ORIGINAL ARTICLE

Cost-Effectiveness Analysis of the Use of Probiotics for the Prevention of *Clostridium difficile*–Associated Diarrhea in a Provincial Healthcare System

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OBJECTIVE. To conduct a full economic evaluation assessing the costs and consequences related to probiotic use for the primary prevention of *Clostridium difficile*–associated diarrhea (CDAD).

DESIGN. Cost-effectiveness analysis using decision analytic modeling.

METHODS. A cost-effectiveness analysis was used to evaluate the risk of CDAD and the costs of receiving oral probiotics versus not over a time horizon of 30 days. The target population modeled was all adult inpatients receiving any therapeutic course of antibiotics from a publicly funded healthcare system perspective. Effectiveness estimates were based on a recent systematic review of probiotics for the primary prevention of CDAD. Additional estimates came from local data and the literature. Sensitivity analyses were conducted to assess how plausible changes in variables impacted the results.

RESULTS. Treatment with oral probiotics led to direct costs of CDN $24 per course of treatment per patient. On average, patients treated with oral probiotics had a lower overall cost compared with usual care (CDN $327 vs $845). The risk of CDAD was reduced from 5.5% in those not receiving oral probiotics to 2% in those receiving oral probiotics. These results were robust to plausible variation in all estimates.

CONCLUSIONS. Oral probiotics as a preventive strategy for CDAD resulted in a lower risk of CDAD as well as cost-savings. The cost-savings may be greater in other healthcare systems that experience a higher incidence and cost associated with CDAD.

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Clostridium difficile is an anaerobic, spore-forming bacterium responsible for *C. difficile* infections (CDI) including *C. difficile*-associated diarrhea (CDAD), pseudomembranous colitis, and toxic megacolon, which can lead to sepsis and death.[1,2] The incidence and severity of CDI has increased in healthcare settings over the past decade with increases in patient transfer to the intensive care unit, colectomy, and deaths due to CDI.[1] A substantial financial burden has been associated with this changing epidemiology. Patients with CDI require isolation, supportive therapy for underlying complications arising from CDI, and specific antibiotic therapy for *C. difficile*.[3] On average these patients spend an extra 1–3 weeks in hospital compared with noninfected patients, and the increased duration of hospitalization has been a major contributor to increased costs.[3]

A major risk factor for hospitalized patients to acquire *C. difficile* is antecedent antibiotic exposure.[4] Probiotics are live organisms thought to improve the microbial balance of the gut flora and to reduce the risk of colonization by *C. difficile* and other pathogenic bacteria.[5] Probiotics are increasingly available as capsules and food supplements sold in health food stores and supermarkets and have been suggested as a means of both preventing and treating CDI.[5]

A recent Cochrane systematic review and meta-analysis suggested that when probiotics are routinely given with antibiotics they reduce the risk of developing CDI, specifically CDAD,[5] which may correspondingly reduce the associated increased treatment costs and extended length of stay in acute care facilities. Therefore, a full economic evaluation assessing the costs and consequences related to probiotic use is required.

METHODS

Overview

A cost-effectiveness analysis was conducted to evaluate the impact of oral probiotics on the incidence and cost of CDAD among hospitalized patients. The target population was all

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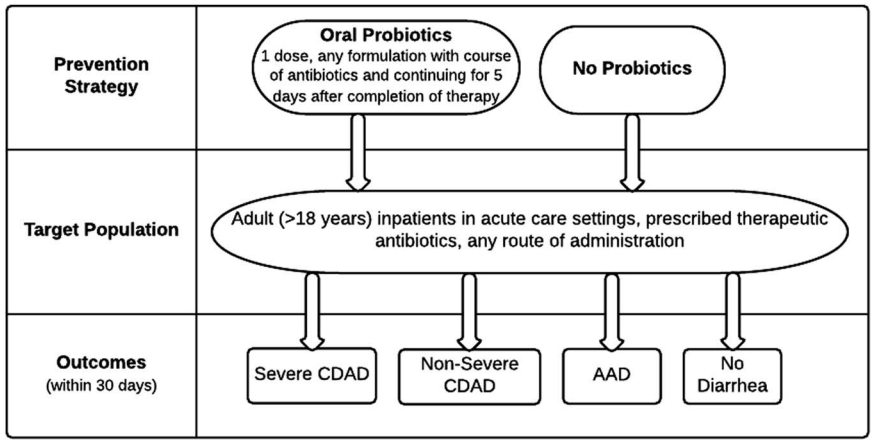

FIGURE 1. Structure of decision tree showing the flow of patients and outcomes considered in the cost-effectiveness analysis. AAD, antibiotic-associated diarrhea; CDAD, *Clostridium difficile*-associated diarrhea.

adult (>18 years) inpatients in acute care settings who were prescribed therapeutic antibiotics regardless of route of administration.

The preventive intervention was the administration of 1 dose of oral probiotics in any formulation with the course of antibiotics and continuing for 5 days following the completion of therapy (ie, the probiotic group). The alternative strategy was no probiotic given to the target population. The cost-effectiveness analysis was conducted from the perspective of a publicly funded healthcare system.

Decision Model Design and Assumptions

The impact of probiotic use on the proportion of patients developing CDAD was modeled using decision analysis. Within each treatment strategy, a patient at risk of CDAD could transition to one of several clinical states, including CDAD, severe CDAD, antibiotic-associated diarrhea (AAD), or no diarrhea (Figure 1), with the risk based on the results of the Cochrane review of probiotics. The time horizon considered in the cost-effectiveness analysis was 30 days to account for duration of antibiotics, duration of probiotic use, and patient follow-up time as measured in the clinical trials and the occurrence of severe CDAD during a hospitalization. The economic model was developed and analyzed using standard approaches as recommended by the Canadian Agency of Drugs and Technologies in Health guidelines and with conventional software (TreeAge Pro Healthcare; TreeAge).[6]

To ensure face validity, the model was reviewed by expert members of the provincial antimicrobial stewardship committee, consisting of pharmacists and infectious disease physicians. A series of consistency checks was completed and the model was calibrated to ensure the outputs were consistent with the model inputs. The main assumptions in this model were as follows:

- For patients developing CDAD, the probability of severe CDAD was the same in both strategies.
- Probiotics lowered the risk of AAD, consistent with the findings of the Cochrane review.
- Probiotics reduced the duration of symptoms and contact precautions among patients with AAD but not with CDAD.[7]
- Adverse events related to probiotic use are negligible and were not included in the model.[5,8]
- CDAD patients incurred a higher healthcare cost than non-CDAD patients, but the cost for managing patients with CDAD is equal in both strategies. Since the incremental cost of CDAD on hospitalization was uncertain, 3 methods were used to estimate the incremental cost. In the base case, the incremental cost of CDAD was based on a published systematic review of the literature of attributable costs of healthcare-associated infections.[9] In sensitivity analyses, we used estimates from randomized trials, taking the average per diem hospital costs from Alberta hospitalization data and assuming that only severe CDAD was associated with incremental costs.
- Metronidazole was used to treat non-severe CDAD patients, whereas vancomycin was used to treat severe CDAD patients.

Data Inputs

The effectiveness measure for the use of oral probiotics for preventing CDAD was based on 23 efficacy studies included in a Cochrane review (Table 1).[5] The inclusion criteria were randomized controlled trials reporting incidence outcomes for CDAD, adult and pediatric participants receiving antibiotic therapy for any reason, and interventions comparing probiotics (any strain or dose) versus placebo, an alternative prophylaxis, or no treatment for the prevention of CDAD. Studies using probiotics for the treatment of CDAD were excluded.

Of the patients who develop CDAD, the proportion developing severe CDAD was derived from a 1-year retrospective study of hospital inpatients at least 18 years of age who had positive *C. difficile* toxin results.[10] Severe CDAD patients were defined as having at least 1 of the following criteria: (1) death

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TABLE 1. Base Case Estimates of Risk and Effectiveness

Variable	Parameter estimate	Range	Reference
Risk of CDAD and AAD in patients not receiving oral probiotics			
Risk of AAD	0.221	0.05–0.28	Goldenberg et al[5]
Risk of CDAD	0.055	0.01–0.10	Goldenberg et al[5]
Risk of severe CDAD	0.122	0.05–0.286	Henrich et al[10]
Contact isolation days, AAD	6.40	4.6–8.2	Gao et al[7]
Contact isolation days, CDAD	7.0	5.0–18.0	AHS IPC
Risk of CDAD and AAD in patients receiving oral probiotics			
Relative risk AAD	0.600	0.49–0.72	Goldenberg et al[5]
Relative risk CDAD	0.360	0.26–0.51	Goldenberg et al[5]
Risk of severe CDAD	0.122	0.05–0.286	Henrich et al[10]
Contact isolation days, AAD	3.64	3.02–4.26	Gao et al[7]
Contact isolation days, CDAD	7.0	5.0–18.0	AHS IPC
Length of treatment, days			
Metronidazole, 250 mg, 6x/day	10.0	7.0–14.0	AHS Pharmacy
Vancomycin, 125 mg, 4x/day	10.0	7.0–14.0	AHS Pharmacy
Length of oral probiotics, days	15.0	12.0–20.0	Gao et al[7]

NOTE. AAD, antibiotic-associated diarrhea; AHS, Alberta Health Services; CDAD, *Clostridium difficile*–associated diarrhea; IPC, Infection Prevention and Control.

TABLE 2. Base Case Cost Estimates

Variable	Parameter estimate[a]	Range	Reference
Incremental cost of CDAD			
Nonprobiotic group	$11,862.57	$9,584.65–$14,268.71	Zimlichman et al[9]
Probiotic group	$11,862.57	$9,584.65–$14,268.71	Zimlichman et al[9]
Contact precautions			
Isolation room cost, per day	$41.67	…	AHS IPC
Nursing cost donning and doffing PPE, per day	$34.83	…	AHS IPC
Gowns, per day	$21.88	…	AHS IPC
Gloves, per day	$7.15	…	AHS IPC
Total costs per day	$105.53	$79.15–$131.91	AHS IPC
Isolation terminal cleaning, once per patient	$24.68	$18.51–$30.85	AHS IPC
C. Diff Quik Chek Complete Assay			
2-step algorithm test	$30.31	$3.0–$31.0	Calgary Laboratory Services
Treatment			
Metronidazole, 250 mg, 6x/day, per capsule,	$0.37	$0.28–$0.46	AHS Pharmacy
Vancomycin, 125 mg, 4x/day, daily total	$4.76	$3.57–$5.95	AHS Pharmacy
Oral probiotics, per day	$1.57	$0.11–$3.50	AHS Pharmacy

NOTE. AHS, Alberta Health Services; CDAD, *Clostridium difficile*–associated diarrhea; IPC, Infection Prevention and Control; PPE, personal protective equipment.
[a]All costs actualized to 2015 Canadian dollars.

within 30 days after onset of symptoms or positive assay in which CDI was a major contributor, (2) at least 1 intensive care unit admission in which CDI was a major contributor, (3) colectomy or other surgery directly attributed to *C. difficile*, or (4) intestinal perforation in the presence of CDI.

Costs

Since the analysis was using the perspective of a publicly funded healthcare system, only direct medical costs of CDAD were considered (Table 2). Direct nonmedical costs, time costs to patients and families, and productivity costs were not included. All costs were converted into 2015 CDN$ using the Bank of Canada currency convertor and the fixed basket of goods and services of the 2015 Consumer Price Index. Given the short time horizon, discounting was not required.

The cost of oral probiotics was based on a commercially available product in Canada. In addition to the probiotic costs, the incremental hospitalization costs, cost of isolating a patient on contact precautions, microbiologic testing to identify *C. difficile* bacteria, CDAD treatment agents, and the cost of longer hospital stays were considered. The CDAD treatment

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agents included the antibiotics commonly used in the cases of CDAD infections, metronidazole and/or vancomycin. Antibiotic and probiotic unit costs were derived from the AHS Pharmacy Procurement and Inventory Department.

Point estimates of the incremental cost associated with hospitalization of CDAD patients were taken from a published systematic review of the PubMed literature (1986 through April 2013) for the estimation of attributable costs. The authors used Monte Carlo simulation to generate 95% confidence intervals of the attributable costs.[9]

The cost per day of contact precautions was derived from a review of daily costs for patients on CDAD precautions in 2012 at a local, large urban hospital in Alberta. The isolation room costs included the daily revenue loss from a private room. The costs for donning and doffing personal protective equipment were determined by the nurses' average hourly wage and the number of minutes per hour nurses spent donning and doffing such equipment. The isolation terminal cleaning costs were derived from the time and cost for enhanced cleaning of an isolated patient's room following discharge. Costs of microbiologic testing for the identification of *C. difficile* using the *C. difficile* Quik Chek Complete Assay (TECHLAB, Blacksburg, VA) were provided by the centralized laboratory, Calgary Laboratory Services.

Sensitivity Analysis

To assess variability in parameter values, extensive 1-way sensitivity analyses across ranges outlined in Tables 1 and 2 were conducted to assess whether plausible changes in any variable would result in the oral probiotic strategy being more costly. Three 2-way sensitivity analyses were conducted varying ranges of the relative risk of either CDAD or AAD with the incremental cost of CDAD; and varying the risk of both CDAD and AAD. A variety of scenarios to assess uncertainty were considered (Table 3), including a best-case scenario using the results from a publication by Gao et al.[7] That clinical trial reported a better effectiveness estimate of probiotic use for the reduction of CDAD than in the base case (95% reduction vs 64% reduction). A worst-case scenario excluding the study by Gao et al[7] was also assessed.

RESULTS

Base Case

The Cochrane review of probiotics found that the risk of CDAD was reduced from 5.5% in those not receiving oral probiotics to 2% in those receiving oral probiotics. Treatment with oral probiotics led to direct costs of $24 per course of treatment per patient. Use of the oral probiotic strategy resulted in an average overall cost of $327 per patient treated, compared with $845 per patient in the usual care strategy (average savings of $518 per patient treated with oral probiotics). Use of oral probiotics was a dominant strategy since this option reduced the proportion of patients who develop CDAD, thereby reducing the need for CDAD treatment, contact precautions, prolonged hospitalizations, and testing for *C. difficile* compared with the no-probiotic group, despite the cost of introducing oral probiotics.

Sensitivity and Scenario Analysis

One-way sensitivity analysis of each estimate showed the use of oral probiotics would be cost-saving across all clinically plausible variations. The 2-way sensitivity analyses in the base case also showed cost-savings across all clinically plausible variations and combinations. A variety of scenarios were considered to further assess uncertainty. Plausible variations in parameters that would result in the oral probiotic strategy being more costly were not identified (Table 3). This model was most sensitive to simultaneous changes to the relative risk and incidence of CDAD. When the risk of CDAD was low at 1% and the relative risk of CDAD was 0.99 the use of oral probiotics was associated with the lowest cost-savings per patient of $73. The highest cost-savings per patient was observed when the Gao et al[7] estimates were used ($3,098). Here the incidence of CDAD was high at 25% and the use of oral probiotics was associated with a 95% reduction in the proportion of patients developing CDAD (relative risk, 0.05) (Table 3).[7]

Another 2-way sensitivity analyses within the scenarios were conducted to assess the impact of changing 2 important parameters at a time. The most influential variables were the relative risk of CDAD and the incremental cost of CDAD. When isolation costs were excluded, the results demonstrated that when the relative risk of CDAD with oral probiotics was higher than 0.85 (ie, 15% reduction in CDAD) and the incremental cost of managing a patient with CDAD was less than approximately $2,250 (Figure 2), the oral probiotic strategy becomes more costly than the nonprobiotic strategy.

DISCUSSION

Additional demonstrated that the use of 1 capsule per day of oral probiotics by all hospitalized adults receiving a therapeutic course of antibiotics resulted in a lower risk of CDAD and cost-savings of $518 per person treated using the perspective of a publicly funded healthcare system. Multiple areas within the healthcare system will see reductions in spending. Patients will experience improvements in the quality of care through reduced lengths of stay, fewer days on isolation, and fewer complications due to CDAD.

Decision analytic modeling was used to assess the impact of probiotics on the incidence and cost associated with CDAD, information not fully reported by the Cochrane review assessing effectiveness of probiotics. The modeling also allowed for the assessment of uncertainty and variability relating to the evaluation.[11] Although the model findings are robust, a number of important factors need to be considered in the

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TABLE 3. Scenario Analysis Results

Scenario	Incremental risk of CDAD		Incremental cost-savings associated with oral probiotic strategy
	Parameter	estimate	
Base case			
Risk of CDAD	0.055	−0.04	−$518.00
Relative risk of CDAD	0.36		
Risk of AAD	0.221		
Relative risk of AAD	0.6		
Varying incremental cost of CDAD			
Low	$9,584.65	−0.04	−$438.00
High	$14,268.71		−$603.00
Excluding Gao et al[7] relative risk estimates			
Risk of CDAD	0.047	−0.03	−$400.00
Relative risk of CDAD	0.435		
Risk of AAD	0.198		
Relative risk of AAD	0.65		
Relative risk and incidence estimates only from Gao et al[7]			
Risk of CDAD	0.238	−0.23	−$3,098.00
Relative risk of CDAD	0.048		
Risk of AAD	0.44		
Relative risk of AAD	0.34		
Less effective oral probiotic on reduction of CDAD			
Risk of CDAD	0.055	−0.01	−$79.00
Relative risk of CDAD	0.99		
Less effective oral probiotic on reduction of AAD			
Risk of AAD	0.221	−0.04	−$484.00
Relative risk of AAD	1.0		
Less effective oral probiotic on reduction of CDAD and AAD			
Risk of CDAD	0.055	−0.03	−$403.00
Relative risk of CDAD	0.51		
Risk of AAD	0.221		
Relative risk of AAD	0.72		
Less effective oral probiotic on reduction of CDAD and lower incidence of CDAD			
Risk of CDAD	0.01	0.00	−$73.00
Relative risk of CDAD	0.99		
Excluding isolation costs			
Daily isolation costs	$0.00	−0.04	−$399.00
One time terminal cleaning	$0.00		
Per diem hospital costs and length of stay instead of incremental cost of CDAD			
Incremental cost of CDAD	$0.00	−0.04	−$2,786.00
Average length of stay with no probiotics	10 days		
Average length of stay with probiotics	8 days		
Per diem medical costs for 10 days	$1,105.55		
Per diem surgical costs for 10 days	$1,833.44		
Per diem medical costs for 8 days	$1,112.58		
Per diem surgical costs for 8 days	$1,879.76		
Incremental costs of CDAD applied only to the severe CDAD group			
Incremental cost of CDAD to severe group on no probiotics	$11,862.57	−0.04	−$152.00
Incremental cost of CDAD to severe group on probiotics	$11,862.57		
Excluding laboratory and antibiotic treatment costs			
2-step algorithm test	$0.00	−0.04	−$514.00
Metronidazole	$0.00		
Vancomycin	$0.00		

NOTE. AAD, antibiotic-associated diarrhea; CDAD, *Clostridium difficile*–associated diarrhea.

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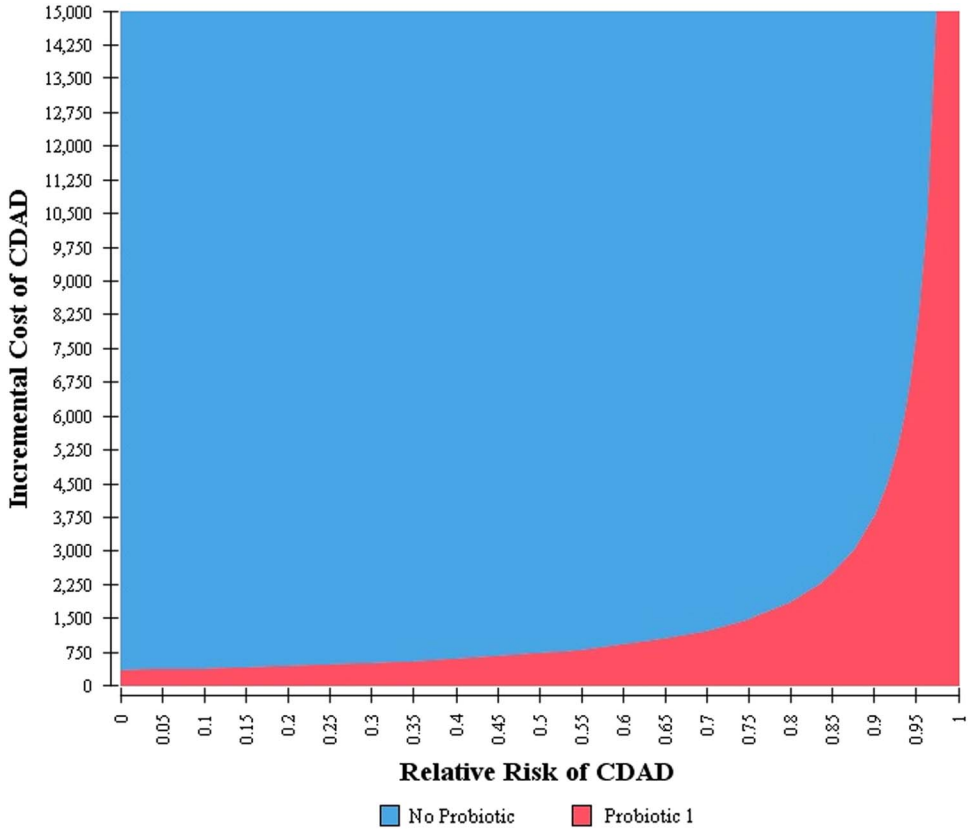

FIGURE 2. Two-way sensitivity analysis on the relative risk of *Clostridium difficile*–associated diarrhea (CDAD) and incremental cost of CDAD (in CDN $) when isolation costs are excluded. The no probiotic strategy is more costly in the blue area. The oral probiotic strategy is more costly in the red area.

interpretation of the results. First, the effectiveness measure of oral probiotics was based on a meta-analysis of 23 clinical trials of low (n = 16) to moderate (n = 7) quality as defined in the Cochrane review.[5] Although all studies showed an overall trend that probiotics reduce the incidence of CDAD and AAD, there was heterogeneity in the studies in terms of the probiotics, study populations, and secondary outcomes addressed. The studies had decreased precision due to a small number of events and no study assessed adverse events due to CDAD. For the model, all probiotic strains were assumed to perform equally well in reducing the risk of CDAD and AAD. This was supported in the Cochrane review's probiotic species subgroup analysis and the lack of clear evidence that there is a biological difference in the effectiveness of different strains of probiotics.[5,12]

One key element that was not well reported in the studies included in the Cochrane review was the duration of patients' hospitalization and the associated costs. Therefore, to estimate the increase in healthcare costs incurred by patients with CDAD, the results of a systematic review on healthcare-associated infections that identified 2 studies estimating the incremental cost of hospitalized CDAD patients were used in the base case.[9] Moreover, the results did not vary when other estimates of the incremental cost of CDAD were considered, including the results of 3 studies referenced in the Cochrane review that provided information on a patient's length of stay for both treatment groups.[13] To consider the possibility that the cost-savings associated with AAD and CDAD were overestimated, we also modeled a scenario where patients with CDAD incurred higher costs only when they had severe CDAD, and a scenario where isolation costs were excluded since this was largely driven by the frequency of AAD. In both cases, cost-savings were lower but still present. The 2-way sensitivity analysis suggested that probiotics would not result in a cost-savings if the relative risk of CDAD was greater than 0.85 and if the incremental cost was less than $2,250. Studies have found that the attributable costs of CDAD are likely to be much higher than this estimate and therefore it is unlikely that a loss in investment would occur.[9,14–17]

Previous studies assessing the economic impact of probiotic use were limited to cost and cost-consequence analyses.[14,18] These evaluations differed from this study in that they modeled older target populations (ie, inpatients ≥50 years of age); used a single study evaluating the effectiveness of probiotics for the prevention of CDAD, unlike this study, which used 23 randomized controlled trials for the effectiveness estimate; evaluated only one type of probiotic; and overall did not conduct a full economic evaluation. Our transparent model

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can be used by decision makers in different settings to estimate cost savings that might be expected in their hospital by substituting local estimates of baseline risk and costs for CDAD.

There were some limitations to this model. First, the model addresses only one strategy in the reduction of CDAD, but there are other infection prevention and control strategies that may be appropriate to assess in conjunction with probiotic use (eg, environmental decontamination technologies, alcohol-based hand rub, and dedicated patient equipment). These alternative strategies were not evaluated in the model owing to inadequate data on their costs and their efficacy was not evaluated in the Cochrane review. Second, the Cochrane review did not report the impact of probiotics on the occurrence of severe CDAD. It was assumed that the proportion of severe CDAD was reduced similarly to the risk of CDAD. Third, the target population was adult inpatients from all clinical groups despite evidence that the burden of CDAD varies between particular groups of patients.[19] A subgroup analysis in the Cochrane review suggested that there was no difference in the effectiveness of probiotics in the reduction of CDAD by age. The effectiveness of probiotics among adult inpatients was also supported by another systematic review and meta-analysis of randomized control trials.[12] More recently, the use of probiotics for the prevention of CDAD was implemented in a community hospital in Quebec Canada similar to the proposed strategy in this evaluation, resulting in a 73% reduction of CDAD over a 10-year period with no adverse events.[8,20]

In conclusion, the current model demonstrates that the introduction of oral probiotics as a preventive strategy for CDAD in hospitalized adults who are receiving a therapeutic course of antibiotics reduced the risk of CDAD and resulted in a cost-savings of $518 per person treated. Extrapolating to a population with more than 380,000 hospitalizations per year, the publicly funded healthcare system would expect to spend $2.2 million on oral probiotics but could expect overall cost-savings of $44 million considering the base case (data not shown). The cost-savings may be greater in other healthcare systems that experience higher incidences and costs associated with CDAD. Health policy decision makers should consider prioritizing funding for concomitant oral probiotics among hospitalized patients receiving therapeutic antibiotics.

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