HEALTH ECONOMIC EVALUATION OF PROBIOTIC PROPHYLAXIS IN CRITICAL ILLNESS FOR PREVENTION OF HEALTHCARE-ASSOCIATED INFECTIONS: SYSTEMATIC REVIEW, STUDY PROTOCOL AND COST-EFFECTIVENESS ANALYSIS

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A Thesis Submitted to McMaster University School of Graduate Studies in Partial Fulfillment of the Requirements for the Degree of Masters of Science

McMaster University

TITLE: HEALTH ECONOMIC EVALUATION OF PROBIOTIC PROPHYLAXIS IN CRITICAL ILLNESS FOR PREVENTION OF HEALTHCARE-ASSOCIATED INFECTIONS: SYSTEMATIC REVIEW, STUDY PROTOCOL AND COST-EFFECTIVENESS ANALYSIS

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Abstract:

Ventilator-associated pneumonia (VAP) is the most common healthcare-associated infection in the intensive care unit, resulting in a high burden of illness, mortality and increased cost. The literature around the cost-effectiveness of probiotics in prevention of health-care associated infections has not been previously well-described, and a definitive health economic evaluation alongside a well-designed randomized control trial assessing probiotic prophylaxis has not been previously performed.

This thesis consists of 3 separate manuscripts (with 2 published in peer-reviewed journals and 1 pending). The theme of this thesis was to: (1) describe the literature about the cost-effectiveness of probiotics in hospitalized patients in preventing healthcare-associated infections; (2) design a protocol for an economic evaluation alongside a randomized control trial (RCT) examining probiotic prophylaxis of VAP; and then (3) perform and analyze the health economic evaluation presented in the protocol.

The first component of this thesis is a systematic review of probiotic prophylaxis of healthcare-associated infections in hospitalized patients. We performed an extensive search including multiple databases which found 7 studies. Probiotics demonstrated favourable cost-effectiveness in 6 of 7 (86%) economic evaluations, with 3 studies being manufacturer-supported, all suggesting cost-effectiveness. Certainty of cost-effectiveness evidence was very low due to risk of bias, imprecision and inconsistency using the GRADE approach. Hence further RCTs with economic evaluations were stated as a solution.

The second component of this thesis is a study protocol for an economic evaluation alongside the Probiotics to Prevent Severe Pneumonia and Endotracheal Colonization Trial (PROSPECT), which assessed the efficacy of probiotic prophylaxis in the prevention of healthcare-associated infections (specifically VAP).

The third component of this thesis is the cost-effectiveness analysis performed utilizing the individual patient data from PROSPECT to produce the economic evaluation (E-PROSPECT). As of the date of thesis submission, PROSPECT is still pending publication, and hence E-PROSPECT is also pending analysis and publication. However, I have prepared a draft manuscript (along with figures and tables) that will be produced at the conclusion of E-PROSPECT for thesis committee review.

ACKNOWLEDGEMENTS

I would like to express my sincerest gratitude to my thesis committee. I am truly thankful for these individuals on the committee.

Deborah Cook has been the best mentor, supervisor, colleague and most importantly, friend that anyone could ask for. She has gone above and beyond to help not only with this thesis, but also help with career and providing opportunities that I would otherwise be a part of. Her expertise, guidance, patience and encouragement throughout this educational process have been incomparable. I would not be here today without her advice and generous heart, allowing me to be a part of her team and project. I am forever in debt to her. Thank you from the bottom of my heart.

Bram Rochwerg has been an amazing lead Master's supervisor, mentor, colleague and friend as well. Thank you taking me on even through a reference from a colleague (even without meeting me first), and I hope the mutual work we have done together has lived up to that billing. Thank you for being an inspirational collaborator and role model, a person who I wish to emulate in my clinical and research career. Thank you for encouraging me in my research, but also my career aspirations, and thank you for always being someone I can talk to about anything and everything related to critical care. I cannot thank you enough.

Feng Xie has been my main health economics professor, mentor and colleague. Thank you for guiding me through this new research realm and introducing me to this fascinating and burgeoning field. Thank you for the ability to teach the discipline of health economic evaluation with methodological rigour, for your astute attention to detail, and for the patience to answer all our questions and educating us in economic evaluations alongside critical care trials. Hopefully we can continue collaborations in the future as our work intertwines. Thanks you for everything you've done. I am forever grateful.

To my clinical and research colleagues: John Basmaji, Jean-Eric Tarride, Gord Blackhouse, Ian Ball, Claudio Martin, Jennie Johnstone, Rob Fowler, Nicole Zytaruk, Alyson Takaoka, Chris Martin, Doug Austgarden, Ana Igric, Guilio Didiodato, Stewart Aitken, Adarsh Tailor, Sean Bagshaw, Dennis Djogovic and Shelley Duggan, Oleksa Rewa, Brian Buchanan, Rob Arntfield, Hailey Hobbs - your contributions, guidance, teaching, assistance, support and faith in me is most appreciated. Thank you as well.

To my parents Sam and Anita, and my sister Winnie: Thank you for being my support throughout my life, and also my loving family who encouraged and helped me become the person I am today. Thank you for helping me throughout my education and through all my trials and tribulations.

To all my friends, family and colleagues: thank you for supporting me and cheering me on. It is most appreciated.

And most importantly, to my loving wife Andrea: Thank you for being there throughout my life, our marriage and through my winding career. Thank you for having the patience to walk through this with me, and your understanding and support throughout all the ups and downs. Thank you for being such a wonderful mother to our puppies and our family, and I am eternally grateful for you.

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DECLARATION OF ACADEMIC ACHIEVEMENT

This thesis is submitted in partial fulfillment of the requirements for the Master of Science program in Health Research Methodology. The work takes the form of a sandwich thesis, consisting of three separate, but related manuscripts with regards to probiotic prophylaxis to prevent healthcare-associate infections in critically ill patients.

Vincent Lau is the first author of all three manuscripts and the principle investigator of the health economic evaluation with senior supervision from Drs. Bram Rochwerg (lead), Deborah Cook and Feng Xie.

Vincent Lau led the systematic review (along with Drs. Bram Rochwerg, Deborah Cook and Feng Xie, John Basmaji), which included the title and abstract review, case report form generation, data abstraction, analysis and GRADE application.

Vincent Lau led the E-PROSPECT protocol development, alongside Drs. Bram Rochwerg, Deborah Cook, Feng Xie and Rob Fowler.

Vincent Lau also led the E-PROSPECT cost-effectiveness analysis (in progress pending results of PROSPECT), alongside Drs. Bram Rochwerg, Deborah Cook, Feng Xie and Rob Fowler.

Vincent wrote the first draft of each manuscript prior to group revisions. All other co-author contributions are listed at the end of each chapter.

This health economic evaluation (E-PROSPECT) and PROSPECT is funded by the Canadian Institute for Health Research, McMaster University, St. Joseph's Healthcare Hamilton, Canadian Frailty Network, Physicians Services Incorporated of Ontario, the Hamilton Academic Health Sciences Organization and the Academic Medical Organization of Southwestern Ontario.

CHAPTER 1: INTRODUCTION

Ventilator-associated pneumonia is a healthcare-associated infection in critically ill patients

Ventilator-associated pneumonia (VAP) is a healthcare-associated infection that is hospital acquired, developing 48 hours or more after initiation of invasive mechanical ventilation. In critically ill patients, the evaluation and diagnosis of suspected VAP involves a thorough clinical history, physical examination and investigations that may include complete blood count, chest radiography, respiratory tract and blood cultures[1]. The 2005 American Thoracic Society definition of VAP includes the presence of: (1) a new lung infiltrate on chest imaging (with clinical evidence that the infiltrate is of infectious etiology); plus at least 2 of the following findings: (2) new onset of fever >38^{O}C; (3) leukocytosis or leukopenia; (4) purulent secretions; and/or (5) decline in oxygenation[2].

However, a recent systematic review and meta-analysis has revealed the pooled sensitivity (range: 61.4-88.9%) and specificity (range: 26.1-79.6%) for various clinical indicators of VAP to have poor accuracy, including: fever, purulent secretions, infiltrate on chest radiography, endotracheal aspirate, protected specimen brush, broncho-alveolar lavage and Clinical Pulmonary Infection Scores >6[3]. Therefore, there is no universal definition for VAP and the longstanding discussion regarding the consequences of different diagnostic criteria persists[2–4].

Ventilator-associated pneumonia is common, confers a poor outcome, and is costly

VAP is the most common healthcare-associated infection in the ICU, resulting in a high burden of illness and is a leading cause of death for hospital-acquired infections[5–7]. A 2005 systematic review found a pooled cumulative VAP incidence of 23% (95% confidence interval (CI): 19%–27%) in randomized controlled trials (RCTs) and 10% (95% CI: 7–13%) in observational studies[6]. Ventilator-associated pneumonia is associated with a two-fold attributable risk of dying in the intensive care unit (ICU) (odds ratio [OR] 2.02, 95% CI: 1.2–3.6). The cost attributed to VAP ranges from US $10,000 to $13,000 per patient[6].

Prevention of ventilator-associated pneumonia is important

Comprehensive clinical practice guidelines have been developed to address prevention of VAP associated morbidity and mortality in ICUs[5]. The Canadian Patient Safety Institute has estimated hospital mortality to be ~46% for ventilated patients who develop VAP compared to ~32% for non-VAP patients[7], with the attributable mortality of VAP being approximately 13%[8]. Thus, VAP prevention is a patient-important safety goal during critical illness[5,8,9].

Various jurisdictions employ different VAP prevention interventions, which may include some or all of the following measures as part of usual care: head-of-bed elevation, other positional bed strategies (e.g. kinetic bed), oro-endotracheal tubes with subglottic secretion drainage, oral hygiene care (including oral decontamination with chlorhexidine or iodinated solutions), daily assessment for extubation, early initiation of enteral nutrition, prophylactic antibiotics (e.g. intravenous or aerosolized, nasal, topical), and ventilator circuit changes for new or soiled circuits[5,7,10(p)]

Recent re-evaluation of very low to moderate evidence has revealed the effectiveness of chlorhexidine oral decontamination[12,13]and head-of-bed elevation[14] now questions their indiscriminate use and inclusion in VAP bundles. And despite pre-existing VAP bundles, the incidence of VAP remains high in ventilated patients[6]. Therefore, further studies exploring additional interventions for VAP prevention, including selective decontamination of the digestive

tract (SDD)[15], and probiotics[12–15], need to have strong evidence-based studies of effectiveness backing their inclusion.

Probiotics appear to prevent healthcare-associated infections

Probiotics are defined as "live microorganisms which when administered in adequate amounts may confer a potential health benefit on the host[16]. They are reported to enhance gut barrier function, reduce host pathogenic bacterial load, modify gut microbiota, and modulate the immune system[17–20]. Meta-analyses of probiotic trials suggest benefits including a reduced incidence of healthcare-associated infections[21–24].

Prior meta-analyses of RCTs (Table 1) suggest that probiotics administered to critically ill mechanically ventilated patients were associated with a ~26-38% lower VAP rate, and a ~20% lower infection rates with no differences in ICU or hospital mortality[12,25–28]. However, the largest meta-analysis included 30 small, mostly low quality single-center RCTs (n=18-300, 2972 total patients). This meta-analysis yielded point-estimates (lower VAP rate: risk ratio 0.74 [95% CI: 0.61-0.90, p=0.002; and lower infection rates: risk ratio 0.80 [95% CI: 0.68-0.95], p=0.009) that were derived from high clinical heterogeneity and potential publication bias[12]. This precludes strong clinical recommendations, and indicates that further high quality clinical trials are needed to evaluate whether probiotics are beneficial for VAP prevention.

Further evidence suggests that probiotics can reduce the incidence of diarrhea - specifically *Clostridioides difficile*-associated diarrhea (CDAD), which can cause pseudomembranous colitis, toxic megacolon, and death[29]. A recent Cochrane systematic review and meta-analysis of 31 RCTs including 8672 adult and pediatric, hospitalized patients receiving antibiotics (for any reason) demonstrated that concurrent administration of probiotics prevented CDAD as compared with placebo (based on moderate certainty evidence). The cost of treatment for CDAD is expensive, and thus imposes a substantial financial burden on the health care system[29].

Thesis justification: Importance to study cost-effectiveness of probiotics

Probiotics confer an extra (albeit, low) drug acquisition cost, and thus represent an added cost to usual care to prevent VAP. However, if probiotics prevent VAP, then it is worth knowing if probiotics are cost-ineffective, cost-neutral, cost-effective or even cost-saving[30]. This underscores the need for comparative economic and clinical effectiveness research to inform bedside practice, clinical guidelines and policy makers[30,31].

Despite prior systematic reviews and meta-analyses investigating the effect of probiotic prophylaxis for prevention of VAP[12], no systematic reviews had summarized the economic evaluations of probiotic prophylaxis in hospitalized patients.

Only one prior health economic evaluation has examined probiotics to prevent VAP in a cost-benefit analysis (CBA) using a Markov model. Prophylactic probiotics demonstrated cost-benefit per VAP case averted and dominance of probiotics over placebo with usual care[10].

However, no prior cost-effectiveness analyses (CEA) have been designed alongside a large rigorous RCT evaluating probiotic prophylaxis in preventing VAP. There is an increasing advocacy for the science of value in healthcare[32]. Some have stated that CEAs should be mandatory alongside clinical-effectiveness research to aid in guideline development and public healthcare decision-making policy[31].

Therefore, as part of this thesis, I conducted a systematic review of economic evaluations of probiotic prophylaxis in hospitalized patients. The objective of this systematic review was to summarize cost or cost-effectiveness evidence of probiotic strategies (different doses and strains) in preventing healthcare-associated infections (e.g. VAP, CDAD and

antibiotic-associated diarrhea [AAD]) in hospitalized adult patients. This is presented in Chapter 2, and is the first component of the thesis.

Methodological issues addressed in this chapter include: synthesizing cost-effectiveness, cost-utility or cost-benefit for health economic evaluations across multiple outcomes (VAP, CDAD, AAD), different perspectives, discounting and time-horizons (precluding a conventional meta-analysis); interpreting data in the context of other healthcare-associated infection prevention strategies; evaluating the risk of bias for multiple inputs (e.g. RCTs, observational studies, surveys) for model-based economic evaluations; applying the GRADE approach to economic evaluations; and, assessing roles of funding and sponsorship on economic evaluation outcomes.

The Probiotics to Prevent of Severe Pneumonia and Endotracheal Colonization Trial (PROSPECT)

To answer the question of whether probiotic prophylaxis can prevent healthcare-associated infection like VAP in critically ill patients, the Probiotics to Prevent Severe Pneumonia and Endotracheal Colonization Trial (PROSPECT) was conducted[13–15]. PROSPECT is a randomized, double-blinded multicenter controlled trial (ClinicalTrials.gov number: NCT01782755). PROSPECT used a central system for concealed 1 randomization of patients (in variable unspecified block sizes, stratified by center and by medical, surgical or trauma admission status) to either 1×10^{10} colony forming units (CFU) of *L. rhamnosus* GG (iHealth, Inc.) or an identical placebo suspended in tap water administered twice daily via feeding tube in the ICU. PROSPECT enrolled 2653 critically ill patients between October 2013 and March 2019 throughout 44 ICUs (41 in Canada, 2 in the United States and 1 in Saudi Arabia)[15]. PROSPECT analysis is ongoing and publication of study results is thus pending.

Protocol for a health economic evaluation alongside PROSPECT (E-PROSPECT)

The second component of this thesis centers on the design of a protocol for a health economic evaluation alongside PROSPECT (E-PROSPECT). This study protocol is presented in Chapter 3. I developed this economic evaluation protocol prospectively before PROSPECT results were available to minimize bias and confounding, and maximize efficiency.

Methodological issues addressed in this chapter include: developing a prospective, *a priori* study protocol for a health economic evaluation alongside an RCTs to minimize bias; statistical analysis plan for calculating incremental effectiveness (per-patient event rates or proportions of between group event-rates); calculation of total costs using a bottom-up approach of line-item resource utilization multiplied by mean unit costs estimation from various jurisdictions; justifications for short time-horizons, lack of health-related quality-of-life outcomes and cost-utility analysis; planned uncertainty (non-parametric bootstrapping) and sub-group analyses; and calculation of the cost-effectiveness analyses using incremental costs and effects.

Results of a cost-effectiveness analysis economic evaluation of probiotic prophylaxis to prevent ventilator-associated pneumonia

The third component of this thesis is the cost-effectiveness analysis of PROSPECT (E-PROSPECT). This study is presented in Chapter 4. The recent multi-center blinded trial comparing the effectiveness of probiotics with usual care (probiotics group) versus usual care without probiotics (usual care group)[13–15] has not yet been analyzed. Results of the trial are pending at the time of this thesis submission. Pilot data have been collected for E-PROSPECT

and I have prepared a draft manuscript (along with figures and tables) that will reflect the final E-PROSPECT manuscript.

Methodological issues addressed in this chapter include: pilot testing for acquisition of missing unit costs for various line-item resources; use of imputation or a mean unit cost approach for missing unit costs across jurisdictions; use of "standard" dosage for non-titratable medications and "medium" dosage for titratable medications; assumptions made for estimating resource use; and presentation of outcomes from CEA (resource utilization and mean unit cost tables, cost-effectiveness plane using non-parametric bootstrapping for uncertainty analysis, incremental cost-effectiveness ratios, and cost-effectiveness acceptability curves for various willingness-to-pay thresholds).

Summary of Methodological Issues, Future Directions and Thesis Conclusions

Chapter 5 presents the methodological challenges faced as part of this thesis, and how I addressed them, the strengths and limitations of this work, potential future directions for this research which I plan, and the conclusions of this thesis.

Tables (Chapter 1)

Table 1: Summary of findings from recent systematic reviews assessing probiotic prevention of ventilator-associated pneumonia (2014 to present)

Author & Date	# of RCTs included in MA	# of patients (pooled)	VAP rate reduction (probiotics vs. placebo)	Overall infection rate (probiotics vs. placebo)	ICU Mortality (probiotics vs. placebo)	Hospital Mortality (probiotics vs. placebo)	GRADE used	Methodological Strengths/Limitation
Su 2020	13*** (6 double-blinded RCTs	1975	All studies: OR 0.62 (95% CI: 0.45-0.85; p=0.003) Double-blind RCTs: OR 0.72 (95% CI: 0.44-1.19; p=0.2)	N/A	OR 0.95 (95% CI: 0.67-1.34; p=0.77)	N/A	No	Restricted retrieval strategy, limited data collection for inclusion criteria; methodological quality low; high RoB for individual studies; statistical heterogeneity; potential publication bias
Chen 2018	10***	1403	OR 0.69 (95% CI: 0.54-0.88; p=0.003)	N/A	OR 0.95 (95% CI: 0.67-1.33; p=0.76)	OR 0.86 (95% CI: 0.62-1.18; p=0.35)	No	Unclear to high RoB; potential publication bias; statistical heterogeneity
Weng 2017	13***	1969	RR 0.73 (95% CI: 0.60–0.89; p=0.002)	N/A	RR 0.97 (95% CI: 0.74–1.27; p=0.82)	RR 0.81 (95% CI: 0.65–1.02; p=0.07)	No	Methodological quality low; Unclear to high RoB; failure to detect publication bias; significant heterogeneity
Manazares 2016	30***	2972	RR 0.74 (95% CI: 0.61-0.90, p=0.002	RR 0.80 (95% CI: 0.68-0.95, p=0.009)	N/A	RR 0.98 (95% CI: 0.82-1.18, p=0.85)	No	Potential publication bias; unable to perform subgroup analysis for all clinical outcomes due to limited number of studies
Bo 2014	8***	1083	OR 0.70 (95% CI: 0.52-0.95; p=0.02)	N/A	OR 0.84 (95% CI: 0.58-1.22; p=0.37)	OR 0.78 (95% CI: 0.54-1.14; p=0.20)	Yes	Moderate/higher RoB in half of the studies, low in the other half; statistical heterogeneity

CI: confidence interval, GRADE: Grading of Recommendations, Assessment, Development and Evaluation, ICU: intensive care unit, MA: meta-analysis, N/A: not available, OR: odds ratios, RCT: randomized control trial, RoB: risk of bias, RR: relative risk/risk ratio, VAP: ventilator-associated pneumonia

***Meta-analyses included studies with a wide variety of probiotics strains, daily doses and length of administration of therapy

CHAPTER 2: Manuscript #1 - Probiotics in hospitalized patients: a systematic review of economic evaluations

Manuscript #1 Summary: Based on our systematic review, probiotics may be economically attractive intervention drugs for preventing ventilator-associated pneumonia, *Clostridioides difficile*-associated diarrhea, and antibiotic-associated diarrhea in adult hospitalized patients. However, certainty about cost-effectiveness evidence is very low.

Reference: Lau VI, Rochwerg B, Xie F, Johnstone J, Basmaji J, Balakumaran J, Iansavichene A, Cook DJ. Probiotics in hospitalized adult patients: a systematic review of economic evaluations. *Can J Anesth* Published Online First: 12 November 2019. doi:10.1007/s12630-019-01525-2

Probiotics in hospitalized patients: a systematic review of economic evaluations

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Key Words: Probiotics, critical care, economics, systematic review, infection

Manuscript Word Count: 3000
Abstract Word Count: 248

Competing Interests
Several of our authors (Deborah Cook, Jennie Johnstone, Bram Rochwerg) are co-investigators in PROSPECT (Probiotics: Prevention of Severe Pneumonia and Endotracheal Colonization Trial).

Career Funding
DJ Cook holds a Canada Research Chair in Knowledge Translation in Intensive Care Medicine from the Canadian Institutes of Health Research.

Tweet: "Probiotics appear to be cost-effective for prevention of certain healthcare-associated infections, although the quality of evidence is very low. Future trials examining probiotics should incorporate cost data to inform bedside practice, clinical guidelines and policy makers."

Abstract

Purpose: Probiotics may prevent healthcare-associated infections such as VAP, CDAD, and other adverse outcomes. Despite their potential benefit, there are no summative data examining the cost-effectiveness of probiotics in hospitalized patients. This systematic review (SR) summarized studies evaluating the economic impact of using probiotics in hospitalized adult patients.

Methods: We searched MEDLINE, EMBASE, CENTRAL, ACP Journal Club, and other EBM Reviews (inception to Jan 31, 2019) for health economics evaluations examining the use of probiotics in hospitalized adults. Independently and in duplicate, we extracted data study characteristics, risk of bias, effectiveness and total costs (medications, diagnostics/procedures, devices, personnel, hospital) associated with healthcare-associated infections (VAP, CDAD and AAD). We used Grading of Recommendations Assessment, Development and Evaluation (GRADE) methods to assess certainty in the overall cost-effectiveness evidence.

Results: Of 721 citations identified, we included 7 studies. For the clinical outcomes of interest, there was 1 randomized control trial (RCT)-based health economic evaluation, and 6 model-based health economic evaluations. Probiotics demonstrated favourable cost-effectiveness in 6 of 7 (86%) economic evaluations. Three of the 7 studies were manufacturer-supported, all which suggested cost-effectiveness. Certainty of cost-effectiveness evidence was very low due to risk of bias, imprecision and inconsistency.

Conclusion: Probiotics may be economically attractive intervention drugs for preventing VAP, CDAD, AAD in adult hospitalized patients. However, certainty about their cost-effectiveness evidence is very low. Future RCTs examining probiotics should incorporate cost data to inform bedside practice, clinical guidelines and healthcare policy.

Systematic review registration: PROSPERO CRD42019129929.

Background

Probiotics are defined as "live microorganisms, which when administered in adequate amounts, confer a health benefit on the host."[33] Mechanisms by which probiotics offer potential health benefits are not yet fully elucidated. They may include enhanced gut barrier function, reduced gastrointestinal pathogenic bacterial load through competitive inhibition, modification of the gut microbiome, and modulation of the host immune system. These effects may reduce the incidence of healthcare-associated infections.[17,20]

Probiotics have been studied in randomized controlled trials (RCT) in a variety of conditions in the hospital setting with evidence suggesting benefits, including the reduction of healthcare-associated infections.[21,22] In the intensive care unit (ICU), probiotics have been studied for the prevention of ventilator-associated pneumonia (VAP).[12,20] Multiple probiotic strains (i.e. *Lactobacillus*, *Bifidobacterium, Saccharomyces)* and doses have been systematically reviewed; a meta-analysis reveals a risk reduction of 0.74 for VAP (95% CI: 0.61-0.90, $P = 0.002$), demonstrating a potential effect across species[12]. As the most common healthcare-associated infection in ICU, VAP is associated with a two-fold attributable risk of death, and an attributable cost of USD $10,000–13,000 USD/patient.[6]

Further evidence suggests that probiotics can reduce the incidence of diarrhea, specifically CDAD, which can cause pseudomembranous colitis, toxic megacolon, and death.[29] A Cochrane systematic review (SR) and meta-analysis of 31 RCTs including 8672 patients receiving concurrent administration of probiotics (any dose, any strain) and antibiotics demonstrated that probiotics prevented CDAD as compared with placebo (based on moderate certainty evidence), with heterogeneous evidence for a specific species or dose effect.[29] The cost of treatment for CDAD is expensive ($8911-30,049 USD/patient).[34]

Among critically ill patients, the clinical effectiveness of probiotics in preventing VAP, CDAD, and other infectious outcomes was evaluated in a recently-completed but as yet unpublished multi-center RCT (Probiotics: Prevention of Severe Pneumonia and Endotracheal Colonization Trial - PROSPECT; NCT01782755), with additional RCTs ongoing (PRINCESS: Probiotics to reduce infections in care home residents; ISRCTN16392920).

Health economic evaluations produce important evidence to inform clinical decisions and health policy creation. The objective of this SR is to summarize cost or cost-effectiveness evidence of a broad spectrum of strategies involving probiotics (different doses and strains) in hospitalized adult patients. The research question was: In hospitalized adult patients (population), do probiotics (intervention: any strain, any dose) versus placebo/no treatment (comparator: usual care) demonstrate cost-effectiveness in preventing healthcare-associated infections: VAP, CDAD and AAD?

Methods

Data Sources and Searches

Our search strategy is outlined in Appendix Supplement 1. Searches were performed by a clinical librarian (AI) with experience in conducting electronic literature searches; searches underwent PRESS (Peer Review of Electronic Search Strategies) by a professional librarian and our authors. No publication type or language restrictions were applied.

To identify additional potentially relevant studies, we also checked reference lists of identified articles within our SR search, to examine what source inputs were utilized in their economic evaluations.

Study Selection and Quality Assessment

Two reviewers independently assessed each citation and applied inclusion/exclusion criteria (Figure 1). Two reviewers (VL/JB) independently screened abstracts in the first stage, and full-text screening in the second stage. Disagreements were resolved through a third

reviewer (BR/FX). We listed the characteristics of the included studies (Table 1). Quality of studies was critically appraised (Table 2) using the Joanna Briggs Institute for Critical Appraisal of Economic Evaluations tool[35] and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[36] Our SR has been registered in PROSPERO (international prospective register of systematic reviews): CRD42019129929 (www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=129929). Our SR search commenced before registration, and data extraction was underway (but not completed) when registered (started Jan 31, 2019, registration was April 25, 2019).

Data Extraction

Independently and in duplicate, our reviewers (VL/JB) extracted data using pre-developed abstraction forms (Appendix Supplement 2). We attempted to contact study authors for all study-related data, if not previously published. All currencies were converted to Canadian Dollar (CDN) for the year 2018 utilizing the World Bank Official Exchange Rate.[37] Incremental costs, effectiveness outcomes or cost-effectiveness ratios were presented in Table 3.

Risk of Bias Assessment

Randomized control trials used as data sources for the health economic evaluation were assessed using the Cochrane Collaboration Risk of Bias (ROB) tool.[38] Non-randomized trials were assessed using the Newcastle-Ottawa Scale (NOS).[39] Surveys were assessed using the ROB tool from the McMaster University Clinical Advances Through Research and Information Translation (CLARITY).[40] The assessment schemas are found in Appendix Supplement 3 or in the footnotes of Appendix Supplement 4A-D.

For model-based economic designs, we assessed ROB in the contributing inputs from multiple source studies for the models. We decided *a priori* that, if each source input in a particular economic model had low ROB, the overall model would likely have a low ROB (even for varied types of studies: RCTs to surveys). If any source study had an unknown/high ROB (identified as the weakest link), the entire economic evaluation would be assessed an unknown/high ROB. For source articles drawn from SRs, guidelines documents or economic evaluations, we did not assess ROB unless that source was not previously assessed in Appendix Supplement 4A-D. We did not assess ROB when data were derived from an externally established public database (i.e. Consumer Price Index).

Data Synthesis and Analysis

We summarized the economic evaluation data (e.g. resource utilization, costs, cost-effectiveness ratios) in terms of point estimates and 95% CIs or ranges, if available. Categorical variables were reported as counts/proportions. Given the heterogeneity among the included studies, we could not conduct a meta-analysis. This review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines.[41]

Grading of Recommendations Assessment, Development and Evaluation (GRADE)

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Table 4) to assess the following domains: ROB, indirectness, imprecision, inconsistency and other considerations. Certainty in evidence from RCTs started as high, while observational studies started as low. Final quality was rated: high, moderate, low or very low[42].

Results

Study Comparisons, Populations and Format

Out of 721 records identified through database searches, 147 duplicates were removed and 526 excluded based on the title/abstract as irrelevant. The full-text of 48 papers was retrieved for comprehensive evaluation, of which 41 were excluded (Figure 1).

Of 7 studies included in this SR (Table 1), 1 study was a RCT-based cost-effectiveness analysis (CEA)[10]. Six studies were model-based economic evaluation using cost-effectiveness analysis (CEA) or incremental cost[43–48]. Two also reported cost-utility analysis (CUA).[43,47] One evaluation investigated VAP;[10] 6 investigated CDAD,[43–48] and 3 investigated AAD.[43,46,48]

Study Perspectives, Time Horizon and Funding

Three studies were conducted in the United States,[10,44,47] 2 in the United Kingdom,[43,46]1 in Canada,[30] and 1 in Belgium.[33] Four studies were conducted from the societal perspective[10,43,48] (aggregation of all perspectives, taking into account time costs, opportunity costs and community preferences: i.e. patient, payer, hospital)[49] and 7 from the perspective of a specific payer (4 public, 3 private payers).[10,43–48] The time horizon (duration of time for follow-up, over which health outcomes and costs are calculated) ranged from 3-52 weeks. A probiotic manufacturer supported 3 of 7 (43%) studies.[20,22,24]

Study Quality and **Risk of Bias**

Study quality is summarized in Table 2. Two studies obtained effectiveness data from meta-analysis,[21,23] while 7 studies obtained data from RCTs or observational trials.[18–24] All performed sensitivity analyses.[18–24]

For assessing ROB in RCTs (Appendix Supplement 4A), 3 studies[43–45] had a low ROB, while 4 studies[27,31,32,34] had unclear/high ROB. Common ROB issues were: selection, performance, detection, attrition and reporting bias. For observational study ROB (Appendix Supplement 4B), there were 6 high quality cohort observational studies,[26–31] and 10 low quality cohort study[32–40]. Common ROB were: selection (only selected group of patients for representativeness of intervention cohort, no description of non-exposed non-intervention cohort, and no demonstration that outcome of interest was not present at start of study), comparability (study did not control for age, antibiotic/probiotic exposure /additional factors), and outcome (short follow-up).

For case-control studies ROB (Appendix Supplement 4C), there was 1 high quality study,[41] and 1 low quality study[42]. Common ROB were: selection (no description of case definition, representativeness shows potential for selection bias, no description of control – case-study only, no description of source), comparability (study did not control for age, antibiotic/probiotic exposure/additional factors), and outcome (no method of ascertainment for controls, non-response rate and different with no designation).

For surveys ROB (Appendix Supplement 4D), there was 2 high quality studies,[43,44] with 2 studies with a mix of low/high ROB.[18,45] Common ROB issues were: low response rates (<50%), missing data (>15% within questionnaires), no evidence of reliability/validity for survey instrument).

Cost and Effect Estimates

The cost and effect estimates are shown in Table 3. Individual natural units and unit cost per resource are presented in Appendix Supplement 5.

<u>Ventilator Associated Pneumonia</u>

One evaluation investigated VAP (Table 3). Using a Markov model for a cost-benefit analysis, prophylactic probiotics (with subglottic endotracheal tubes) demonstrated cost benefit for preventing VAP, with a willingness-to-pay (WTP) of $50,000-100,000 USD ($70,807-141,614 CDN) per case of VAP averted (median cost estimate of $15,958 [$7000-35,000] ($22,623 CDN [$9913-49,566]) per VAP case). The incremental cost-effectiveness ratio (ICER) between

probiotics and no probiotics showed dominance of probiotics over placebo (with usual care). Sensitivity analysis showed continued dominance in a multiple scenarios (reducing cost of VAP, increasing hourly nursing wages). There was a substantial increase in cost savings with probiotics when VAP risk reduction was increased versus placebo.[10]

Clostridioides-difficile Associated Diarrhea

Among 6 studies examining the cost-effectiveness of probiotics in CDAD (Table 3), 4 studies found probiotics to be cost-effective/incremental cost-saving,[20,22–24] one study showed no difference[43], and one study showed cost-effectiveness in certain scenarios.[47]

Fansi et al. found a cost-savings dose response for probiotics vs. placebo. There was cost-savings of $1968 USD ($2152.40 CDN) for a single dose of probiotics (per CDAD case prevented) compared to placebo. For a double dose of probiotics per day, there was $2661 USD ($2910.34 CDN) cost-savings when compared to placebo.[20] Leal et al. demonstrated cost-savings of $538.25 CAD per patient ($339.78 CAD for probiotics vs. $878.03 CAD for usual care) for CDAD.[45]

Shen et al. demonstrated a cost-savings of $840 USD ($1150.27 CDN) per case of CDAD averted, with dominance of probiotics (lower cost, higher effectiveness) in the base case. However, there were scenarios (i.e. young patients) in which the ICER was not cost-effective [(age 18-44, CDAD risk 0.6%: ICER $884,100 USD/quality-adjusted life-year (QALY) ($1,196,609 CDN/QALY)].[47] Furthermore, Allen et al. showed there was no difference in total health-care costs between probiotics (£8020 GBP; 95% CI: £7620-8420) ($15,629 CDN; 95% CI $14,850-16,409) and placebo (£8010 GBP; 95% CI: £7600-8420) ($15,601 CDN; 95% CI $14,811-16,409).[43]

Antibiotic-Associated Diarrhea

Among 3 studies examining the cost-effectiveness of probiotics for AAD (Table 3), 2 studies found probiotics to be cost-effective,[22,24] with one study showing no difference between probiotics and placebo.[19]

Lenoir-Wijnkoop et al. showed a mean cost-savings of £339 GBP ($642.94 CDN) per hospitalized patients for probiotics vs. no treatment for prevention of AAD.[22] Vermeesch et al. found cost savings of €50.30 [$75.74 CDN] using a bottom-up approach and €28.10 [$42.31 CDN] (top-down) per AAD patient treated with antibiotics for a payer's perspective. From a hospital/societal perspective, there was cost savings of €95.20 [$143.35 CDN] (bottom-up) and €14.70 [$22.13 CDN] (top-down) per AAD patient treated with probiotics.[19]

Conversely, Allen et al. found that probiotics were not cost-effective, with an ICER for AAD prevention of £4531.36 GBP [£3439.80-5622.92] ($8830.58 CDN [6703.39-10957.79]), and a base-case cost-utility of £189,662 ($369,608 CDN) per QALY, for a willingness-to-pay threshold of <£20,000 ($38,975 CDN)/QALY.[19]

Sponsorship, Economic Perspective, Trial vs. Model Based, and Placebo vs. No Probiotic Subgroup Comparisons

Overall, of the 7 studies included, 6 (86%) economic evaluations favoured probiotics as cost-effective/cost-savings in the base case. Three studies (43%) were sponsored by the manufacturer (*Lactobacillus acidophilus/casei/paracasei)*. All 3 reported favourable findings towards probiotics. Three of 4 studies without manufacturer sponsorship favoured probiotics. Publication bias cannot be excluded.

The 1 trial-based economic evaluation did not show cost-effectiveness for its outcome[43], while all 6 model-based evaluations showed cost-effectiveness in their base cases and certain sensitivity analyses[10,44–48]. For economic perspective subgroups, 6 of 7 (86%) payer perspectives were cost-effective, while 2 of 3 (66%) of societal perspectives were cost-effective. For comparators control arms (placebo vs. no probiotic subgroups), 2 of 3 (66%) with placebo

control arms were cost-effective, while 4 of 4 (100%) with no treatment/usual care control arms were cost-effective.

GRADE Assessment

The GRADE assessment[46] (Table 4) found very low certainty of evidence for probiotic use for VAP, CDAD and AAD.

The outcome of VAP included 1 model-based economic evaluation. We downgraded for ROB (serious ROB from multiple model inputs with unclear/high ROB) and imprecision (serious for only 1 study in analysis).[10]

The outcome of CDAD included 6 health economic evaluations (1 RCT-based and 5 model-based). We downgraded for ROB (serious: multiple model inputs with unclear/high ROB), inconsistency (serious: 1 not cost-effective, 5 cost-effective) and imprecision (confidence interval crosses zero for one RCT economic evaluation, with many small studies included).[19–24]

The outcome of AAD included 3 health economic evaluations (1 RCT-based and 2 model-based). We downgraded for ROB (serious: multiple model inputs with unclear/high ROB), inconsistency (serious: 1 study not cost-effective, while 2 studies cost-effective) and imprecision (serious: confidence intervals crossing zero the largest RCT to date, with many small studies included).[19,22,24]

Discussion

In this SR of economic evaluations of probiotics in hospitalized adult patients, we found that most of the studies suggest probiotics are cost-saving/cost-effective in preventing VAP, CDAD or AAD.[18–24] However, the largest trial-based RCT paired with a health economic evaluation to date found no difference in clinical outcomes, and no cost-effectiveness/cost-utility[43]. The conclusions drawn from the collective studies in this SR are based on very low certainty evidence from the ROB and GRADE assessments, precluding strong inferences or definitive recommendations regarding probiotics.

We found no prior SRs focused on economic evaluations of probiotic prophylaxis in hospitalized patients, hence we conducted our own. Among economic evaluations included in this review, incremental costs/ICERs were expressed in costs per healthcare-associated infection event prevented, but heterogeneity in reporting prevented meta-analysis conduction. Further, variable time horizons make comparisons of economic evaluations problematic (specifically ICERs) as costs and resource utilization may change over different time **horizons.** Changes in time horizons or perspectives can lead to differing parameters (costs [direct vs. indirect], or outcomes [patient vs. payer]). Many studies only reported incremental costs, rather than true ICERs. Results from different perspectives, time horizons and variable incremental cost reporting all represent disparate cost outcomes, which need to be interpreted carefully within context.

Moreover, there are large ranges in WTP, which are difficult to interpret with no conventional WTP benchmarks for prevention of VAP, CDAD, and AAD. Different countries may differ on values quality of life and WTP, making benchmarks difficult to establish across jurisdictions. Cost-utility parameters (like cost per life-year or QALY gained) were less commonly reported. If cost per QALYs were available, it would help to inform economic comparisons with other healthcare interventions.

Compared to other infection-prevention strategies, probiotics appear to be similarly cost-effective. A study examining concomitantly administered central-line associated bloodstream infection (CLABSIs) and VAP programs combined documented ICERs of $14,250.74 USD ($20,533.24 CDN)/life-year gained and $23,277.86 ($33,540.02 CDN)/QALY.[47] Multifaceted quality improvement programs for reducing CLABSIs in ICUs have demonstrated dominance (lower cost, higher effectiveness) in 80% of model scenarios using probabilistic sensitivity analysis.[48] A proactive model infection-control program for multi-drug resistant (MDR) organisms

in general-surgical ICUs showed and ICER of $3804 USD ($5320.01 CDN) per case averted of transmission of MDR organisms in 1 year compared with standard infection control. For a WTP threshold of $14,000 USD ($19,579.43 CDN) per transmission averted, there is a 42% probability of being cost-effective, and 100% probability when WTP thresholds were $22,000 USD ($30,767.68 CDN).[49] These similarities suggest that adoption of probiotics for prevention of healthcare-associated infections could be cost-effective.

New interventions studied in economic evaluations are occasionally sponsored by drug manufacturers. This potentially introduces bias in model construction and interpretation of results. In a retrospective analysis of 107 studies in 5 leading medical journals with regard to outcome and sources of funding, trials sponsored by pharmaceutical companies were more likely to favour the new drug over traditional therapy.[50,51]

In our SR, 3 studies were funded by manufacturers and all found the sponsored intervention to be more economically attractive, which could suggest potential publication bias (although this does not prove its presence). This is tempered by 3 of 4 peer-review funded studies that also demonstrated cost-effectiveness. Hence, methodologically rigorous trials with concomitant economic evaluations from peer-review funded studies are needed to ensure proper interpretation of results.

Strengths of our review include adherence to rigorous methodology, consisting of a comprehensive search strategy, broad eligibility criteria, and study selection by 2 independent adjudicators to minimize selection bias.[42] We conducted data abstraction and appraisal in duplicate, using established criteria for assessing economic evaluations.[11] We performed assessments of study quality employing ROB assessments, including assessment of source studies utilized in model-based economic evaluations[38–40] We performed assessment of level of certainty using GRADE.[42] We also addressed the relationship of for-profit industry sponsorship potentially influencing the reporting of economic evaluations.

This review also has limitations. The inclusion of only 7 studies influences precision. Rare product-specific complications such as probiotic-induced complications (i.e. bacteremia) are unclear, underscoring need for additional safety data. Overall GRADE certainty of evidence was very low for all outcomes, rendering conclusions non-definitive. Our review included only adult patients and may not be applicable to pediatric populations. Reports that were evaluated varied widely with respect to patient population, time-horizon of therapy, and payer perspective, which challenges the generalizability and interpretation of these findings.

Conclusion

This SR found that probiotics may be an economically attractive strategy for the prevention of healthcare-associated infections in most studies. However, our GRADE summary indicates a very low quality/certainty of evidence, such that inferences are weak regarding the health economic evaluation of probiotics in adult hospitalized patients. Future RCTs should include concomitant economic evaluations, including clinical outcomes and costs associated with probiotics, to inform bedside practice, clinical guidelines, and healthcare policy. To this end, an economic evaluation of PROSPECT (E-PROSPECT) is planned.

Acknowledgements

We are grateful to the Canadian Critical Care Trials Group (CCCTG) and the Canadian Institute of Health Research (CIHR) who have supported PROSPECT. We also thank Juanita Meyer (Library Services, London Health Sciences Center) for her assistance with the full-text acquisition and search strategy.

Author Contributions

Vincent Lau, Bram Rochwerg, Feng Xie, John Basmaji, Jana Balakumaran, Alla Iansavichene, Jennie Johnstone and Deborah Cook have: (1) made substantial contributions to

conception and design, acquisition of data, analysis and interpretation of data; (2) drafted the submitted article and revised it critically for important intellectual content, and (3) provided final approval of the version to be published.
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Tables

Table 1: Summary of Health Economic Studies of Probiotics

Study	Study Design	Patient Population	Economic Perspective	Time Horizon	Comparison	Cost (Currency/Year)	Primary Clinical Outcome	Primary Economic Outcome
Trial Based Health Economic Analysis								
Allen et. al (2013)	Cost-effectiveness Cost-utility (trial based economic analysis)	Elderly hospitalized adults >65 years (medical, surgical) treated with antibiotics	Payer, Societal	12 weeks	*Lactobacillus* or *Bifidobacterium* vs. placebo	British £ (2012)	AAD CDAD	Total health-care costs ICER cost for AAD ICER per QALY
Model Based Health Economic Analysis								
Branch-Elliman et. al (2015)	Cost-benefit analysis Cost-effectiveness analysis (model based decision tree analysis)	Adult medical-surgical patients (mechanical ventilation >12 hours)	Payer, Societal	4 weeks	Probiotics, subglottic endotracheal tubes, VAP prevention bundles, chlorhexedine oral care, selective oral decontamination, selective gut decontamination, silver endotracheal tubes	USD $ (2013)	VAP	Cost-benefit ratio per VAP prevented
Fansi et. al (2012)* **	Cost-effectiveness (model based decision tree analysis)	Adult hospitalized patients (50-70 years), hospitalization of 5 or more days, and antibiotic therapy of at least 3 days but no more than 14 days	Payer	3 weeks	*Lactobacillus acidophilus/casei* vs. placebo	USD $ (2009)	CDAD	Cost savings per dose
Leal et. al (2016)	Cost-effectiveness analysis (model based decision tree analysis)	Adult (>18 years) hospitalized patients treated with antibiotics	Payer	4 weeks	*Lactobacillus acidophilus/casei* vs. no treatment	CDN $ (2015)	CDAD	Cost savings per CDAD avoided
Lenoir-Wijnkoop et. al (2014) * **	Cost-effectiveness (model based decision tree analysis)	Elderly hospitalized patients (>65 years) treated with antibiotics	Payer	Until recovery/ death	Fermented milk (FM) with *Lactobacillus paracasei* vs. placebo	British £ (2010)	AAD CDAD	Cost savings per AAD avoided
Shen et. al (2017)	Cost-effectiveness Cost-utility (model based decision tree analysis)	Hospitalized adults (mean age: 68 years)	Payer	52 weeks	*Lactobacillus acidophilus/casei/Saccharomyces boulardii* vs. no treatment	USD $ (2013)	CDAD	ICER cost for CDAD ICER per QALY
Vermeersch et. al * (2018)**	Cost-effectiveness (model based decision tree analysis)	Hospitalized adults (mean age: 68 years)	Payer/ Societal	Until hospital discharge/death	*Saccharomyces boulardii* vs. no treatment	Euro € (2017)	AAD (non-complicated) CDAD (complicated)	Cost savings per patient for AAD &. CDAD

AAD: Antibiotic associated diarrhea, **CDAD**: Clostridium Difficile associated diarrhea, **CDN**: Canadian, **CFU**: colony-forming units, **GBP**: Great Britain Pound, **ICER**: incremental cost-effectiveness ratio, **ICU**: intensive care unit, **FM:** fermented milk, **NR**: not reported, **RCT**: randomized control trial, **QALY**: quality-adjusted life year, **USD**: United States Dollar, **VAP**: ventilator-associated pneumonia

***** - industry sponsored study**

Table 2: Critical appraisal of study articles (modified Joanna Briggs Institute Critical Appraisal Tool for Economic Evaluations)

Paper	Were the outcomes accurately measured?	Were the costs accurately measured?	Do incremental costs and outcomes differ between subgroups?	Are prophylaxis benefits worth the harm and costs?	Generalizability: could other patient populations expect similar outcomes?	Generalizability: could other patient populations expect to experience similar costs?
Allen et. al (2013)	Yes	Yes - data from literature, databases, reference costs	Yes	Equivocal (no benefit and no difference in cost)	Yes	Yes
Branch-Elliman et. al (2015)	Yes	Yes - data from literature, databases, reference costs	Yes	Yes	Yes	Yes
Fansi et. al* (2012)**	Yes	Yes – data from a hospital, consumer price index, pharmacy Red Book	Yes	Yes	Yes	Yes
Leal et. al (2016)	Yes	Yes - data from literature, Alberta pharmacy and infection control, laboratory services, consumer price index	Yes	Yes	Yes	Yes
Lenoir-Wijnkoop et. al* (2014)**	Yes	Yes - data from literature and local price lists	Yes	Yes	Yes	Yes
Shen et. al (2017)	Yes	Yes - data from literature, databases, consumer price index	Yes	Yes	Yes	Yes
Vermeersch et. al* (2018)**	Yes	Yes - data from literature, databases, consumer price index	Yes	Yes	Yes	Yes

NR: not reported

***** - industry sponsored study**

- Modified from the Joanna Briggs Institute Critical Appraisal Tool for Economic Evaluations (Gomersall et al.)

Table 3: Incremental costs, effects and cost efficacy ratios for the probiotics vs. comparator (placebo/no treatment/usual care)

Reference	Costs **Inputs**	**Clinical Effects Inputs** (healthcare-associated infections avoided, life-years or QALYS gained)	**Incremental Outputs** (**Incremental Costs, Incremental Cost Benefit or Cost Effectiveness Ratios -** cost per healthcare associated-infection avoided or life-years or QALYS gained)	Subgroup Analysis	Sensitivity Analysis	Most economically attractive drug
Allen et. al (2013)	Total health-care costs per patient did not differ significantly between the probiotic (£8020; 95% CI £7620 to £8420) & placebo arms (£8010; 95% CI: £7600 to £8420) Probiotics: ($15629 CDN; 95% CI $14850 to $16409) Placebo: ($15601 CDN; 95% CI $14811 to $16409)	Probiotics and occurrence of AAD/CDAD: No difference with probiotics usage and placebo for AAD (10.8 v.10.4%), RR 1.04 [95% CI: 0.84-1.28, p=0.71] or CDAD: Probiotics (12/1470, 0.8%), vs. Placebo (17/1491, 1.2%), RR 0.71 [95% CI: 0.34-1.47, p=0.35]	**Incremental Cost** (AAD): **£8.74 GBP [95% CI: −£4.32-21.78]** **$17.03 CDN [95% CI: -8.42-42.44]** **ICER:** Base Case Analysis: **£22,701 GBP** per QALY **($44,239.07 CDN** per QALY)	Yes	Yes	No difference (base case)
Branch-Elliman et. al (2015)	VAP: $15,975 USD [$7000-35000] per case ($22,623 CDN [$9913-49566]) Probiotics cost: $2.18 USD [Range: $1-10] ($3.09 CDN [Range: $1.42-14.16])	Primary outcome: VAP risk reduction (RR): 0.48 (Range: 0.1-0.9) (Model effects inputs: 83.8% ICU survivors, 20% VAP, 15.4% mortality, 1% remained in ICU)	**Incremental cost benefit ratio**: Low estimate for VAP: $7000-14,000 USD ($9913-19826 CDN) vs. willingness to pay threshold of $50,000-100,000 ($70,809-141,617 CDN) per VAP case Prophylactic probiotics and subglottic endotracheal tube are cost-effective for preventing VAP	Yes	Yes	Probiotics, suction ETT, VAP Bundle (base case)
Fansi et. al (2012)* **	Hospital care for CDAD patient (per day hospitalized): $1424.16 USD ($2016.85 CDN) $2.50 USD ($3.55 CDN) (Lactobacillus acidophilus/casei, per dose - unit)	Probiotic-double dose (Pro-2) (15.5%) lower AAD vs. Probiotic-single dose (Pro-1) (28.2%) with each probiotic lower AAD incidence vs. placebo (44.1%). In patients with AAD, Pro-2 (2.8 days) & Pro-1 (4.1 days) had shorter symptom duration vs. placebo (6.4 days). Pro-2 (1.2%) had lower CDAD incidence vs. Pro-1 (9.4%). Each treatment group had a lower CDAD incidence vs. placebo (23.8%). Gastrointestinal symptoms were less common in the treatment groups vs. placebo and in Pro-2 vs. Pro-1.	Estimated mean per patients savings **(incremental cost)**: $1968 USD ($2152.40 CDN) - single dose $2661 USD ($2910.34 CDN) - double dose vs. compared with the placebo option (if used an average of 13 days by all patients at risk of developing AAD and CDAD)	Yes	Yes	Probiotics (base case)
Leal et. al (2016)	Cost of probiotics: $24 CDN CDN/treatment (2018): $24.94 CDN Costs of CDAD: $11,862 CDN ($12326.60 CDN 2018)	Risk of CDAD vs. cost of probiotics Lower risk of CDI: 5.5 vs. 2.0%	**Incremental Cost:** Cost savings: $518 CDN ($538.25 CDN 2018)/patient Patients treated with oral probiotics lower overall cost compared with usual care (CDN $327 [$339.78 CDN 2018] vs. $845 [$878.03 CDN 2018])	Yes	Yes	Probiotics (base case)
Lenoir-Wijnkoop et. al (2014)* **	Non-severe CDAD patient (1st, 2nd, 3rd line): £2502, £3104, £2808 GBP ($4745.24, $5586.98, $5225.59 CDN) Severe CDAD patient (1st, 2nd, 3rd line): £6292, £6236, £5110 GBP ($11933.27, $11827.06, $9691.51 CDN)	Probiotic group, 12% (7/57) developed AAD compared to 34% (19/56) in the placebo group (P = 0.007). None of the patients randomized to the FM with probiotic developed CDAD, while 17% (9/53) in the placebo group developed CDAD (P = 0.001). Risk ratio (RR) for the total population from Hickson's study was 0.35 (12/34)	**Incremental cost**: Probiotic intervention to prevent AAD generated estimated mean cost savings of £339 ($642.94 CDN) per hospitalized patient over the age of 65 years and treated with antibiotics, compared to no preventive probiotic. **Incremental cost savings**: £243 ($460.87 CDN)/case treated with antibiotics by preventing non-CDAD £96 ($182.07)/case treated with antibiotics through preventing CDAD	Yes	Yes	Probiotics (base case)
Shen et. al (2017)	CDAD (inpatient cost per case): $7670 USD [3830-11500] CDAD (outpatient cost per	Probiotic efficacy vs. no treatment: <0.73 RR, baseline risk CDAD>1.6%, risk of probiotic-associated	**Incremental cost**: Cost savings of $840 USD ($1150.27 CDN)/case of CDAD averted **Base Case (Age 65-84, CDI risk 2.9%):**	Yes	Yes	Probiotics **(in certain scenarios: Base case - age 65-84**

	case): $440 USD [210-620] CDAD (inpatient cost per case): $10502.98 CDN [5244.65-15747.62] CDAD (outpatient cost per case): 602.52 CDN [287.57-849.00]	bacteremia/fungemia (<0.26%)	**Probiotics dominant (-$13 USD incremental cost [$17.60 CDN], +0.00005 QALYs) - Probiotics dominated no probiotics (less costly, greater QALYs)** **ICERs (scenarios): Probiotics RR 0.51 (WTP: $100,000 USD ($135,348 CDN))** **Age 18-44, CDI risk 0.6%: ICER $884,100 USD/QALY ($1,196,609 CDN/QALY) - not cost effective** **Age 45-64, CDI risk 1.5%: ICER $156,100 USD/QALY ($211,277.73 CDN/QALY) - not cost effective** **Age 65-84, CDI risk 1.2%: ICER $1,257,100 USD/QALY ($1,701,455.69 CDN/QALY) - not cost effective** **Age >85, CDI risk 3.8%: Probiotics dominant (-$31 USD incremental cost [$41.96 CDN], +0.00014 QALYs)** **ICER:** $19,200 USD ($26,291.70 CDN)/QALY if baseline CDAD risk was low <1.2%			**& CDI risk 2.9%, Age >85, CDI risk 3.8%)**
Vermeersch et. al* (2018)**	AAD – non-complicated (cost per case): €277 Euros [$417.90 CDN] (hospital)- €2150.3 [3237.78 CDN] (societal) CDAD - complicated (inpatient cost per case): €588.8 Euros [$886.58 CDN] (hospital)- €2239.1 [$3371.49 CDN] (societal)	Base case: AAD: 9.6% (71/743 patients), CDAD 5.6% (4/71 AAD patients) AAD RRR 48% *S. boulardii* vs. no treatment CDAD RRR 47% *S. boulardii* vs. no treatment	**Incremental Cost:** Cost savings of €50.3 Euros [$75.74 CDN] (bottom-up) and €28.1 [$42.31 CDN] (top-down) per AAD patient treated with antibiotics (health care provider) **Incremental Cost:** Cost savings of €95.2 Euros [$143.35 CDN] (bottom-up) and €14.7 [$22.13 CDN] (top-down) per AAD patient treated with antibiotics (hospital/societal)	Yes	Yes	Probiotics (base case)

AAD: Antibiotic associated diarrhea**, CDAD:** *Clostridium Difficile* associated diarrhea, **CDN:** Canadian Dollar, **ETT:** Endotracheal tube, **GBP:** Great Britain Pound, **RR:** risk reduction, **RRR:** relative risk reduction, **US:** United States, **VAP:** ventilator associated pneumonia, **WTP**: willingness-to-pay threshold

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Adjusted to Canadian Dollar (CDN) - 2018

Table 4: Grading of Recommendations Assessment, Development and Evaluation (GRADE) of Probiotics Systematic Review Outcomes: VAP, CDAD, AAD.

Author(s): Vincent Lau, Bram Rochwerg, Feng Xie, Jennie Johnstone, John Basmaji, Jana Balakumaran, Alla Iansavichene, Deborah J. Cook
Date: July 30, 2019
Question: Probiotic compared to no probiotic/no treatment/usual care for as a cost-effective intervention to prevent adverse sequelae of antibiotics (healthcare associated infections)
Setting: Hospitalized adult patients

Certainty assessment							Impact	Certainty	Importance
№ of studies	**Study design (sources)**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Prevention of ventilator associated pneumonia (VAP)[1]									
1	1 model based health economic evaluation (observational studies)[a]	serious [b]	not serious	not serious	serious	none	Branch-Elliman *et al.* constructed a cost-benefit decision model with a Markov model based on multicenter observational data. One hundred twenty unique combinations of VAP prevention strategies were examined. Probiotics, along with subglottic suction ET tubes, and the Institute for healthcare Improvement VAP Prevention Bundle was the preferred strategy for best cost-benefit ratio.	⊕◯◯◯ Very Low	CRITICAL
Prevention of *Clostridium Difficile* associated diarrhea (CDAD)[2-7]									
6	6 model based health economic evaluations (randomised and observational trials)[b], 1 RCT based health economic evaluation	serious [b]	serious [c]	not serious	serious [d]	none	*Allen et al. concluded no difference in total health-care costs per patient the probiotic & placebo arms. All other studies concluded that probiotic was a cost-effective intervention to prevent CDAD. On this basis, there were serious concerns about inconsistency.* *Allen et al. suggested that probiotic reduces and increase risk of CDAD (RR 0.71 [95% CI: 0.34-1.47, p=0.35]). This, in addition to the weight of the study based on the sample size, raised serious concerns about imprecision.*	⊕◯◯◯ Very Low	CRITICAL
Prevention of antibiotic associated diarrhea (AAD)[2,5,7]									
3	3 model based health economic evaluations (randomised and observational trials)[e], 1 RCT based health economic evaluation	serious [b]	serious [c]	not serious	serious [d]	none	*In the PLACIDE study, Allen et al concluded no difference in total health-care costs per patient the probiotic & placebo arms. All other studies concluded that probiotic was a cost-effective intervention to prevent AAD. On this basis, there were serious concerns about inconsistency.* *The PLACIDE study suggested that probiotic reduces and increase risk of AAD (RR 1.04 [95% CI: 0.84-1.28, p=0.71]). This, in addition to the weight of the study based on the sample size, raised serious concerns about imprecision.*	⊕◯◯◯ Very Low	CRITICAL

AAD: antibiotic associated diarrhea, **CDAD:** *Clostridium Difficile* associated diarrhea, **CI:** Confidence interval, **ET:** endotracheal tube, **RCT:** randomized control trial**, RR:** relative risk, **VAP:** ventilator-associated pneumonia

Explanations

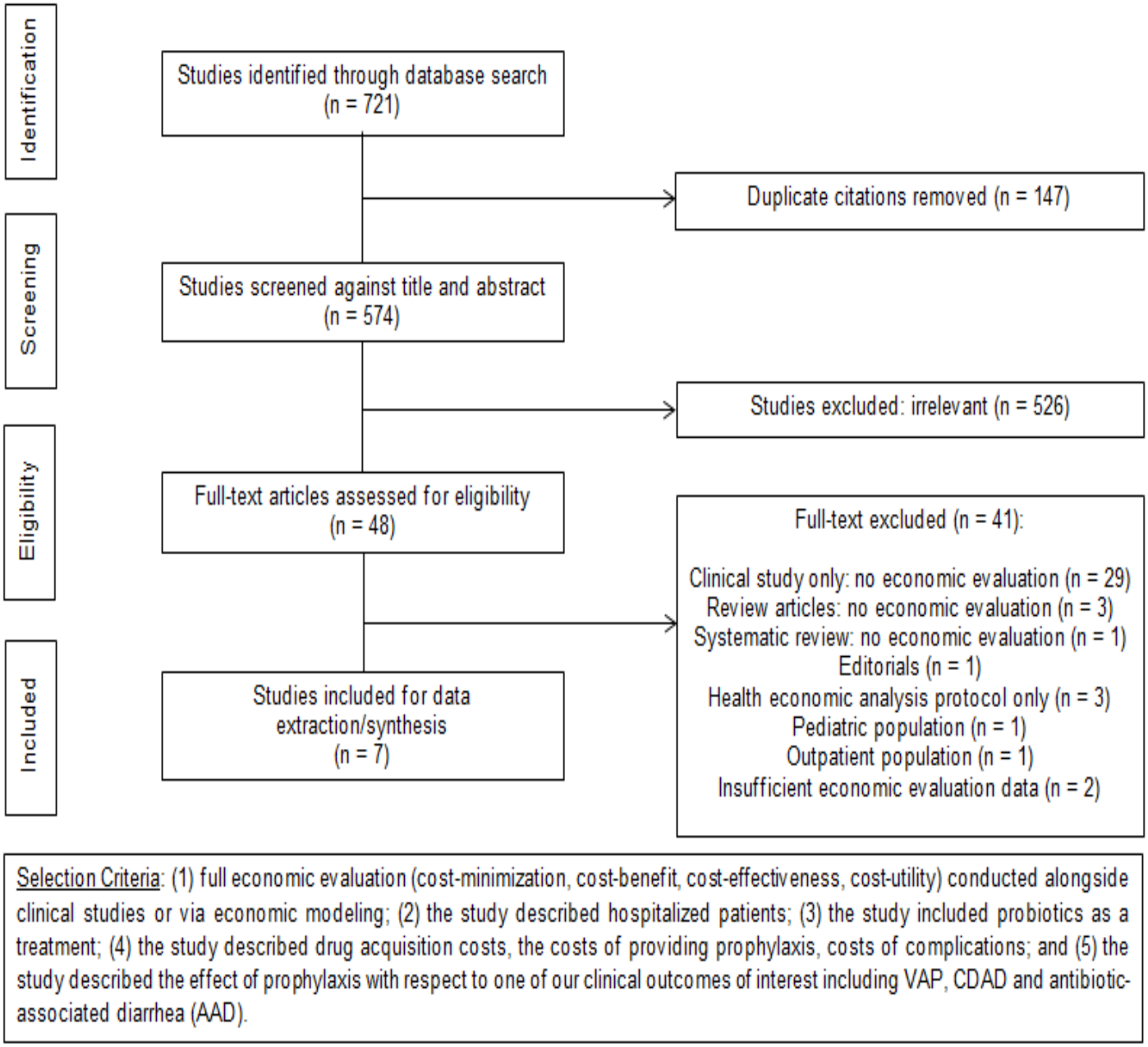
a. Decision tree analysis with observational studies as input (no RCTs)

b. Multiple source data, observational cohort/case-control studies, and surveys had high risk of bias which downgraded this category

c. Inconsistency came from one study (Allen et al.) found no benefit in the use of probiotics to prevent CDAD, and concluded that they were not cost effective, while all other studies concluded that probiotics had a benefit for AAD/CDAD. There was no pooled estimate with a 95% CI, as the outcomes for some of the studies were not available or were too heterogeneous to pool (i.e. cost per treatment (with multiple dose regimens of probiotics) vs. incremental cost-effectiveness ratios vs. cost-utility vs. cost-savings).
d. Confidence interval crosses 0 for Allen et al. study, and many of the included studies were small
e. Included RCT, decision tree analysis, and systematic reviews/meta-analyses was used for source data (6 RCTs)

Figures

Figure 1: E-PROSPECT PRISMA Flow Diagram



Selection Criteria: (1) full economic evaluation (cost-minimization, cost-benefit, cost-effectiveness, cost-utility) conducted alongside clinical studies or via economic modeling; (2) the study described hospitalized patients; (3) the study included probiotics as a treatment; (4) the study described drug acquisition costs, the costs of providing prophylaxis, costs of complications; and (5) the study described the effect of prophylaxis with respect to one of our clinical outcomes of interest including VAP, CDAD and antibiotic-associated diarrhea (AAD).

Appendix

Appendix Supplement 1: Search strategy

We searched Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica database **(**Embase**)**, American College of Physicians (ACP) Journal Club, and Cochrane Central Register of Controlled Trials (CENTRAL) electronic databases via Ovid interface from inception to Jan 31, 2019. We also searched Evidence Based Medicine (EBM) Reviews' selected subset of Economic Evaluation databases (Database of Abstracts of Reviews of Effects (DARE) and NHS Economic Evaluation Database (NHS EED)) from inception to first quarter of 2016 (latest date of creation for all records within database-archived version).

A sensitive search strategy (Appendix 1) identified relevant economic evaluation studies using of probiotics for prophylaxis in hospitalized adults (age ≥18 years) and was based on a combination of the following subject headings and free-text keywords using alternative word spellings and endings: *probiotics, synbiotics, costs, cost analysis, economics, economic analysis/evaluation, critical illness, intensive care units, hospital units, inpatients, and hospitalization.*

Database: Ovid MEDLINE(R) ALL <1946 to Jan 31, 2019> (Jan 31th, 2019)

Search Strategy:

---

1 probiotics/ or synbiotics/ or exp Lactobacillus/ or exp Bifidobacterium/ (36082)
2 (probiotic$ or synbiotic$ or bifidus$ or bifidogenic$ or bifido$ or bifidobacter$ or bifido-bacter$ or lactobacill$).mp. or (beneficial adj3 bacter$).tw,kw. (52541)
3 or/1-2 (52541)
4 exp "Costs and Cost Analysis"/ or exp Economic Evaluation/ or exp Pharmacoeconomics/ or exp Economics, hospital/ or exp Economics, medical/ or Economics/ or exp models, economic/ or "Value of Life"/ or ec.fs. (491561)
5 (cost$ or economic$ or reimburs$ or pharmacoeconomic$).tw,kw. (709720)
6 ((value or values or valuation) adj2 (money or monetary or life or lives)).tw,kw. (4462)
7 ((((willingness adj1 pay) or sensitivity) adj analys?s) or quality adjusted life expectanc$).tw,kw. (26864)
8 or/4-7 (1015053)
9 3 and 8 (1330)
10 (decision adj1 (tree$ or analy$ or model$)).ti,ab. (14725)
11 "Quality of Life"/ or (QOL or QOLY or QOLYs or HRQOL or QALY or QALYs).ti,ab. or (quality$ adj2 life$).tw. (285029)
12 quality-adjusted life years/ or (life year$ adj3 (adjusted$ or quality-adjusted$)).tw. (16544)
13 or/10-12 (301202)
14 3 and 13 (502)
15 limit 3 to "economics (best balance of sensitivity and specificity)" (803)
16 9 or 14 or 15 (1781)
17 critical$.jw,ja,jn. or critically$.tw. or exp Critical Care/ or intensive care units/ or *Critical Illness/ or ((critical$ or intensive) adj care).mp. or (intensive care unit$ or ICU or intensive therapy unit$).mp. or apache/ or apache.tw. (350663)
18 exp Respiration, Artificial/ or exp Ventilators, Mechanical/ or Pneumonia, Ventilator-Associated/ (78012)
19 (ventilat$ adj2 (artificial$ or mechanical$ or pneumon$)).tw. (52385)
20 (respirat$ adj2 (artificial$ or assisted$ or mechanical$)).tw. (2920)
21 (respirat$ adj2 failure$).tw. (27352)

22 (ventilat$ adj3 patient$).mp. or (ventilat$ and patient$).ti. or (ventilat$ and patient$).ab. /freq=3 (32607)
23 (PPV and (pressure or ventilat$)).tw. (1058)
24 (positive adj3 pressure adj5 (ventilat$ or respir$)).tw. (8862)
25 or/18-24 [ventilated patients search concept] (134664)
26 or/17,25 (444844)
27 16 and 26 (61)
28 exp Hospitalization/ or exp hospital units/ or exp hospitals/ or patients/ or inpatients/ or outpatients/ or pharmacy service, hospital/ or exp Drug Prescriptions/ or hospital$.mp. or (patients$ or inpatient$ or outpatient$ or in-patient$ or out-patient$ or tertiary$ or (out$ adj2 hospital$) or ambulat$ or same day or same-day or admission$ or admitted$).tw,kw. (6080532)
29 28 and (9 or 15) (247)
30 27 or 29 (280)
31 limit 30 to "all adult (19 plus years)" (49)
32 limit 30 to "all child (0 to 18 years)" (58)
33 30 not (32 not (31 and 32)) (237)
34 33 and adult$.ti. (14)
35 33 and (pediatr$ or paediatr$ or child$ or adolescent$ or infan$ or newborn$ or boy$1 or neonat$).ti. (14)
36 33 not (35 not (34 and 35)) (226)
37 remove duplicates from 36 (221)

****
Database: Embase Classic+Embase <1947 to Jan 31, 2019> (Jan 31, 2019)
Search Strategy:
---
1 probiotic agent/ or synbiotic agent/ or exp *Lactobacillus/ or exp *Bifidobacterium/ (43323)
2 (probiotic$ or synbiotic$ or bifidus$ or bifidogenic$ or bifido$ or bifidobacter$ or bifido-bacter$ or lactobacill$ or (beneficial adj3 bacter$)).tw,kw. (55137)
3 or/1-2 (64150)
4 exp *Economic Aspect/ or exp *Cost/ or *Reimbursement/ or pe.fs. [Pharmacoeconomics] (499919)
5 (cost$ or economic$ or reimburs$ or pharmacoeconomic$).tw,kw. (928773)
6 ((value or values or valuation) adj2 (money or monetary or life or lives)).ti,ab. (6098)
7 ((((willingness adj1 pay) or sensitivity) adj analys?s) or quality adjusted life expectanc$).ti,ab. (40333)
8 or/4-7 (1279874)
9 3 and 8 (1994)
10 (decision adj1 (tree$ or analy$ or model$)).ti,ab. (21203)
11 *"Quality of Life"/ or (QOL or QOLY or QOLYs or HRQOL or QALY or QALYs).ti,ab. or (quality$ adj2 life$).tw. (377968)
12 *quality adjusted life year/ or "quality of life index"/ or (life year$ adj3 (adjusted$ or quality-adjusted$)).tw. (20840)
13 or/10-12 (397483)
14 3 and 13 (899)
15 limit 3 to "economics (best balance of sensitivity and specificity)" (1045)
16 9 or 14 or 15 (2772)
17 *critically ill patient/ or critically$.tw. or *Critical Illness/ or exp *intensive care/ or *intensive care unit/ or ((critical$ or intensive) adj care).mp. or icu.tw. or (intensive care unit$ or ICU or intensive therapy unit$).mp. or *apache/ or apache.tw. (601767)

18 exp *artificial ventilation/ or exp *assisted ventilation/ or (ventilat$ adj2 (artificial$ or mechanical$)).tw. or ventilator associated pneumonia/ (142764)
19 (ventilat$ adj2 (artificial$ or mechanical$ or pneumon$)).tw. (81176)
20 (respirat$ adj2 (artificial$ or assisted$ or mechanical$)).tw. (5520)
21 (respirat$ adj2 failure$).tw. (45637)
22 (ventilat$ adj3 patient$).mp. or (ventilat$ and patient$).ti. or (ventilat$ and patient$).ab. /freq=3 (53824)
23 (PPV and (pressure or ventilat$)).tw. (1962)
24 (positive adj3 pressure adj5 (ventilat$ or respir$)).tw. (12752)
25 or/18-24 [ventilated patients search concept] (200715)
26 or/17,25 (696858)
27 16 and 26 (91)
28 exp *hospital care/ or exp *hospital/ or *hospitalization/ or exp *"hospital cost"/ or exp *hospital infection/ or exp *hospital patient/ or exp *hospital management/ or (hospital$ or inpatient$ or in-patient$).tw,kw. (4094480)
29 28 and (9 or 15) (334)
30 27 or 29 (373)
31 limit 30 to (adult <18 to 64 years> or aged <65+ years>) (90)
32 limit 30 to (embryo or infant or child) (61)
33 30 not (32 not (31 and 32)) (323)
34 33 and adult$.ti. (22)
35 33 and (pediatr$ or paediatr$ or child$ or adolescent$ or infan$ or newborn$ or boy$1 or neonat$).ti. (25)
36 33 not (35 not (34 and 35)) (303)
37 remove duplicates from 36 (292)

****

Database: EBM Reviews - ACP Journal Club <1991 to Jan 31, 2019>, EBM Reviews - Cochrane Central Register of Controlled Trials <April 2018>, EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>
Search Strategy:
---

1 (probiotic$ or synbiotic$ or bifidus$ or bifidogenic$ or bifido$ or bifidobacter$ or bifido-bacter$ or lactobacill$).mp. or (beneficial adj3 bacter$).tw,kw. (5067)
2 ec.fs. (23293)
3 (cost$ or economic$ or reimburs$ or pharmacoeconomic$).tw,kw. (75674)
4 ((value or values or valuation) adj2 (money or monetary or life or lives)).ti,ab. (525)
5 ((((willingness adj1 pay) or sensitivity) adj analys?s) or quality adjusted life expectanc$).ti,ab. (3092)
6 or/2-5 (78940)
7 1 and 6 (213)
8 (decision adj1 (tree$ or analy$ or model$)).ti,ab. (1245)
9 (QOL or QOLY or QOLYs or HRQOL or QALY or QALYs).ti,ab. or (quality$ adj2 life$).tw. (60440)
10 quality-adjusted life years/ or (life year$ adj3 (adjusted$ or quality-adjusted$)).tw. (7742)
11 or/8-10 (61488)
12 1 and 11 (265)
13 critical$.jw,ja,jn. or critically$.tw. or ((critical$ or intensive) adj care).mp. or (intensive care unit$ or ICU or intensive therapy unit$).mp. or apache.tw. (24227)

14 (ventilat$ adj2 (artificial$ or mechanical$ or pneumon$)).tw. (7105)
15 (respirat$ adj2 (artificial$ or assisted$ or mechanical$)).tw. (522)
16 (respirat$ adj2 failure$).tw. (2287)
17 (ventilat$ adj3 patient$).mp. or (ventilat$ and patient$).ti. or (ventilat$ and patient$).ab. /freq=3 (7329)
18 (PPV and (pressure or ventilat$)).tw. (147)
19 (positive adj3 pressure adj5 (ventilat$ or respir$)).tw. (1764)
20 or/13-19 (31449)
21 (7 or 12) and 20 (12)
22 hospital$.mp. or (patients$ or inpatient$ or outpatient$ or in-patient$ or out-patient$ or tertiary$ or (out$ adj2 hospital$) or ambulat$ or same day or same-day or admission$ or admitted$).tw,kw. (721318)
23 7 and 22 (163)
24 21 or 23 (163)
25 24 and adult$.ti. (11)
26 24 and (pediatr$ or paediatr$ or child$ or adolescent$ or infan$ or newborn$ or boy$1 or neonat$).ti. (39)
27 24 not (26 not (25 and 26)) (124)
28 7 and 27 (124)
29 remove duplicates from 28 (120)
****

Appendix Supplement 2: Data extraction form

Data	**Extractor #1**	**Extractor #2**
• Type of health economic evaluation		
• Perspective		
• Time horizon		
• Year of study and currency		
• Patient group		
• Probiotic genus/species and comparators		
• Clinical outcomes		
• Incremental effects as 'events avoided', 'life-years' or quality adjusted life-years (QALYs) gained'		
• Health care resource uses and unit costs (including source articles)		
• Incremental costs or incremental cost-effectiveness ratio		
• Results of any sensitivity analyses		
• Country in which the study was performed		
• Declared source of funding		

Appendix Supplement 3: Risk of bias (RoB) assessment methods

Randomized control trials used as data sources for the included health economic evaluation were assessed using the Cochrane Collaboration Risk of Bias (ROB) tool (Appendix Supplemental Table 4A). We examined the following domains: selection bias (adequate sequence generation, allocation concealment), performance bias (blinding of participants/study personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data addressed), reporting bias (free from selective reporting), and other bias. Assessment used an ordinal scale of low, medium/unknown and high ROB for RCTs.[20]

Non-randomized trials were assessed for ROB using the Newcastle-Ottawa Scale (NOS), examining the following domains: selection (max score of 4), comparability (max score of 2) and exposure (max score of 3) (Appendix Supplemental Table 4B) for cohort and case-control studies (Appendix Supplemental Table 4C).[21]

Quality of the studies were based on either good (3-4 stars in selection domain and 1-2 stars in comparability domain and 2-3 stars in outcome/exposure domain), fair (2 stars in selection domain and 1-2 stars in comparability domain and 2-3 stars in outcome/exposure domain) or poor (0-1 star in selection domain or 0 stars in comparability domain or 0-1 stars in outcome/exposure domain) quality. **Each of the criteria for the NOS scales for cohort/case-control studies are found in the footnotes of Appendix Supplemental Tables 4B & 4C.**[21]

Surveys were assessed using the ROB tool from the McMaster University Clinical Advances Through Research and Information Translation (CLARITY) group examining the following domains: source population, response rate, missing data, clinical sensibility of the survey and reliability/validity of the survey instrument (Appendix Supplemental Table 4D). Each of the criteria for the NOS scales for cohort/case-control studies are found in the footnotes of Appendix Supplemental Table 4D. Assessment used an ordinal scale of “no, probably no, probably yes and yes” for surveys.[22,23]

For model-based designs, we assessed ROB in each of the multiple contributing source studies in the models. **If one the contributing types (RCTs to surveys) of studies had an unknown/high ROB (identified as the weakest link), we concluded that the entire economic evaluation would be assessed an unknown/high ROB**. For source articles drawn from SRs, guideline documents or health economic evaluations, we did not assess ROB given that the sources previously assessed in Appendix Supplemental Table 4A-D. We did not assess risk of bias when data were derived from an externally established public database (i.e. Consumer Price Index, etc.).

Appendix Supplement 4A-B: Risk of bias table

Supplement 4A: Risk of Bias Assessment for Source Clinical Studies Utilized in Health Economic Analysis of Probiotics (Randomized Control Trials)

	Adequate sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding or participants/study personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data addressed (attrition bias)	Free from selective reporting (reporting bias)	Free from other bias
Source Studies: Allen et al. (2013)							
None							
Source Studies: Branch-Elliman et al. (2015)							
Esteban et. al. (2002)							
US Department of Labour Statistics (2014)****	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Pharmacy Red Book (2014)****	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Source Studies: Fansi et al. (2012)							
Gao et. al (2010)							
Consumer Price Index (2009)****	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Pharmacy Red Book (2006)****	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Source Studies: Leal et al. (2016)							
Goldenberg et. al. (2013)*	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Gao et. al (2010)							
Zimlichman el. al (2013)**	N/A	N/A	N/A	N/A	N/A	N/A	N/A
AHS IPC****	N/A	N/A	N/A	N/A	N/A	N/A	N/A
AHS Pharmacy****	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Calgary Laboratory Services****	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Source Studies: Lenoir-Wijnkoop et al. (2014)							
Hickson et al. (2007)							
Lowry et al. (2010)							
Louie et al. (2011)							
British National Formulary (2009)****	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Department of Health Reference Costs (2009-10)****	N/A	N/A	N/A	N/A	N/A	N/A	N/A
PSSRU Unit Costs of Health & Social Care (2010)****	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Source Studies: Shen et al. (2017)							

Goldenberg et. al. (2013)*	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Allen et al. (2013)***							
Lenoir-Wijnkoop et al. (2014)***							
McFarland et al. (2002)							
Lucado et. al (2006)*	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Didari et al. (2014)*	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Abou Chakra et al. (2014)*	N/A	N/A	N/A	N/A	N/A	N/A	N/A
McFarland et al. (1999)*	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Surawicz et al. (2013)**	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Kwon et al. (2015)*	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Healthcare Cost and Utilization Project (HCUP) (2015)****	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Centers for Medicare and Medicaid Services Fee Schedule (2015)****	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Consumer Price Index (2013)****	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Pharmacy Red Book (2012)****	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Konijeti et al. (2014)***	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Park et al. (2012)***	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Trallori et al. (1997)***	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cohen et al. (2010)**	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Dellinger et al. (2013)**	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Source Studies: Vermeersch et al. (2018)							
Goldenberg et. al. (2013)*	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Hempel et. al. (2012)*	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cleemput et. al (2012)****	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Swartenbroekx et. al (2012)****	N/A	N/A	N/A	N/A	N/A	N/A	N/A

AHS: Alberta Health Services, **HCUP:** Healthcare Cost and Utilization Project, **IPC:** Infection Prevention and Control, **PSSRU:** Personal Social Services Research Unit, **US:** United States

Low risk of bias  **Unknown risk of bias**  **High risk of bias** 

* Systematic reviews/meta-analyses
**Guideline documents
***Health economic analyses
****Public/hospital databases

Supplement Table 4B. Risk of Bias Assessment for Source Clinical Studies Utilized in Health Economic Analysis of Probiotics (Observational Studies – Utilizing the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies)

	Selection (max 4 stars)	Comparability (max 2 stars)	Outcome (max 3 stars)
Source Studies: Allen et al. (2013)	N/A	N/A	N/A
Source Studies: Branch-Elliman et al. (2015)	N/A	N/A	N/A
Source Studies: Fansi et al. (2012)			
Song et. al (2008)	****	**	***
Source Studies: Leal et al. (2016)	N/A	N/A	N/A
Source Studies: Lenoir-Wijnkoop et al. (2014)			
Pepin et al. (2006)	****	**	***
Miller et al. (2002)	*	0	**
Source Studies: Shen et al. (2017)			
Miller et al. (2002)	*	0	**
Salminen et al. (2002)	****	**	***
Van Walraven et al. (2014)	****	**	***
Lessa et al. (2015)	****	**	***
Kuntz et al. (2012)	****	**	***
Source Studies: Vermeersch et al. (2018)			
Elseviers et al. (2015)	*	*	0
Kyne et al. (2002)	*	0	*
Dubberke et al. (2008)	*	0	*
Song et. al (2008)	****	**	***
Lawrence et. al (2008)	*	0	*
Riley et. al (2008)	*	0	*
Miller et al. (2002)	*	0	**
Ananthakrishnan et al. (2008)	*	0	*
Kofsky et al. (1991)	*	0	*
Wassenberg et al (2010)	*	*	0

Selection

1) Representativeness of intervention cohort:
    a. Truly representative of average, treated probiotic patient in hospital*
    b. Somewhat representative of average, treated probiotic patient in hospital*
    c. Only selected group of patients
    d. No description of derivation cohort
2) Selection of non-intervention cohort:
    a. Drawn from same community as intervention/exposed cohort*
    b. Drawn from different source
    c. No description of the derivation of the non-exposed cohort
3) Ascertainment of intervention:
    a. Health record*
    b. Structured interview*
    c. Written self-report
    d. No description
4) Demonstration that outcome of interest was not present the start of the study:
    a. Yes*
    b. No

Comparability

1) Comparability of cohorts on the basis of the design or analysis:
    a. Study controls for age, antibiotic/probiotic exposure*
    b. Study controls for an additional factors*

Outcome

1) Assessment of outcome:
    a. Independent blind assessment*
    b. Record linkage*
    c. Self report
    d. No description
2) Was follow-up long enough for outcomes:

a. Yes (median duration of follow-up 4 weeks)*
b. No

3) Adequacy of follow-up cohort:
   a. Complete follow-up*
   b. Minimal loss to follow-up (<20%)*
   c. Follow-up rate <80% and no description of losses to follow-up
   d. No statement

Supplement Table 4C. Risk of Bias Assessment for Source Clinical Studies Utilized in Health Economic Analysis of Probiotics (Observational Studies – Utilizing the Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies)

	Selection (max 4 stars)	Comparability (max 2 stars)	Exposure (max 3 stars)
Source Studies: Allen et al. (2013)	N/A	N/A	N/A
Source Studies: Branch-Elliman et al. (2015)	N/A	N/A	N/A
Source Studies: Fansi et al. (2012)			
Suneshine and McDonald (2006) – case report only	0	0	*
Source Studies: Leal et al. (2016)			
Henrich et al. (2009)	****	**	***
Source Studies: Lenoir-Wijnkoop et al. (2014)	N/A	N/A	N/A
Source Studies: Shen et al. (2017)	N/A	N/A	N/A
Source Studies: Vermeersch et al. (2018)	N/A	N/A	N/A

Selection

1) Is the case definition adequate?:
    a. Yes, with independent validation*
    b. Yes (i.e. record linkage), or based on self-reports
    c. No description
2) Representativeness:
    a. Consecutive or obvious representative series of cases*
    b. Potential for selection biases or not stated
3) Selection of controls:
    a. Hospital controls*
    b. No description
4) Definition of controls:
    a. No history of disease (end-point)*
    b. No description of source

Comparability

1) Comparability of cases and controls on the basis of design or analysis:
    a. Study controls for age, antibiotic/probiotic exposure*
    b. Study controls for an additional factors*

Outcome

1) Ascertainment of outcome:
    a. Secure medical record*
    b. Structured interview where to blind to case/control status*
    c. Interview not blinded to case/control status
    d. Written self-report or medical record only
    e. No description
2) Same method of ascertainment of cases and controls:
    a. Yes*
    b. No
3) Non-response rate:
    a. Same rate for both groups*
    b. Non-respondents described
    c. Rate different and no designation

Supplement Table 4D. Risk of Bias Assessment for Source Clinical Studies Utilized in Health Economic Analysis of Probiotics (Evidence Partners and CLARITY for Risk of Bias of Surveys)

	Source population	Response Rate	Missing Data	Survey Clinical Sensible	Reliability/Validity of Survey Instrument
Source Studies: Allen et al. (2013)	N/A	N/A	N/A	N/A	N/A
Source Studies: Branch-Elliman et al. (2015)					
Branch-Elliman et. al (2013)					
Source Studies: Fansi et al. (2012)	N/A	N/A	N/A	N/A	N/A
Source Studies: Leal et al. (2016)	N/A	N/A	N/A	N/A	N/A
Source Studies: Lenoir-Wijnkoop et al. (2014)					
Baeur et al (2011)		Probably 			
Source Studies: Shen et al. (2017)					
Magill et al. (2014)					Probably 
Sullivan et al. (2006)					
Source Studies: Vermeersch et al. (2018)	N/A	N/A	N/A	N/A	N/A

CLARITY: Clinical Advances through Research and Information Translation

High risk of bias  **Low risk of bias** 

Risk of Bias Instrument for Cross-Sectional Surveys of Attitudes and Practices (Agarwal et. al, evidencepartners.com)

1) Is the source population representative of the population of interest?
2) Is the response rate adequate?
3) Is there little missing data?
4) Is the survey clinically sensible?
5) Is there any evidence for the reliability and validity of the survey instrument?

Appendix Supplement 5: Costing Data (Natural Units, Unit Costs and/or Total Costs)

Cost Variable (Total Cost)	Allen et. al (2013)	Branch-Elliman et. al (2015)	Fansi et. al (2012)***	Leal et. al (2016)	Lenoir-Wijnkoop et. al (2014)***	Shen et. al (2017)	Vermeersch et. al (2018)***
Diagnostics/Procedures							
Microbiology testing	£45.28-54.94 [27.51-109.88] (unit) $88.24-107.07 CDN [53.61-214.13] [NHS Reference Costs, Curtis L.]	NR	$32.16 USD ($45.67 CDN) (unit, Clostridium Difficile screen) [Hospital database]	$30.31 CDN ($31.52) (unit, Clostridium Difficile Quick Check Complete Assay (2-step algorithm test)) [Calgary Laboratory Services]	NR	NR	NR
Diagnostic and therapeutic protocols	£69.65 ($135.73 CDN) (unit) (NHS Reference Costs, Curtis L.)	NR	NR	NR	NR	NR	NR
CBC	NR	NR	NR	NR	NR	NR	NR
Urea/WBC/LFT	NR	NR	NR	NR	NR	NR	NR
CRP	NR	NR	NR	NR	NR	NR	NR
Abdominal XR	NR	NR	NR	NR	NR	NR	NR
Flexible Sigmoidoscopy	NR	NR	NR	NR	NR	NR	NR
Stool Culture (Toxin/WBC/C&S/ Clostridium Difficile PCR)	NR	NR	NR	NR	NR	NR	NR
Fecal transplant	NR	NR	NR	NR	NR	$3150 USD [1580-4730] ($4313.48 CDN [2163.59-6477.07]) (total) [Redbook, HCUP]	NR
Colectomy	NR	NR	NR	NR	NR	$37290 USD [18650-55940] ($51063.38 CDN [25538.54-76601.92]) (total) [Konejeti et al.]	NR
Medication/Drugs							
Antibiotics	Probiotic: £865.09 ($1685.86 CDN) Placebo: £829.29 ($1616.10 CDN) (total, including staff time) [Joint Formulary Committee]	NR	$0.23 USD ($0.33 CDN) (Metronidazole, per dose - unit) $11.76 USD ($16.70 CDN) (Vancomycin, per dose - unit) [Consumer Price Index]	$0.37 CDN ($0.38) (Metronidazole, per capsule – unit) $4.76 CDN ($4.95) (Vancomycin, per day – unit) [Alberta Health Services Pharmacy]	NR	$1490 USD [750-2240] ($2040.34 CDN [1027.02-3067.36]) (Vancomycin, full course - total) [Redbook, HCUP]	NR
Probiotics	Probiotic: £73.02 ($142.30 CDN), Placebo: £0.00 ($0.0) (total, including staff time) [Joint Formulary Committee]	$2.18 USD [Range: $1-10] ($3.09 CDN [Range: $1.42-14.16]) (unit) [Pharmacy Red Book]	$2.50 USD ($3.55 CDN) (Lactobacillus acidophilus/casei, per dose - unit) [Consumer Price Index]	$1.57 CDN ($1.63) Probiotics (per day - unit) [Alberta Health Services Pharmacy]	NR	$70 USD [40-110] ($95.86 CDN [54.77-150.63]) (full course - total) [Redbook, HCUP]	€12.40 ($18.67 CDN) (*S.Boulardii CNCM I-745*) [Elseviers/RIZIV/INAMI]
Medications	NR	NR	NR	NR	Non-Severe: £35 ($66.50 CDN) (CDAD) vs. £1 ($1.90 CDN) (non-CDAD) Severe: £92 ($174.80 CDN) (CDAD) vs. £2 ($3.80 CDN) (non-CDAD) (unit) [British National Formulary, 2009; Department of Health Reference	NR	NR

					Costs, 2009/10; PSSRU Unit Costs of Health and Social Care, 2010]		
Diarrhea Treatment	Probiotic: £4531.36 ($8830.59 CDN) Placebo: £473.23 ($922.22 CDN) (total) [Joint Formulary Committee]	NR	NR	NR	NR	NR	NR
AAD Treatment	Probiotic: £1742.15 ($3395.05 CDN) Placebo: £2220.38 ($4327.01 CDN) (total) [Joint Formulary Committee]	NR	NR	NR	NR	NR	NR
Oral decontamination	NR	$13.30 USD [Range: 5-25] ($18.84 CDN [Range: 7.08-35.40]) (unit) [Pharmacy Red Book]	NR	NR	NR	NR	NR
Digestive decontamination	NR	$17.92 USD [Range: 9-45] ($25.38 CDN [Range: 12.75-63.73]) (unit) [Pharmacy Red Book]	NR	NR	NR	NR	NR
Devices/Equipment							
Cleaning/laundry/disposables	£57.15-95.73 ($111.37-186.56 CDN) (unit) [NHS Reference Costs, Curtis L.]	NR	NR	NR	NR	NR	NR
Gowns	NR	NR	NR	$21.88 CDN ($22.76) (gowns per day – unit) [AHS IPC]	NR	NR	NR
Gloves	NR	NR	NR	$7.15 CDN ($7.44) (gloves per day – unit) [AHS IPC]	NR	NR	NR
Terminal cleaning	£20.76 [16.61-24.91] ($40.45 CDN [32.37-48.54]) (unit) [NHS Reference Costs, Curtis L.]	NR	NR	$24.08 CDN ($25.04) (total) [AHS IPC]	NR	NR	NR
Daily cleaning	£9.54 [7.63-11.45] ($18.59 CDN [14.87-22.31]) (unit) [NHS Reference Costs, Curtis L.]	NR	NR	NR	NR	NR	NR
Spot cleaning & changing	£32.85 [26.28-39.42] ($64.02 CDN [51.21-76.82]) (unit) [NHS Reference Costs, Curtis L.]	NR	NR	NR	NR	NR	NR
Standard ETT	NR	$3.07 USD [Range: 0-10] ($4.35 CDN [Range: 0-14.16]) (unit) [Manufacturer]	NR	NR	NR	NR	NR
Silver ETT	NR	$50 USD [Range:	NR	NR	NR	NR	NR

		30-60] ($70.81 CDN [Range: 42.49-84.97]) (unit) [Manufacturer]					
Suction ETT	NR	$17.16 USD [Range: 10-100] ($24.30 CDN [Range: 14.16-141.62]) (unit) [Manufacturer]	NR	NR	NR	NR	NR
VAP bundle	NR	$33.32 USD [Range: 33.32-150] ($47.19 CDN [Range: 47.19-212.43]) (unit) [Manufacturer]	NR	NR	NR	NR	NR
Oral care	NR	$38 USD [Range: 38-150] ($53.81 CDN [Range: 53.81-212.43]) (unit) [Manufacturer]	NR	NR	NR	NR	NR
VAP bundle & oral care	NR	$71.32 USD [Range: $71-300] ($101.00 CDN [Range: 100.55-424.85]) (unit) [Manufacturer]	NR	NR	NR	NR	NR
Personnel							
Physician costs	£194.76 [103.01-259.67] ($379.54 CDN [200.74-506.40]) (unit) [NHS Reference Costs, Curtis L.]	NR	NR	NR	Non-Severe: £141 ($267.90 CDN) (CDAD) vs. £74 ($140.60 CDN) (non-CDAD) Severe: £192 ($364.80 CDN) (CDAD) vs. £147 ($279.30 CDN) (non-CDAD) (consultation – unit) £36.5 ($69.35 CDN) (specialist referral – unit) £47 ($89.30 CDN) (GP referral – unit) £6.9 ($13.11 CDN) (junior doctor – unit) £43.8 ($83.22 CDN) (gastroenterology – unit) [British National Formulary, 2009; Department of Health Reference Costs, 2009/10; PSSRU Unit Costs of Health and Social Care, 2010]	$210 USD [110-320] ($287.57 CDN [150.63-438.19]) (specialist referral – unit) [Centers for Medicare and Medicaid Services Fee Schedule]	NR
Nurse costs	Probiotic: £105.38 ($205.36 CDN) Placebo: £90.94 ($177.22 CDN) (unit) [NHS Reference Costs, Curtis L.]	$33.32 USD [Range: 25-120] ($47.19 CDN [Range: 35.40-169.94]) (unit – per hour) [US Department of Labor Statistics (median nursing wages)]	NR	$34.83 CDN ($36.22) (Nurse donning/doffing PPE per day – unit) [AHS IPC]	£10 ($19 CDN) (district nurse – unit) [British National Formulary, 2009; Department of Health Reference Costs, 2009/10; PSSRU Unit Costs of Health and	NR	€ 0.63 ($0.95 CDN)/minute nursing time spent [Elseviers/RIZIV/INAMI]

					Social Care, 2010]		
Allied staff costs	Probiotic: £759.71 ($1480.50 CDN) Placebo: £738.34 ($1438.86 CDN) (unit) [NHS Reference Costs, Curtis L.]	NR	NR	NR	£45 ($85.50 CDN) (pharmacist – unit) [British National Formulary, 2009; Department of Health Reference Costs, 2009/10; PSSRU Unit Costs of Health and Social Care, 2010]	NR	NR
Societal productivity loss	NR	NR	NR	NR	NR	NR	€290.22 ($437.00 CDN)/day [Cleemput]
Hospital Cost							
Lost bed day (closure)	£334.17 ($651.22 CDN) (unit) [NHS Reference Costs, Curtis L.]	NR	NR	NR	NR	NR	NR
Ward closure	£9356.76 ($18234.19 CDN) (unit) [NHS Reference Costs, Curtis L.]	NR	NR	NR	NR	NR	NR
Diarrhea (case per day)	£81.40 ($158.05 CDN) (unit) [NHS Reference Costs, Curtis L.]	NR	NR	NR	NR	NR	NR
Hospital in-patient day	£267.34-401.00 ($520.98-781.46 CDN) (unit) [NHS Reference Costs, Curtis L.]	NR	$1424.16 USD ($2022.31 CDN) (Hospital care for CDAD patient per day hospitalized) (unit) [Hospital database]	NR	Non-Severe: £2268 ($4309.20 CDN) (CDAD) vs. £1614 ($3066.60) (non-CDAD) Severe: £5588 ($10617.20 CDN) (CDAD) vs. £2897 ($5504.30 CDN) (non-CDAD) (unit) [British National Formulary, 2009; Department of Health Reference Costs, 2009/10; PSSRU Unit Costs of Health and Social Care, 2010]	NR	NR
General ward	NR	NR	NR	NR	£530 ($1007 CDN) (unit) [British National Formulary, 2009; Department of Health Reference Costs, 2009/10; PSSRU Unit Costs of Health and Social Care, 2010]	NR	NR
Single ward	NR	NR	NR	NR	£479 ($910 CDN) (unit) [British National Formulary, 2009; Department of Health Reference Costs, 2009/10; PSSRU Unit Costs of Health and Social Care, 2010]	NR	NR
VAP Cost	NR	$15975 [Range: 7000-35000] ($22623.38 CDN [Range: 9913.22-49566.09]) (total) [Safdar, Restrepo, Kollef, Institute for Health Care	NR	NR	NR	NR	NR

		Improvement]					
AAD cost	NR	NR	NR	NR	NR	NR	€1250.60 [277.40-2150.3] ($1883.08 CDN [417.69-3237.79]) (bottom up) €1248.7 ($1880.22 CDN) (top-down) [Elseviers/RIZIV/INAMI]
CDAD cost	NR	NR	NR	NR	NR	$7670 USD [3830-11500] ($10502.98 CDN [5244.64-15747.62]) (inpatient cost per case – total) $440 USD [210-620] ($602.52 CDN [287.57-849.00]) (outpatient cost per case – total) [Redbook, HCUP]	€1339.50 [588.80-2239.10] ($2016.94 CDN [866.58-3371.50]) (bottom up) €1337.50 ($2013.93 CDN) (top-down) [Elseviers/RIZIV/INAMI]
CDAD Relapse (one-time cost)	NR	NR	NR	NR	NR	NR	€11868.50 ($17870.88 CDN)/episode [Elseviers/RIZIV/INAMI]
Probiotic induced bacteremia/fungemia	NR	NR	NR	NR	NR	$18280 USD [9140-27420] ($25031.87 CDN [12515.94-37547.81]) (total) [Redbook, HCUP]	NR
Isolation room	NR	NR	NR	$41.67 CDN ($43.34) (per day – unit) [AHS IPC]	NR	NR	€133.89 ($201.60 CDN)/day [Elseviers/RIZIV/INAMI]
Total Cost	Probiotic: £8020.11 ($15629.36 CDN) Placebo: £8011.37 ($15612.33 CDN) (CDAD, total) [NHS Reference Costs, Curtis L.]	NR	NR	NR	NR	NR	NR

AAD: Antibiotic associated diarrhea**, AHS:** Alberta Health Services, **C&S:** Culture and sensitivity**, CBC:** complete blood count, **CDAD:** *Clostridium Difficile* associated diarrhea, **CRP:** C-reactive protein, **ETT:** Endotracheal tube, **Euro: €, GBP**: Great Britian Pound (£), **HCUP:** Healthcare Cost and Utilization Project, **IPC:** Infection Prevention and Control, **LFT:** liver function tests, **NHS:** National Health Service, **PCR:** polymerase chain reaction, **PPE:** personal protective equipment, **PSSRU:** Personal Social Services Research Unit, **RIZIV/INAMI:** National Institute for Health and Disability Insurance, **US:** United States, **VAP:** ventilator associated pneumonia, **WBC:** white blood cell count, **XR:** X-ray
[Ranges] in brackets/square parentheses (if reported)
***** - industry sponsored study**

CHAPTER 3: Manuscript #2 - Economic Evaluation alongside the Probiotics to Prevent Severe Pneumonia and Endotracheal Colonization Trial (E-PROSPECT): Study Protocol

Manuscript #2 Summary: The objective of E-PROSPECT is to determine the incremental cost effectiveness of *Lactobacillus rhamnosus* GG with usual care versus usual care without probiotics in critically ill patients. E-PROSPECT will be performed from the public healthcare payer's perspective over a time horizon from ICU admission to hospital discharge. This study protocol outlines the health economic evaluation methodology associated with performing a cost-effectiveness analysis alongside PROSPECT.

Reference: Lau VI, Cook DJ, Fowler R, Rochwerg B, Johnstone J, Lauzier R, Marshall JC Basmaji J, Heels-Ansdell D, Thabane L, Xie F. Economic Evaluation alongside the Probiotics to Prevent of Severe Pneumonia and Endotracheal Colonization Trial (E-PROSPECT): Study Protocol. *BMJ Open 2020 (accepted)*

Economic Evaluation alongside the Probiotics to Prevent Severe Pneumonia and Endotracheal Colonization Trial (E-PROSPECT): Study Protocol

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Key Words: Probiotics, critical care, economics, infection, PROSPECT, cost-effectiveness, ventilator-associated pneumonia

Manuscript Word Count: 3017

Abstract Word Count: 315

Abstract

Introduction

Ventilator-associated pneumonia (VAP) is a common healthcare-associated infection in the intensive care unit (ICU). Probiotics are defined as live microorganisms that may confer health benefits when ingested. Prior randomized trials suggest that probiotics may prevent infections such as VAP and *Clostridioides difficile*-associated diarrhea (CDAD). PROSPECT (Probiotics to Prevent Severe Pneumonia and Endotracheal Colonization Trial) is a multicenter, double-blinded, randomized controlled trial comparing the efficacy of the probiotic *Lactobacillus rhamnosus* GG with usual care versus usual care without probiotics in preventing VAP and other clinically important outcomes in critically ill patients admitted to the ICU.

Methods and Analysis

The objective of E-PROSPECT is to determine the incremental cost effectiveness of *Lactobacillus rhamnosus* GG plus usual care versus usual care without probiotics in critically ill patients. E-PROSPECT will be performed from the public healthcare payer's perspective over a time horizon from ICU admission to hospital discharge.

We will determine probabilities of in-ICU and in-hospital events from all patients alongside PROSPECT. We will retrieve unit costs for each resource use item using jurisdiction-specific public databases, supplemented by individual site unit costs if such databases are unavailable. Direct costs will include medications, personnel costs, radiology/laboratory testing, operative/non-operative procedures and per-day hospital 'hoteling' costs not otherwise encompassed. The primary outcome is the incremental cost per VAP prevented between the two treatment groups. Other clinical events such as CDAD, antibiotic-associated diarrhea (AAD), and in-hospital mortality will be included as secondary outcomes. We will perform pre-specified subgroup analyses (medical/surgical/trauma; age; frailty status; antibiotic use; prevalent vs. no prevalent pneumonia) and probabilistic sensitivity analyses for VAP, then generate confidence intervals using the non-parametric bootstrapping approach.

Ethics and Dissemination

Study approval for E-PROSPECT was granted by the Hamilton Integrated Research Ethics Board (HIREB) of McMaster University on July 29, 2019. Informed consent was obtained from the patient or substitute decision maker in PROSPECT. The findings of this study will be published in peer-reviewed journals.

Strengths and limitations of this study:

Strengths of this protocol:

- *A priori* study protocol with prospective clinical and economic data collection with representation from international jurisdictions.

- The balance of randomization reduces risk of bias in the cost-effectiveness analysis occurring on patient level.

Limitations of this protocol:

- A relatively short time-horizon.

- Primary outcome of incremental cost to avoid a clinical event (cost-effectiveness approach), rather than a cost-utility approach (incremental cost per quality-adjusted life year).

Background

Ventilator-associated pneumonia (VAP) is the most common healthcare-associated infection in the intensive care unit (ICU), resulting in a high burden of illness.[6,8] A 2005 systematic review found a pooled cumulative VAP incidence of 23% (95% confidence interval (CI): 19%–27%) in randomized controlled trials (RCTs) and 10% (95% CI: 7–13%) in observational studies.[6] In addition, VAP is associated with a two-fold attributable risk of dying in the ICU (odds ratio (OR) 2.02, 95% CI: 1.2–3.6), and the cost attributed to VAP ranges from US $10,000 to $13,000 per patient.[6] Thus, VAP prevention is a patient-important safety goal during critical illness.[5,8,9]

Probiotics are defined as "live microorganisms which, when administered in adequate amounts, confer a potential health benefit on the host.[16,33] They are reported to enhance gut barrier function, reduce host pathogenic bacterial load, modify gut microbiota, and modulate the immune system.[17–20] Probiotics studies suggest benefits including reduced incidence of healthcare-associated infections.[21–24] A recent meta-analysis of RCTs suggests that probiotics administered to critically ill mechanically ventilated patients were associated with a 26% lower VAP rate (95% CI: 10–39%) and 20% lower infection rates overall (95% CI: 5–32%).[12] However, these findings arose from 30 small, mostly low quality single-center RCTs (n=18–300, 2972 total patients in the meta-analysis), yielding imprecise estimates and results with uncertain internal and external validity.[12]

Further, probiotics may reduce the incidence of diarrhea, specifically *Clostridioides difficile*-associated diarrhea (CDAD), which can cause serious complications such as pseudomembranous colitis, toxic megacolon, and death.[29] In a recent Cochrane systematic review and meta-analysis of 31 RCTs including 8672 patients who were receiving antibiotics and concurrent probiotics, moderate certainty evidence suggested that probiotics were effective at reducing the burden of CDAD for patients and the healthcare system.[29]

We recently performed a systematic review of economic evaluations examining probiotics in hospitalized patients, evaluating their cost-effectiveness for reducing VAP, CDAD and antibiotic-associated diarrhea (AAD), while also identifying variables that could drive costs.[76] From 721 potentially relevant studies, 7 met the eligibility criteria. Probiotics appear to be either cost-effective or cost-saving in 6 of 7 studies compared to other prophylactic strategies within usual care to prevent healthcare-associated infection in acutely ill hospitalized patients. However, Grading of Recommendations Assessment, Development and Evaluation (GRADE) evaluations indicated a high risk of bias and very low quality/certainty of clinical evidence, such that cost-effectiveness evidence on the use of probiotics in adult hospitalized patients was weak. Furthermore, probiotic manufacturers funded 3 of 7 (43%) studies, all of which were reported as either cost-effective or cost-saving.[76] Some probiotic economic evaluations were designed after the results of the trial were published.

Therefore, we have designed this economic evaluation (E-PROSPECT) alongside the multicenter PROSPECT (ClinicalTrials.gov number: NCT01782755), assessing the incremental cost effectiveness ratio (ICER) of probiotics versus usual care for critically ill adult patients.[13–15]

METHODS

Overview of PROSPECT

PROSPECT is a randomized, double-blinded multicenter controlled trial. It used a central system for concealed 1:1 ratio to randomize patients (in variable unspecified block sizes, stratified by center and by medical, surgical or trauma admission status) to either 1×10^{10} colony forming units (CFU) of *L. rhamnosus* GG (iHealth, Inc.) or an identical placebo suspended in tap water administered twice daily via feeding tube in the ICU.[15] PROSPECT has enrolled 2653 critically ill patients between October 2013 and March 2019 throughout 44 ICUs (41 in Canada, 2 in the United States and 1 in Saudi Arabia). Patients, healthcare providers, investigators and research personnel were all blinded to group allocation. Sample size calculation has been previously described.[13–15]

E-PROSPECT design

The primary objective of E-PROSPECT is to estimate the incremental cost per VAP prevented arising from a prevention strategy of using probiotics with usual care (the probiotics arm) versus usual care without probiotics (the usual care arm) during hospitalization. Our secondary analyses of ICERs include healthcare-associated complications (CDAD, AAD) and mortality.[13–15] Our economic evaluation will be performed from the public healthcare payer's perspective,[77] over the time horizon of the ICU admission to hospital discharge or death (Table 1). Our economic evaluation protocol was developed (Table 1) according to established CHEERS (Consolidated Health Economic Evaluation Reporting Standards) and international cost-effectiveness analysis (CEA) guidelines.[36,78]

Clinical outcomes

Clinical outcomes that will be examined in E-PROSPECT are described with definitions in Supplemental Table 1 that were previously described from PROSPECT.[15] Clinical events such as VAP (primary outcome), CDAD, AAD and hospital mortality (secondary outcomes) will be gleaned from PROSPECT, with a statistical analysis methodology previously described.[15] For the dichotomous outcomes, we will use time-to-event analyses. Hazard ratios and associated 95% confidential intervals will be estimated using a stratified Cox proportional hazards model. For continuous outcomes, we will report estimates of the difference between intervention and control groups, 95% confidence intervals (CIs) and associated p-values.[15]

These dichotomous outcomes with proportions and continuous outcomes with point-estimates (e.g. length of stay, which will be used for calculation of resource utilization) will be used to calculate both incremental costs (resource utilization) and effects. Incremental effects will be defined as the difference in per-patient event rates or the difference in proportion of a clinical event (e.g. VAP) between groups.

Health care resource utilization

Based on our systematic literature review[76] and published evidence,[13–15] we identified a list of relevant health care resource items that includes medications, physician/personnel utilization, diagnostic radiology/laboratory testing, and operative/non-operative procedures and per-day hospital 'hoteling' costs not otherwise encompassed. Antimicrobial use in ICU will be defined as days of therapy (DOT), defined daily dose (DDD) of therapy and antimicrobial-free days (AFDs).[79,80] Only systemic antimicrobials will be captured whether prophylactic or therapeutic in intent. Topical creams, eye/ear drops and inhaled antimicrobials will be excluded. We will also document the duration of mechanical ventilation, ICU and hospital length of stay and mortality. The health care resource uses will be collected alongside PROSPECT. For missing resource use data, we will choose appropriate imputation methods according to the type and distribution of the missing data.[81,82] Otherwise, we will utilize an appropriate "standard dose" for non-titratable medications (e.g. chlorhexidine), and a clinically appropriate "medium dose" for titratable medications (e.g. vasopressors or inotropes).

Unit costs

Unit costs for health care resource items will be identified through jurisdiction-specific (regions/provinces/states which manage health care delivery in their area) public databases (e.g. pharmacy drug formularies, physician billing schedule of benefits, Medicare/Medicaid reimbursement manuals, labour department wages/salaries, manufacturer costs). When there is a small sample or distribution of unit costs (i.e. a provincial jurisdiction may have the same cost for a particular procedure), we will estimate the standard error if possible, or incorporate a ±25% error around the mean unit cost distribution.

For unit costs not represented in public databases, we will obtain site-specific unit costs from the participating PROSPECT sites. We will first conduct a pilot study of unit cost acquisition at a convenience sample of 9 participating centers (Canadian: British Columbia, Alberta, Manitoba, Ontario, Québec, Nova Scotia; US: Minnesota, Missouri; and Saudi Arabia) to request a list of unit costs (Supplemental Table 2: E-PROSPECT unit cost data extraction table). The site investigator or research coordinator will then contact the most appropriate individual in each hospital's accounting, human resources, pharmacy, radiology or laboratory departments to obtain the unit costs. [83] In all cases, costs will be requested (if available). If only charges are known, then we will attempt to convert to costs by the institution's cost-to-charge estimate for that item, where it exists [83].

Direct costs will be presented in the pre-specified cost categories (Supplemental Table 2). Assumptions regarding resource utilization are presented in Supplemental Table 3. We will assess direct unit costs for study product-related resources associated with outcomes of VAP, CDAD, AAD and mortality. If a specific line-item unit cost is not attainable for a specific jurisdiction,[83] we will: 1) ask another site within the same jurisdiction for missing unit costs; 2) derive a cost-ratio from acquired line-items (i.e. drug costs both known in 2 jurisdictions), then using the cost-ratio impute the missing line-item unit costs for the missing jurisdiction (by multiplying the cost-ratio against a known jurisdiction's acquired line-item to impute the line-item unit cost for the missing jurisdiction). 3) If line-item unit costs are still missing after multiple imputation (with missing variables), a mean unit cost approach will be utilized for the remaining jurisdictions which did report unit costs.

The pilot phase may inform amendments to our protocol. For example, if a unit cost for a particular line-item is deemed to be small and/or has a low clinical incidence rate, then that line-item may be removed from the final analysis. Items without a difference in clinical outcome/resource utilization between intervention and control groups but which contribute substantially to costs may still be retained (even if little to no incremental difference in costs would exist between the two arms) in order to maintain face validity and accurately reflect the magnitude of costs for hospitalization of a critically ill patient. Once the list of line-items has been pared down to those which are deemed to be cost drivers, and clinically relevant while also feasible to obtain, the remaining line-item list will be surveyed across a sampling of individual sites from each representative jurisdiction from PROSPECT.

Unit cost data will be summarized among all sites, and by country, to explore variability across centers and countries and to improve the generalizability of results. Visible outliers will be reconfirmed with individual hospital contacts. Participating sites will be queried to determine if particular costs have changed substantially (for example, by more than 25%), beyond inflationary or deflationary changes, over the course of the study. If there are substantial changes that have occurred over time, we will use the mean unit costs adjusted for inflation over the mean duration of the trial.[83]

Cost analysis

The cost for each resource use item will be calculated by multiplying the natural resource utilization units by the unit cost. The total cost per patient will be the sum of the cost of

items utilized from the time of randomization until discharge from hospital or death. The incremental mean cost will be estimated by calculating the difference in the total per patient costs between the two groups. All costs will be converted to 2019 United States dollars, accounting for annual inflation.[37,84–87] We plan on using international currency conversion, instead of purchase power parity (PPP)-based conversions, because health-specific PPPs are not available for all participating countries, and non-health PPP conversion rates vary substantially over the period of the analysis.[37] Country-specific costs will be considered only in sensitivity analyses.

Incremental costs will be calculated using the difference in mean per patient cost between the two treatment arms. We have developed a costing operations manual outlining this process (Supplemental Appendix 4: E-PROSPECT costing manual). [37]

Base-Case Cost Effectiveness Analyses

Means (standard deviations) or frequency (percentage) will be used to describe effect and cost estimates wherever appropriate. Chi-square tests and two-sample t-test comparisons will be used as appropriate to compare baseline characteristics between the two arms. The primary outcome will be based on the intention-to-treat principle and will form the clinical event estimates for the economic evaluation. Regression analyses may be performed if there is residual confounding, based on previously described methodology[15].

The base case incremental cost-effectiveness ratio (ICER) is the ratio of incremental costs per VAP prevented of probiotics versus usual care during the period of hospitalization (from ICU admission to hospital discharge or death). The incremental mean costs will be estimated from all patients in both groups based on multiplying the resource unit cost by resource utilization as described above. The incremental mean effects will be derived from PROSPECT, where incremental effects were defined as the difference in per-patient event rates or the difference in proportion of a clinical event (e.g. VAP) between groups[30,83]. In secondary analysis we will also calculate ICER using other clinical outcomes (i.e., CDAD, AAD, mortality). If there is dominance in cost effectiveness (i.e. one treatment is better at lower cost than the other treatment), we will present the difference in cost and effect separately, without calculating the ICER for the base case analysis. When there is no difference in clinical outcomes, we will present incremental cost and effects separately, without calculating an ICER for the base case analysis.

Subgroup analyses

As subgroup analyses, we will investigate specific patients who may have differential effects and costs as compared to the entire population, including: diagnostic category (medical, surgical, trauma);[6] age <65 years, 65-75 years and >75 years;[88,89] frailty status (baseline Clinical Frailty Score $\geq$5 of 9 versus);[90] patients who received/did not receive antibiotics within 2 days of randomization;[15] prevalent (present at the time of enrollment) vs. no prevalent pneumonia.[15]

Uncertainty analyses

Because patient characteristics and costs may differ in different jurisdictions and outside clinical trials settings, and there will be uncertainty associated in the estimation of each group's clinical outcomes and separately in the associated group's costs, we have prospectively planned an uncertainty analysis to explore how ICERs may change with plausible ranges in costs of probiotics.

To test the robustness of our results (and determine the uncertainty associated with cost and effects estimation), we will perform a probabilistic sensitivity analysis of pairs of known costs and effects, using non-parametric bootstrapping techniques to generate 95% confidence intervals. We will perform 1000 bootstrap simulations in the following manner: each simulation will draw the same number of patients per group (as per intention-to-treat), with replacement (for

both events and cost) in pairs. For each sample, the difference in event rate and cost was calculated, obtaining 1000 pairs of differences in cost and event rate.[91,92] Cost effectiveness acceptability curves will be used to present the probability of probiotics being cost effective over a wide range of willingness-to-pay thresholds.[77]

Scenario analyses will also be performed with variations of estimates of pairs of potentially influential variables (i.e. costs of probiotics, per day cost of care in ICU and hospital wards) across plausible ranges (variation of costs: 50-150%) to explore potential cost differences in higher- and lower-spending health care jurisdictions to determine if different estimates change the overall results.

All analyses will be undertaken using Excel (Microsoft Corp, Redmond Washington, US), and SAS (Cary, North Carolina, US).

Patient and Public Involvement

Patients or the public were not involved in the development of the research question, design, or conduct, or reporting, or dissemination plans of our research. The burden of the intervention was not assessed the patients themselves.

Ethics and Dissemination

Research ethics approval for E-PROSPECT was granted by the Hamilton Integrated Research Ethics Board (HIREB) of McMaster University (project identifier: REB#:15-322). Informed consent was obtained from each participant in PROSPECT, or their substitute decision-maker, in accordance with local REB approvals. We anticipate that a majority of sites participating in E-PROSPECT will consider central HIREB approval as satisfactory to obtain additional non-specific patient-based costing data from their center. All economic data, as with trial data, will be de-identified, maintained in a password-protected and encrypted laptop or desktop, in locked offices. All de-identified datasets, technical appendices and statistical code will be published alongside the economic evaluation. Knowledge translation of the results will be disseminated to patients, public and healthcare providers through peer-review journals. The CHEERS checklist has been completed (Supplemental Appendix 5).

Discussion

PROSPECT is the largest trial undertaken of probiotic usage for VAP prophylaxis in critically ill patients. Although probiotics have been shown in prior trials to prevent VAP and CDAD, their relative effects, side-effects and cost-effectiveness remain uncertain. PROSPECT will determine whether probiotics reduce the frequency of VAP and other healthcare-associated complications during critical illness.[13–15] An economic evaluation jointly considers both costs and effects between alternative treatment options. Thus, physicians, administrators and policy-makers can know whether a new treatment provides good value for the healthcare expenditure. E-PROSPECT will answer these questions and address the cost-effectiveness of probiotics for VAP prevention. The literature currently has a paucity of health economic evaluations, illustrating the importance of E-PROSPECT.[93]

Strengths and Limitations

Some aspects of our methodology have potential limitations. First, the time-horizon is relatively short, with no outpatient follow-up (only reporting in-hospital outcomes). Other studies have utilized relative, non-fixed time horizons in health economic evaluations,[30] including those investigating probiotics.[46,48] We will carefully interpret these cost-effectiveness ratios in context from the short time horizon. Second, our primary outcome is the incremental cost to avoid a VAP event and other clinically important outcomes, not the incremental cost per quality-adjusted life year gained in a cost-utility analysis [77]. PROSPECT is not designed to measure long-term

outcome or downstream life expectancy (hence no lifetime time horizon). However, if PROSPECT shows a difference in hospital survival due to probiotics, this will be addressed as a secondary outcome. As with all efficacy trials, the generalizability and external validity of a health economic evaluation concurrently performed with an RCT may not represent the same treatment effects and costs as in routine clinical practice.

E-PROSPECT has several advantages.[94] First, we reduce the potential for investigator hypothesis-driven biases by pre-specifying our parameters of analysis (subgroup and sensitivity analysis) for the health economic evaluation prior to unblinding of the trial. Second, trial randomization can reduce bias and confounding according to different baseline characteristics between study groups. Third, the concurrent collection of clinical and economic data can reduce the costs of data collection and minimize the possible problem of missing data if attempting to obtain it retrospectively. Fourth, we have chosen to gather costs from healthcare systems from multiple countries participating in the PROSPECT trial. We anticipate a wide variability in institutional reporting patient-specific cost accounting.[30,83] Although this has the potential to introduce variability in cost estimates, this approach will also likely enhance the generalizability of our results. Finally, timely economic data can be useful to healthcare policy-makers to aid in resource allocation decisions. There are several clinician-researchers that are advocating for the embracing the science of value in healthcare,[95] while others state that cost-effectiveness analysis should be mandatory in clinical-effectiveness research to aid in clinical guideline development and public healthcare decision policy.[31] By conducting our economic analysis concurrent with the PROSPECT trial, we take advantage of each of these strengths.[83]

Acknowledgements

PROSPECT was designed by the PROSPECT Steering Committee and improved by Drs. Dawn Bowdish, Michael Surette and Erick Duan, the PROSPECT Investigators and Research Coordinators and the Canadian Critical Care Trials Group. We are grateful for the commitment of all our colleagues in participating centers, and staff at the Methods Center for their expertise including Nicole Zytaruk, Lois Saunders, Shelley Anderson-White, Mary Copland, Megan Davis, France Clarke and Alyson Takaoka.

Funding

This economic evaluation (E-PROSPECT) and PROSPECT is funded by the CIHR, McMaster University, St. Joseph's Healthcare Hamilton, Canadian Frailty Network, Physicians Services Incorporated of Ontario, the Hamilton Academic Health Sciences Organization and the Academic Medical Organization of Southwestern Ontario. DJC is a Canada Research Chair of the Canadian Institutes of Health Research. Study products were donated by i-Health, Inc., the manufacturers of *L. rhamnosus GG*; however, no funding for either the trial itself or the economic evaluation was received from the manufacturers of any probiotic or other agent involved in VAP prevention or treatment.

None of the funders played a role in the conception, design, conduct, oversight, analysis, interpretation or decision to submit this manuscript for publication or in the preparation, review or approval of the manuscript.

Footnotes

Conflicts of interests

The authors declare that they have no competing interests.

Authors contributions

Conception and design: VL, DJC, BR, FX, JJ, RF.

Manuscript writing: VL, DJC, BR, FX, JJ, RF.

Critical revision and final approval of the manuscript: VL, DJC, BR, FX, JJ, RF, JB, FL, JM, LT, DHA.

Obtained funding: DJC, JJ, FL, JM, LT.
Administrative, technical or material support: FX, BR, DJC, JJ, DHA, LT.
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Tables

Table 1: Summary of economic evaluation framework

Question:	Is the use of probiotics as compared to standard care without probiotics cost-effective for the prevention of VAP and other clinically important outcomes in critically ill medical-surgical patients in PROSPECT?
Perspective:	Public payer (in-hospital costs)
Setting:	Ventilated ICU patients (44 centers, 3 countries: 41 Canada, 2 USA, 1 Saudi Arabia)
Comparators:	Probiotics (*Lactobacillus rhamnosus* GG) with standard of care versus standard care without probiotics
Time Horizon:	From ICU participant admission to hospital discharge/death (non-fixed time span)
Discount Rate:	No discounting (no long term follow-up over 1 year)
Clinical Outcomes:	VAP, CDAD, AAD, length of stay and mortality (ICU and hospital)
Costs:	Direct medical costs associated with treatment and complications (ICU and ward costs, personnel, medications, laboratory tests, diagnostic testing and procedures/surgeries)
Evaluation:	Primary outcome: Incremental cost-efficacy ratios (ICERs) per in-hospital VAP event avoided Secondary outcomes: ICERs for other clinically important outcomes: (i.) Incremental cost per CDAD avoided (ii.) Incremental cost per AAD avoided (iv.) Incremental cost per death avoided
Currency (price date):	United States Dollars (2019)
Uncertainty:	Non-parametric bootstrapping to produce confidence intervals (probabilistic sensitivity analysis) Cost sampling from various hospitals (stratified by: location) Sensitivity analyses to deal with structural and methodological uncertainty

AAD = antibiotic associated diarrhea; CDAD = *Clostriodiodes difficile* associated diarrhea; ICER = incremental cost-efficacy/effectiveness ratio; ICU = intensive care unit; PROSPECT = Probiotics: Prevention of Severe Pneumonia and Endotracheal Colonization Trial; US = United States; VAP = ventilator-associated pneumonia;

Supplemental Table 1: Definitions of clinical outcomes

Clinical Outcome	Definition	Source/Rationale
Ventilator-associated pneumonia (VAP)	The primary outcome is adjudicated VAP. Clinically suspected VAP at participating sites is being centrally adjudicated independently and in duplicate by 2 physicians blinded to allocation and center, informed by the following standardized definition: receiving invasive mechanical ventilation for > 2 days, when there is a new, progressive or persistent radiographic infiltrate on chest radiograph plus any 2 of the following: 1) fever (temperature >38°C) or hypothermia (temperature <36°C); 2) relative leukopenia (<3.0 x 106/L) or leukocytosis (>10 x 106/L); 3) purulent sputum	The American College of Chest Physicians (ACCP) definition did not provide thresholds for leukopenia or leukocytosis. Therefore, the thresholds were obtained from Morrow et al [Morrow] as their VAP definition was also based on the ACCP definition [Grossman]. Any disagreement in adjudication will be resolved through discussion and consensus. Acknowledging that there is no universally accepted gold standard VAP definition [9], and that in non-immunocompromised patients, routine invasive testing is not associated with improved outcomes [Canadian Critical Care Trials Group], we are also collecting data to allow VAP reporting according to several other definitions [96–99].
Early VAP	Pneumonia arising on day 3, 4 or 5 after the initiation of mechanical ventilation.	We are classifying VAP by early VAP and late VAP, as the etiologic organisms may differ, the antimicrobials prescribed may differ, and the prognosis is often worse for late VAP [100,101]. We will also report a composite outcome of early VAP, late VAP, and post-extubation pneumonia, adjudicated independently and in duplicate by 2 physicians. For the timing of all pneumonia outcomes, we use days rather than hours to inform the classification.
Late VAP	Late VAP is defined as VAP arising on day 6 of mechanical ventilation or later, and including up to 2 days after discontinuation of mechanical ventilation (also relevant for patients with a	

	tracheostomy)	
Post-extubation pneumonia	Pneumonia arising in the ICU following discontinuation of mechanical ventilation (3 or more days after discontinuation), labeled post-extubation pneumonia, to avoid suppressing potentially relevant lung infections that arise in ICU	
Diarrhea	Diarrhea in the ICU: • World Health Organization definition (≥3 loose or watery bowel movements per day • Bristol Stool classification for loose or watery stool (type 6 or 7)	We will record each bowel movement and define diarrhea incorporating 2 metrics [33,102]
Clostridioides difficile–associated diarrhea (CDAD)	Clostridioides difficile in the ICU and prior to discharge from hospital: diarrhea (as previously defined) and laboratory confirmation of C. difficile or colonoscopic or histopathologic findings demonstrating pseudomembranous colitis	Definition from Cohen et al. [103]. Will be adjudicated independently and in duplicate by 2 physicians
Antibiotic-associated diarrhea (AAD)	AAD: diarrhea (as above) defined as following the administration of antibiotics, any day antibiotics are administered or within 1 day after starting any antibiotic	Definition from Thibault et al. [104]
Other healthcare–associated infections	Any infection acquired during the ICU stay, including bloodstream infection, intravascular catheter-related bloodstream infection, intra-abdominal infection, C. difficile infection, urinary tract infection, skin and soft tissue infection, and others.	These individual infections are classified using definitions adapted from the International Sepsis Forum Consensus Conference on Definitions of Infection in the Intensive Care Unit [97], as adapted in prior studies [96]. We will also report a composite outcome of any infections (including pneumonia) acquired during the ICU stay. Secondary infectious outcomes (other than pneumonia and C. difficile) are being centrally adjudicated by 1 physician blinded to allocation and center, based on review of data collected at each participating site.
Serious adverse events (SAE)	Defined as isolation of Lactobacillus spp. in a culture from a sterile site or as the sole or predominant organism cultured from a non-sterile site and results in:	The rationale for our approach to SAEs [Guidance Document for Industry] accords with our guidelines

	1) persistent or significant disability or incapacity; 2) that is life-threatening, or; 3) that results in death	for academic drug trials in critical care [105]. Any culture obtained by the ICU team and processed by the clinical microbiology laboratory as positive for Lactobacillus spp. is recorded. Any such bacterial sample is sent to a McMaster University research laboratory for strain genotyping to evaluate consistency with the administered L. rhamnosus GG strain

Supplemental Table 2: Healthcare resource utilization and unit costs (per jurisdiction)

Cost Categories	Natural Units	Unit Cost	Total Cost	Source

Study-related drugs
• probiotics *(Lactobacillus rhamnosus GG)*
• antibiotics:
  ○ pipercillin-tazobactam
  ○ ceftriaxone
  ○ ceftazidime
  ○ azithromycin
  ○ vancomycin
  ○ metronidazole
  ○ levofloxacin
  ○ imipenem
  ○ meropenem
  ○ amoxicillin-clavulin
  ○ cefuroxime
  ○ linezolid
  ○ cefazolin
  ○ cloxacillin
  ○ ciprofloxacin
  ○ gentamicin
  ○ trimethoprim-sulfamethoxazole
• steroids
  ○ dexamethasone
  ○ methylprednisone
  ○ hydrocortisone
  ○ prednisone
• stress ulcer prophylaxis
  ○ cimetidine
  ○ ranitidine
  ○ famotidine
  ○ nizatidine
  ○ lansoprazole
  ○ dexlansoprazole
  ○ pantoprazole
  ○ esomeprazole
  ○ omeprazole
  ○ rabeprazole
• laxatives/motility agents
  ○ domperidone
  ○ metoclopramide
  ○ erythromycin
  ○ senna
  ○ dulcolax
  ○ golytely
  ○ glycerin
  ○ lactulose
  ○ colace				

○ citro-mag ○ PegLyte ○ pancreatic enzymes ○ enema • opiates ○ morphine ○ hydromorphone ○ demerol ○ fentanyl ○ oxycodone ○ percocets				
Laboratory testing • complete blood count • creatinine • arterial blood gas • lactate • albumin • blood cultures • urine cultures • sputum/tracheal aspirate/bronchoalveolar lavage cultures • *C. difficile* polymerase chain reaction (PCR), toxin assays, ELISA, cell culture, LAMP • other aerobic/anaerobic cultures ○ thoracentesis ○ paracentesis				
Personnel (*per diem or hourly wage)* • most responsible physician ○ ICU ○ Hospital • consultation physicians • nursing • pharmacist • respiratory therapist • physical therapist • social work • ICU administrative and/or clerical staffing				
Radiology • portable chest or abdominal radiographs • computerized tomography (CT) scan: chest, abdomen, pelvis, sinusitis, head • MRI: head, chest, joint • abdominal ultrasound				

Procedural costs:
• central venous catheter, peripherally inserted central catheter, arterial lines
• chest tube
• naso- or oro-gastric tube
• percutaneous endoscopic gastrostomy (PEG) tube
• tube feed
• fiber
• protein supplement
• ventilator circuit changes
• endotracheal tubes (with or without subglottic suction)
• invasive ventilation (ventilator days)
  ○ heat moisture exchange
  ○ heated humidifier
• non-invasive positive pressure ventilation
• high-flow nasal cannula
• vasopressor/inotropic agents
• VAP prevention bundles
  ○ chlorhexidine usage
  ○ bacterial filters
  ○ oral decontamination
  ○ gut decontamination
  ○ oral antibiotic paste
• colonoscopy (cautery, epinephrine injection)
• echocardiograms (transthoracic/transesophageal)
• bronchoscopy
• thoracostomy
• tracheostomy
• interventional radiology drain
• intermittent hemodialysis
• continuous renal replacement therapy
• fecal management device				

Operative costs • laparotomy (toxic megacolon, bowel perforation) • colectomy • thoracotomy • open abdominal wound (vacuum-assisted closure (VAC) devices) • surgeon				

• surgical assistant • anesthesiology • nursing				
Overhead costs • ICU days • ward days				

CT = computerized tomography; ELISA = enzyme-linked immunosorbent assay; ICU = intensive care unit; LAMP = loop-mediated isothermal amplification; MRI = magnetic resonance imaging; NM = nuclear medicine; PEG = percutaneous endoscopic gastrostomy; PCR = polymerase chain reaction; PROSPECT = Probiotics: Prevention of Severe Pneumonia and Endotracheal Colonization Trial; US = United States; VAC = vacuum-assisted closure; VAP = ventilator-associated pneumonia;

Supplemental Table 3: Health economic evaluation assumptions

Assumption	Rationale
Prophylactic and therapeutic probiotic administration outside the ICU • If no prophylactic/therapeutic probiotics was used prior to trial enrollment, we will assume study product (*Lactobacillus rhamnosus* GG prophylaxis or placebo) will be used for duration of stay in the ICU with no other probiotic co-administration; • If open label probiotics were used in the ICU, we will assume study product (*Lactobacillus rhamnosus* GG prophylaxis or placebo) will still be used for duration of stay in the ICU (co-administered); • After the duration of ICU stay (transfer to the ward), we assume that there will be no further probiotic administration	Ward-based/pre-admission ICU prophylactic and therapeutic probiotic administration was not directly measured
Variability in investigations and treatment practice of disease/illness • Based on variability in incidence of disease/illness, we will investigate the incidence of each illness severity, and average resource utilization for a particular illness. • We will utilize the mean costs for a particular illness (we will attempt to directly derive this variability from the case report forms)For patients who undergo multiple investigations, treatment (medications/procedures/surgeries) for a particular disease/illness, we will assume the lowest number of potential interventions to treat the disease/illness, as well as mean resource utilization for such events from PROSPECT	Various clinical diagnoses will have variability in severity, and therefore, variability in the way they are investigated and treated (i.e. *C. difficile* could be investigated/treated with only culture assay, abdominal x-ray and antibiotics to colectomy). Based on prior scoping reviews for VAP/CDAD, there will be variability in the resource utilization of each treatment/test based on illness severity, which may drive differences in resource utilization

Investigations of other infectious outcomes • For those illnesses that are only investigated if positive or indeterminate cultures are detected (i.e. endocarditis), we will assume there is a potential minimum and maximal resource utilization that would be used to investigate/treat a specific diagnosis • Certain assumptions will need to be made for healthcare resource utilization for certain services, investigations, procedures/surgeries, as they may not be explicitly captured in PROSPECT, but can be gleaned indirectly from the case report forms • For example: o central-line blood stream infections would be assumed to warrant a replacement or previous venous or arterial catheters; o broncho-alveolar lavage (BAL) cultures were assumed to have a bronchoscopy procedure to perform them o CDAD was assumed to have an abdominal x-ray (at a minimum) for radiological investigation ▪ At a maximum, a proportion of patients would receive at CT abdo, colonoscopy/flexible sigmoidoscopy, laparotomy, colectomy, fecal transplant, vacuum-assisted closure device o empyema/lung abscess would be assumed to be diagnosed by CT chest, and treated with a chest tube (with a proportion of patients with tissue plasminogen activator into the pleural cavity, or VATS thoracotomy with decortication and irrigation and debridement) o abdominal x-rays can be used to count the number of abdominal drains inserted ▪ a proportion of patients were assumed to receive an abdominal ultrasound, CT abdo, MRI abdo o we will assume that a positive blood culture with specific organisms (known to cause endocarditis) would warrant a transthoracic echocardiogram ± transesophageal echocardiogram; o confirmed endocarditis would be investigated with a transthoracic echocardiogram ± transesophageal echocardiogram o mediastinitis would be assumed to be	There are certain investigations or interventions that would be expected to be associated with various disease state suspicions (and given correct circumstances, we would assume these would be tested/treated in these ways)

diagnosed by CT or MRI chest ▪ at a maximum, they would receive an thoracotomy/sternotomy for an I&D and potential VAC dressing o initiation (on the first day) of intermittent hemodialysis or continuous renal replacement therapy would incur a cost of central venous hemodialysis line placement o suspected meningitis/encephalitis case would warrant a lumbar puncture ± CT or MRI head; o osteomyelitis would warrant a NM scan or MRI; o biliary tract infections would be assumed to have at minimum an abdominal ultrasound; ▪ At a maximum, a proportion of patients would receive at CT abdo, ERCP, percutaneous transhepatic cholecystostomy (PTC) tube, cholecysectomy o pancreatic infections would be assumed to have at minimum an abdominal ultrasound; ▪ At a maximum, a proportion of patients would receive at CT abdo, MRI abdo, abdominal drain or aspiration o typhilitis would be assumed to have at minimum an abdo X-ray; ▪ At a maximum, a proportion of patients would receive at CT abdo o toxic megacolon would be assumed to have at minimum an abdo X-ray; ▪ At a maximum, a proportion of patients would receive at CT abdo o urinary tract infection would be assumed to have at a urinalysis and urine culture o sinusitis would be assumed to have investigations at baseline ▪ At a maximum, a proportion of patients would receive at CT head o septic arthritis would be assumed to have an aspiration culture at a minimum ▪ At a maximum, a proportion of patients would receive an orthopedic surgery for I&D o PEG tube insertion would be assumed to be placed when 1st record on the daily data form of PEG tube utilization (Daily Form 4.2 of 3) o Tracheostomy insertion would be assumed to be placed when 1st record on the daily	

data form (Daily Form 4.1 of 3 – Mechanical airway in place today)	
Imputation of missing data • For those patients with missing data from a clinical outcomes perspective, multiple imputation methods will be utilized – including generalized estimating equations (GEEs) • For missing unit costs (which are not attainable from public jurisdiction databases or trial site-specific inquiries), we will utilize costing-ratio methodology	We will utilize standard multiple imputation methods to handle missing clinical outcome data, or costing-ratio methodology for missing unit costs

BAL = broncho-alveolar lavage; CDAD = C. Difficile-associated diarrhea; CT = computerized tomography; CXR = chest x-ray; ERCP = endoscopic retrograde cholangio-pancreatography; ICU = intensive care unit; I&D: irrigation & debridement; MRI = magnetic resonance imaging; NM = nuclear medicine; PEG = percutaneous endoscopic gastrostomy; PCR = polymerase chain reaction; PROSPECT = Probiotics: Prevention of Severe Pneumonia and Endotracheal Colonization Trial; US = United States; VAC = vacuum-assisted closure; VAP = ventilator-associated pneumonia; VATS = video-assisted thorascopic surgery

Supplemental Appendix 4: E-PROSPECT Costing Manual

E-PROSPECT: The economic evaluation of PROSPECT (Probiotics: Prevention of Severe Pneumonia and Endotracheal Colonization Trial)

Operations Manual

Costing Methodology and Definitions

Data Collection

Clinical Outcomes: Clinical data on every patient will be collected as part of PROSPECT. Site coordinators have already participated in the main clinical randomized controlled trial (RCT), and undergone intensive training session to review the methods and case report forms (CRFs) of the main trial. The Methods Centre at McMaster University will manage PROSPECT data, providing patient characteristics, tests, treatments, and outcomes (e.g., infections, adverse events, duration of stay in ICU and hospital, and mortality in ICU and hospital). We will obtain variable names from the Methods Centre at McMaster to associate them with costs.

Resource utilization: To determine the incremental cost of patients receiving probiotics compared to placebo (with usual care), the resources consumed by patients in PROSPECT will be collected. Enrolled patients are in the intensive care unit (ICU), and are randomized to receive probiotics or placebo, with daily follow-up to identify relevant outcomes. In determining incremental costs, only resources which differ between the two treatment groups need to be identified. However, because the resources that will differ are uncertain, the economic evaluation will be conducted alongside to the RCT as a sub-study, with all important resources being ascertained and analyzed. Once resources are identified, resource utilization and the unit costs of each item for each given patient needs to be calculated.

For purposes of a health economic evaluation, resources will be translated into monetary values. Resource utilization variables associated with the direct medical costs of critically ill patients include: (1) medications; (2) laboratory testing; (3) personnel; (4) radiology testing; (5) procedures/surgeries, and (6) complications/adverse clinical outcomes. Overhead costs include: (1) ICU costs and (2) ward costs. A comprehensive list of direct medical resource utilization elements associated with critically ill patients will be identified. Previous studies (Fowler et al. - Pilot) discovered that public and private-funded institutions have considerable variability in patient costing, and that line-by-line item costs are not available routinely. Many summary cost measures tend to “roll-up” individual items costs rather than listing them as unit costs, which would not allow for a linkage of costs and clinical events (the later measured as part of the PROSPECT CRFs).

This previously established cost-gathering methodology (Fowler et al. – Pilot) captures hospital-specific line item costs, according to important variables that we anticipate will drive costs and possible cost-effectiveness. These “big ticket items” are determined by: (1) a systematic review (SR) of probiotics economic evaluations for preventing healthcare-associated infections (ventilator-associated pneumonia, *Clostridiodes difficile*-associated diarrhea, antibiotic-associated diarrhea) in hospitalized patients (Lau 2019), (2) the PROSPECT CRFs, and (3) experts in healthcare-associated infections in the ICU. If additional costing and utilization information cannot be gleaned from these sources, then certain methodological assumptions (Table 4) will be made regarding resource utilization for potential routine utilization for specific diagnoses/complications.

Further to this, we will be conducting a pilot phase of unit cost acquisition at a sampling of sites to determine which unit costs can be feasibly obtained. It is possible that the pilot phase of this work may inform changes to this protocol, as well as the analysis of the economic evaluation. For example, if a unit cost for a particular line-item is deemed to be small and not a major driver of costs, then that line-item may be removed from the final analysis. The same would apply if a specific line-item has a low clinical incidence rate or no difference in clinical outcome/resource utilization between intervention and control groups, as little to no incremental difference in costs would exist between the two arms. Once the list of line-items has been pared down to those which are deemed to be major cost drivers, clinically relevant, but also feasible to obtain, this new line-item list will be surveyed across all sites.

Unit costs will be obtained from various sources including: (1) departments within participating hospitals, (2) provincial/state/country source databases. Costs conversion will involve collecting costs in their natural currency units from the participating center, and then converting to American dollars in the year of publication (2020). Discounting will not be applied for short-term (<1 year) time-horizon events.

Unit Costs

A unit cost differs from a charge:

- Costs are the expenses incurred by the hospital for the service/procedure rendered.
- Charge is the amount that hospital requires drug companies/researchers to pay for a service/procedure to be conducted at their hospital. A charge usually consists of the cost of performing the service/procedure plus a mark-up fee.
- Hospitals may have a charge-to-cost conversion for unit costs – which we will try to obtain.

Unit costs will be obtained by several methods:

1) Hospital budgets

Ideally, all costs would reflect expenses in the hospital budget. This information will be obtained from hospital financial departments if available. However, in most cases, unit costs are not available for reasons such as: item costs are presented in bulk quantity costs, or item costs are several years outdated, or prices cannot be disclosed due to agreement with suppliers.

2) Government reimbursement

If hospital budget costs are not available, costs will be obtained from government sources/databases. In public healthcare systems, the country's government is mostly accountable for reimbursements of services rendered. We will obtain unit costs from a government schedule of benefits, which delineate the reimbursement for each procedure or test by laboratories, hospitals and healthcare professionals. If the schedule of fees is unavailable or have restricted access, the information will be collected through contact with medical professionals (i.e. pharmacist, ICU manager, etc.) from PROSPECT-associated hospitals. In jurisdictions in which there is a mix of both private and public healthcare (i.e. US), the total private health care fee (i.e. Medicare Benefits Schedule Book) or equivalent government medical benefits schedule may be used.

3) Charge to Cost Ratios

If costs cannot be acquired, the amount that a hospital charges for a procedure, either to patients or to investigators for clinical trials will be used where cost-to-charge ratios are

available. We will use cost:charge ratios that relate to individual costs, as opposed to "rolled-up" ratios, as much as possible.

General Costing Procedures

The PROSPECT site investigators list (maintained by the McMaster Methods Centre) will be used to identify who to initially contact for costing information. An introductory e-mail will be sent to select site investigators (and to the research coordinator, if known) to inform them of E-PROSPECT and to request their assistance to obtain costing information from their site during the pilot phase of unit cost acquisition. If there is no response by the PROSPECT site investigators, individuals will be contacted 2 more times via telephone, email. If there is still no response, or if the site investigators decline to participate, the site's unit costs will be excluded from analysis. Once pilot phase testing is completed, the new line-item unit cost list will be sent to all sites for the remaining unit costs which could not be acquired from public databases.

The general procedure for initiating the costing exercise at each hospital will be as follows:

1. We will contact the PROSPECT site investigator and research coordinator to identify the most appropriate person to identify the requested costs.

2. We will contact these individuals, inform them of E-PROSPECT, and request the hospital-related costs. In some cases, PROSPECT site investigators may prefer to contact these individuals themselves. The e-mail (below) will be sent to contacts.

3. For each cost item, we will ask about the relevant person at the hospital who is most responsible for knowing/determining the hospital-specific cost (e.g. radiology, pharmacy, ICU personnel) will be contacted.

4. We will ask if a hospital specific cost exists for each variable.

5. We will determine if the cost is an actual cost, or "charge". If the item is a charge, a hospital line-item specific cost-to-charge ratio will be required.

6. If the cost is generalizable to a broader geography (health region laboratory cost, provincial physician reimbursement rate, etc.), then we will obtain these costs from the investigators and compare these to the hospital specific costs. Significant discrepancies will be further interrogated to determine whether the difference is real, and which best approximates actual cost (vs. charge). Notations will be made on the dataset and used for future decisions about which numbers to apply to the eventual economic analyses. The list of study variables, definitions, and documentation examples for sources of variable values is below.

Sample Communication to Identified Individuals at E-PROSPECT Sites

Dear colleague,

I am helping with the economic evaluation of the PROSPECT study (E-PROSPECT). We are in the process of gathering costing data on key variables and suspected drivers of cost from all sites involved in PROSPECT (in Canada, the US, and Saudi Arabia). The site principal investigator(s)/research coordinator(s) has passed on your contact information as an individual who could hopefully assist us with ***unit cost*** *collection for E-PROSPECT.*

Our goal primarily is:

To collect unit costs for specific items in PROSPECT, NOT for any patient-specific data*.*

We are looking for the unit costs to be listed in your **local currency** for this **year (2019)**.

A unit cost is defined as:

A **unit cost** is the **expenditure/cost** spent on **one unit** of a particular medication, diagnostic test, investigation, procedure, surgery or personnel in health care.

For example:

- For a specific antibiotic (i.e. ceftriaxone), we are looking for the unit cost for this medication
    - The specific cost (unit cost) at the particular dose (1 unit) that your institution pays for the medication *(*i.e. Ceftriaxone: $50.00 CDN per 1 gram of medication)
- For a specific diagnostic test (i.e. echocardiogram), we are looking for the unit cost per 1 test *(i*.e. transthoracic echocardiogram: $119.00 CDN per 1 echocardiogram)
- For a specific personnel (i.e. nurse), we are looking for the per diem (day) cost for that staff member *(*i.e. Nurse: $200.00 CDN per day)
- For overhead cost, we are looking for the per diem (day) cost for 1 day stay in the ICU and 1 day stay on the ward
    - *We request the per diem day cost broken down into its component parts (i.e. personnel, devices, etc.), as we will need to ensure that we do not double-count the cost of items*

- Attached to this costing manual (and also in the data extraction spreadsheet) are key variables we are hoping to obtain from your site

- If either yourself, or someone else at your center is able to put us in touch with someone to contact at your site, that would be greatly appreciated.

- Sometimes there is a costing person attached to ICU or a costing/charging department. Sometimes we have found it necessary to track down someone in radiology, pharmacy, ICU, lab services, etc. Could you please put us on the right track with names/emails or by forwarding this request?

- We would like to include your names in the publications arising from this work.

Thanks very much for your help and continued support of PROSPECT.

Sincerely,

Dr. Vincent Lau, MD, FRCPC, McMaster HRM MSc(c)

Supervised by: Drs. Deborah J. Cook, Bram Rochwerg, Feng Xie, Jennie Johnstone and Rob Fowler

E-PROSPECT UNIT COST LIST

Pharmacy Costs - Just Tell us Who to Contact:

- probiotics *(Lactobacillus rhamnosus GG)*
- antibiotics:
    - pipercillin-tazobactam
    - ceftriaxone
    - ceftazidime
    - azithromycin
    - vancomycin
    - metronidazole
    - levofloxacin
    - imipenem
    - meropenem
    - amoxicillin-clavulin
    - cefuroxime
    - linezolid
    - cefazolin
    - cloxacillin
    - ciprofloxacin
    - gentamicin
    - trimethoprim-sulfamethoxazole
- steroids
    - dexamethasone
    - methylprednisone
    - hydrocortisone
    - prednisone
- stress ulcer prophylaxis
    - cimetidine
    - ranitidine
    - famotidine
    - nizatidine
    - lansoprazole
    - dexlansoprazole
    - pantoprazole
    - esomeprazole
    - omeprazole
    - rabeprazole
- laxatives/motility agents
    - domperidone
    - metoclopramide
    - erythromycin
    - senna
    - dulcolax
    - golytely
    - glycerin
    - lactulose
    - colace
    - citro-mag
    - PegLyte

    - pancreatic enzymes
    - enema
- opiates
    - morphine
    - hydromorphone
    - demerol
    - fentanyl
    - oxycodone
    - percocets

Clinical Laboratory Costs - Just Tell us Who to Contact:

- complete blood count
- creatinine
- arterial blood gas
- lactate
- albumin
- blood cultures
- urine cultures
- sputum/tracheal aspirate/bronchoalveolar lavage cultures
- *C. difficile* polymerase chain reaction (PCR), toxin assays, ELISA, cell culture, LAMP
- other aerobic/anaerobic cultures
    - thoracentesis
    - paracentesis

General ICU and Ward Costs/Personnel - Just Tell us Who to Contact:

- most responsible physician
    - ICU
    - Hospital
- consultation physicians (general surgery, thoracic surgery, gastroenterology, infectious disease specialists, respirology)
- nurse
- pharmacist
- respiratory therapist
- physical therapist
- social worker
- ICU clerk
- ICU days (generic cost)
- ward days (generic cost)

Radiology Costs - Just Tell us Who to Contact:

- portable chest radiograph
- portable abdominal radiograph
- computerized tomography (CT) scan: chest, abdomen, pelvis, sinusitis, head
- MRI: head, chest, joint
- abdominal ultrasound

Procedural Costs - Just Tell us Who to Contact:

- central venous catheter, peripherally inserted central catheter, arterial lines
- chest tube
- naso- or oro-gastric tube

- percutaneous endoscopic gastrostomy (PEG) tube
- tube feed
- fiber
- protein supplement
- ventilator circuit changes
- endotracheal tubes (with or without subglottic suction)
- invasive ventilation (ventilator days)
    - heat moisture exchange
    - heated humidifier
- non-invasive positive pressure ventilation
- high-flow nasal cannula
- vasopressor/inotropic agents
- VAP prevention bundles
    - chlorhexidine usage
    - bacterial filters
    - oral decontamination
    - gut decontamination
    - oral antibiotic paste
- colonoscopy (cautery, epinephrine injection)
- echocardiograms (transthoracic/transesophageal)
- bronchoscopy
- thoracostomy
- tracheostomy
- interventional radiology drain
- intermittent hemodialysis
- peritoneal dialysis
- continuous renal replacement therapy
- fecal management device

Cost reimbursed by the governing authority to the primary physician for procedure that is rendered at a hospital. Costs often include a Professional component, and a Technical component.

The *professional component* consists of:

A. Providing clinical supervision, including approving, modifying and/or intervening in the performance of the procedure where appropriate, and quality control of all elements of the technical component of the procedure.
B. Performance of any clinical procedure associated with the diagnostic procedure which is not separately billable (e.g. injections which are an integral part of the study) and of any fluoroscopy.
C. Where appropriate, post-procedure monitoring, including intervening except where this constitutes a separately billable service.
D. Interpreting the results of the diagnostic procedure.
E. Providing premises for any aspect(s) of A and D that is(are) performed at a place other than the place in which the procedure is performed.

The *technical component* consists of:

A. Preparing the patient for the procedure.

B. Performing the diagnostic procedure or assisting in the performance of fluoroscopy.
C. Making arrangements for any appropriate follow-up care.
D. Providing records of the results of the procedure to the interpreting physician.
E. Discussion with, and providing information and advice to, the patient or patient's representative(s), whether by telephone or otherwise, on matters related to the service.
F. Preparing and transmitting a written, signed and dated interpretive report of the procedure to the referring physician.
G. Providing premises, equipment, supplies and personnel for all specific elements of the technical and professional components except for the premises for any aspect(s) of A and D of the professional component that is(are) not performed at the place in which the procedure is performed.

Operative Costs - Please tell us who to Contact:

- laparotomy (toxic megacolon, bowel perforation)
- colectomy
- thoracotomy
- open abdominal wound (vacuum-assisted closure (VAC) devices)
- surgeon
- surgical assistant
- anesthesiology
- nursing

Definition of Variables, Source Documentation for Values

NOTE THAT DEFINITIONS MAY DIFFER ACROSS JURISDICTIONS. PLEASE USE THE DEFINITIONS AS A GUIDELINE.

Drug costs

Unit cost to be paid by the hospital to the drug company as negotiated between the hospital and the drug company. The cost is usually found in the hospital drug formulary, or is known to the hospital pharmacy contact.

Supplemental Appendix 5: CHEERS Checklist - **Items to include when reporting economic evaluations of health interventions**

Section/item	Item No	Recommendation	Reported on page No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 2
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Page 4-5
		Present the study question and its relevance for health policy or practice decisions.	Page 4-5
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Page 5
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 5
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 5
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 5
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 5
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 5, Table1
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 5
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Page 5, 8
	11b	*Synthesis-based estimates*: Describe fully	Not applicable

Section/item	Item No	Recommendation	Reported on page No
		the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Not applicable
Estimating resources and costs	13°	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Page 5-6
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Not applicable
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 5-7
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Not applicable
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Table 4
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Page 6-7
Results			
Study parameters	18	Report the values, ranges, references, and,	Page 5-7

Section/item	Item No	Recommendation	Reported on page No
		if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Page 5-7
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	Page 5-7
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Not applicable
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Page 7
Discussion			
Study findings, limitations, generalizability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge.	Page 7
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 9
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal	Page 15

Section/item	Item No	Recommendation	Reported on page No
		Editors recommendations.	
For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist			

CHAPTER 4: Manuscript #3 - Economic Evaluation alongside the Probiotics to Prevent Severe Pneumonia and Endotracheal Colonization Trial (E-PROSPECT): Cost-Effectiveness Analysis

Manuscript #3 Summary: The objective of E-PROSPECT is to determine the incremental cost effectiveness of *Lactobacillus rhamnosus* GG with usual care versus usual care without probiotics in critically ill patients. The results of this manuscript are still pending results from PROSPECT. However, we will present the methodology and health economic outputs (Tables and Figures) that would be expected to be produced from this cost-effectiveness analysis.

Reference: In preparation

Economic Evaluation alongside the Probiotics to Prevent of Severe Pneumonia and Endotracheal Colonization Trial (E-PROSPECT): Cost-Effectiveness Analysis

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Key Words: Probiotics, critical care, economics, infection, PROSPECT, cost-effectiveness, ventilator-associated pneumonia

Abstract

Background/Importance: Ventilator-associated pneumonia (VAP) is a common healthcare-associated infection in the intensive care unit (ICU). Probiotics are defined as live microorganisms that may confer health benefits when ingested. Prior randomized trials suggest that probiotics may prevent infections such as VAP and *Clostridioides difficile*-associated diarrhea (CDAD). PROSPECT (Probiotics to Prevent Severe Pneumonia and Endotracheal Colonization Trial) is a multicenter, blinded, randomized controlled trial comparing the efficacy of the probiotic *Lactobacillus rhamnosus* GG versus placebo in preventing VAP and other clinically important outcomes in critically ill patients.

Objective: To evaluate the cost-effectiveness of probiotics with usual care (probiotics group) versus usual care without probiotics (usual care group).

Methods, Setting and Participants: E-PROSPECT was an economic evaluation conducted alongside PROSPECT (October 2013 to March 2019). We adopted a public healthcare payer's perspective over a time horizon from ICU admission to hospital discharge. We derived baseline characteristics and probabilities of in-ICU and in-hospital events. We measured healthcare resource utilization and costs in 2019 United States Dollar among 2653 critically ill patients in 44 centers in 3 countries (9 jurisdictions).

Main Outcomes and Measures: Incremental cost-effectiveness ratios (ICERs) were used to compare between the probiotics group and the usual care group during hospitalization. Primary outcome is incremental cost per VAP averted, with secondary outcomes of cost per CDAD, AAD and mortality. Uncertainty was dealt with nonparametric bootstrapping, and scenario analyses.

Results: Total costs per patient were $xx,xxx (95% confidence interval [CI]: $xx,xxx-$xx,xxx) for xxxx patients who received probiotics compared with $xx,xxx (95% CI: $xx,xxx-$xx,xxx) for xxxx patients who did not receive probiotics (incremental cost, -$xxxx [95% CI: -$xxxx-$xxxx]; P = 0.xx). The incremental cost-effectiveness ratios were $xxxxx (95% CI: xxxxx-xxxxx) per VAP event averted, $xxxxx (95% CI: xxxxx-xxxxx) per CDAD event averted, $xxxxx (95% CI: xxxxx-xxxxx) per ADAD event averted, and $xxxxx (95% CI: xxxxx-xxxxx) per death averted. Cost-effectiveness acceptability curves revealed that a usual care strategy with probiotics remained dominant (most effective, less costly) for the outcome of VAP. In scenario analyses, the probiotics strategy remained least costly unless probiotics acquisitions costs increased from $x to $xxx per dose, and was consistent among higher- and lower-spending health care systems. The majority of parameter variability and scenario analyses did/did not change the outcomes.

Conclusion: From a public healthcare payer's perspective, the use of probiotics in addition to usual care for VAP prevention among critically ill patients will be evaluated in this economic analysis.

Background

Ventilator-associated pneumonia (VAP) is the most common healthcare-associated infection in the intensive care unit (ICU), resulting in a high burden of illness.[6,8] VAP prevention is a patient-important safety goal during critical illness.[5,8,9,106]

Probiotics are defined as "live microorganisms which, when administered in adequate amounts, confer a potential health benefit on the host."[16] They are reported to enhance gut barrier function, reduce host pathogenic bacterial load, modify gut microbiota and modulate the immune system.[17–20] Probiotics studies suggest benefits including reduced incidence of healthcare-associated infections, including VAP[12,21–24,107] and *Clostridioides difficile*-associated diarrhea (CDAD).[29]

A recent multi-center blinded, randomized trial (PROSPECT [Probiotics to Prevent of Severe Pneumonia and Endotracheal Colonization Trial]) compared the effectiveness of probiotics (probiotics group) versus placebo (usual care group).[13–15] Results of the trial concluded that xxx [Cook PROSPECT Manuscript – *pending publication*].

Probiotics have a minor additional drug acquisition cost associated with their utilization (in addition to usual care). However, whether probiotics are used in practice will depend on the preventive effect of probiotics on healthcare-associated infection outcomes and the reduced ICU consumption associated with probiotic use. This endorses the need for comparative economic and clinical effectiveness research to inform bedside practice, clinical guidelines and policy.[31,32]

We conducted this economic evaluation following a protocol designed *a priori* [Lau E-PROSPECT Protocol] and concurrently with the conduct of PROSPECT [Cook PROSPECT Manuscript]. We measured costs (resource utilization) and clinical effectiveness (outcomes and complications) to determine the incremental cost-effectiveness of probiotics in addition to usual care versus usual care in critically ill ICU patients.

Methods

Design

The primary objective of E-PROSPECT was to estimate the incremental costs per VAP prevented arising from a prevention strategy of probiotics with usual care (probiotics group) versus usual care without probiotics (usual care group) during hospitalization. Secondary outcomes included incremental costs to prevent other healthcare-associated complications (CDAD, AAD) and mortality[13–15] *&* [Cook PROSPECT manuscript, Lau E-PROSPECT protocol BMJ Open]. We performed the economic evaluation from the public healthcare payer's perspective, over the time horizon of the ICU admission to in-hospital discharge or death. We developed the economic evaluation according to established economic evaluations guidelines, including cost-effectiveness analysis recommendations[78] and Consolidated Health Economic Evaluation Reporting Standards (CHEERS),[36] as shown in our Supplemental Appendix 1.

The statistical analysis plan was pre-specified as part of the economic evaluation of the PROSPECT protocol (E-PROSPECT) before trial completion and unblinding (ClinicalTrials.gov number: NCT01782755) [Cook PROSPECT manuscript, Lau E-PROSPECT protocol BMJ Open].

We obtained research ethics board approval in all participating centers for the clinical trial. Informed consent was obtained from each participant in the trial or their substitute decision-maker. Research ethics approval for this economic evaluation was granted by the Hamilton Integrated Research Ethics Board (HIREB) of McMaster University (project identifier: REB#:15-322) to include non-patient-based costing data.

Patients

PROSPECT was an international randomized trial in which clinicians, adjudicators and patients were blinded. Critically ill (medical, surgical or trauma) patients received either probiotics (1×10^{10} colony forming units (CFU) of *L. rhamnosus* GG [iHealth, Inc.] or identical placebo suspended in tap water administered twice daily via feeding tube while in the ICU.

Inclusion/exclusion criteria have been described elsewhere.[15] In summary, patients were: adults ≥18 years old, anticipated to be mechanically ventilated ≥ 72 hours, and were eligible to receive probiotics or placebo. We excluded patients who had potential for increased risk of iatrogenic probiotic infection (specific immunocompromised groups), risk for endovascular infection, severe acute pancreatitis, percutaneously-inserted feeding tubes in-situ, strict contraindications or inability to receive enteral medications, or if there was intent to withdraw advanced life support.

From October 2013 to March 2019, we randomized 2653 critically ill patients in PROSPECT. Unit costs were recorded after the last patient was recruited but during the patient follow-up, and prior to PROSPECT analysis and publication. Overall, 1332 patients were allocated to Group A and 1321 patients to Group B. Three patients were excluded from all analyses (they received no study product and had no data collection, as described in PROSPECT) [Cook PROSPECT manuscript].

After exclusion, there were 2650 patients included in the analysis, with 1332 patients in Group A and 1318 patients in Group B (see prior CONSORT diagram) [Cook PROSPECT manuscript]. The main analyses were based on the intention-to-treat principle, which also informed clinical events and costs measured in the economic analyses. Baseline characteristics and findings are summarized in Supplemental Appendix 2.

Clinical outcomes

We collected the clinical effects, frequency or proportions, per-patient event rates and clinical complications for all patients enrolled in PROSPECT. The primary clinical outcome was the difference in VAP event rates. Secondary clinical outcomes included difference in event rates of CDAD, antibiotic-associated diarrhea (AAD) and mortality. PROSPECT was designed and powered to evaluate differences in the rate of VAP events between the probiotics group and placebo group rather than differences in mortality (secondary outcome). Given the in-hospital time horizon and emphasis on VAP events, we did not directly measure health-related quality of life (quality-adjusted life-years [QALY]) or extrapolate lifetime outcomes.

Unit costs

We developed a line-item list of unit costs/healthcare resource use with total costing methodology described elsewhere [*Lau E-PROSPECT protocol - pending*].

Unit costs were captured for follow categories: medications, physician/personnel, diagnostic radiology/laboratory testing, operative/non-operative procedures and per-day hospital 'hoteling' costs not otherwise encompassed (E-PROSPECT costing manual, E-PROSPECT Unit Cost Data Extraction) [*Lau E-PROSPECT protocol - pending*]. We defined overhead/'hoteling' unit costs as direct non-medical costs (general services/procedures which benefit more than one patient at a time, (e.g. utility).[77,94] We collected ward or ICU per diem costs (disaggregated where possible) based on length of stay as the only overhead costs ('hoteling' costs). The disaggregated unit costs reported by each institution was checked for double-counting of previously acquired line-items in other cost categories (i.e. personnel), and duplicate line-items were removed.

Unit costs published by public healthcare payers (e.g. schedule of benefits) were our preferred source. For unit costs not available through the public sources, we performed a pilot study at 9 centers (representing the 9 different jurisdictions) to determine these costs for

PROSPECT patients in different healthcare systems [*Lau E-PROSPECT protocol - pending*] from that hospital's accounting, human resources, pharmacy, radiology or laboratory].[30,83]

If a specific line-item unit cost was not attainable for a specific jurisdiction, we: 1) asked another site within the same jurisdiction for missing unit costs; 2) used multiple imputation or derived a cost-ratio from previously acquired line-items (i.e. drug costs both known in 2 jurisdictions) to impute the missing unit costs [*Lau E-PROSPECT protocol - pending*]. 3) used a mean unit cost approach was utilized for the remaining jurisdictions which did report unit costs [Lau E-PROSPECT protocol BMJ Open].[30,83]

We requested institution-specific unit costs from participating centers (if missing from public databases); if charges were known, we converted to costs by using the institution's cost-to-charge estimated for that item. We recorded professional costing (performance, interpretation, or both), and technical costs for procedures when applicable. We used mean unit costs (with estimated standard errors if possible, or ±25% around the mean unit cost distribution if no distribution existed).

Health care resource use

Healthcare resource use was collected for 2653 patients (1332 in Group A, 1321 in Group B) enrolled from all 44 hospitals in 3 countries (41 in Canada, 2 in the United States and 1 in Saudi Arabia). Healthcare resource use was captured for the same unit cost categories above.

Total costing calculation and statistical analytic plan

All 9 jurisdictions were invited to participate in the costing component of the economic evaluation (with one center representative of each jurisdiction).

The E-PROSPECT steering committee will review evidence underlying the relative importance of cost variables [*Lau E-PROSPECT protocol - pending*], taking into account the unit cost magnitude alongside incremental differences in resource utilization between groups. If a unit cost for a particular line-item is deemed to be small and/or infrequent (and therefore unlikely to influence the incremental difference in total costs), then that line-item was removed from the final analysis. Items without a difference in resource utilization between probiotic and placebo groups but which contribute substantially to costs will be retained (even if little to no incremental difference in costs would exist between the two arms) to maintain validity and accurately reflect the magnitude of costs for hospitalization of a critically ill patient.

At the patient level, individual resource utilization (frequency or event rates of medications administered, laboratory and radiological tests incurred, other procedures or operations performed, per-day personnel costs, and ICU or ward days) will be multiplied by jurisdiction unit costs to calculate individual total costs (total cost = unit cost per resource x all patient's individual resource utilization). This approximates the total inpatient costs for each patient from the time of ICU admission until discharge from hospital or death [Lau E-PROSPECT protocol].

Total groups costs will be calculated for the probiotics and usual care groups by summing each of the individual patient costs. Incremental costs were taken as the difference in per-patient costs between groups. We defined incremental effects as the different in per-patient event rates between groups (or the differences in proportions of clinical effects between group). For missing data, we will choose appropriate imputation methods according to the type and distribution of the missing data.[81,82] Appropriate "standard dose" for non-titratable medications (e.g. chlorhexidine) and a clinically appropriate "medium dose" for titratable medications (e.g. vasopressors or inotropes) will be estimated for various medications. Furthermore, we used various assumptions (see Appendix 1) to estimate other missing resource utilization.

The incremental cost-effectiveness ratio (ICER) will be measured the ratio of incremental costs per incremental effects of probiotics versus usual care during the period of hospitalization

(from ICU admission to hospital discharge). Each of the clinical outcomes (VAP, CDAD, AAD, and mortality) will be used to calculate the incremental cost per episode prevented.

We planned to use descriptive analyses means (with standard deviations), counts (and proportions), or frequencies (percentage) to describe baseline characteristics, effect, and cost estimates, wherever appropriate. We will use standard parametric or non-parametric tests (Chi-square tests and two-sample t-test comparisons) where appropriate to compare differences between the two groups. Statistical significance for differences among *a priori* comparisons was set at p = 0.05 (2-sided).

We plan to adjust all costs to 2019 US dollars, accounting for inflation and currency exchange rates.[37,84–86] International currency conversion will be used instead of purchase power parity (PPP)-based conversions, because health-specific PPPs were not available for all participating countries.

Subgroup analyses

For pre-specified subgroup analyses (Supplemental Appendix 9) from PROSPECT, we planned to investigate specific patients who may have differential effects and costs as compared to the entire population, including: diagnostic category (medical, surgical, trauma);[6] age <65 years, 65-75 years and >75 years;[88,89] frailty status (baseline Clinical Frailty Score $\geq$5 versus <5);[90] patients who received/did not receive antibiotics within 2 days of randomization;[15] prevalent (present at the time of enrollment) vs. incident pneumonia.[15]

Sensitivity and scenario analyses

To assess the uncertainty associated with cost and effects estimation, we planned perform a probabilistic sensitivity analysis, using non-parametric bootstrapping techniques to generate 95% confidence intervals (CIs). We plan to perform 1000 bootstrap simulations in the following manner: each simulation drew xxxx patients per group, with replacement (for both events and cost) in pairs. For each sample, the difference in event rate and cost was calculated, obtaining 1000 pairs of differences in cost and event rate to generate an incremental cost-effectiveness plot (Figure 1). We will plot results on a cost-effectiveness plane (Figure 1) per VAP averted, and also demonstrated the probability of probiotics' cost-effectiveness on a cost-effectiveness acceptability curve (CEAC) for various willingness-to-pay (WTP) thresholds (Figure 2). For secondary outcomes of CDAD, AAD and mortality, we will present corresponding cost-effectiveness planes (Supplemental Appendix 3-5) and CEACs (Supplemental Appendix 6-8).

We will also perform scenario analyses with variations of estimates of pairs of potentially influential variables (i.e. costs of probiotics, per day cost of care in ICU and hospital wards) across plausible ranges (variation of costs: 50-150%) to explore potential cost differences in higher- and lower-spending health care jurisdictions to determine if different estimates change the overall results.

Primary analysis will be undertaken using Excel (Microsoft Corp, Redmond Washington, US), and SAS (Cary, North Carolina, US).

Oversight

Study operations, methods, submission for funding, and manuscript generation were coordinated by the E-PROSPECT steering committee (VL, DC, FX, RF, BR, JJ, FL, JM).

Results

Results of PROSPECT and E-PROSPECT are pending at the time of this MSc thesis submission. However, we will present the framework of the results and discussion sections forthcoming in this chapter.

Characteristics of study population

Patient characteristics of the E-PROSPECT trial are the same as those of the main RCT (2653 patients randomized to the Group A [n=1332] or Group B [n=1321]). The mean age of these mechanically ventilated patients was 59.8 years, 40.1% were female, and 76.5% were in the ICU with medical admitting diagnoses.

There were 3 patients (0 in Group A, 3 in Group B) who, after randomization, were discovered to have a safety-related exclusion criterion. These patients were not included in the intention-to-treat analysis as they did not receive any study product, and they did not have any further daily data collection [*Cook PROSPECT Manuscript - pending*]. Therefore, 2650 patients (1332 patients in Group A and 1318 patients in Group B) were used to determine resource utilization and total cost calculations.

Clinical outcomes and incremental effects

The main findings and clinical outcomes (events rates) of PROSPECT are described in Table 1.

For the primary outcome, there were xxxxxx (no/significant) differences in effects between groups, with numerically xxxxxxx events of VAP xxxx in the probiotics versus the usual care group (Table 1). For the secondary outcome, there was xxxxxx (no/significant) differences in effects between groups for CDAD or AAD. There were xxxxx (no/significant) differences in mortality. Patients in the probiotic group had xxxxxxx (substantially increased/decreased/no difference) duration of mechanical ventilation and xxxxxx (shorter/longer/no difference) length of stay in ICU and hospital overall in the usual care group.

The incremental effects as the difference in proportions of VAP events between groups was 0.xx [95% CI:]. The incremental effects as the difference in proportions of CDAD events between groups was 0.xx [95% CI:]. The incremental effects as the difference in proportions of AAD events between groups was 0.xx [95% CI:]. The incremental effects as the difference in proportions of mortality events between groups was 0.xx [95% CI:].

Resource use, costs and incremental costs

Resource utilization is outlined in Table 1 for the following categories: medications used, laboratory and radiological investigations performed, procedures and operations performed for trial-related effects, complications, and personnel and institution resources consumed during ICU stay, until hospital discharge or death.

Table 1 lists mean unit costs for: medications, laboratory and radiological investigations, procedures/operations, complications, and personnel and overhead daily institution per diem costs. Supplemental Table 2 lists individual jurisdictional unit costs for the above categories.

Among all patients, the mean post-randomization hospital costs of care per patient who received usual care without probiotics was $xx,xxx [95% CI: $xx,xxx-xx,xxx] compared with $xx,xxx ([95% CI: $xx,xxx-xx,xxx] for patients who received probiotics with usual care. The total incremental cost between groups was $x,xxx,xxx, favouring xxxxxxxx (probiotics/usual care/no difference). The mean cost difference was -$xxxx [95% CI: -$xxxx to $xxxx]; p=0.xx; and was associated with xxxx VAP rates and CDAD (Table 3).

Cost-Effectiveness Analysis

Using cost-effectiveness analysis methodology and conventional cost metrics to prevent VAP events, xxxxxxxxx was the xxxxxxx (dominant/dominated) strategy to prevent VAP, given its xxxxxx (lower/higher) costs combined with xxxxx (better/worse) effects (Table 2). The cost-effectiveness plane shows probiotics are cost-xxxxxxx for VAP prevention, and potentially even cost-xxxxxxx (saving) (Figure 1).

The incremental cost-effectiveness ratios are presented in Table 2. Cost-effectiveness plots for CDAD, AAD and mortality are presented in Supplemental Figures 3-8. There was also xxxxxxxx (no difference/differences also) for CDAD, AAD and mortality.

Subgroup Analyses

The trial considered 5 pre-specified subgroups according to diagnostic category (medical, surgical, trauma);[6] age <65 years, 65-75 years and >75 years;[88,89] frailty status (baseline Clinical Frailty Score ≥5 versus <5);[90] patients who received/did not receive antibiotics within 2 days of randomization;[15] prevalent (present at the time of enrollment) vs. incident pneumonia.[15]

There were xxxxxxx (no/some) significant sub-group interactions detected (xxxxxx: listed subgroups with differences if applicable) (Supplemental Figure 9) for differences in resource use and/or cost-effectiveness.

Sensitivity and scenario analyses

The cost-effectiveness plane and cost-effectiveness acceptability curves (CEACs) are presented in Figures 1 and 2. Using non-parametric bootstrapping, probiotics were xxxxxx (more/less/equally) effective and xxxxxxxx (more/less/equally) costly than usual care in xx% of simulations (Figures 1 & 2), and VAP prophylaxis with probiotics was associated with cost-xxxxxxxxx (effectiveness, neutrality, ineffectiveness, savings) (Figure 1).

As unit costs may vary substantially across 9 jurisdictions (44 centers in 3 countries), we examined their variations on the result of cost-effectiveness. We first examined the relative influence of all individual unit costs and found that higher per-day xxxxxxxxxxx (hoteling/overhead) and xxxxxxx (ventilator days) costs were the largest contributors to between group differences in costs of care. Costs for patients who received probiotics remained xxxxxxxx (lower/higher) than for usual care without probiotics when varying medication, daily hoteling, personnel, procedural/surgical and laboratory/diagnostic imaging costs across standard deviations, or ±25% when cost distributions were uncertain.

Scenario analyses were performed with variations of estimates of pairs of potentially influential variables (e.g. per day cost of care in ICU and hospital wards) across plausible ranges (variation of costs: 50-150%) to explore potential cost differences in higher- and lower-spending health care jurisdictions to determine if different estimates change the overall results.

Discussion

We found that prevention of VAP using the probiotics *Lactobacillus rhamnosus GG* with usual care was xxxxxxx (less/more) costly than placebo with usual care and was associated with xxxxxxx (higher/lower/similar) rates of VAP. There were xxxxxxx (higher/lower/similar) rates of CDAD and AAD, and with xxxxxx (higher/lower/similar) mortality. Sensitivity analyses demonstrated that a strategy using probiotics was most effective, least costly xx% of the time, and remained xxxxxxx (more/less/similar) costly unless the drug acquisition cost of *Lactobacillus rhamnosus GG* was increased by more than x fold.

These findings are important for ventilated adult critical care patients, demonstrating a xxxxxxxx (cost-effective/cost-savings/cost-neutral/non-cost-effective) rationale with probiotics being xxxxxx (xxxx costly, xxxx effective) alongside clinical effectiveness knowledge from PROSPECT. For example, if an ICU with 1000 medical-surgical admissions per year uses probiotics alongside usual care, the annual incremental cost-xxxxxx may be between $xxxxxxxx to $xxxxxxxx with similar or outcomes, despite the individual drug acquisition cost of probiotics being $x.xx per day.

These findings supplement PROSPECT in terms of xxxxxxxxxxx (cost-effectiveness/cost-neutral/non cost-effective) [*Cook PROSPECT manuscript - pending*]. These findings (complement/contradict) prior systematic reviews on cost-effectiveness of probiotics for

preventing healthcare-associated infections.[76] Our CEA on probiotics alongside prior SRs for effectiveness[12,25–28] helps enhance the existing evidence on probiotic prophylaxis.

Ventilator-associated pneumonia prevention bundles include multiple interventions (e.g. chlorhexidine oral decontamination and head-of-bed elevation). However, recent re-evaluation of very low to moderate evidence for chlorhexidine oral decontamination[108,109] and head-of-bed elevation[110], which now questions their indiscriminate use and inclusion in VAP bundles. Further studies exploring additional interventions for VAP prevention, including selective decontamination of the digestive tract (SDD),[111] and probiotics,[12,14,15] need to have strong evidence-based studies of effectiveness backing their inclusion. To date, there are no current guidelines which either strongly or weakly recommend routine use of probiotics in standard-of-care VAP prevention bundles. Some guidelines did not recommend routine probiotics use,[112,113] while others do not mention probiotics at all.[2,4,5,114] Pairing PROSPECT alongside E-PROSPECT with evidence for both potential xxxxxxxx (effectiveness and cost-effectiveness) will potentially allow for xxxxxx (integration) of probiotics into VAP bundles.

Compared to other infection-prevention strategies, probiotics appear to be xxxxxxx (similarly) cost-effective and potentially cost-saving for VAP prevention. A study examining concomitantly administered central-line associated bloodstream infection (CLABSIs) and VAP programs combined documented ICERs of $14,250.74 USD/life-year gained and $23,277.86/ QALY.[71] A prior cost-benefit analysis using a Markov model revealed prophylactic probiotics demonstrated cost benefit for preventing VAP, with a willingness-to-pay (WTP) threshold of $15,958 per VAP case averted. The incremental cost-effectiveness ratio (ICER) between probiotics and no probiotics showed dominance of probiotics over placebo (with usual care).[10] Hence, our findings are likely xxxxxxx (aligned/out-of-keeping) with other healthcare-associated infection prevention strategies, from a clinical prevention but also economic standpoint. However, there are no prior benchmark WTP thresholds for VAP prevention. Therefore, individual jurisdictions will need to determine their own WTP for probiotics and VAP prevention (as there is no common denominator like QALYs or prior VAP bundle CEA WTP thresholds for comparison). Xx (If/as) the probiotics were xxxxxxxxx (cost-effective) at a very low WTP threshold, or even xxxxxxxxxxxx (dominant and cost-saving), it would be xxxxxxx (easier/harder) to suggest wider implementation.

Sensitivity analysis indicates the relative importance of various factors in the incremental cost differences between strategies, especially xxxxxxxxx (ICU and hospital length of stay and ventilator days) being most influential. Reductions in xxxxxxxxx VAP (e.g. xxxxxxxx) complications also led to xxxxx (lower) costs among patients receiving probiotic prophylaxis with *Lactobacillus rhamnosus GG*, emphasizing the robustness of this analysis.

There are several strengths of this health economic evaluation. The protocol is prospectively designed with collection of predetermined costs and effects (including subgroup and sensitivity analyses) alongside a randomized control trial to minimize bias. Many other economic analyses are designed after unblinding of results from the primary trial, potentially leading to investigator hypothesis-driven biases. Another strength is that clinical effects and costs are based on trial-based, patient-level data (rather than model-based, hypothetical cohorts and inputs incorporated from multiple sources in the literature), increasing internal validity with both costs and effects more representative of the study cohorts. Furthermore, the ability to capture jurisdictional costs and effects with their own distributions and variance, allows a more precise estimate of between-group differences, which increases external validity and generalizability [Lau E-PROSPECT protocol BMJ Open]. And finally, our study was peer-review funded rather than supported by the manufacturer of probiotics with the peer-review funding agency playing no role in the study design, conduct, analysis, interpretation or decision to publish.

There are also limitations of this study. First, the relatively short-time horizon (time to in-hospital discharge/death) could potentially miss additional costs associated with downstream

health consequences (e.g. physiotherapy, rehabilitation, home oxygen, etc.) secondary to VAP. Future studies in critical care research could investigate longer-term or lifetime time horizons, which is a general recommendation.[115,116] Second, a lack of QALY metrics may censor important differences in quality-of-life that may not be fully captured by clinical outcome events alone (e.g. VAP, CDAD, AAD). For future studies, a cost-utility analysis approach could be suggested. Third, as all RCTs primarily assess efficacy rather than effectiveness, generalizability and external validity of this health economic evaluation may not represent the same treatment effects and costs as in routine clinical practice.[30] And finally, although PROSPECT and E-PROSPECT compared the probiotic *Lactobacillus rhamnosus GG* with placebo and usual care, this may not be generalizable to all types of probiotics for both effectiveness & cost-effectiveness. Results may differ with other species, strains and doses.

Nevertheless, the findings of PROSPECT and E-PROSPECT will inform decisions about using probiotics to minimize VAP risk and the associated potential healthcare expenditures. As probiotics are shown to be xxxxxxxxxxx (cost-effective/cost-saving), their integration can inform bedside practice, clinical guideline development and aid health policy decision-makers. Individual jurisdictions or countries will also need to take into account their own individual willingness-to-pay thresholds for clinical event prevention, as those thresholds may affect their prescribed guidelines.[76]

Conclusions

In conclusion, from a public healthcare payer's perspective (considering the time horizon from ICU admission to hospital discharge), VAP prophylaxis with *Lactobacillus rhamnosus GG* in critically ill medical-surgical patients was xxxx (more/less) effective and had similar or xxxxx (lower/higher) costs than usual care without probiotics (xxxxxxxxxx – cost-effective, cost-saving, cost-neutral, not cost-effective). These findings were driven by xxxxx (decreased/increased) ICU/hospital length of stay and duration of mechanical ventilation, decreased incidence of VAP, decreased mortality). Both clinical efficacy and cost-effectiveness evidence can aid in jurisdictional guideline development and health policy decision-making.

Acknowledgements

PROSPECT was designed by the PROSPECT Steering Committee and improved by Drs. Dawn Bowdish and Erick Duan, the PROSPECT Investigators and Research Coordinators and the Canadian Critical Care Trials Group. We are grateful for the commitment of all our colleagues in participating centers, and staff at the Methods Center for their expertise including Nicole Zytaruk, Lois Saunders, Shelley Anderson-White, Mary Copland, Megan Davis, France Clarke and Alyson Takaoka.

Funding and Conflicts of Interest

This economic evaluation (E-PROSPECT) and PROSPECT was funded by the CIHR, McMaster University, St. Joseph's Healthcare Hamilton, Canadian Frailty Network, Physicians Services Incorporated of Ontario, the Hamilton Academic Health Sciences Organization and the Academic Medical Organization of Southwestern Ontario. DJC is a Canada Research Chair of the Canadian Institutes of Health Research. Study products were donated by i-Health, Inc., the manufacturers of *L. rhamnosus GG*; however, no funding for either the trial itself or the economic evaluation was received from the manufacturers of any probiotic or other agent involved in VAP prevention or treatment.

None of the funders played a role in the conception, design, conduct, oversight, analysis, interpretation or decision to submit this manuscript for publication or in the preparation, review or approval of the manuscript.

CHAPTER 5: Methodological Issues, Future Directions and Thesis Conclusions

Presented here are the methodological challenges faced as part of this thesis, how they were addressed, future directions for this area of research, and the conclusions based on this thesis.

Methodological Issues with Probiotics Economic Evaluations Systematic Review (Chapter 2)

Due to the heterogeneity of methodology, economic evaluation reporting (cost-effectiveness, cost-utility, or cost-benefit), time-horizons, discount rates, perspectives and outcomes (VAP, CDAD, AAD), we were unable to perform quantitative meta-analysis. I addressed these issues by creating a descriptive summary table of each individual article in the SR, and narratively summarizing the individual economic evaluations. Heterogeneity of outcomes also made comparison alongside other healthcare-associated infection prevention strategies (e.g. CLABSIs) challenging. In order to overcome this limitation in the data, future trialists and health economists should measure health-related quality-of-life (HRQoL) and adopt a cost-utility analysis (CUA) approach using a common denominator of QALYs.

Evaluating risk of bias (RoB) in multiple types of studies and inputs for model-based economic evaluations was also challenging. Unlike a trial-based economic evaluation, which bases their resource use and clinical outcome data on a single source (e.g. RCT), model-based economic evaluations often use multiple source inputs. In order to overcome this challenge, multiple risk of bias evaluative tools (e.g. Cochrane RCT RoB tool[38], Newcastle-Ottawa Scale for observational studies (cohort & case-control)[39], and CLARITY Evidence Partners tool for surveys)[40,117] were required and varied depending on study design. As we were without guidance on how best to combine these RoB evaluations, we developed the following a *priori* approach: if each source input in a particular economic model had low ROB, the overall model-based economic evaluation would be low ROB (even for varied types of input studies). If any source study had an unknown or high ROB, then the entire economic evaluation would be assessed an unknown or high ROB[76], which is consistent with our usual approach to RoB.

GRADE does not recommend including evidence on cost-effectiveness. Since economic evaluations make underlying assumptions which may differ from that of guideline developers, GRADE instead recommends that resource use and costing should both be described in the SoF table,[70] rather than costing alone. However, our SR revealed a paucity of resource use costing data,[76] precluding its addition to the SoF table. Applying resource use would also be a departure from the traditional GRADE system for guideline development[70]. Therefore, in order to overcome these challenges, we maintained adherence to the standard GRADE reporting one might use in an interventional review, which revealed very low certainty of evidence regarding cost-effectiveness for probiotic prophylaxis for the outcomes of VAP, CDAD and AAD.[76]

Finally, assessing roles of funding/sponsorship with subgroup analysis, demonstrating that all economic evaluations with industry-sponsorship showed cost-effectiveness in favour of probiotics, while 3 out of 4 studies without industry sponsorship showed cost-effectiveness (as part of a subgroup analysis investigating funding/sponsorship). However, the 1 study which showed no difference in effectiveness or economic outcomes was the largest and only RCT-based CEA/CUA assessment, which had peer-review sponsorship.[76] Therefore, sponsorship bias was addressed in our SoF assessment and accounted in GRADE assessment of RoB, which changed downgraded this category to serious. Furthermore, because of a low number of studies in our SR, we could not address the issue of publication bias by using typical Egger's weighted regression for continuous outcomes (e.g. cost-effectiveness) assessment of funnel plot asymmetry[118] or Begg's/arcsine tests for dichotomous (e.g. VAP, CDAD, AAD) outcomes.[119,120] Despite the absence of a quantitative analysis, we overcame this with a comprehensive search that documented every instance of industry sponsorship, and reviewed

trial registrations where applicable[43]. In the end, we attempted to address publication bias with these methods to the best of our ability. Perhaps a future updated SR after an increased number of publications assessing probiotic health economic evaluations would be required to assess publication bias.

The conclusions of this systematic review (published in the Canadian Journal of Anesthesia),[76] pointed to the importance of future large, rigorous RCTs with concomitant health economic evaluations and peer-reviewed funding to improve the quality and certainty of the evidence regarding cost-effectiveness of probiotic prophylaxis for healthcare-associated infections.

Methodological Issues with E-PROSPECT protocol (Chapter 3)

There were also some methodological issues that were encountered while developing this health economic evaluation protocol alongside a randomized control trial (PROSPECT).

To reduce the potential for investigator hypothesis-driven biases and post-hoc analysis, we developed a prospective, *a priori* study protocol for the cost-effectiveness analysis which is to occur alongside a randomized control trial with pre-specified statistical analysis plan (SAP) prior to unblinding. Concomitant clinical/economic data acquisition also reduces missing data while increasing research efficiency. The multi-centered jurisdictions help increase generalizability by assessing variation for both costs and effects in different areas. Given that PROSPECT completed recruitment in February 2019, it was important and timely for this protocol to be published prior to the unblinding and publication of PROSPECT study results.

Our statistical plan includes: (1) calculating incremental effectiveness between groups as either per-patient event rates or proportion of a clinical event (e.g. VAP) from PROSPECT; (2) planned uncertainty (non-parametric bootstrapping) and sub-group analyses (previously defined in PROSPECT); and, (3) calculation of incremental costs using a bottom-up approach of line-item resource utilization multiplied by mean unit costs estimation from various jurisdictions. All these methods address estimating the most accurate mean costs (derived from resource use) and effects (derived from health consequences) from the bottom-up, and assessing uncertainty by building 95% confidence intervals using the non-parametric bootstrapping approach. These methods serve to derive the incremental cost-effectiveness (separately if dominant or dominated, ICER if in quadrant I, III or cost-neutral) of probiotics for VAP, CDAD, AAD and mortality prevention.

One other methodological issue to address for this protocol was the justification for short, non-fixed time-horizon cost-utility outcomes without assessment of health-related quality-of-life (HRQoL). As the PROSPECT trial followed patients from randomization to hospital discharge, the time horizon was expected to be non-fixed, as time-to-hospital discharge is expected to be variable between patients and groups. Long term clinical consequences for VAP, CDAD, or AAD would not be expected, hence: (1) the use of a short time horizon in-keeping with our healthcare payer perspective for in-hospital costs; (2) no use of discounting as outcomes >1 year are not expected, and (3) no extrapolation for longer-term outcomes (even though VAP could potentially cause ARDS). PROSPECT did not include HRQoL in case-report forms, hence we could not calculate quality-adjust-life years or apply cost-utility analysis methodology. We also did not extrapolate these outcomes for these patients given the original CEA design for the E-PROSPECT protocol. Future studies could incorporate QALYs and CUA methodology to address these issues.

Despite these limitations, the planned protocol for E-PROSPECT was finalized and published in BMJ Open.

Methodological Issues with E-PROSPECT cost-effectiveness analysis (Chapter 4)

Prior methodological issues raised during the protocol development also gave rise to further issues during the CEA of PROSPECT.

For unit costs line-items that were not obtainable from public databases, we performed pilot testing from the 9 jurisdictions of PROSPECT. During this phase, many line-items were acquired, with a few more missing second to jurisdictional disclosure factors. We addressed the remaining missing unit costs by either imputation or a mean unit cost approach across jurisdictions (similar to previous CEAs).[30]

Multiple assumptions were needed regarding resource use from PROSPECT CRFs, as not all resource use was measured quantitatively, but nominally (e.g. checkboxes for presence/absence of procedures/surgeries and drugs with no counts or dosage). We addressed with the following assumptions. We chose "standard doses" for non-titratable medications (e.g. lansoprazole 30 milligrams oral daily) which would otherwise be the normal dose for that drug. For titratable medications (e.g. norepinephrine infusion), a "medium dose" (e.g. 10 micrograms/minute) was chosen as it would estimate the potential mean dosage of each medication a typical ICU patient may consume. This methodology has been previously described [30] For estimating resource use from a given procedure/surgery, we used the lowest number of resource use was estimated for any particular health outcome/consequence. For example, if a patient underwent a surgery (e.g. colectomy for CDAD), we would estimate the lowest utilization of medications (e.g. antibiotics), laboratory/radiology investigations (e.g. *C. difficile* assay, CT abdominal scan), personnel (e.g. ICU nursing, RTs, etc.), procedural/surgical (e.g. surgeon, anesthetist) use and hoteling (e.g. ICU/ward per day) associated with a procedure/surgery without increased complications (e.g. without repeat laparotomies). Although this may underestimate difference between groups (and bias cost-effectiveness towards the null hypothesis), we elected to take this conservative approach to estimating resource use in measuring differences between groups. We elected not to amplify differences in resource use, even if there were repeated complications of the same procedure/surgery. This conservative bias would ensure that if differences in resource use did exist, then we would more likely to conclude these differences to be true.

We focused our incremental CEA on including cost drivers with two main principles: (1) line-items with significant unit costs; (2) items with significant between-group differences. That gave us the ability to exclude unit costs line-items if they did not meet these 2 principles. For example, ICU length of stay would be expected to be included in the incremental analysis given its high unit cost per ICU day, alongside potential between-group differences in length of stay. In contrast, a medication (e.g. senna) may be excluded based on its low unit cost, but also if there are no significant between-group differences in resource use. This methodology would ensure that our CEA would include main cost drivers of between-group differences (with differences in either resource use and/or unit costs). The presentation of outcomes from the PROSPECT CEA provided some methodological issues. Our main cost-effectiveness (CE) plane using non-parametric bootstrapping for uncertainty analysis could only present each separate outcome on their own plots (VAP, CDAD, AAD and mortality), as opposed to a CE plane with a common effect denominator like QALYs, in which all interventions and their outcomes could be plotted. Same would apply to CEACs with various WTP thresholds. This speaks to future incorporations of HRQoL/QALYs into critical care outcomes research mentioned previously, allowing a common denominator like cost per QALY to compare interventions across different illnesses/disciplines/disease states/populations.

External validity has been helped by addressing variation between jurisdictions for this cost-effectiveness analysis. All CEA trial data must be taken into context, as there are no benchmark WTP thresholds for VAP, CDAD, AAD or mortality from these illnesses. Jurisdictions must also account for own individual WTP thresholds for healthcare-associated infection event prevention, as WTP may affect a jurisdiction's prescribed guidelines or health-policy decision-making.

Future Directions

Future areas of research in the field of probiotics and healthcare-associated infections could examine strain-specific & dosage-specific regimens (as PROSPECT primarily examined *Lactobacillus rhamnosis GG*) to see how costs and effects may differ.

Future studies should involve collaborations between health economists and trialists to help design RCTs which are developed alongside health economic evaluations to increase efficiency (by reducing missing cost and effect outcome data collection) and reducing bias (by pre-specified economic evaluation SAPs alongside RCTs).

Furthermore, health economists and trialists should work towards validating specific HRQoL measures in critically ill populations, so that QALYs can be used to implement CUA methodology alongside RCTs. These future trials can hopefully take even longer term time-horizons and even broader economic societal perspectives, in order to enhance their contributions of the health economic evaluation under the umbrella of health technology assessment[77].

Thesis Conclusions

Based on our systematic review, there is very low certainty evidence supporting the cost-effectiveness of probiotic prophylaxis to prevent VAP and other healthcare-associated infections (despite the majority demonstrating cost-effectiveness or even cost-savings).[76]

As part of this research program, we developed a health economic evaluation protocol and planned a cost-effectiveness analysis alongside a multicenter trial [Lau E-PROSPECT Protocol BMJ Open]. The findings of the E-PROSPECT analysis will help to inform bedside clinicians, will be incorporated into clinical guidelines, and will inform health policy regarding healthcare resource allocation for the prevention of VAP and other healthcare-associated infections.

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