

**Curriculum Vitae**  
**Emily L. Heil, PharmD**

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**Degree and Date to be Conferred:** Master of Science, December 2020

**Education**

University of North Carolina at Chapel Hill, Eshelman School of Pharmacy, 2009  
PharmD

University of North Carolina at Chapel Hill, 2007  
B.S., Pharmaceutical Science

**Post Graduate Training**

**Infectious Diseases Pharmacy Resident (PGY2)**, University of North Carolina Hospitals, Chapel Hill, NC. 2010-2011.

**Pharmacy Practice Resident (PGY1)**, University of North Carolina Hospitals, Chapel Hill, NC. 2009-2010.

**Professional Experience**

**Associate Professor**, Department of Pharmacy Practice and Science, University of Maryland School of Pharmacy, Baltimore, MD. 2019-Present.

**Clinical Associate Professor (secondary appointment)**, Department of Medicine, Division of Infectious Diseases, University of Maryland School of Medicine, Baltimore, MD. 2019-Present.

**Infectious Diseases Clinical Pharmacy Specialist**, University of Maryland Medical Center, Baltimore, MD. 2011-Present.

**Clinical Instructor**, University of North Carolina Eshelman School of Pharmacy, Chapel Hill, NC. 2009-2011.

**Certifications**

Board Certified Infectious Diseases Pharmacist, 2013, 2019.

Board Certified Pharmacotherapy Specialist, 2010, 2017.

Maryland Pharmacist License #20231

### **Select Peer Reviewed Publications (2018-Present)**

\*complete listing available at:

<https://pubmed.ncbi.nlm.nih.gov/?term=Heil%2C+Emily%5BAuthor%5D&sort=date>

1. **Heil EL**, Tamma PD. Cefiderocol: The Trojan Horse Has Arrived but will Troy Fall? *Lancet Infect Dis* 2020 (epub ahead of print). [Invited Editorial].
2. Reed BN, Noel ZR, **Heil EL**, Shipper AG, Gardner AK. Surveying the selection landscape: A systematic review of processes for selecting postgraduate year 1 pharmacy residents and key implications. *J Amer Coll Clin Pharm* 2020 (epub ahead of print). Doi:10.1002/jac5.1334. [Review].
3. Mouradjian MT, **Heil EL**, Sueng H, Pandit NS. Virologic suppression in patients with a documented M184V/I mutation based on the number of active agents in the antiretroviral regimen. *SAGE Open Med* 2020;8:205031210960570. [Original research]/
4. **Heil EL**, Bork JA. It's a marathon, not a sprint: Antimicrobial Stewardship in the ICU. *Crit Care Med* 2020 (epub ahead of print). [Invited Editorial].
5. Ajaka L\*, **Heil E**, Schmalzle S. Dalbavancin in the Treatment of Bacteremia and Endocarditis in People with Barriers to Standard Care. *Antibiotics* 2020 (epub ahead of print). [Original Research].
6. Weber DJ, Talbot TR, Weinmann A, Mathew T, **Heil E**, Stenehjem E, Duncan R, Gross A, Stinchfield P, Baliga C, Wagner J, Schaffner W, Echevarria K, Drees M on behalf of the Society of Healthcare Epidemiology of America. Policy statement from the Society for Healthcare Epidemiology of America (SHEA): Only medical contraindications should be accepted as a reason for not receiving all routine immunizations as recommended by the Centers for Disease Control and Prevention. *Infect Control Hosp Epi* 2020. Doi:10.1017/ice.2020.342. [Policy Statement].
7. Claeys KC, **Heil EL**, Loughry N, Chainani S, Hitchcock S, Johnson JK, Leekha S. Management of Gram-negative bloodstream infections in the era of rapid diagnostic testing: Impact with and without antibiotic stewardship. *Open Forum Infect Dis* 2020 (epub ahead of print). [Original Research].
8. Narayanan S, Chua JV, **Heil E**. COVID-19: Pitfalls in Offering Research Participation as Therapy in Clinical Settings. *J Gen Intern Med* 2020 (epub ahead of print). Doi:10.1007/s11606-020-06158-6. [Commentary].
9. Bhat P\*, Noval M\*, Doub J, **Heil E**. COVID-19 and PCP Co-infection in a Severely Immunocompromised 25-year old Patient. *Int Journal of Infect Dis* 2020 (epub ahead of print). Doi: 10.1016/j.ijid.2020.07.061. [Case report].

10. Doub J, **Heil E**, Ntem-Mensah A, Neeley R, Ching P. Rifabutin use in Staphylococcus biofilm infections: A case series. *Antibiotics* 2020 (epub ahead of print). [Case series].
11. Strich J, **Heil EL**, Masur H. Considerations for Empiric Antimicrobial Therapy in Sepsis and Septic Shock in an Era of Antimicrobial Resistance. *J Infect Dis* 2020;222:s119-s131. [Review].
12. Phe K, **Heil EL**, Tam V. Optimizing Pharmacokinetics/Pharmacodynamics of Antimicrobial Management in Patients with Sepsis: A Review. *J Infect Dis* 2020;222:s132-s141. [Review].
13. Rhee C, Chiotos K, Cosgrove SE, **Heil EL**, Kadri SS, Kalil AC, Gilbert DN, Masur H, Septimus EJ, Sweeney DA, Strich JR, Winslow DL, Klompas M. Infectious Diseases Society of America Position Paper: Recommended Revisions to the National Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) Sepsis Quality Measure. *Clin Infect Dis* 2020 (epub ahead of print). DOI:10.1093/cid/ciaa059. [Invited Commentary].
14. **Heil EL**, Aitken SL, Nix DE, Drew R, Rose WE, Davis SL, Justo JA, Fish DN, Pogue JM. Recommended Revisions to the National SEP-1 Sepsis Quality Measure: A commentary by the Society of Infectious Diseases Pharmacists on the Infectious Diseases Society of America Position Paper. *Pharmacother* 2020;40(4):368-71. Doi:10.1002/phar.2384. [Invited Commentary].
15. Claeys KC, Brade K, **Heil EL**. Should vancomycin AUC(/MIC)-based therapeutic drug monitoring (by Bayesian or 2-point PK equations) become standard for patients with confirmed for suspected invasive MRSA Infections? *Can J Health-Syst Pharm* 2020 (epub ahead of print). [Review].
16. Blackman A\*, **Heil EL**, Devanathan A, Pandit NS. The effect of veno-arterial extracorporeal oxygenation and nasogastric tube administration on the pharmacokinetic profile of abacavir, lamivudine, and dolutegravir: a case report. *Antiviral Ther* 2020 (epub ahead of print). [Case Report].
17. Bork JA, Claeys KC, **Heil EL**, Banoub M, Leekha S, Sorkin J, Kleinberg M. The positive impact of infectious diseases consultation on antimicrobial appropriateness in hospitalized patients with antimicrobial stewardship oversight: a propensity-score matched study. *Antimicrob Agents Chemother* 2020 (epub ahead of print). [Original Research].
18. Vega A\*, **Heil EL**, Blackman A, Banoub M, Johnson JK, Leekha S, Claeys KC. Evaluation of the addition of IV metronidazole to PO vancomycin therapy in critically ill patients with non-fulminant, severe *C. difficile* infection. *Pharmacotherapy* 2020 (epub ahead of print). [Original Research].

19. Mattingly TJ, **Heil EL**. The Economics of Penicillin Allergy: Still Scratching the Value Surface. *Clin Infect Dis* 2020 (epub ahead of print). [Invited Commentary].
20. Masich AM\*, Vega AD\*, Callahan P\*, Herbert A\*, Fwoloshi S, Zulu P, Chanda D, Chola U, Mulenga L, Hachaambwa L, Pandit NS, **Heil EL**, Claassen CW. Antimicrobial usage at a large teaching hospital in Lusaka, Zambia. *PLOSOne* 2020;15(2):e022855. [Original Research].
21. Pizzuti AG, Patel KH, McCreary EK, **Heil EL**, Bland CM, Chinaeke E, Love LB, Bookstaver PB. Views by Healthcare Practitioners of Social Media as an Educational Resource in Healthcare. *PLoSOne* 2020;15(2):e0228372. [Original Research].
22. Fornaro R\*, **Heil E**, Claeys K, Sheikh F, Naqvi F, Chou J, Oketch E, Mansour D, Zarowitz B, Brandt N. Identifying and bridging the gaps in antimicrobial stewardship in post-acute and long-term care. *J Gerontologic Nurs* 2020; 46(1):8-13. [Original research].
23. Kalaria S, Gopalakrishnan M, Heil E. A population pharmacokinetics and pharmacodynamic approach to optimize tazobactam activity in critically-ill patients. *Antimicrob Agent Chemother* 2020 (epub ahead of print). [Original research].
24. Noval M\*, Banoub B, Claeys KC, Heil EL. The Battle is On: New Beta-lactams for the Treatment of Multidrug Resistant Gram-Negative Organisms. *Curr Infect Dis Report* 2020;22(1) doi:10.1007/s11908-020-0710-9. [Review]
25. Masich AM\*, Kalaria SN, Gonzales JP, **Heil EL**, Tata AL, Claeys KC, Patel D, Gopalakrishnan M. Vancomycin pharmacokinetics in obese patients with sepsis and septic shock. *Pharmacotherapy* 2020 (epub ahead of print). [Original Research].
26. Pogue JM, Heil EL. Laces out Dan! The role of tazobactam based combinations for invasive ESBL infections in a post-MERINO world. *Expert Opin Pharmacother* 2019 (epub ahead of print), DOI: 10.1080/14656566.2019.1663827. [invited commentary].
27. Johnson M, Jones B, **Heil E**, Stover K, Trone S, Fulford M, Bland C. Self-Perceived knowledge and confidence regarding infectious diseases of advanced pharmacy practice experience students. *Curr Pharm Teach Learn* 2019 (epub ahead of print). [Original Research].
28. Deming M, Mark A, Nyemba V, **Heil EL**, Palmeiro RM, Schmalzle SA. Cognitive biases and knowledge deficits leading to delayed recognition of cryptococcal meningitis. *IDCases* 2019 e00588. [Case series].

29. Freedman SR, Ravichandran BR, Masters BM, Bromberg JS, Haririan A, Saharia KS, **Heil EL**, Sparkes TM. Clinical Outcomes of Valganciclovir Prophylaxis in High Risk (D+/R-) Renal Transplant Recipients Experiencing Delayed Graft Function. *Transplant Infect Dis* 2019;00:e13125. [Original Research].
30. Bork JT, **Heil EL**, Berry S, Lopes E, Dave R, Gilliam BL, Amoroso A. Dalbavancin Use in Vulnerable Patients Receiving Outpatient Parenteral Antibiotic Therapy for Invasive Gram-Positive Infections. *Infect Dis Ther* 2019;8(2):171-84. DOI: 10.1007/s40121-019-0247-0. [Original Research].
31. Claeys KC, Hopkins T, Brown J, **Heil EL**. Pharmacists' Perceptions of Implementing an Area Under the Concentration Time Curve Pharmacist-to-Dose Program at a Large Academic Medical Center. *J Am Coll Clin Pharm* 2019;2(5):482-7. [Original Research].
32. Mattingly TJ, Meninger S\*, **Heil EL**. Penicillin skin testing in methicillin-sensitive staphylococcus aureus bacteremia: A cost-effectiveness analysis. *PLoS ONE* 2019; 14(1):e0210271. [Original Research].
33. Bland CM, Bookstaver PB, Griffith NC, **Heil EL**, Jones BM, Justo JA, Staicu ML, Torney NP, Wall GC. From Theory to Practice: A Practical Guide for Pharmacists to Implement Penicillin Allergy Skin Testing. *Am J Health Syst Pharm* 2019;76:136-47. [Commentary].
34. Gallagher JC, Satlin MJ, Elabor A, Saraiya N, McCreary EK, Molnar E, El-Beyrouy C, Jones BM, Dixit D, **Heil EL**, Claeys KC, Hiles J, Vyas NM, Bland CM, Suh J, Biason K, McCoy D, King MA, Richards L, Harrington N, Guo Y, Chaudhry S, Lu X, Yu D. Ceftolozane-tazobactam for the treatment of multidrug-resistant *Pseudomonas aeruginosa* infections: A multicenter study. *Open Forum Infect Dis* 2018;5(11):ofy280, doi:10.1093/ofid/ofy280. [Original Research].
35. Vega A\*, Hynicka L, Claeys KC, **Heil EL**. Effectiveness of Eight Weeks of Ledipasvir/Sofosbuvir for Hepatitis C in HCV/HIV-coinfected Patients. *Antivir Ther* 2018 (epub ahead of print). [Original Research].
36. Claeys KC, Schlaffer KE, **Heil EL**, Leekha S, Johnson JK. Validation of an Antimicrobial Stewardship Driven Verigene Blood-Culture Gram-Negative Treatment Algorithm to Improve Appropriateness of Antibiotics. *Open Forum Infect Dis* 2018;5(10) doi:10.1093/ofid/ofy233. [Original Research].
37. **Heil EL**, Nicolau DP, Farkas A, Roberts JA, Thom KA. Pharmacodynamic target attainment for cefepime, meropenem and piperacillin/tazobactam using a pharmacokinetic/pharmacodynamic-based dosing calculator in critically ill patients. *Antimicrob Agent Chemother* 2018; 62:e01008-18. [Original Research].

38. Plazak ME\*, Tamma PD, **Heil EL**. The Antibiotics Arms Race: Current and Emerging Pharmacotherapy for the Treatment of *Klebsiella pneumoniae* Carbapenemase (KPC)-Producing Bacteria. *Expert Opin Pharmacother* 2018 (epub ahead of print). [Review].
39. Lewis PO, **Heil EL**, Covert KL, Cluck DB. Treatment Strategies for Persistent Methicillin-Resistant *Staphylococcus aureus* Bacteremia. *J Clin Pharm Ther* 2018;43:614-25 doi:10.1111/jcpt.12743. [Review].
40. **Heil EL**, Claeys KC, Mynatt RP, Hopkins TL, Brade K, Watt I, Rybak MJ, Pogue JM. Making the Shift to Area Under the Curve-Based Vancomycin Dosing: The Why and the How. *Am J Health Syst Pharm* 2018;75:1986-95. [Commentary].
41. Outpatient Stewardship Working Group: Blanchette L, Gauthier T, **Heil E**, Klepser M, Madaras Kelly K, Nailor M, Wei W, Suda K. The Essential Role of Pharmacists in Antibiotic Stewardship in Outpatient Care: An Official Position Statement of the Society of Infectious Diseases Pharmacists. *J Am Pharm Assoc* 2018;58(5):481-4. doi:10.1016/j.japh.2018.05.013. [Commentary].
42. **Blanco N**, O'Hara LM, Robinson GL, Brown J, **Heil E**, Brown CH, Stump BD, Sigler BW, Belani A, Miller HL, Chiplinski AN, Perlmutter R, Wilson L, Morgan DJ, Leekha S. Healthcare worker perceptions toward computerized clinical decision support tools for *Clostridium difficile* Infection reduction. *Am J Infect Control* 2018; doi:10.1016/j.ajic.2018.04.204 (epub ahead of print). [Original Research].
43. **Claeys KC**, **Heil EL**, Pogue JM, Lephart PR, Johnson JK. The Verigene Dilemma: Gram-negative Polymicrobial Bloodstream Infections and Clinical Decision Making. *Diag Microbiol Infect Dis* 2018;91:144-6. doi 10.1016/j.diagmicrobio.2018.01.012. [Original Research]. Citations: 1.
44. **Pogue JM**, **Heil EL**, Lephart P, Johnson JK, Mynatt RP, Salimnia H, Claeys KC. An Antibiotic Stewardship Program Blueprint for Optimizing Verigene BC-GN within an Institution: a Tale of Two Cities. *Antimicrob Agents Chemother* 2018;62(5). doi: 10.1128/AAC.02538-17. [Original Research].
45. **Heil EL**, Pineles L, Mathur P, Morgan DJ, Harris AD, Srinivasan A, Thom KA and the CDC Epicenters. Accuracy of provider-selected indications for antibiotic orders. *Infect Control Hosp Epidemiol* 2018;39:111-3. [Original Research].
46. **Mattingly TJ**, Fulton A\*, Lumish R\*, Williams A\*, Yoon S\*, Yuen M\*, **Heil EL**. The cost of self-reported penicillin allergy: a systematic review. *J Allergy Clin Immunol Pract* 2018;6:1649-54. doi: 10.1016/j.jaip.2017.12.033. [Systematic Review].

47. Claeys KC, Hopkins TL, Vega A\*, **Heil EL**. Fluoroquinolone restriction as an effective antimicrobial stewardship intervention. *Curr Infect Dis Report* 2018;20(5):7. doi: 10.1007/s11908-018-0615-z. [Review].

### **Select Invited Presentations (2018-Present)**

1. *Strategies to Avoid Stewardship Burnout*. SHEA Antimicrobial Stewardship Best Practices Pre-Meeting Workshop. ID Week 2020 Virtual Conference. October 2020. [National]. ACPE/CME Continuing Education Lecture (invited).
2. *COVID-19 Therapeutics*. Maryland Society of Health-System Pharmacy Fall Seminar. Baltimore, MD. October 2020. [Local]. ACPE Continuing Education Lecture (invited).
3. *Adapting Antibiotic Stewardship Practices During a Public Health Emergency*. Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria Public Meeting. Washington, DC. September 2020. [National] (invited).
4. *Updates in COVID-19 Therapeutics – Pediatric Edition*. University of Maryland Department of Pediatrics Grand Rounds. Baltimore, MD. June 2020. [Local]. ACCME Continuing Education Lecture (invited).
5. *Updates in COVID-19 Therapeutics*. University of Maryland Department of Medicine Grand Rounds. Baltimore, MD. May 2020. [Local]. ACCME Continuing Education Lecture (invited).
6. *Antibiotic Stewardship Workforce: integrating non-infectious diseases pharmacists into antibiotic stewardship activities*. Society of Healthcare Epidemiology of America Decennial Meeting, Atlanta, GA. March 2020. [National]. ACCME/ACPE Continuing Education Lecture (invited). (Canceled due to COVID19)
7. *Tip of the CAP: CAP Management in 2019*. American College of Clinical Pharmacy Annual Meeting, New York City, NY. October 2019. [National]. ACPE Continuing Education Lecture. (Invited).
8. *Definitive Treatment for Penicillin Allergies: How Do We Improve Antimicrobial Stewardship?* ASM Microbe, San Francisco, CA. June 2019. [National]. ACCME/ACPE Continuing Education Lecture (invited).
9. *Penicillin Allergy: The Inpatient Approach*. Hippo Education – Primary Care Reviews and Perspectives. May 2019. [National]. ACCME Continuing Education Lecture (invited).
10. *The Role of Antibiotic Allergies in Antimicrobial Stewardship in Long-Term Care*. Maryland Department of Health/Peter Lamy Center. April 2019. [State]. (Invited).

11. *Goodbye Fluoroquinolone Use, Hello Reduced C.difficile Rates.* Maryland SPARC Collaborative. March 2019. [State]. (Invited).
12. *Probiotics: What Do We Tell Our Patients?* Edmund G. Beacham 46<sup>th</sup> Annual Current Topics in Geriatrics Conference, Baltimore, MD. March 2019. [National]. ACCME Continuing Education Lecture (Invited).
13. *HIV & HCV.* American College of Clinical Pharmacy Last Chance Infectious Diseases Review Webinar. September 2018. [National]. Lecture (Invited).
14. *Microbiology, Antibiograms, and Anti-Infective Basics 101.* Maryland Long-Term Care Stewardship Summit, Columbia, MD. September 2018. ACPE No. 0025-0000-18-112-L04-P. [State]. Lecture (Invited).
15. *Stewardship PR: Marketing your Program.* Making a Difference in Infectious Diseases Annual Meeting, Orlando, FL. May 2018. [National]. Workshop (Invited).
  - a. Encore at Maryland Campaign for Appropriate Antibiotic Use monthly webinar. May 2018. [State].
16. *Penicillin Allergy: Practice and Policies.* Making a Difference in Infectious Diseases Annual Meeting, Orlando, FL. May 2018. [National]. Workshop (Invited).
17. *Combating Drug Resistant Gram-Negative Infections: Giving Conventional Antibiotics New Capabilities.* Making a Difference in Infectious Diseases Annual Meeting Satellite Symposium, Orlando, FL. May 2018. [National]. Lecture (Invited).
18. *Pharmacokinetic Dosing of Antimicrobials.* Duke School of Medicine Infectious Diseases Grand Rounds, Durham, NC. April 2018. [Local]. ACCME Continuing Education Lecture (Invited).
19. *Probiotic Stewardship.* Edmund G. Beacham 45<sup>th</sup> Annual Current Topics in Geriatrics Conference, Baltimore, MD. February 2018. [National]. ACCME Continuing Education Lecture (Invited).
20. *Strategies and Opportunities for Reducing the Incidence of Clostridium difficile Colitis in the Hospital.* Society of Hospitalist Medicine, Maryland Chapter Meeting, Columbia, MD. January 2018. [State]. Lecture (Invited).

### **Honors and Awards**

1. American Association of Colleges of Pharmacy Teacher of the Year. University of Maryland School of Pharmacy. May 2019. (Professional)

achievement, Local).

2. Medication Safety Award. Maryland Society of Health-System Pharmacy. November 2016. (Professional achievement, State).
3. Clinical Practice Award. American College of Clinical Pharmacy Infectious Diseases Practice and Research Network. October 2016. (Professional achievement, National).
4. Pharmacist of the Year. Maryland Society of Health-System Pharmacy. November 2015. (Professional achievement, State).
5. Preceptor of the Year. University of Maryland Residency and Fellowship Programs. June 2014. (Professional achievement, Local).
6. Medication Safety Award. Maryland Society of Health-System Pharmacy. May 2013. (Professional achievement, State).
7. Linda Rodgers Memorial Award. Kappa Epsilon Professional Pharmacy Fraternity, Grand Council. June 2008. (Professional achievement, National).
8. Phi Lambda Sigma Leadership Society. Eshelman School of Pharmacy, University of North Carolina at Chapel Hill. Inducted 2007. (Professional achievement, local).
9. Rho Chi Pharmacy Honor Society, Xi Chapter. Eshelman School of Pharmacy, University of North Carolina at Chapel Hill. Inducted 2007. (Professional achievement, local).

### **Teaching Experience**

**Course Manager**, Infectious Diseases Therapeutics I & II. University of Maryland School of Pharmacy. 2016-Present.

**Instructor**, Clinical Pharmacokinetics. University of Maryland School of Pharmacy. 2017-Present.

**Instructor**, Pharmacotherapy. University of Maryland School of Pharmacy. 2017-Present.

**Instructor**, Host Defense and Infectious Diseases. University of Maryland School of Medicine. 2017-Present.

## Abstract

Title of Thesis: Probiotic Use for the Primary Prevention of *Clostridioides difficile* infection

Emily L. Heil, PharmD, MS in Clinical Research Candidate, 2020

Thesis Committee Chair: Surbhi Leekha, MBBS, MPH; Associate Professor, Department of Epidemiology and Public Health

Primary prevention of *C. difficile* infection (CDI) is a priority for hospitals and probiotics have the potential to interfere with colonization and/or infection with *C. difficile* offering an opportunity to enhance ongoing primary prevention strategies. The overall objective of this study was to evaluate the impact of a hospital-wide computerized clinical decision support system tool to prescribe probiotics to eligible adult patients receiving antibiotics for the primary prevention of CDI. After implementation of the tool, the odds of CDI was 1.41 in eligible patients compared to the pre-intervention time period (aOR 1.41, 95% CI 1.11, 1.79). A propensity score matched analysis showed that patients who received probiotics did not have lower rates of CDI compared to those who did not (OR 1.46, 95% CI 0.87, 2.45). Based on these findings, the use of probiotics for the primary prevention of CDI is not supported.

Probiotic Use for the Primary Prevention of *Clostridioides difficile* infection

by  
Emily Heil

Thesis submitted to the Faculty of the Graduate School of the  
University of Maryland, Baltimore in partial fulfillment  
of the requirements for the degree of  
Master of Science  
2020

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## List of Abbreviations

APR-DRG-ROM	All patient refined diagnosis related groups risk of mortality
APR-DRG-SOI	All patient refined diagnosis related groups severity of illness
BPA	Best Practice Alert
BMT	Bone Marrow Transplant
CCDSS	Computerized clinical decision support system
CDC	Centers for Disease Control and Prevention
CDI	<i>Clostridioides difficile</i> Infection
CDR	Clinical data repository
CFU	Colony Forming Units
CI	Confidence Interval
HSCRC	Health Services Cost Review Commission
ICD-10	International Classification of Diseases, 10 <sup>th</sup> Revision
ICU	Intensive Care Unit
IMC	Intermediate Care Unit
IQR	Interquartile range
ITS	Interrupted time series
NHSN	National Healthcare Safety Network
NPO	Nothing by mouth
OR	Odds ratio
PS	Propensity Score
QBR	Quality Based Reimbursement
SD	Standard Deviation

SIR	Standardized Infection Ratio
UMMC	University of Maryland Medical Center
UMMS	University of Maryland Medical System

## **Background and Significance:**

*Clostridioides difficile* is a spore-forming, Gram-positive, anaerobic bacteria that can cause life-threatening diarrhea and colitis and is considered an “Urgent Threat” by the Centers for Disease Control and Prevention.<sup>1</sup> Over 450,000 infections and 15,000 deaths are attributed annually to *C. difficile* and approximately 30% of patients treated for a primary episode of *C. difficile* infection (CDI) experience a recurrence<sup>2-4</sup>. *C. difficile* infections increase patient and healthcare system costs through extended length of hospital stay, re-hospitalizations, laboratory testing, and additional medications. Primary prevention of CDI is challenging given that CDI occurs as a result of complex host, agent and environmental factors. Despite many interventions CDI rates have not decreased to the degree of other hospital-acquired infections and decreasing CDI rates remains a priority in many institutions to improve patient and economic outcomes.

The human intestinal microbiota is an essential ‘organ’ that carries out multiple activities ranging from catabolism and bioconversion of complex molecules to synthesis of a wide range of compounds that can have an effect on both the microbiota and the host.<sup>5</sup> Disruption of the beneficial functions of the microbiota can lead to disease, including CDI, and intentional manipulation of the microbiota is an important area of research for novel therapeutic targets.<sup>5</sup>

Alterations in gut microbiota, usually from antimicrobial therapy, play a key role in the pathogenesis of CDI. Healthy adults are protected from *C. difficile* colonization and disease by the colonization resistance conferred by their normal bacterial flora. Disturbances in

colonic flora by antimicrobials, acid suppressing medications and/or chemotherapy leads to a loss of colonization resistance and thus the host becomes vulnerable to CDI and CDI recurrences<sup>6</sup>. Unfortunately, when the microbiota is unable to restore resistance to colonization by *C. difficile*, patients face increased risk of recurrent infection.

Probiotics are live microorganisms which when administered in adequate amounts confer a health benefit on the host<sup>7</sup>. The rationale for probiotic administration to patients at high risk for CDI is re-inoculation of the disturbed indigenous microbiota secondary to antibiotic administration and emerging data that certain strains can inhibit binding of *C. difficile* toxin to the intestinal brush boarder.<sup>8</sup> Utilization of probiotics therefore offers an opportunity to enhance ongoing primary prevention strategies.

Multiple meta-analyses of randomized controlled trials have shown that ingestion of certain probiotic strains during antibiotic therapy reduces the risk of antibiotic associated diarrhea and *C. difficile* infection<sup>9-13</sup>. A probiotic formulation of *Lactobacillus acidophilus* CL1285, *Lactobacillus casei* LBC80R, and *Lactobacillus rhamnosus* CLR2 (Bio-K+) was shown to be safe and effective in decreasing rates of *C. difficile* at a community hospital in Quebec during an outbreak of the *C. difficile* NAP1/027/BI strain<sup>14</sup>. A dose-ranging study found that a dose of 100 billion colony forming units (CFU) of Bio-K+ was associated with a lower incidence of CDI compared to placebo and a dose of 50 billion CFU<sup>15</sup>. Most recently, a before and after study of Bio-K+ administration to eligible inpatients receiving antibiotics at a tertiary-care medical center found a lower incidence of CDI in the second half of the year of observation (IRR 0.8; 95% CI, 0.5-1.1; P=0.13)<sup>16</sup>.

Optimizing the use of probiotics for primary CDI prevention in hospitalized patients requires balancing safety and efficacy. Probiotics are not benign agents and particularly in immunocompromised patients and/or patients with central venous access when the products are manipulated can be associated with invasive infection.<sup>17</sup> Timing is key with probiotics when used for primary prevention of CDI with a decrement in efficacy for every day of delay in starting probiotics, and maximal impact when probiotics are administered within 2 days of antibiotic initiation.<sup>18</sup> Therefore, a narrow window of probiotic eligible patients at high risk for CDI exists and initiation of probiotics early in the antibiotic course is essential. Utilization of a computerized clinical decision support system (CCDSS) based tool built to alert prescribers for patients at high-risk for CDI without contraindications to inpatient probiotic administration to order probiotics at the time of initial concomitant antibiotic order could promote optimal use of this primary prevention strategy.

The standardized infection ratio (SIR) for CDI at the University of Maryland Medical Center (UMMC) had decreased from 1.12 to 0.85 from fiscal year 2017 to fiscal year 2018 with the implementation of numerous interventions including antimicrobial stewardship efforts focusing on fluoroquinolone reduction, improvement of the quality of environmental cleaning, and efforts to reduce unnecessary testing (e.g., testing in the presence of laxative use). Additionally, in October of 2018, the testing process changed from DNA detection alone to a two-step reporting with DNA followed by toxin EIA. Despite these interventions, the incidence of CDI at UMMC in early 2019 remained above the national SIR target of 0.7 and at other hospitals within the University of Maryland Medical System (UMMS). Of note, the SIR is a summary measure that adjusts

for facility and/or patient factors that contribute to HAI risk, and is used to track hospital-acquired infections such as CDI at national, state and local levels over time.<sup>19</sup> The goal of this project is to pilot a guideline and CCDSS-based tool to facilitate probiotic utilization for primary prevention of CDI at four medical centers in the University of Maryland Medical System.

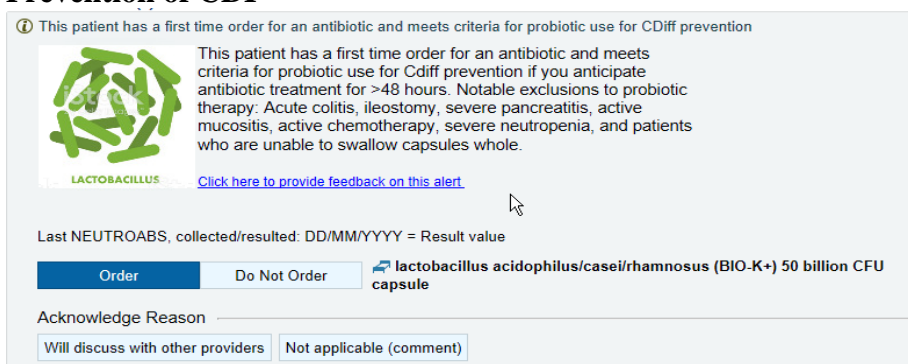
### **Methodology:**

The overall objective of this study was to evaluate the impact of a hospital-wide guideline and CCDSS-based tool to prescribe probiotics to eligible adult patients receiving antibiotics for the primary prevention of *Clostridioides difficile* infection. The first aim was to evaluate the change in incidence of overall hospital-onset CDI before and after CCDSS implementation, and the second aim was to evaluate change in hospital-onset CDI in patients eligible for probiotics before and after CCDSS implementation. A subgroup analysis of post-intervention patients who received probiotics was also performed.

Intervention: A “best practice alert” (BPA) was built in the EPIC electronic medical record (EPIC Systems Corporation, Verona, WI) and launched at the four included UMMS hospitals in May of 2019. The BPA prompted prescribers to order probiotic capsules (Bio-K+, Laval, Quebec, Canada) containing 100 billion CFUs of probiotic (*L. acidophilus*, *L. casei*, *L. rhamnosus*) for qualifying patients at the time of initial qualifying systemic antibiotic prescription. Qualifying patients were inpatients at increased risk of CDI due to age greater than 50 years, initiation of select systemic antibiotic therapy with an anticipated antibiotic need of greater than 48 hours (Appendix 1) and able to take medications by

mouth. Antibiotics selected were those that are systemically absorbed and known to be associated with higher risk of CDI. Antibiotics with minimal association with CDI (e.g., linezolid) or minimal systemic absorption (e.g., nitrofurantoin) were excluded. To ensure safety of the intervention, the BPA was designed to not fire on patients at higher risk of adverse effects, namely invasive infection, secondary to probiotic administration. Therefore the BPA excluded patients if their problem or medication list included acute colitis, ileus or perforation; ileostomy; patients with known, severe acute pancreatitis; severe neutropenia (ANC <500); active chemotherapy; active mucositis; bone marrow or solid organ transplant; other immunosuppression including high-dose steroids or biologics; and active NPO orders. Additionally, the BPA did not fire on patients located in oncology and transplant units in Hospital 1 and in the intensive care unit at Hospital 3. The BPA was built to make the ordering of probiotics easy for providers with only “2-clicks” from the BPA to complete the order. The BPA was also designed to optimize timing of probiotics by coordinating probiotic initiation with the initiation of the qualifying antibiotic.

**Figure 1: CCDSS Best Practice Alert to Promote Ordering of Probiotics for Primary Prevention of CDI**



The screenshot shows a clinical alert interface. At the top, a header reads: "This patient has a first time order for an antibiotic and meets criteria for probiotic use for CDiff prevention". Below this is a green circular icon containing several green capsules, with the word "LACTOBACILLUS" written underneath. To the right of the icon, the alert text states: "This patient has a first time order for an antibiotic and meets criteria for probiotic use for Cdiff prevention if you anticipate antibiotic treatment for >48 hours. Notable exclusions to probiotic therapy: Acute colitis, ileostomy, severe pancreatitis, active mucositis, active chemotherapy, severe neutropenia, and patients who are unable to swallow capsules whole." Below the text is a blue link: "Click here to provide feedback on this alert". Underneath the link, it says "Last NEUTROABS, collected/resulted: DD/MM/YYYY = Result value". There are two buttons: a blue "Order" button and a grey "Do Not Order" button. To the right of these buttons is a small icon of a capsule and the text "lactobacillus acidophilus/casei/rhamnosus (BIO-K+) 50 billion CFU capsule". At the bottom, there is a section for "Acknowledge Reason" with two buttons: "Will discuss with other providers" and "Not applicable (comment)".

Additionally, clinical pharmacists reviewed antibiotic orders to support probiotic prescription in appropriate patients along with periodic compliance assessments made by

the antimicrobial stewardship team. The corresponding guideline for the BPA aims for the 3-strain probiotic mixture to be initiated within 12 hours of the initial antibiotic dose, continued daily during the patient's antibiotic course and for 5 days after the final dose of antibiotic (appendix 2). Patients who are discharged prior to the completion of their antibiotic and probiotic courses could be provided with a prescription for Bio-K+ at discharge. Education regarding the guidelines and BPA was provided to prescribers and pharmacists prior to launch at the four participating hospitals. Education was also provided to nursing to ensure probiotics were administered safely without capsule manipulation and proper hand hygiene before and after administration.

A brief overview of the study aims can be found in Table 1 on the following page.

**Table 1: Study Methodology Overview**

Aim	Patient Population	Design	Outcomes Measured	Analytic Method
1: Evaluate change in incidence of hospital-onset CDI before and after the probiotics intervention among all hospitalized patients				
1a. Change in SIR as reported to CDC/ NHSN	All hospitalized patients at the four participating hospitals	Quasi-experimental before and after evaluation	% change in SIR	Descriptive
1b. Change in CDI incidence			CDI incidence level change and slope change	Interrupted time series analysis
2. Patient-level analysis of change in hospital-onset CDI before and after the probiotics intervention				
2a. CDI incidence among patients eligible for probiotics	Hospitalized patients >50 years of age receiving a qualifying antibiotic with a length of stay >2 days in the pre- and post-intervention periods	Quasi-experimental study of patients eligible for probiotic administration before and after implementation of the CCDSS	CDI incidence before and after CCDSS implementation in qualifying patients	Chi-square test
2. a1. Adjust incidence for covariates associated with CDI			CDI incidence before and after CCDSS implementation adjusted for confounders	Multivariate analysis
2. a2. Quantify adherence to CCDSS BPA			Hospitalized patients where the CCDSS BPA 'fired' during their stay	% of unique patients where the BPA resulted in a probiotic order
2b. CDI incidence among patients who received probiotics versus those who did not	Hospitalized patients >50 years of age receiving a qualifying antibiotic with a length of stay >2 days in the post-intervention period	Quasi-experimental study of patients eligible for probiotic administration after implementation of the CCDSS	CDI incidence by receipt of probiotics adjusted for covariates impacting probiotic prescription	Propensity score matching of groups and Chi-square test
2 b1. CDI incidence by PCR testing			CDI incidence by PCR testing	
2 b2. CDI incidence by toxin testing			CDI incidence by toxin testing	Chi-square or Fisher's exact test
2c. Evaluate safety of probiotics	All hospitalized patients in the post-intervention period with a blood culture positive for <i>Lactobacillus</i> spp.	Retrospective review of all hospitalized patients with the culture of interest in the post-intervention period	Quantification of number of blood cultures positive for <i>Lactobacillus</i> spp. attributable to use of probiotics	Descriptive

Table 1 Continued				
3. Evaluate cost implications of probiotics intervention				
3a. Quantify costs of Bio-K+ during the post-intervention period	McKesson Pharmacy Purchasing Data	Financial evaluation of intervention costs and potential cost avoidance benefits in the post-intervention period	Amount spent on probiotics (Bio-K+) dispensed	Descriptive
3b. Quantify HSCRC penalty changes based on SIR changes	Maryland HSCRC QBR reporting records		Financial penalty change (increase/decrease) based on QBR performance	Descriptive

**Aim 1:** *To evaluate CDI Rates for All Patients Before and After Implementation of Probiotics*

Study design: This was a quasi-experimental before-and-after study at four hospitals in the University of Maryland Medical System. A 13-month baseline period (April 1, 2018-April 30, 2019) and a 13-month intervention period (June 1, 2019-June 30, 2020) was assessed including a 1-month run-in period (May 2019) during the implementation of the probiotic guideline and CCDSS tool.

Measures:

1a) Laboratory identified *C. difficile* infections have been required for public reporting since July 1, 2013 through the Center for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) and used for Maryland hospital quality-based reimbursement by the Maryland Health Service Cost Review Center (HSCRC).<sup>20</sup> The NHSN defines hospital-onset CDI as a positive laboratory test result for *C. difficile* toxin A and/or toxin B or any detecting of toxin-producing *C. difficile* organisms by culture or other laboratory means on an unformed stool specimen that conforms to the container after 4 or more days of the patient’s hospital stay.<sup>21</sup> Incidence is used to determine the SIR, that

is, the ratio of observed cases compared to predicted cases. The number of predicted cases is calculated by the CDC using a negative binomial regression model. The number of predicted events is risk adjusted for inpatient community-onset prevalence rate, medical school affiliation, number of ICU beds, total number of inpatient beds, facility type, reporting from an Emergency Department (ED) or 24-hour observation unit and CDI test type.<sup>19</sup>

1b) The incidence rate of total reportable hospital-onset CDI in all inpatients in the pre- and post-intervention periods was assessed. CDI incidence was defined as the number of hospital-onset CDI cases divided by the patient census per quarter and was calculated for each individual hospital and an aggregate of the four hospitals combined. CDI incidence rate was reported as CDI cases per 10,000 patient days and did not include any of the risk adjustment that the SIR does. Due to the change to a two-step testing process mid-way through the pre-intervention period, DNA positivity via PCR testing was the primary outcome for CDI and was counted regardless of the results of the toxin EIA.

Data collection:

1a) Quarterly data reported to the CDC/NHSN on hospital-onset CDI for the four hospitals was retrieved from CDC/NHSN database for April 2018 through June of 2020. This data included the total number of hospital-onset CDI cases, the corresponding patient census for the quarter, the expected number of CDI cases and the calculated SIR.

1b) The CDC/NHSN reported number of hospital-onset CDI cases and patient census was used to calculate the rate of hospital-onset CDI per quarter for the four hospitals individually and in aggregate.

Analysis:

1a) The difference in SIR in the pre- and post-intervention periods was calculated as a percentage change.

1b) Interrupted time series (ITS) analysis was conducted using segmented regression to compare overall hospital-onset CDI incidence in the post- and pre-implementation periods for the four individual hospitals individually and in aggregate using ordinary least squares regression. Level change after the implementation of the CCDSS was evaluated along with slope change between the two time period. The following model was used:

$$Y_t = \beta_0 + \beta_1 * \text{time}_t + \beta_2 * \text{implementation} + \beta_3 * \text{time after implementation}_t + \varepsilon_t,$$

where  $Y_t$  is the CDI incidence in quarter  $t$ , with  $t$  taking values from 1 (for April 2018) to 9 (for April 2020).  $\beta_0$ : intercept and the slope  $\beta_1$ : average quarterly change in the CDI incidence before the implementation.  $\beta_2$ : the immediate effect of the implementation (i.e., the change in level of the CDI incidence immediately after the implementation).  $\beta_3$ : the changes in the slope of the quarterly CDI incidence after the implementation, compared to the slope  $\beta_1$  for the segment before the implementation. The variable *implementation* is 0 before July 2019 and 1 for observations on or after July 2019. The variable *time after implementation* measured the time units after the implementation; it was 0 for April 2018 to April 2019 and took values 1 to 4 for the quarters from July 2019 to April 2020.

Level (immediate) change after the implementation of the CCDSS was not expected to be attributable to the intervention whereas a decrease in slope (gradual) between the two time periods would support the potential improvement in rates due to the intervention.

Since the ordinary least squares regression was applied in time series data, the regression

model was augmented with an autoregressive model for random error to solve the violation of the independent errors assumption. We used the following autoregressive error model of order k:

$$Y_t = \beta_0 + \beta_1 * \text{time}_t + \beta_2 * \text{implementation} + \beta_3 * \text{time after implementation}_t + v_t,$$

$$v_t = \gamma_1 v_{t-1} - \gamma_2 v_{t-2} - \gamma_3 v_{t-3} - \dots - \gamma_k v_{t-k} + \varepsilon_t,$$

where  $\varepsilon_t \sim \text{IN}(0, \sigma^2)$ . The Yule-Walker method was used to perform the stepwise autoregressive process and then select the correct order of the autoregressive error model. Each model fit with autocorrelation was assessed using the white noise probability plot, autocorrelation functions (ACF) plot, and partial ACF plot.

All statistical analyses were done using SAS Version 9.4 (SAS Institute, Inc. Cary, NC).

**Aim 2:** *Patient-level analysis of change in hospital-onset CDI before and after the probiotics intervention*

Study design:

2a) We sought to describe the change in hospital-onset CDI in patients who would have qualified for the probiotic intervention in the post-intervention period through a quasi-experimental study of patients eligible for the CCDSS intervention in the pre- and post-intervention periods.

2b) To conduct a patient-level analysis of the association between probiotic use and CDI, we conducted a cohort study of eligible patients who received probiotics versus eligible patients who did not receive probiotics in the post-intervention time period with propensity score matching to account for potential differences in patients who were prescribed probiotics.

2c) Safety of probiotics was assessed through an evaluation of all blood cultures positive for *Lactobacillus* spp. during the post-intervention time period

Participants: Patients in the pre- and post-intervention periods who were eligible to receive probiotics based on the BPA (e.g., age >50 years, on one of the included units, receiving an eligible antibiotic and admitted for >2 days) were included. For aim 2b, only patients in the post-intervention period were included (June 2019-June 2020). The safety population was an assessment of all hospitalized patients with blood cultures positive for *Lactobacillus* spp. in the post-intervention time period.

Measures:

2a) *CDI Rates by CDI PCR in Patients Eligible for the BPA Based on Age and Antibiotics*

The incidence of hospital-onset CDI among patients who would have qualified for probiotics in the post-intervention period based on age greater than 50 years and receipt of a qualifying antibiotic in the pre-period was compared to the post-period. CDI was defined as patients with a positive *C. difficile* toxin gene DNA assay on stool test sent due to clinical suspicion of CDI. Since the testing process changed to two-step in the middle of the pre-intervention period, we used DNA positivity for the outcome and counted these as positive regardless of the results of the toxin EIA. As a balance measure, we evaluated potential change in *C. difficile* testing intensity by comparing the frequency at which patients were tested hospital wide in the pre and post-periods.

2.a1) *CCDSS BPA Adherence*. A secondary outcome was to assess the adherence to the probiotic guideline. Adherence to the probiotic guideline was assessed through the CCDSS tool identifying how often the best-practice alert resulted in a probiotic order in eligible patients.

2b) *CDI PCR Positivity Rate in Patients who Received Probiotics*. The primary outcome was to evaluate if probiotic receipt has a protective effect on the risk of CDI by measuring incidence of CDI in patients who received probiotics compared to those who did not. As only patients in the post-intervention time period were included in this part of the analysis, CDI was assessed as both CDI PCR positivity and separately as CDI toxin positivity.

2c) *Probiotic Safety*. Safety was assessed through a review of all positive blood cultures from the microbiology laboratory across the 4 hospitals for cases of invasive *Lactobacillus* spp. infections in the post-intervention time period. Charts were reviewed to determine if patients had received probiotics during the index admission with the positive culture or in the three months prior to hospital admission. Medical notes were reviewed to determine if the culture was deemed clinically significant or contamination by the patient's care team and if any treatment was received.

Data collection:

2a) Data was abstracted from the Clinical Data Repository (CDR) and validation of data from 100 charts (across all sites) was done. For the primary outcome of CDI, laboratory results for any *C. difficile* tests performed at the UMMC microbiology laboratory (which

performs testing for all included hospitals) including test type (e.g., DNA PCR, toxin EIA) and corresponding results were gathered. To assess patients who were eligible for probiotic administration in the two study periods, a listing of patients over the age of 50 years who received one of the qualifying antibiotics (appendix 1) and had a hospital length of stay of at least 2 days was obtained. Covariates for these patients included demographic data, hospital (e.g., Hospital 1, 2, 3 or 4), hospital unit at time of qualifying antibiotic prescription, all antibiotics prescribed during hospital stay, any proton pump inhibitors (PPIs) or H2 antagonists prescribed during the hospital stay, International Classification of Diseases, 10<sup>th</sup> Revision (ICD-10) codes, all patient refined diagnosis related groups (APR-DRGs) for severity of illness (i.e., the extent of physiologic decompensation or organ system loss of function) and risk of mortality (i.e., likelihood of dying)<sup>22</sup>, hospital length of stay and patient disposition. Elixhauser comorbidity indices were calculated from the ICD-10 data.<sup>23</sup> Hospital units were grouped into medical/surgical floors, intermediate care units (IMC), intensive care units (ICU), emergency department (ED), peri-operative areas and operating room (OR), cancer or transplant units, and other. Antibiotics received were categorized into four classes: CDI high risk (clindamycin, third generation cephalosporins, fluoroquinolones), carbapenems (imipenem/cilastatin, meropenem, ertapenem), other broad-spectrum beta-lactams (piperacillin/tazobactam, cefepime, ceftaroline, aztreonam, ceftazidime/avibactam, ceftolozane/tazobactam) and narrow spectrum beta-lactams (cefoxitin, amoxicillin/clavulanate, ampicillin/sulbactam, cefazolin, cephalexin).

2a1) A report of unique firings of the CCDSS BPA was obtained from Epic to evaluate adherence to the BPA. The report included each firing of the BPA along with action taken by the prescriber and any corresponding probiotic orders.

2b) Analysis for aim 2b used the same data from 2a above.

2c) A report of all blood cultures from the UMMC microbiology laboratory (which provides microbiology laboratory services for all included hospitals) positive for *Lactobacillus* spp. during the post-intervention time period was used to conduct chart review to determine if the patients had received probiotics during the index hospital stay or in the preceding 90 days.

Analysis:

2a) For the evaluation of patients who would have qualified for probiotics, quantitative variables were expressed as mean  $\pm$  standard deviation (SD) or median and interquartile range (IQR), as appropriate and categorical variables were expressed as frequency/proportion. Descriptive statistics were used to summarize patient demographic and clinical characteristics. Bivariate associations between patient characteristics and time period (exposure) and between patient characteristics and CDI (outcome) were measured using Chi-square test, Fisher's exact test and Wilcoxon rank-sum test. Due to the large sample size, Cliff's delta and Cramer's V were computed to evaluate the significance of differences in the pre- and post-intervention characteristics. Cramer's V is a statistical test to measure effect size of categorical variables to show the magnitude of effect as the significance test (Chi-square) does not tell the degree of effect. A Cramer's V of  $<0.10$  with 1 degree of freedom is considered a small effect size.<sup>24</sup> Similarly, Cliff's Delta is a non-parametric effect size measure that quantifies that amount of differences where  $|d| < 0.147$  is considered a negligible effect and  $|d| < 0.33$  a small effect.<sup>25</sup> Multivariable analysis was done to evaluate the association between the primary exposure (study period)

and outcome (CDI) adjusting for potential confounding variables. For the multivariable regression models, covariates were considered statistically significant at the  $P < 0.10$  level in univariable analysis or if determined to be clinically important. Covariates considered for model inclusion were patient demographics (age, sex), hospital location and unit at time of antibiotic prescription, antibiotic grouping, severity of illness indications (APR DRG SOI, APR DRG ROM), Elixhauser co-morbidity score, hospital length of stay and receipt of PPIs. Correlation coefficients (greater than .70) were used to identify multicollinearity between pairs of covariates. The results of the logistic regression analyses are reported as odds ratios (OR) with 95% confidence intervals (CI). The Hosmer-Lemeshow test and the area under the receiver operating characteristics (ROC) curve were used to assure goodness of fit and discriminatory power of the constructed model.

2b) The association between the primary exposure (receipt of probiotics) and outcome (CDI by CDI PCR) was evaluated. To account for differences in patients who received probiotics versus those who did not, a propensity score (PS) matching method was applied. The propensity score was performed using variables that may influence prescription of probiotics for patients and risk factors for CDI by using ordinary logistic regression. Variables thought to influence likelihood of probiotic prescription and included in the propensity score were hospital location and hospital unit at time of antibiotic order, age, sex, Elixhauser score, APR DRG SOI and antibiotic class. Additional variables that may impact risk of CDI included receipt of a PPI or H2 antagonist, and hospital length of stay. To form matched sets of patients who did and did not receive probiotics who share a similar propensity score optimal one-to-one matching using the logit of the propensity score (PS)

with 0.3 caliper width as the matching metric was conducted.<sup>26</sup> Matching was performed without replacement. To assess the performance of the PS model in discriminating between patients who received probiotics and those who did not, the absolute standardized differences were used to evaluate covariate balances. Although no universal threshold exists, a goal of <10% for the absolute standardized difference indicates good balance. Plots of standardized differences of means provided a visual inspection of the balance between covariates. Another balance diagnostic used was the covariate variance between the probiotics and no-probiotics group with a value close to 1 indicating good balance on the covariate, and values <0.5 or >2 indicating far imbalance. Once the PS matching completed acceptably balanced groups, relative risk of the effects of probiotics (exposure) on CDI by PCR testing (outcome) was calculated. The number of patients with CDI toxin testing was small, therefore bivariate analysis was done to evaluate for any associations between patient characteristics and CDI by toxin testing and were measured using Chi-square or Fisher's exact test and Wilcoxon rank-sum test. Analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

### ***Aim 3 Cost Impact of the Intervention***

Third, we assessed cost implications of the guideline by collecting expenditures on probiotics in the post-period utilizing pharmacy purchase data and Maryland HSCRC lost revenue secondary to CDI in the pre-period and post-period.

## Results

Four hospitals from the University of Maryland Medical System were included in the study. A description of the hospital characteristics can be found in Table 2.

**Table 2: Participating Hospital Characteristics**

Hospital	Hospital-Type	Bed Size	Other Comments
1	Tertiary Academic Medical Center	757	>150 ICU beds, Cancer Center including bone marrow transplant, and large transplant service
2	Community teaching hospital	179	18 ICU beds
3	Community teaching hospital	285	Cancer center, 36 ICU beds
4	Rehabilitation and Orthopedic hospital	137	Traumatic brain injury, spinal cord and stroke rehab with many same-day/short-stay orthopedic surgeries

### Aim 1

#### *CDI Rates for All Patients Before and After Implementation of Probiotics*

1a. The SIR of hospital-onset CDI reported to the CDC NHSN in the post-intervention periods decreased across all 4 hospitals compared to the pre-intervention period (Table 3).

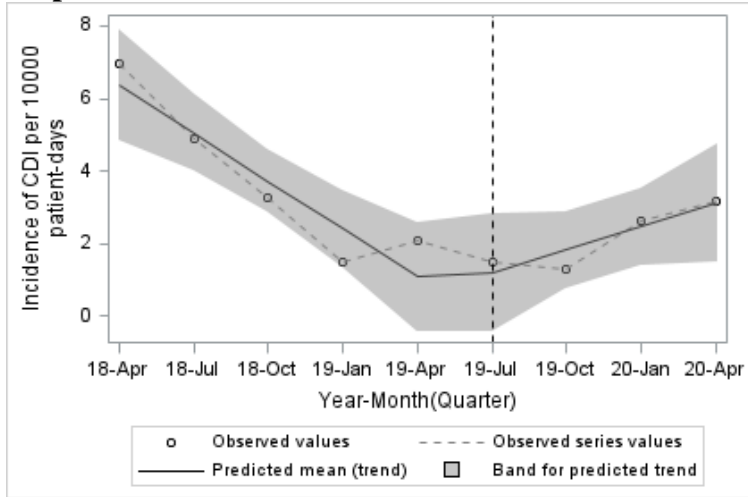
**Table 3: Hospital-onset *C. difficile* Infection SIRs for the four participating hospitals pre-intervention and post-intervention**

Facility	SIR for Pre-Intervention Period	SIR for Post-Intervention Period	% Improvement in SIR
1	0.63	0.40	-36.2%
2	0.59	0.28	-52.3%
3	0.79	0.25	-67.8%
4	1.50	1.27	-15.4%

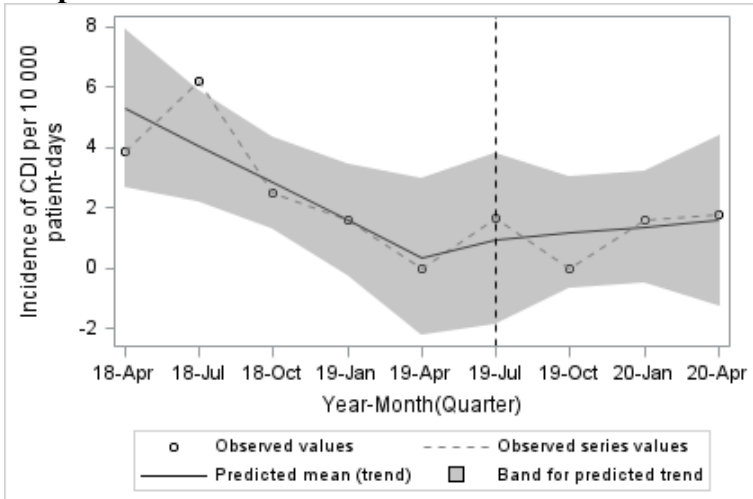
1b. When evaluating CDI incidence for all hospitalized patients, there was a pre-intervention decrease in CDI per 10 000 patient days with a significant immediate level change, however, the incidence of CDI per 10 000 patient days significantly increased again after the implementation (change in slope 1.4 cases per 10 000 patient days per quarter,  $p=0.001$ ). Evaluating CDI rates by quarter using segmented regression, hospital 1 had a significant pre-intervention trend with the incidence of CDI decreasing by 1.3 per 10,000 patient-days per quarter ( $p=0.003$ ). There was a non-significant level decrease after the implementation of probiotics; however, the incidence of CDI per 10 000 patient-days significantly increased overall after the implementation (from -1.3 to 0.7, change in slope 2.0 incidences per quarter ( $p=0.005$ )). Hospital 2's results estimate a significant pre-intervention trend with the incidence of CDI per 10 000 patient-days decreasing by 1.2 incidences per quarter ( $p=0.03$ ). There was a non-significant level change and slope change after the implementation of probiotics. The incidence of CDI per 10 000 patient-days at Hospital 3 had a significant immediate (level change, 6.8 lower) effect but no sustained (slope change) effect after the intervention. The incidence of CDI per 10000 patient days at Hospital 4 had no immediate (level change) or sustained (slope change) effects in the post-intervention period (Table 4, Figure 2).

**Figure 2. Changes in the incidence of CDI per 10 000 patient-days after the implementation of the CCDSS**

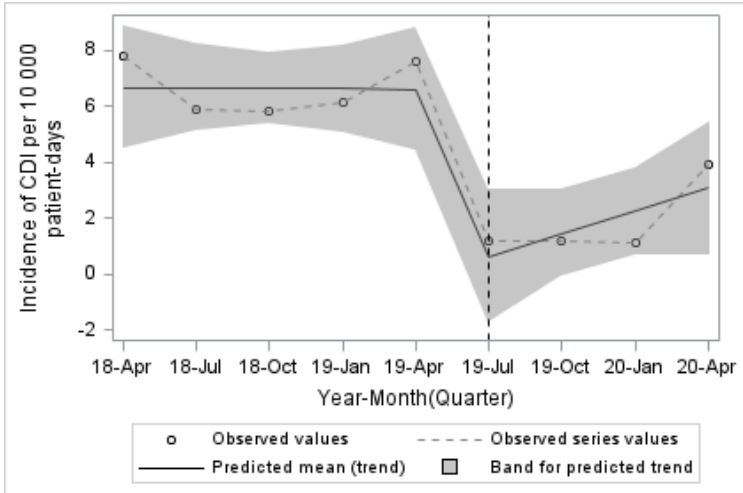
**Hospital 1**



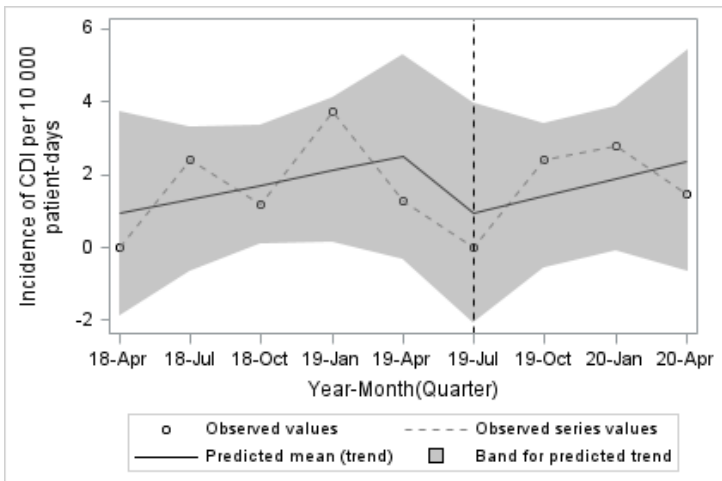
**Hospital 2**



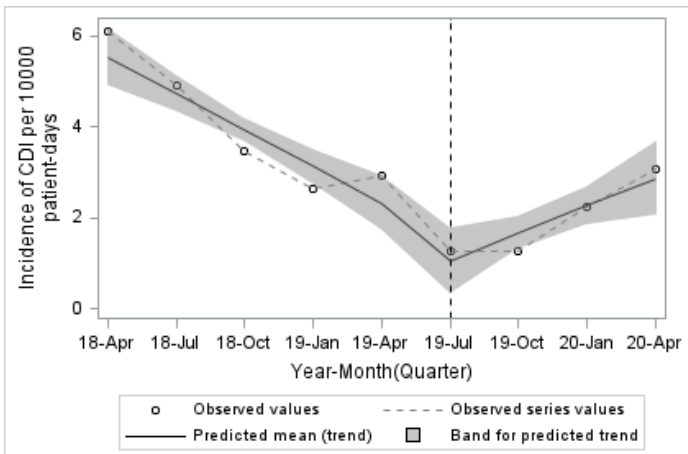
### Hospital 3



### Hospital 4



### All Hospitals Combined



**Table 4. Changes in the incidence of CDI per 10 000 patient-days after the implementation**

Hospital	Trend in the pre-INT (95% CI)	p value	Level change in the INT (95% CI)	p value	Change in slope (95% CI)	p value
1	-1.3 (-1.9, -0.8)	0.003	-0.55 (-3.3, 2.3)	0.64	2.0 (0.8, 3.1)	0.005
2	-1.2 (-2.3, -0.2)	0.03	0.4 (-4.5, 5.3)	0.84	1.4 (-0.4, 3.3)	0.10
3	-0.02 (-0.9, 0.9)	0.96	-6.8 (-10.8, -2.7)	0.008	0.8 (-0.7, 2.4)	0.23
4	0.4 (-0.7, 1.6)	0.42	-2.0 (-7.2, 3.3)	0.36	0.09 (-1.8, 2.1)	0.91
All	-0.8 (-1.0, -0.6)	0.001	-1.9 (-3.2, -0.6)	0.02	1.4 (0.9, 1.9)	0.001

## **Aim 2**

### *2a) CDI Rates by CDI PCR in Patients Eligible for the BPA Based on Age and*

#### *Antibiotics*

Focusing on patients eligible for the BPA based on age >50 and qualifying antibiotic and assessing CDI by CDI PCR positivity, there were 17,536 patients in the pre-intervention group and 15,023 in the post-intervention group. Baseline characteristics between the two groups are listed in Table 5. Patients in the post-intervention group were older, had a higher median APR DRG risk of mortality score and were less likely to have received a PPI and less likely to have had a *C. difficile* test sent compared to the pre-intervention group although these differences had negligible to small effect sizes are unlikely to be clinically important.

**Table 5: Differences in Baseline Characteristics of Patients Eligible for Probiotic Administration in the pre-intervention and post-intervention periods**

Characteristic	Pre-Intervention (n=17536)	Post-Intervention (n=15023)	P-value	Effect Size
Age (years), median (IQR)	64 (58, 73)	65 (58, 74)	<0.0001	Negligible Cliff's delta=-0.03
Male, n(%)	9393 (53.6)	8204 (54.6)	0.093	Small effect Cramer's V=0.01
Length of stay (days), median (IQR)	4 (1,9)	4 (1,10)	0.5	
Elixhauser Score, median (IQR)	4 (2, 6)	4 (2, 6)	0.2	
APR DRG Severity of Illness, median (IQR)	3 (2, 4)	3 (2, 4)	0.5	
APR DRG Risk of Mortality, median (IQR)	3 (2, 3)	3 (2, 4)	<0.0001	Negligible Cliff's delta=-0.03
Received Probiotics, n(%)	8 (0.05)	2489 (16.6)	<0.0001	
Received Proton Pump Inhibitors, n (%)	5991 (34.5)	4632 (31.2)	<0.0001	Small effect Cramer's V=-0.04
NPO, n(%)	8547 (48.7)	7272 (48.4)	0.5	
Hospital, n(%)			0.0012	
• 1	10797 (61.6)	9016 (60)		
• 2	2422 (13.8)	2134 (14.2)		
• 3	2759 (15.7)	2586 (17.2)		
• 4	1558 (8.9)	1287 (8.6)		
Unit n(%)			0.0043	Small effect Cramer's V=0.02
• Floor	3074 (17.5)	2819 (18.8)		
• IMC	695 (4)	530 (3.5)		
• ICU	2484 (14.2)	2236 (14.9)		
• ED	4496 (25.6)	3808 (25.4)		
• OR	1624 (9.3)	1363 (9.1)		
• Cancer/Transplant	731 (4.2)	643 (4.3)		
• Other	4432 (25.3)	3624 (24.1)		
<i>C. difficile</i> Test Sent	1242 (7.1)	930 (6.2)	0.001	Small effect Cramer's V=-0.02

Table 5 Continued				
	Pre- Intervention (n=55932)	Post- Intervention (n=46064)		
Antibiotic Class*, n(%)			<0.0001	Small effect Cramer's V=0.02
• High-risk CDI	10110 (18.3)	8540 (18.5)		
• Carbapenems	2463 (4.5)	1841 (4.0)		
• Other broad-spectrum beta-lactams	33200 (59.9)	27326 (59.3)		
• Narrow-spectrum beta lactams	9619 (17.4)	8357 (18.1)		
	Pre- Intervention (n=17325)	Post- Intervention (n=14855)		
Modified Antibiotic Classes			0.2	Small effect, Cramer's V =0.008
• High-risk CDI	7313 (42.2)	6388 (43)		
• Others	10012 (57.8)	8467 (57)		
• Carbapenems	1258 (7.3)	988 (6.7)	0.03	Small effect, Cramer's V =-0.01
• Others	16067 (92.7)	13867 (93.3)		
• Broad-spectrum beta-lactams	5577 (33.4)	4945 (33.8)	0.5	Small effect, Cramer's V =0.004
• Others	11126 (66.6)	9691 (66.2)		
• Narrow spectrum beta-lactams	7476 (43.2)	6550 (44.1)	0.09	Small effect, Cramer's V =0.01
• Others	9849 (56.8)	8305 (55.9)		
Frequency missing = 8711 (APR DRG SOI), 8711 (APR DRG ROM), 293 (Elixhauser), 379 (antibiotic class), 349 (PPI)				
*High-risk CDI antibiotics included fluoroquinolones, clindamycin and third-generation cephalosporins. Other broad-spectrum beta-lactams included piperacillin/tazobactam, cefepime, ceftaroline, aztreonam, ceftazidime/avibactam, ceftolozane/tazobactam). Narrow spectrum beta-lactams included cefoxitin, amoxicillin/clavulanate, ampicillin/sulbactam, cefazolin, cephalixin.				

**Table 5-1: Bivariable analysis of CDI positivity by PCR testing and patient characteristics**

Characteristics	Total (n=32180)	CDI PCR		p-value	Effect size
		Not tested /Negative (n=31895)	Positive (n=285)		
Age, median(IQR)	65(58, 73)	65(58, 73)	66(60, 74)	0.07	Negligible Cliff's delta = -0.03
Sex, n(%)				0.8	Small effect df=1, Cramer's V=-0.001
Female	14791(46.0)	14658(46.0)	133(46.7)		
Male	17388(54.0)	17236(54.0)	152(53.3)		

Table 5-1 Continued					
<b>Length of stay, median(IQR)</b>	4(1, 10)	4(1, 9)	14(6, 26)	<0.0001	Negligible Cliff's delta = -0.003
<b>Hospital location, n(%)</b>				<0.0001	Small effect df=1, Cramer's V=0.05
Floor	5887(18.3)	5847(18.3)	40(14.0)		
IMC	1225(3.8)	1206(3.8)	19(6.7)		
ICU	4716(14.7)	4654(14.6)	62(21.8)		
ED	8297(25.8)	8217(25.8)	80(28.1)		
OR	2961(9.2)	2959(9.3)	2(0.7)		
Cancer/Transplant	1368(4.3)	1325(4.2)	43(15.1)		
Other	7726(24.0)	7687(24.1)	39(13.7)		
<b>APR DRG SOI, median(IQR)</b>	3(2, 4)	3(2, 4)	4(3, 4)	<0.0001	Negligible Cliff's delta = 0.005
<b>APR DRG ROM, median(IQR)</b>	3(2, 3)	3(2, 3)	3(3, 4)	<0.0001	Negligible Cliff's delta = -0.03
<b>Elixhauser score, median (IQR)</b>	4(2, 6)	4(2, 6)	5(4, 7)	<0.0001	Negligible Cliff's delta = -0.006
<b>NPO, n(%)</b>				0.003	Small effect df=1, Cramer's V=0.02
No	16415(51.0)	16295(51.1)	120(42.1)		
Yes	15765(49.0)	15600(48.9)	165(57.9)		
<b>Modified Antibiotic class, n(%)</b>					
High risk group	13701(42.6)	13570(42.5)	131(46.0)	0.2	Small effect df=1, Cramer's V=0.007
Others	18479(57.4)	18325(57.5)	154(54.0)		
Carbapenem	2246(7.0)	2177(6.8)	69(24.2)	<0.0001	Small effect df=1, Cramer's V=0.06
Others	29934(93.0)	29718(93.2)	216(75.8)		
broad spectrum beta-lactams	10522(33.6)	10327(33.3)	195(68.7)	<0.0001	Small effect df=1, Cramer's V=0.07
Others	20817(66.4)	20728(66.7)	89(31.3)		
Narrow spectrum beta-lactams	14026(43.6)	13966(43.8)	60(21.1)	<0.0001	Small effect df=1, Cramer's V=-0.04
Others	18154(56.4)	17929(56.2)	225(78.9)		
<b>PPI</b>				<0.0001	Small effect df=1, Cramer's V=0.04
No	21578(67.1)	21449(67.2)	129(45.3)		
Yes	10602(32.9)	10446(32.8)	156(54.7)		

Table 5-1 Continued					
<b><i>C.difficile</i> test sent</b>				<0.0001	Medium effect df=1, Cramer's V=0.4
No	30010(93.3)	30010(94.1)	0		
Yes	2170(6.7)	1885(5.9)	285(100)		

In patients eligible for probiotic administration in the pre-intervention group, 132 (0.75%) patients had CDI compared to 153 (1.02%) in the post-intervention group (p=0.01). APR DRG SOI and APR DRG ROM scores were highly correlated (r=0.80) so only APR DRG SOI was included in the model. Controlling for age, sex, length of stay, APR DRG Severity of Illness score, Elixhauser score, antibiotic class, receipt of PPIs and hospital unit, the odds of CDI was 1.4-fold greater in the post-intervention group compared to the pre-intervention group (95% CI, 1.13, 1.84 p=0.003) [Table 6].

**Table 6. Multivariable analysis of CDI positivity by PCR testing adjusted for factors associated with CDI**

Outcome	Variables	Adjusted odds ratio (95%CI)	p-value
<b>CDI PCR (positive)</b>	<b>Intervention</b>		
	Pre	Ref	
	Post	1.41 (1.13, 1.84)	0.003
	<b>Age</b>	1.01(0.99, 1.02)	0.4
	<b>Sex</b>		
	Male	Ref	
	Female	1.18(0.93, 1.51)	0.17
	<b>Length of stay</b>	1.01 (1.00, 1.02)	<0.0001
	<b>Hospital unit</b>		
	Floor	Ref	
	IMC	1.74(0.99, 3.06)	0.053
	ICU	0.96(0.61, 1.49)	0.8
	ED	1.42(0.93, 2.16)	0.1
	OR	0.50 (0.11, 2.11)	0.3
	Cancer/Transplant	2.24(1.40, 3.58)	0.008
	Other	0.93 (0.58, 1.48)	0.8
<b>APR_DRG_SOI</b>	2.07(1.66,2.59)	<0.0001	

Table 6 Continued			
<b>Elixhauser score</b>	1.03(0.97, 1.09)		0.3
<b>Antibiotic class</b>			
High-risk CDI group vs others	0.81(0.62, 1.05)		0.1
Carbapenem vs. Others	1.41(1.03, 1.91)		0.03
Broad spectrum beta-lactams vs. Others	1.31(0.97, 1.77)		0.08
Narrow spectrum beta-lactams vs. Others	0.54(0.38, 0.74)		0.0001
<b>PPI Yes vs No</b>	1.38(1.07, 1.78)		0.01
<b>NPO Yes vs No</b>	0.89 (0.68,1.17)		0.4
Note: The overall model was significant (likelihood $\chi^2$ (17) = 357 with a p<0.0001 and pseudo R <sup>2</sup> of 11.6%. The Hosmer and Lemeshow $\chi^2$ (8) statistic was 4.23, with a p-value of 0.84. The area under the receiver-operating curve (AUC) was 0.80. All these goodness-of-fit tests denote good model fit.			

Changes in CDI PCR positivity rates were driven by hospital 1 and were unchanged at the other 4 sites. Rates of CDI in units where the CCDSS BPA would not have fired based on the patient populations (e.g., the oncology and transplant units at hospital 1 and the ICUs at hospitals 1 and 3) were statistically unchanged between the time periods but did increase by 17 cases (Table 7).

**Table 7: CDI PCR Positivity Rates by Hospital**

CDI Positivity by Hospital, n(%)	Pre-Intervention	Post-Intervention	P-value
Hospital 1	89/10797 (0.82)	108/9016 (1.20)	0.008
• Hospital 1 removing Cancer Center and Transplant	71/10066 (0.71)	83/8373 (0.99)	0.03
• Hospital 1 ICUs	22/2278 (0.97)	32/2070 (1.55)	0.085
• Hospital 1 Cancer Center and Transplant	18/731 (2.46)	25/643 (3.89)	0.13
Hospital 2	17/2422 (0.70)	17/2134 (0.80)	0.71
Hospital 3*	24/2759 (0.87)	26/2586 (1.01)	0.61
Hospital 4	2/1558 (0.13)	2/1287 (0.16)	0.85

\*no cases in the pre- or post-groups in the Hospital 3 ICU

Across all hospitals, there was overall no change in CDI PCR Positivity rates depending on the type of unit where the patient's antibiotics were initiated with the exception of the ICUs and cancer/transplant centers which did have numeric increases in their rates (Table 8).

**Table 8: CDI PCR Positivity Rates by Unit Type**

CDI Positivity by Unit, n(%)	Pre-Intervention	Post-Intervention	P-value
Floor	16/3074 (0.52)	24/2819 (0.85)	0.12
IMC	10/695 (1.44)	9/530 (1.7)	0.72
ICU	25/2484 (1.01)	37/2236 (1.65)	0.051
ED	41/4496 (0.9)	39/3808 (1.02)	0.60
OR	1/1624 (0.06)	1/1363 (0.07)	0.90
Cancer/Transplant	18/731 (2.46)	25/643 (3.9)	0.13
Other	21/4432 (0.88)	18/3624 (0.50)	0.88

As a balancing measure for the use of CDI PCR as the primary measure of CDI due to the change in testing methodology in the pre-intervention period, we evaluated the frequency of *C. difficile* tests sent in the pre- and post-intervention groups. In the pre-BPA time period, 0.93% of patients had a *C. difficile* test sent compared to 1.14% of patients in the post-BPA time period (p=0.10).

#### 2a1) CCDSS BPA Adherence

During the study period, the BPA fired on 5203 unique patients resulting in an order for probiotics in 2392 (46%) patients. Adherence to the BPA (acceptance of the intervention resulting in an order for Bio-K+) varied between institutions with orders for Bio-K+

occurring in 87.6% of patients where the BPA fired at hospital 4, followed by 68.6% at hospital 3, 44% at hospital 2 and 34% at hospital 1.

*2b) CDI PCR Positivity Rates in Patients who Received Probiotics*

In the post-intervention group, 2489 patients received probiotics. Most of these orders (96%) were as a direct result of the CCDSS BPA with only 4% of the orders for probiotics generated outside of the BPA. The unadjusted odds ratio for positive CDI PCR in the patients who received probiotics compared to those who did not receive probiotics was 1.48 (95% CI, 1.01 to 2.16,  $p=0.043$ ). When adjusting for length of stay, APR DRG severity of illness score, hospital unit at the time of the BPA firing, antibiotic class and receipt of PPIs, the odds ratio for positive CDI PCR was 1.54 (95% CI, 1.002-2.38) for those who received probiotics compared to those who did not. To account for differences in patients who received probiotics versus those who did not, propensity score matching was done based on age, sex, length of stay, APR DRG severity of illness score, Elixhauser score, antibiotic class, receipt of PPI or H2 antagonist, hospital, and hospital unit. The resultant matched sample consisted of 2174 matched pairs (87.3% of patients receiving probiotics were successful matched to a patient not receiving probiotics with a similar value of the logit of the propensity score). The characteristics between the patients who received probiotics (BioK) versus those who did not are presented in Table 9. The standardized differences ranged from a low of -0.14 to a high of 0.07 with a median of 0.0016 (IQR - 0.17, 0.021). The variance ratios ranged from 0.58 to 1.58. The only characteristic for which the standardized difference was  $>0.01$  was hospital location 4, which represented the smallest hospital with the highest rate of CCDSS adherence limiting the options for

matching. Overall, the aforementioned analyses indicate that the means and variances of the variables were similar between the probiotics treated patient group and the matched sample.

**Table 9. Patient characteristics across receipt of probiotics (BioK) in the non-propensity matched group and the propensity matched group**

Characteristics	Non-PS matched				PS matched			Standardized difference	Variance ratio
	Total (n=14855)	BioK No (n=12366)	BioK Yes (n=2489)	p value	Total (n=4348)	BioK No (n=2174)	BioK Yes (n=2174)		
Age, median (IQR)	65 (58, 74)	65 (58, 73)	67 (60, 77)	<0.01	67 (60, 77)	67 (60, 77)	67 (60, 77)	0.0048	0.97
Sex, n(%)				<0.01					
Female	6747 (45.4)	5544 (44.8)	1203 (48.3)		2089 (48.1)	1054 (48.5)	1035 (47.6)	0.018	0.99
Male	8107 (54.6)	6821 (55.2)	1286 (51.7)		2259 (51.9)	1120 (51.5)	1139 (52.4)	-0.018	0.99
Length of stay, median (IQR)	4 (1, 10)	4 (1, 9)	6 (3, 12)	<0.01	7 (4, 13)	6 (3, 12)	7 (4, 14)	0.0091	0.65
Hospital unit, n(%)				<0.01					
Floor	2814 (18.9)	1757 (14.2)	1057 (42.5)		1855 (42.7)	904 (41.6)	951 (43.7)	-0.049	1.01
IMC	530 (3.6)	306 (2.5)	224 (9.0)		395 (9.1)	186 (8.6)	209 (9.6)	-0.043	1.11
ICU	2234 (15.0)	2042 (16.5)	192 (7.7)		364 (8.4)	175 (8.1)	189 (8.7)	-0.018	1.07
ED	3804 (25.6)	3362 (27.2)	442 (17.8)		789 (18.2)	405 (18.6)	384 (17.7)	0.024	0.96
OR	1351 (9.1)	1339 (10.8)	12 (0.5)		23 (0.5)	11 (0.5)	12 (0.6)	-0.0027	1.09
Cancer/Transplant	637 (4.3)	630 (5.1)	7 (0.3)		19 (0.4)	12 (0.6)	7 (0.3)	0.012	0.58
Other	3485 (23.5)	2930 (23.7)	555 (22.3)		903 (20.8)	481 (22.1)	422 (19.4)	0.070	0.91
APR DRG SOI, median (IQR)	3 (2, 4)	3 (2, 4)	3 (2, 4)	0.2	3 (2, 4)	3 (2, 4)	3 (2, 4)	-0.017	0.80
Elixhauser score, median (IQR)	4 (2, 6)	4 (2, 5)	5 (3, 6)	<0.01	5 (3, 7)	5 (3, 7)	5 (3, 7)	-0.0069	0.96
Hospital, n(%)				<0.01					
1	8932 (60.1)	8059 (65.2)	873 (35.1)		1628 (37.4)	833 (38.3)	795 (36.6)	0.038	0.98
2	2061 (13.9)	1585 (12.8)	476 (19.1)		859 (19.8)	434 (20.0)	425 (19.6)	0.012	0.98
3	2577 (17.4)	1626 (13.2)	951 (38.2)		1560 (35.9)	793 (36.5)	767 (35.3)	0.029	0.99
4	1285 (8.7)	1096 (8.9)	189 (7.6)		301 (6.9)	114 (5.2)	187 (8.6)	-0.14	1.58
Antibiotic class, n(%)									
High risk group	6388 (43)	4922 (39.8)	1466 (58.9)	<0.01	2598 (59.8)	1299 (59.7)	1299 (59.7)	0	1

Table 9 Continued									
Others	8467 (57)	7444 (60.2)	1023 (41.1)		1750 (40.2)	875 (40.3)	875 (40.3)		
Carbapenem	988 (6.7)	800 (6.5)	188 (7.6)	0.04 8	365 (8.4)	183 (8.4)	182 (8.4)	0.0016	1.0
Others	13867 (93.4)	11566 (93.5)	2301 (92.4)		3983 (91.6)	1991 (91.6)	1992 (91.6)		
Broad spectrum beta-lactams	4945 (33.8)	3997 (32.6)	968 (39.8)	<0.0 1	1919 (44.1)	991 (45.6)	928 (42.7)	0.059	0.99
Others	9691 (66.2)	8227 (67.4)	1464 (60.2)		2429 (55.9)	1183 (54.4)	1246 (57.3)		
Narrow spectrum beta-lactams	6550 (44.1)	575 (46.6)	794 (31.9)	<0.0 1	1396 (32.1)	677 (31.1)	719 (33.1)	-0.040	1.03
Others	8305 (55.9)	661 (53.4)	1695 (68.1)		2952 (67.9)	1497 (68.9)	1455 (66.9)		
<b>PPI</b>				<0.0 1					
No	10234 (68.9)	8619 (69.7)	1615 (64.9)		2789 (64.1)	1402 (64.5)	1387 (63.8)		
Yes	4621 (31.1)	3747 (30.3)	874 (35.1)		1559 (35.9)	772 (35.5)	787 (36.2)	-0.014	1.0
<b>H2 Antagonist</b>				0.2					
No	10848 (73.0)	9007 (72.8)	1841 (74.0)		3140 (72.2)	1557 (71.6)	1583 (72.8)		
Yes	4007 (27.0)	3359 (27.2)	648 (26.0)		1208 (27.8)	617 (28.4)	591 (27.2)	0.026	0.97

The cumulative CDI incidence by PCR testing was 0.016 in patients receiving probiotics. Those in the probiotic group had 1.46 times the risk of CDI by PCR testing compared to those who did not receive probiotics (RR=1.46; 95% CI, 0.87-2.45, p=0.15).

2b2) Because post-intervention testing was two-step, we repeated the analysis using toxin-positive as the CDI outcome. In both the non-PS matched and the PS-matched groups, receipt of probiotics was not associated with a difference in CDI by toxin testing. No other characteristics were identified as associated with CDI by toxin testing from bivariate analysis (Table 10).

**Table 10: Bivariate analysis of CDI by *C. difficile* Toxin Assay in the non-PS matched and PS-matched groups**

Characteristics	Non-PS matched			p-value	PS matched			p-value
	Total (n=14855)	CDI Toxin			Total (n=4348)	CDI Toxin		
		Not tested /Negative (n=14836)	Positive (n=19)			Not tested /Negative (n=4341)	Positive (n=7)	
<b>Probiotics (BioK), n(%)</b>				1.0				1.0
No	12366 (83.2)	12350 (83.2)	16 (84.2)		2174 (50)	2170 (50)	4 (57.1)	
Yes	2489 (16.8)	2486 (16.8)	3 (15.8)		2174 (50)	2171 (50)	3 (42.9)	
<b>Age, median(IQR)</b>	65 (58, 74)	65 (58, 74)	70 (66, 81)	0.01	68 (60, 77)	68 (60, 77)	81 (66, 84)	0.1
<b>Sex, n(%)</b>				0.8				0.7
Female	6747 (45.4)	6739 (45.4)	8 (42.1)		2098 (48.3)	2094 (48.2)	4 (57.1)	
Male	8107 (54.6)	8096 (54.6)	11 (57.9)		2250 (51.7)	2247 (51.8)	3 (42.9)	
Unknown								
<b>Length of stay, median(IQR)</b>	4(1, 10)	4(1, 10)	16 (9, 30)	<0.0001	7(4, 13)	7(4, 13)	15 (12, 30)	0.1
<b>Hospital location, n(%)</b>				0.4				0.3
Floor	2184(18.9)	2809(18.9)	5(26.3)		1856 (42.7)	1853 (42.7)	3(42.9)	
IMC	530(3.6)	530(3.6)	0		398(9.2)	398(9.2)	0	
ICU	2234(15.0)	2230(15.0)	4(21.1)		383(8.8)	382(8.8)	1(14.3)	
ED	3804(25.6)	3796(25.6)	8(42.1)		777(17.9)	774(17.8)	3(42.9)	
OR	1351(9.1)	1351(9.1)	0		20(0.5)	20(0.5)	0	
Cancer/ Transplant	637(4.3)	637(4.3)	0		18(0.4)	18(0.4)	0	
Other	3485(23.5)	3483(23.5)	2(10.5)		896(20.6)	896(20.6)	0	
<b>APR DRG SOI, median(IQR)</b>	3(2, 4)	3(2, 4)	4(3, 4)	0.002	3(2, 4)	3(2, 4)	4(3, 4)	0.4
<b>APR DRG ROM, median(IQR)</b>	3(2, 4)	3(2, 4)	3(3, 4)	0.04	3(2, 3)	3(2, 3)	3(3, 4)	0.9
<b>Elixhauser score, median (IQR)</b>	4(2, 6)	4(2, 6)	6(3, 8)	0.02	5(3, 7)	5(3, 7)	6(5, 9)	0.9
<b>Modified Antibiotic class, n(%)</b>								
High risk group	6388(43)	6382(43.0)	6(31.6)	0.4	2598 (59.7)	2594 (59.8)	4(57.1)	1.0
Others	8467(57)	8454(57.0)	13 (68.4)		1750 (40.3)	1747 (40.2)	3(42.9)	
Carbapenem	988(6.7)	981(6.6)	7(36.8)	0.0001	372(8.6)	370(8.5)	2(28.6)	0.1
Others	13867 (93.3)	13855 (93.4)	12 (85.7)		3976 (91.4)	3971 (91.5)	5(71.4)	
broad spectrum beta-lactams	4945(33.8)	4931(33.7)	14 (73.7)	0.0004	1906 (43.8)	1903 (43.8)	3(42.9)	1.0

Table 10 Continued								
Others	9691(66.2)	9686(66.3)	5(26.3)		2242 (56.2)	2438 (56.2)	4(57.1)	
Narrow spectrum beta-lactams	6550(44.1)	6544(44.1)	6(31.6)	0.4	1385 (31.9)	1383 (31.9)	2(28.6)	1.0
Others	8305(55.9)	8292(55.9)	13 (68.4)		2963 (68.1)	2958 (68.1)	5(71.4)	
<b>Modified Antibiotic class duration, median(IQR)</b>								
High risk group	1(0, 2)	1(0, 2)	1.5 (0, 2)	0.5	1(0, 3)	1(0, 3)	2 (1, 2.5)	0.7
Others	1(0, 2)	1(0, 2)	2(1, 4)	0.02	1(0, 2)	1(0, 2)	1(1, 10)	0.4
Carbapenem	1(0, 3)	1(0, 3)	1(0, 6)	0.9	1(0, 3)	1(0, 3)	0.5(0, 1)	0.3
Others	1(0, 2)	1(0, 2)	2(1, 2.5)	0.02	1(0, 3)	1(0, 3)	2(2, 3)	0.09
Broad spectrum beta-lactams	1(0, 2)	1(0, 2)	1(0, 2)	0.7	1(0, 3)	1(0, 3)	1(0, 2)	0.8
Others	0(0, 1)	0(0, 1)	2(2, 3)	0.005	1(0, 3)	1(0, 3)	2.5(1.5, 6.5)	0.1
Narrow spectrum beta-lactams	1(0, 1)	1(0, 1)	1.5(1, 7)	0.045	1(0, 2)	1(0, 2)	5.5(1, 10)	0.2
Others	1(0, 2)	1(0, 2)	2(0, 2)	0.2	1(0, 3)	1(0, 3)	2(1, 2)	0.8
<b>PPI</b>				0.3				0.7
No	10234 (68.9)	10223 (68.9)	11 (57.9)		2822 (64.9)	2818 (64.9)	4(57.1)	
Yes	4621(31.1)	4613(31.1)	8(42.1)		1526 (35.1)	1523 (35.1)	3(42.9)	
<b>H2 Antagonist</b>				0.007				0.4
No	10848 (73.0)	10840 (73.1)	8(42.1)		3083(70.9)	3079(70.9)	4(57.1)	
Yes	4007(27.0)	3996(26.9)	11(57.9)		1265(29.1)	1262(29.1)	3(42.9)	
<b>Hospital, n(%)</b>				0.6				0.7
1	8932(60.1)	8917(60.1)	15(79.0)		1629(37.5)	1626(37.5)	3(42.9)	
2	2061(13.9)	2060(13.9)	1(5.3)		838(19.3)	837(19.3)	1(14.3)	
3	2577(17.4)	2575(17.4)	2(10.5)		1585(36.5)	1583(36.5)	2(28.6)	
4	1285(8.7)	1284(8.7)	1(5.3)		296(6.8)	295(6.8)	1(14.3)	

### 2c) Probiotic Safety

All cases of *Lactobacillus* bacteremia were reviewed post implementation and no cases were identified in patients receiving Bio-K+ during the index admission or within the three months prior. No additional safety signals were identified, but rates of potential minor adverse events such as bloating or gas were not assessed.

### ***Aim 3 Cost implications of the intervention***

During the post-intervention period, a total of \$70,212.43 was spent on the Bio-K+ probiotics preparation across the four institutions. Due to the percent improvements in the SIRs, the system gained \$1,898,820 in penalty decreases through the Maryland Health Services Cost Review Commission (HSCRC) quality-based reimbursement (QBR) program for hospitals 1-3; hospital 4 is not included in the QBR program.

### **Discussion**

In this study implementing a CCDSS tool to facilitate prescription of probiotics for the primary prevention of CDI, probiotics were not found to be protective. In fact, incidence of CDI was higher in patients who received probiotics versus patients who did not, although this was not statistically significant when controlling for other risk factors for CDI. Overall uptake of the intervention was moderate with about half of the patients who qualified for probiotics per the CCDSS receiving them.

Many studies have evaluated the use of probiotics for the prevention of CDI. A systematic review and meta-analysis in 2012 of twenty randomized controlled trials in adult or pediatric patients receiving antibiotics with a primary outcome of CDI found that probiotics reduced the incidence of CDI by 66% (RR=0.34; 95% CI 0.24-0.49). Outcomes were similar in both adults and children when comparing lower ( $\leq 10$  billion CFU/d) or higher ( $> 10$  billion CFU/d) doses and different probiotic species. The observed effect was increased when comparing supplements with multiple species versus single species although this effect was not statistically significance.<sup>27</sup> Subsequently in 2013, a Cochrane

review also evaluated the safety and efficacy of probiotics for the prevention of CDI in adults and children. Studies comparing probiotics at any dose or strain versus placebo, alternate prophylaxis or no treatment were included. They included 23 studies with 4213 number of patients and identified rates of CDI were 2% in the probiotics group compared to 5.5% in the placebo or no treatment group (RR=0.36; 95% CI 0.26 to 0.51) with a moderate quality of evidence and no significant heterogeneity ( $p=0.75$ ;  $I^2=0\%$ ).<sup>9</sup> Both reviews may have been compromised by methodologic inconsistencies and neither focused on hospitalized patients taking antibiotics. The largest randomized controlled trial for the use of probiotics was the PLACIDE trial from 2013 which was a randomized, double-blind, placebo controlled trial to evaluate if a probiotic preparation would reduce the frequency of antibiotic-associated diarrhea or *C.difficile* diarrhea in inpatients greater than 65 years of age admitted to a hospital and receiving at least one antibiotic therapy. The probiotic preparation consisted of two strains of *L. acidophilus* and two strains of *Bifidobacteria* given to patients for 21 days. The study had lengthy exclusion criteria limiting the generalizability to a larger population including immunocompromised patients, ICU status, heart disease with a prosthetic valve, CDI in the last 3 months, pre-existing gastrointestinal diseases such as inflammatory bowel disease or J/G-tube feeds. There were 1470 patients in the microbial preparation group versus 1471 in the placebo group and the incidence of CDI was 0.8% in the microbial preparation group compared to 1.2% in the placebo group (RR 0.71; 95% CI 0.34-1.47;  $p=0.35$ ). The overall low rate of CDI in the study suggests the study may have had insufficient power to detect an effect and that the results of the study may not be generalizable to a higher incidence setting.<sup>28</sup>

Taking into account the PLACIDE trial, another systematic review was done in 2017 and focused on only studies with hospitalized patients receiving antibiotics. Data from 19 studies comprising 6261 patients found a risk reduction of 58% in patients receiving probiotics suggesting a number needed to treat of 43 to prevent one case of CDI and that probiotics given within 2 days of antibiotic initiation produced a greater risk reduction for CDI (RR 0.32; 95% CI 0.22-0.48) compared to later admission (RR 0.70; 95% CI 0.40-1.23).<sup>18</sup>

Given the promise of early use of probiotics to prevent hospital-acquired CDI, we sought to implement a CCDSS tool to facilitate uptake in patients at risk of CDI due to age and receipt of select antibiotics. In selecting a microbial preparation, we chose a multi-strain agent containing 3 *Lactobacillus* spp. that has demonstrated efficacy in previous studies including a randomized controlled trial and a single center before-and-after quality improvement initiative.<sup>15,29-31</sup> The dose of 100 billion CFU/day was chosen based on a dose finding study that greater CDI reduction for the 100 billion CFU dose compared to a 50 billion CFU dose or placebo in 255 hospitalized patients receiving either a penicillin, cephalosporin or clindamycin during their hospital stay.<sup>15</sup> The decision to build a CCDSS tool to facilitate use was important as experience using this agent based on education, manual intervention and/or physician discretion alone has shown low uptake and no benefit.<sup>16,32</sup> Additionally, the CCDSS was designed to optimize timing of probiotic initiation in relation to the start of qualifying antibiotics. Our study had moderate uptake rates of probiotic prescription with nearly 50% of patients recommended for probiotics for

CDI prevention receiving them; with higher rates of adherence noted at the two community hospitals and the rehabilitation center compared to the academic medical center.

One of the primary challenges with probiotic use in an inpatient setting is the risk for rare but serious adverse effects. While the more common side effects of probiotics are benign, such as gas, bloating and hiccups; the bigger concern with probiotics is the potential for bacteremia or fungemia either from translocation of bacteria from the intestines or direct inoculation in patients with central venous access. Cases of *Saccharomyces* fungemia secondary to probiotic use have been described in patients who are critically ill, receiving nutrition enterally or have central venous catheters as the organisms can be spread on healthcare workers hands.<sup>17,33</sup> Risk factors for bacteremia or fungemia unfortunately overlap with common risk factors for *C. difficile*, namely immunocompromised hosts or critical illness.<sup>34,35</sup> Our BPA was designed with safety first and foremost, and therefore did not fire in patients with risk factors for bacteremia or fungemia, including patients with an NPO status (e.g., unable to swallow the Bio-K+ capsules whole), patients on cancer or transplant units, and patients receiving immunosuppressant medications. Patients in an ICU unable to swallow medications by mouth were excluded due to the risks of manipulating the Bio-K+ capsules and potential inoculation of central venous catheters. Exclusion of patients both at high-risk of CDI but also high-risk of adverse effects secondary to probiotics may have tempered any potential impact from probiotic use. Although non-statistically significant likely due to effect size, numerically rates of CDI in patients located in an ICU, cancer or transplant unit who were not eligible for the CCDSS tool did increase in the post-implementation period.

A recent patient-level meta-analysis provided moderate quality of evidence that probiotics may be useful and safe for preventing CDI using 18 randomized controlled trials with individual participant data for 6851 patients. Probiotics reduced CDI odds in the unadjusted model (OR 0.37; 95% CI 0.25-0.55) and adjusted model (OR 0.35; 95% CI, 0.23-0.55), and that multispecies probiotics were more beneficial than single species probiotics. Importantly, patients taking 2 or more antibiotics and in hospital settings where risk of CDI is  $\geq 5\%$  had the biggest benefit.<sup>13</sup> It should be noted that the small studies that demonstrate the biggest benefit of probiotics in the two meta-analyses described above have very large effect sizes but the populations had very high first-episode CDI prevalence rates (23.8% and 40%).<sup>15,36</sup> In our study, CDI rates were already relatively low and more similar to the PLACIDE study population, and the BPA flagged regardless of number of antibiotics received which could limit the potential impact of primary prophylaxis.

Our study is strengthened by the inclusion of multiple hospitals that represent diverse practice settings and patient populations, including comprehensive evaluations of intervention adherence and safety. We analyzed CDI data with multiple analyses and outcomes (e.g., SIR, CDI incidence by PCR testing, CDI incidence by toxin testing) helped to drill-down the true effect of probiotics as evaluation of risk-adjusted SIR alone would have made it seem the use of probiotics was beneficial. Use of propensity score matching allowed us to evaluate the potential impact of probiotic administration while controlling for potential differences in patients who did and did not receive probiotics.

This study has several limitations. First, the *C.difficile* testing strategy in our healthcare system changed from a PCR-based test alone to a two-step testing process where the PCR was followed by a confirmatory Toxin EIA to help distinguish colonization from infection. However, the intervention occurred six months after the two-step testing was implemented which should have allowed for adequate time for the change due to testing to be established. Additionally, we did only assess PCR positivity rates in this study and as a counter measure evaluated *C. difficile* testing rates in both study periods to assure testing rates remained similar before and after implementation of the BPA. While the BPA was implemented after many additional *C.difficile* targeting interventions had already been made across the hospitals, it is possible that other interventions may have confounded the potential benefit of probiotic use. As seen in the ITS analysis, CDI rates at the participating hospitals had all begun to decline sharply prior to the implementation of the BPA due to other interventions beyond the two-step testing including participation in a state-wise CDI reduction collaborative, new restrictions on *C. difficile* test orders and antimicrobial stewardship interventions targeting fluoroquinolones. It is also important to consider that the SIR reported to the CDC NHSN which did decline over the study period provides risk adjustment, whereas we evaluated CDI incidence without any risk adjustment. Our rates of toxin positivity in the post-intervention group were extremely low, but proportional to the PCR positivity rates indicating that many of the cases counted as positive in the analysis of CDI incidence by PCR likely included cases that would not have been considered clinically significant or treated. It is unclear why administration of probiotics would have potentially worsened incidence of CDI as noted in the unadjusted analysis of patients who

did or did not receive probiotics post-intervention, but we suspect may be due to residual confounding that was not accounted for in our analysis.

Acceptance of the BPA and subsequent ordering of Bio-K+ was higher than expected and what has been noted in other studies, but still many patients who potentially qualified ultimately did not receive the intervention, and we were unable to evaluate compliance with the full course of probiotics in patients who were discharged while still receiving antibiotics. Additionally, our follow-up period of 13 months post intervention may not have been adequate as a similar study identified a shift in CDI rates beginning at least six months after the implementation of probiotics.<sup>16</sup> The modest benefit of probiotics has been primarily demonstrated in first-episodes of CDI but not on the treatment or prevention of recurrence, and in our study we did not differentiate between initial and recurrent episodes of CDI.<sup>37</sup>

While probiotics may ultimately have a role in CDI prevention, utilization in hospitalized patients is limited by safety concerns as the highest-risk populations for CDI overlap with patients where concern over probiotic use is high. Benefit may be seen in the population of patients we used probiotics in, but larger studies with longer follow-up periods would be needed to confirm given our baseline low CDI positivity rates.

Appendix 1

Systemic Antibiotics Included or Excluded from the Computerized Clinical Decision Support System Tool

Included Antibiotics	Excluded Antibiotics
<ul style="list-style-type: none"> <li>• Ampicillin/sulbactam</li> <li>• Amoxicillin/clavulanate</li> <li>• Piperacillin/tazobactam</li> <li>• Cefazolin</li> <li>• Ceftriaxone</li> <li>• Cefotaxime</li> <li>• Ceftazidime</li> <li>• Cefdinir</li> <li>• Cefoxitin</li> <li>• Cephalexin</li> <li>• Cefepime</li> <li>• Ceftaroline</li> <li>• Ceftazidime/avibactam</li> <li>• Ceftolozane/tazobactam</li> <li>• Meropenem</li> <li>• Imipenem</li> <li>• Ertapenem</li> <li>• Aztreonam</li> <li>• Ciprofloxacin</li> <li>• Levofloxacin</li> <li>• Moxifloxacin</li> <li>• Clindamycin</li> </ul>	<ul style="list-style-type: none"> <li>• Antimycobacterial agents (e.g., rifampin, rifabutin, ethambutol, pyrazinamide, isoniazid)</li> <li>• Daptomycin</li> <li>• Doxycycline</li> <li>• Fosfomycin</li> <li>• Linezolid</li> <li>• Metronidazole</li> <li>• Minocycline</li> <li>• Nitrofurantoin</li> <li>• Tetracycline</li> <li>• Tigecycline</li> <li>• Vancomycin (IV &amp; PO)</li> </ul>

## Appendix 2: Probiotic Use Guideline



**Purpose:** To establish guidelines for the safe use of probiotics for prevention of *C. difficile* infection (CDI) for adult patients at the University of Maryland Medical Center (UMMS).

### BACKGROUND

Despite ongoing infection control interventions, CDI remains a challenge at UMMC and other institutions. Probiotics have the potential to prevent colonization and infection with *C. difficile*, thus offering an opportunity to enhance our primary prevention strategies at UMMC and hospitals throughout the University of Maryland Medical System (UMMS). Although current data is limited by heterogeneity in probiotic dose, species and formulation, there is evidence that early administration of probiotics, close to the time of the first dose of antibiotics, can reduce the risk of CDI by more than 50% in hospitalized patients.<sup>1</sup>

### Probiotic<sup>2</sup>

- Live microorganisms which when administered in adequate amounts confer a health benefit on the host
- Mechanisms of action
  - Modulation of content of gut microbiota
  - Maintenance of gut barrier integrity
  - Modulation of local immune response
- Major probiotic bacteria genera
  - *Lactobacillus*
  - *Bifidobacterium*
- Composition – varies by product
  - Formulary product: *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus rhamnosus* (Bio-K+®) 50 billion CFU/capsule

### UTILIZATION

#### Probiotics for the prevention of inpatient CDI

#### Qualifying Patients:

- >50 years of age
- New start antibiotics, anticipated antibiotic need of >48 hours
- Able to take medications by mouth

#### Exclusions

- Acute colitis (including *C. difficile* infection), ileus or perforation
- Ileostomy
- Patients with known severe acute pancreatitis not tolerating tube feeds
- Severe neutropenia (ANC <500  $\mu$ L)
- Active chemotherapy or active mucositis
- Bone marrow or solid organ transplant within previous 6 months
- Other immunosuppression (high-dose steroids, biologics)
- Patients only receiving antibiotics with limited systemic absorption (e.g., nitrofurantoin, fosfomycin, PO vancomycin) or antibiotics with minimal association with *C. difficile* (e.g., vancomycin,

tetracyclines, tigecycline, linezolid, daptomycin, metronidazole, rifampin, rifabutin, ethambutol, pyrazinamide, isoniazid)

#### Procedure

- Probiotic capsules should be prescribed for daily administration during an antibiotic course and for 5 days after the final dose of antibiotics
  - A best-practice-alert (BPA) in Epic will fire for potentially eligible patients and encourage providers to consider ordering Bio-K+ at the time of initial antibiotic prescription. The BPA will only fire for the first qualifying antibiotic prescription and will not fire for patients already on antibiotics or probiotics.
- Probiotics should ideally be administered within 12 hours of the initial antibiotic dose.

#### Safety Issues with Probiotic use in Inpatients<sup>3-8</sup>

- Probiotic use has been rarely associated with the development of bacteremia and fungemia.
- Probiotics can be spread via healthcare worker's hands.
- Manipulation of capsules can lead to substantial air contamination – organisms can persist for up to 2 hours on surfaces in a patient's room when the capsules are manipulated.

#### Guidelines for Safe Use:

- Probiotics must not be used in patients who are unable to take PO medications and swallow probiotic capsules whole
- Nurses should change gloves between probiotic administration and manipulation of central venous access
- Probiotics should not be used in the following areas: NICU, BMT Unit, C8

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