

## ORIGINAL ARTICLE

# Effectiveness of Probiotic for Primary Prevention of *Clostridium difficile* Infection: A Single-Center Before-and-After Quality Improvement Intervention at a Tertiary-Care Medical Center

William E. Trick, MD;<sup>1</sup> Stephen J. Sokalski, DO;<sup>2</sup> Stuart Johnson, MD;<sup>3</sup> Kristen L. Bunnell, PharmD;<sup>4</sup> Joseph Levato, PharmD;<sup>2</sup> Michael J. Ray, MPH;<sup>1</sup> Robert A. Weinstein, MD<sup>1</sup>

**OBJECTIVE.** To evaluate probiotics for the primary prevention of *Clostridium difficile* infection (CDI) among hospital inpatients.

**DESIGN.** A before-and-after quality improvement intervention comparing 12-month baseline and intervention periods.

**SETTING.** A 694-bed teaching hospital.

**INTERVENTION.** We administered a multispecies probiotic comprising *L. acidophilus* (CL1285), *L. casei* (LBC80R), and *L. rhamnosus* (CLR2) to eligible antibiotic recipients within 12 hours of initial antibiotic receipt through 5 days after final dose. We excluded (1) all patients on neonatal, pediatric and oncology wards; (2) all individuals receiving perioperative prophylactic antibiotic recipients; (3) all those restricted from oral intake; and (4) those with pancreatitis, leukopenia, or posttransplant. We defined CDI by symptoms plus *C. difficile* toxin detection by polymerase chain reaction. Our primary outcome was hospital-onset CDI incidence on eligible hospital units, analyzed using segmented regression.

**RESULTS.** The study included 251 CDI episodes among 360,016 patient days during the baseline and intervention periods, and the incidence rate was 7.0 per 10,000 patient days. The incidence rate was similar during baseline and intervention periods (6.9 vs 7.0 per 10,000 patient days;  $P = .95$ ). However, compared to the first 6 months of the intervention, we detected a significant decrease in CDI during the final 6 months (incidence rate ratio, 0.6; 95% confidence interval, 0.4–0.9;  $P = .009$ ). Testing intensity remained stable between the baseline and intervention periods: 19% versus 20% of stools tested were *C. difficile* positive by PCR, respectively. From medical record reviews, only 26% of eligible patients received a probiotic per the protocol.

**CONCLUSIONS.** Despite poor adherence to the protocol, there was a reduction in the incidence of CDI during the intervention, which was delayed ~6 months after introducing probiotic for primary prevention.

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While many proven interventions have successfully reduced certain healthcare-associated infections (HAIs),<sup>1</sup> *Clostridium difficile* infection (CDI) remains common in many institutions. Strategies to reduce the risk of CDI (eg, reduced antimicrobial use and enhanced environmental cleaning)<sup>2</sup> have been difficult to sustain across facilities. One challenge specific to controlling CDI is that the condition results in diarrhea, facilitating environmental surface contamination.<sup>3,4</sup> In addition, *C. difficile* spores are resistant to alcohol-based hand gel<sup>5</sup> and most disinfectants used for room cleaning.<sup>6</sup> To test a control strategy enhanced by the use of probiotics, we collaborated with the Illinois Department of Public Health to identify hospitals with high CDI rates as reported to the Centers for Disease Control and Prevention (CDC) that were actively engaged in infection prevention efforts (eg, hand hygiene and environmental

disinfection). We contacted these hospitals and identified a large teaching hospital with the capacity to implement a probiotic-based quality improvement intervention.

Although most CDI cases can be treated with antibiotics, primary prevention is critical for the following reasons: (1) almost 1 in 5 treated patients experiences a recurrence, and each recurrence increases the likelihood of treatment failure; (2) infected patients serve as a reservoir for ongoing transmission; and (3) implementation of contact isolation precautions can have deleterious consequences for patients.<sup>7</sup> Also, CDI can result in severe disease, leading to colectomy and death. Because *C. difficile* is spread between patients,<sup>8</sup> primary prevention reduces the risk of exposure for other patients.

Some probiotic strains hold promise to interfere with colonization and/or infection with *C. difficile*. The appeal of

Affiliations: 1. Department of Medicine, Cook County Health & Hospitals System, Chicago, Illinois; 2. Division of Infectious Diseases, Advocate Christ Medical Center, Oak Lawn, Illinois; 3. Loyola University Medical Center, Maywood, Illinois; 4. College of Pharmacy, University of Illinois, Chicago, Illinois.

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probiotics is in part due to relative safety and public acceptance, which is supported by a substantial body of evidence suggesting efficacy.<sup>9–11</sup> The interpretation of clinical trials is complicated by differences in probiotic agents and intended use, that is, primary versus secondary prevention. If proven effective, certain probiotic strains would be a relatively simple, safe, low-cost solution likely to be accepted by patients.

We evaluated the impact of a hospital-wide policy to prescribe a probiotic mixture to eligible adult antibiotic recipients. We chose an agent (Bio-K+, Laval, Quebec, Canada) containing 3 *Lactobacillus* spp: *L. acidophilus* (CL1285), *L. casei* (LBC80R), and *L. rhamnosus* (CLR2). This agent has been proven effective and safe by meta-analysis<sup>11</sup> of 3 randomized trials<sup>12–14</sup> and in a single center before-and-after quality improvement initiative.<sup>15</sup> We report our findings from this quality improvement intervention.

## METHODS

### Setting and Population

We performed a before-and-after quality improvement intervention at a 694-bed teaching hospital near Chicago, Illinois. We compared 12-month baseline (October 1, 2012, through September 30, 2013) and intervention periods (November 1, 2013, through October 31, 2014). October 2013 served as a 1-month run-in period, during which probiotic distribution was implemented. We excluded all patients on neonatal, pediatric, and oncology units. To minimize the risk of adverse events, we excluded patients with leukopenia (white blood cell count <1,000 cells per mm<sup>3</sup>), pancreatitis, or transplant recipients regardless of unit location. The institutional review board deemed this study to be a quality improvement intervention, and full review was waived.

### Intervention

Patients who were to receive their initial dose of antibiotics at the project hospital were prescribed probiotic capsules (Bio-K+, Laval, Quebec, Canada) containing 100 billion colony-forming units (CFUs) of probiotic, which had previously been confirmed.<sup>16</sup> The organisms were *L. acidophilus* (CL1285), *L. casei* (LBC80R), and *L. rhamnosus* (CLR2); alphanumeric designations represent a company-assigned trademark. The 3-strain probiotic mixture was to be initiated within 12 hours of the initial antibiotic dose; thus, patients receiving antibiotics before hospital admission were ineligible. Recipients of perioperative antibiotic prophylaxis were also excluded. Patients restricted from oral intake were not given probiotic capsules; however, those receiving enteral tube feedings were provided with a commercially available liquid slurry of the same probiotic preparation. The 3-strain probiotic mixture was administered during the antibiotic course and for 5 days after the final dose of antibiotic. Discharged patients were sent home with probiotic to complete their

entire course. Inpatient probiotic distribution required pharmacist review of antibiotic prescriptions including a manual review of an automated printout of clinically ineligible patients. We were unable to build probiotic distribution through the clinical decision support system.

### Observational Hospital-Level Study

Our primary outcome was the incidence of hospital-onset CDI among all patients on eligible units. We used a clinical definition of CDI,<sup>17</sup> requiring the presence of symptoms, determined by the hospital epidemiologist, and detection of *C. difficile* in stool. *Clostridium difficile* was detected by polymerase chain reaction (Xpert PCR assay, Cepheid, Sunnyvale, CA) during the entire project. We did not monitor patients after hospital discharge. We calculated the incidence rate ratio (IRR) and 95% confidence intervals (CIs) expressed per 10,000 patient days. We used segmented regression analysis to compare the incidence during baseline and intervention periods, reporting deviations in level (ie, test for immediate intervention effect) and slopes (ie, test for a delayed intervention effect). Given the decline in incidence during the final 6 months of the intervention and based on previously identified postintervention delays in reducing CDI,<sup>18</sup> we performed a post hoc analysis comparing the incidence between the initial and final 6 months of the intervention. We obtained the number of community-onset (CO) cases of *C. difficile* reported to the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) during the project period, which included emergency department patients and those cultured during their first 3 hospital days; rates were reported by quarter. We evaluated the trend in CO cases and included the number of CO cases in the segmented regression models. To evaluate *C. difficile* testing intensity, we evaluated the frequency at which patients were tested hospital-wide, and we compared the proportion of tests positive for *C. difficile* toxin between baseline and intervention periods. We routinely conducted in-person meetings at the project hospital, during which no changes in infection prevention programs and no new antibiotic stewardship initiatives were reported.

### Case-Control Study

To conduct a patient-level analysis, we performed a matched case-control study, sampling patients hospitalized during the intervention. We selected CDI case patients who were eligible to receive probiotic (ie, receipt of a therapeutic course of antibiotics on an intervention unit, without clinical exclusions, and not receiving antibiotics on admission), and who developed CDI  $\geq 24$  hours after antibiotic exposure. Control patients (ie, no CDI identified) were pair-matched to case patients by age ( $\pm 10$  years), temporal proximity of antibiotic initiation date ( $\pm 10$  days), and geographic proximity (hospital unit) when antibiotics were started. Control patients had to

have been hospitalized for at least 4 days and exposed to a course of at least 1 antibiotic on the list of high-risk antibiotics received by at least 1 case patient. We recorded data on age, sex, race–ethnicity, daily exposure to probiotic and antibiotics, timing of initial probiotic relative to initial antibiotic dose, presence of tube feeding, comorbidities, prior hospitalizations at the same facility, preadmission location (eg, home, hospital, long-term care facility), use of a proton pump inhibitor, and severity of illness and risk of mortality (range, 1–4 for each score) recorded at discharge. We inputted these data into proprietary software embedded in the electronic medical record (3M Health Information Systems, St Paul, MN).<sup>19,20</sup> We defined per-protocol probiotic administration in the following 2 ways: (1) complete adherence to protocol (ie, on-time administration and no missed days) and (2) on-time administration of the first dose and receipt of  $\geq 80\%$  of inpatient doses.<sup>21</sup> We did not monitor postdischarge probiotic receipt. We collected daily administration of probiotic and antibiotics.

### Statistical Analysis

We compared cases to controls using the 2-sample *t* test and the McNemar  $\chi^2$  test. To evaluate the protective effect of the probiotic mixture adjusting for exposure time, we performed survival analyses. We censored controls at the same duration of time from initial antibiotic exposure to when their corresponding case patient developed CDI, so the at-risk periods were similar. We constructed Cox proportional hazards regression models for time-varying covariates, inclusive of interaction terms. We constructed conditional logistic regression models with the dependent variable as case status (yes/no). In conditional logistic regression models, we summed probiotic and antibiotic exposure days and modeled cumulative exposure for each patient.

## RESULTS

### Observational Study

For eligible hospital units, there were 177,184 patient days during the baseline period and 182,832 patient days during the intervention period. More *C. difficile* assays were performed in the baseline than in the intervention period: 210 versus 186 per 10,000 patient days ( $P < .001$ ). However, the percentage of tests positive for *C. difficile* (ie, number of tests positive per number of tests performed  $\times 100$ ) was similar during the baseline period (19%) and the intervention period (20%). The CDI incidence was similar in the baseline and intervention periods: 6.9 versus 7.0 per 10,000 patient days ( $P = .95$ ). When we compared baseline and intervention periods by regression analysis, the decreasing incidence observed during the intervention was not significantly different from the baseline (Figure 1). We observed a decreased incidence of CDI during the second half of the intervention period (months 7–12)

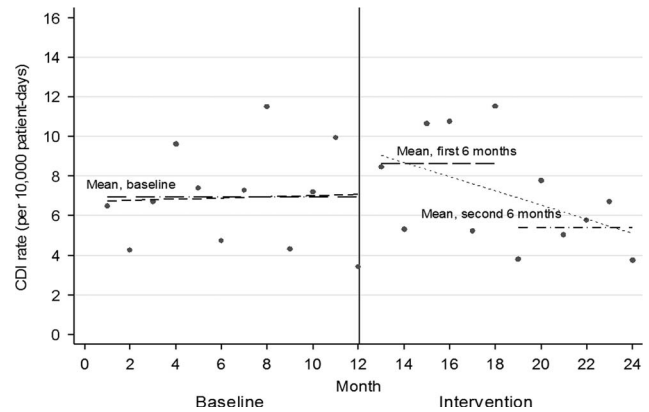


FIGURE 1. Comparison of CDI rates between the baseline and intervention periods. Antibiotic recipients in the intervention period were to receive probiotic. <sup>a</sup>Short-dash lines represents the fitted slope from the regression models; long-dash lines represent the mean values. Statistical tests: level change, baseline to intervention ( $P = .29$ ); slope change, baseline to intervention ( $P = .22$ ); incidence difference, baseline to last 6 months of the intervention (IRR, 0.8; 95% CI, 0.5–1.1;  $P = .13$ ); incidence difference, first to last 6 months of the intervention (IRR, 0.6; 95% CI, 0.4–0.9;  $P = .009$ ).

compared to the first half of the intervention period: 5.4 versus 8.6 per 10,000 patient days (IRR, 0.6; 95% CI, 0.4–0.9;  $P = .009$ ). When compared to the baseline, we detected a trend toward a lower incidence in the second 6 months of the intervention that did not reach statistical significance (IRR, 0.8; 95% CI, 0.5–1.1;  $P = .13$ ) (Figure 1). We observed a nonsignificant decrease in community-onset cases during the project period. However, adjustment for this decline in the regression models did not appreciably change our results.

### Case-Control Study

When we reviewed the medical records of patients who developed CDI during the intervention period ( $N = 128$ ), slightly more than half (68, 53%) were included in the case-control study. Potential case patients were excluded for the following reasons: no in-hospital antibiotic receipt (21, 16%); preoperative antibiotic prophylaxis (16, 12%); clinically ineligible (11, 9%); CDI within 24 hours of antibiotic receipt (6, 5%); receiving antibiotics before hospitalization (3, 2%); unable to match to a control patient (2, 2%); and unavailable medical record for 1 patient.

Among the 136 patients (68 matched pairs) in the case-control study, 35 (26%) received the probiotic according to the protocol (ie, dosed on time and every eligible day); 36 (26%) received no probiotic; 29 (21%) received their first dose late; 25 (18%) missed doses; and, 11 (8%) received their first dose late and missed doses. Using 80% of doses received as the threshold for per-protocol dosing, 48 (35%) received the probiotic intervention per protocol. Among the 103 patients for whom the dosage form was recorded, most received

capsules alone (66%); a substantial minority (34%) received at least 1 dose as slurry. The mean age was 67 ( $\pm 14$  SD) years and the mean length of stay was 17 ( $\pm 14$  SD) days. On average, case patients had a worse severity of illness than control patients: 3.7 versus 3.3 ( $P = .004$ ). The most common sources of admission were home (62%), nursing home (24%), or inter-facility acute-care transfer (11%).

Case patients were no less likely to have received probiotic than control patients: 18 of 68 (26%) versus 17 of 68 (25%). The mean number of days of probiotic receipt was similar for case patients and control patients: 4.4 days versus 3.9 days, respectively. In multivariable models, we found no protective effect from probiotics by either conditional logistic regression or proportional hazards models. By conditional logistic regression, factors associated with CDI were tube feeding (adjusted odds ratio [aOR], 4.6; 95% CI, 1.3–17;  $P = .02$ ), chronic kidney disease (aOR, 4.2; 95% CI, 1.1–17;  $P = .04$ ), high severity of illness (aOR, 2.6; 95% CI, 1.1–6.2,  $P = .03$ ), and peptic ulcer disease (OR, 5; 95% CI, 2.4–250;  $P = .007$ ). Probiotic receipt did not reduce CDI risk (aOR, 0.95; 95% CI, 0.8–1.2;  $P = .65$ ).

Because missed doses were common, we looked for patterns associated with missing a probiotic dose. Missing a dose was not associated with presence of a feeding tube, sex, comorbidity, or day of the week. Because of variability in staffing, we expected that a specific day of the week might be associated with missing doses, but we detected no differences in probiotic receipt across days of the week.

## DISCUSSION

In this large before-and-after evaluation of a probiotic agent to prevent CDI among hospital patients receiving antibiotic therapy, we found a possible delayed benefit from the intervention. Meta-analyses summarizing individual randomized controlled trials provide evidence that certain probiotic agents can significantly reduce the risk of CDI.<sup>9–11</sup> Despite consistent findings across probiotic formulations (ie, low between-study heterogeneity), one challenge facing clinicians and institutions is to select the optimal probiotic agent. Here, 2 major decision points are (1) whether to choose bacterial probiotic (usually inclusive of a *Lactobacillus* spp.) or yeast probiotic (eg, *Saccharomyces boulardii*) and (2) whether the agent should have >1 organism. Such choices are driven by evidence of efficacy, safety, and cost. Because evidence from 3 randomized controlled trials and a single-center before-and-after study showed similar reductions in CDI, we chose a multispecies formulation comprising *L. acidophilus* (CL1285), *L. casei* (LBC80R), and *L. rhamnosus* (CLR2).<sup>12–15</sup> Although our implementation did not reduce overall CDI incidence during the entire 12-month intervention period, we found a reduction in CDI during the final 6 months of the intervention.

The delayed reduction in CDI rate is consistent with the following prior studies. In a before-and-after intervention similar to ours, the CDI rate declined several months after introduction of probiotic.<sup>15</sup> In a separate intervention focused

on the detection of *C. difficile* with isolation of patients, the decline in CDI rate was not immediate but occurred over time.<sup>18</sup> We speculate that the delayed probiotic effect could be due to several independent or synergistic factors. First, our intervention hospital had a relatively high baseline rate of CDI, which might have contributed to high-density environmental contamination. The effectiveness of a probiotic may be related to the environmental burden of *C. difficile* spores; for example, probiotic might be more effective during relatively low-inoculum exposures. Thus, a reduction in environmental burden (eg, surface contamination) would be needed before probiotic effect is realized. Such an explanation is supported by the known prolonged environmental survival of *C. difficile* spores.<sup>22</sup> Second, probiotics might reduce the excretion of viable organisms, and because the intensity of environmental contamination contributes to patient acquisition,<sup>23</sup> a gradual reduction in contamination would lead to reduced patient acquisition over time. Third, the possible 'herd effect' likely to result from saturating high-risk patients with probiotics was not achieved during our intervention given the substantial proportion of case patients ineligible for probiotic receipt (41%). Fourth, given the before-and-after design, enhancements or deteriorations in infection control practices may have been unrecognized by the project team. However, there were no changes in environmental cleaning policies, antimicrobial stewardship activities, or modifications to other infection control policies during the study period. Specifically, the laboratory assay (PCR) results for *C. difficile* toxin detection remained constant throughout the baseline and intervention periods.

Because we were unable to electronically extract patient-level antibiotic and probiotic receipt data, we evaluated the association between probiotic receipt and CDI through a matched case-control study. To control for known major confounders, we matched case-control pairs on age, patient-care unit, and date of onset for antibiotic administration. We found that cases had higher severity-of-illness scores than controls; however, after adjusting for severity of illness, we found no protective effect from the probiotic. Despite this negative finding, we expect that there were critical unmeasured factors that increased risk of CDI among case patients. Ideally, we would have had comprehensive assessments of each patient's severity of illness on initiation of antibiotics. Also, prehospitalization antibiotic exposure data would have been a useful surrogate for disruption of a patient's microbiome, but it was not available.<sup>24</sup>

It is possible that the probiotic mixture had a beneficial effect unmeasured in the case-control study, such as modulating *C. difficile* in antibiotic recipients who were colonized but not symptomatic. Such a possibility is suggested by Freedberg et al<sup>25</sup> in their proposed 'herd effect' of antibiotics, wherein antibiotics taken by individual patients puts other patients at risk for CDI.<sup>25</sup> In the study by Freedberg et al, receipt of antibiotics by prior hospital room occupants was associated with increased risk for CDI in subsequent occupants

of the same room. Their hypothesis is that antibiotics promote *C. difficile* proliferation and subsequent environmental contamination in colonized, but not necessarily symptomatic, patients. Our data were also limited by the fact that we did not have the resources to monitor antibiotic recipients after hospital discharge, a time during which patients remain at high risk to manifest CDI and when the full effect of probiotic receipt might be realized.

Despite the largely proven safety of the probiotic mixture, we and clinical staff were concerned about potential harms, particularly clinical infections by probiotic organisms. We believed that the 3 *Lactobacillus* spp were low risk given the frequency of patient exposure to probiotics and uncommon recovery from clinical specimens. During our intervention, only a single episode of *Lactobacillus* bacteremia was recorded for a probiotic recipient. When we performed blinded genetic analysis of the patient's isolate to those recovered from the 3-strain probiotic capsules, we determined that the bacteremia was unrelated to probiotic receipt.<sup>26</sup> Regarding safety, in prior studies, side effects were either reduced or unchanged in probiotic recipients compared with controls.<sup>27,28</sup>

A fundamental limitation of our project was low intervention fidelity among intended recipients, and a substantial number of at-risk patients were ineligible for the intervention (eg, pre-hospital or perioperative antibiotic receipt, clinical ineligibility, and no in-hospital antibiotic receipt). Through a chart review for the case-control study, we discovered that only 1 in 4 eligible antibiotic recipients received probiotic per protocol. Among those not receiving the intervention per protocol, the most common event was complete omission of probiotic, that is, not a single administered dose. Monitoring probiotic distribution during the intervention was performed, but the results were inconsistent with our retrospective chart review. Particularly influential factors impeding probiotic receipt were (1) frequent initiation of antibiotics before admission, either in the community or emergency room; (2) intention to administer only perioperative antibiotics; and (3) our system of probiotic distribution required manual evaluation of eligibility lists by pharmacists combined with the need for episodic pharmacy staffing with temporary personnel during the intervention. Anecdotally, patient refusal was rare and clinician refusal was uncommon. Future projects that pair probiotic with antibiotic administration would benefit (1) from an electronic, automated clinical decision support rule; (2) from the inclusion of emergency room patients; and (3) from possibly relaxing criteria for clinical eligibility (eg, a lower leukopenia threshold or requiring active pharmacologic immunosuppression for transplant recipients).

In conclusion, we found a decreased rate of CDI during the final 6 months of a 12-month before-and-after quality improvement intervention of a 3-strain probiotic mixture for primary prevention of CDI. The delayed effect is consistent with prior literature and may have been related to poor fidelity to the protocol for probiotic administration and a delayed gradual reduction in environmental contamination. Our quality

improvement intervention in a large hospital encountered substantial implementation challenges. It is critical that such real-world applications are evaluated and reported to guide future quality-improvement research efforts based on the lessons learned. Given the foundation of evidence supporting probiotics to prevent CDI, interventions that achieve better distribution of probiotic and focused environmental cleaning before intervention and control periods are needed to quantify the impact of probiotics on CDI.

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Address correspondence to William E. Trick, MD, Collaborative Research Unit, 1900 W Polk Street, Ste 1600, Chicago, IL 60612 (wtrick@cookcountyhhs.org).

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