PROBIOTICS AND ITS GASTRO-INTESTINAL PROTECTIVE MECHANISMS DURING ANTIBIOTIC THERAPY: A TRAINING FOR AMBULATORY CARE CLINIC PROVIDERS

A DOCTOR OF NURSING PRACTICE PROJECT SUBMITTED TO THE GRADUATE DIVISION OF THE UNIVERSITY OF HAWAI'I AT MĀNOA IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

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ABSTRACT

Problem. Antibiotic resistance is growing with the CDC describing it as one of the biggest public health challenges of our time (Centers of Disease Control and Prevention [CDC], 2020). A major risk factor of developing antibiotic resistance is not completing the full course of antibiotic treatment. One identified cause of patients not completing the full course is the occurrence of antibiotic associated diarrhea (AAD). The recent increase in research on probiotics has shown effectiveness in the prevention and treatment of AAD when taken concurrently with the antibiotics. The VA Pacific Islands Health Care System (VAPHICS) treats many infections with oral antibiotics. However, data shows scarce numbers of providers placing orders of probiotics with their antibiotic prescriptions. This illustrates a possible knowledge gap between providers within the VAPHICS and the most current research on the use of probiotics in the clincal setting.

Purpose. The purpose of this project was to increase the number of co-prescriptions of probiotics with antibiotics to potentially improve health outcomes through the delivery of evidence-based probiotic education.

Methods. A probiotic education session for providers was developed and disseminated. Effectiveness was measured by comparing the number of prescriptions of probiotics, antibiotics, and co-prescriptions of the two, over a three-month period prior to implementation against the same data post implementation. The in-service session was evaluated by a pre- and post-presentation questionnaire assessing knowledge, attitude, and behavior of probiotic use.

Results. Data analysis showed no improvement in the number of co-prescriptions of probiotics with antibiotics. However, data illustrated a 41% increase in the number of probiotic prescriptions alone, after delivery of the in-service by the providers who attended. The providers'

knowledge, attitude, and behavior also improved in comparison of pre- and post-presentation questionnaires showing they felt more knowledgeable on the use of probiotics, its safety, and availability at the VA. After the presentation, providers felt that probiotics had a larger role in clinical medicine and were more likely to discuss the initiation of probiotics with their patients.

Discussion. The provision of probiotics with antibiotic prescriptions has shown to reduce the risk of AAD and may help to address the growing pandemic of antibiotic resistance. Providers who gain knowledge of probiotic use and benefits has the long-term implication of benefitting the health and wellbeing of patients.

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List of Abbreviations

AAD	Antibiotic associated diarrhea
ACC	Ambulatory Care Clinic
CDC	Centers for Disease Control and Prevention
CITC	Collaborative Institutional Training Initiative
CME	Continuing Medical Education
EBP	Evidence-based practice
HIPAA	Health Insurance Portability and Accountability Act
VA	Department of Veteran's Affairs
VAPIHCS	VA Pacific Islands Health Care System
WHO	World Health Organization

Introduction

The Centers of Disease Control and Prevention (CDC) reports 2.8 million people each year are diagnosed with an antibiotic resistant infection, with more than 35,000 of those cases resulting in death (Centers of Disease Control and Prevention [CDC], 2020). Antibiotic resistance is growing with the CDC describing it as one of the biggest public health challenges of our time (CDC, 2020). The World Health Organization (WHO) summarizes the consequences of antibiotic resistance reporting its occurrence leads to longer hospital stays, higher medical cost, and increased mortality (World Health Organization [WHO], 2020).

A major risk factor of developing antibiotic resistance is not completing the full course of antibiotic treatment. One identified cause of patients not completing the full course is the occurrence of antibiotic associated diarrhea (AAD) with up to a 39% occurrence rate (Agamennone et al., 2018; Blaabjerg, Artzi, & Aabenhus, 2017; Mullish &Williams, 2018). Antibiotic use often results in disruption of the normal microbiota resulting in colonic pathogen overgrowth or metabolic imbalances that can lead to AAD. However, not completing the full antibiotic course results in bacteria strengthening, changing, and developing bacterial resistance (Mckonnen, Merenstein, Fraser, & Marco, 2020; Ouwehand, Forssten, Hibberd, Lyra, & Stahl, 2016). The recent increase in research on probiotics has shown effectiveness in the prevention and treatment of AAD when taken concurrently with antibiotics. This may decrease the risk of premature antibiotic discontinuation, ultimately decreasing the risk of developing antibiotic resistant bacteria (Ouwehand et al., 2016).

The VA Pacific Islands Health Care System (VAPIHCS) treats many infections with oral antibiotics. However, data shows a scarce number of providers placing orders of probiotics with

their antibiotic prescriptions. This illustrates a possible knowledge gap of the most current research on the use of probiotics in providers within the VAPHICS.

Background

VA Pacific Islands Health Care System, provides outpatient and mental health services to approximately 50,000 Veterans residing in the state of Hawaii, American Samoa, Saipan and Guam. This EBP project took place at the main Ambulatory Care Clinic (ACC) located in Honolulu, HI serving approximately 18,487 men and women Veterans. All patients seen at the ACC are adults, with the majority being between the ages of 25-84 years old. This clinic provides primary care, women's health services, specialty care, mental health services, imaging, pharmacy, social services, and more.

To assess the pre-implementation status of probiotic and antibiotic usage at the ACC, the VAPIHCS pharmacy was consulted. Analysis showed 430 antibiotic prescriptions and 69 probiotic prescriptions were placed during the months of February, March, and April 2021. Of the 430 prescriptions of antibiotics, only six were found to have co-prescriptions with probiotics prescribed and all six were prescribed by the same physician. Additionally, data showed a total of 66 providers that prescribed antibiotics and only 24 providers that prescribed probiotics within the 3-month time period.

Problem Statement

As noted above, there was a limited number of co-prescriptions of probiotics with antibiotic prescriptions at the ACC and its satellite clinics located throughout Hawaii. Providers' practice of placing orders for oral antibiotics and the additional order for probiotics is dependent on individual providers discretion, preferences, and familiarity of probiotics. This was identified as a clinical and knowledge limitation.

PICOT Question

Will there be an increase in the co-prescription of probiotics with oral antibiotics over a 3-month period post implementation following an evidenced-based provider education session on the use of probiotics to providers within the VAPIHCS?

Purpose & Objectives

The purpose of this project was to develop, implement, and evaluate a probiotic educational class for providers at the main ACC and Hawaii satellite outpatient clinics with the goal of increasing provider knowledge of best practice and use of probiotics and increase the number of probiotic prescriptions given out to patients receiving oral antibiotic treatment with the intention to improve patient outcomes.

Objectives:

1. Obtain number of probiotics being prescribed with antibiotics over a 3-month period, prior to implementation;
2. Develop provider training;
3. Increase ACC provider knowledge of probiotic usage by offering a training regarding probiotic use and its GI protective mechanisms; and
4. Obtain number of probiotics prescribed with antibiotics after a 3-month period post educational in-service to assess for effectiveness.

Conceptual Framework

The Stetler model (Stetler, 2010) was used to guide the development of this evidence-based educational-based project. This model focuses on how to create formal change within an organization by the identification, evaluation, and implementation of the most current evidence-based research. The model includes five phases: Phase I: Preparation, Phase II: Validation, Phase III: Comparative Evaluation/ Decision Making, Phase IV: Translation/Application, Phase V: Evaluation.

Literature Review

Search Strategy

A literature search to support this evidence-based practice (EBP) project was conducted using CINAHL, PubMed, and Google Scholar. The search period spanned from August 2020 through June 2021. The search terms and phrases included: “probiotic”, “antibiotic”, “diarrhea”, “antibiotic-associated diarrhea”, “pathophysiology”, “antibiotic resistance”, “safety”, “prevention”, “treatment”, “strain-specificity”, and “disease-specificity.” Search terms were combined using Boolean operators (AND/OR) and truncations to alter the sensitivity of searches. The search yielded 1,450 publications.

Inclusion/ Exclusion Criteria

Studies considered for review met the following inclusion criteria: Full-text articles; focused on adult population (>18 years old) taking antibiotics and/or probiotics; impact of probiotics on antibiotic associated diarrhea; safety of probiotics; and dosage- and strain-specificity of probiotics. Exclusion criteria included the following: publications limited to pediatric patients or animal-based research; published prior to January 2015; and articles not published in English. Narrowing the search to the exclusion and inclusion criteria resulted in 156 articles. After reviewing the titles, 139 articles were excluded that were found be duplicates or failed to address the PICOT question.

Additional inclusion criteria were imposed to guide the selection of the articles - all chosen articles were required to be meta-analysis and/or systematic reviews corresponding to the highest level of evidence, level I. After reviewing the abstracts of the remaining 43 articles that met the additional inclusion criteria, 21 articles were excluded based on the abstracts failing to

address the PICOT question. The remaining 22 articles that met the additional inclusion criteria and addressed the PICOT question were selected and critically appraised using Mosby's Quality of Evidence rating system.

Synthesis of Evidence

In a review of the articles, six themes emerged: (a) Antibiotic associated diarrhea, (b) probiotics, (c) probiotics in the treatment/ or prevention of AAD, (d) dose- and strain- specificity of probiotics, (e) safety of probiotic use, and (f) low use of probiotics by providers.

Antibiotic associated diarrhea (AAD). Antibiotics disturb the normal microbiota of the gastrointestinal tract through varying mechanisms of action, causing microbiota dysbiosis evidenced by the development of AAD (Agamennone, Krul, Rijkers, & Kort, 2018; Jafarnejad et al., 2016; Mullish & Williams, 2018; Silman, Konnikova, & Gerber, 2017). AAD is a common adverse effect from the use of antibiotics with up to a 39% occurrence rate (Agamennone et al., 2018; Blaabjerg, Artzi, & Aabenhus, 2017; Mullish &Williams, 2018). Oral antibiotics can cause AAD, with a higher incidence noted with aminopenicillins, cephalosporins and clindamycin (Blaabjerg et al., 2017). Additionally, adverse symptoms of antibiotic use, such as AAD, may detour the patient from continuing and completing the recommended full course of antibiotic treatment, leading to opportunistic microorganisms' ability to overcome and develop further antibiotic resistance (Mckonnen, Merenstein, Fraser, & Marco, 2020; Ouwehand, Forssten, Hibberd, Lyra, & Stahl, 2016).

Probiotics. Probiotics are live microorganisms that have a beneficial effect on human health and wellness (Agamennone et al., 2018; Guarino, Guandalini, & Lo, 2015; Kim, et al., 2019). Benefits of probiotics include support of the immune system; prevention, improved

prognosis and/ or treatment of obesity, diabetes, varying gastrointestinal diseases as well as disturbances in mental health (Agamennone et al., 2018; Islam, 2016; Kim, et al., 2019; Mckonnen et al., 2020). The use of probiotics is expanding rapidly with 3.9 million Americans identifying as using some form of pro- or pre-biotic in 2015, a four-fold increase from 2007 (Preidis, Weizman, Kashyap, & Morgan, 2020; Su et al., 2020).

Probiotics in treatment and/ or prevention of AAD. Studies demonstrate AAD incidence, duration, and/or severity may be reduced by the co-administration of probiotics with oral antibiotic treatment (Blaabjerg et al., 2017; Kim et al., 2019; Ouwehand et al., 2016). Though the exact mechanism of action of probiotics on ADD is unknown, literature hypothesizes probiotics increase the beneficial bacteria in the gut to flourish, thereby decreasing the overtaking of pathogenic bacteria in the intestines, stimulating the immunity, and provoking competition for nutrients (Blaabjerg et al., 2017; Jafarnejad et al., 2016; Kim et al., 2019; Liu, Tran, & Rhoads, 2018; Mckonnen et al., 2020; Wilkins & Sequoia, 2017). Research has found the use of antibiotics can alter the gut microbiome up to two months post antibiotic use (Blaabjerg et al., 2017; Kim et al., 2019; Mckonnen et al., 2020). Therefore, continued probiotics treatment, past antibiotic completion, could be beneficial to preserve and restore the gut microbiome and decrease the risk of further infections.

Strain & dose specificity of probiotics. Recent literature is focusing on the importance of probiotic strain-, dose-, and disease- specific use of probiotics (Wilkins & Sequoia, 2017). Studies have found probiotic species most specific for prevention and treatment of AAD to be *Lactobacillus rhamnosus* and secondly *Saccharomyces boulardii* (Agamennone et al., 2018; Blaabjerg et al., 2017; Guarino et al., 2015; Kim et al., 2019; Mcfarland, Evans, & Goldstein, 2018; Wilkins & Sequoia, 2017). As researchers are finding increased evidence on the

significance of specificity of probiotic strains and dosage, more studies are being published with findings and recommendations for providers and consumers. For example, one study by Agamennone et al. (2018) recommended a minimal daily dose of 10^9 CFU twice a day, of the probiotic strain *L. rhamnosus* GG in the prevention of AAD. Other studies have agreed on a dose-related relationship where there is a higher response rate with higher caliber dosages, specifically more than 10^5 CFU per day, than when compared to lower dosages of less than 10^5 CFU per day (Blaabjerget al., 2017; Guarino et al., 2015; Wilkins & Sequoia, 2017). Findings of probiotics being strain and dose specific per condition being treated, shows importance of more research, education and development of guidelines that need to be initiated and provided to healthcare providers for effective therapy (Mcfarland et al., 2018).

Safety of probiotic use. Overall, the use of probiotics has been found to be safe and effective in treating and/or preventing a variety of gastrointestinal conditions (Agamennone et al., 2018; Blaabjerg et al., 2017; Islam, 2016; Kim et al., 2019). The rare adverse effects noted in literature appear to be mild and included nausea, headache, metallic taste, loss of appetite, epigastric discomfort, or flu-like symptoms (Blaabjerg et al., 2017). There have been rare occurrences of overuse of specific probiotics that have been reported to cause bacteremia, sepsis, or endocarditis cautioning use in patients with weakened immune systems, severe inflammatory digestive organs, or women who are pregnant (Agamennone et al., 2018; Islam, 2016; Kim et al., 2019; Silverman et al., 2017).

Low use of probiotics by providers. Several studies identified a key factor in the low use of probiotics by providers being due to a lack in confidence, secondary to a lack of knowledge or education on the use of probiotics in the clinical setting (Ababneh et al., 2020; Arshad et al., 2021; Sanders et al., 2018; Wilson & Whitehead, 2019). With the recent rapidly

expanding amount of research on probiotics, it is important providers are made aware of the latest findings to provide the highest level of care to their patients. Though many providers feel there is a place for probiotics in the clinical setting, multiple studies have found that providers may lack confidence in probiotic use (Ababneh et al., 2020; Wilson & Whitehead, 2019). The lack of confidence was linked to a decreased use of probiotics and is thought to be due to a deficiency in education (Ababneh et al., 2020; Wilson & Whitehead, 2019). For example, one study of 205 physicians and pharmacist found only a half (51.5%) felt they had fair knowledge on probiotics (Ababneh, et al. , 2020). About half (59%) had positive attitudes towards probiotics, but only 41% had ever recommended probiotics (Ababneh et al., 2020). In another study, Arshad et al. (2021) found of 405 providers, only 15% considered themselves of having good knowledge, 15.6% had acceptable practices, while 89.1% had a positive attitude towards the use of probiotics. In another study of 1068 providers, the majority had positive attitudes towards the use of probiotics, yet their behavior of prescribing and recommending probiotics to their patients were not congruent (Wilson & Whitehead, 2019). The same study, Wilson and Whitehead (2019) found the more a provider considered themselves knowledgeable on the use of probiotics, the more likely they were to prescribe. These studies show despite the majority of providers having a positive attitude toward the use of probiotics, there was a low level of confidence in knowledge, and a low number of providers having had ever recommended their use to patients, insinuating the need and influence an evidenced based education on the use of probiotics could have in provider behavior.

Summary of Evidence

The synthesis of the articles demonstrated: (1) The use of probiotics may restore and maintain normal gut-health; (2) probiotics in the treatment of varying disease processes are dose-

, species-, and disease-specific, (3) probiotic use is regarded as safe in individuals not affected by immunocompromising diseases, and (4) the low use of probiotics by providers may be due to a knowledge gap in the latest finding on probiotics.

Methods

Project Design

This quality improvement project design consisted of developing, implementing, and evaluating an evidenced-based provider education on the use of probiotics to providers at the VA ACC and its satellite clinics. The VA ACC and its satellite clinics are located throughout Hawaii.

Stakeholders

The stakeholders involved in the development of the project were the project committee members, the organization's leadership EBP council, the nurse scientist, medical providers, pharmacy, and clinical education department within the VAPIHCS. Committee team members included the DNP project committee chair, DNP Committee third reader, and the DNP project content expert (VA Gastroenterologist). This DNP student oversaw the development and delivery of the probiotic education material.

Participants

The in-service was delivered at a bi-monthly meeting offered to all providers and staff within the VAPIHCS via email invite. Attendees included physicians, physician assistants, nurse practitioners, registered nurses, licensed practical nurses, and clinical staff. There was a total of 84 attendees, 11 of which identified as a physician, physician assistant, or nurse practitioner that satisfied inclusion into this project. The sampling design was a non-probability convenience sample as providers were invited via email invite.

Intervention

Educate providers on the use and benefits of probiotics. The intervention involved the development of an evidenced based in-service educational offering on the use and benefits of co-

prescription of probiotics with antibiotics (see Appendix A for the Probiotic Class PowerPoint Slides) to VAPIHCS providers. The intervention was chosen to improve provider knowledge on the use of probiotics in a clinical setting and encourage co-prescriptions when ordering antibiotics. The intervention session included a questionnaire, PowerPoint slides and a verbal presentation of the information by the DNP student. The content of the in-service covered: (1) The background of AAD; (2) background of probiotics; (3) use of species-specific probiotics in the treatment and prevention of AAD; (4) the safety, precautions and contraindications in the use of probiotics, and (5) probiotic species currently offered on formulary by the VA pharmacy.

Following the development and vetting of the in-service PowerPoint presentation by the VA Gastroenterologist (the Project's content expert), the DNP student collaborated with VAPIHCS Education Department and Chief of Primary Care to coordinate the delivery of the in-service to VAPHICS providers during one of the organizations bi-monthly meetings. The presentation was delivered via Microsoft Teams, a virtual meeting platform, on November 24, 2022. The class lasted approximately 30 minutes with 15 minutes for comments and questions.

Data Collection

Evaluation of knowledge and attitudes regarding probiotic use in the clinical setting. To evaluate for changes in provider knowledge and attitudes on probiotic use in the clinical setting, the DNP student collaborated with the VA's Nurse Scientist and DNP Project Chair to develop a pre- and post-presentation evaluation questionnaire (see Appendix B). The questionnaire was uploaded and administered to attendees before and after the presentation using Microsoft forms, a web-based survey site that is secured, and provided by the VA. The questions on the form represented knowledge, attitudes, and behavior shown in Table 1.

Table 1. ***Pre- & Post-Training Questionnaire***

Pre- & Post-Training Questionnaire
1. Of patients who take oral antibiotics, up to what percent experienced diarrhea as an adverse effect?
2. Which two probiotic strains are found to be most specific for prevention and treatment of AAD?
3. What is your overall knowledge and understanding regarding probiotic use for the prevention and treatment of AAD?
4. What is your overall level of knowledge regarding available pro biotic options at the VA?
5. How confident are you in your knowledge of probiotic safety of use and contraindications?
6. Please respond to the following statement: Probiotics have a place in clinical medicine.
7. How likely are you discuss initiation of probiotic with the veteran?

Questions 1 and 2 consisted of knowledge-based questions with a single correct answer. Questions 3, 4, and 5 consisted of questions measuring the provider's confidence in their knowledge. These questions were coded using a five-point Likert scale, with a negative score (-2) indicating low confidence in knowledge and a positive score (+2) indicating high confidence in knowledge. The scores for questions 3, 4, and 5 were added and averaged. Questions 6 and 7 evaluated attitudes and behaviors, and were coded using a five-point Likert scale, with a negative score (-2) indicating low support of utilizing probiotics and a positive score (+2) indicating high support in the use of probiotics.

Number of probiotics being prescribed with antibiotics over a 3-month period. To evaluate for changes in prescibing behavior among providers who attended the class, the number of three types of prescriptions were accounted for including: (1) antibiotics; (2) probiotics, and (3) the co-prescriptions of the two. Numbers were collected over three months prior to delivery of the in-service (February, March, and April 2021) and once again over the three months post-delivery of the in-service (December 2021, January 2022, February 2022). Numbers were recorded, compared, and analyzed to assess for trends and effectiveness of the in-service. Data

was recorded using a spreadsheet kept in the DNP student's folder on the Laulima course site (see Appendix D). Laulima is the University of Hawai'i learning management system, and was approved for DNP students' use to store their DNP Project data.

Analysis

Despite studies showing most providers having a positive attitude towards the use of probiotics in the clinical setting, there was a low level of confidence in the providers knowledge, and a low number of providers having ever recommended their use to their patients (Ababneh et al., 2020; Wilson & Whitehead, 2019). A gap in education on the latest findings of probiotics has been identified as a probable factor in this lack of confidence and therefore could contribute to a lower number of probiotics being prescribed (Ababneh et al., 2020; Arshad et al., 2021; Sanders et al., 2018; Wilson & Whitehead, 2019).

The intended outcome of the project was to educate PCPs at VAPIHCS regarding the latest evidence-based research on the use and benefits of probiotics. The implementation of the class on probiotics encouraged and reassured providers in the use of probiotics with prescriptions of antibiotics to decrease the risk of AAD. This was to encourage quality improvement in patient care, to result in decreased risk of AAD, decreased risk of premature discontinuation of antibiotics secondary to AAD, ultimately decreasing the risk of developing antibiotic resistance.

The in-service was implemented with pre-and post-questionnaires and analysis of the number or antibiotic and probiotic prescriptions were used to assess the effectiveness of the class. The data from the results were exported to Excel for statistical analysis.

Approvals and Human Subjects Consideration

UH IRB. The author completed the Collaborative Institutional Training Initiative (CITI) Training for research ethics and compliance, and Health Insurance Portability and Accountability

Act (HIPAA) Training on patient privacy protections. This DNP Project involved making judgements about a program to improve or further develop program effectiveness and inform decisions and future programming within an organization (University of Hawaii Human Studies program personal communication, August 2, 2018). All these tasks were related to quality improvement and did not produce generalizable knowledge. Thus, this project did not require IRB application and review.

VA EBP Council. Although this project did not require an IRB application for approval, it underwent the mandatory VA EBP Council review and approval process. Measurements and data collection were kept confidential. All other information was kept private.

Results

Pre- and Post-Training Questionnaires

Eleven providers from the VAPIHCS attended the meeting on November 24, 2022. Eight (73%) completed the pre-class questionnaire, and six (55%) completed the post-class questionnaire. Comparison of the pre- and post-presentation questionnaires, question 1 and question 2 (Figure 1), showed improvement in knowledge of AAD and probiotics. Analysis of question 1, showed prior to attending the in-service, 62% of participants believed only up to 5% of patients taking antibiotics experience AAD as an adverse effect (Figure 1). No participants choose the correct answer of 40% (Figure 1). After the teaching, there was a 50% improvement rate where 50% of participants choose the correct answer of 40% (Figure 1).

However, when asked to select the two most specific strains of probiotics found to prevent and treat AAD, the correct selection of *Lactobacillus rhamnosus* decreased from 37% to 25%, but the other correct strain, *Saccharomyces boulardii*, increased from 13% to 50% (Figure 1). Despite the discrepancy, after combining the two answers, averaging them out, and comparing the pre- and post- data, analysis still showed a 17.5% improvement overall in identifying the two strains found most effective in prevention and treatment of AAD.

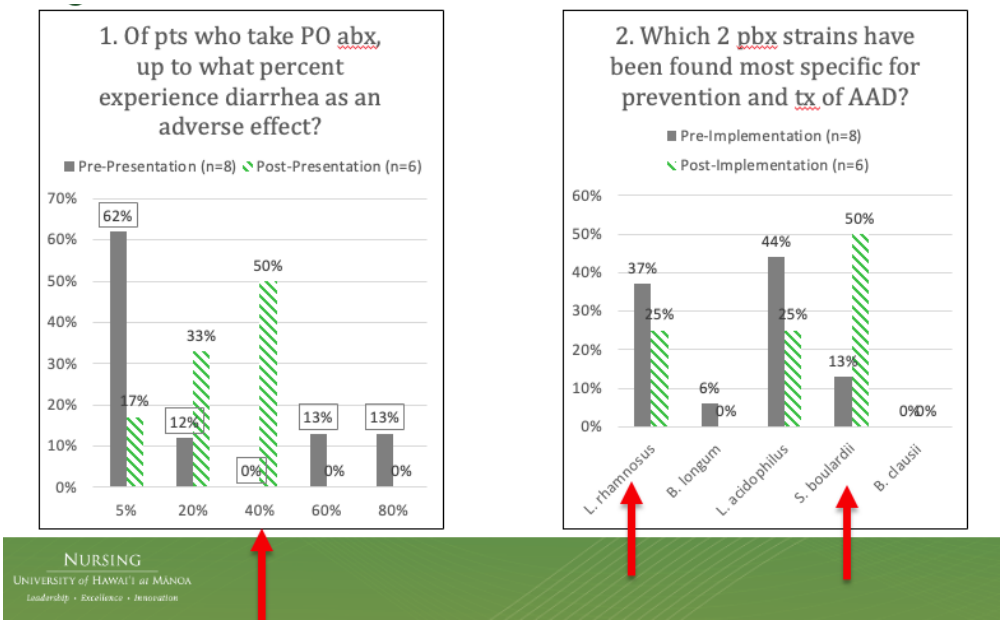


Figure 1. Results of Question 1 & 2

The providers' mean scores for questions 3, 4, and 5 were all less than 0, indicating a low level of perceived knowledge on the understanding of probiotics use for the prevention and treatment of AAD and available probiotics options on formulary at the VA (Table 2). Despite the gap in knowledge, question 6 and question 7, attitude- and behavior-based questions, respectfully, had a mean value above the midpoint of 0, showing "some" support in the utilization of probiotics prior to the class. This finding could be interpreted as providers being interested and open to the use of probiotics, but just "unsure" due to a gap in education and could further illustrate a gap in knowledge being a culprit of low prescriptions of probiotics, consistent with finding in the review of literature.

Table 2. *Pre-Presentation Questionnaire Results*

Question	Mean Value	ST DEV
3. What is your overall knowledge and understanding regarding probiotic use for the prevention and treatment of antibiotic associated diarrhea?	-0.75	1.16
4. What is your overall level of knowledge regarding available probiotic options at the VA?	-1.25	0.89
5. How confident are you in your knowledge of probiotic safety of use and contraindications?	-0.25	1.16
6. Please response to the following statement: Probiotics have a place in clinical medicine.	0.75	1.04
7. How likely are you to discuss initiation of a probiotic with a veteran?	0.125	1.45

The post-presentation survey shows an improvement in the providers responses for questions 3, 4, 5, and 6 (Table 3). Comparison and analysis of the mean values pre- versus post-presentation indicate after the class, the providers felt more knowledgeable on the use probiotics for the prevention and treatment of AAD, its safety, and availability at the VA. These values also show that providers attitudes and behavior may have been affected after the delivery of the presentation where they left feeling like probiotics have a bigger role in clinical medicine and are more likely to discuss the initiation of probiotics with their patients. The standard deviation was <1 for six out of the seven post-presentation questions, indicating normal distribution, with the variance in the results being close to the mean.

In analysis of the post presentation data found in Table 3, the mean values display an improvement in the provider responses for all five questions indicating after the class, providers felt more knowledgeable on the use of probiotics for the prevention and treatment of AAD, its safety, and availability at the VA. These values also show providers attitudes and behavior may

have been affected after the delivery of the presentation where they left feeling that probiotics have a bigger role in a clinical setting and are more likely to discuss the initiation of probiotics with their patients. The standard deviation was <1 for six out of the seven post-presentation questions, indicating normal distribution, with the variance in the results being close to the mean.

Table 3. *Post-Presentation Questionnaire Results*

Question	Mean Value	ST DEV
3. What is your overall knowledge and understanding regarding probiotic use for the prevention and treatment of antibiotic associated diarrhea?	0.67	0.82
4. What is your overall level of knowledge regarding available probiotic options at the VA?	0.5	1.05
5. How confident are you in your knowledge of probiotic safety of use and contraindications?	1.33	0.51
6. Please response to the following statement: Probiotics have a place in clinical medicine.	1.33	0.82
7. How likely are you to discuss initiation of a probiotic with a veteran?	1.17	0.75

Number of Probiotic and Antibiotic Prescriptions

The number of probiotic prescriptions ordered by participants over a three-month period increased from 16 prescription made prior to attending the in-service, to 39 prescriptions ordered after, seen in Table 4, indicating a 41% increase.

Unfortunately, for all providers, the data showed no co-prescriptions of probiotics with antibiotic prescriptions placed during the phase of the post-implementation data collection period (Table 4).

Table 4. *Number of Prescriptions Pre- vs Post-Implementation*

	February 2021-April 2021			December 2021-February 2022		
ID	# Ab prescriptions	# Probiotic prescriptions	# Ab with probiotic co-prescriptions	# Ab prescriptions	# Probiotic prescriptions	# Ab with probiotic co-prescriptions
1	New hire	New hire	New hire	5	6	0
2	8	5	0	11	6	0
3	2	6	0	9	4	0
4	5	1	0	5	0	0
5	1	0	0	21	19	0
6	11	2	0	10	0	0
7	15	0	0	17	1	0
8	16	0	0	6	0	0
9	New hire	New hire	New hire	4	0	0
10	4	0	0	3	0	0
11	22	3	0	13	3	0
Total	**84**	**16**	**0**	**104**	**39**	**0**

Discussion

Summary

The goal of this DNP project was to increase co-prescriptions of probiotics with antibiotic prescriptions at the VA in Hawaii by creating and disseminating an evidence-based education on the use of probiotics targeted to providers to result in improved patient outcomes and practice improvement. Prior to implementation, a review of the number of probiotic prescriptions with antibiotics prescriptions within the ACC showed to be minimal with only one physician that was ordering the co-prescription to five patients in the given time frame of February 2021- April 2021, while within the period there was a total of 430 antibiotic prescriptions ordered. Considering the scarce number of co-prescriptions and the most current evidence on the potential benefits in the use of probiotics, the DNP student identified a potential knowledge gap between the providers and the use of probiotics in the medical setting as described in the literature review section of this paper.

Though the development and delivery of an evidence-based in-service on the use of probiotics did not show an increase in the co-prescription of probiotics with antibiotic prescriptions, there was an average increase of 41% in the number of probiotics prescriptions when comparing pre- and post-implementation data of the providers who attended the in-service. Pre- and post-presentation questionnaires showed an improvement in the knowledge on the use of probiotics in relation to AAD, the safety in use of probiotics, and the availability within the VA formulary. Furthermore, post-presentation questionnaires illustrated a change in providers attitude and behavior where they felt the use of probiotics have a place in clinical medicine and were reported they were more likely to discuss the use of probiotics with their patients.

Limitations

Several limitations and barriers were identified within this quality improvement project. One identified drawback was the low number of providers that attended the in-service and the low number of providers who participated in the pre- and post-teaching questionnaire. Low attendance may have been due to being conducted the day prior to Thanksgiving holiday where many employees take the day off. The offering of the in-service on another day was considered but there was no other availability to present within the time constraints of this projects timeline and what the VA had to offer.

Other possible barriers of attendance may have included a lack of interest in the topic covered in the meeting, shortage of time due to workload, patient appointments coninciding with the time of the meeting, and/or technological difficulties as the in-service was delivered virtually.

Of the eleven providers who attended only eight participated in the pre-questionnaire, and only six participated in the post-questionnaire. Time constraints prevented application and obtainment of Continuing Medical Education (CME) credits to offer the providers as an incentive that may have increased attendance and participation in questionnaires.

Another limitation identified included the limited supply of various species of probiotics on formulary in the VAPIHCS. Specifically, the VAPIHCS formulary did not carry the two species of probiotics found most specific in the prevention and treatment of AAD, *L. rhamnosus* or *S. boulardii.* The pharmacy only carried *L. acidophilus*. Despite the attempt to obtain the species-specific probiotics, the process of such acquisitions was complex and outside the timeframe of this DNP project but could be considered for future innovation of the project.

There were several potential threats to internal validity identified in analysis of the number of pre- and post-presentation prescriptions. In addition to the class, one explanation of

the increase may be due to a potential skew in data by provider ID #1 placing six prescriptions for antibiotics after attending the presentation, but being a new hire, had no contribution in pre-implementation data. Also, provider ID #5 showed a significant increase in probiotic prescriptions after attending the class, but on further analysis this was congruent with a significant increase in antibiotic prescriptions as well. There is a possibility the provider always had prescribed probiotics prior to the class but due to external factors such as being on leave or data collection error, were not represented in the pre-implementation data. Therefore, the increase in the number of probiotics prescribed by this provider may have not been a direct effect of the attendance to class.

Cost of managing AAD was not included since the scope of the PICO question addressed changes in provider's probiotic prescribing behavior rather than the actual management of AAD.

Sustainability

Lessons learned from implementation resulted in some recommendations for future variations of this project.

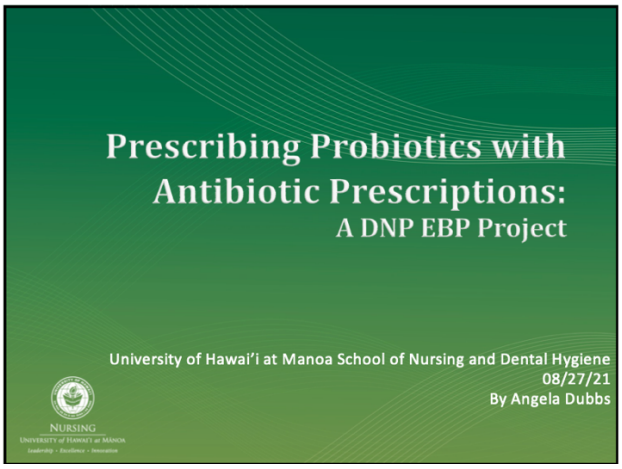
1. The in-service could be recorded and added to the VA's online education system. This would allow the material to be easily accessed at the providers convenience and available for continued periodic teachings such as during onboarding of new hires.
2. Applying for and obtaining CME credits for attendance and completion of pre- and post-implementation questionnaires may work as an incentive in provider participation.
3. Collaboration with the VA's Clinical Applications Coordinators to develop automated prompts in the electronic medical record that would suggest an order of probiotics once providers place orders for antibiotics may help increase co-prescriptions.

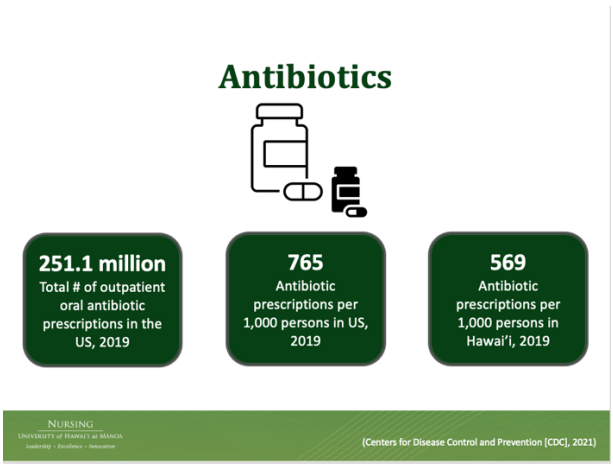
4. Collaborate with pharmacy to obtain the specific species of probiotics, *L. rhamnosus* and/or *S. boulardii* that are shown to be most effective in the prevention and treatment of AAD, to be added to the VA formulary. At the time of the project the pharmacy only carried *L. acidophilus*.
5. Investigating the associated cost related to AAD, including missed days at work, social cost, and physiological cost such as outcomes of shifts in electrolytes, and possible visits to the emergency department, in addition to the physical cost of the probiotic co-prescriptions.

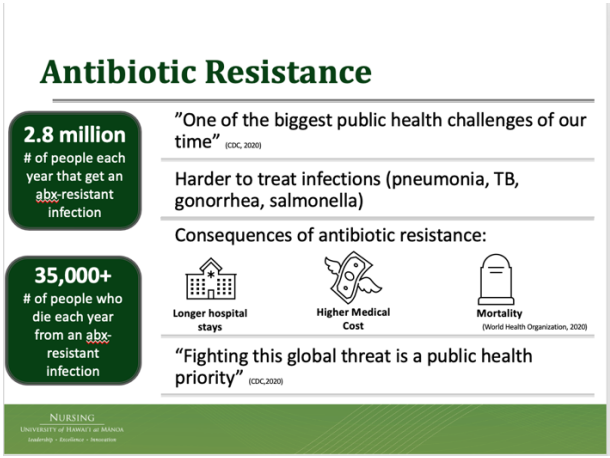
Conclusion

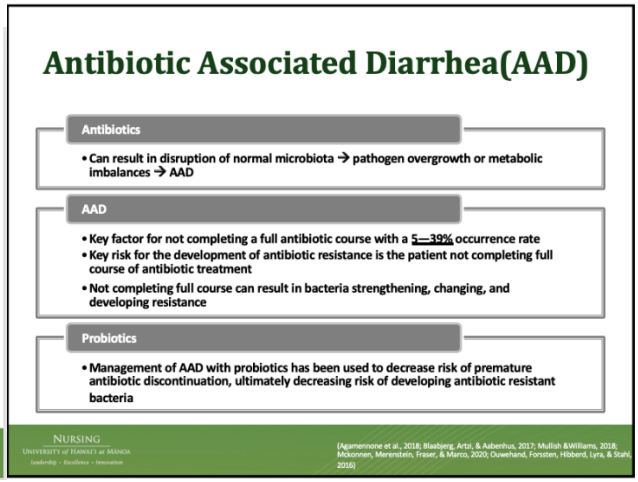
During this project eleven providers attended the presentation on the use of probiotics. Eight completed the pre-questionnaire, six completed the post-questionnaire. Despite there being no increase in the number of probiotic co-prescriptions with antibiotic prescriptions, as well as some barriers of time and limited attendance, the project resulted in a 41% increase the number of independent probiotic prescriptions by attendees. The simplicity of recording the presentation and the project design, coupled with use of systems and infrastructure already in place means that future iterations are sustainable. This project provides a foundational model for other clinics and health systems to use to improve the health and quality of life of their Veteran patient populations.

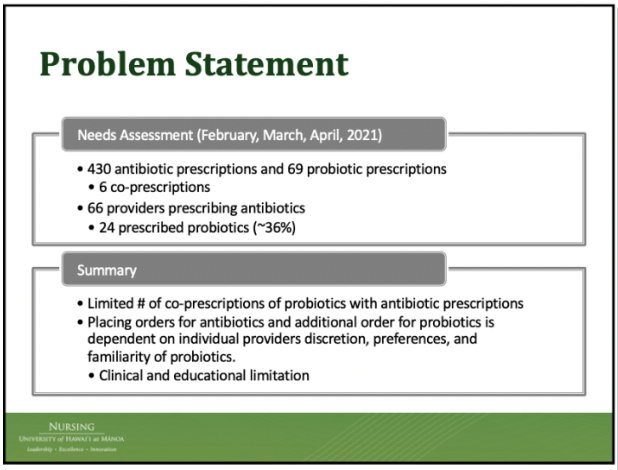
Appendix A: Probiotic Class PowerPoint Slides

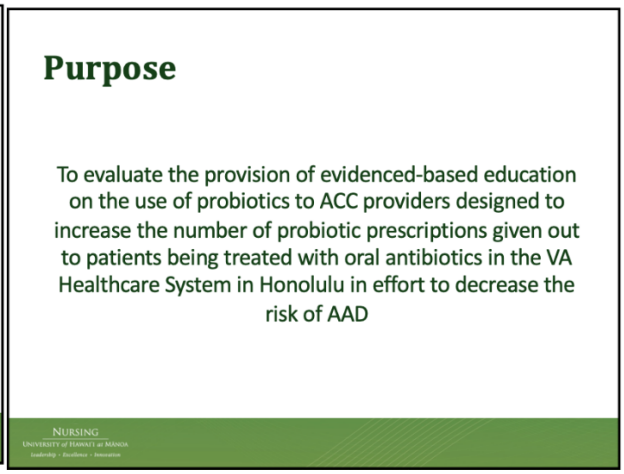












Literature Review

Search Strategy

- Literature search conducted August 2020-June 2021
- CINAHL, PubMed, Google Scholar
- Search terms: "probiotic", "antibiotic", "antibiotic-associated diarrhea", "antibiotic-resistance", "strain-specificity", "disease-specificity", "prevention", "treatment", "safety"
- 1,450 publications

Inclusion/Exclusion Criteria

- Inclusion: Full-text, adult population, impact of probiotics on AAD, safety of probiotics, dosage- and strain- specificity of probiotics
- Exclusion Criteria: Published prior to January 2015, articles not in English, duplicates
- 43 publication

Abstracts reviewed for relevance

- 17 publications selected and critically appraised using Mosby's Quality of Evidence rating system
- All meta-analysis and/or systemic reviews corresponding to the highest level of evidence, Level I, encompassing over 728 RCT and other meta-analysis.

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Synthesis of Evidence

Five Themes

- Antibiotic associated diarrhea (AAD)
- Probiotics
- Probiotics in the treatment/ or prevention of AAD
- Dose- and strain-specificity of probiotics
- Safety of probiotic use

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Antibiotic Associated Diarrhea (AAD)

Occurrence rate

- 5% -40% (Agamennone et al., 2018; Blaabjerg, Artzi, & Aabenhus, 2017; Mullish &Williams, 2018)

Pathophysiology

- Antibiotics disturb the normal microbiota of the GI tract through varying mechanisms of action, causing microbiota dysbiosis
  (Agamennone, Krul, Rijkers, & Kort, 2018; Jafarnejad et al., 2016; Mullish & Williams, 2018; Silman, Konnikova, & Gerber, 2017)

High risk oral antibiotics

- Aminopenicillins, cephalosporins, clindamycin
  (Blaabjerg et al., 2017)

Consequences

- Non-compliance → leading to opportunistic microorganisms' ability to overcome and develop further antibiotic resistance
  (Mckonnen, Merenstein, Fraser, & Marco, 2020; Ouwehand, Forssten, Hibberd, Lyra, & Stahl, 2016)

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Probiotics

Probiotics (Agamennone et al., 2018; Guarino, Guandalini, & Lo, 2015; Kim, et al., 2019)

- Live microorganisms that have a beneficial effect on human health and wellness

Benefits (Agamennone et al., 2018; Islam, 2016; Kim, et al., 2019; Mckonnen et al., 2020)

Immunity	Obesity	Diabetes	GI Diseases	Mental Health
Support of immunity	Prevention, improved prognosis and/or treatment of obesity	Prevention, improved prognosis and/or treatment of diabetes	Prevention, improved prognosis and/or treatment of varying GI diseases	Prevention, improved prognosis and/or treatment of mental health disturbances

Prevalence of use (Preidis, Weizman, Kashyap, & Morgan, 2020; Su et al., 2020)

- 3.9 million Americans identifying as using some form of pro- or pre-biotic in 2015, a four-fold increase from 2007

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Probiotics for Treatment and/or Prevention of AAD

MOA

- Probiotics increase the beneficial bacteria in the gut to flourish, decreasing the overtaking of pathogenic bacteria in the intestines, stimulating the immunity, and provoking competition for nutrients (Blaabjerg et al., 2017; Jafarnejad et al., 2016; Kim et al., 2019; Liu, Tran, & Rhoads, 2018; Mckonnen et al., 2020; Wilkins & Sequoia, 2017)

Findings

- AAD incidence, duration, and/or severity may be reduced by the co-administration of probiotics with oral antibiotic treatment (Blaabjerg et al., 2017; Kim et al., 2019; Ouwehand et al., 2016).
- Antibiotics can alter the gut microbiome up to two months post antibiotic use (Blaabjerg et al., 2017; Kim et al., 2019; Mckonnen et al., 2020)
  - **Continued probiotics treatment, past antibiotic completion, could be beneficial to preserve and restore the gut microbiome and decrease the risk of further infections**

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Strain & Dose Specificity of Probiotics for AAD

Key Point

- Recent literature is focusing on the importance of probiotic strain-, dose-, and disease- specific use of probiotics
- (Wilkins & Sequoia, 2017)

Species

- ***Lactobacillus rhamnosus***
- ***Saccharomyces boulardii***
- (Agamennone et al., 2018; Blaabjerg et al., 2017; Guarino et al., 2015; Kim et al., 2019; Mcfarland, Evans, & Goldstein, 2018; Wilkins & Sequoia, 2017)

Dose

- $>10^5$ CFU per day
- Dose-related relationship: higher response rate with higher caliber dosages, specifically more than 10^5 CFU per day, than when compared to lower dosages of less than 10^5 CFU per day
- (Blaabjerget al., 2017; Guarino et al., 2015; Wilkins & Sequoia, 2017)

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Available Probiotic Options at the VA

- Lactobacillus acidophilus (25 million CFU/capsule) – On formulary
  - Recommended dose: 50 billion CFU/day (DynaMed, 2021)
- Saccharomyces boulardii: Non formulary (drug request)
  - Recommended dose: 1 billion CFU/capsule BID (250mg PO BID) (DynaMed, 2021)

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Safety of Probiotics Use

Safety

- Overall, the use of probiotics has been found to be safe and effective (Agamennone et al., 2018; Blaabjerg et al., 2017; Islam, 2016; Kim et al., 2019)

Adverse Effects

- Rare & mild
- Nausea, headache, metallic taste, loss of appetite, epigastric discomfort, or flu-like symptoms (Blaabjerg et al., 2017)

Caution

- Immunocompromised, severe inflammatory digestive organs, pregnancy (Agamennone et al., 2018; Islam, 2016; Kim et al., 2019; Silverman et al., 2017)

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Summary of Evidence

Probiotic use may restore and maintain normal gut-health

Probiotics for the treatment of varying disease processes are dose-, species-, and disease-specific

Probiotic use is regarded as safe in individuals not affected by immunocompromising diseases

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Pretty please fill out the post-presentation questionnaire

☺

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Appendix B: Pre and Post Presentation Evaluation Tool

Probiotic Training
Pre-Training Questionnaire

1. **Of patients who take oral antibiotics, up to what percent experience diarrhea as an adverse effect?**

☐	☐	☐	☐	☐
5%	20%	40%	60%	80%

2. **Which 2 probiotic strains has been found to be most specific for prevention and treatment of antibiotic associated diarrhea?**

☐	☐	☐	☐	☐
Lactobacillus rhamnosus	*Bifidobacterium longum*	*Lactobacillus acidophilus*	*Saccharomyces boulardii*	*Bacillus clausii*

3. **What is your overall level of knowledge and understanding regarding probiotic use for the prevention and treatment of antibiotic associated diarrhea?**

☐	☐	☐	☐	☐
Very Low	Low	Moderate	High	Very High

4. **What is your overall level of knowledge regarding available probiotic options at the VA?**

☐	☐	☐	☐	☐
Very Low	Low	Moderate	High	Very High

5. **How confident are you in your knowledge of probiotic safety of use and contraindications?**

☐	☐	☐	☐	☐
Not Confident	Slightly Confident	Somewhat Confident	Confident	Very Confident

6. **How likely are you to discuss initiation of a probiotic with a Veteran?**

☐	☐	☐	☐	☐
Very Unlikely	Unlikely	Somewhat Likely	Likely	Very Likely

7. **Please respond to the following statement: Probiotics have a place in clinical medicine.**

☐	☐	☐	☐	☐
Highly Disagree	Disagree	Neutral	Agree	Highly Agree

Probiotic Training
Post-Training Questionnaire

1. **Of patients who take oral antibiotics, up to what percent experience diarrhea as an adverse effect?**

☐	☐	☐	☐	☐
5%	20%	40%	60%	80%

2. **Which 2 probiotic strains has been found to be most specific for prevention and treatment of antibiotic associated diarrhea?**

☐	☐	☐	☐	☐
Lactobacillus rhamnosus	*Bifidobacterium longum*	*Lactobacillus acidophilus*	*Saccharomyces boulardii*	*Bacillus clausii*

3. **What is your overall level of knowledge and understanding regarding probiotic use for the prevention and treatment of antibiotic associated diarrhea?**

☐	☐	☐	☐	☐
Very Low	Low	Moderate	High	Very High

4. **What is your overall level of knowledge regarding available probiotic options at the VA?**

☐	☐	☐	☐	☐
Very Low	Low	Moderate	High	Very High

5. **How confident are you in your knowledge of probiotic safety of use and contraindications?**

☐	☐	☐	☐	☐
Not Confident	Slightly Confident	Somewhat Confident	Confident	Very Confident

6. **Please respond to the following statement: Probiotics have a place in clinical medicine.**

☐	☐	☐	☐	☐
Highly Disagree	Disagree	Neutral	Agree	Highly Agree

7. **How likely are you to discuss initiation of a probiotic with a Veteran?**

☐	☐	☐	☐	☐
Very Unlikely	Unlikely	Somewhat Likely	Likely	Very Likely

Appendix C: Data Collection Forms

Pre-Implementation Antibiotic and Probiotic Prescriptions By Providers Who Attended Presentation

	February 2021			March 2021			April 2021		
ID	# Ab prescriptions	# probiotic prescriptions	# Ab with probiotic co-prescriptions	# Ab prescriptions	# probiotic prescriptions	# Ab with probiotic co-prescriptions	# Ab prescriptions	# probiotic prescriptions	# Ab with probiotic co-prescriptions
1	New hire	New hire	New hire	New hire	New hire	New hire	New hire	New hire	New hire
2	4	1	0	4	2	0	0	2	0
3	0	1	0	2	2	0	0	3	0
4	5	0	0	0	0	0	0	1	0
5	1	0	0	0	0	0	0	0	0
6	4	0	0	3	1	0	4	1	0
7	4	0	0	6	0	0	5	0	0
8	7	0	0	4	0	0	5	0	0
9	New hire	New hire	New hire	New hire	New hire	New hire	New hire	New hire	New hire
10	1	0	0	1	0	0	2	0	0
11	7	1	0	5	1	0	10	1	0
Total	**33**	**3**	**0**	**25**	**6**	**0**	**26**	**8**	**0**

Post-Implementation Antibiotic and Probiotic Prescriptions By Providers Who Attended Presentation

	December 2021			January 2022			February 2022		
ID	# Ab prescriptions	# probiotic prescriptions	# Ab with probiotic co-prescriptions	# Ab prescriptions	# probiotic prescriptions	# Ab with probiotic co-prescriptions	# Ab prescriptions	# probiotic prescriptions	# Ab with probiotic co-prescriptions
1	1	4	0	1	1	0	3	1	0
2	5	3	0	2	2	0	4	1	0
3	1	1	0	3	1	0	5	2	0
4	5	0	0	0	0	0	0	0	0
5	8	7	0	8	7	0	5	5	0
6	4	0	0	4	0	0	2	0	0
7	5	0	0	3	0	0	9	1	0
8	1	0	0	1	0	0	4	0	0
9	1	0	0	1	0	0	2	0	0
10	0	0	0	2	0	0	1	0	0
11	5	1	0	7	1	0	1	1	0
Total	**36**	**16**	**0**	**32**	**12**	**0**	**36**	**11**	**0**

Summary of Antibiotics and Probiotic Prescriptions Pre- and Post-Presentation of Providers Who Attended Presentation

	February 2021-April 2021			December 2021-January 2022		
ID	# Ab prescriptions	# probiotic prescriptions	# Ab with probiotic co-prescriptions	# Ab prescriptions	# probiotic prescriptions	# Ab with probiotic co-prescriptions
1	New hire	New hire	New hire	5	6	0
2	8	5	0	11	6	0
3	2	6	0	9	4	0
4	5	1	0	5	0	0
5	1	0	0	21	19	0
6	11	2	0	10	0	0
7	15	0	0	17	1	0
8	16	0	0	6	0	0
9	New hire	New hire	New hire	4	0	0
10	4	0	0	3	0	0
11	22	3	0	13	3	0
Total	**84**	**16**	**0**	**104**	**39**	**0**

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