for evaluation of PS improvements has been debated for many years (16;17). We used the rules of evidence described by the Cochrane Effective Practice and Organisation of Care (EPOC) Group: randomized control studies, controlled clinical trials, controlled before-and-after studies and interrupted time series (18).

Second, the **choice of comparator** will have a major influence on the results of a cost effectiveness analysis. Any intervention will look good if compared with an unattractive alternative. The standard of care is often an appropriate comparator.

Third, several potential **analytic approaches** can be used. In a **cost effectiveness analysis**, an incremental cost effectiveness ratio is the additional cost divided by the number of life years gained. Life year gained is an appropriate choice when death is the outcome of interest, but may not be appropriate for other outcomes, such as adverse events. In a **cost utility analysis**, an incremental cost-utility ratio uses estimates the incremental cost to improve health-related quality of life, or quality adjusted life year (QALY). These cost-utility ratios can be compared across many disease states. Unfortunately, health related quality of life estimates used to create cost utility ratios are unknown for many PS targets. In a **cost consequence analysis**, a cost consequence ratio estimates the incremental cost per event avoided. Cost consequence ratios are easier to calculate, but can make comparisons between different studies or conditions difficult.

Finally, as in the economic burden of illness studies, the **choice of perspective**, the **choice of time horizon** and the **attribution of healthcare resources** to the management of a PS target, rather than the patient's underlying condition, are also important.

We did not include budget impact analyses in our review. Budget impact analyses predict how an intervention will impact spending on a target condition (19). Budget impact analyses do not explicitly incorporate evidence of effectiveness, and often do not specify economic perspectives or time horizons.

OBJECTIVES

Our objectives were to:

1. Summarize the scope and quality of published studies on the economic burden of adverse events in the acute care setting.
2. Summarize the scope and quality of published comparative economic evaluations (cost effectiveness analyses) of PS improvement strategies in the acute care setting.
3. Estimate the economic burden of adverse events on the Canadian acute care system.
4. Provide a framework and guidelines for performing economic burden studies and comparative economic evaluations (cost effectiveness analyses) in PS.

METHODS

IDENTIFICATION OF PS TARGETS

Our first step was to develop a list of PS targets in the acute care hospital setting. We used an iterative process with co-investigators (n=9), informed by prior systematic reviews (20), Canadian provincial government PS priorities, Canadian Patient Safety Institute (CPSI) improvement priorities and the American Healthcare research and Quality (AHRQ) Patient Safety Net website

We selected our targets based on three characteristics:

- A clinical outcome (e.g., hospital-acquired methicillin-resistant Staphylococcus aureus [MRSA] infection) or a surrogate with an established link to a clinical outcome (e.g. MRSA colonization).
- High specificity as a measure of PS, as opposed to being a naturally occurring condition.
- A sufficiently long history of measuring this outcome in the literature, such that some studies on the economic burden or cost effectiveness can be expected.

We presented our initial list of PS targets to over 200 delegates at the 2010 Halifax pre-conference plenary session on the economics of PS, and five members of our pre-conference advisory group: Dr. Sven Grisvold (past editor of Acta Anaesthesiologica Scandinavica); Dr. Kathleen Sutcliffe (Gilbert and Ruth Whitaker Professor of Business Administration and Professor of Management and Organizations, University of Michigan); and Mr. Steven Lewis, Mr. Blair Sadler, and Mr. Joseph Gebran (CPSI).

We selected eight PS targets (Table 1), including six sub-categories of nosocomial colonization and infections.

Table 1: List of PS Targets

1. Adverse Events, Including Adverse Drug Events
2. Nosocomial colonization and infections a. Ventilator-associated pneumonia b. Catheter-associated urinary tract infection c. Antibiotic-resistant organism colonization d. Antibiotic-resistant organism infection e. Catheter-associated bloodstream infection f. Clostridium difficile-associated disease g. Surgical wound infection
3. Nosocomial pressure ulcers
4. Wrong-site surgery
5. Retained surgical foreign bodies
6. Contrast-induced nephropathy
7. Nosocomial venous thromboembolism
8. Nosocomial fall-related injuries

SYSTEMATIC REVIEW OF PUBLISHED LITERATURE

We then conducted a systematic review of published literature. Our goal was to identify, review, and summarize the scope and quality of evidence of published economic evaluations in the area of PS.

We searched the MEDLINE database for articles published between 2000 and 2010 (using the following search terms for costs: "costs and cost analysis," "cost-effectiveness," "cost," and "financial management, hospital."

We developed search terms for each PS target. We expected to find any cost effectiveness analyses related to these conditions through these search terms. We wanted to ensure that all relevant economic literature was captured, so we also searched specific PS improvement strategies: hand hygiene, rapid response teams, bundles, checklists, automatic stop orders, and bar-coding. (Table 2)

Table 2: Search Terms for PS Targets and PS Improvement Strategies

PS TARGETS	SEARCH TERMS
1. Adverse Events, Including Adverse Drug Events	- "adverse events" and "prevent" - "medical errors"
2. Nosocomial colonization and infections	- "cross infection" or "infection control" - "nosocomial" or "hospital acquired" or "healthcare associated infection" or "healthcare associated infection" or "HAI" - "catheterization" - "drug resistance" - "methicillin-resistant staphylococcus aureus" - "bata-lactam resistance" - "vancomycin resistance" - "clostridium difficile" - "surgical wound infections" - "ventilator associated pneumonia" - "VAP"
3. Nosocomial pressure ulcers	- "nosocomial" or "hospital acquired" or "healthcare associated infection" or "healthcare associated infection" or "HAI" - "pressure ulcers"
4. Wrong-site surgery	- "medical errors" and "surgery" - "wrong site surgery"
5. Retained surgical foreign bodies	- "foreign bodies" - "surgical equipment" - "retained"
6. Contrast-induced nephropathy	- "nephrosis" or "nephropathy" - "contrast media" or "contrast induced" or "radiocontrast"
7. Nosocomial venous thromboembolism	- "venous thromboembolism" - "pulmonary embolism" - "venous thrombosis" - "deep-vein thrombosis" - and "prevent"
8. Nosocomial Fall Related Injuries	- "accidental falls" - "fall related injuries" - "fall injury"

PS IMPROVEMENT STRATEGIES	SEARCH TERMS
9. Hand Hygiene	- "hand washing" - "hand hygiene"
10. Rapid Response Team	- "hospital rapid response team" - "rapid response team"
11. Bundles	- "bundle" and "intervention" - and "safety"
12. Checklists	- "checklist" and "patient"
13. Automatic Stop Orders	- "automatic stop order" - "automatic stop date"
14. Bar-Coding	- "bar code"

All citations were reviewed by two investigators. Eligible studies included original research with a cost effectiveness analysis or burden of illness analysis. All reviews, editorials, and articles with no costing information in the abstract were excluded. All remaining abstracts were independently reviewed by two co-investigators. Full publications of any abstracts considered potentially relevant were retrieved. Two co-investigators reviewed all eligible articles using the Drummond Checklist (3). Studies that did not have costing methods were excluded.

We submitted the first version of this report to the CPSI on May 31st, 2011. In November 2011, we became aware of a newly published significant cost effectiveness analysis. We chose to update our search for cost effectiveness analyses through to November 2011 so this significant analysis could be included in our review.

ASSESSMENT OF STUDY QUALITY

(Appendix 1)

Economic studies are conducted using recognized frameworks that can be modified for specific target conditions (13;14). Drummond and Jefferson constructed a checklist to evaluate the quality of economic studies in healthcare that is used worldwide (3;15) (see *Appendix 1*). We used the entire Drummond Checklist (3) to evaluate the quality of cost effectiveness analyses. The Drummond Checklist rates 35 parameters as present (yes), absent (no), not clear, and not applicable. For the burden of illness studies, the Drummond Checklist was modified to 22 items, excluding those items required only for cost effectiveness analyses. We arbitrarily assigned one point for each item present, then calculated a total score. Scores are presented as means and medians for the number of yes parameters.

Cost effectiveness analyses require evidence of effectiveness of the PS improvement strategy that is being evaluated. We used the rules of evidence described by the Cochrane Effective Practice and Organisation of Care (EPOC) Group: randomized control studies, controlled clinical trials, controlled before-and-after studies, and interrupted time series analyses (18). Uncontrolled before-after studies do not provide sufficient evidence of effectiveness of a PS improvement strategy.

Two independent reviewers evaluated each manuscript. If the scores were within five points, then the higher of the two scores was taken. We discussed and resolved discrepancies between reviews of five or more points. We had no difficulty resolving these discrepancies and achieving consensus. We made some standard assumptions to facilitate our reviews. For example, most studies took a short-term acute care hospital perspective, so discounting was not relevant.

Our third objective was to estimate the economic burden of adverse events on the Canadian acute care system. We used data obtained from our systematic review wherever possible. We also sought additional data from the Canadian Adverse Events Study (1) and data from the Canadian Institute for Health Information (2) on Canadian estimates on the incidence of PS targets, including estimates of preventability, Canadian estimates of the population at risk for each PS target, and Canadian estimates of the attributable length of stay, or attributable costs for each PS target.

RESULTS

SCOPE OF PUBLISHED RESEARCH

Our initial search yielded 2,151 citations, of which 207 were considered potentially relevant. We reviewed these 207 full manuscripts, and identified 61 economic burden studies and five cost effectiveness analyses that met our inclusion criteria. We excluded the remaining 141 articles for the following reasons: they did not study an intervention directed at a PS target (n=5), were review papers with no primary data or analysis (n=6), were not conducted in an acute care setting (n=8), or did not report any costing methodology (n=101). We then excluded 19 cost effectiveness analyses that did not report, or cite, adequate evidence of effectiveness based on the Cochrane collaboration guidelines for quality improvement effectiveness studies (18). Of these 19 exclusions, the effectiveness data described or cited were uncontrolled observational cohort studies (n=8) (21-28), hypothetical evidence without clinical evidence (n=6) (29-34), or uncontrolled before-after studies (n=5) (35-39). Finally, we excluded two cost effectiveness analyses of specific strategies for reducing contrast induced nephropathy due to narrow patient subgroups (40;41).

Table 3: Summary of 61 Studies Reporting 68 estimates of the Economic Burden of PS Targets in Acute Care.

	NUMBER OF STUDIES	MEAN METHODOLOGIC FEATURE SCORE [MEDIAN, RANGE]	STUDY DESIGN
Adverse Events and Adverse Drug Events	8	13 [13, 12-16]	Retrospective cohort study (n=5), prospective cohorts with nested cases and controls (n=2), case series (n=1)
Nosocomial Infections (not otherwise specified)	10	14 [15, 12-16]	Prospective study (n=1), retrospective cohort (n=5), retrospective case control study (n=3), decision model (n=1)
Surgical Site Infections	8	14 [14.5, 11-17]	Prospective study (n=1), retrospective cohort (n=3), retrospective case control study (n=2), nested case control (n=2)
Nosocomial Bloodstream Infections	10	14 [15, 9-18]	Prospective study (n=1), retrospective cohort (n=3), retrospective case control study (n=5), case series (n=1)
Nosocomial Sepsis	2	17 [17.5, 15-20]	Prospective cohort (n=1), retrospective cohort (n=1)
Nosocomial Rotavirus Infections	3	14 [14, 13-15]	Prospective cohort (n=1), prospective case series (n=1), nested case control (n=1)
Nosocomial Urinary Tract Infection	4	13 [15,9-15]	Prospective cohort (n=1), retrospective cohort (n=2), retrospective case control (n=1)

	NUMBER OF STUDIES	MEAN METHODOLOGIC FEATURE SCORE [MEDIAN, RANGE]	STUDY DESIGN
Nosocomial Pneumonia	4	14 [13-15]	Prospective cohort (n=2), prospective/ retrospective case control (n=1), retrospective case control (n=1)
Nosocomial Respiratory Tract Infection	3	15 [15, 15-15]	Retrospective cohort (n=1), retrospective case control (n=1), one case control (n=1)
Miscellaneous Nosocomial Infections	12	15 [14.5, 12-20]	Prospective nested case control (n=1), Case control (n=1), retrospective case series (n=4), retrospective case control (n=2), retrospective cohort (n=3), retrospective nested case control (n=1),
Nosocomial Venous Thromboembolism	2	17 [17, 16-18]	Decision analysis (n=1), Retrospective observational cohort study (n=1)
Nosocomial Falls	3	15 [15, 14-16]	Prospective cohort (n=1), case series (n=2)
TOTAL	**68**		

ECONOMIC BURDEN STUDIES

(Table 3, Appendices 3-9)

Adverse events, including adverse drug events (eight studies)

(Appendix 3)

We identified eight studies of the economic burden of AEs and ADEs published since 2000. The mean and median Drummond Checklist scores were 13.9 out of 22 (63 per cent) and 13.5, respectively. The scores ranged from 12 to 16. The articles are summarized in *Appendix 3*.

Five of these studies used a retrospective cohort study design, and relied on regression analyses to determine the attributable costs. Of these, two articles broadly focused on any AE or hospital-acquired complication (42;43). An additional article evaluated the economic burden of a broad range of AEs, in patients with spinal cord injuries (44). One article included five specific AEs: medication errors, patient falls, urinary tract infections, pneumonia and pressure ulcers (45). Another article evaluated costs related only to surgical AEs, but did not further define them (46). The three remaining studies related to AEs were either case series (47) or prospective cohorts with nested cases and controls (48;49). Two of these studies defined a case as any AE (48) or a case leading to a medical dispute (47). One burden study specifically evaluated adverse drug events (49).

Costs[1] attributable to AEs were reported to be US$3,857 (CAN$6,124) (48) and AUS$11,846 (CAN$12,648) (43) per case in two studies. In patients with spinal cord injury, the cost attributable to general AEs was AUS$7,359 (CAN$7,857), but was significantly higher for specific complications; for example, procedural complications in these patients were associated with additional costs of AUS$21,821(CAN$23,299) (44). The cost attributable to adverse drug events specifically was reported to be US$2,162 (CAN$4,028) per ADE (49). In another study, medication errors in medical and surgical cases were associated with costs of US$334 (CAN$402) and US$525 (CAN$632), respectively (45). Additional length of stay related to AEs of any type ranged from 0.77 days to 32 days. Three of the eight articles did not collect length-of-stay data.

In summary, studies of adverse events used variable methods, different definitions of adverse events, and different methods for attributing costs. Attributable costs of adverse events ranged from US$2,162 (CAN$4,028) to AUS$11,846 (CAN$12,648); medication errors had an attributable cost of US$334 (CAN$402) to AUS$525 (CAN$632).

Nosocomial Infections

(Appendix 5)

• General Nosocomial Infections (10 studies)

We identified 10 studies of the economic burden of general nosocomial infections, not otherwise specified by type of infection. These included one prospective design, five retrospective cohort designs, three retrospective case-control designs, and one study used a decision model. Analytic methods included regression analysis, including linear regression, multivariate regression, and ordinary least-squares regression analysis. The mean Drummond Checklist score for these articles was 13.5 out of 22 (61 per cent). The median score was 14. The scores ranged from 11 to 16 out of a total of 22.

In general hospital populations, the cost per case of hospital-acquired infection ranged from US$2,027 (CAN$2,265) to US$12,197 (CAN$22,400) (52-58). Hospital-acquired infections cost US$2,767 (CAN$3,091) in gastrectomy patients (58) and €11,750 (CAN$27,796) (59) in neonates. The estimated costs of hospital-acquired infections over one fiscal year in New Zealand in medical and surgical patients were US$4,569,826 (CAN$8,392,705) and US$3,900,922 (CAN$7,164,231), respectively (60).

• Surgical Site Infections (eight studies)

We found eight studies of the economic burden of surgical site infections. Study designs included prospective cohort (N=1), retrospective cohort (N=3), retrospective case-control (N=2), and two nested case-control designs. The mean Drummond Checklist scores for these articles were 14 out of 22 (64 per cent). The median score was 14. The scores ranged from 12 to 17 out of a total of 22.

1 All costs are reported in their original currency. For comparison purposes, they have also been converted to 2010 Canadian dollars based on the Bank of Canada currency converter and inflation calculator (50;51). Each cost was first converted to Canadian dollars of the same year indicated in the study; the converted cost was then inflated to 2010. Due to conversion and inflation rates fluctuating yearly, the proportion of the original cost compared to the 2010 Canadian cost is not the same. The 2010 Canadian costs were used for comparison purposes only and do not reflect how much Canada spent in each safety target.

Three studies reported the average cost per case of surgical site infection in a general patient population to be US$1,051 (CAN$1,174) (52), €1,814 (CAN$3,268) (61), and 19,638 Swiss francs (CAN$21,392) (62). In orthopaedic patients, the median attributable cost of surgical site infection was US$17,708 (CAN$31,527) (63). Surgical site infection in patients after colorectal procedures, head-and-neck cancer-related surgery, coronary artery bypass graft procedures, and low transverse Caesarean delivery were associated with costs of US$13,746 (CAN$16,560) (64), €16,000 (CAN$26,273) (65), AUS$12,419 (CAN$14,934) (66), and US$2,852 (CAN$3,107) to US$3,529 (CAN$3,845) (67) per case, respectively.

• Nosocomial Bloodstream Infections (11 studies)

We found 10 studies of the economic burden of nosocomial bloodstream infections. These included one prospective, three retrospective cohort, five retrospective case-control, and one case series. The mean Drummond Checklist score for these articles was 13.5 out of 22 (61 per cent). The median score was 14.5. The scores ranged from 10 to 16 out of a total of 22.

In general European patient populations, nosocomial bloodstream infection was associated with costs ranging from €1,814 (CAN$3,268) to €16,706 (CAN$29,950) (52;61;68-71). One American study reported average incremental costs of US$19,427 (CAN$23,404) (72). In a pediatric ICU, nosocomial bloodstream infection was estimated to cost US$39,219 (CAN$71,500) (73). Very low-birth-weight infants with nosocomial bloodstream infection incurred average total costs US$54,539 (CAN$101,621) higher than those without the infection (74). S. aureus bacteraemia in patients with prosthetic implants was associated with US$67,439 (CAN$123,469) in costs per nosocomial case, in one prospective case series (75).

• Nosocomial Sepsis (two studies)

In one retrospective cohort study, nosocomial sepsis was associated with mean additional costs of US$27,510 (CAN$50,523) (76) per case. In one prospective cohort, ICU-acquired sepsis was associated with a mean increase of €39,908 (CAN$65,644) in total costs per case (77). The mean and median Drummond Checklist scores for these articles were 16.5 out of 22 (75 per cent). The scores ranged from 13 to 20 out of a total of 22.

• Nosocomial Rotavirus Infection (three studies)

One prospective cohort study estimated the costs associated with nosocomial rotavirus infection in children under 30 months of age, but did not provide a per-case result; this study estimated that the national cost of all cases in one year in Italy is €8,019,155 (CAN$12,787,889) (78). Rotavirus in children under 48 months of age was associated with €2,442 (CAN$5,144) in costs per case in one prospective case series (79). One prospective study with a nested case control reported €1,930 (CAN$3,337) in mean excess costs per case (80). The mean Drummond Checklist score for these articles was 13.3 out of 22 (60 per cent). The median score was 14. The scores ranged from 12 to 14 out of a total of 22.

• Nosocomial Urinary Tract Infection (four studies)

We found four studies of the economic burden of nosocomial urinary tract infections. These included one prospective, two retrospective cohort, and one retrospective case-control study. The average costs attributable to urinary tract infection ranged from US$589 (CAN$1,114) to US$14,300 (CAN$26,645) (52;61;81;82). The mean Drummond Checklist score for these articles was 12.5 out of 22 (57 per cent). The median score was 13. The scores ranged from 9 to 15 out of a total of 22.

• Nosocomial Pneumonia (four studies)

Nosocomial pneumonia was associated with average additional costs of 2,255 Argentinian pesos ($1,309 CAN) (83) and €17,000 ($27,915 CAN) (65) in two studies. One German article detailed both a prospective case control and a retrospective case control, reporting average excess costs of DM 14,606 ($14,840 CAN) and DM 29,610 ($30,085 CAN), respectively (84). In one study, the average cost attributable to ventilator-associated pneumonia in a pediatric ICU was US$51,157 ($61,630 CAN) (85). The mean Drummond Checklist score for these articles was 14 out of 22 (64 per cent). The median score was 13.5. The scores ranged from 13 to 16 out of a total of 22.

• Nosocomial Respiratory Tract Infection (three studies)

Three studies reported on the economic burden of nosocomial respiratory tract infections. These included one retrospective cohort, one retrospective case-control, and one case-control study. The mean Drummond Checklist score for these articles was 15 out of 22 (68 per cent). The median score was 15. All three scores were 15 out of a total of 22.

Single-site respiratory tract infections were associated with additional mean costs of €2,421 (CAN$4,362) (61) and US$4,287 (CAN$4,789) (52) in two studies, respectively. In one additional study, a case was defined as an infection of nosocomial respiratory syncytial virus; this infection was associated with a mean US$9,414 (CAN$16,788) per case (86).

• Nosocomial Antibiotic-Resistant Organisms (four studies)

In one Irish hospital, postoperative methicillin-resistant Staphylococcus aureus (MRSA) infection incurred additional costs of £6,485 (CAN$14,484) (87). One case-control study reported the attributable costs of vancomycin-resistant Enterococcus infection in the medical ICU and in hospital to be US$7,873 (CAN$14,414) and US$11,989 (CAN$21,950), respectively (88). In one drug-resistant S. typhimurium outbreak in a Turkish neonatal ICU, cases incurred charges US$1,082 (CAN$1,427) higher than controls (89). A pertussis outbreak incurred total hospital costs of US$30,282 (CAN$43,917) and US$43,893 (CAN$63,657) in two hospitals (90). One retrospective case-control study defined a case as a multidrug-resistant infection of Acenitobacter bowmanii in burn patients, and reported a mean additional cost per case of US$98,575 (CAN$181,038) (91).

• Nosocomial Clostridium Difficile-Associated Disease (one study)

One prospective study with a nested case control reported a median incremental cost of €7,147 (CAN$10,809) per case of Clostridium difficile–associated disease (CDAD) (92).

• Other Nosocomial Infections (10 studies)

The mean Drummond Checklist score for these articles was 12.7 out of 22 (58 per cent). The median score was 13. The scores ranged from 10 to 18 out of a total of 22. During a P. aeruginosa outbreak, it was retrospectively estimated that infected patients who had been on mechanical ventilation incurred excess costs of €18,408 (CAN$28,109) (93). Another retrospective case series investigated the economic impact of a norovirus outbreak that affected patients and staff, and did not provide a per-case cost estimate; dividing the total outbreak costs by the given number of case infections yields a crude estimate of €890 (CAN$1,359) per case (94). Another similar study yielded an estimate of US$2,452 (CAN$4,489) per case of outbreak-related norovirus (95). The attributable costs during a Salmonella outbreak in one Australian tertiary care complex were reported in total costs rather than per case, and dividing by the number of cases yields an estimate of AUS$2,308 (CAN$3,222) per case (96).

• Summary

In summary, studies of the economic burden of nosocomial infection are heterogeneous in methodological characteristics, country setting, case definitions, and patient populations. A summary estimate was not possible. Nevertheless, most studies describe significant costs attributable to hospital-acquired infections. For example, in general hospital populations, the cost per case of hospital-acquired infection ranged from US$2,027 (CAN$2,265) to US$12,197 (CAN$22,400) (52-54;54-57).

Nosocomial Venous Thromboembolism

(Appendix 8)

We identified two burden studies published since 2000. The mean and median Drummond Checklist scores were 17 and 17, respectively (77 per cent). The scores ranged from 16 to 18.

One study focused on nosocomial deep-vein thrombosis (DVT) after hip replacement surgery (97). The cost of DVT was modelled in patients undergoing total hip replacement surgery, with Markov decision analysis. The article reported the annual per-patient cost of DVT to be US$3,798 (CAN$6,975), with discounted lifetime costs US$3,069 (CAN$5,696). Costs of DVT-related complications were US$3,817 (CAN$7,010) for post-thrombotic syndrome with ulcer, and US$6,604 (CAN$12,219) for pulmonary embolism. A retrospective U.S. study of DVT (n=15,679), PE (n=7,653), and post-thrombotic syndrome (n=624) found annual attributable direct medical costs of $16,832 (CAN$24,411) for DVT, $18,221 (CAN$26,426) for PE, $24,874 (CAN$36,074) for combined DVT and PE, and $4,726 (CAN$6,854) for post thrombotic syndrome. This study did not explicitly distinguish cases of nosocomial DVT, but 78 per cent of the study cohort had abdominal or orthopaedic surgery prior to the index VTE event (98).

Nosocomial Falls

(Table 3 and Appendix 9)

We reviewed three burden of illness studies related to nosocomial falls. The mean Drummond Checklist score was 12.7 out of 22 (58 per cent). The median score was 13. The scores ranged from 12 to 13 out of a total of 22. These articles are summarized in detail in *Appendix 9*.

Two of three burden studies were case series (99;100). The third study had a prospective cohort design (101). One study (101) identified cases only in patients over 60 years of age. One study focused on legal compensation rather than hospital-related costs (100), and neither of the other two articles (99;101) clearly stated what methods were used for determining attributable costs. There was one additional case-control study that reported attributable length of stay, but not costs (102).

Oliver found that 60.5 per cent of legal claims related to in-hospital falls resulted in payment of costs or damages, with mean payment of £12,945 (CAN$28,721) (100). Nurmi provided the cost per treatment of an in-hospital fall, estimated at €944 (CAN$1,876) (101). The third study did not describe costs per case or per fall, but did provide the total estimated attributable cost of all cases included in the study; dividing by the provided number of cases yields a crude estimate of £1,667 (CAN$4,321) per case (99).

COST EFFECTIVENESS ANALYSES

(Table 4, Appendix 4)

We identified five cost effectiveness analyses that were based on at least one study of effectiveness with adequate methods. These five analyses reported a total of seven cost effectiveness comparisons.

Adverse Drug Events

One comparative analysis studied the impact of various strategies for reducing potential adverse drug events (103). The methodological feature score was 27/35. Pharmacist-led medication reconciliation was the only strategy with adequate effectiveness data, based on one randomized trial and several non-randomized controlled trials (104-108). Pharmacist-led medication reconciliation dominated over a strategy of no reconciliation (103). The main limitation of this analysis was the assumption that a reduction in potential adverse drug events leads to a reduction in preventable adverse drug events.

Transfusion-related Adverse Events in Critically Ill Patients

One analysis compared the strategy of erythropoietin to reduce transfusion related adverse events to standard care in critically ill patients (109). The methodologic feature score was 28/35. Effectiveness data was derived from a randomized clinical trial, where outcomes were measured as units of recombinant human erythropoietin needed to reduce allogeneic blood transfusions (110). The strategy of giving erythropoietin had an incremental cost of US$4,700,000 (CAN$6,816,309) to avoid one transfusion-related adverse event (109).

Vascular Catheter Associated Bloodstream Infection

One analysis compared chlorhexidine gluconate and povidone-iodine for catheter site care, with an outcome of catheter-related bloodstream infections in a Thailand hospital (111). The methodologic feature score was 25/35. The effectiveness data came from a meta-analysis based on several randomized controlled trials (112). Chlorhexidine gluconate was a dominant strategy over povidone-iodine in both central-line catheter and peripheral-line catheter sites, showing a cost savings of 304.49 baht (CAN$9.98) per central line catheters and 13.56 baht (CAN$0.45) per peripheral catheter, with fewer infections (111). A similar analysis published three years earlier yielded a similar result; chlorhexidine was a dominant strategy, showing a cost savings of US$113 (CAN$209) per catheter used, and fewer infections (113).

One analysis compared the Keystone ICU Patient Safety Program in six hospitals to usual care. The Keystone ICU Patient Safety Program included 2 key components: *(a)* a Comprehensive Unit-Based Safety Program, which included interventions to improve safety culture, teamwork, and communication; a daily goals sheet; and other communication tools; and *(b)* specific interventions to improve compliance with evidence-based care to reduce central line associated blood stream infections. The methodologic feature score was 20/35. The effectiveness data came from an interrupted time series study (114). The main finding was that the Keystone ICU patient safety program had low development and implementation costs. The intervention cost about $5,404 per case of central line associated blood stream infection averted, and the cost of a central line associated blood stream infection is $12,208 to $56,167. Therefore the intervention can be considered economically dominant (115).

Retained Surgical Foreign Body

One cost effectiveness analysis was related to retained surgical foreign bodies (116). This analysis compared eight strategies: no sponge tracking, standard counting, universal radiography without counting, universal radiography with standard counting, selective mandatory radiography for high-risk operations, bar-coded sponges, and radiofrequency-tagged sponges. The methodologic feature score was 24/35. The effectiveness data came from a randomized control study and diagnostic test studies (117-119). Detection of surgical foreign bodies can be considered a diagnostic test; some of the evidence for effectiveness came from studies that evaluated the sensitivity and specificity of standard surgical counting compared to other detection methods, such as routine postoperative radiography. Standard counting was predicted to prevent 82 per cent of retained surgical sponges with an incremental cost of US$1,500 (CAN$1,676) for each surgical foreign body detected, compared to a strategy of no counting. Bar-coded sponges would prevent 95 per cent of retained surgical sponges, with an incremental cost of US$95,000 (CAN$106,132) for each surgical foreign body detected, compared to a strategy of standard counting. Selective mandatory radiography for high-risk operations, universal radiography without counting, and universal radiography with standard counting were less effective and more expensive than bar-coded sponges. The downstream costs of retained surgical foreign bodies were not included in this study, as these costs have not been described. If these downstream costs were included, then standard counting would probably be the dominant strategy compared to no counting, and bar-coded sponges would be more economically attractive (116).

We did not identify any eligible cost effectiveness analyses for the remaining PS targets or for the other improvement strategies. We did identify relevant but incomplete evidence related to venous thromboembolism prophylaxis, which we will summarize in our discussion.

Table 4: Cost effectiveness of PS Improvement Strategies

SAFETY TARGET	INTERVENTION	COMPARATOR	INCREMENTAL COST EFFECTIVENESS RATIO
Catheter-associated bloodstream infection (111), ((115))	Chlorhexidine gluconate skin preparation	Poviodine skin preparation	Dominant; economically attractive
	Keystone ICU Patient Safety program [2]	Usual care	Dominant; economically attractive
Potential adverse drug events (103)	Pharmacist medical reconciliation	Standard care	Dominant; economically attractive
Retained surgical foreign body prevention (116)	Standard surgical count	No count	$1,500 to avoid one retained surgical sponge; probably economically attractive
Retained surgical foreign body prevention (116)	Bar-code-identified surgical sponges	Standard surgical count	$95,000 to avoid one retained surgical sponge; uncertain economic attractiveness
Transfusion-related adverse events (109)	Erythropoietin	Standard care	US$4,700,000 (CAN$6,816,309) to avoid one transfusion related event; economically unattractive

2 The Keystone ICU Patient Safety Program included 2 key components: *(a)* a Comprehensive Unit-Based Safety Program, which included interventions to improve safety culture, teamwork, and communication; a daily goals sheet; and other communication tools; and *(b)* specific interventions to improve compliance with evidence-based care to reduce CLABSI

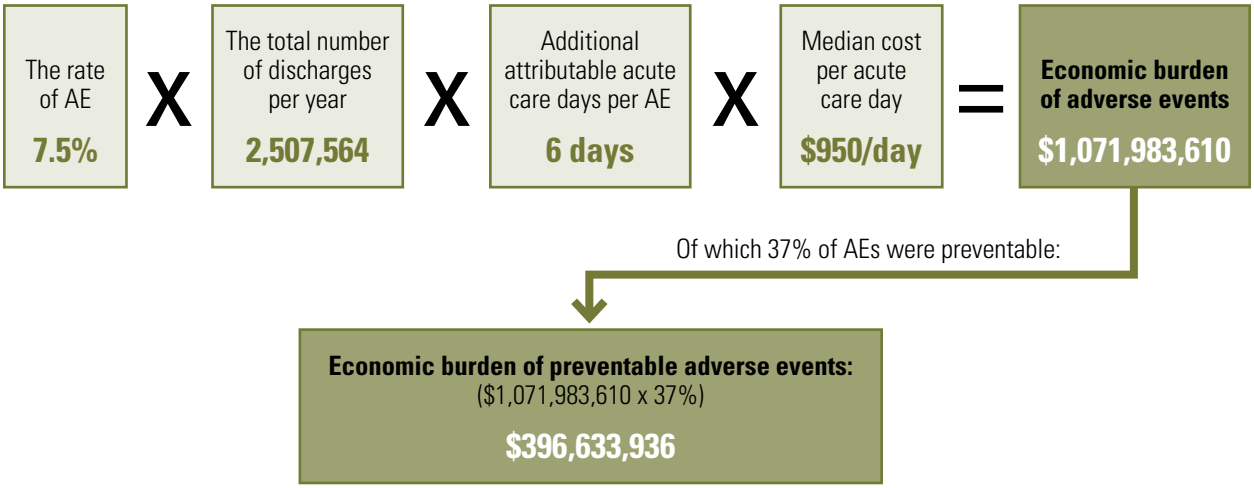
ECONOMIC BURDEN OF PATIENT SAFETY IN ACUTE CARE IN CANADA

Overall Cost

We calculated a preliminary estimate of the overall cost of AEs to the system, using the following estimates:

- The Canadian Adverse Events Study estimated that the rate of AE was 7.5 per cent (1).
- In 2009–2010 there were 2,507,564 acute care hospital discharges (20,117,526 acute care bed days) for patients 20 years or older (120).
- The Canadian Adverse Events Study (1) found that an additional six acute care days were attributable to each adverse event.
- The median cost per day in a Canadian acute care hospital was $950 (2008/2009) (121).
- The Canadian Adverse Events Study estimated that 37 per cent of adverse events were preventable (1).

We used these parameters for our preliminary estimate of the economic burden of AE in Canada in 2009–2010:



Our preliminary estimate of the economic burden of AE in Canada in 2009–2010 is $1,071,983,610 ($1.1 billion), including $396,633,936 ($397 million) for preventable AEs. If we substitute the estimated attributable costs for adverse events identified in our systematic review, these estimates would be higher. Our estimate does not include costs of care after discharge, or societal costs of illness, such as loss of functional status of occupational productivity.

We then attempted to estimate the economic burden of specific PS targets from a Canadian perspective, based on at least one valid economic burden study. We sought additional estimates of the following variables:

- Estimates of the incidence rate for the PS target
- Estimates of preventability rate
- Attributable Cost per event, based on our systematic review
  - Attributable length of stay
  - Attributable cost
- Population at risk.

We were able to calculate preliminary estimates for Clostridium difficile-associated disease, MRSA infection, VRE infection, and surgical site infection. We consider these to be very rough estimates due to the lack of preventability data for most events, and the limited number of economic burden studies, none of which report primary Canadian data.

Clostridium Difficile-Associated Disease (CDAD)

The Canadian incidence rate of hospital-acquired CDAD infection in adult patients is 4.6 cases per 1,000 patient admissions and 65 per 100,000 patient-days (122). Specific measures of preventability of CDAD are not known, but nosocomial infections are considered to be 20–70 per cent preventable. We used a conservative estimate of 37 per cent preventability, based on the Canadian Adverse Events Study (1). Based on our systematic review, the attributable cost of CDAD is €7,147 (CAN$10,809) (92). In 2009–2010 there were 2,507,564 adult acute care hospital discharges (127). Using these estimates, the economic burden of CDAD is $46.1 million (Table 3).

Methicillin-Resistant Staphylococcus Aureus (MRSA) Infection

There were approximately 2.70 MRSA infections per 1,000 admissions in Canada in the year 2006 (123). We used the baseline estimate of 37 per cent preventability from the Canadian Adverse Events Study (1). Based on our systematic review, the attributable cost of these infections is £6,485 (CAN$14,484) (87). In 2009–2010 there were 2,507,564 adult acute care hospital discharges. Using these estimates, the economic burden of MRSA is $36.3 million (Table 3).

Vancomycin-Resistant Enterococci (VRE) Infection

There were approximately 0.052 nosocomial acute care VRE infections per 1,000 admissions in Canada in 2006 (124). We used the baseline estimate of 37 per cent preventability from the Canadian Adverse Events Study (1). Based on our systematic review, the attributable costs of these infections are US$7,873 (CAN$14,414) and US$11,989 (CAN$21,950), respectively (88). In 2009–2010 there were 2,507,564 acute care hospital discharges (127). Using these estimates, the economic burden of VRE is $695,411 (Table 3).

Surgical Site Infections (SSI)

Approximately 4 per cent of patients undergoing surgical procedures in Ontario between 1992 and 2006 developed SSIs during their index acute care stay. Most of these infections related to abdominal, urologic, gynaecologic, and musculoskeletal procedures (125). Approximately 65 per cent of SSIs can be considered preventable (126). Based on our systematic review, we found wide ranges for the cost of an SSI, depending on the type of surgical site infection. We will use the conservative low estimate of US$1,051 (CAN$1,174). According to the CIHI Discharge Abstract Database for 2009–2010, there were 799,513 surgical discharges in Canada (127). Using these estimates, a conservative low end estimate of the economic burden of SSIs is $24.4 million (Table 3).

Table 5: Estimating the economic burden of specific PS targets in Canadian Acute Care Hospitals

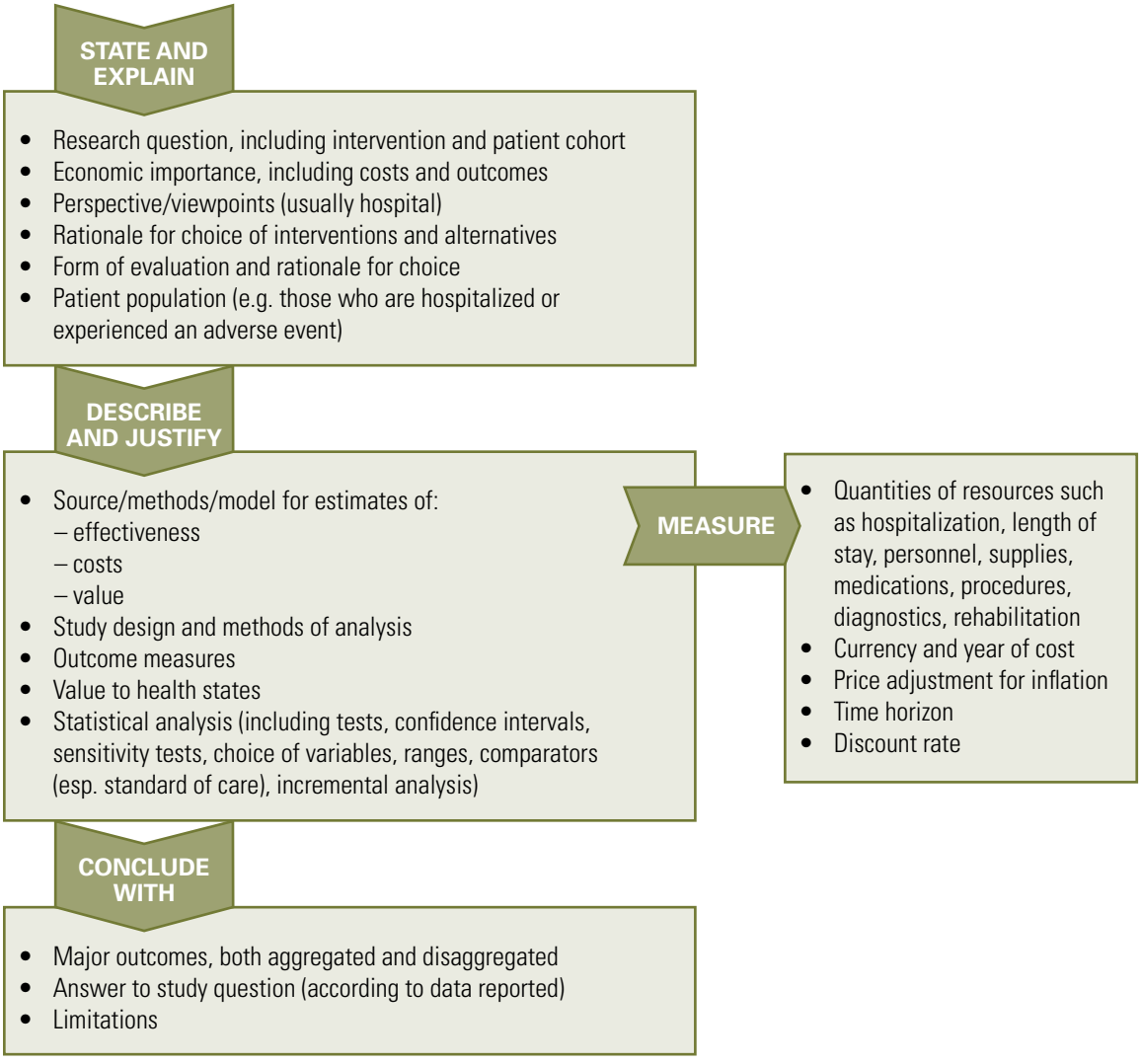
PS TARGET	INCIDENCE RATE	PREVENTABILITY	COST PER CASE	POPULATION	TOTAL COST
CDAD	4.6/1,000 patient admission	37%	$10,809	2,507,564	$46,131,449
MRSA infection	2.7/1,000 patient admission	37%	$14,484	2,507,564	$36,283,237
VRE Infection	0.052/1,000 patient admission	37%	$14,414	2,507,564	$695,411
Surgical site infection	4.0/100 surgeries	65%	$1,174	799,513	$24,404,335

GUIDELINES AND FRAMEWORK FOR ECONOMIC EVALUATIONS IN PATIENT SAFETY

We found that the many economic evaluations in PS have methodological gaps, suggesting that guidelines for performing or assessing economic research in PS are required. Such guidelines could be based on the Drummond checklist, as we found that most of the parameters in the Drummond checklist that are required for economic evaluations could be directly applied to the PS area. *Appendix 2* explains how they can be applied, and highlights items for which special consideration is required for PS.

Figure 1 provides a summary of these guidelines in the form of a framework. For more details and selected examples, refer to *Appendix 2*. We selected examples from the included studies wherever possible. However, we occasionally chose suitable examples from studies that were ultimately excluded from our review.

Figure 1 – Framework for economic evaluations in patient safety



DISCUSSION

The majority of economic burden studies that we identified had no costing methodology. The remaining economic burden studies reported wide estimates of the economic burden, due to variations in case definitions, patient populations, costing methodology, and study setting. The majority of studies reported the economic burden of adverse events and nosocomial infections. We found that the reported attributable costs of adverse events ranged from US$2,162 (CAN$4,028) to AUS$11,846 (CAN$12,648). In general hospital populations, the cost per case of hospital-acquired infection ranged from US$2,027 (CAN$2,265) to US$12,197 (CAN$22,400). Nosocomial bloodstream infection was associated with costs ranging from €1,814 (CAN$3,268) to €16,706 (CAN$29,950).

We found five comparative economic analyses that reported a total of seven comparisons based on at least one effectiveness study of adequate methodologic quality. Based on these limited studies, pharmacist-led medication reconciliation, the Keystone Michigan ICU Intervention for central line associated blood stream infections, chlorhexidine for vascular catheter site care and standard surgical sponge counts were economically attractive PS improvement strategies.

Our preliminary estimate of the economic burden of AE in Canada in 2009–2010 was $1,071,983,610 ($1.1 billion), including $396,633,936 ($397 million) for preventable adverse events. This estimate does not include the direct costs of care after hospital discharge, or societal costs of illness, such as loss of functional status or occupational productivity.

We found significant gaps in the economic methods, which is consistent with the few prior reviews of the economics of patient safety in the acute care setting. A 2005 review identified 165 PS articles that included an economic analysis as an objective, but 35 per cent of these articles provided no economic analysis, and 25 per cent provided no primary economic data. The remaining studies had significant gaps in their costing methodology, and only 16 per cent conducted sensitivity analyses that could address these limitations (128). Another review of economic evaluations of patient safety programs identified 40 studies published between 2001–2004, none of which provided sufficient information about both the cost of the prevention program and the cost of the AE being targeted (129). A 2005 review of cost effectiveness analyses related to bloodstream infections found that the existing analyses were characterized by low data quality, lack of transparency, short time-horizons, and narrow economic perspectives (130).

We did not find cost effectiveness analyses for many improvement strategies that are well known to the safety improvement community. Some improvement strategies, such as rapid response teams to reduce adverse events, or smart infusion pumps to reduce adverse drug events, have not been consistently effective in evaluative studies (131;132). Other improvement strategies, such as improving venous thromboembolism prevention or bar coded medication administration, have sufficient evidence of effectiveness, but we were unable to identify an appropriate cost effectiveness analysis.

Although we did not find any recent cost effectiveness analyses on improvement programs in venous thromboembolism based on adequate evidence of effectiveness, we speculate that such an analysis would likely find such programs to be economically attractive. Prevention of venous thromboembolism is a leading safety best practice, based on a large body of high-quality effectiveness evidence for many

prophylaxis regimens (20;133). First, there are numerous economic analyses published before 2000 showing that many forms of prophylaxis are economically attractive compared to no prophylaxis (134-136). The most economically attractive choice among various forms of thromboprophylaxis in specific patient subgroups remains an active area of research, which was beyond the scope of our review (26;27;29-31). Second, gaps in thromboprophylaxis are well described (137;138). Third, computer reminders, standardized order sets, and audit and feedback can improve adherence to appropriate venous thromboembolism prophylaxis (139;140). Despite this significant body of knowledge, we found no published cost effectiveness analyses that explicitly cited adequate evidence of effectiveness for safety improvement programs. One cost-effectiveness analysis evaluated implementation of clinical guidelines on thromboprophylaxis, but this analysis used effectiveness estimates from a single-site uncontrolled before-and-after study. The study assumed that guideline implementation would be 100 per cent effective with no incremental costs beyond the cost of administering prophylaxis (36). Implementing VTE risk assessment and ensuring adequate prophylaxis for medical and surgical patients would likely reduce total costs by £0.9 million (2007 currency) from the perspective of a national healthcare system, according to a large budget-impact analysis published by the National Institute for Clinical Effectiveness (NICE) in the United Kingdom in 2010. This was not a cost effectiveness analysis, because it did not model the effectiveness of guideline implementation, and did not consider any incremental costs of developing, organizing, implementing, and maintaining national and local VTE prevention improvement programs. Despite these limitations, the NICE analysis suggests that ensuring adequate VTE prophylaxis in the acute care setting could be economically attractive (141). Finally, an analysis that was published after we completed our review found that a hypothetical program that increased compliance with thromboprophylaxis in critical care from 85 to 95 per cent had an incremental cost effectiveness ratio of approximately $25,000 per quality adjusted life year gained, which would generally be considered economically attractive (142).

Our review also found limited cost effectiveness data related to prevention of adverse drug events, even though there are many well-known medication safety improvement strategies. We identified one analysis showing that medication reconciliation by clinical pharmacist was a dominant strategy, based on reductions in potential adverse drug events. We acknowledge that the relationship between preventing potential adverse drug events and preventable adverse drug events remains an area of uncertainty in PS improvement.

Bar-coded medication administration, with electronic medication administration records, reduces potential adverse drug events, based on one study with adequate evidence of effectiveness (143). However, we could not find an economic analysis of bar-coded medication administration that cited evidence other than from simple before-after comparisons (144). We also excluded one cost effectiveness analysis (144) because it did not cite effectiveness data of sufficient quality on rounding clinical ward pharmacists. One Canadian economic analysis of a computerized order entry system to prevent adverse drug events was excluded due to lack of effectiveness data on ADE rates for their computerized physician order entry (CPOE) system (145). When effectiveness data from other systems were included in their analysis, the incremental cost of their CPOE system was estimated at US$12,700 (CAN$18,704) per ADE prevented, which would make their CPOE system a moderately attractive healthcare intervention (145). As expected, this result was sensitive to the effectiveness and cost of the CPOE system, as well as the baseline rate of ADEs at the hospital.

We identified several cost effectiveness analyses related to hand hygiene that cited only evidence from before-and-after studies. One analysis found that alcohol-based hand hygiene product was cheaper and faster, and yielded better hand hygiene compliance, than a detergent-based antiseptic (146), but there was no data on adherence and no data on the impact of safety targets. Another study found that failure to perform hand hygiene by a healthcare worker moving between two unknown MRSA status patients incurred a mean cost per noncompliant event of US$1.98 (CAN$2.16) (if leaving a room with unknown MRSA status) to $52.53 (if leaving a room of a patient known to be MRSA-positive) (147).

We can make several additional recommendations from our review of cost effectiveness analyses in PS. First, we identified many cost effectiveness analyses that were not based on adequate effectiveness data. Safety improvement programs should consider the EPOC standards when planning their program evaluations. Simple before after studies are insufficient bases for drawing conclusions about effectiveness and cost effectiveness. Second, we did not identify economic analyses that explicitly considered the impact of PS on economically important parameters such as staff retention, staff absenteeism, and patient (market) retention. These parameters should be considered in future cost effectiveness analyses in PS. Third, the relative value of investing in PS improvement as opposed to investing in other healthcare interventions, such as new treatments or diagnostic tests, has not been explicitly considered in cost effectiveness analyses. The relative societal value of improving safety over improving care of primary clinical conditions should be considered in future cost effectiveness analyses in PS. Finally, we found no data on the health-related quality of life for many PS targets. Studies of the health-related quality of life associated with PS targets are needed to inform comparative cost-utility analyses with other interventions.

We calculated a preliminary estimate that the economic burden of adverse events in Canada in 2009–2010 was $1.1 billion, including $397 million for preventable adverse events. We consider this a preliminary estimate, and we emphasize that it is based on information that was not obtained as part of our systematic review. We are unaware of prior estimates of the economic burden of adverse events on the Canadian acute care system. For comparison, the most expensive medical condition within the Canadian acute care system in 2005 was acute myocardial infarction (CAN$511 million [2005], or CAN$556 million [2010]) (2). The estimated 1,128,404 acute hospital bed days used each year to care for patients who suffer any adverse event is similar to the total number of acute hospital bed days in Manitoba each year. The estimated 417,509 acute hospital bed days used each year to care for patients who suffer a preventable AE is equivalent to the total number of acute hospital bed days in Newfoundland and Labrador each year.

We attempted to use our review to estimate the economic burden of specific PS targets, but most necessary data for such estimates was lacking. We consider our estimates to be crude and preliminary. We did find a recent estimate of the cost of ventilator associated pneumonia (VAP) to the Canadian healthcare system is CAN$46 million (possible range: $10 million to $82 million) per year (148). This estimate was primarily based on an estimated 1,150 ventilator days per 100,000 Canadians, which yielded 388,009 ventilator days. The attributable ICU length of stay due to VAP is 4.3 days, and the cost for a critical care bed is CAN$2,396 per day (149), giving a total of CAN$10,303. Approximately 55 per cent of VAP was considered preventable (126). Using these estimates, the economic burden of VAP in Canada is $23.3 million.

LIMITATIONS

Our review has several important limitations.

First, we focused on studies published between 2000-2011 and indexed in MEDLINE. Studies outside of our search strategy may contain potentially useful data. For example, we did not include a 2010 study by the Society of American Actuaries, that was not indexed in MEDLINE (150). We may have missed other studies not published in the traditional literature. However, our major finding that 61 per cent of studies provide no or limited costing methodology would be unchanged by inclusion of a few additional studies.

Second, we focused on the acute care hospital setting because it consumes a significant proportion of Canadian healthcare expenditures, and because a large number of evaluative PS studies have been conducted in the acute care setting. The economic perspective should extend beyond the acute care hospital, as only 22-66 per cent of the economic burden of AEs in acute care are borne by the hospital (151;152). Future work could focus on the economic burden and cost effectiveness of safety improvement strategies in other settings, such as long-term care and the community.

Third, we did not evaluate the interrater reliability of our methodologic reviews. Our review method was designed to yield higher methodologic ratings, as we always took the higher rating of the two reviewers, yet we still identified a significant lack of methodologic features.

Fourth, we arbitrarily assigned one point for each methodologic feature, so that we could report a simple summary measure of methodologic features. However, we recognize that methodologic features are not all equally important.

Fifth, the heterogeneity in study methods and methodologic features made it impossible to generate summary estimates of economic burden.

Sixth, we chose to apply the rules of evidence of effectiveness from the Cochrane Effective Practice and Organisation of Care (EPOC) Group. We acknowledge that some may not share the opinion that uncontrolled before-after studies are insufficient evidence of effectiveness.

SUMMARY

In summary, we found that most studies of the economic burden of PS in acute care do not report any costing methodology. We found wide estimates of the economic burden from these 61 studies, due to variations in case definitions, patient populations, costing methodology, and study setting. The majority of studies reported the economic burden of adverse events and nosocomial infections.

We found five comparative economic analyses that reported a total of seven comparisons based on at least one effectiveness study of adequate methodologic quality. Based on these limited studies, pharmacist-led medication reconciliation, the Keystone Michigan ICU Intervention for central line associated blood stream infections, chlorhexidine for vascular catheter site care, and standard surgical sponge counts were economically attractive PS improvement strategies.

We calculated a preliminary estimate of the economic burden of AE in Canada in 2009–2010 was $1,071,983,610 ($1.1 billion), including $396,633,936 ($397 million) for preventable adverse events.

CONCLUSIONS

1. The majority of published studies on the economic burden of PS in acute care describes no costing methodology.
2. For studies that report a costing methodology, there is variability in methods for measuring and attributing costs.
3. Most studies report on the economic burden of adverse events and nosocomial infections.
4. The reported attributable costs of adverse events ranged from US$2,162 (CAN$4,028) to AUS$11,846 (CAN$12,648). In general hospital populations
5. The cost per case of hospital-acquired infection ranged from US$2,027 (CAN$2,265) to US$12,197 (CAN$22,400). Nosocomial bloodstream infection was associated with costs ranging from €1,814 (CAN$3,268) to €16,706 (CAN$29,950).
6. We found only five comparative economic analyses of PS improvement strategies in the acute care setting based on adequate evidence of effectiveness based on guidelines from the Cochrane Effective Practice and Organisation of Care (EPOC) Group.
7. Based on these limited analyses, the following PS improvement strategies are economically attractive:
    - Pharmacist-led medication reconciliation to prevent potential adverse drug events was the dominant strategy (improved safety and lower cost) when compared to no reconciliation.
    - The Keystone ICU Patient Safety Program to prevent central line associated bloodstream infections was the dominant strategy compared to usual care. The Keystone ICU Patient Safety Program included two key components: *(a)* a Comprehensive Unit-Based Safety Program, which included interventions to improve safety culture, teamwork, and communication; a daily goals sheet; and other communication tools; and *(b)* specific interventions to improve compliance with evidence-based care to reduce central line associated blood stream infections.
    - Chlorhexidine for catheter site care to prevent catheter-related bloodstream infections was the dominant strategy when compared to povidone-iodine.
    - Standard counting was associated with a cost of US$1,500 (CAN$1,676) for each surgical foreign body detected, when compared to a strategy of no counting.
8. We estimate that the economic burden of preventable adverse events in the Canadian acute care system was approximately $397 million in 2009-2010.
9. Safety improvement programs should consider the EPOC standards when planning their program evaluations.
10. Cost effectiveness analyses should explicitly consider the impact of patient safety on economically important parameters such as staff retention, staff absenteeism and patient (market) retention.
11. Cost effectiveness analyses should explicitly consider the societal value of improving safety over improving care of primary clinical conditions.
12. Studies of the health-related quality of life associated with PS targets are needed.
13. Guidelines for performing or assessing economic research in PS could be based on the Drummond Checklist (3) *(Appendix 2)*.

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APPENDICES

Appendix 1: Drummond Checklist

Each parameter is scored yes, no, not clear, or not applicable.

STUDY DESIGN
The research question is stated.
The economic importance of the research question is stated.
The viewpoint(s) of the analysis are clearly stated and justified.
The rationale for choosing the alternative programmes or interventions compared is stated.
The alternatives being compared are clearly described.
The form of economic evaluation used is stated.
The choice of form of economic evaluation is justified in relation to the questions addressed.
DATA COLLECTION
The source(s) of effectiveness estimates used are stated.
Details of the design and results of effectiveness study are given (if based on a single study).
Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies).
The primary outcome measure(s) for the economic evaluation are clearly stated.
Methods to value health states and other benefits are stated.
Details of the subjects from whom valuations were obtained are given.
Productivity changes (if included) are reported separately.
The relevance of productivity changes to the study question is discussed.
Quantities of resource use are reported separately from their unit costs.
Methods for the estimation of quantities and unit costs are described.
Currency and price data are recorded.
Details of currency of price adjustments for inflation or currency conversion are given.
Details of any model used are given.
The choice of model used and the key parameters on which it is based are justified.
ANALYSIS AND INTERPRETATION OF RESULTS
Time horizon of costs and benefits is stated.
The discount rate(s) are stated.
The choice of discount rate(s) is justified.
An explanation is given if costs or benefits are not discounted.
Details of statistical tests and confidence intervals are given for stochastic data.
The approach to sensitivity analysis is given.
The choice of variables for sensitivity analysis is justified.
The ranges over which the variables are varied are justified.
Relevant alternatives are compared.
Incremental analysis is reported.
Major outcomes are presented in a disaggregated as well as aggregated form.
The answer to the study question is given.
Conclusions follow from the data reported.
Conclusions are accompanied by the appropriate caveats.

Appendix 2: Economic Evaluation Guidelines for PS based on the Drummond Checklist

Parameter	Description	Application to PS	Example from PS literature review*
STUDY DESIGN			
The research question is stated.	The research question being investigated should consist of the type of study, comparators, disease state, and the perspective for the analysis.	For economic burden studies, a clear description of the patient cohort (e.g., patients with nosocomial CDAD) is given. For cost effectiveness analyses, clear descriptions of the interventions and the comparators are given.	Example: "This paper presents a model which quantifies the extent of the burden in terms of the number of catheterized patients who acquire a UTI and the costs incurred by the hospital section,and identifies the potential benefits of introducing the routine use of silver alloy coated catheters to reduce them." (24)
The economic importance of the research question is stated.	There should be a statement describing that treatments/medications/programs are costly (or increasing in cost or using a number of additional resources over standard of care) but they are associated with some sort of benefit or improvement.	For patient safety analyses, outcomes may include infections (or infections avoided); complications (or complications avoided); hospitalization (or hospitalizations avoided); admissions (or admissions avoided); and/or errors (or errors avoided).	Example: "A central difficulty in this field is that clinical trials would require randomization of >100,000 patients to reliably detect a significant reduction in actual retained surgical sponge (RSS) events. As an alternative approach, decision-analytic simulation offers a viable opportunity to compare proposed strategies, estimate their relative cost effectiveness, and facilitate the integration of new research findings." (116)
The viewpoint(s) of the analysis are clearly stated and justified.	A statement indicating the perspective/ viewpoint of the analysis is required, as the perspective of the analysis sets up the framework for the required resources in the analysis. Possible perspectives include the hospital, healthcare system, payer-perspective, and society. The jurisdiction of the perspective (e.g., country, region) should be highlighted.	For patient safety analyses, a clear description of the perspective is required as it provides the framework for the eligible resources and costing. The majority of patient safety economic analyses have considered the health institution/hospital perspective, although the economic impact of patient safety includes direct costs of care after discharge, and indirect (societal) costs such as lost productivity.	Example: "All costs were calculated from the point of view of the healthcare system." (29)
The rationale for choosing the alternative programmes or interventions compared is stated.	A clear rationale for choosing the comparators should be presented. Justification may include improved outcomes of one intervention over another, decreased resource consumption associated with one intervention over another, and/or improved quality of life for one comparator. Indicate whether existing treatment is standard of care, or recommended by treatment or management guidelines.	This applies to patient safety analyses.	Example: Regenbogen et al explicitly summarize all strategies for detecting retained surgical sponges in their analysis (116).

Parameter	Description	Application to PS	Example from PS literature review*
The alternatives being compared are clearly described.	A statement clearly describing the comparators used in the analysis is required. The description should include dosing and administration if relevant. The standard of care for this analysis should be determined. Comparators excluded or not considered in the analysis may be discussed.	This applies to patient safety analyses.	Example: "The Michigan Keystone ICU Patient Safety Program was based on the Johns Hopkins Quality and Safety Research Group (QSRG) improvement program and facilitated by QSRG faculty. It included 2 key components: (a) a Comprehensive Unit-Based Safety Program, which included interventions to improve safety culture, teamwork, and communication; a daily goals sheet; and other communication tools; and (b) specific interventions to improve compliance with evidence-based care to reduce CLABSIs and VAP that were derived using the QSRG method for Translating Evidence into Practice." (115)
The form of economic evaluation used is stated.	A statement on the type of analysis conducted is required, namely cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-minimization analysis (CMA), cost-benefit analysis (CBA), or cost-consequence analysis (CCA).	This applies to patient safety analyses.	Example: "Following this clinical audit, our aim was to perform a cost-effectiveness analysis comparing the period before and after implementation of the clinical guidelines, to estimate the impact of the adopted clinical guidelines on costs and benefits at the hospital level, taking into account possible complications and adverse events." (36)
The choice of form of economic evaluation is justified in relation to the questions addressed.	The choice of economic evaluation should be justified with statements on costs and benefits.	This applies to patient safety analyses.	Example: "Following this clinical audit, our aim was to perform a cost-effectiveness analysis comparing the period before and after implementation of the clinical guidelines, to estimate the impact of the adopted clinical guidelines on costs and benefits at the hospital level, taking into account possible complications and adverse events." (36)

Parameter	Description	Application to PS	Example from PS literature review*
DATA COLLECTION			
The source(s) of effectiveness estimates used are stated.	The literature search used should be explained along with definitions for included or excluded studies. Clinical outcomes used in the analysis should be described. Sources of clinical outcomes may be published literature, administrative databases, or case series. The quality of the clinical data according to evidence-based algorithms should be described.	This applies to patient safety analyses.	Example: "The clinical literature search was performed by an information specialist using a peer-reviewed search strategy. The following bibliographic databases were searched through the Ovid interface: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Biosis Previews, The Cochrane Library, and the Centre for Reviews and Dissemination databases. The search strategy comprised controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were vancomycin, metronidazole, and C. difficile. The clinical search was not restricted by publication date, but was restricted to English and French language publications. Methodological filters were applied to limit retrieval to systematic reviews, randomized controlled trials, controlled clinical trials, and observational studies. See Appendix 2 for the detailed search strategies. (Search was run on October 28, 2009). Grey literature (literature that is not commercially published) was identified by searching the websites of health technology assessment and related agencies, professional associations, clinical trials registries, and other specialized databases. Google and other Internet search engines were used to search for additional information. These searches were supplemented by hand-searching through the bibliographies and abstracts of key papers and conference proceedings, and through contacts with appropriate experts and agencies. Three manufacturers (Sanofi-Aventis Canada Inc., Ferring Pharmaceuticals Canada, and Iroko International LP) were contacted to request unpublished clinical studies. Two reviewers independently screened the titles and abstracts of all citations that were retrieved in the literature search. The data from Louie et al.'s trial are used in the base-case analysis, because these are the only data available that included patients known to be infected with the NAP1 strain." (153)
Details of the design and results of effectiveness study are given (if based on a single study).	A clear description of type of study design (e.g., randomized controlled study), comparators, and duration of the study should be provided. Peer-reviewed published studies are preferred over unpublished ones.	This applies to patient safety analyses.	Example: "A retrospective case-matched before-after study was completed. Critically ill burn patients using a Bowel Management System were matched with similar patients managed before introduction of the device based on gender, total body surface area burned, burn location, ventilation days, and hospital length of stay." (35)
Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies).	For more than one study, the number of studies pooled as well as the pooling technique should be clearly described.	This applies to patient safety analyses.	Example: "The error types included in the model are not exhaustive, but represent the most frequently observed errors in a recent systematic review of medication error literature." (144)

Parameter	Description	Application to PS	Example from PS literature review*
The primary outcome measure(s) for the economic evaluation are clearly stated.	Primary outcome measures typically include life years or quality-adjusted life years. For patient safety analyses, primary outcomes could include complications, infections, adverse events, errors, hospitalizations, or length of stay.	This applies to patient safety analyses.	Example: "The cost-effectiveness of DVT prophylaxis was measured in three ways: cost per DVT prevented, cost per fatal PE prevented, and cost per life-year saved." (154)
Methods to value health states and other benefits are stated.	Valuations of health states are used in cost-utility analyses. A clear statement outlining whether or not health preference values were considered in the economic analysis should be provided. Methodologies for their measurement (e.g., Health Utility Index, EQ5D, time trade-off) should be described.	This applies to patient safety analyses.	Example: "Quality-adjusted life year (QALY) weights for mild-to-moderate post-thrombotic syndrome (PTS) and severe PTS were based on standard gamble utilities obtained from healthy volunteers. Decrements in utility for recurrent VTE and treatment complications were expressed in days lost equivalent to the length of hospital stay." (97)
Details of the subjects from whom valuations were obtained are given.	Valuations of health states are used in cost-utility analyses. A clear statement outlining size, demographic information, and clinical condition (e.g., complication, infection) should be provided.	This applies to patient safety analyses in which the appropriate patient population may be those who are hospitalized or have experienced a medical error or complication.	Example: "Utility estimates for those requiring dialysis were based on average scores from hemodialysis subjects." (40)
Productivity changes (if included) are reported separately.	Productivity changes are typically used in economic analyses with a societal perspective.	For patient safety analyses, productivity changes may also be applicable to staffing changes at an institutional level.	Example: There were no cost effectiveness evaluations with lost productivity parameters. Lost productivity was not applicable based on the acute hospital perspective.
The relevance of productivity changes to the study question is discussed.	A justification of inclusion of productivity changes should be included for the patient safety analysis.	For patient safety analyses, relevant reasons include impact of patient safety issues on staff turnover and personnel over time.	Example: There were no cost effectiveness evaluations with lost productivity parameters. Lost productivity was not applicable based on the acute hospital perspective.

Parameter	Description	Application to PS	Example from PS literature review*
Quantities of resource use are reported separately from their unit costs.	Sources of the resources information should be provided. Resources identified and used in the economic evaluations should be provided.	For patient safety analyses, these may include hospitalization, length of stay, personnel, supplies, medications, procedures, diagnostics, and rehabilitation. Although not commonly used, legal action may be important to consider from an institutional perspective. Sources may include registries or administrative databases.	Example: "[W]e conducted a series of semistructured interviews with staff in each of the 6 hospitals to determine the inputs into intensive care before and after the implementation of the intervention. These interviews followed a set questionnaire focusing on the principal activities of each type of staff and the time spent on each activity. In each hospital, these interviews included the following staff categories and numbers of individuals: -ICU director • Intensivists [2-3] • Other physicians [2-3] • ICU nurses [3-4] • Keystone ICU team leaders [1-2] • Senior-level hospital administrators [1-2] • Infection prevention staff [1-2] • Pharmacists [1-2] The cost categories collected included the following: -*Initial education and training* expenses for the Keystone ICU project, including time spent organizing and planning the training and education sessions, communicating and meeting with representatives from the MHA and the Keystone Center, and other preparation for the program. Material costs include facility rental, transportation, supplies, and food. -*Capital purchases* and investments associated with the intervention, including necessary equipment such as BSI line carts and central line insertion carts. -*Ongoing time spent on the intervention*, including continued training and meetings, as a percentage of total time commitment for each staff category. -*Average annual salary* for each category of personnel working in the ICU, including nurses (by category), physicians (by category), administrators, support staff, and other specialist staff (e.g., pharmacists), over the study time period. Salary information includes the complete value of reimbursement to employees in the category in question—including overtime and benefits such as health insurance and retirement. -*Product purchases* related to sustaining the intervention, including chlorohexidine, oral care kits, and sterile central line dressing kits." (115)

Parameter	Description	Application to PS	Example from PS literature review*
Methods for the estimation of quantities and unit costs are described.	Methods to estimate resources should be described. Unit costs should be described.	For patient safety analyses, the sources of the resource and cost should be provided.	Example: "Overall costs for the Vancomycin Resistant Enteroccoci surveillance and infection control program were estimated using the hospital's step-down cost allocation system, which recorded line-item cost data per resource consumed and total cost per hospital admission. MICU costs were estimated from these data by dividing the patient's total hospitalization cost by total days of hospitalization and then multiplying the quotient by the patient's total MICU-days. This data system also provided hospital reimbursement data, type of insurance, case-mix index, and DRG. Variable — Cost -gown — $0.75 each -gloves — $0.07/pair -hand hygiene — $0.10/use -nursing time — $27/hour -isolation cart set up — $18.00 -VRE-negative — $12.13 -VRE-positive — $24.29" (88)
Currency and price data are recorded.	Provide year of costs and currency.	This applies to patient safety analyses.	Example: "Cost in Thailand in 2005 Baht." (111).
Details of currency of price adjustments for inflation or currency conversion are given.	Provide inflation and currency calculations.	This applies to patient safety analyses.	Example: "All costs were adjusted to 2003 United States dollars (US$1=CAN$1.4=Euro 0.885)." (41)
Details of any model used are given.	Provide a figure or text description of any model used to determine the economic value of a program. Provide choices and occurrence rates and justification for those rates.	This applies to patient safety analyses.	Example: "A decision tree model was developed that described a series of error points and subsequent error detection points in pathways through the medication process in a generic secondary care setting." (144).
The choice of model used and the key parameters on which it is based are justified.	Justification for the model structure and parameters should be provided. Justification may include that the structure is part of published management guidelines.	This applies to patient safety analyses.	Example: "The hypothetical cohort in the decision analysis model included hospitalized patients requiring either a peripheral or central vascular catheter for short-term use (average duration, <10 days). Because the risk of CLBSI differs for central and peripheral venous catheters (24), we analyzed these cohorts separately. We considered "central vascular catheters" to include central venous, peripherally inserted central venous, pulmonary arterial, and hemodialysis catheters and introducer sheaths, whereas "peripheral vascular catheters" included peripheral venous and peripheral arterial catheters." (111)

Parameter	Description	Application to PS	Example from PS literature review*
ANALYSIS AND INTERPRETATION OF RESULTS			
Time horizon of costs and benefits is stated.	The time horizon for the study should be clearly stated.	For patient safety analyses, the majority of the published studies have used the institutional perspective and thus the time horizon is the duration of stay. Dependent on the patient safety target, complications may lead to long-term consequences in terms of morbidity and rehabilitation and should be considered in the economic evaluation.	Example: "Using decision analysis and an analytic horizon of a lifetime, we calculated the cost effectiveness of three different VTE prophylaxis strategies in trauma patients with severe injuries admitted to their ICU who were believed to have a contraindication to pharmacological VTE prophylaxis for up to 2 weeks because of a risk of major bleeding." (27)
The discount rate(s) is (are) stated.	The discount rate should be stated. Usual discount rates range from 0% to 5%.	For patient safety analyses, short time horizons (<1 year) do not have a discount rate.	Example: "Finally, the model was run using alternative discount rates (0% and 5%)." (97)
The choice of discount rate(s) is justified.	The discount rate should be justified. Usual discount rates range from 0% to 5% and are based on health technology assessment agencies.	This applies to patient safety analyses.	Example: There were no cost effectiveness evaluations with justification of discount rates.
An explanation is given if costs or benefits are not discounted.	For analyses conducted over a time horizon of less than one year, a discount rate is not applied.	This applies to patient safety analyses.	Example: "Because the follow-up for this analysis is less than one year, the cost and outcomes were not discounted." (153)
Details of statistical tests and confidence intervals are given for stochastic data.	Statistical analyses should be outlined.	This applies to patient safety analyses.	Example: "The model was analysed by sampling 10,000 input parameter sets based on the probability that they represent the optimal set. Additional parameter values were sampled from probability distributions representing severity of incident pADEs, intervention effectiveness, implementation costs, and pADE cost and QALYs effects. The RRs and cost parameters were represented as log normal distributions: bounded at zero with a long tail representing the small likelihood of limited and even negative effectiveness or large costs respectively." (103)
The approach to sensitivity analysis is given.	The analysis should provide information on whether deterministic or probabilistic sensitivity analyses were conducted.	This applies to patient safety analyses.	Example: "Because there is uncertainty in our effectiveness estimates for the sponge-tracking technologies, we computed cost-effectiveness ratios across a range of efficacy estimates, including the circumstance in which they completely eliminate RSS. To evaluate the effect of variability in cost estimates for the technologies, we also evaluated the sensitivity of our estimates to differentiate cost." (116)
The choice of variables for sensitivity analysis is justified.	Choice of parameters evaluated in the sensitivity analyses should be justified. Justification includes some language around quality of estimates used in the base case, reproducibility of the estimates used in the base case, representativeness of the estimates used in the base case, and availability of the estimates used in the base case.	This applies to patient safety analyses.	Example: "Several parameters were changed to determine the impact of our four main assumptions on the net benefits of gowns." (88)

Parameter	Description	Application to PS	Example from PS literature review*
The ranges over which the variables are varied are justified.	Ranges include minimum, maximum, and/or 95% confidence intervals.	This applies to patient safety analyses.	Example: "The variation between 60 to 140 patient contacts yielded net benefits of $388,664 and $450,017, respectively. The variable of 1 to 4 cultures per patients resulted in net benefits of $418,188 and $421,464, respectively. The variation in costs of labor and materials results in net benefits of $406,488 and $435,426, respectively." (88)
Relevant alternatives are compared.	A statement clearly describing the comparators used in the analysis is required. Descriptions should include dosing and administration. The standard of care for this analysis should be determined. Comparators excluded or not considered in the analysis may be discussed.	This applies to patient safety analyses.	Example: "In our model, either an ultrasound strategy incorporating unilateral duplex Doppler examination of the proximal veins of the lower extremity catheterized by a femoral central venous line or no ultrasound was chosen." (30)
Incremental analysis is reported.	An incremental ratio should be provided. These may include the incremental cost per outcome avoided, where outcome may be defined as a life year gained, QALY, and/or clinical consequence (e.g., infection).	This applies to patient safety analyses.	Example: "Dominant and ICERs of £184 per QALY; £184." (103)
Major outcomes are presented in a disaggregated as well as aggregated form.	Cost and benefit outcomes should be presented in disaggregated form. Large cost buckets for disaggregation may include hospitalization, personnel, medications, and legal.	This applies to patient safety analyses.	Example: "Overall hospital cost; adverse drug reaction cost; contrast media cost (Table III)." (40)
The answer to the study question is given.	Based on the objective proposed, provide the answer to the question.	This applies to patient safety analyses.	Example: "Use of prophylactic hemofiltration in patients at high risk for contracting nephropathy may be potentially cost effective only if certain conditions are satisfied, and its attractiveness is materially diminished when compared to other strategies." (41)
Conclusions follow from the data reported.	Based on the objective proposed, provide the answer to the question.	This applies to patient safety analyses.	Example: "Use of prophylactic hemofiltration in patients at high risk for contracting nephropathy may be potentially cost effective only if certain conditions are satisfied, and its attractiveness is materially diminished when compared to other strategies." (41)
Conclusions are accompanied by the appropriate caveats.	Limitation of the analysis should be reported. Limitations should be divided into quality-, structural-, and parameter-related issues.	This applies to patient safety analyses.	Example: "The results indicate that pharmacist-led medicines reconciliation is likely to be the most cost-effective intervention, although it is difficult to assess whether the model has captured all of the relevant ncertainty. There are also likely to be other interventions, particularly IT-based interventions, for which evidence of effectiveness was not available." (103)

*Some examples are chosen from studies that were ultimately excluded from our final report

Appendix 3: Economic Burden – Adverse Events (AEs)

Study, Drummond Checklist Score	Design	Method for Estimating Attributable Cost	Resources Used	Source of Resource Cost (Curr, Year)	Sample Population (Time Horizon)	Case Definition	Incidence	Incremental LOS	Estimated Incremental Cost
Aoki, 2008 (47) Drummond Checklist score = 16	Case series	Multivariate logistic analysis	Positive legal compensation in medical disputes	Medical dispute records (US$, 2007; converted from JP yen)	155 resolved medical dispute cases in Japan (1989–1998)	Any medical dispute case resolved during the study period	Not available	Not available	Legal compensation for an AE claim was mean $38,937, median $7,417
Hoonhout, 2009 (42) Drummond Checklist score = 16	Retrospective cohort	Multivariate multi-level analysis	Direct medical costs, based on additional LOS and additional medical procedures	Dutch guideline prices of 2003, corrected for 2004 (€, 2004)	7,926 patients in 21 Dutch hospitals (Aug. 2005–Oct. 2006)	Any AE: an unintended injury resulting in temporary/ permanent disability, death, or extra LOS, caused by healthcare	5.7%	University hospitals: 10.1 additional days; general: 8.9 additional days	Excess costs of all AEs: mean €4,446 per AE; excess costs of preventable AEs: mean €3,634 per pAE
Kaushal, 2007 (48) Drummond Checklist score = 15	Prospective with nested case control	Matched case-control, linear regression model	Charges, actual variable costs, actual fixed costs, actual direct variable costs, and actual direct fixed costs	Hospital TSI database (US$, 2002/3)	108 cases matched with 375 controls in 1 hospital ICU and CCU (July 2002–June 2003)	Any AE, detected via observation, reports, and guided implicit chart abstraction	Not available	ICU AEs: 0.77 additional days; cardiac ICU AEs: 1.08 additional days	$3,961 in the MICU; $3,857 in the CCU
Ehsani, 2006 (43) Drummond Checklist score = 14	Retrospective cohort	Simple linear regression modelling	Total cost of per-patient care from database (not further described)	Patient-level costing dataset of the Victorian Department of Human Services (AU$, year unclear)	Total of 979,834 admissions, 45 hospitals in Victoria, Australia (June 2003–July 2004)	Any AE identified via diagnosis codes	6.9% had at least one AE	10 additional days	$11,846 per AE
New, 2010 (44) Drummond Checklist score = 13	Retrospective cohort	Ordinary least squares regression analysis	LOS, surgical and medical procedures, laboratory tests	Hospital accounting database (AU$, 2004)	1,605 spinal cord injury patients, in 45 campuses of 26 Australian health services (June 2003–June 2004)	At least one AE or hospital-acquired complication (HAC) in a patient with spinal cord injury (SCI)	38% of multi-day SCI episodes had at least one incident complication	32 additional days	Additional costs, any complication: AU$7,359; UTI: $23,705; procedural complications: $21,821; anemia: $18,047; pressure ulcer: $17,882

Study, Drummond Checklist Score	Design	Method for Estimating Attributable Cost	Resources Used	Source of Resource Cost (Curr, Year)	Sample Population (Time Horizon)	Case Definition	Incidence	Incremental LOS	Estimated Incremental Cost
Senst, 2001 (49) Drummond Checklist score = 13	Prospective with nested case control	Case control, multiple linear regression model	Charges converted to costs	Prospectively recorded charges (US$, year unclear)	3,187 admissions in one US healthcare network incl. four hospitals and 26 clinics (53-day study period, 1998)	Adverse drug event: an injury caused by the use, disuse, or misuse of a drug via error or despite proper usage	4.2%	1.2 additional days	$2,162 per adverse drug event
Morris, 2003 (46) Drummond Checklist score = 12	Retrospective cohort	Cause and effect analysis	Hospital charges, costs, legal fees and indemnity payments, legal write-offs	Unclear (assumed US$, year unstated)	130 cases out of 32,100 patients over age 13 (Jan. 1, 1995–Dec. 6, 1999)	Surgical AEs, not further specified	0.4%	Not available	Total legal payment for the study group (126) was $8.2 million
Pappas, 2008 (45) Drummond Checklist score = 12	Retrospective cohort	Regression analysis	Nursing staff hours per patient day, clinical outcomes, patient-level data	Cost-accounting system/I Eclipsys TSI (US$, year unstated)	3,200 inpatients in two hospitals from US hospital databases, location unspecified (24-month window, date unspecified)	Nosocomial AEs (medication error, fall, UTI, pneumonia, and pressure ulcer)	Medical patients: 21.5%; surgical patients: 14.4%	Not available	Medical patients: $1,029 per AE; surgical patients: $903 per AE

Appendix 4: Cost Effectiveness Analysis Summary Table

Study, Drummond Checklist Score, Funding	Type of Analysis, Modelling Method	Effectiveness Data Safety Improvement Strategies	Cost Data	Cohort and Time Horizon for Analysis	Main Outcome Measures and Discounting	Results of Base Case Analysis	Results: Sensitivity Analysis	Limitations
ADVERSE DRUG EVENTS								
Karnon 2009 (103) Drummond Checklist score = 25 Funding not stated	Cost utility Decision analytic model	One randomized trial of pharmacist-led medication reconciliation (104) Pharmacist-led medication reconciliation	Case control studies (155-157); Case series with attributable costs (157)	Patients at risk of medication error due to lack of medication reconciliation	Cost per QALY gained No discounting	Pharmacist-led medication reconciliation is a dominant strategy	Economic attractiveness is based on £1,695 per QALY gained, when costs of intervention are high and effectiveness is low	Effectiveness based on single small randomized controlled trial; no utility measures available so these were estimated
TRANSFUSION-RELATED ADVERSE EVENTS IN CRITICALLY ILL PATIENTS								
Shermock 2005 (109) Drummond Checklist score = 23 Funding not stated	Cost effectiveness Decision analytic model	Randomized control trial (110) Use of EPO in preventing transfusion-related AEs	Randomized control trial (110)	Patients at risk of contracting transfusion-related AEs	Cost to avoid one transfusion-related AE No discounting	Incremental cost: $4,700,000 to avoid one transfusion-related AE, $25,600,000 to avoid one serious transfusion-related AE, and $71,800,000 to avoid a likely fatal transfusion-related AE EPO is not an economically attractive option for reducing transfusion-related AE	Results withstood extensive sensitivity analysis Risk rates were the cost drivers when estimating upper and lower bound of the confidence interval	Single estimate of effectiveness

Study, Drummond Checklist Score, Funding	Type of Analysis, Modelling Method	Effectiveness Data Safety Improvement Strategies	Cost Data	Cohort and Time Horizon for Analysis	Main Outcome Measures and Discounting	Results of Base Case Analysis	Results: Sensitivity Analysis	Limitations
VASCULAR CATHETER ASSOCIATED BLOODSTREAM INFECTION								
Maenthaisong 2006 (111) Drummond Checklist score = 25 Funded by Thailand Research Fund	Cost-effectiveness Decision analytic model	Prospective observational study (158)	Published reports from national health security office (159)	Catheterized patients at Siriraj hospital, Thailand, for the duration of hospitalization	Incidence of catheter-related bloodstream infections (CRBSI) and death related to CRBSI No discounting	Chlorhexidine gluconate showed a cost savings of 304.49 Baht in central line catheter sites and 13.56 Baht per catheter in peripheral line catheter site Chlorhexidine is a more cost-effective strategy over poviodine iodine for prevention of CRBSI	Chlorhexidine gluconate increased direct medical costs by 3.29 Baht. Cost of CRBSI was the cost driver in worst-case scenario, but did not increase rate of CRBSI nor death due to CRBSI	None listed
Waters 2011 (115) Methodologic feature score = 20 Funded by Blue Cross Blue Shield of Michigan through the Michigan Health and Hospital Association	Cost-effectiveness Decision analytic model	Interrupted time series (114)	Activity-based Costing through interviews with staff	Patients at risk of CLABSIs Three year time horizon	Cases of CLABSI averted by the intervention for each hospital No discounting	Intervention cost was about $3,375 per infection averted and considered economically dominant	If the median hospital infection rate was used as the main outcome rather than the mean then cost per infection averted is $4,725	Results may not be generalizable outside of Michigan and did not include longer term healthcare costs
RETAINED SURGICAL FOREIGN BODY								
Regenbogen 2009 (116) Drummond Checklist score = 24 Funding not stated	Cost effectiveness analysis Decision analytic model	Randomized control study (117) and epidemiology studies (118;119) Comparing standard counting against alternative strategies: universal or selective x-ray, bar-coded sponges (BCS), and radiofrequency-tagged (RF) sponges	Published literature (160;161) OR managers at the hospital, University of California, San Francisco Medical Center, and the Hospital of the University of Pennsylvania	Average risk of inpatient operation from published literature (117-119;162) Duration of hospitalization	RSS incidence and cost-effectiveness ratios for each strategy No discounting	Standard count $1,500 per RSS averted; Bar-coded sponges $95,000 per RSS averted; Routine intraoperational radiology over $1 million per RSS averted	As incidence of nUTIs lowered, a higher percentage of infections was needed in order to cover the cost of the intervention	Effectiveness estimates are crude and somewhat uncertain because of little direct clinical evidence

Appendix 5: Economic Burden–Nosocomial Infections

Study, Drummond Checklist Score	Design	Method for Estimating Attributable Cost	Resources Used	Source of Resource Cost (Curr, Year)	Sample Population (Time Horizon)	Case definition	Incidence	Incremental LOS	Estimated Incremental Cost
Puzniak, 2004 (88) Drummond Checklist score = 19	Case control	Matched 1:1 by DRG, APACHE II score ±2, age ±5	Patient's total hospitalization costs, microbiology costs, healthcare staff time, LOS, and MICU LOS	Hospital database, step-down cost allocation system (US$, year unstated)	Patients admitted ≥24 hours to a US medical intensive care unit (MICU) (1 July 1997–Dec. 31, 1999)	Positive screening for Vancomycin-resistant Enterococcus (VRE)	Not available	MICU: 4 attributable days Hospital: 8.3 attributable days	MICU: $7,873 attributable Hospital: $11,989 attributable
Adrie, 2005 (76) Drummond Checklist score =20	Retrospective analytic cohort of prospective database	Model, multiple linear regression	Direct ICU and medical costs, unit costs of ICU resources, overheads and other fixed costs	Prospective database, microcosting (€, 2001)	1,698 patients hospitalized for more than 48 hours in six ICUs (Apr. 1997–Dec. 2000)	Severe sepsis: infection, ≥2 criteria for systemic inflammatory response syndrome, and ≥1 criterion for organ dysfunction	19.96%	Not summarized	$27,509.49
Chen, 2005 (53) Drummond Checklist score = 15	Retrospective analytic cohort	Stratified analysis and regression model	LOS, physician services, medical and surgical procedures, laboratory, and radiology, unit costs	Hospital database (US$, 2001)	778 patients admitted to three ICUs in one hospital between (Oct. 2001–June 2002)	Any nosocomial infection (BSI, UTI, SSI, etc.) confirmed by culture, symptoms, and an attending physician	10.2% had at least one nosocomial infection	18.2 additional days	$3,306 additional costs per case patient
Penel, 2005 (65) Drummond Checklist score =16	Prospective cohort with a post hoc analysis	Unclear	LOS. Estimation of per diem cost, incl. rooming, lab, medications, and procedure costs	Macrocosting: LOS multiplied by estimation of per diem cost (€, 2005)	261 patients who had undergone head/neck cancer surgery in one hospital (Jan. 1997–Dec. 1999)	Based on the Centres for Disease Control 1992; surgical site infection (SSI), postoperative pneumonia (PP)	SSI: 36% PP: 13% SSI and PP: 5%	SSI: 16 days in additional mean LOS PP: 17 days SSI and PP: 31 days	SSI: €16,000 increase in mean direct medical costs; PP: €17,000; Both SSI and PP: €35,000
Baggett, 2007 (90) Drummond Checklist score =15	Retrospective case series	Standardized interviews with hospital staff and review of contact tracing logs	Direct costs: personnel time, laboratory, and medication costs; Indirect: hospital staff furloughs	Hospital database, microcosting (US$, 2004)	Two hospitals experiencing a nosocomial pertussis outbreak (Jul. 25–Sep. 15, 2004)	A cough illness lasting ≥14 days with symptoms of whooping cough and/or isolation of B. pertussis or confirmed by PCR or culture	Incidence was 10/1,475 persons exposed	Not available	Total cost per nosocomial case, Hospital A: $43,893; Hospital B: $30,282

Study, Drummond Checklist Score	Design	Method for Estimating Attributable Cost	Resources Used	Source of Resource Cost (Curr, Year)	Sample Population (Time Horizon)	Case definition	Incidence	Incremental LOS	Estimated Incremental Cost
Weber, 2008 (62) Drummond Checklist score =17	Prospective with nested case control	Matched 1:1 by age ±5yrs, procedure code, and NNIS risk index	LOS, ICU LOS, patient charges, and antibiotic costs	Microcosting from hospital accounting database (Swiss franc, assumed 2001)	6,283 surgical procedures in one Swiss hospital (2000-2001)	All surgical site infections at one Swiss hospital	2.98%	16.8 additional days	Mean additional hospital cost was 19,638 Swiss francs
Zingg, 2005 (95) Drummond Checklist score =15	Retrospective case control	Matched 1:2 by age, gender, LOS, underlying disease category	Direct: loss of revenue, additional microbiological diagnosis	Hospital database, microcosting (US$, 2001/2002)	16 case patients and 32 control patients during a norovirus outbreak (2001 and 2002)	A person who developed acute diarrhea, nausea, and vomiting during the norovirus outbreak	Attack rate 13.9% among patients and 29.5% among healthcare workers	Not available	$2,452 per case ($40,675 total direct outbreak costs ÷ 16 case patients)
Chu, 2005 (75) Drummond Checklist score =16	Prospective case series	Not stated	All infection-related diagnostic tests and surgical procedures, and inpatient and outpatient costs	Hospital accounting system (US$, 2002)	298 patients with a prosthetic implant and S. aureus bacteremia (whether nosocomial / community-acquired) (Sept. 1994–Sept. 2002)	Positive blood culture for S. aureus bacteremia, ≥72 hours post admission, in a patient with ≥1 prosthetic implant	Not available	Mean 33 additional days	Attributable cost per case: $67,439
Roberts, 2003 (163) Drummond Checklist score =16	Retrospective cohort	Ordinary least-squares regression and economic models	Units of each resource used by patient	Data abstracted from medical records, microcosting (US$, 1998)	246 patients in one urban teaching hospital (Jan.–Dec. 1998)	Any HAIs, according to Center for Disease Control and Prevention's National Nosocomial Infection Surveillance	15.2%	10.7 additional days	Incremental costs attributable to suspected HAI: $6,767; Confirmed HAI: $15,275
Chen, 2009 (52) Drummond Checklist score =15	Retrospective analysis of a prospectively assembled cohort	Generalized linear modeling	Medical and surgical procedures, medications, lab investigation, ICU bed-days, items	Hospital database, microcosting (US$, 2007, converted from Taiwanese dollars)	401 NIs in 320 of 2,757 patients, in four ICUs in one hospital in Taiwan (2003–2004)	BSI, UTI, SSI, respiratory tract infection, "and others" diagnosed ≥48 hours after admission to ICU	14.5 NI episodes per 100 admissions	Not available	$10,015

Study, Drummond Checklist Score	Design	Method for Estimating Attributable Cost	Resources Used	Source of Resource Cost (Curr, Year)	Sample Population (Time Horizon)	Case definition	Incidence	Incremental LOS	Estimated Incremental Cost
Payne, 2004 (74) Drummond Checklist score = 15	Retrospective cohort	Multiple regression	Charges converted to costs	Hospital charges (converted to costs), Centers for Medicare and Medicaid Services (US$,1999)	2,809 patients in 17 neonatal ICUs, very low birth weight (VLBW) (1998–1999)	BSI after third postnatal day, with symptoms of infection and 5+ days antibiotic treatment after diagnosis	Nosocomial BSI: 19.7%	The mean LOS of VLBW infants with nBSI was 32.49 days longer than those without	The mean incremental cost was US$54,539
Mahieu, 2001 (59) Drummond Checklist score = 15	Retrospective cohort with nested case control	Matched by gestational age and early post-natal co-morbidity factors	Charges and LOS	Charges from hospital discharge abstracts and patient files (€, 1995)	515 neonates in one Belgian neonatal ICU (NICU) (Oct. 1993–Dec. 1995)	Infections ≥48hr after admission to NICU and treated with IV antibiotics for 5+ days were considered nosocomial	13% incidence of one or more HAI	Mean 24 additional days	Mean extra charge with HAI was €11,750
Blot, 2005 (68) Drummond Checklist score = 15	Retrospective case control	Linear regression analysis, and matched 1:1 or 1:2 by APACHE II score, principal diagnosis, ICU LOS	Duration of mechanical ventilation, LOS, hospital costs	Patient hospital invoices (€, 2002)	36,836 patients (192 cases) were admitted to one general ICU in Belgium (1992–2002)	Catheter-related bloodstream infection: positive culture results, and clinical signs of sepsis	5.2 cases BSI per 1000 admissions, or 1 case per 1000 catheter-days	10 days attributable	Attributable costs €13,585
Elward, 2005 (73) Drummond Checklist score =14	Prospective cohort	Multiple linear regression analysis	Direct medical costs of PICU and hospital stay	Hospital accounting database (US$, 1999/2000)	911 admissions, incl. 56 case patients under age 18 in one US PICU (Sept. 1, 1999–May 31, 2000)	Bloodstream infections in PICU patients, recognized pathogen isolated from blood >48 hrs post admission	Rate of BSI: 13.8 per 1000 central venous catheter days	Not available	Attributable PICU direct costs: $39,219
Defez, 2007 (61) Drummond Checklist score =15	Retrospective case control	Matched 1:1 by age, sex, ward, LOS before infection, DRG, and McCabe index	Lab tests, radiology, surgery, antimicrobial agents, rate per day of hospital bed (est.)	Reimbursement from La Nomeclature Générale des Actes Professionnels and hospital pharmacy accounting database (€, 2004)	1,703 infected patients from previous study, 30 randomly chosen for each infection site, total 150. One French hospital. (2001–2003)	Patients with single-site nosocomial infection	Not available	Not available	Additional cost (mean €) by site of infection, UTI: 574; Surgical site: 1,814; Respiratory tract: 2,421 Bloodstream: 953; Other: 1,259

Study, Drummond Checklist Score	Design	Method for Estimating Attributable Cost	Resources Used	Source of Resource Cost (Curr, Year)	Sample Population (Time Horizon)	Case definition	Incidence	Incremental LOS	Estimated Incremental Cost
Graves, 2003 (60) Drummond Checklist score = 15	Decision model	Monte Carlo simulation	Estimated literature cost per bed-day, literature estimates of increased LOS, medical and surgical services	Database and literature values for NZ hospitals (US$, year unstated)	Any/all recorded admissions, New Zealand hospitals (1998–1999)	Hospital-acquired infection reported in database	No overall incidence reported	Not collected in study	Not reported per case. Estimated national costs of HAI over fiscal year in NZ, Medical patients: US$4,569,826; Surgical: US$3,900,922
Macartney, 2000 (86) Drummond Checklist score =15	Case control	Matched 1:1 by age, principal discharge diagnosis, same RSV season, and number of secondary diagnoses	Direct medical costs	Hospital accounting database (US$, 1996)	All patients admitted to one Philadelphia paediatric hospital over eight RSV seasons (1988–1996)	Nosocomial Respiratory Syncytial Virus (RSV) infection	88 nosocomial RSV cases out of 90,174 patients	Attributable LOS for nosocomial RSV was 7.8 days	Mean cost to hospital per RSV NI was $9,419/ case
Olsen, 2010 (67) Drummond Checklist score = 12	Retrospective cohort	Generalized least squares (GLS) and propensity score matched-pairs	Department actual cost components multiplied by patient charge codes (pharmacy, room and board, and procedures)	Barnes-Jewish Hospital cost accounting database (US$, 2008)	1,616 women who under-went low transverse caesarean delivery at one tertiary care hospital (July 1999–June 2001)	Patients diagnosed with surgical site infection (SSI) and/or endometritis (EMM) after surgery	Incidence of SSI: 5.0% EMM: 7.6%	Not available	SSI: attributable cost was $3,529 by GLS, $2,852 by propensity method; EMM: $3,956 by GLS, $3,842 by propensity method
Orsi, 2002 (69) Drummond Checklist score = 13	Retrospective case control	Matched 1:2 by pre-infection LOS, primary diagnosis, ward, central venous catheter, age ±5, and sex	Single-day hospital cost, increased LOS	Data from clinical and micro-biological records collected by infection control team (€, year unclear)	105 included cases, each matched with two controls at one teaching hospital in Rome, Italy (Jan. 1994–June 1995)	Bloodstream infection: isolated pathogen(s) in the blood, plus one or more related symptoms, ≥48 hours after admission	Diagnosed in 2% of screened patients	Attributable LOS 19.1-19.8 days (mean), 13-15 days (median)	Additional €15,413 expenditure per case
Spearing, 2000 (96) Drummond Checklist score =13	Retrospective cohort	Unclear	Direct costs incl. medical costs, outbreak investigation, lost productivity costs, and miscellaneous	Medical records data and Medicare costs (AU$, 1996)	52 cases in a 600-bed tertiary care complex during an outbreak of Salmonella (December 1996)	Not detailed; cases of Salmonella during the outbreak	Not available	Not available	AU$2,308 (US$1,827) per case (Total outbreak cost AU$120,000 or US $95,000 ÷52 cases)

Study, Drummond Checklist Score	Design	Method for Estimating Attributable Cost	Resources Used	Source of Resource Cost (Curr, Year)	Sample Population (Time Horizon)	Case definition	Incidence	Incremental LOS	Estimated Incremental Cost
Brilli, 2008 (85) Drummond Checklist score =13	Retrospective case control	Matched by primary and underlying diagnoses, and ventilation days. When possible: surgical procedure, PRISM score ±10, age ±1 yr, and sex	Hotel costs; surgical, medical, and laboratory procedures; supplies; blood products; radiology; and other professional fees	Microcosting from hospital accounting database (US$, year unspecified)	13 case patients matched to control patients 1:1 in one paediatric ICU (FY 2005–FY 2007)	Paediatric ICU patients with Ventilator-Associated Pneumonia (VAP)	7.8 cases per 1,000 ventilator days in FY 2005	8.7 attributable days	Attributable VAP costs per patient: $51,157
Dietrich, 2002 (84) Drummond Checklist score = 14	Prospective case control	Matched 1:1 based on severity of disease, age ±15, primary ward, status of ventilation, immunosuppression, gender, LOS	All resources consumed for diagnosis, treatment, nursing and hospital stay, including materials and personnel	Hospital accounting database (DM, 1998/1998)	48 cases and 66 controls (resulting in 29 matched pairs) in one German teaching hospital, five ICUs (May 1998–Mar 1999)	Nosocomial pneumonia, diagnosed according to the criteria of the Centers for Disease Control and Prevention (CDC), Atlanta	Not available	5, 6.55, and 7.4 excess days on ventilation, in ICU and in hospital, respectively	Excess cost per case: DM 14,606 from the hospital perspective
Dietrich, 2002 (84) Drummond Checklist score = 14	Retrospective case control	Matched 1:1 based on severity of disease, age ±15, primary ward, status of ventilation, immunosuppression, gender, LOS	All resources consumed for diagnosis, treatment, nursing and hospital stay, including materials and personnel	Hospital accounting database (DM, 1998/1998)	37 matched pairs in one German teaching hospital, admitted to one of two neurosurgical wards (Feb. 1997–Dec. 1998)	Nosocomial pneumonia, diagnosed according to the criteria of the Centers for Disease Control and Prevention (CDC), Atlanta	Not available	5,14.03 and 10.14 excess days on ventilation, in ICU and in hospital, respectively	Excess cost per case: DM 29,610 from hospital perspective
Fretz, 2009 (94) Drummond Checklist score = 13	Retrospective case series	Unclear	Revenue loss, nursing, diagnostic procedures, pharmacy, and costs of creating an isolation ward	Hospital department-specific costs (€, year unspecified)	90 infected patients and staff of an Austrian hospital during a norovirus outbreak (Dec. 2006–Feb. 2007)	Positive stool specimen for norovirus by RT-PCR ≥48 hours following admission	Not applicable	Not available	The total cost of the outbreak for the Department of Internal Medicine was €80,138

Study, Drummond Checklist Score	Design	Method for Estimating Attributable Cost	Resources Used	Source of Resource Cost (Curr, Year)	Sample Population (Time Horizon)	Case definition	Incidence	Incremental LOS	Estimated Incremental Cost
Fruhwirth, 2001 (79) Drummond Checklist score = 14	Prospective case series	Unclear	Direct medical costs, direct non-medical (e.g., food), and indirect costs (e.g., productivity loss)	Hospital database, microcosting (€, 1997/ 1998)	33 cases of nosocomial rotavirus infection in children <48 months, in Austria (Dec. 1997--May 1998)	Rotavirus-positive diarrhea, nosocomial if onset was >48 hours after admission	Risk for contracting nosocomial RV was 2.59 per 1,000 hospital days during peak RV season (Dec–May), <48 months of age	Not available	Case cost average €2,442
Lee, 2010 (58) Drummond Checklist score = 13	Retrospective cohort	Linear regression models	Third-party payer's overall hospital costs, increased LOS (post-surgical), and antibiotic costs	Quality Indicator/ Improvement Project (QIP) database (US$, 2007, converted from JP yen)	1058 gastrectomy patients from 10 Japanese hospitals (Apr .2004–Jan. 2007)	Diagnosed with any hospital-acquired infection (HAI)	HAI incidence 20.3%	10.6 days attributable	Attributable HAI costs: $2,767 (range $1,035–6,513)
Piednoir, 2003 (80) Drummond Checklist score = 14	Prospective cohort with nested case control	Matched 1:1 by primary diagnoses, date of admission ±7 days, age ±3 months, sex, and pre-infection LOS	All expenses sustained by the hospital: medical, preventative, staff costs, and fixed costs	Medical records and hospital accounting database (€, 2001/2002)	23 cases matched 1:1, in one French paediatric hospital (1 Dec. 2001–Mar. 31, 2002)	Rotavirus-positive stool via qualitative enzyme-linked immunosorbent assay (ELISA) ≥48 hours post admission	Attack rate: 6.6%; Incidence: 15.8 per 1,000 hospital days	4.9 additional days	Mean excess cost due to nosocomial rotavirus infection: €1,930
Whitehouse, 2002 (63) Drummond Checklist score =12	Prospective case control	Matched 1:1 by type of operative procedure, NNIS risk index, age ±5, surgery within the same year, and surgeon	Total direct costs from database, representing sum of costs required to provide healthcare services	Hospital accounting database, microcosting (US$, 1997)	59 cases, each matched with one control, in one US hospital (1997–1998)	Orthopaedic surgical site infection: superficial incisional, deep incisional, or organ/space	SSI Cases: 59 (out of approximately 6000 patients undergoing orthopedic surgery)	Cases: median LOS 6 days; Controls: median LOS 5 days; Incremental LOS: 1 day	Cases: median total direct cost: $24,344USD; Controls: median total direct cost: $6,636USD; Total attributable cost for all patients was $867,039USD
Rosenthal, 2004 (83) Drummond Checklist score = 13	Prospective with nested case control	Matched 1:1 by ICU type, hospital and year of admittance, sex, age, and severity of illness (ASIS score)	Fixed cost per bed-day, defined daily antibiotic doses, LOS	Hospital finance department (Argentinian pesos [$], year unclear)	307 case patients (pneumonia), 307 control patients in three hospitals over 5 years (1998–2002)	Nosocomial pneumonia according to definition from the Centers for Disease Control and Prevention	5.79% developed nosocomial pneumonia	Mean 8.95 additional days	Mean extra total cost for cases was AG$2,255

Study, Drummond Checklist Score	Design	Method for Estimating Attributable Cost	Resources Used	Source of Resource Cost (Curr, Year)	Sample Population (Time Horizon)	Case definition	Incidence	Incremental LOS	Estimated Incremental Cost
Brun-Buisson, 2003 (77) Drummond Checklist score = 13	Prospective cohort with retrospective measurement of costs	Costing model, no further effort (Chaix et al., 1999)	All resources used and direct costs (of fluids, drugs, blood products and procedures)	Hospital accounting database and previously built costing model created in this ICU (€, 2001)	424 patients in one Paris, France ICU (1997–1998)	Patients with sepsis, clinically or microbiologically documented, ≥48 hours after admission	ICU-acquired sepsis: 23%	19 additional days compared to patients with no sepsis	Nosocomial cases incurred average total costs €39,908 higher than patients with no sepsis
Fuller, 2009 (164) Drummond Checklist score = 12	Retrospective cohort	Linear regression model	Charges converted to costs	Health Services and Cost Review Commission, Maryland; Office of Statewide Planning and Development, California (US$, 2008)	2,496,212 admissions in Maryland and California (Maryland: FY2008; California: FY2006)	Any negative event or outcome that results from the process of inpatient care	4–5.6% of patients had one hospital-acquired potentially preventable complication; 1.6–2.2% had multiple	Not available	Maryland: $626,416,710 (9.63% of total claims) associated with potentially preventable complications
Kilgore, 2008 (55) Drummond Checklist score = 13	Retrospective cohort	Multivariable regression models and restricted models	Total, variable costs of inpatient care, and LOS	Cardinal Health-MedMined database (US$, 2007)	1,355,647 admissions during 69 months from 55 hospital databases (March 2001–Jan 2006)	Any nosocomial infection, identified via Nosocomial Infection Marker (NIM)	Overall NIM rate was 4.3%	5.4 additional days	NIMs are associated with excess total costs of $12,197
Mahmoud, 2009 (64) Drummond Checklist score = 13	Retrospective analytic cohort	Logistic regression	Medical and surgical procedures, hotel costs, nursing, pharmacy, ICU, supplies, and laboratory procedures	Large US hospital database: Premier Perspective database (US$, 2005/6)	25,825 patients undergoing colorectal procedures, in US database of 196 hospitals (Jan. 2005–June 2006)	Incisional surgical site infections, superficial or deep as defined by the U.S. Centers for Disease Control and Prevention	SSI incidence: 3.7%	LOS with postoperative complications is 3–11 days longer than without	Mean total direct costs incurred by treating SSI: $13,746 ± 13,330
Bou, 2009 (93) Drummond Checklist score = 11	Retrospective case series	Multiple linear regression analysis	ICU hospital costs only: treatments and diagnostic procedures	Hospital finance department, microcosting (€, year unspecified)	67 ICU patients during a P. aeruginosa outbreak at one ICU in Spain (July–Sept 2003)	Any patient who developed the infection after ≥48 hours on mechanical ventilation	Incidence of outbreak associated with pseudomonas infection; 17/67	38 additional days	€18,408 average extra ICU costs per case patient

Study, Drummond Checklist Score	Design	Method for Estimating Attributable Cost	Resources Used	Source of Resource Cost (Curr, Year)	Sample Population (Time Horizon)	Case definition	Incidence	Incremental LOS	Estimated Incremental Cost
Festini, 2010 (78) Drummond Checklist score = 12	Prospective cohort	Unclear	LOS, estimated cost of hospital day based on DRG, and lost productivity of patients' parents	Hospital accounting databases, wage data provided by Italian Central Bank (€, year unclear)	608 children under 30 months of age in four Italian hospitals (2006–2008)	Hospital acquired, positive rapid rotavirus testing	Incidence of NRVI was 5.3%	1.7 days additional	Nationally in Italy, est. €8,019,155.44/ year (based on increased LOS)
Jenney, 2001 (66) Drummond Checklist score = 12	Retrospective cohort with nested case control	Matched 1:1 by gender, age ±5, NNIS risk index scores	LOS, antibiotic costs, salaries, utilities, and overhead costs	Hospital finance department (AU$, 1999)	1,377 CABG (coronary artery bypass graft) procedures; 125 cases in an Australian hospital (1996–1998)	Surgical site infection (SSI) after CABG, defined according to Centers for Disease Control and Prevention (CDC)	SSI incidence: 9.1%	1.36 mean additional days	Mean excess cost: $12,419/case
Pirson, 2008 (71) Drummond Checklist score = 11	Retrospective case control	Matched 1:1 by APR-DRG and severity of illness	Salaries, hotel costs, drugs, ICU, medical and surgical procedures, laboratory, and diagnostics	Université Libre de Bruxelles costing database (€, 2003)	3 Belgian hospitals (2003 and 2004)	Cases were defined as bacteraemia that developed ≥48 hours after admission	Incidence of HAB: 1.4% and 1.2% in 2003 and 2004	Attributable LOS: 6.1 days (ICU); 30 days (non-ICU)	Mean additional cost of HAB was €16,709
Tambyah, 2010 (81) Drummond Checklist score = 11	Prospective cohort data analyzed retrospectively	Patient records reviewed by investigators	Laboratory costs, LOS, and medications	Hospital charges were converted to costs via cost-to-charge ratio (US$, 1998)	1,497 catheterized patients in one U.S. University hospital (1997–1998)	Nosocomial UTI, defined as new bacteriuria or funguria exceeding 103 CsFU/mL	14.9% of catheterized patients	Not available	Average attributable treatment cost: $589
Vonberg, 2008 (92) Drummond Checklist score = 10	Prospective with nested case control	Matched 1:3 by DRG in 2006, pre-infection LOS, Charlson comorbidity index ±1	"General charge for each day of care," and "some patient costs" (unclear)	Hospital finance department (€, year unstated)	45 nCDAD cases, 1:3 case:control in one German tertiary care hospital (Jan.–Dec. 2006)	Positive EIA or culture for CDAD, nosocomial if onset is ≥72 hours after admission	10–16% of patients are carriers of c.dif, at risk for CDAD; incidence of CDAD not available	Median 7 additional days	Median incremental cost: €7,147/CDAD case

Study, Drummond Checklist Score	Design	Method for Estimating Attributable Cost	Resources Used	Source of Resource Cost (Curr, Year)	Sample Population (Time Horizon)	Case definition	Incidence	Incremental LOS	Estimated Incremental Cost
Sheng, 2005 (57) Drummond Checklist score = 11	Retrospective case control	Matched 1:1 by age ±2, sex, underlying illness, operation(s), admission date ±28 days, ward, diagnosis, and severity	Costs of stay, medication, laboratory procedures, materials and services, and nursing care	Hospital finance departments (US$, 2002)	273 adult case-control pairs, from two community hospitals and one tertiary medical centre (Oct.– Dec. 2002)	Patients aged ≥16 years with onset of any infection ≥48 hours after admission or within one week of discharge	Not available	19.67 additional days	$5,189 in mean additional costs
Esatoglu, 2006 (56) Drummond Checklist score = 11	Retrospective case control	Matched 1:1 by age, gender, clinic, and primary diagnosis of the infected patients	LOS, medical goods/ materials, drugs, tests, beds, treatments, and other costs	Unspecified, presumably hospital accounting database (US$, 2001)	57 patients with HAI, matched 1:1, in one hospital in Ankara, Turkey (Sept.–Dec. 2001)	Any hospital-acquired infection, not further described	Not available	Mean 23 additional days	HAI mean additional cost: US$2,026.70
Kilgore, 2008 (72) Drummond Checklist score = 11	Retrospective cohort	Regression analysis	"Fixed and variable costs of care"	Hospital accounting database (US$, 2006)	1,355,647 admissions during 69 months from 55 hospital databases (March 2001–Jan. 2006)	Nosocomial BSIs, non-duplicate isolate collected ≥3 days after admission	Nosocomial BSIs identified in 0.93% of admissions	Not available	Incremental costs: $19,427
Plowman, 2001 (54) Drummond Checklist score = 14	Prospective cohort	Linear regression model	Resources, LOS; care and treatment; paid staff time; nursing costs; unit costs for laboratory, radiology and other diagnostic procedures	Costs estimated for specialty via interviewing healthcare professionals, hospital database (GBP£, year unclear)	4,000 adults in one general hospital in London, England (Apr. 1994–May 1995)	Any hospital-acquired infection	Incidence of HAIs: 7.8%	14.1 additional days	Mean additional costs due to HAI at any site: £3,154 (model estimate £2,917)
Wilson, 2004 (91) Drummond Checklist score = 11	Retrospective with nested case control	Matched 1:1 to controls with ≥20% total body surface burns	Hospital charges converted to costs	Hospital finance department; opaque costing methods (US$, 2001)	34 burn patients who acquired nosocomial MDRAB (Jan.–Dec. 2004)	Nosocomial multidrug resistant infection (Acenitobacter Bowmanii) (MDRAB)	16% of 217 burn patients acquired MDRAB	11 additional days	Mean additional cost: $98,575

Study, Drummond Checklist Score	Design	Method for Estimating Attributable Cost	Resources Used	Source of Resource Cost (Curr, Year)	Sample Population (Time Horizon)	Case definition	Incidence	Incremental LOS	Estimated Incremental Cost
Anil, 2009 (89) Drummond Checklist score = 10	Retrospective case control	Matched 1:1 based on birth weight ±10%, sex, gestational age ±2 wks, ventilation, anti-microbial therapy, and use of CVC/ TPN	Charges per patient and actual financial burden of outbreak; not detailed further	Hospital discharge abstracts via the hospital's central finance service (US$, assumed 2005)	22 cases in one Turkish neonatal ICU, drug resistant S. typhimurium outbreak (15 to 29 March, 2005)	Positive stool/ rectal swab or fluid culture for S. typhimurium	Attack rate 30.5%	9.8 additional days	$1081.84 more charges per case compared to control
Pirson, 2005 (70) Drummond Checklist score = 10	Retrospective case control	Matched (ratio unstated) by APR-DRG	Administrative, general services costs, medical charges, LOS, and drugs	Hospital cost centres, medical records data, and invoicing data (€, 2001)	46 cases of HAB in one Belgian hospital (2001)	An infection of bacteraemia developed ≥48 hours after admission	0.56% incidence	21.1 additional days	Average additional costs: €12,853
Watters, 2009 (87) Drummond Checklist score = 10	Retrospective cohort	Unclear	Antibiotics, high dependency unit and intensive therapy unit facility use, and prolonged LOS	Unspecified, presumably hospital accounting/ finance database (£, year unstated)	55 patients who had undergone head and neck surgery in one Irish hospital (over 1 year; year unspecified)	Positive MRSA screening in postoperative period after head and neck surgery	25 patients (45%) became MRSA positive in the post-operative period	Difference in mean LOS: 45 days	Additional cost: £6,485; mean extra antibiotic cost: £1,700
Morse, 2001 (82) Drummond Checklist score = 9	Retrospective cohort	Unclear	Only "overall costs" of hospital stay after operation; not detailed further	Hospital case costing system, EP Si (US$, year unstated)	118 bowel surgery patients aged 65 to 79, and 33 aged >80, with Medicare in one hospital (Jan 2008- March 2009)	"Never events:" hospital-acquired complications that are not reimbursed by Medicare	42.4% of study patients experienced a "never event"	Not available	Catheter-related UTI: $14,300 extra costs; Vascular catheter infection: $16,400 extra costs
Mauldin, 2008 (165) Drummond Checklist score = 16	Retrospective case series	Segmented regression analysis for interrupted time series, univariate and multivariate	LOS, ICU LOS, drug costs, laboratory and medical procedures, and adjusted hospital charges	Hospital database (US$, 2005)	187 patients with MRSA, 19 patients with VRE infections in one U.S. hospital (2000–2005)	Patients diagnosed with either VRE or MRSA	Not available	Not available	Total mean costs, MRSA patients: $110,493; VRE patients: $115,260

*Dietrich, 2002 (84) is one paper detailing two different studies. The studies were separated in this table for clarity.

Appendix 6: Economic Burden–Nosocomial Venous Thromboembolism

Study, Drummond Checklist Score	Design	Method for Estimating Attributable Cost	Resources Used	Source of Resource Cost (Curr, Year)	Sample Population (Time Horizon)	Case Definition	Incidence	Incremental LOS	Estimated Incremental Cost
Caprini, 2003 (97) Drummond Checklist score = 18	Decision analysis (Markov)	Univariate analysis	Patient care protocols, healthcare staff time, diagnostic tests, supplies, hospitalizations, and procedures	Literature data (US$, year unstated)	Two hypothetical cohorts similar to all US patients undergoing total hip replacement surgery (THRS) in the U.S. (1995–1996)	Deep-vein thrombosis (DVT)	Literature information only	Literature information only	Annual per-patient cost of DVT: $3,798
MacDougall 2006 (98) Drummond Checklist score = 16	Retrospective observational cohort study	Linear model with log-link function and gamma distribution	Treatment strategy, length of hospital stay, physician office, emergency room, outpatient claims, ancillary services, and pharmacy utilization	Actual healthcare plan payments for services only	Patients with a DVT or PE diagnosis code during the study period (Jan. 1, 1997–Mar. 31, 2004)	Deep-vein thrombosis (DVT), and pulmonary embolism (PE)	Literature information only	Mean LOS DVT = 10 days, PE = 9 days, DVT and PE = 10 days	Annual direct medical costs of $16,832 ($24,411 CAN) for DVT, $18,221 ($26,426 CAN) for PE, $24,874 ($36,074 CAN) for combined DVT and PE, and $4,726 ($6,854 CAN)

*Only gives incidence of PTS, PEs given post-surgical DVT.

Appendix 7: Economic Burden–Nosocomial-related Falls

Study, Drummond Checklist Score	Design	Method for Estimating Attributable Cost	Resources Used	Source of Resource Cost (Curr, Year)	Sample Population (Time Horizon)	Case Definition	Incidence	Incremental LOS	Estimated Incremental Cost
Nurmi, 2002 (101) Drummond Checklist score = 13	Prospective cohort	Unclear	Emergency room visits, outpatient visits, LOS, and radiology	Hospital accounting database (€, 1999)	1,056 patients treated in four institutions in Finland (Feb. 1, 1993–Jan. 31, 1994)	Falls among ambulatory patients over 60 years within the study period	1,398 falls per 1000 person years. 30% of falls resulted in injury	Not available	Average cost per treating a fall: €944
Oliver, 2008 (100) Drummond Checklist score = 13	Case series	N/A	Legal payments	NHS Litigation Authority Database of clinical negligence claims (GBP£, year unspecified)	479 clinical negligence claims resulting from in-hospital falls in England (1995–2006)	Any closed clinical negligence claim resulting from in-hospital falls within the time period	Not applicable	Not applicable	60.5% of claims resulted in payment of costs or damages, with mean payment GBP£12,945/claim
Nadkarni, 2005 (99) Drummond Checklist score = 12	Case series	Unclear	Operation procedures, non-operative treatment, and LOS	Southport and Ormskirk Hospital Risk Management Department; Hospital Finance Department (GBP£, year unspecified)	42 cases, of Southport and Ormskirk Hospital Risk Management Department incident forms (Jan. 2000–Dec. 2002)	Orthopaedic injuries sustained by inpatients falling on the hospital wards	Not available	Mean 4.1, median 3 additional weeks	GBP £1,667 per case (total GBP £70,000 ÷ 42 cases)

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