Cost-Effectiveness Analysis of Probiotic Use to Prevent *Clostridium difficile* Infection in Hospitalized Adults Receiving Antibiotics

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Background. Systematic reviews with meta-analyses and meta-regression suggest that timely probiotic use can prevent *Clostridium difficile* infection (CDI) in hospitalized adults receiving antibiotics, but the cost effectiveness is unknown. We sought to evaluate the cost effectiveness of probiotic use for prevention of CDI versus no probiotic use in the United States.

Methods. We programmed a decision analytic model using published literature and national databases with a 1-year time horizon. The base case was modeled as a hypothetical cohort of hospitalized adults (mean age 68) receiving antibiotics with and without concurrent probiotic administration. Projected outcomes included quality-adjusted life-years (QALYs), costs (2013 US dollars), incremental cost-effectiveness ratios (ICERs; $/QALY), and cost per infection avoided. One-way, two-way, and probabilistic sensitivity analyses were conducted, and scenarios of different age cohorts were considered. The ICERs less than $100 000 per QALY were considered cost effective.

Results. Probiotic use dominated (more effective and less costly) no probiotic use. Results were sensitive to probiotic efficacy (relative risk <0.73), the baseline risk of CDI (>1.6%), the risk of probiotic-associated bactermia/fungemia (<0.26%), probiotic cost (<$130), and age (>65). In probabilistic sensitivity analysis, at a willingness-to-pay threshold of $100 000/QALY, probiotics were the optimal strategy in 69.4% of simulations.

Conclusions. Our findings suggest that probiotic use may be a cost-effective strategy to prevent CDI in hospitalized adults receiving antibiotics age 65 or older or when the baseline risk of CDI exceeds 1.6%.

Keywords. antibiotic-associated diarrhea; *Clostridium difficile*; cost-effectiveness; prevention; probiotic.

A total of 453 000 cases of *Clostridium difficile* infection (CDI) were estimated to occur in the United States in 2011 resulting in more than 29 000 deaths and healthcare costs of up to $4.8 billion [1]. Disease recurrence occurs in 20%–60% of patients [2]. Major independent risk factors for CDI include antibiotic use, hospitalization, and increasing age [3]. Improved prevention of CDI would have substantial public health benefits.

Coadministration of different probiotics with antibiotics may decrease disturbance of the gastrointestinal microbiome preventing *C difficile* colonization and CDI [4]. Although published data on probiotic efficacy for CDI appears conflicting, a Cochrane systematic review with meta-analysis found probiotic use efficacious, whereas a latter published large, multicenter randomized controlled trial (RCT) did not [5]. However, the RCT was underpowered and included patients receiving their first probiotic dose up to 7 days after the initial antibiotic dose. Most recently, a systematic review with meta-regression analysis incorporating this trial found that timely probiotic use was efficacious, with loss of efficacy for every day in delay, emphasizing for the first time the importance of giving the probiotic within 2 days of the first antibiotic dose [6].

Current guidelines from the American College of Gastroenterology (ACG) and the Society for Healthcare Epidemiology of America do not recommend probiotics for primary prevention of CDI, whereas a recent modified Delphi panel recommended use of *Lactobacillus acidophilus* and *Lactobacillus casei* to prevent CDI in subjects taking antibiotics [7–9]. In light of these conflicting recommendations and data, providing guidance on scenarios in which probiotic use is optimal in clinical practice is needed. We conducted a cost-effectiveness analysis of probiotic use for prevention of CDI in hospitalized adults receiving antibiotics.

METHODS

Analytic Overview

We developed a decision analytic model (Figure 1) programmed in TreeAge Pro 2015 software (TreeAge Software,
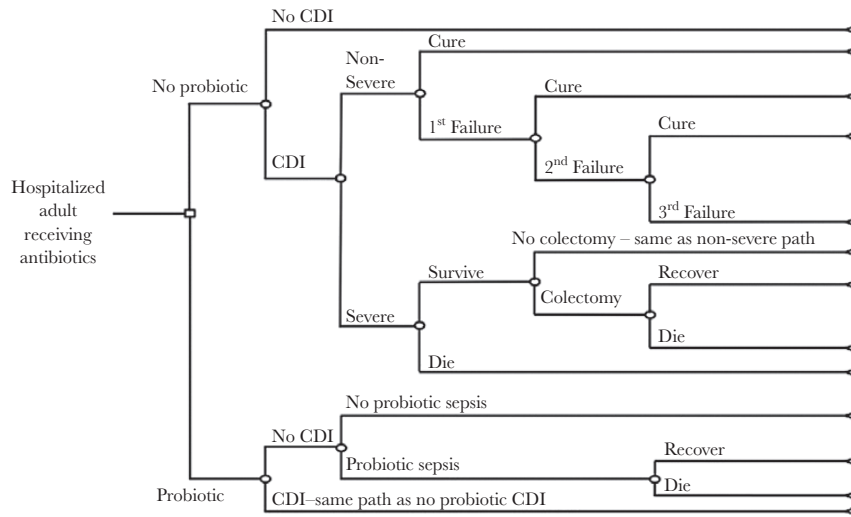
Figure 1. Decision analytic model schematic. CDI, *Clostridium difficile* infection.

Williamstown, MA) to investigate the cost-effectiveness of probiotic use compared with no probiotic use to prevent CDI in a hypothetical cohort of hospitalized adults receiving antibiotics. Model outcomes included quality-adjusted life-years (QALYs) gained, cases of CDI averted, and costs (2013 US dollars) associated with probiotics and CDI. Costs were converted to US 2013 dollars using the consumer price index [10]. Incremental cost-effectiveness ratios (ICERs) were calculated as the additional cost per QALY gained compared with no probiotic administration. Strategies that resulted in higher costs and shorter QALY gained or those with a higher ICER compared with a more effective strategy were considered inefficient ("dominated") and removed from final incremental comparisons. The analysis was conducted from a healthcare system perspective. The ICERs less than $100 000 per QALY were considered cost effective [11].

Sensitivity and Scenario Analyses
Model inputs were varied in one-way and two-way sensitivity analyses to evaluate individual parameter uncertainty. To investigate overall model uncertainty, we performed probabilistic sensitivity analysis using Monte Carlo simulation to vary model inputs using distribution types listed in Table 1. In accordance with recommended practices [12], we assigned gamma distributions to cost inputs and beta distributions for quality-of-life and probability inputs. Beta and gamma distributions were derived using estimates of mean and standard deviations based on published data (Supplementary Table 1). We conducted 10 000 iterations sampling from the probability distributions to calculate the ICER for each iteration. Results are reported as a cost-effectiveness acceptability curve representing the probability (ie, percentage of iterations) in which probiotic administration is preferred at various willingness-to-pay values. Only variables with distributions listed in Table 1 were included in the probabilistic sensitivity analysis.

To further explore uncertainty in probiotic efficacy and baseline CDI risk, we considered base and worst case scenarios. We also considered scenarios with different age cohorts (18–44, 45–64, or ≥85) accounting for age-related quality of life, all-cause mortality, and CDI risk and severity (Supplementary Table 2).

Model Overview
The model assumed the decision to use probiotics occurred at initiation of antibiotics and continued for 21 days. Individuals who did not develop CDI could survive or die based on published 1-year mortality rates for hospitalized adults [13]. Those who developed CDI could experience nonsevere CDI or severe CDI. *Clostridium difficile* infection treatment could be curative or fail; treatment failure was due to recurrent disease or primary treatment failure. Colectomy and death only occurred in patients with severe CDI. Recurrent disease was comparable in severity [14]. Patients cured from CDI had the same all-cause mortality as those without CDI. Antibiotic courses were based on ACG and Infectious Diseases Society of America guidelines [7, 8]. Subjects with relapsing or refractory CDI, defined as 3 prior treatment failures, were assumed to undergo curative fecal microbiota transplant [7]. The time horizon for CDI costs and effects was 1 year. Death due to other causes not attributable to CDI was assumed to occur, on average, 6 months after index hospitalization.

Probiotic Efficacy
Probiotic efficacy was modeled as the relative risk (RR) reduction of CDI with probiotic use compared with no probiotic use. Based on prior meta-analysis, in the base case, we estimated that probiotics conferred a RR of 0.51 in the base case and a RR of 0.85 in the worst-case scenario [15]. We considered specific probiotic formulations, *L. acidophilus* + *L. casei* (RR = 0.21; 95% confidence interval [CI], 0.11–0.42) and *Saccharomyces boulardii* (RR = 0.47; 95% CI, 0.24–0.94), based on findings in meta-analysis subgroups

Table 1. Model Input Parameters

Inputs	Base Case	One-Way Sensitivity Analysis Range	Distributions in Monte Carlo Simulation	References
Relative risk of CDI with probiotic use	0.51	0.35–0.85	Beta	[15]
Risk of CDI, %	2.9	1.2–5.0	Beta	[5, 17, 18]
Risk of probiotic bacteremia/fungemia, %	0.02	0–1.0	Beta	[23, 32]
CDI Outcomes, %				
Severe CDI	18	7–48	Beta	[19]
CDI recurrence				
First	22	12–64	Beta	[19]
Second	42	30–60	Beta	[14]
Third	53	45–65	Beta	[22, 38]
Colectomy[a]	0.9	0.3–6.2	Beta	[20]
Mortality, %				
All cause	22	4–64	Beta	[13]
CDI attributable[b]	5	3–10	Beta	[1, 20, 39]
Probiotic bacteremia/fungemia	12	0–32	Beta	[16, 32]
Costs, 2013 US $				
CDI				
Inpatient[c]	7670	3830–11 500	Gamma	
Outpatient	440	210–620	Gamma	[30, 40]
Specialist referral	210	110–320	Gamma	[40]
Treatment[d]				
Vancomycin taper	1 490	750–2 240	Gamma	[7, 26]
FMT[e]	3 150	1580–4730	Gamma	[26, 37]
Colectomy	37 290	18 650–55 940	Gamma	[37]
Probiotic course	70	40–110	Gamma	[26]
Probiotic bacteremia/fungemia	18 280	9140–27 420	Gamma	[25]
Quality of Life				
Adult without CDI	0.827	0.736–0.922	Beta	[24]
Adult with CDI				
Nonsevere	0.600	0.500–0.700	Beta	[41]
Severe				
No colectomy	0.550	0.450–0.650	Beta	[41]
Post-colectomy	0.500	0.400–0.600	Beta	[41]
Initial				
Late	0.787	0.696–0.882	Beta	[25]
Bacteremia/fungemia	0.550	0.450–0.650	Beta	[41]
Time in a health state, days				
CDI[f]				
Nonsevere	10	4–14	n/a	[7, 8]
Severe	14	10–21	n/a	[7, 8]
Initial postcolectomy	90	30–180	n/a	[25]
Bacteremia/fungemia	7	3–14	n/a	[42]

Abbreviations: CDI, *Clostridium difficile* infection; FMT, fecal microbiota transplant; n/a, not applicable.

[a]Colectomy was input as the probability of CDI requiring colectomy (0.9%) divided by the base case of severe CDI (18%).

[b]CDI-attributable mortality included the probability of mortality after colectomy (41%, 25%–80%) [43].

[c]Inpatient cost ($7670) was the weighted average of the probability of CDI as the primary diagnosis (0.33) multiplied by average cost ($9830) and the probability of CDI being a secondary diagnosis (0.67) multiplied by average cost ($6600) [16, 17, 27–29].

[d]Treatment with oral metronidazole and vancomycin for initial treatment and first recurrence was assumed to be included in the inpatient and outpatient costs.

[e]FMT was the sum of the costs of vancomycin before FMT ($1960), FMT preparation and instillation ($120), testing of the recipient ($120) and donor ($540), and colonoscopy ($410) [26, 37].

[f]Time spent in CDI and probiotic bacteremia/fungemia health states was based on recommended treatment durations [7, 8].

[15]. The risk of CDI with probiotic administration was the product of the baseline risk of CDI and the RR.

Baseline Risk of *Clostridium difficile* Infection

The baseline risk of CDI without probiotic administration was determined from the Healthcare Cost and Utilization Project (HCUP) [16]. We used the incidence rate for the 65–84 age cohort (151 CDI cases per 10 000 inpatient stays) based on mean age (68) of CDI cases in HCUP [17]. To derive age-specific CDI risk, we used the age-stratified CDI incidence rates reported in HCUP (CDI cases per 10 000 hospital stays). We assumed 51.9% of hospitalized patients receive antibiotics based on results of a nationally representative point prevalence study of antibiotic utilization [18]. Age-specific CDI risk was

calculated based on CDI cases per 10 000 hospital stays for each cohort divided by the probability of receiving antibiotics during a hospital stay (Table 1). We also considered a worst-case scenario of baseline CDI risk of 1.2% [5].

Clostridium difficile Infection Outcomes

The probabilities of CDI first recurrence (22%) and severe CDI (18%) were based on a systematic review [19]. *Clostridium difficile* infection-associated colectomy (0.9%) and CDI-attributable mortality (5.0%) were based on the median incidence of study findings from a literature review during endemic periods [20]. For nonsevere CDI, the probability of outpatient treatment was 52% for the initial episode and 80% for recurrence [21]. Severe CDI was assumed to require hospitalization. Equivalent recurrence rates were assumed for severe or nonsevere CDI [2]. The probability of a second (42%) or third recurrence (53%) was from a prospective study and a Delphi panel estimate [14, 22].

Probiotic Bacteremia/Fungemia

For the purposes of the analysis, probiotic bacteremia/fungemia was assumed to include cases of sepsis attributable to ingestion of organisms in probiotic formulations. We assumed a risk of probiotic bacteremia/fungemia (0.02%) based on surveillance data from Finland [23]. Mortality due to probiotic-related bacteremia/fungemia (12%) was based on that reported for other causes of sepsis in HCUP [16].

Quality of Life

Quality-adjusted life-years are a measure of health-related quality of life for a given health state that incorporates a score from 0 to 1 with 0 representing death and 1 representing perfect health. Weights are multiplied by the time spent in the health state. The baseline QALY weight (0.827) was derived from the median

EQ-5D assigned to patients aged 60–69 from a nationally representative study of the US population [24]. No data on health-related quality of life specific to CDI have been published. Several published cost-effectiveness analyses on CDI have incorporated QALY estimates from inflammatory bowel disease or chemotherapy-associated diarrhea, and we therefore used the same QALY estimates as the best available alternative. For colectomy survivors, we used 2 QALY weights to represent the immediate postcolectomy period and the late postcolectomy period [25].

Costs

Costs were derived from Red Book [26], HCUP [16], and published literature [27–29]. The inpatient CDI cost was the weighted average of the principal and secondary diagnosis costs [16, 17, 27–29]. The outpatient CDI cost was the sum of laboratory and office visit costs [30]. Additional costs for third recurrence included GI referral and vancomycin taper. Probiotic cost was the average wholesale price of a 21-day course of *S. boulardii* and *L. acidophilus* + *L. casei* [26]. Probiotic bacteremia/fungemia cost was the cost of sepsis reported in HCUP [16].

RESULTS

In the base case, the probiotic strategy was both less costly and resulted in a greater number of QALYs, and therefore probiotics dominated no probiotics (Table 2). In the worst-case scenario, the probiotic strategy was more costly with minimally increased QALYs resulting in an ICER of $1 257 100/QALY, which was above our willingness-to-pay threshold of $100 000/QALY.

Probiotics were dominant for the age cohort ≥85 years, but these were not cost-effective strategies for age cohorts 18–44 years and 45–64 years, with respective ICERs of $884 100/QALY and $156 100/QALY (Table 2). In a scenario modeling the

Table 2. Cost-Effectiveness Results Comparing No Probiotic Use to Probiotic Use to Prevent CDI in Cohorts Aged 18–44, 45–64, 65–84 (by base case and low risk of CDI), and ≥85

Strategy	Cost ($)	Incremental Cost ($)	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER[a] ($/QALY)
Age 18–44 (CDI baseline risk = 0.6% and probiotic efficacy RR = 0.51)					
No probiotic	31	—	0.9010	—	—
Probiotic	90	59	0.9011	0.0001	884 100
Age 45–64 (CDI baseline risk = 1.5% and probiotic efficacy RR = 0.51)					
No probiotic	82	—	0.7909	—	—
Probiotic	116	34	0.7911	0.0002	156 100
Age 65–84 (CDI baseline risk = 2.9% and probiotic efficacy RR = 0.51)					
Probiotic	163	—	0.7354	—	—
No probiotic	176	13	0.7349	−0.0005	Dominated[b]
Age 65–84 (CDI baseline risk = 1.2% and probiotic efficacy RR = 0.51)					
No probiotic	72	—	0.7355	—	—
Probiotic	135	63	0.7356	0.0001	1 257 100
Age ≥85 (CDI baseline risk = 3.8% and probiotic efficacy RR = 0.51)					
Probiotic	183	—	0.5969	—	—
No probiotic	214	31	0.5955	−0.0014	Dominated[a]

Abbreviations: CDI, *Clostridium difficile* infection; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years; RR, relative risk.

[a]ICERs may not calculate directly due to rounding.

[b]Dominated describes scenarios in which no probiotic use is less effective and more costly.

cost-effectiveness of specific probiotic formulations, *L. acidophilus* and *L. casei* dominated both no probiotics and *S. boulardii* at base case. If baseline risks of CDI were low (1.2%), *L. acidophilus* and *L. casei* remained cost effective with an ICER of $19 200/QALY (Supplementary Figure 1 and Supplementary Table 3).

When CDI cases averted were used as an outcome measure instead of QALYs, probiotics remained cost-saving. In the no probiotic strategy, our model predicted 29 cases of CDI per 1000 patients compared with 15 cases per 1000 patients with probiotics. The net cost-saving per case of CDI averted was $840.

Sensitivity Analyses

The most influential variables were the risk of probiotic bacteremia/fungemia, risk of CDI, probiotic relative risk, and probiotic cost. In one-way sensitivity analysis, probiotics remained the preferred strategy at a $100 000/QALY threshold except when the risk of probiotic bacteremia/fungemia was greater than 0.26% (Supplementary Figure 2), the risk of CDI was less than 1.6% (Figure 2), probiotic RR was greater than 0.73, or probiotic cost was greater than $130. Results were stable to changes in other model inputs across plausible ranges (Supplementary Table 4).

In the worst-case scenario, the ICER became <$100 000/QALY when the baseline risk of CDI exceeded 5.2% (Figure 2), probiotic RR was less than 0.36, or probiotic cost was less than $10. A two-way sensitivity analysis varying the baseline risk of CDI and probiotic efficacy demonstrates that for CDI risk between 1% and 6%, probiotics remained cost effective for RR values <0.85 (Figure 2).

Probabilistic sensitivity analysis found probiotics cost effective in 69.4% of simulations at a $100 000/QALY willingness-to-pay threshold. A cost-effectiveness acceptability curve and incremental cost-effectiveness scatter plot illustrate the probability of probiotics being the optimal strategy in the majority of simulations for all willingness-to-pay thresholds (Figure 3A and B).

DISCUSSION

Our study is the first to evaluate the cost-utility of probiotics for prevention of CDI among hospitalized adults in the United States. Incorporating published data on probiotics, CDI costs and outcomes, we found probiotics to be economically attractive across a wide range of plausible values, but not in all scenarios. In the base case, probiotics dominated no probiotics, but probiotics had an unfavorable ICER of $1.26 million/QALY in our worst-case scenario.

Two prior cost-benefit analyses conducted in the United Kingdom and the Canadian health systems found probiotics to be cost saving [22, 31]. Although many of our model inputs were more conservative than both prior economic analyses, we also found probiotics to be cost-saving in our base case analysis and in the majority of simulations in our probabilistic sensitivity analysis.

In our scenario analyses, we found use of *L. acidophilus* + *L. casei* to be economically favorable compared with *S. boulardii*. We also found age to be an important consideration
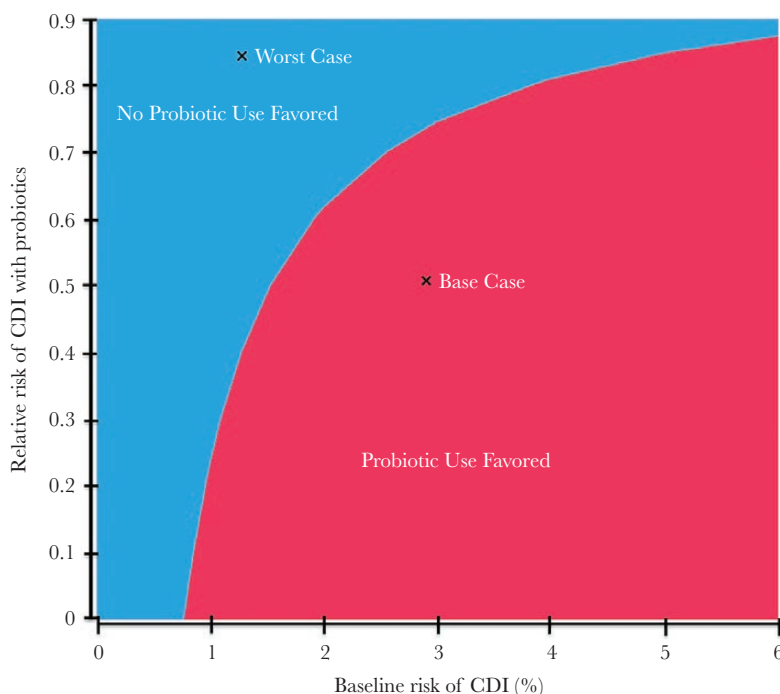

Figure 2. Cost-effectiveness of probiotic use for *Clostridium difficile* infection (CDI) prevention at a willingness-to-pay threshold of $100 000/quality-adjusted life-years: two-way sensitivity analysis varying probiotic efficacy and baseline risk of CDI.
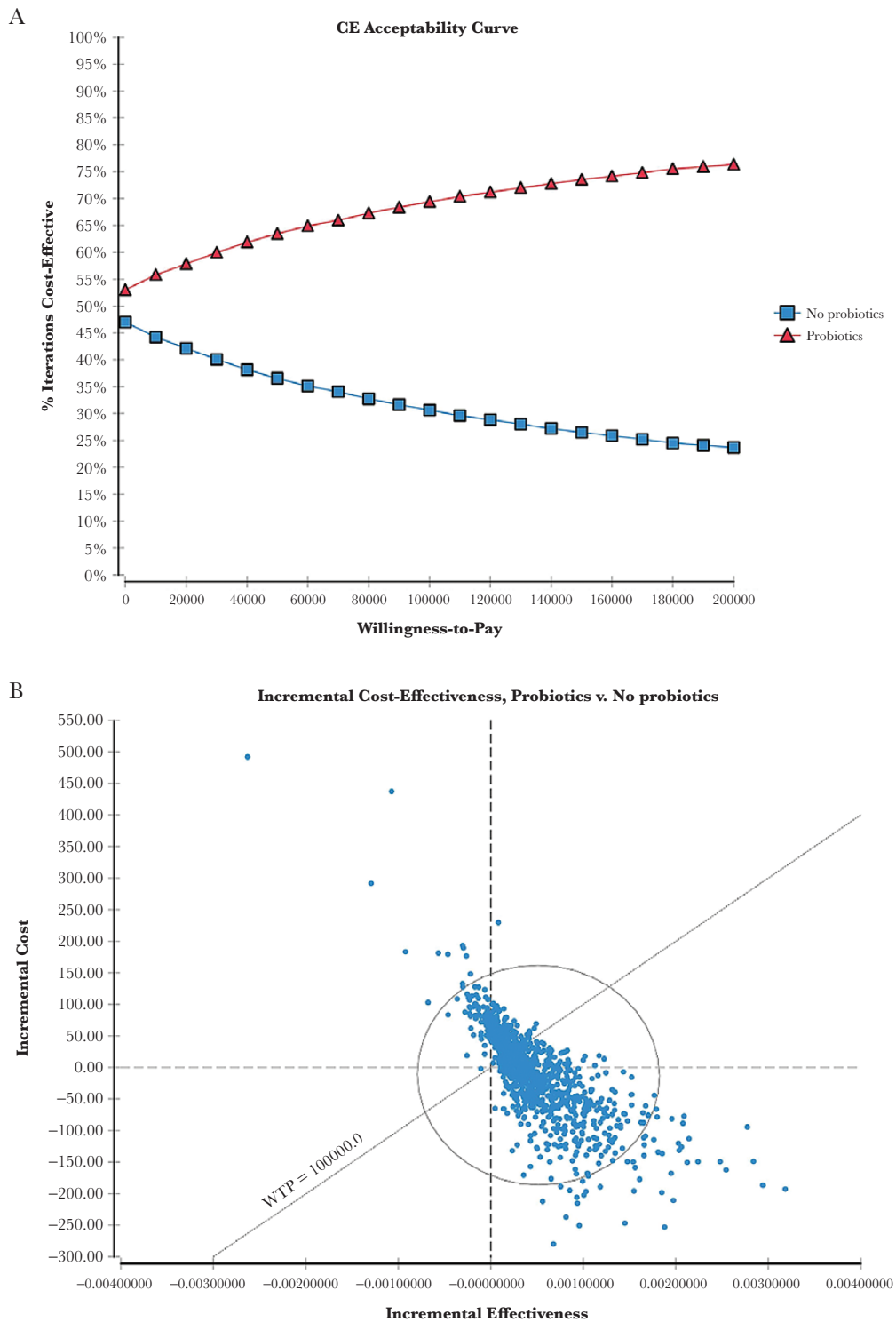
Figure 3. Probabilistic sensitivity analysis of probiotic use versus no probiotic use for prevention of *Clostridium difficile* infection acceptability curve at different willingness-to-pay (WTP) thresholds (A) and incremental effectiveness and cost (B). CE, cost-effectiveness.

with cost-effectiveness results becoming more favorable with increasing age—probiotic use dominated no probiotic use in subjects aged ≥65, but probiotic use was not cost effective in younger cohorts.

The risk of probiotic bacteremia/fungemia was another important determinant of cost-effectiveness. Bacteremia/fungemia due to probiotics has been rarely reported in the literature and primarily limited to case reports [23, 32]. A systematic

review of probiotic safety found that high-risk groups for systemic infection included immune-compromised, post-surgical, critically ill, long-time-hospitalized, and elderly patient populations [32]. There are also data to suggest probiotics may be safe in immunocompromised patients including human immunodeficiency virus and post-transplantation [33, 34]. No events of probiotic bacteremia/fungemia occurred in the RCTs [15, 32, 35], but patients at increased risk, such as immunocompromised and critically ill populations, were excluded from the studies. Although most studies exclude subjects with chronic gastrointestinal diseases because of possible confounding effects on stool output, a few clinical trials suggest the safety of using probiotics among patients with inflammatory bowel disease [36]. Estimates of the incidence of probiotic-associated bacteremia/fungemia may be limited due to possible underreporting of events in clinical practice. Our base case assumption for probiotic bacteremia/fungemia may be conservative because one study found only 16.7% of episodes of *Lactobacillus* bacteremia matched the species in probiotic formulations [23]. We found the risk of probiotic bacteremia/fungemia would need to exceed our base case estimate (0.02%) by more than 10-fold for probiotics to no longer be cost effective in the base case. Given the overlap in patient populations at risk for both CDI and probiotic-associated complications, future clinical trials should examine safety and efficacy of probiotics for CDI prevention in these high-risk sub-populations.

Our study has the following limitations. First, the quantity and quality of published data on the topic varied widely, limiting the precision of our inputs. Nevertheless, we based our estimates on the highest quality evidence and considered a wide range of plausible values in sensitivity analyses. Second, the restrictive inclusion criteria in clinical trials evaluating probiotics prevents complete assessment of sub-populations in which probiotics may be optimal or potentially harmful. Third, the variety of probiotic species and doses studied limits the ability to inform decision-making around selection of specific regimens. Based on available evidence, our analysis suggests that *L. casei* and *L. acidophilus* may be preferred over *S. boulardii*. Fourth, the baseline risk of CDI, an important determinant of cost-effectiveness, may be challenging to apply to clinical decision-making because of the difficulty in precisely quantifying such risk at the individual patient level. Although certain antibiotic classes, such as clindamycin, fluoroquinolones, and cephalosporins, are well established risk factors for CDI, the effectiveness of probiotics on CDI prevention based on antibiotic class are unknown. We attempted to account for these limitations by extensive sensitivity analyses including a worst-case scenario and scenarios with different age cohorts. In our model, when CDI risk exceeded 1.7%, probiotics were cost effective, which suggests that our findings apply primarily to patients receiving high-risk antibiotics. Fifth, no formal quality-of-life studies of CDI have been conducted. We chose our QALYS based on previously published cost-effectiveness analyses

of CDI, estimating QALYs based on those reported in the inflammatory bowel disease population [37]. Sixth, a myriad of definitions have been used in the literature to define severe CDI. We incorporated the best available data from a recent large systematic review of 68 studies using the definition of any complication, fulminant colitis, intensive care unit admission, and shock or death [19]. Seventh, because comorbidities correlate with increased risk of CDI, patients with CDI may have higher all-cause mortality than those who do not have CDI. Although our analysis assumed all-cause mortality was equivalent in patients with and without CDI, this assumption was conservative and would only bias against the favorability of probiotics.

Despite these limitations, our analysis has the following strengths. First, we incorporated QALYs, the gold standard for health economic evaluations, to capture CDI-associated morbidity and mortality and for comparison with other diseases. Second, we modeled CDI outcomes such as recurrence, colectomy, and mortality, whereas neither prior analysis included all of these important complications of CDI. Third, we considered various scenarios with different age cohorts, probiotic species, and accounted for the risk of probiotic bacteremia/fungemia. Fourth, in contrast to prior published studies, we included probabilistic sensitivity analysis and a cost-effectiveness acceptability curve, which is a recommended best-practice for reporting results of health economic models [12].

CONCLUSIONS

In summary, our findings suggest that probiotic use could be a cost-effective means to prevent CDI when CDI risk exceeds 1.6%. Our results were sensitive to the risk of CDI, probiotic efficacy, the risk of probiotic sepsis, probiotic cost, and age. Although further studies are needed to clarify the optimal dose, species, duration, and patient population, our findings suggest that probiotics may be a cost-effective means to prevent CDI in hospitalized adults receiving antibiotics based on efficacy assumptions from published meta-analyses.

and critical revision of the manuscript for important intellectual content. A. M. contributed to study concept and design, acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and statistical analysis. B. B. contributed to analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and statistical analysis. M. S. S. contributed to study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, and study supervision.

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