A Survey of Current Practices and Factors Associated with Health Care Professionals' Use of Probiotics

by

Yenly Catherine Londono Calle

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Abstract

Probiotics are live microorganisms which confer a health benefit to the host. The literature strongly supports the benefits of probiotic therapy in preterm infant populations, specifically in the prevention of necrotizing enterocolitis (NEC) and mortality. To this end, probiotics are routinely given to premature infants in several European and Asian countries. However, in spite of the current evidence and neonatal feeding practices elsewhere, probiotic supplements are rarely prescribed in nurseries in North America. Furthermore, there is little or no literature on factors which affect clinical decision-making regarding probiotic supplementation.

The study implemented a cross-sectional descriptive survey. The purpose of this study was to: (i) describe current practices involving probiotic supplementation of preterm infant enteral feeds; and (ii) identify factors that affect willingness of health care professionals to support the use of probiotics. Probiotic use was examined in Neonatal Intensive Care Units (NICUs) in Canada and the United States using two cross-sectional internet-based surveys. Survey #1 focused on current practices and targeted neonatologists who serve as clinical directors or department heads. The results were analysed using descriptive statistics. Survey #2 addressed factors that affect probiotic supplementation of preterm infant feedings, and had two versions: the first version targeted physicians and nurse practitioners whereas version 2 targeted neonatal nurses. The development of Survey #2 was guided by the Theoretical Domain Framework which evaluates factors which may affect the willingness of Health Care Professionals to support the use of probiotics in neonatal practice. The results of survey #2 were analysed using Chi-Square, Fisher's Exact Test, and One-Way ANOVA.

The results of the study indicated that only a small proportion of NICUs are administering probiotics to preterm infants and practices vary. The most significant factors influencing clinical

decision-making regarding probiotic supplementation were knowledge about probiotics and the evidence, perceptions about the evidence and safety of probiotics, and knowledge about probiotics and clinical guidelines. Improving knowledge about probiotics, addressing safety issues of probiotics products, expanding the evidence base, and developing clinical guidelines may contribute to increased use of probiotics in NICUs.

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Chapter One: Introduction

Probiotics are live microorganisms which, when consumed in adequate amounts, confer a health benefit to the host (Guarner & Schaafsma, 1998). These microorganisms include bacteria such as *Bifidobacter sp*. and *Lactobacillus sp*., both of which are found in natural foods such as yoghurt and kefir. These species are also found as commensal or beneficial bacteria in the human gastrointestinal tract. There is good evidence that probiotics are efficacious in decreasing preterm infant (<37 weeks gestational age (Gleason & Sherin, 2012)) mortality and in decreasing the risk of diseases such as necrotizing enterocolitis (NEC) (Khalid Alfaleh, Anabrees, Bassler, & Al-Kharfi, 2011; Jacobs et al., 2013). Meta-analyses published in 2011, 2012 and 2013 unambiguously support the use of probiotics for the prevention of NEC and the reduction of mortality for this population (Khalid Alfaleh et al., 2011; Bernardo et al., 2013; Wang, Dong, & Zhu, 2012). Furthermore, several studies provide evidence that there are additional health benefits conferred by the use of probiotics in premature infants. These include: improvement of neurological outcomes (Romeo et al., 2011), prevention of nosocomial pneumonia (Rojas et al., 2012), prevention of sepsis (Awad et al., 2010), decreased allergies (Cukrowska et al., 2002), increased body weight (Mohan , Koebnick, & Schildt, 2006), and improvement in intestinal motility (Braga, da Silva, de Lira, & de Carvalho Lima, 2011). Taken together, probiotics appear to be both safe and efficacious.

In spite of the evidence cited above, probiotics are rarely prescribed in neonatal practice in North America. I am aware of only one Canadian NICU where probiotics use is a standard of care for preterm infants (Dr. Keith Barrington, *personal communication,* February 2, *2013*), and only three American nurseries where probiotics are used routinely (Li, Rosito, & Slagle, 2013; N. Rabovsky, personal communication, April 19, 2012; P. Gal, personal communication, May

22, 2013). In contrast, probiotics have been used for several years in neonatal units in Finland (Luoto, Isolauri, & Lehtonen, 2010a), France (Bonsante, Iacobelli, & Gouyon, 2012), Germany (Mohan et al., 2006), Greece (Costalos C, Skouteri V, & Gounaris A, 2003), Italy (Manzoni et al., 2011a), Saudi Arabia (K. Alfaleh, personal communication, May 22, 2013), and Taiwan (Lin et al., 2008).

The hesitance of clinicians in North America to introduce probiotic supplements into clinical practice is in obvious contrast to the standards in other parts of the world and clearly warrants further investigation. On this basis, an extensive literature review using databases such as CINAHL, Pubmed, Scopus, Embase, and the Cochrane library was performed. The search, which will be described in the next chapter, was conducted by focussing on current practices and factors which may affect the implementation of probiotics as a standard of practice in newborn care. In this literature review, several gaps and/or disparities in the literature were identified with respect to the range of current practices in North America, clinical practice guidelines, medical opinions regarding the evidence supporting probiotic use, and factors which influence the willingness of medical and nursing staff to use probiotics in enteral feeds for premature infants. For example, few physicians' opinions regarding the use of probiotics have been published, and these differ widely (Agostoni et al., 2010, Tarnow-Mordi, Wilkinson, Trivedi, & Brok, 2010). Differences in opinions also extend to the rigor of research in the area. At least one meta-analysis has been criticized for its lack of homogeneity with respect to the Randomized Control Trials (RCT) on probiotics and the presence of confounders, as well as other factors (Khalid Alfaleh, Anabrees, & Bassler, 2010). Potential safety issues regarding probiotics supplementation have also been highlighted (Jenke,Ruf, Hoppe, Heldmann, & Wirth, 2011; Kunz, Noel, & Fairchok, 2004) and there seem to be institutional barriers regarding probiotics supplementation

(Barrington, 2013). Although this review provides insights into possible obstacles to probiotic supplementation, no peer-reviewed research has been published which rigorously examines clinical decision-making around this practice. Combined with a paucity of information on current practices in North America, and a lack of understanding of the factors associated with health care professionals' decision to use probiotics for preterm infants, the purpose of this study is therefore to: (i) describe current practices around probiotic supplementation in preterm infant enteral feeds in Canada and the united Sates, (ii) identify factors that affect clinical decision making regarding probiotic use for preterm infants.

This study is significant because it may yield useful information that will enhance our understanding of some of the barriers to implementing what has been deemed by some clinicians as one of the most promising new treatments in neonatal practice. Despite some of the concerns noted above, it nonetheless appears that probiotics yield significant improvements in preterm infant health outcomes; thus, it is important to understand current practices and factors which constitute barriers to its advancement.

This thesis is comprised of six chapters in addition to the introduction. In Chapter two, I provide a definition of probiotics and present a review of pertinent literature on their purported health benefits. In this chapter I also discuss the state of science related to current practices of probiotic supplementation in U.S and Canada, as well as factors that may affect probiotic supplementation. In Chapter three I explain some theories of behavior change. In addition, this chapter constitutes a description of the theoretical framework which supports this study, together with my research questions. In chapter four I detail the designs and methods utilized in my thesis research, together with ethical considerations. In chapter 5, I describe the results of this study.

Finally, in chapter 6 I present the discussion, study strengths and limitations. I end this chapter with recommendations for future research, practice and policy.

Chapter Two: Literature Review

A comprehensive review of select databases was performed, including CINAHL, Pubmed, Scopus, Embase, and the Cochrane library. I used the following terms singly and/or in combination: allergies, brain, bacteremia, barriers, *Bifidobacteria*, behavioral theories, doctors, decision making, preterm infants, knowledge, lactobacillus, Evidence Based Medicine (EBM), Evidence Based Practice (EBP), *lactobacillus*, models and theories of behavior change, necrotizing enterocolitis (NEC), neonate, newborn, nurse, nutrition, preterm, probiotic, neurologic, nurse, practice, sepsis, and regulations of probiotics. Articles retrieved included those not listed in the search strategy but which were derived as secondary sources.

Based on the information retrieved in the search, I synthesize and review herein several key themes from the literature review, including definitions of probiotics, the importance of intestinal microflora, putative mechanisms of action of probiotics, and patterns of bacterial colonization of the neonatal gut. In subsequent sections of chapter II, I summarize studies demonstrating the efficacy of probiotics in preventing gastrointestinal pathologies including NEC, as well as other benefits of probiotics for premature infants. In the state of science of this chapter, I describe current practices and factors which might negatively influence the implementation of probiotic use in U.S and Canada.

Review of Relevant Literature about Probiotics

Probiotics. The term probiotics originates from the Latin preposition “pro” which means “for” and the Greek adjective *βιωτικός* biotic. The noun *βίος* means “life” (Hamilton-Miller, Gibson, & Bruck, 2003). Therefore, etymologically, “probiotic” means “for life” which implies that life is present. The latest, widely-accepted definition of probiotics was given by Guarner and Schaafsma (1998), who describe probiotics as, “living microorganisms that on ingestion in

certain numbers exert health benefits beyond inherent basic nutrition". This definition was adopted in a joint report in 2001 (FDA/WHO) about probiotics. The two most important criteria for a probiotic is that the microorganisms (bacteria or yeast) must be alive at the time of ingestion, and that they must provide a health benefit (Sanders, 2009).

The most common probiotics are *Bifidobacterium* and *Lactobacillus,* which can be consumed in certain processed and unprocessed foods, or in the form of capsules, pills, drops and powder preparations. These and other probiotic species may be found in foods such as yoghurt and cheese, especially aged cheese. They can also be found in natural sources such as expressed breast milk and some products made by fermentation processes such as kefir, sour cream, airan, soya sauce and tofu.

Misconceptions about the definition of probiotics are prevalent in the literature, in which the word has been wrongly defined or interchangeably used with "commensal bacteria" and "live active cultures". Sanders (2009) clarified these issues by explaining that candidate probiotics are frequently isolated from the pool of native, putatively-beneficial bacteria found in humans; however, it is not correct to parallel probiotics with native commensal microbes. Probiotics are not synonymous with "live active cultures" because live cultures are microbes associated with foods, often as food fermentation agents. Many of these agents have not been directly tested for health benefits, whereas probiotics are live microbes that have been shown to have a health effect, as stated previously. It is important to recognize the classification of bacteria resident in the gut that are not necessarily beneficial to the host. I present a summary of the relevant types of bacteria and their functions, in Table 1, Appendix A.

Functions of Gut Microflora. The gut microbiota, also referred to as the intestinal microbiome, is widely recognized as being important for intestinal health. Furthermore,

maintenance of homeostasis within the gut microbiome has both local and systemic implications. With respect to the gastrointestinal environment, the microflora has three important functions: metabolic, trophic and protective (Francisco Guarner & Malagelada, 2003). Bacteria produce short-chain fatty acids and vitamins, and participate in mucosal epithelial cell proliferation and differentiation. The gut microflora also induces maturation of host immunity and protects the host from colonization by pathogens, while intestinal bacteria are believed to mitigate the risk of gastrointestinal cancers (de Moreno de LeBlanc & Perdigón, 2010). Given this perspective, the gut microflora can be viewed as a "microbial organ" (Peterson, Frank, Pace, & Gordon, 2008) that has a critical influence on human health. For example, bacteria have been demonstrated to modulate a variety of intestinal disorders in adults, including: inflammatory bowel diseases (Guandalini et al., 2010); bowel cancer (de Moreno de LeBlanc & Perdigón, 2010); ulcerative colitis (Sang, 2010); irritable bowel syndrome (Moayyedi et al., 2010); obesity (Luoto et al., 2010a); eczema (Kim et al., 2009); cholesterol levels (Huang, Wang, Cheng, & Zheng, 2010; Lye, Rusul, & Liong, 2010; Ramasamy, Abdullah, Wong, Karuthan, & Ho, 2009); and diarrhoea secondary to oral antibiotics (Kale-Pradhan, Jassal, & Wilhelm, 2010). This emerging picture of the importance of intestinal microbes in human health is being extended to the premature infant as well, where they also appear to have significant developmental benefits. Before reviewing the detailed benefits that probiotics confer upon premature infants, it is pertinent to describe both the mechanisms of the action of probiotics and the bacterial colonization of the neonatal gut.

Mechanism of Action of Probiotics. To understand the mechanism of the action of probiotics, it is important to first review intestinal immunity. In addition to the barrier function of the intestinal mucosa, intestinal immunity can be viewed as being either 'innate, or 'acquired'. Innate immunity is a natural host defense mechanism that does not rely on antibodies for its

responses to pathogens. In contrast, acquired or adaptive immunity develops progressively after contact with microorganisms, and is based on specific recognition of antigens by antibodies (Yoon, 2010). Interactions with intestinal microflora involve both types of immune responses, and are critical components of infant health. I focus herein on microbial interactions within the innate system, which is primarily modulated by Toll-Like Receptors (TLRs) (Basith, Manavalan, Lee, Kim, & Choi, 2011).

TLRs are transmembrane proteins found in intestinal epithelial cells (as well as many other cell types, and they belong to the IgG superfamily. TLRs recognize or bind relatively non-specifically to a variety of broadly-conserved microbial products (including bacterial DNA and cell wall components). In so doing, TLRs facilitate the innate immune response to a variety of bacteria, viruses, fungi, and parasites (Gewirtz,2011). This in turn triggers the production of chemokines and cytokines, which are biological mediators that have key roles in innate immunological responses to pathogens. TLRs enhance local and systemic immunity, increasing or decreasing anti-inflammatory responses, modulating gut permeability to bacteria and toxins, and suppressing pathogens associated with NEC (Millar, Wilks, & Costeloe, 2003). TLRs also work by sensing injury in the intestine and then limiting damage by modulating apoptosis, depressing pro-inflammatory pathways and by promoting epithelial cell proliferation (Vijay-Kumar et al., 2006 ; Zeng et al., 2006). TLRs increase the production of trefoil, a glycoprotein which has an important role in wound healing and repair in the intestinal mucosa (Podolsky, Gerken, Eyking, & Cario, 2009). In contrast, dysregulation of TLRs can induce mucosal inflammation (Garlanda et al., 2007) and carcinogenesis (Fukata et al., 2007; Xiao et al., 2007). The interactions listed above may be dysregulated in premature infants due if, in turn, Intestinal bacterial colonization is altered or disrupted**.**

Numerous mechanisms are believed to mediate the benefits of probiotics. Some probiotics strains increase the production of IgA, whichis a key component of mucosal defense, neutralizing pathogenic microorganisms (Anand, Leaphart, Mollen, & Hackam, 2007; van der Waaij, Mesander, Limburg, & van der Waaij, 1994). IgA in the luminal mucus layer of the intestine binds to pathogens, thus decreasing their capacity to access and adhere to microvilli of enterocytes and colonocytes (Sherman, Ossa, & Johnson-Henry, 2009). An increase in IgA has been observed in infants receiving probiotics. In a double-blind placebo-controlled trial, infants that received a probiotic mixture (*Lactobacillu*s GG, *L. rhamnosus, B breve and Propionibacterium freudenreichii* ssp. *Shermanii*) had higher post-treatment fecal IgA levels than the placebo group (Viljanen et al., 2005). Similar findings were found in other randomized control trials (RCTs) in infants who received *L casei*, *L acidophilus*, *B subtilis* and *Enterococcus faecalis* (Yu Wang, Gao, Zhang, Shi, & Ren, 2014).

Some probiotic strains also appear to increase the production of mucins (MUC2 and MUC3) from human intestinal cells (Mack, Michail, Wei, McDougall, & Hollingsworth, 1999). Mucins protect the intestinal mucosal barrier by preventing the binding of pathogenic microorganism to the mucosal epithelial cells (Mack et al., 1999) and increase the removal of pathogens from the intestine (Linden, Sutton, Karlsson, Korolik, & McGuckin, 2008). A deficient mucous coat could facilitate the development of NEC (Anand et al., 2007). In addition, mucins cells secret trefoil factors which are antibacterial peptides (Sherman et al., 2009). Both mucins and trefoil factors are the first intestinal barrier defense against pathogens (Plaut, 1997). In addition to being part of the mucosal barrier, trefoil factors perform functions in cell immigration (an essential activity for healing) and apoptosis, which help to preserve epithelial surface integrity (Taupin, Kinoshita, & Podolsky, 2000). As discussed in the subsequent section, the intestinal microbiome of preterm

infants is recognized as a key component of intestinal and systemic health, and has developmental implications.

Bacterial Colonization of the Neonatal Gut. Several parameters affect bacterial colonization of the neonatal gut. These include mode of delivery, environmental exposure, diet and antibiotics (Dominguez-Bello, Blaser, Ley, & Knight, 2011). Preterm infants delivered by Caesarean (C)-section are not exposed to vaginal and faecal microbes such as *Bifidobacteria*, *Bacteroides*, *Fragilis group* and *Escherichia coli* (Marques et al., 2010). The lack of this 'natural' exposure results in fewer *Bifidobacteria* and the widespread presence of *Clostridium difficile*, which is a serious intestinal pathogen (Biasucci, Benenati, Morelli, Bessi, & Boehm, 2008, Biasucci et al., 2010, Penders et al., 2006). There is a notable correlation between lack of exposure to vaginal and fecal microbes and to the susceptibility of infants to certain pathogens and diseases. For example, 64 % - 82% of all cases of skin infection with methicillin-resistant *Staphylococcus aureus* (MRSA) were in newborns delivered by caesarean (C)-section (Center for Disease Control and Prevention, 2006). In one meta-analysis that included 23 studies, there was a 20% increase in the risk of asthma in children who had been delivered by C-section (Thavagnanam, Fleming, Bromley, Shields, & Cardwell, 2008). In another meta-analysis of 20 studies it was shown that children born by C-section have a 20% higher risk of developing childhood-onset type 1 diabetes compared to those born vaginally (Cardwell et al., 2008).

Environmental factors can also contribute to the settlement of the first microbiota in infants. Infants confined to neonatal intensive units are potentially exposed to a higher load of pathogens, and this can alter the microbiome (Mshvildadze, 2008). Such infants have a predominance of coliforms, bacteroides, and clostridia (Fanaro, Chierici, Guerrini, & Vigi, 2003;Penders et al., 2006). It has been documented that diet, not surprisingly, also affects gut colonization. Several

studies have reported a lower abundance of *Bifidobacteria* and a higher abundance of aerobic bacteria in the gastrointestinal microbiota of formula-fed infants relative to breast-fed infants (Hopkins, Macfarlane, Furrie, Fite, & Macfarlane, 2005). Breast-fed infants harbor a fecal microbiota that has a two-fold increase in *Bifidobacteria* compared to formula-fed infants (Bezirtzoglou, Tsiotsias, & Welling, 2011) . This might be due to the fact that that human milk contains up to 10^9 live bacteria per liter with a predominance of *Bifidobacteria* (Gueimonde, Laitinen, Salminen, & Isolauri, 2007). Human milk also contains oligosaccharides that serve as an energy source for *Bifidobacteria* growth (Garrido, Dallas, & Mills, 2013).

Premature infants who have delayed enteral feedings typically also experience a delay in intestinal colonization by commensal bacteria (Martin & Walker, 2008). Antibiotics negatively affect the composition of the infant gut microbiota by increasing anaerobic species and by delaying colonization with *Lactobacillus* sp. This in turn increases colonization with *Klebsiella* and *Staphylococci* species (Magne, Suau, Pochart, & Desjeux, 2005). In premature infants, the combined effects of immaturity, duration of stay in NICU and the use of broad spectrum antibiotics delay the establishment of a beneficial bacterial community and enable the growth of potentially pathogenic bacteria (Martin & Walker, 2008; Mshvildadze, 2008).

It has been suggested that optimization of intestinal microflora has beneficial effects on digestive tolerance and growth (Jacquot et al., 2011a). Initial bacterial colonization has repercussions for the permanent microbiota in adults. Enteral feeds and bacteria both constitute sources of antigens that are essential for the neonatal immune system to become competent and functional. Initial exposure to these antigens can affect long-term immune competence, particularly via maturation of dendritic cells and regulatory T-cells (Calder et al., 2006; Blümer, Pfefferle, & Renz, 2007). Disruption of this process through inappropriate colonization, or via

secondary reactions to antibiotic therapy have been linked to long- term health consequences including immune-related disorders such as eczema, allergic rhinitis, and inflammatory bowel disease (Conroy, Shi, & Walker, 2009; Kelly, King, & Aminov, 2007). Furthermore, dysregulation of the bacterial microflora has been linked to pathologies such as NEC in premature infants(Claude & Walker, 2001). In the following section, I provide a description of the benefits of probiotic use in the premature infant population.

Benefits of Probiotic Use on Premature Infants

The benefits of probiotics in premature infants include: a) a reduction in the incidence and severity of NEC and other parameters of gastrointestinal health; b) improved neurological outcomes; c) a reduction in pneumonia associated with ventilation (PAV); d) increased vitamin production; e) a reduction in duration of hospitalization; and f) increased weight gain.

Impact on NEC and gastrointestinal health. One of the most significant pathologies of premature infants is NEC which is the most common inflammatory intestinal disorder in premature infants. NEC remains a leading cause of morbidity and mortality in neonatal intensive care units (Hunter, Upperman, Ford, & Camerini, 2008). The overall incidence of NEC in Canada is 5.1%, with incidences varying from 1.3% to 12.9% (median = 4.6%) (Yee et al., 2012). Inappropriate colonization of the gut by pathogenic bacteria has been linked to NEC, as has a decreased bacterial intestinal flora. Colonization by commensal bacteria is necessary for the healthy development and maturation of the newborn intestine (Dai & Walker, 1998). The intestine of the preterm infant tends to be colonized by pathogenic microorganisms and has a decreased microflora (Jacquot et al., 2011; Yunwei Wang et al., 2009). This dysregulation of the gut microbiota in the preterm infant is one of the factors that makes these infants vulnerable to developing NEC (Claude & Walker, 2001).

Probiotics potentially regulate the imbalance in the gut's microbiota (Richardson et al., 2010). There are several studies which show the efficacy of probiotics in preventing NEC, including several randomized, controlled trials (RCTs) which provide encouraging evidence regarding the benefits of probiotics. A recent meta-analysis of 20 eligible trials (including trials performed in China randomizing 3816 preterm infants) unambiguously concludes that probiotics reduce the risk of mortality by 44% and decrease the risk of NEC by 67% in probiotics-fed infants vs placebo (Wang, Dong, & Zhu, 2012). Other meta-analyses with different methodological procedures had similar results, reporting a significant reduction of NEC and mortality (Khalid Alfaleh et al., 2011)Bernardo et al., 2013). Significantly, in the RCTs included in this meta-analysis, there were no reported cases of sepsis related to probiotics supplements. Similarly, a large RCT that randomized 1099 infants reported that *B. infantis*, *S. thermophilus*, and *B. lactis* reduced NEC (Bell stage 2 or higher) by 2.0% in the probiotic group versus 4.4% in the placebo group (Jacobs et al., 2013). This RCT was not powered to detect NEC reduction by birth or weight; however, it appeared that NEC was prevented only in infants weighing ≥1000 g and at ≥28 gestational age. Therefore, there was no indication that probiotics were beneficial for infants weighing < 1,000 grams (Jacobs et al., 2013). In addition, in another RCT involving preterm infants receiving *Lactobacillus sporogenes* (Sari et al., 2011), there was no apparent reduction of NEC (Sari et al., 2011). From these studies, it appears that the efficacy of probiotics in decreasing the risk of NEC depends of the strain that is being used.

Another systematic review reported that, "there is insufficient evidence to recommend routine probiotics" (p. 6) (Mihatsch et al., 2012). From a review of the literature, another theme is that there are concerns regarding safety issues and probiotic supplementation. Patient safety and other issues affecting probiotic supplementation are further discussed within the context of the 'state of

science'.

Probiotics have also been reported to yield favorable feeding outcomes. Previous clinical studies have shown that probiotics significantly decrease feeding intolerance in premature infants (Indrio et al., 2008; Sari et al., 2011). In one RCT, infants with at least one episode of feeding intolerance were significantly lower in the probiotics group that was fed with *L. sporogenes* when compared with the control group (44.5% vs. 63.1%, respectively) (Sari et al., 2011). In addition, infants receiving the probiotic species *B. breve and L. casei* have enhanced intestinal motility when compared with the placebo group (Braga et al., 2011). Infants receiving *L. reuteri* have improvement of gastric emptying when compared to the placebo group (Indrio et al., 2009).

Other clinical studies on premature infants indicated that probiotics significantly reduced the time to reach full enteral feedings (Hu et al., 2010; Indrio et al., 2008; Samanta et al., 2009; Sari et al., 2011). For instance, one RCT reported that the number of days to reach full enteral feeding was significantly low (13.76±2.28 vs. 19.2 ±2.02 days) in infants who received probiotics mixture (*B. infantis, B. bifidum, B. longum and L. acidophilus*) (Samanta et al., 2009). Similar results were reported in another RCT conducted with infants who weighed >1000g. The time to reach full enteral feeding was significantly shorter in the probiotic group that received *B. longum* and *L. rhamnosus GG* (16 d; 13–20 days) than in the placebo group (19 d; 15–26 days) (Rouge, Piloquet, Butel, Rochat F, & Ferraris L, 2009).

Neurological outcomes. Previous *in vitro* and clinical studies have shown that probiotics may influence brain development. Recent findings indicated that the immune response generated by probiotics is involved in the control of neuronal proliferation and differentiation in the brain (Akira, Uematsu, & Takeuchi, 2006) and in enhanced brain healing (Arslan, de Kleijn, Timmers,

Doevendans, & Pasterkamp, 2008). In animal models, early intestinal colonization by microflora has been shown to affect motor control and anxiety behavior (Heijtz et al., 2011). Such findings positively reflect on the potential for probiotics to attenuate or in some cases mitigate hypoxic-ischemic (HI) brain injury (Wu et al., 2010), and thereby significantly improve neurological outcomes in preterm infants (Romeo et al., 2011), and possibly improve autism (J. B. Adams, Johansen, Powell, Quig, & Rubin, 2011).

Pneumonia associated with ventilation (PAV). In a randomized controlled study of premature infants receiving mechanical ventilation, a statistically significant reduction of ventilator-associated pneumonia (VAP) was reported after *Bifidobacterium* administration (X.-L. Wu, Li, Zhou, Wu, & Wu, 2011). Similarly, the results of another RCT indicated a lower rate of nonsocomial pneumonia in the probiotic group receiving *L. reuteri* vs. placebo probiotic group (2.4% vs. 5.0%, respectively) (Rojas et al., 2012). The justification for the expected benefit of probiotics was theorized to be due to the potential to prevent infection via the "stomach-oropharynx-respiratory tract"; *Bifidobacterium* can decrease gastric pH, gastric bacterial colonization and feeding intolerance (Bailey & Yeung, 2011;Wu et al., 2011).

Vitamin production. Clinical studies on humans and in vitro studies reported that specific probiotic species produce a variety of vitamins. Studies indicated that probiotics can produce vitamin K (Cooke, Behan, & Costello, 2006; Morishita, Tamura, Makino, & Kudo, 1999). One clinical study, infants with vitamin K deficiency had lower numbers of *Bifidobacteria* than healthy infants (Benno, Sawada, Mitsuoka.,1985). Similarly, probiotics can increase folic acid production (D'Aimmo, Mattarelli, Biavati, Carlsson, & Andlid, 2012; Kim et al., 2009; Strozzi & Mogna, 2008). An *in vitro* study reported that two strains of *Lactobacillus* (*sakei and plantarum*) produced high levels of folate (about 100 µg/L) (Masuda et al., 2012). Probiotics can

also increase plasma levels of other vitamins in humans. The consumption of probiotics and conventional yogurt increases thiamine (B1) and riboflavin (B2) in healthy women (Fabian, Majchrzak, Dieminger, Meyer, & Elmadfa, 2008). Although studies showing an increase in the levels of vitamin B1 and B2 due to probiotics in infants were not found, it does not discount the possibility. Morevoer, the results of an *in vitro* study reported that *L. reuteri* CRL1098, was able to produce cobalamin (vitamin B12) (Taranto, Vera, Hugenholtz, De Valdez, Sesma, et al, 2003).

Reduction in hospitalization. Clinical studies have shown a significant reduction in days of hospitalization of premature infants when probiotics are used (Rojas et al., 2012; Samanta et al., 2009). One RCT showed that the duration of hospital stay was significantly lower in the probiotic group receiving a mixture of *B. infantis, B. bifidum, B. longum* and *L. acidophilus* compared with the control group (17.17 ± 3.23day vs. 24.07 ± 4.0 days) (Samanta et al., 2009). Also, in another RCT duration of hospitalization was lower in infants ≥1500g receiving *L. reuteri* when compared with the placebo group (32.5 days vs 37 days) (Rojas et al., 2012).

Weight gain. Some studies have shown more rapid weight increase in premature infants receiving probiotics vs. placebo (Hu, Zhou, Xu, & Lin, 2010; Kitajima et al., 1997); however, other studies do not report any difference in weight gain (Costalos et al., 2003; Sari et al., 2011). As noted earlier, these contradictory results may be due to the use of different strains of probiotics. For instance, one RCT reported that the time to regain birth weight was lower in infants receiving probiotic supplements (*B. longum, L. bulgeriaus* and *S. thermophilus*) compared to the placebo group (6.8±1.2 days vs 7.7±1.6 days; $P<0.05$) (Hu et al., 2010). Another study reported that weight gain was significantly greater in the colonised infants with *B. breve* between 4 and 8 weeks of life (Kitajima et al., 1997).

State of Science

In this section I discuss current practices, and factors that might affect the use of probiotics supplementation for premature infants in U.S. and Canada. Knowledge gaps in the literature review are also identified.

Current Practices in Canada and the United States

There is a conspicuous lack of information in the literature regarding current practices on the use of probiotics in Canada and the United States. However, probiotic supplementation in preterm feeds has been implemented in a small number of facilities in U.S and Canada. The description of current practices in the NICUs within Canada and the United States will include the following: a) indications for treatment, b) type(s) of probiotic(s), c) dosages and formulations, d) contraindications, and e) criteria for discontinuation. A summary of current probiotic supplementation practices in Canada and the United States is presented in Table 2, Appendix B.

Indications. In U.S. and Canada indications for probiotics include preterm birth and/or infants receiving antibiotics. I found one NICU in Canada (K. Barrington, personal communication, February 2, 2013) and three NICUs in U.S. where probiotics are routinely given to premature infants and/or infants on prolonged use of antibiotics (Li, Rosito, & Slagle, 2013; N. Rabovsky, personal communication, April 19, 2012; P. Gal, personal communication, May 22, 2013).

At Kaiser Medical Center in San Francisco, CA the criteria for starting probiotic supplementation includes infants at ≤34 weeks and/or weight <1500 gr, and <24 hours after birth, or with prolonged antibiotic treatment (N. Rabovsky, personal communication, April 19, 2012). At California Pacific Medical Center in San Francisco, CA the criteria is infants born ≤33 weeks and/or weight <1500 gr (Li, Rosito, & Slagle, 2013). At Women's Hospital of

Greensboro in North Carolina the criteria is infants <1500g or >1500g and also receiving antibiotics (P. Gal, personal communication, May 22, 2013).

At Sainte Justine University Health Center in Montreal, PQ probiotics supplementation is initiated at <33 weeks or weight <1500g, when enteral nutrition starts and is not indicated in infants with prolonged use of antibiotics (K. Barrington, personal communication, February 2, 2013).

Types of probiotics. With respect to the types of probiotic in use, two of the four NICUs in U.S. and Canada use probiotics with multiple strains of *Lactobacillus*, *Bifidobacterium* and/or *Streptococcus*. OneAmerican NICU administers ABC Dophilus®, a powder that has strains of *Bifidobacterium* and *Streptococcus* (*S. thermophilus, B. infantis, B. bifidium)* (Li et al., 2013). In the Canadian NICU the pre/probiotic in use is FloraBaby ^{MD}, a powder that contains *Lactobacillus*, *Bifidobacterium* and prebiotic (*L. rhamnosus, B.breve, B. bifidum, B. infantis, B. longum* and Fructo-oligosaccharide) (K. Barrington, personal communication, February 2, 2013). The other two NICUs in U.S. reported routine use of a single strain (*L. Reuteri Protectis*) with the commercial name of Biogaia® (Hunter et al., 2012, N. Rabovsky, personal communication, April 19,2012; P. Gal, personal communication, May 22, 2013,

Dosages and formulations. In U.S and Canada doses are quite diverse among NICUs, likely due to the fact that different strains of probiotics and different presentations (powder/drops) are being used. For example, in the Canadian NICU FloraBaby^{MD} is given in doses of 2 x 10^9 UFC (K. Barrington, personal communication, February 2, 2013). In two NICUs in the United States, the Biogaia ® formulation (*L. Reuteri*) is given in one NICU at a dose of 0.17 ml (5 drops) daily (N. Rabovsky, personal communication, April,19, 2012), and at the other NICU the dose is 0.2ml daily (P. Gal, personal communication, May 22, 2013). In the other North American NICU ABC

Dophilus® is given in very low birth weight (VLBW) infants (1000g-1500g) in a dose of 1.05 x 10^9 CFUs/day and in extremely low birth weight (ELBW) infants (<1000g) the dose is 0.5 x 10^9 CFUs/day (Li et al., 2013).

Contraindications. The American and Canadian NICUs provided several contraindications for not giving probiotics. In two of the American NICUs, infants not eligible for receiving probiotics administration include: those receiving inotropic support (Dopamine, Dobutamine, Epinephrine), infants on continuous gastric suctioning, infants with an active gastric lesion and/or GI bleeding present, infants with a surgically transected gut (until well healed) and infants having symptoms of, or are suspected of, having definitive NEC. These symptoms include abdominal distension, abdominal peritonitis, pneumoperitoneum or pneumotosis on x-ray and/or bilious residuals (N. Rabovsky, personal communication, April 19, 2012). The single Canadian NICU identified as giving probiotics had the same contraindication as NICUs in the United States; however this Canadian NICU also uses some relative contraindications. For example, probiotics may not be given to patients with neonatal asphyxia, NEC grade III antecedents, and acquired immunosuppression (more than 2 weeks of dexamethasone 0.3 mg/kg/hr or hydrocortisone 8mg/kg/hr) (K. Barrington, personal communication, February 2, 2013). One of the American NICUs located in North Carolina did not provide any information about contraindications. The contraindications found are supported by relatively recent literature that illustrates that probiotics should not be administered in patients with a short gut, immunosuppression and special medical conditions due to pediatric cases of probiotic bacteremia (De Groote, Frank, Dowell, Glode, & Pace, 2005; Kunz, Noel, & Fairchok, 2004; Land et al., 2005).

Discontinuation. Criteria for discontinuation of probiotic therapy is variable among North American NICUs identified as implementers of probiotics. There are 2 NICUs in the U.S. located in California which discontinue probiotics when the premature infant reaches a corrected gestational age of 36 weeks or with discharge home or to another facility (Li, Rosito, & Slagle, 2013; N. Rabovsky, personal communication, April 19, 2012). There is one American NICU located in North Carolina in which probiotics are given until at least 34 weeks but often continue administering probiotics until close to discharge to be on the safe side (P. Gal, personal communication, May 22, 2013). In the Canadian NICU probiotic supplementation is stopped at 34 weeks post conceptional age if by that time the patient is receiving all nutrition orally or the infant is transferred to another health care unit (K. Barrington, personal communication, February 2, 2013).

Factors Affecting Probiotics Supplementation

Despite the evidence supporting the use of probiotics, the lack of implementation suggests that certain factors may be negatively impacting the adoption of preterm probiotic supplements in U.S. and Canada. In order to understand what factors negatively affect the use of probiotics, barriers that affect any Evidence Based Medicine (EBM) and/or Evidence Based Practice (EBP) will be discussed in the subsequent section, followed with specific factors found in the literature that possibly affect probiotic supplementation.

Barriers to implementing EBM/EBP. Taken together, there appears to be evidence from a number of meta-analyses which conclude that probiotics supplementation greatly decreases the risk of NEC and mortality in the premature infant (Khalid Alfaleh et al., 2011)Bernardo et al., 2013; Wang, Dong, & Zhu, 2012). Despite the evidence, this practice has not been implemented widely in U.S and Canada. Understanding the barriers to implementing EBM or EBP can help us

to further understand the factors that might affect the support for the use of probiotics in preterm infants' feeds.

EBM, is also known as EBP when it is applied to other health care professions (Dogherty, Harrison, Graham, Vandyk, & Keeping-Burke, 2013). The practice of EBM involves the integration of a critical analysis of the current best evidence from systematic research along with doctors' clinical experience and patient preferences in clinical decision making regarding the care of individuals (Krahn & Naglie, 2008, Sackett, Rosenberg, Gray, Haynes, & Richardson, 1996). Barriers that affect the use of EBM by neonatologists are not well-documented in the literature. However, there is extensive literature that discusses the barriers to the use of EBM by general practitioners (GPs). A systematic review of 22 quantitative and qualitative studies reported that the barriers confronting GPs to apply EBM are related to evidence, GPs' experience and expertise, barriers related to the patients' preferences, and barriers related to the general practice setting (Zwolsman, te Pas, Hooft, Wieringa-de Waard, & van Dijk, 2012). To clarify, it was found that doctors had difficulties regarding the evidence itself. The evidence was perceived to be of inadequate quality, contradictory, and too extensive. In addition, it was shown that some doctors doubted the quality of the evidence. The most mentioned barrier in this study was having access to the evidence itself. Regarding barriers related to the GPs' preferences and expertise, this systematic review described a quantitative study in which 72% of the GPs reported encountering barriers to the application of EBM (Trevena, Irwig, Isaacs, & Barratt, 2007). This same review reported that GPs are usually not positive about the usefulness of EBM because they will have to precisely follow the evidence. Moreover, previous life or clinical experience impacts the use of evidence. It was found that opinions of peers encourage the use of EBM. This review also indicated that having insufficient knowledge and skills to critically appraise the

evidence tends to influence the use of EBM. The training needed to develop these necessary skills is lacking. Additionally, for GPs it is difficult to evaluate applicability of the EBM. In reference to barriers related to the patients' preferences, this review showed that patients' inclinations and beliefs have a major influence on EBM. For example, when the EBM recommendation of the doctor does not match the patient's viewpoint, there is a barrier to use EBM. On the other hand, it can be difficult for doctors to explain EBM to the patients. The systematic review also found many barriers related to general practice settings. The major barriers for doctors are the applicability of EBM in their practices. There are notable differences between the patients in clinical trials and the patients in general practice, namely there is a heightened fear of injury or adverse effects in general practice. Moreover, there are barriers in relation to the heavy work load encountered in general practice, and the time required for using EBM was identified as a barrier. Lack of administrative and institutional supports are also barriers for the use of EBM. In this systematic review the authors reported that doctors feel they need financial resources for the use of EBM, and from their perspective, practicing medicine is more cost effective than searching for EBM.

The major factors that affect the use of EBM of this systematic review are comparable to those mentioned in other studies about barriers experienced by GP trainee doctors (Te Pas, van Dijk, Bartelink, & Wieringa-De Waard, 2013), residents (van Dijk, Hooft, & Wieringa-de Waard, 2010), doctors from other disciplines (Bhandari et al., 2003), and nurses (Dogherty et al., 2013, Solomons & Spross, 2011). In addition to the barriers mentioned above, a survey of knowledge and perceptions of the access to EBP of 660 maternal and infant health practitioners in South East Asia reported that EBP had been heard of by 58%, but the majority did not understand the concept (Martis, Ho, Crowther, & SEA-ORCHID Study Group, 2008). In

addition, the same survey reported that the most frequent sites used were Google and PubMed. The Cochrane Library had been heard of by 47% of respondents, of whom 51% had access, but the majority did not use it or used it less than once per month. This last study showed that although there is evidence to guide practice many HCPs are not aware of it. It is suspected that some of the barriers mentioned regarding the use of EBP or EBM can be extrapolated to the use of the evidence regarding probiotic supplementation.

Specific factors that might interfere in the use of probiotic supplements. No research papers were found which addressed all factors that affect implementation of probiotics. Publications about opinions, pros and cons about the use of probiotics and safety issues, together with some criticisms to the meta-analysis done by (Khalid Alfaleh et al., 2010) were identified. Collectively, these publications suggest a range of factors that might interfere with the use of probiotics as a standardized practice in neonatal nurseries. These factors include: i) safety issues; ii) methodological controversies regarding the evidence; and iii) institutional barriers.

Safety issues. Safety issues create concerns among HCPs and possibly restrain them from the implementation of probiotics. These concerns include those related to the current regulatory system under which probiotics fall in North America. Other barriers are related to the safety of this practice in the premature infant population, and concerns about long term outcomes. Therefore, safety concerns will be discussed in terms of the following: *a) current regulations, b) safety of clinical supplementation; and c) long term outcomes*.

Current regulations. The current regulations regarding probiotics in U.S. and Canada potentially influence the decision-making process as to whether probiotics supplements in premature infant feeds are given. Probiotics supplements do not fall under current drug regulations. As such, they might not be considered safe to be administered in this particularly

vulnerable population. For instance, in Canada probiotics are not considered drugs, and are considered health products subject to natural health product regulations which are issued by Health Canada. In order to be sold in Canada, any health product undergoes rigorous quality control measures that verify that the product contains what the label claims (Health Canada, 2012). Once Health Canada has assessed a product and decided it is safe, effective and of high quality, it issues a product licence along with an eight-digit Natural Product Number (NPN) (Health Canada, 2012). Health Canada issued a product license to the probiotic brand Biogaia Drops (L. reuteri) with the intended use for decreasing episodes (duration) of crying in infants suffering from colic. Another probiotic which received a product license from Health Canada is FloraBaby (*L. rhamnosus, B. breve, B. bifidum, B. infantis, B. longum, and* Fructooligosaccharide). The purpose of FloraBaby is to support intestinal/gastrointestinal health. Health Canada had also issued a product license to probiotic brands such as ibsium (Saccharomyces cerevisiae) and Pharmax Hlc Replenish (*B. animalis, B. bifidum, L. acidophilus, L. salivarius*). Both products are recommended for reducing symptoms of irritable bowel syndrome. Although Canadian regulations ensure quality of probiotics products, the fact that probiotics are not under the current drug regulations and do not require more rigorous testing than any other health product likely contribute to their lack of implementation in Canada. It is suspected that the lack of awareness of Canadian quality control regulations of natural health products might affect implementation.

In contrast, American regulations regarding probiotics are notably different from those used in Canada. In the United States probiotics are considered a dietary supplement and do not require approval by the FDA for the claims of safety or quality of the product (FDA, 2010). In fact, the FDA only verifies labeling or safety of the product in cases when the product is marketed as a

drug. The lack of insightful quality control by the FDA may allow consumers to ingest dietary supplements that are not safe. For instance, there have been misleading quality claims regarding probiotics products in the United States, and concerns regarding contamination. One study indicated that a remarkably high percentage (69%) of commercial products did not contain the components advertised on product labels (Drago, Rodighiero, Celeste, Rovetto, & De Vecchi, 2010). In 2012, a probiotics product named iFlora® Kids Multi-Probiotic and iFlora™ 4-Kids Powder were recalled due to its possible contamination with salmonella (FDA, 2012). Given the impact of regulations generated by the American FDA, current regulations in the US likely affect the use of probiotics with the premature population in other countries. HCPs have expressed concerns about the non-licensure of probiotics by regulatory authorities (Millar, Wilks, Fleming, & Costeloe, 2012; Neu & Shuster, 2010). Other neonatologists are concerned about the regulatory status of probiotics in the United States because of the perception that probiotics will remain in a 'regulatory purgatory', neither approved nor unproved, which potentially prevents this evidence-based treatment from becoming a standard of care (Janvier, Lantos, & Barrington, 2013). Despite this, the approval of probiotics as drugs appears to be approaching. In August of 2013 the FDA designated the probiotic strain *Lactobacillus reuteri* as an orphan drug. The orphan designation is with respect to the prevention of necrotizing enterocolitis in preterm infants with birth weight less than or equal to 1500 grams (FDA, 2013). The Orphan Drug Act defines "medical food" as "a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation" (FDA, 2013. p. 1). This incorporation of *Lactobacillus reuteri* as an orphan drug might encourage the prescription of

probiotics in nurseries in the United States.

Safety of clinical supplementation. There are contradictory opinions regarding the safety of probiotics therapy. For instance, Agostoni et al (2010) claimed there is "not enough available evidence to indicate that the use of probiotics or prebiotics in preterm infants is safe" (p.90). In contrast, Guthman et al., (2010) cited that there is evidence from clinical trials with preterm infants that probiotics are "both safe and well tolerated" (p.284). In several European countries, probiotic supplements have been routinely given to preterm infants for several years, and multiple retrospective studies validate their safety (Bonsante,Iacobelli, & Gouyon, 2012; Luoto et al., 2010; Manzoni et al., 2011a).

Based on the available literature, my interpretation is that there is sufficient evidence supporting the overall safety and efficacy of probiotics. It is important, however, to mention certain caveats: namely, that some medical complications, treatments or medications likely preclude the use of probiotics. For example, *Lactobacillus* bacteremia has been reported in infants with short gut syndrome and other disadvantageous medical conditions such as immunosuppression (De Groote et al., 2005; Kunz, Noel,& Fairchok,2004; Land et al., 2005). In addition, *Bifidobacterium* septicemia has been associated with postoperative probiotic therapy in an infant with omphalocele (Ohishi et al., 2010). Reflective of such concerns, in U.S. nurseries where probiotic supplementation is routine, infants are not eligible to receive oral probiotics if they have medical conditions such as active gastric lesions, GI bleeding or surgically-transected gut (until well healed) (N. Rabovsky, personal communication, April 19, 2012). Safety of the probiotic therapy has also been questioned due to the results of one RCT which indicated that in patients with advanced acute pancreatitis, probiotics are associated with increased mortality and do not actually reduce the risk of additional infections (Besselink et al., 2008).

In the same vein, some HCPs have safety concerns in relation to the Extremely Low Birth Weight (ELBW) infants. They considered that it cannot be affirmed that probiotics are safe in the highest risk population for development of NEC, who is, ELBW (< 1000gr) (Eaton & Hall, 2013). This claim is substantiated by the under-representation of this population in RCTs, and by one reported episode of sepsis in the ELBW (Jenke, Ruf and Hoppe, 2012). It was also claimed that standard culture techniques are not reliable in detecting probiotic bacteria, and sepsis related to probiotics species might be therefore be under-represented. Similarly, other authors mentioned that the potential detection of sepsis is unreliable due to the fact that most laboratory blood culture media do not support anaerobic probiotic growth (Garland, Jacobs, & Tobin, 2010). In contrast, a retrospective cohort study in the U.S. comparing the rates of NEC in neonates with birth weight ≤ 1000 episode, did not report any adverse event related to the probiotic strain that was used. In this study the incidence of NEC was significantly lower in the neonates who received *L. reuteri* than neonates that were not treated (2.5% versus 15.1%). The rates of late-onset gram-negative or fungal infections in this study were not statistically different (22.8 versus 31%) (C. Hunter et al., 2012).

long term outcomes. Other authors have expressed other safety concerns related to the unknown long-term outcomes after probiotic supplementation. Some researchers affirmed that the introduction of live bacteria species into a constantly refilling culture environment (the infant intestine) may result in a life-long presence of the organism in question (Beattie, Hansen, & Barclay, 2010). In addition these authors mentioned that the pioneer role that bacteria may have in influencing host gene expression; hence, ongoing colonization make the possibility of long term sequelae an important concern. Similarly, Frost & Caplan (2013) argued that probiotic supplementation alters immunity in preterm infants such that they are susceptible to

development of chronic diseases. These authors based this on two studies in the area of allergy. One study reported that *Lactobacillus acidophilus* might increase allergy sensitization in infants (one year follow up) of women with allergy (Taylor, Dunstan, & Prescott, 2007). Another study reported that infants of mothers who received *Lactobacillus GG* have a decreased overall risk for developing eczema during the first 7 years of life (Kalliomäki, Salminen, Poussa, & Isolauri, 2007). However, in this same study rhinitis and asthma tended to be more common in the probiotic group, urging for more research in different populations using other probiotic strains (Kalliomäki et al., 2007).

Despite the criticism and concerns, other comprehensive studies evaluating long-term outcomesin infants that have received probiotics do not show any adverse effects from probiotic therapy. For example, one recent meta-analysis reported that prenatal and/or early-life probiotic administration reduces the risk of atopic sensitization and decreases the total IgE level in children, but did not significantly reduce the risk of asthma/wheeze (Elazab et al.,2013). In reference to long-term neurodevelopmental outcomes, two studies have been published. A prospective follow-up study of very low weight infants who received *L. acidophilus* and *B. infantis* reported that there were no significant differences in growth and neurodevelopmental outcomes at 3 years corrected age (Chou et al., 2010). Similarly, another study reported that oral *L. sporogenes* given to very low weight infants did not affect growth, neuromotor, neurosensory and cognitive outcomes at 18 to 22 months corrected age (Sari et al., 2012).

Methodological controversies regarding the evidence. The meta-analysis done by Alfaleh, Anabrees, & Bassler (2010) generated a vast controversy among HCPs. Some views made the evidence appear unreliable and emphasized several procedural flaws (Neu & Shuster, 2010). On the other hand, another author claimed that this was one of the most substantial pieces

of evidence when compared to other recent interventions in neonatology (Janvier et al., 2013). The putative methodological errors and issues of the meta-analysis in question are the following: *a) confounders; b) lack of information; c) variety of the studies included; and d) lack of clear evidence to establish an optimal practice e) applicability of RCTs.*

Confounders. One criticisms is that meta-analyses fail to give sufficient information regarding the feed regimen used in probiotic trials (Soll, 2010). Feed regimen is considered one of the most important confounders for some authors (Beattie et al., 2010), and this criticism is based on two important aspects of the feed regimen. First, infants exclusively fed maternal or donor milk have significantly lower incidence of NEC when compared with those fed by formula alone (Boyd, Quigley, & Brocklehurst, 2007; Quigley, Henderson, Anthony, & McGuire, 2007). Second, breast milk contains prebiotics in the form of oligosaccharide and probiotics such as *Lactobacillus and Bifidobacterium* (Beattie et al., 2010). In response to this cofounder, Deshpande, Rao, Patole, &Bulsara, (2010) argued that, "despite preferential use of breast milk (with pro- and prebiotics) in most of the units, the incidence of definite NEC has not declined significantly" (p.1). They also affirmed that, "units with high standard of care and low baseline event rates in the population at risk are not expected to benefit significantly by the probiotics supplementation" (p.1). They conclude that, "even a 10% reduction in death or serious disease is significant" (p.1). Another associated confounder that has been discussed from some of the critics of the recent meta-analysis is the environmental cross- contamination that occurred in some RCTs. This concern is supported with the data from a pilot data collected during a RCT. The introduction of *Bifidobacterium breve* BBG during the RCT resulted in 35% of the infants in the placebo group being colonised by this specific probiotic strain (Costeloe, 2012). In

addition, other RCTs in infants have shown that environmental cross-contamination can occur with probiotics products (Kitajima et al., 1997; Mohan et al., 2006).

Lack of information. Other authors raised concerns about probiotics based on the lack of information in the original studies included in the meta-analysis regarding causes of death and increased sepsis seen in certain subgroups in individual studies. For example, among the smallest babies in the Lin et al., (2008) multicenter trial there were 12 babies in the probiotic group who developed sepsis (Neu & Shuster, 2010). However, in this RCT, Lin et al., (2008) reported that the pathogens in the cases of sepsis in the RCT were most often related to catheter-related infections in both groups and none of the positive blood cultures yielded *Lactobacillus* or *Bifidobacterium* spp.

Variety of the studies included. One of the major criticisms against the meta-analysis was the inclusion of a large number of different probiotics and protocols. Several authors criticize this approach (Eaton & Hall, 2013; Frost & Caplan, 2013; Neu & Shuster, 2010; Szajewska & Shamir, 2010). Szajewska & Shamir, (2010) argued that pooling data on different probiotics might result in misleading conclusions for several reasons. First, every specific strain has different benefits due to the immunomodulatory effects in the host (O'Mahony et al., 2005; Wickens et al., 2008). Second, probiotics differ by organism (e.g. lactic acid bacteria and yeast), therefore each microorganism has different pathogenic mechanisms. As a result, their safety and efficacy may differ (Canani et al., 2007). Third, the doses of probiotics may be important (Basu, Chatterjee, Ganguly, & Chandra, 2007; Basu, Paul, Ganguly, Chatterjee, & Chandra, 2009; Misra, Sabui, & Pal, 2009; Whorwell et al., 2006). Finally, it has been suggested that probiotics responses vary in different populations (Arvola et al., 1999(M. R. Thomas et al., 2001); Vanderhoof et al., 1999). These authors concluded that there is a risk of generalizing the results

of meta-analysis to other probiotics. Similar views are given by Liao (2010), who indicated that one of his major concerns in reference to such meta-analyses is whether it is appropriate to retrieve data on different probiotic microorganisms. The same author also pointed out that the effects observed in each clinical trial can only be ascribed to the specific probiotic strain(s) tested.

In response to this criticism about pooling data from different RCTs Tarnow-Mordi, Wilkinson, Trivedi, & Brok, (2010) argued that putting together interventions of the same class affects Cochrane review of antibiotics, beta blockers, steroids, tocolytics, contraceptives, surfactants, immunoglobulins, ventilation, hypothermia and many others. They conclude that a lack of heterogeneity justify pooling probiotics, and that no neonatal systematic review has a greater effect size for mortality and lower p value that the meta-analysis by Alfaleh et al., (2010). They also affirmed that disapproval of this by future evidence would be unprecedented (Ioannidis & Lau, 2001). They added that, if pooling is confined to *bifidobacterium*, the RR for death is 0.34 (0.20-0.55,$p<0.0001$, n=1386). In addition, Tarnow-Mordi et al., (2010) encourages physicians to import and if parents wish, prescribe previously evaluated probiotics using published regimens (Bin-Nun et al., 2005; Lin HC et al., 2005; Lin et al., 2008; Samanta et al., 2009). They also offer sharing procedures for this and for monitoring extraneous microorganism and stool colonization. They affirmed that "the evidence that probiotics reduce mortality calls for major changes in practice" (p.1)

Deshpande, Rao, Patole, & Bulsara, (2010) suggested that, given the lack of statistical heterogeneity, the consistent benefits despite significant variations of probiotics strains and protocols across the range of participating units from different parts of the world reflects the strengths rather than the weaknesses, considering the broad perspective of the meta-analysis.

They also add that reproducibility of the results in different set-ups is desirable. Also, it has been suggested that pooling data helps to identify the most promising microorganism, as well as the research questions to be addressed in future studies (Szajewska & Shamir, 2010).

Lack of clear evidence necessary to establish an optimal practice. HCPS stated that the results of the meta-analysis are not clear in guiding future practice and many questions regarding probiotics supplementation remain. However, others insist that the evidence is enough and RCTs are not necessary (Girish Deshpande et al., 2010a). For instance, some authors said that despite the studies and meta-analyses, we still do not know which probiotic product to use, the doses, when the therapy should be initiated, what infant population should receive it and , if probiotic routine is safe (Eaton & Hall, 2013). Similarly, Neu, (2011) argued that the available trials do not permit a decision to be made in reference to the optimum strain, doses, and protocol. Therefore, some professionals seem to feel that more evidence is required before probiotics are accepted as an established therapy (Beattie et al., 2010). HCPs encourage further target studies of the efficacy, safety and mechanism of action of probiotics (Eaton & Hall, 2013). Other authors affirmed that larger probiotics trials are needed (Garland et al., 2010;Neu, 2011). Similar views are shared by Millar et al., (2012) who argued that there is a need for trials with adequate statistical power and sufficient duration of follow-up individually to provide clear clinical answers.

In response to these critics, Deshpande et al., (2010) stated that placebo controlled trials are not required to address each and every issue related to probiotics in preterm neonates, they also affirm that improving access to "safe and effective" probiotics is a priority. They insisted that probiotics as an intervention has completed a full circle, from basic science (Caplan et al., 1999; Siggers et al., 2008) and cohort studies (Hoyos, 1999), to conclusive meta-analysis (Girish

Deshpande, Rao, Patole, & Bulsara, 2010b), routine use (Satoh, Shinohara, & Umezaki, 2007), and long term follow up (Chou et al., 2010). They expressed the view, “it is time to acknowledge the elephant in the room and provide all evidence (for and against) to the parents in a clear, honest, and transparent manner, and let them decide” (p.1). They also emphasized that, “the belief that we know what is best for our patients needs to be discarded” (p.1).

With respect to the general controversy about probiotics (Janvier et al., 2013) stated that the debate about probiotics is similar to that on other therapies in neonatology, such as antenatal steroids, the use of inhaled nitric oxide or hypothermia after perinatal asphyxia. In these interventions, some experts were convinced by the data while others not, thereby requiring more rigorous studies. These authors argued that the data supporting probiotics as effective and safe is significant compared with others recent innovation therapies in infants such as inhaled nitric oxide for hypoxic respiratory failure (Finer & Barrington, 1996), hypothermia for hypoxic ischemic encephalopathy (Jacobs, Hunt, Tarnow-Mordi, Inder, & Davis, 2008), and antenatal steroids for preterm (Roberts & Dalziel, 2006). They stated that the biggest difference in the current debate about probiotics from previous debates is that they do not require special skills to administer and they can be obtained by anyone at health and grocery stores. Many parents, in fact, give them to their children at home. They stated that probiotics therefore, raise many ethical questions. For example, what can a neonatologist do if a parent not only requests probiotics formulation but brings probiotics to the hospital? What if a mother administers the probiotic herself in her breast milk?. These authors also raised other questions such as, “Should parents be encouraged to give probiotics? Prohibited from doing so? Tactically ignored?”(p.117). These authors believe that this is a perfect situation for shared decision making. In reference to performing further randomized control trials, these authors believe that doctors should allow

parents to choose probiotics or randomization, and that participation in a RCT should not be the requirement for receiving probiotics. They also suggested that doctors and hospitals should have a standardized probiotic product available. They advised that parents be informed of the results from the trials, including the information of the reduced mortality and lack of adverse effects in those studies.

Based on the review of the literature, one of the major concerns regarding the implementation of probiotics appears to be a disagreement over the evidence itself. However, this has not been empirically determined, and therefore supports the need for a research study explicitly testing whether this, and/or other issues are indeed key barriers to implementation of probiotics in preterm infant feeds.

Applicability of RCTs. There are concerns about the applicability of meta-analysis of studies on probiotics for premature infants in U.S. and Canadian settings. HCPs have questioned the quality of the evidence, given that none of the RCTs included in the past meta-analysis were from the U.S. where conditions may possibly be different (Neu & Shuster, 2010). For instance, Clinical trials on probiotics done in different settings have conflicting results possibly due to the immune properties and genetics variances of the host, and the strain specific characteristics of probiotics (Kalliomäki et al., 2007, Kopp, Hennemuth, Heinzmann, & Urbanek, 2008;Sampath et al., 2015). Another factor that possibly affects the applicability of meta-analyses on probiotic use in North American settings is the differences in the incidence of NEC (Alfaleh, Anabrees, & Bassler, 2010; AlFaleh & Anabrees, 2014). The incidence of NEC in some North American NICUs are very low (5.1%) (Yee., et al 2012) in comparison with the NEC rates in infants that received probiotics in the RCT included in past meta-analyses (Alfaleh, Anabrees, & Bassler, 2010, AlFaleh & Anabrees, 2014). Therefore, adopting probiotic therapy in a low incidence

setting may not be appropriate if adverse events are a concern given that infants who are not at risk of NEC would have chances to develop adverse effects [e.g. septicemia], even if the probability is low (Ofek Shlomai, Deshpande, Rao, & Patole, 2014). Because of these concerns regarding meta-analysis of probiotic studies in North America, HCPs urged "a high quality confirmative NEC prevention trial in U.S. using probiotics in at-risk infants" (Abrahamsson, Rautava, Moore, Neu, & Sherman, 2014, p. 392). This study has the potential to provide neonatologists in the U.S and Canada new evidence that can greatly influence clinical practice (Abrahamsson et al., 2014).

In summary, HCPs do not trust the evidence for three possible reasons. First, HCPs believe that the evidence has many flaws. For instance, the way that the meta-analysis was performed received multiple criticisms. Secondly, the evidence does not appear reliable in the opinion of some HCPs because of the safety issues with current regulation of probiotics product and probiotic therapy, and the possibility of negative long term outcomes claimed by some authors. Third, there is contradictory evidence. There is one meta-analysis (Mihatsch et al., 2012) that reported that there is insufficient evidence to demonstrate that probiotics are safe which contradicts the results of the other 3 meta-analyses about probiotics (Girish Deshpande et al., 2010b; Bernardo et al., 2013; Wang, Dong, & Zhu, 2012).

The issues related to the evidence might raise uncertainties about the efficacy and safety of this practice, in addition to specifically-identified safety concerns. It has been documented that HCP uncertainty influences decision making processes in the area of medicine. The degree of uncertainty is high in areas where clinical science is evolving and, "objective and convincing data are unavailable, and accepted or common treatment patterns are not shared by all practitioners" (p.415-415) (Mittman, Tonesk, & Jacobson, 1992). Probiotics for premature

infants is one area of research that is evolving. Besides the 4 meta-analyses that have been performed in the past 3 years (Alfaleh et al., 2011; Bernardo et al., 2013; Mihatsch et al., 2012, Wang, Dong, & Zhu, 2012) a large RCT was recently performed (Jacobs et al., 2013). In addition, among HCPs there seems to be no consensus about the efficacy of probiotics because of the different interpretations of the evidence as described above. Again, these issues have not been empirically evaluated for their significance as barriers to clinical implementation, thereby underscoring the need for my proposed research.

Institutional barriers .The controversies that generated the latest meta-analyses might affect the decision making process about probiotic. However, even when professionals overcome these barriers, they possibly face institutional barriers. Dr. Barrington (Barrington, 2013) a neonatologist at Saint Justine University Center in Montreal, described in his neonatal research blog (URL: http://neonatalresearch.org/) the processes required before probiotics became a standardized practice in the NICU at Hospital St. Justine. He indicated that, in his workplace the first inquires about using probiotics were unfruitful and that the pharmacy committee was reluctant. Probiotic supplementation became standardized practice only after a mother of a preterm infant inquired about the possibility of giving her infant to probiotics. After several infants were given in that NICU (being purchased by parents). Later, administrative events took place in order that probiotics were provided by the hospital and became a standardized practice in the nursery. For instance, at this hospital, probiotic supplementation required approval by the pharmacy committee and infection control committee. In addition, professionals from the infection disease committee grew the organisms that were in the probiotics product in the laboratory to verify the absence of pathogens. Dr. Barrington stated that he had received several communications from HCPs that wanted to administer probiotics in their nurseries. However, he

metnioned that there are often roadblocks and some reluctance from either the infection control or pharmacy and therapeutic committee (or both) (Barrington, 2013).

In summary, after describing all the possible factors that might affect the use of probiotics, it appears that there are four schools of thought among HCPS regarding the use of probiotics. One group seems convinced by the data and started implementing probiotic supplementation in the nurseries (K. Alfaleh, personal communication, May 22, 2013; K. Barrington, personal communication, February 2, 2013; Bonsante et al., 2012; Hunter et al., 2012) Li, Rosito, & Slagle, 2013(Manzoni et al., 2011a) (Luoto et al., 2010a). A second group believes that more evidence is needed before probiotics can be safely standardized as a routine practice (Beattie et al., 2010; Eaton & Hall, 2013; Soll, 2010; Garland et al., 2010; Neu, 2011; Millar et al., 2012). A third group of professionals is concerned about the quality of probiotic products that are offered in U.S. because the current FDA regulations do not warrant the quality of a probiotic product (Neu & Shuster, 2010, Michael Millar, Wilks, Fleming, & Costeloe, 2012). The second and third group of HCPs might be part of the same group because they possibly share the same positions about the evidence and regulatory issues. A fourth group of professional are those who are willing to implement probiotics in the nurseries but they face institutional barriers (Barrington, 2013). A possible fifth group are those professionals that might not be aware of the evidence or do not know how to interpret it (Dogherty et al., 2013). Again, these have not been verified empirically, and the relative proportion HCPs in these groups would likely weigh the significance of specific barriers.

Knowledge Gaps

There are currently no extant studies which evaluate either the range of practices in U.S. and Canada or current factors that are impeding the use of probiotics in the nurseries. Regarding

current practices, as was evidenced above, only two practices in U.S. have been published and the other two are known by personal communications. Also, it is likely that practices are only published after they have been implemented for several years. For instance, a probiotic implementation protocol in the United States was published after a cohort study of 8 years (Li et al., 2013). It is quite possible that the practice is being implemented in other nurseries in North America while not being available for public knowledge. It is therefore important to conduct a cross-sectional survey that can inform the current practice preferences in U.S and Canada.

Regarding factors that are affecting probiotics supplementation, no study was found that looked at barriers for probiotic implementation. However, as evidenced above, it seems that a group of professionals believe that more evidence is needed before being completely confident to implement this practice. Another group of HCPs may be convinced about the evidence but may also be facing institutional barriers. Another group might want to implement the practice but distrust the quality of available products. Additionally, it is possible that there are other groups of professionals that might face different issues such as lack of skills to appraise the evidence, lack of motivation, lack of peer support, lack of resources in the hospital to have access to the evidence, lack of knowledge about probiotics, and lack of time for decision making along with other issues. Little is known about the ratios of these groups are. Several questions continue to remain unanswered such as whether there is lack of knowledge about probiotics, how many professionals who are willing to give probiotics face but institutional barriers limiting their efforts? Are most of the professionals waiting for more evidence? Are the majority of HCPs unaware of the evidence? Is the decision-making process difficult? Are there other barriers? Are professionals planning to implement this practice in the long term?

The largest RCT on probiotics was done in Australia and New Zealand (Jacobs et al., 2013). In this study, 1099 premature infants were randomized with respect to treatment. The result indicated that the probiotic combination (*B. infantis*, *S. thermophilus*, and *B. lactis*) reduced NEC of Bell stage 2 or more (2.0% versus 4.4%) in spite of breast milk feeding initiation rates of 96.9% in both groups. The authors of this RCT concluded that the probiotics *B infantis*, S *thermophilus*, and *B. lactis* significantly reduced NEC of Bell stage 2 or more in very preterm infants and that intervention with these probiotic strains appears to be safe. It is possible that those professionals that wanted larger RCTs get answers to questions and concerns regarding safety, doses and effectiveness of probiotics in preventing NEC. Therefore, it is important to know if this new evidence has an impact of HCPs attitudes towards probiotic supplementation.

Furthermore, recently, the Cochrane Neonatal Review Group held a webinar in Canada bout probiotics and prebiotics in October 31, 2013 (K. Barrington & Janvier, 2013). In this webinar the significant benefits of probiotics in preventing NEC were discussed, together with successful experiences of neonatologists in Canada implementing the therapy. The presentation encouraged HCPs to implement probiotics in premature infants. It is important to know if the webinar caused a positive impact on HCPs willingness to implement probiotics. Thus, the survey implemented in this study will test if the awareness of probiotic supplementation in other North American NICUs has an impact in clinical decision making process about this practice.

Given the paucity of data about current practices and the lack of studies that specify in detail the barriers for probiotic supplementation, it is necessary that a study be done that investigates both current practices and factors that are affecting the decision making process for implementing this practice.

Chapter Three: Theories and Framework

This chapter presents a review of relevant theories which includes a discussion of behavior change theories. This chapter also gives a description of the theoretical framework by which this study is supported, together with the research questions.

Behavior Change Theories

Decision-making processes can be studied in light of theories of behavior change. Adoption of a practice implies a behavior change, therefore it is important to assess all factors which may influence and interfere in the process of adoption of a practice.

In order to understand factors that are involved in the decision making process with respect to probiotic supplementation, it is important to review some of the major theories and models that explain key elements underpinning behavioral change. Two theories and one model which have been used to analyze behavior change in health related behaviors, and which have been applied widely in health research are respectively: a) Social Cognitive Theory (SCT**)**; b) Theory of Planned Behavior (TPB); and 3) The Transtheoretical Model (TTM).

Social cognitive theory. SCT was earlier termed 'Social Learning Theory' (SLT) (Bandura & Walters, 1963) and later renamed by Bandura (1986) in his book *Social Foundations of Thought and Action*. SCT postulates that human behavior is comprised of three components which interact with each other reciprocally. These components are behavior, environmental factors, and personal factors (cognition, affect and biological events) (Bandura, 1986). The interaction among these three factors results in behavior change (Bandura, 1986). SCT gives special importance on the potential of human beings. SCT emphasizes that five basic human capabilities describe a human being (Bandura, 1986). The first one is ***symbolizing capability***, which is the human ability to create symbols from human experiences. These symbols have meanings which

the person later uses as a guide in further actions. ***Vicarious capability*** refers to the ability to learn from observing the behavior of other people and the consequences they experience. ***Forethought capability*** refers to the ability of having a prior thought about consequences of a behavior. People motivate themselves and guide their actions using this capability. ***Self-regulatory capability*** refers to setting internal standards and self-evaluative reactions to our own behavior. Self-satisfaction is gained by meeting the anticipated standards and dissatisfaction results from below-standard performance. The last capability is ***self-reflective capability***, which is the ability to think about our own thought process. This capability permits humans to self-examine and critique their own behavior.

SCT incorporates a set of constructs that are determinants of behavior change. These include knowledge, outcome expectations, outcome expectancies, situational perception, environment, self-efficacy, self-efficacy in overcoming impediments, goal setting or self-control, and emotional coping (Bandura, 2004). ***Knowledge*** refers to learning facts and insights related to an action, idea, object person or situation. Outcome expectations are the anticipation of the probable outcome that would follow as a result of engaging of the behavior under discussion. ***Situation expectancies*** are the values a person places on the possible outcomes that result as a response of a behavior. ***Situational perception*** is the way one perceives their own environment. ***Self-efficacy*** is the confidence in one's own capability to pursue a behavior. ***Self-efficacy in overcoming impediments*** is the confidence that a person has in overcoming obstacles while performing a given behavior. ***Goal setting or self-control*** is the ability of setting goals and developing a plan to perform a chosen behavior. ***Emotional coping*** are the procedures employed by the person to control the emotional and physiological states related to the acquisition of a new behavior.

SCT has been used as the framework for numerous studies including clinician behavior in the management of diabetes (Presseau et al., 2013), attitudes of primary health care physician managers toward research (Jahan & Henary, 2013), defining predictors of exercise participation in female hospital nurses (Pawlak, Connell, Brown, Meyer, & Yadrick, 2005), and predicting sexually risky behavior among adolescent mothers (Koniak-Griffin & Stein, 2006).

SCT has some limitations. The theory poses many constructs which are not always possible to interpret, affecting theory use (Sharma & Romas, 2012). Prochaska (2006) mentioned that this theory lacks arrangement of constructs. Consequently, different researchers used different sets of constructs in different combinations. Prochaska (2006) also noted that SCT interventions principally target those who are ready to change the behavior. In the process such interventions are not applicable to a large part of the population.

Theory of planned behavior. It was earlier named Theory of Reasoned Behavior (TRB) by Fishbein & Ajzen (1975). However, after adding three other constructs (perceived behavioral control, control beliefs and perceived power) it was re-named TPB (Ajzen, 1991). This theory states that behavioral intention precedes behavior and it is determined by attitude toward the behavior and subjective norms. It affirms that people consider the consequences of their behavior before engaging in any action. Also, it emphasises the role of thought in decision making about engaging in behaviors (Ajzen, 1991). There are 11 constructs of the TPB (Ajzen, 1991);Fishbein & Ajzen, 1975).

The first construct is ***behavior***, which is a single action performed by an individual that is observable. The second construct is ***behavioral intention*** which is the thought to perform the behavior which is the immediate determinant of the given behavior. The third construct ***attitude toward the behavior***, is the overall feeling or dislike toward any given behavior. The fourth

construct is ***behavioral beliefs*** which are the beliefs that doing a given behavior leads to certain actions. The fifth construct **is *outcomes evaluations*** which are the values a person gives to each outcome resulting from performance of the behavior. The sixth construct is ***subjective norm*** which refers to a person's belief that most of the significant others in one's life think one should not perform the behavior. The seventh construct is ***normative beliefs*** which are how a person thinks that other people who are a significant in his/her life would like him/her to behave. The eighth construct is ***motivation to comply*** which is the degree to which a person wants to act in accordance to the perceived wishes of those significant in his or her life. The ninth construct is ***perceived behavioral control*** which is how much a person feels he or she is in command of enacting the given behavior. The tenth construct is ***control beliefs*** which are the beliefs about internal and external factors that might inhibit or facilitate the performance of the behavior. The last construct is ***perceived power*** which is the perception about how easy or difficult is to perform the behavior in each condition identified in the control beliefs.

TPB and TRB have been used in multiple health education and health promotion studies. Some of them are smoking cessation (Kim, 2008), predicting binge drinking behavior (Norman, 2011), and multivitamin use among women (Pawlak et al., 2005). TRB and TPB have also been used to analyze HCPs professional behaviors such as physician intention to prescribe emergency conception (Sable, Schwartz, Kelly, Lisbon, & Hall, 2006), determinants of physician's prescribing behavior of methylphenidate (Ponnet, Wouters, Van Hal, Heirman, & Walrave, 2013**),** and hand hygiene among health care workers (McLaws, Maharlouei, Yousefi, & Askarian, 2012)**.**

Although this theory has been useful in health research, it has some limitations. Some authors argue that the limitations of TRB and TBP are that they only predict behavioral intention and

behavior but do not explain behavior change and do not provide guidance for behavior modification (Sharma & Romas, 2012) . Additionally, TRB and TBP do not consider personality related factors, cultural factors, and demographic variables that might influence behavior (Sharma & Romas, 2012). Moreover, these theories do not look at other emotions such as fears which HCPs might face. This is a serious drawback of the theory, given the affect-laden nature of decision making involved in multiple health-based behaviors (Dutta-Bergman, 2003)

The transtheoretical model. The TTM of health behavior is a popular model of behavior change that has been used to analyse the stages of change in health behaviors. Prochaska & Norcross (1979) proposed the early bases of this model which was first named the Stages of Change Model (SOC). The TTM model focuses on explaining behavior change, whereas SCT focuses on factors that influence behavior, while TPB focuses on the cognitive aspects of behavior. The TTM postulates that health behavior change involves progress through five stages of change (Prochaska, 2000; Prochaska, DiClemente, & Norcross, 1992). The first stage is the ***precontemplation stage***, when a person does not have the intention to change in the foreseeable future, usually defined as the first 6 months. There are two categories of people in this stage. First are the uninformed people or less informed people who are unaware of the consequences of their behaviour. Second are people who have experimented with change but have failed in the past so they are no longer looking for change. The second stage is the ***contemplation stage*** which is the stage in which people are aware that a problem exists and are seriously thinking about overcoming it but not immediately. People can be in this stage for long periods. These people have considered the pros and cons of changing their behaviour.

The third stage is the ***preparation stage***, which is the stage that combines intention and behavioral criteria. Individuals in this stage are planning for change in the immediate future,

usually defined as in the next month. Depending on the behavior that the individual desires to change, they have taken some significant steps before they are actually ready to change such as buying some exercise equipment, going to a recovery group, reviewing literature, consulting with colleagues, and so on. The fourth stage is the ***action stage*** in which individuals modify their behavior, experiences, and environment in order to overcome their problem. Action involves the most manifest behavioral changes and requires a considerable commitment of time and energy. The fifth stage is the ***maintenance stage***, in which the person has maintained the change for a period of time, usually considered as 6 or more months. For some behaviors, the maintenance stage can last a lifetime.

The progression through each of these aforementioned stages is not linear, but rather they are considered as cyclical or spiral. In this spiral pattern, individuals can progress from contemplation to preparation to action to maintenance but individuals might go back to an earlier stage and then again progress to higher stages and so on.

The TTM has been used in behavioral research such as predictive modeling for physical activity (Dishman et al., 2009), predicting physician behavior to recommend colonoscopy (Honda & Gorin, 2006), changing sun protection behaviors (Falk & Anderson, 2008), and process of change scale for alcohol misuse (Freyer et al., 2006) among others.

This model has received criticism from researchers who argue that change is a continuous process that cannot be categorized in stages (Davidson, 1992; Littell & Girvin, 2002). Other authors found that categorizing people in stages has several problems (Whitelaw, Baldwin, Bunton, & Flynn, 2000). First, people can move through the stages of the model in minutes. Thus, the validity of self-reported behavior with regards to each stage of the TTM is doubtful.

These are just a few examples of how the SCT, TPB and TTM have been used in health research. Although there are numerous studies related to behavioral change that were supported in the SCT, TPB and TTM, they do have limitations. These limitations impair their application to the proposed study under consideration. SCT, TPB and TTM may not cover all factors that might interfere with behavior change such as barriers related to the documented evidence of a practice, difficulties in the decision making process, emotions, positive views about a practice, and institutional barriers among others. Thus, choosing one of these theories is not appropriate for the proposed research. I could potentially miss evaluating factors that might interfere in probiotic use that are not addressed in any of the above theories. Therefore, I have decided to use the Theoretical Domains Framework (TDF), which is a comprehensive framework that includes several constructs from the previously-mentioned behavioral theories and other theories of behavior change (Michie, 2005). TDF was specifically designed to evaluate factors that influence the implementation of EBP while most of the other behavioural change theories were specifically designed to understand and modify health-related behavior. Therefore, TDF appears to be a better fit with my proposed research, as outlined in the next section.

Framework for the Study

Theoretical domains framework. The TDF is a framework that simplified theories relevant to behavior change in a way that is convenient for researchers working in health services who are seeking explanations for the failure to implement EBP, and /or designing interventions to achieve improved implementation (Michie, 2005). The development of TDF was motivated because of the numerous psychological theories which share overlapping constructs and which have a range of theoretical elaboration that make it difficult to know how to select and apply psychological theories (Michie, 2005). Therefore, the TDF was able to simplify and maximise the accessibility

and usefulness of psychological theory (Michie, 2005). The domains of the framework provide a guide to significant explanations of current behavior and key triggers of behavior change but not the causal process that link theoretical constructs in an articulate explanation of behavior change (Michie, 2005).

The TDF was developed by three groups of scholars, including health psychology theorists, health services researchers (HSR) and health psychologists (HP). The six stages of the scholars' work were: to identify theories and theoretical constructs, simplify the theories into theoretical domains, do an interdisciplinary evaluation, validate the domain list, and pilot-test the interview questions (Michie, 2005). As a result of the teamwork, 12 domains with 112 constructs were derived from 33 psychological theories (a domain is defined as an area of interest; a sphere of thought, action or knowledge and a construct is a concept specially devised to be part of a theory (Michie, 2005)). The team also elaborated some eliciting questions from each domain (Michie, 2005). An example of these questions is summarized in the next table. The domains are on the left side of Table 3.

Table 3

*Examples of Questions for each Domain of the Theoretical Domain Framework**

Domain	Examples of questions related to this domain
Knowledge	Do they know about X? What do they think the evidence is?
Skills	Do they know how to do X? How difficult is it for them to do X?
Social/professional role and identity	Do they think the practice is compatible or in conflict with their professional standards?
Beliefs about capabilities	How confident are they with doing X? What would help them?
Beliefs about consequences	What do they think will happen if they do X? What are the consequences of doing it?
Motivation and goals (intention)	How much do they want to do? How much do they feel they need to do?
Memory, attention and decision process	Is X something they usually do? Will they think to do X? Might they decide not to do X? Why?
Environmental process and resources	To what extend do physical or resource factors facilitate or hinder X?
Social influences	To what extent do social influences facilitate or hinder X?
Emotions	Does doing X evoke an emotional response? If so, what?
Behavioral regulation	What preparatory steps are needed to do X?
Nature of the behaviour	What is the proposed behavior X? Who needs to do what differently?

*As adapted from (Michie, 2005) (p.30)

In 2012, a discriminant content validation of the TDF was performed (Cane, O'Connor, & Michie, 2012a). In the validation process the TDF was refined, adding more domains and removing other domains and constructs. Thus, after the validation procedure, the TDF encompasses 14 domains and 84 constructs. The behavioral experts that participated in the validation of the TDF based the definitions of the domains in the American Psychological Associations' dictionary (2007). The definition of the 14 domains with the correspondent definition and constructs are as follows:

1. Knowledge: An awareness of the existence of something. It has the constructs of knowledge (including knowledge of condition and scientific rationales), procedural knowledge, and knowledge of task environment.

2. Skills: An ability of proficiency acquired through practice**.** The constructs are skills**,** skills development**,** competence**,** ability**,** practice, and skill assessment.

3. Social/professional role and identity: A coherent set of behaviours and displayed personal qualities of an individual in a social work setting. It encompasses the constructs of professional identity, professional role, social identity, identity, professionals, professional boundaries, professional confidence, group identity, leadership, and organizational commitment.

4. Beliefs about capabilities: Acceptance of the truth, reality, or validity about an ability, talent, or facility that a person can put to constructive use. It involves constructs such as self-confidence, perceived competence, self-efficacy, preceived behavioral control, beliefs, self-esteem, empowerment, and professional confidence.

5. Optimism: Confidence that things will happen for the best or that desired goals will be attained. It has the constructs of optimism, pessimism, unrealistic optimism, and identity.

6. Beliefs about consequences: Acceptance of the truth, reality, or validity about outcomes of a behavior in a given situation. The constructs of this domain are beliefs, outcomes of expectancies, characteristics of outcomes of expectancies, anticipated regret, and consequences.

7. **Reinforcement**: Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus. The constructs of this domain are rewards, incentives, punishment, consequences, reinforcement, contingences and sanctions

8. Intentions: A conscious decision to perform behaviour or resolve to act in a certain way. This domain is composed of the constructs of stability of the intentions, stages of change model and TTM and stages of change (precontemplation (not ready), contemplation (getting ready), preparation (ready), action, and maintenance).

9. Goal: Mental representations of outcomes or end stages that an individual wants to achieve. It involves the constructs of stability of intentions, stages of change model, TTM and stages of

change, goal, goal (distal (long term)/proximal (near future), goal priority, goal/target setting, goals (autonomous/controlled) and action planning, and implementation intention.

10. Memory, attention and decision process: The ability to retain information, focus selectively on aspects of the environment and choose between two or more alternatives. It involves the following constructs: memory, attention, attention control, decision making, and cognitive overload/tiredness

11. Environmental context and resources: Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behavior. It is composed by the constructs of environmental stressors, resources/material resources, organizational culture/climate, salient/events/critical incidents, person x environment interaction and barriers and facilitators.

12. Social influences: Those interpersonal processes that can cause an individual to change their thoughts, feeling, or behaviours. It has the constructs of social pressure**,** social norms, group conformity, social support, social comparison, group norms, social support, power intergroup conflict, alienation, group identity, and modelling.

13. Emotions: A complex reaction pattern, involving experiential, behavioral, and psychological elements, by which the individual attempts to deal with a personal significant matter or event. This domain is composed of the constructs of burn-out, fear, anxiety, affect, stress, depression, and positive/negative affect.

14. Behavioral regulation: Anything aimed at managing or changing objectively observed or measured actions. It has the following constructs: self-monitoring, breaking habit, and action planning.

The TDF has been widely used by researchers across several health care systems to explain implementation problems of EBM, to explain health care professional behavior in relation to practices that do not have specific guidelines, to explain errors in a clinical practice, to support implementation interventions, and to guide theory based process evaluation. For example, in Canada it has been used to identify barriers and facilitators to implementing evidence based recommendations on lumbar spine X-rays (Bussières et al., 2012), to guide a theory process evaluation in the Canadian Computed Tomography (CT) trial (Curran et al., 2013) and to develop a theory based knowledge translation to increase physician compliance with best hand hygiene practice (Squires et al., 2013). In the UK it has been used to identify domains relevant to transfusion practices in Intensive Care Units (ICU) and NICUs (Francis et al., 2009), to understand perspectives in making and maintaining behavioral changes in a lifestyle intervention for type 2 diabetes prevention (Penn, Dombrowski, Sniehotta, & White, 2013), and to investigate prescribing errors among trainee doctors (Duncan et al., 2012). In Ireland, it has been used to understand primary care practitioner's clinical behavior to high risk Human Papillomavirus (HPV) (McSherry, Dombrowski, Francis, Murphy, Martin, O'Leary, et al., 2012) . In Australia, examples consist of studies to evaluate theory based interventions for acute low back pain (French et al., 2012; McKenzie et al., 2008; McKenzie et al., 2010), and to investigate experiences of delivering the HPV vaccine to women aged 18-26 years (Brotherton, Leask, Jackson, McCaffery, & Trevena, 2010). The TDF was designed to be used in both qualitative and quantitative research. Therefore, the studies mentioned have used interviews, focus groups, and questionnaires guided by the TDF.

Although the TDF framework was initially designed to be used in context of practices that have clear guidelines, it has been used in studies of practices that do not have clear guidelines,

and those in which the research is evolving (McSherry, Dombrowski, Francis, Murphy, Martin, O'Leary, et al., 2012). Thus, this framework appears suitable for identifying barriers that impede the use of probiotics which, as indicated earlier, does not currently have a standard set of clinical practice guidelines, and about which research findings are still evolving.

Research Questions

This study will address the following research questions:

1) What are the current practices related to the use of probiotics in preterm infants feeds in Canada and the United States?

2) What are the most significant factors that influence the willingness of health care professionals to support the use of probiotics?

The next chapter about methods and procedures will describe the different aspects of the instruments being designed to collect information in order to answer each research question. The data analysis section of the chapter will describe in detail how the responses to each research question will be analyzed.

Chapter Four: Design and Methods

In this chapter, I discuss methods and procedures, which include the following: design elements; survey focus and sample populations; sample design; strategies used to increase response rate; and sample obtained. In addition, I present information about the sample size, and discuss the survey design and questionnaire content as well as pilot testing of the questions. Finally, I describe the data analysis and ethical considerations.

Design

A cross-sectional descriptive survey was implemented. This design was the most appropriate because the research questions in this study were directed at gather data at a specific point of time with the purpose of describing a specific situation (Fink, 2003). For example, the first research question inquiring about current practices was answered by means of a survey that was aimed at describing current practices utilizing probiotics at a specific time. The second research question exploring factors that may affect the use of probiotics was answered by another survey that collected current information about potential factors that may impede probiotic supplementation.

Survey Focus and Sample Populations

For this study, I developed two different internet surveys, both of which targeted various populations with specific inclusion criteria as described below.

Survey 1: This survey focussed on current clinical probiotic practices for premature infants, which targeted medical directors of NICUs. The inclusion criteria included medical directors of NICUs or Special Care Nurseries who can read and write either English or French (Survey 1 in Appendix C). Those respondents who indicated that their unit does not administer probiotics were directed to respond to survey 2 (version 1) (see Appendix D)

Survey 2: This survey was designed to explore factors that may affect clinical decision-making relevant to probiotic supplementation in NICUs, and has two versions which target different sample populations. Version 1 (Appendix D) aimed to sample neonatologists and nurse practitioners, while version #2 sampled nurses who provided direct or indirect care to premature infants (including staff nurses and nurses with any master's degree or specialization such as nurse educator, clinical nurse specialist, and nurse manager) (Survey 2 version 2 in Appendix E)

The inclusion criteria for survey 2 included participants who have worked in NICUs or Special Care Nurseries in the United States and Canada (either full or part-time) for the last 6 months and who can read and write either English or French. Specifically, the inclusion criteria included neonatologists, nurse practitioners and nurses who provide direct or indirect care to infants in NICUs and whose NICU was not using probiotics routinely. The survey was designed in English but was translated into French so it could be completed by health care providers (HCPs) whose language preference is French.

Sample Design, Strategies to Increase Response Rates and Sample Size Obtained

For each survey, different approaches were used to ensure a large and representative sample of HCPs in Canada and the United States. A description of each approach with the strategies to increase response rates and the sample size obtained will be described in detail below for each survey.

Survey 1

Sample design. For this survey, my strategy was to sample medical directors or the heads of NICUs. This was done by using the 2011 Directory of Newborn Intensive Care and Neonatology of the USA and Canada, which is available from the American Academic of Pediatrics. This directory includes names, mailing addresses or/and emails, and phone numbers of all NICU

medical directors across Canada and the United States. In total, this directory had information on 1008 medical directors from the United States and 38 medical directors from Canada.

Strategies to increase response rates. For survey 1 a variety of strategies were used to increase response rates. These strategies targeted factors that might have affected response rate. These factors are the following: a) notifications and reminders; b) invitation design; c) content of the web questionnaire; and d) spam filters.

Notifications and reminders. I used a 'four contact' strategy to increase the number of completed questionnaires, as suggested by Dillman, Smyth, and Christian (2009). This entailed sending a first invitation which was personalized, introduced the recipients to the survey, highlighted why their participation was important, and provided a link to the survey. In this study, the first invitation (see Appendix F) was mailed versus emailed because invitations by mail normally have better response rates (Dillman et al., 2009). The second invitation (see Appendix G) was emailed two weeks after the first invitation allowing sufficient time for the first invitation to arrive by mail. The second invitation was a copy of the first invitation in case the physicians did not receive the first invitation by mail. For those that did receive the first invitation by mail, the second invitation served as a reminder. The third communication (see Appendix H) was a postcard mailed a week after the second invitation reminding and encouraging participants to complete the survey. The postcard was only mailed to physicians who had not completed the survey. The fourth communication was a reminder emailed two weeks after the third invitation was mailed and emphasized the importance of responding and the short time remaining to complete the survey (see Appendix I). Potential participants were tracked using an access code provided in the first invitation letter.

The strategy of sending an invitation letter by mail and another by email ensured that physicians received the invitation to the survey in case the email was rejected by a spam filter. This strategy was previously verified to increase response rates among HCPs (Cho, Johnson, & VanGeest, 2013). Moreover, the postcard included a thank you note for the participant in a personalized way by using a hand written post-script of the note with the complete name of the physicians. This approach has been documented to increase response rates by 40.7% among physicians (Maheux, 1989).

Invitation design. Survey invitations to the medical directors were personalized by including their complete name and job title. This was done because personalized invitations have been shown to have a positive impact on survey response rates (Fan & Yan, 2010). Additionally, some parts of the invitation letter had a web page design (HTML) that included customized font and colors, photographs of the principal investigator, co-supervisors, and a university logo. Design, layout and visual appeal of the invitations, together with the inclusion of the logo of a trust-worthy institution, are important elements to consider in the email invitation (Sue & Ritter, 2007). Careful consideration and inclusion of these elements in an invitation letter have been shown to increase the credibility of the survey and the motivation for individuals to participate (Sue & Ritter, 2007).

Content of the web questionnaire. The content and length of a questionnaire are major factors influencing response rate (Fan & Yan, 2010). The content of survey 1 was of current topical interest in neonatology, given the controversies in the Neonatology community about the use of probiotics in premature infants. Therefore, in the invitation letter to participate in the survey, the importance of the survey topic was included. Given that the length of the survey has

a negative relationship with response rates, efforts were made to keep this survey as short as possible and with a length less than 10 minutes (Fan & Yan, 2010).

Spam filters. The invitation letters and reminders for survey 1 were at risk of being spammed (sent to the junk mail or not received) by email filters of the potential participants; therefore, some strategies were implemented to avoid this issue. For instance, certain phrases or words in the invitation letter were not included in order to avoid email filters. Some of these words and phrases were: free, opportunity, money back, incredible, now only, click here, and buy (Spencer, 2004). Furthermore, only part of the invitation letter were in HTML format, given that when a high percentage of the message has HTML format there is a high risk of being spammed by email filters (Spencer, 2004). In addition, to verify that the invitation letters were not being spammed, a spam testing feature was used in FluidSurvey™.

Sample. The final sample size obtained from the 1045 participants invited to participate in survey 1 was 197 participants, for a response rate of 18.8%. This response rate is lower than that reported in surveys in general (25%) (Braithwaite, Emery, De Lusignan, & Sutton, 2003;Cook, Heath, & Thompson, 2000a). However, this response rate falls within the range of 15%-44% response rates of surveys that targeted medical directors and neonatologists in U.S. (Feltman, Du, & Leuthner, 2012; Hagadorn, Brownell, Lussier, Parker, & Herson, 2014; Laventhal et al., 2011, Schachinger, Stansfield, Ensing, & Schumacher, 2014).

A table with the sample obtained for the survey 1 is provided below.

Table 4

Sample obtained for Survey 1

Source of Sample	# of invitations sent	# responses	Survey response rate (%)	Total response rate (%)

	Canada	*United States*	*Canada*	*United States*	*Canada*	*United States*	
2011 Directory of Neonatologist	38	1005	20	177	52.6	17.6	
Total Participants	1045		197				18.8%

Survey 2 (Version 1)

Sample design. For this survey, neonatologist were sampled by using the 2011 Directory of Newborn Intensive Care and Neonatology of the USA and Canada, which is available from the American Academic of Pediatrics. This directory lists the complete names and the city and state of affiliation with which each neonatologist is affiliated. However, it only lists some emails of neonatologists in Canada and the U.S. In total, 532 neonatologists were invited to participate in the survey. In addition, nurse practitioners across Canada who were members of the Canadian Association of Neonatal Nurses (CANN) were sampled. The CANN assisted the principal investigator by distributing invitations to 38 nurse practitioners to participate in the survey (see Appendix J). In the invitation to the survey it was expressed to CANN members that their participation was anonymous and voluntary.

Strategies to increase response rate. In this survey different strategies were also used to increase response rates. These strategies included the following: a) multiple contacts; b) invitation design; c) content of the web questionnaire; d) incentives; and e) spam filters.

Multiple contacts. In this survey, I used a three-contact strategy to increase the number of completed questionnaires from neonatologists (Dillman et al., 2009). The first invitation letter was sent by email (see Appendix K for the invitation for Neonatologists and Appendix L for Nurse Practitioners). The second follow-up letter was sent by email a week later (see Appendix M for the invitation for Neonatologist and Appendix N for Nurse Practitioners), and the third

follow up letter was sent by email a week after the second follow-up letter (see Appendix O for the invitation for Neonatologists and Appendix P for Nurse Practitioners).

Invitation design. Email invitations to neonatologists were personalized, including the name of the neonatologist and job title. In addition, part of the invitation letter had a web page design (HTML) that included the same features mentioned in survey 1. However, the email invitation sent by the CANN to nurse practitioners was not personalized and did not include a HTLM design.

Content of the web questionnaire. Since the content and length of questionnaires affect response rates, my strategies focused on these parameters. The content of the questionnaire 2 was relevant in Neonatology, given that probiotics are rarely used in U.S. and Canada and there is no research about this topic. Thus, the letter of invitation to the survey highlighted the significance of this topic and the importance of participating. The length of time to complete the questionnaire was 10 minutes as informed by the participants of the pilot testing.

Incentives. HCPs who completed survey 2 (including nurse practitioners and neonatologists) were invited to participated in raffle to win an iPad mini. This incentive was not offered to Medical Directors participating in survey 1 due to the lack of funds to buy another iPad mini. The raffle was managed by the Manitoba Center for Nursing and Health Research. A systematic review about methodologies for improving response rates in surveys of physicians reported that non-monetary incentives (e.g. stickers, pencils, other small prizes) have little or non-significant impact in response rates; however, when there is a draw of large prize there is a positive impact in the response rates (VanGeest, Johnson, & Welch, 2007). The raffle of an iPad mini was a large prize in that it is an expensive product; therefore, it was expected to have a positive impact in the response rates.

Spam filters. The invitation letters and reminders for survey 2 were drafted following the same strategies to avoid email filters mentioned in Survey 1.

Sample estimated. I estimated a response rate of 25% in the internet survey because this was congruent with the literature on response rates in internet surveys (Braithwaite et al., 2003; Cook et al., 2000a). The response rate obtained was 19.8% which was lower than expected. However, this response rate falls within the range of 15%-44% response rates of surveys that target health care professionals in U.S (Feltman et al., 2012; Hagadorn et al., 2014; Laventhal et al., 2011; Schachinger et al., 2014). A table with the sample estimate for the survey 2 (version 1) is provided below.

Table 5

Sample Obtained for Survey 2 (version 1)

Source of Sample	# of invitations sent		# responses		Response rate (%)		Total response rate (%)
	Canada	United States	Canada	United States	Canada	United States	
2011 Directory of Neonatologist	140	392	54	46	38.5	11.7	18.7
Nurse practitioners	38		13		34.2		34.2
Total Participants	570		67	46			19.8

Survey 2 (Version 2)

Sample Design. This survey targeted neonatal nurses, clinical nurse specialists, nurse educators and nurse managers across Canada. It was not possible to sample nurses from the United States given that professional associations were unwilling able to distribute an invitation to their members. The sample of Canadian neonatal nurses was drawn from the members of the

Canadian Association of Neonatal Nurses (CANN). The CANN agreed to send the invitations letters to the CANN's members (see Appendix J for a copy of the email). In addition, the principal investigator invited 18 neonatal nurses from Canada to participate who were recruited in neonatal nurse conferences (see Appendix Q).

Strategies to increase response rate. In this survey different strategies were used to increase response rates. These strategies included the following: a) multiples contacts; b) content of the web questionnaire; c) incentives; and d) spam filters.

Multiple contacts. In this survey I used the three contact strategies suggested by Dillman et al. (2009)**.** Also**,** I followed the recommendations of the strategy regarding the content of each email as described in survey 1**.** The emails were sent by the CANN (see Appendix L, N, P)

Content of the web questionnaire. The content and length of the questionnaire affects response rates as mentioned before; thus efforts were focussed on making the content interesting in the invitation letter and keeping the survey short. The letter of invitation to the survey highlighted the significance of this topic and the importance to participate. Efforts were done to keep the questionnaire as short as possible (less than 10 minutes).

Incentives. Among the health care professionals who completed survey 2 (including nurses and neonatologists), an iPad mini was raffled.

Spam filters. The invitation letters and reminders for survey 2 version 2 were drafted following the same strategies mentioned in Survey 1 in order to avoid email filters. This invitation emails sent by the CANN were not designed using HTLM format because they were sent directly from the CANN. Only the 18 invitations sent by the principal investigator to neonatal nurses who were recruited in conferences had an HTLM format.

Sample obtained. A 25% response rate was expected from the neonatal nurses, given that this is an average response rate for online surveys (Braithwaite et al., 2003; (Cook et al., 2000a). The response rate in this survey was 30% (75 out of 250). However, 19 neonatal nurses quit responding near the beginning of the survey; approximately 22.4 % of the nurses completed the survey.

A table with the sample obtained for the survey 2, version 2 is provided below.

Table 6

Sample Obtained for Survey 2, Version 2

Source of Sample	# of invitations sent	# responses	Response rate (%)	Total response rate (%)
Professional networks	232	71	30.6%	
Conferences	18	4	22%	
Total	250	75		30%

Sample Size

Given that this was primarily a descriptive survey, the sample size obtained was large enough to perform the proposed statistical analysis (i.e., descriptive analysis, chi-square and fisher's exact test). In a consultation with the statistician (Brenden Dufault, personal communication May 25, 2015), the sample obtained was suited for the statistical analyses performed.

Survey Design

This was a non-probability web survey sent to a convenience sample of physicians and nurses in Canada and U.S. (drawn from the membership list of CANN and the Directory 2011 of NICU of the USA and Canada) as described above.

A web survey was preferred as the method of delivery due to several inherent advantages. Web surveys are easily administrated and databases can be used to keep track of who has and

who has not responded. Furthermore, errors related to data entry are minimized since data was not entered manually by the investigator (Greenlaw & Brown-Welty, 2009). The cost is minimal because there are no travel, postage or telephone charges, and/or interviewer costs incurred (Shannon & Bradshaw, 2002). As well, a web survey can reach a large, geographically-scattered population in a short period of time. The period of data collection can be as minimal as one week, although more time may be required in those cases where a follow-up strategy is performed to increase the response rate (Hoonakker & Carayon, 2009; Paolo, Bonaminio, Gibson, Partridge, & Kallail, 2000). The disadvantages of web surveys are few. The response rate in web surveys can be low compared to other survey modes. The response rate of a web survey on average is approximately 11% lower than that of other survey modes (Manfreda, Bosnjak, Berzelak, Haas, & Vehovar, 2008). In addition, studies in the literature reported that email surveys incurred higher percentages of items missing than mail surveys, which results in higher survey errors (Bachmann, Elfrink, & Vazzana, 1996, Paolo et al., 2000). The survey software used for designing the questionnaire was FluidSurvey™ (FluidSurvey, Ontario, Canada), which is an online survey tool with SPSS export.

With respect to the questionnaire, there was no existing survey which evaluated factors that are associated with probiotic use among HCPs; therefore, I designed the entire questionnaire *de novo*. The questionnaire was formulated following the guidelines for crafting good questions proposed by Dillman et al. (2009). The content was guided by the TDF and informed by the aforementioned literature review (Chapter 2). Following the guidelines for designing good questions, every question was worded to ensure that it applied to health care professionals, was technically accurate, and asked one question at a time. Moreover, the questionnaire was phrased using the following principles: use of simple and familiar words; use of specific and concrete

words to specify the concepts clearly; use of as few words as possible to pose the question; use of complete sentences with simple sentence structures; and use of questions that specify the response task.

Questionnaire Design and Content

Survey 1 and the two versions of survey 2 included demographic questions such as the participant's sex, age, profession, location of current work, type of nursery and hospital, and years of experience working in nurseries. This information was needed to describe general characteristics of the HCPs answering the survey and their work place.

Survey 1 (which targets neonatologists who are directors or department heads of NICUs) addressed questions related to current practices, including the following: gestational age, weight or special medical conditions of premature infants for whom probiotics are prescribed, the name of the probiotic product(s), probiotic dosages, method of administration, medical conditions in which probiotics are contraindicated, when they are discontinued, and duration for which this clinical practice is implemented in the NICU. In addition, several questions using Likert scales were included in this survey. One set of questions related to factors which may influence the initiation of administering probiotics. The second set of questions was about possible barriers that were perceived to interfere with the use of probiotics in other NICUs (see survey 1 in Appendix C)

Survey 2 was about factors affecting the use of probiotics for premature infants. This survey was designed to answer the research questions regarding factors that influence the HCPs' use (or lack of use) of probiotics. In survey 2, nurse and physician questionnaires are slightly different in regards to the wording of some questions. For example, in the physician questionnaire, some statements mention "prescribing probiotics" but in the nurse questionnaire, the same statement

was worded differently by mentioning “administering probiotics” rather than prescribing. Given that nurse practitioners prescribe, this group of professionals answered the survey designed for physicians. Both physicians and nurse surveys had the same topics and item numbers (see survey 1 for physicians in Appendix C and for nurses in Appendix E).

The development of survey 2 was guided by the TDF. A set of questions were developed to address each of the domains. Details of how those questions were formulated are explained further. Also, the literature review on probiotics and possible factors affecting implementation of probiotics informed each domain of the TDF. The wording of some statements in survey 2 were guided and adapted from eliciting questions proposed by the consensus group of the TDF (Michie, 2005) and questionnaires found in the literature review that were guided by the TDF. One of these questionnaires was used to investigate practitioner experience related to HPV vaccination (Brotherton et al., 2010), while the other questionnaire assessed difficulties in tobacco use prevention (Amemori, Michie, Korhonen, Murtomaa, & Kinnunen, 2011). These two questionnaires assessed topics of interest using statements with a five point Likert scale ranging from strongly disagree to strongly agree. Therefore, survey 2 in this study used a questionnaire format that incorporated a Likert scale. This questionnaire format also facilitated the implementation of the survey because the time used to answer it was shorter than longer questionnaires with different variations of scale types. In this type of questionnaire using a Likert scale, several statements were made and appeared on the left side of one page screen; answers formatted in the Likert scale were displayed on the right side of the screen. Thus, the person answering the survey did not need to go through several page screens to answer all of the questions. Another format of questionnaire for this study consisted of true and false statements,

which evaluated knowledge about probiotics. This format has previously been validated by the TDF for knowledge evaluation (Brotherton et al., 2010).

The questionnaire for survey 2 encompassed the following twelve domains from the TDF: knowledge; skills; professional role and identity; beliefs about capabilities; beliefs about consequences; optimism; intention; goal; memory, attention and decision process; environmental context and resources; social influences; and emotions. The reinforcement and behavioral regulation domains of the TDF were excluded because these are only applicable in units that have a guideline/policy in the hospital.

The rationale for the statements designed under each domain of the TDF are as follows:

Knowledge

Knowledge about probiotics was evaluated with true and false questions. A question assessing knowledge about a specific health practice or issue of interest along with the other TDF domains is crucial as it has been identified as an important influence on professional health behaviors (Cane et al., 2012a). The questionnaire about knowledge had seven statements which is consistent with other research supported by the TDF (Brotherton et al., 2010). Statements were designed to test knowledge about the definition of probiotics and its properties, sources of probiotics, and common probiotic strains. In addition, knowledge about general awareness on the evidence and probiotics products for premature infants were tested.

Skills

Under this domain, statements tested the ability to prescribe (in the questionnaire for physicians) or administer probiotics (in the questionnaire for nurses). Given the fact that skills are associated with ability acquired through practice, the survey inquired about experience regarding prescription (physicians) or administration (nurses) of probiotics.

Social/professional role and identity

This domain tested whether or not the prescribing or administration of probiotics was in conflict with the professional standards and identity of HCPs. This domain also tested whether or not the lack of current clinical practice guidelines disfavored probiotic supplementation and whether or not HCPs colleagues' professional standards influenced the decision-making process.

Beliefs about capabilities

This domain evaluated HCP's acceptance of the truth about the ability of prescribing or administering probiotics. Therefore, perception of self-competence regarding administration and prescription of probiotics were tested. Taking into account that probiotics supplementation is not a standardized practice widely implemented at the NICUs in U.S. and Canada, it might be possible that HCPs do not feel confident in their abilities regarding the implementation of probiotics.

Optimism

This domain evaluated the confidence that HCPs have about achieving the best outcomes regarding probiotic supplementation for premature infants. Pessimism about this practice was evaluated. It is possible that being optimistic or pessimistic about probiotics supplementation for premature infants might influence the decision regarding implementing this practice.

Beliefs about consequences

The acceptance of the validity of outcomes or concerns regarding the use of probiotics for premature infants was tested under this domain. HCPs' beliefs about the negative consequences of implementing this practice might be affected by the awareness of the literature on cases of *Lactobacillus* bacteremia in infants with short gut syndrome or other disadvantageous medical conditions (De Groote et al., 2005; Kunz, Noel,& Fairchok,2004; Land et al., 2005). Bacteremia

was reported in an extremely low birth weight infant (Jenke et al., 2011). Therefore, a statement about the safety of probiotics was elaborated under this domain.

Intention

This domain was evaluated by determining if health care professionals have made a conscious decision regarding the use of probiotics for premature infants. One of the constructs of this domain is the Trans-theoretical Model and stages of change (Cane et al., 2012a). It was evaluated by asking if the HCPs are looking into the evidence of probiotic supplementation for premature infants and if they are contemplating the possibility of using probiotics (contemplation and preparation). The other stages in this model, such as action and maintenance, were not evaluated because they were evaluated in the goal domain.

Goal

This domain evaluated the mental representation of achieving the implementation of the use of probiotics in the participant's work place. Thus, the physician's willingness to prescribe probiotics in the future was evaluated. Nurses were evaluated for their willingness to recommend the implementation of this practice to doctors. This domain helped to identify if health care professionals are willing to support the use of probiotics in preterm infants.

Memory, attention, and decision process

Only the decision making process was evaluated under this domain because memory and attention are related to practices which already have a guideline in the hospital. As mentioned in the literature review, the decision-making process about implementing probiotics has multiple barriers and many hospitals do not have a guideline. Therefore, statements that evaluated these situations were included.

Environmental context and resources

This domain evaluated some characteristics of the HCPs or their environment which either discourage or encourage the implementation of probiotics for premature infants. A statement regarding concerns about the quality of available products was under this domain. This statement is supported by studies which indicate that commercial probiotic products may not contain the components listed on product labels (Drago, Rodighiero, Celeste, Rovetto, & De Vecchi, 2010). Also, physicians have questioned the quality of probiotics products available for premature infants (Garland, Jacobs, Tobin, 2010). Institutional barriers for probiotics supplementation was tested under this domain, as it has been suggested that HCPs face institutional barriers for implementing probiotics. In addition, other barriers such as lack of time were evaluated because these may constitute barriers for implementing a practice (Amemori, Korhonen, Kinnunen, Michie, & Murtomaa, 2011, (McSherry, Dombrowski, Francis, Murphy, Martin, O'Leary, et al., 2012). Moreover, medical concerns regarding the non-approval of probiotics as drugs as a constraint to use them have been found in the literature (Michael Millar et al., 2012). Consequently, a statement regarding this issue was added to the second survey. In addition, issues such as lack of access to the evidence and the opportunities available to learn about probiotics were evaluated because these problems have also been documented as barriers to implement Evidence Base Practice (Martis et al., 2008).

Social influences

This domain evaluated interpersonal processes which can cause changes of thoughts and behaviors of the HCP regarding the use of probiotics for premature infants. Taking into account that there is a polemic regarding probiotic supplementation for premature infants with divided opinions about this practice (Neu, 2014, Ofek Shlomai et al., 2014). It is important to know if

HCPs are being influenced by the opinions and positions of others regarding this practice .Statements which evaluated the outcomes of discussions about this practice with other professionals and which supported the use of probiotics by the health care team and by administrators were added under this domain. In addition, parents might influence the implementation of probiotics. In RCTs on probiotic supplementation for preterm infants, some parents refused the participation of their preterm infants in the study (Rouge C, Piloquet H, Butel M, Rochat F, & Ferraris L, 2009; Sari et al., 2011). In contrast, Barrington (2013) suggested that some parents requested probiotic supplementation for their premature infants. Hence, a statement about parental influence was added under this domain. Moreover, because of the fact that the implementation of a practice might be influenced by others implementing it, a statement regarding possible influences due to awareness of this practice in other NICUs was included.

Emotions

This domain evaluated the reaction patterns that the implementation of probiotics might evoke in HCPs. As mentioned above, there have been bacteremia cases associated with the use of probiotics; thus, statements regarding fear about causing harm with probiotics were added under this domain.

Questionnaire Testing

Questionnaire testing is an important aspect of quality assurance of this instrument. Thus, two testing stages were implemented: the developmental stage and the question testing stage (De Leeuw et al., 2008).

The developmental stage of this survey required an extensive literature review about probiotics and factors that affect implementation in premature infants. In this stage, the full draft of survey 1, survey 2 (version 1) and survey 2 (version 2) were reviewed. Some questions were

re-worded by the principal investigator and her supervisors. In addition, an experienced neonatologist reviewed the questionnaire content regarding current practices (survey 1) and improved the questions that asked about formulations of probiotics. After those revisions, the three surveys were evaluated by a panel of experts to establish content validity. The panel of experts was composed of five health care professionals (NICU medical director, neonatal nurse, nurse practitioner, a clinical nurse specialist in the NICU, and a clinical educator in the NICU).

The content validity performed by the panel of experts was done using the process as outlined by Waltz, Strickland, and Lenz (2010), which uses the Content Validity Index (CVI) to quantify the extent of agreement between experts. The experts rated each question according to its relevance for answering the research questions, on a 4 point rating scale (1 = not relevant, 2=somewhat relevant, 3= quite relevant, 4 = very relevant). CVI is defined as the proportion of items given a rating of quite/very relevant. A CVI score of 0.80 or better is considered a good content validity item (Polit & Beck, 2012). Most of the questions scored a CVI of more than 0.80. Approximately 6 questions scored a CVI from 0.7 to 0.8. The principal investigator and supervisors closely reviewed those questions and it was decided to remove one question from the questionnaire (in the social influences domain) and to reword the other 5 questions. After the developmental stage, the question testing stage was performed.

The question testing stage (pilot testing) was performed to determine whether questions met all the principles of a good questionnaire, as well as whether the questionnaire flowed as a whole, as suggested by De Leeuw et al. (2008). This stage was done with a sample size of 12 participants, which is similar to recommendations by Fowler (1995). This stage had two phases. In the first phase, 7 Health Care Professionals received a printed copy of the questionnaires (3 neonatologists, 1 medical director, 1 neonatal nurse practitioner, 1 clinical nurse specialist in the

NICU, 1 nurse educator in the neonatal and maternal services). In addition, a nurse and undergraduate student whose first language is French reviewed the French version of the questionnaires. The participants of the question testing stage were asked the following: how long did it take you to complete the questionnaire, are the instructions clear, and how was the overall flow of the questionnaire? It took the participants approximately 8-10 minutes to complete the questionnaire. The instructions and overall flow of the questionnaire were evaluated positively for survey 2. Survey 1 received some suggestions to improve the flow of the questions regarding formulations of probiotics. Thus, the questions regarding formulations were simplified to better capture the formulation of probiotics. Also, those questions were reviewed and improved by a neonatologist to be sure that the questions were clear and well stated.

For survey 2, the subheadings were reworded because several participants pointed out that some headings were not appropriate and were distracting (optimism changed to opinion, beliefs about consequences and beliefs about capabilities changed to beliefs, emotions to feelings). Then, the questionnaires were set up in FluidSurvey™ software to be available online for the participants. Once the questionnaires were in the software, a spam test was performed.

In the second phase of the question testing stage, the online survey was pilot tested by 5 people (3 graduate nursing students, 1 kinesiology professor, and 1 nursing professor). They reviewed that the online questionnaire had correct spelling, clear directions and that the branching and skips of the questionnaire worked. After the developmental and question testing stages were performed, a final version for each survey was created. See surveys in Appendix C (survey 1), D (survey 2, version 1), and E (survey 2, version 2).

Data analysis

The data obtained through the online survey by software FluidSurvey™ was exported in an SPSS file and analyzed using SPSS Grad pack 23.0 for MAC. In addition, support in survey set up and SPSS analysis were received from James Plohman, a research coordinator of the Manitoba Center for Nursing and Health Research (MCNHR). Also, consulting services regarding the data analysis performed were received from Brenden Dufault, a statistician from the University of Manitoba, MCNHR. The next section describes the data analyses conducted.

The number of participants obtained for each survey was described above. Descriptive statistics (i.e. percentages, ranges, frequencies, and means) were used to summarize the demographic characteristics of participants for each survey. The first research question (What are the current practices related to the use of probiotics in preterm infant feeds in Canada and in the United States?) was answered utilizing data collected from survey 1. In survey 1, the medical directors that answered "Yes" about giving probiotics were asked questions related to current practices. A descriptive analysis (i.e., frequencies and percentages) of current practices (product use, dosages, contraindications, when is discontinued, time of use in the NICU), factors that influenced the implementation of this practice and possible barriers for probiotic supplementation in other NICUs in U.S. and Canada were evaluated. Medical directors who answered "No" about giving probiotics in survey 1 were re-directed to answer survey 2 (version 1) questions about factors affecting the implementation of probiotics.

Research question number two (What are the most significant factors that influence the willingness of health care professionals to support the use of probiotics?) was answered utilizing data collected from the two versions of survey 2. The results of each version of survey 2 were analyzed separately due to possible differences between physicians and nurses. In survey 2, the

domain goal was the outcome variable used to evaluate the willingness to support the use of probiotics (i.e., probiotics should be routinely administered to premature infants who meet selected criteria). The other statements that belonged to the 11 domains of the TDF (knowledge, skills, professional role and identity, beliefs about capabilities, beliefs about consequences, optimism, intention, decision making process, environmental context and resources, social influences, and emotions) were the independent variables. Descriptive analyses (frequencies and percentages) were performed for each statement that represented the outcome and independent variables.

In order to answer the second research question and identify what are the most influential factors that influence the willingness of health care professionals to support the use of probiotics, the following statistical analyses were performed:

- Chi-square test of independence was performed to identify relationships between two categorical variables (Polit & Beck, 2012); the independent variable and the outcome variable in a crosstabulated contingence table. To perform both tests, it was necessary to regroup the responses (from both independent and dependent variables) from the Likert scale into 3 groups (strongly disagree and disagree formed a group, uncertain/unsure was one group, and strongly agree and agree were the other group). In those cases were the sample size is small (more than 20% of the contingence cells having a value< 5), the fisher exact test was performed. Fisher exact test is a non-parametric test to measures associations between two categorical variables (Vogt, 2005). Although Fisher exact test is mostly used in 2x2 tables the principles of the test are applicable for greater than two rows and columns (Warner, 2013). Statistical significance was determined when the results of the test had a P-value < 0.05. Those results that were statically significant

revealed what were the most influential factors that influence the willingness of health care professionals to support the use of probiotics.

- One-way ANOVA was used to test for differences in the mean knowledge scores among the three groups representing the outcome variable. Post hoc tests (Tukey HSD and Bonferroni) were used to identify which mean scores were statistically different. This post hoc test only was performed when the one-way ANOVA reported statistical significance ($p < 0.05$). Another test used to assess for mean differences among the three groups was the Kruskall Wallis non-parametric test.

In summary, the descriptive statistics performed for each question that represented domains of the TDF permitted a general depiction of the factors that possibly affect the use of probiotics. However, the inferential analyses, which included chi-square, fisher's exact test and one way ANOVA, helped to answer the second research question by identifying "What are the most significant factors that influence the willingness of health care professionals to support the use of probiotics?"

Ethical considerations

Ethical approval for this study was obtained from Education/Nursing Research Ethics Boards (ENREB) at the University of Manitoba. This study followed the ethical guidelines provided by the Tri-council Policy Statement on ethical conduct for research involving humans (TCPS), which points out that studies should be guided by three core principles: respect for the person, concern for welfare, and justice under any circumstances (Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, & Social Sciences and Humanities Research Council of Canada, 2010). Hence, during the recruitment process, every participant who met the study's inclusion criteria was given the opportunity to participate

regardless of characteristics such as age, culture and ethnicity. The recruitment procedure was carried out by a letter of invitation via email and mail which had a clear and respectful language. In the invitation letter, participants were informed how their email address was obtained.

The data collection procedures (collecting the data, entering the data and storing the data in the computer) and the dissemination of the results were conducted in a manner which maintained confidentiality and privacy, and responses from the survey were kept anonymous. Anonymity was achieved by not asking the participants their identity in the internet survey and by having security codes for entering and accessing data in the computer in which the information was stored. The software (FluidSurvey™) used for this online survey did not record any personal information. Personal information for the raffle of an iPad was collected by a third party (MCNHR). In addition, demographic questions were worded to protect identity of respondents. For example, instead of asking participants their state or province and city of location, participants selected from a region (e.g., Midwest, South, etc.) and instead of asking participants to enter their age, participants selected the appropriate age range (e.g., 25-34, 35-44, etc.). Also, the data will be deleted from the hard drive of the computer that was used for data storage. There were minimal risk associated with this internet survey, as it did not contain questions which could reasonable be construed to cause embarrassment, disturbance, or other psychological effects. It might; however, have caused discomfort as a result of the interruption of daily routines when answering the questionnaire (Westra, Wit, Sukhai, & de Beaufort, 2011). Furthermore, authorization for performing this research was requested from the investigator's thesis committee and the Research Ethics Board at the University of Manitoba. Given that this study was an online survey, it did not require a signed consent form, but participants were informed that their submission of a completed survey would be taken as evidence of their

consent to participate. The letter of invitation to participate in the survey included all the components of a consent form. The components of the consent followed the recommendations by Singer (2008). Thus, the letter of invitation included the research purpose(s), possible benefits, uses of the information collected from the participants, and promises of protection of confidentiality of the information were explained in an attached form. Finally, the voluntary nature of participation and procedures, which allowed the freedom to withdraw from the study at any time, were articulated.

Chapter Five: Results

This chapter presents the results obtained in this study. I will describe the results from survey 1 that targets medical directors, followed by the results of survey 2 (version 1) that targets neonatologists and nurse practitioners and survey 2 (version 2) that targets nurses. At the end of the chapter, a summary is presented.

Survey 1: Medical Directors

This section about the results of survey 1 presents an overview of the response rates by providing details of the responses generated using different communication approaches with the participants. Also, the demographic characteristics of the participants in survey 1 are presented. In this survey we sought to obtain information regarding current practices related to the use of probiotics in NICUs. Medical Directors who were prescribing probiotics were asked questions regarding the current practices (e.g. product, dosages and indications) and also questions regarding factors that affected the implementation of the use of probiotics and barriers they believe affect the implementation of probiotics in other NICUs. This survey also presented information regarding factors that are affecting the implementation of probiotics.

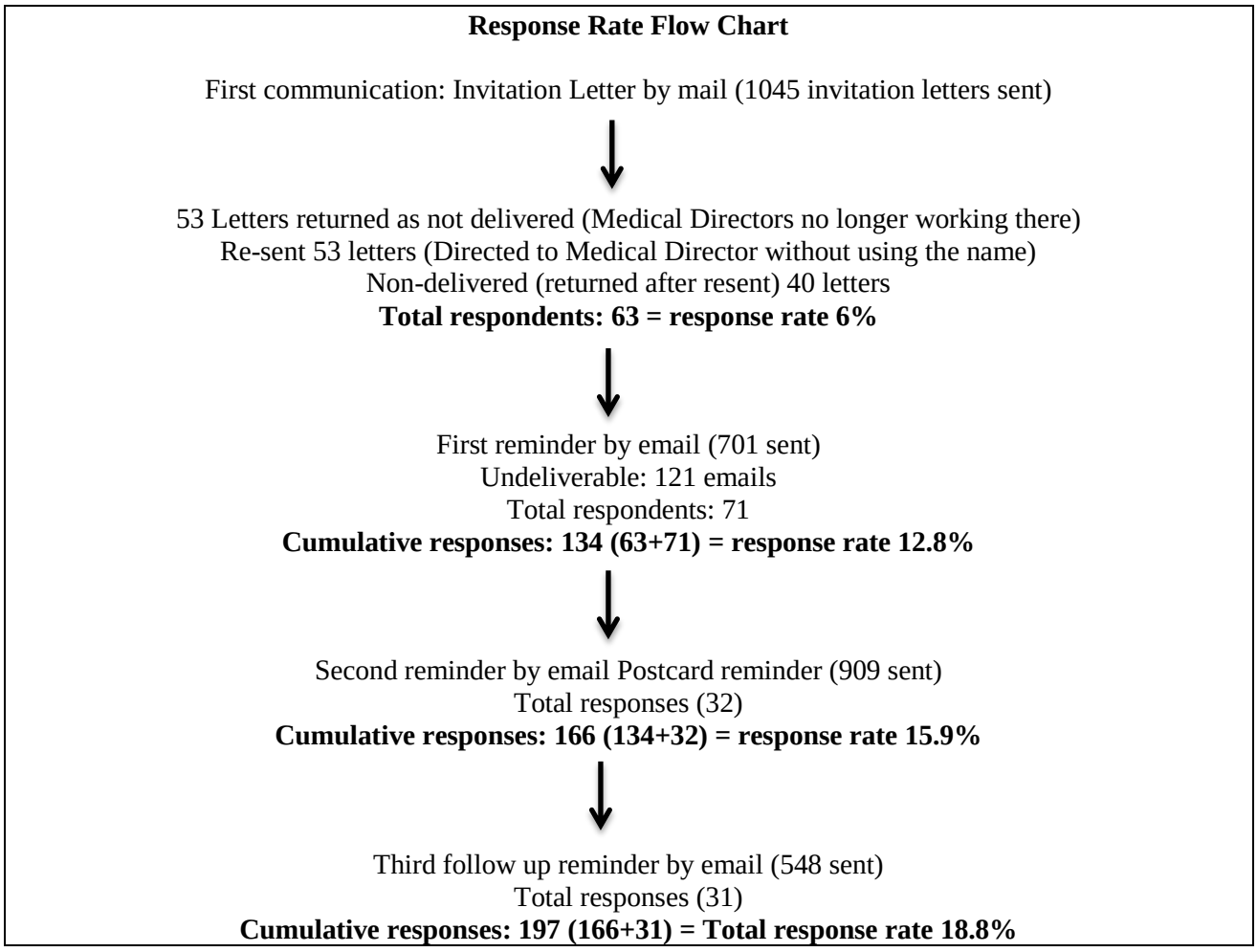
Overview of Responses Rates. Survey 1 had a response rate of 18.8% (197 participants out of 1045 Medical Directors contacted), of whom 10.2% (n=20) were from Canada and 89.8% (n=177) were from the U.S. The response rate among Medical Directors of NICUs in Canada was 52% (20 participants out of 38) and in the U.S. was 17.6% (177 participants out of 1007).

Figure 1 presents a flow chart of the response rates. A four contact strategy (Dillman et al., 2009) was used to maximize response rates in this study. Communications with the participants were as follows:

1) An initial invitation was mailed on December 26, 2014 to 1007 Medical directors in the U.S. and the same invitation was mailed on January 8, 2015 to 38 Medical directors in Canada. The invitation was personalized, printed on university letterhead, and included photographs of the principal investigator, supervisors and committee members (See Appendix F).
2) A first reminder was emailed to 701 NICU Medical Directors on January 19, 2015. It was not possible to send a reminder to all the Medical Directors because their email was not always available in the 2011 Directory of Newborn Intensive Care and Neonatology of the U.S. and Canada. This invitation was personalized, had university logo and photographs of the principal investigator and committee (see Appendix G).
3) A second follow up reminder in the form of a postcard was mailed on January 26, 2015 to participants who did not respond to the previous two invitations. The postcard had an infant picture (royalty rights for the picture were purchased) on the front along with the study title. The back of the postcard had the written name of the participants, a reminder note, and a hand written note that said "Thank you in advance for your participation". Also, the back of the postcard included a photograph of the principal investigator (See Appendix H).
4) A final follow up reminder was emailed on March 3, 2015 to the target population. This reminder was not included in my original proposal and was sent after getting ethical approval for an amendment. It was decided to add a fourth communication in order to increase response rate (See Appendix I).

Figure 1

Response Rate Flow Chart Survey 1



Demographic Characteristics for Survey 1. The demographic characteristics of the participants for survey 1 are presented in Table 7. There were 197 participants in this study. Most (*n*=131 [78%]) of the participants were male. The most prevalent age range was 55-64 years (*n*= 80 [48.8%]), followed by 45-54 years (*n*= 40 [24%]). In Canada, the participants were distributed across Western, Eastern and Central regions. U.S. participants were mostly located in the Midwest (n= 47 [30.5%]) and South (*n*=42 [27.3%]). Most participants worked in tertiary referral centers (*n*=76 [38.6%] and

regional hospitals (*n*= 35 [17.8%]). The majority of the participants had worked in NICUs for more than 20 years (*n*=124 [73.4%]).

Table 7

Demographics Characteristics of Participants

Characteristic (n)	*n (%)*
Sex (168)	
Female	37 (22.0)
Male	131 (78.0)
Age range (167)	
25-34 years	2 (1.2)
34-44 years	14 (8.4)
45-54 years	40 (24.0)
55-64 years	81 (48.5)
Greater than 64 years	30 (18.0)
Location	
Canada (14)	
Western	5 (35.7)
Central	4 (28.6)
Eastern	5 (35.7)
U.S. (154)	
Midwest	47 (30.5)
Northeast	32 (20.8)
South	42 (27.3)
West	33 (21.4)
Current Position in the NICU (166)	
Medical Director	151 (91.0)
Other leadership positions	15 (9.0)
Type of Hospital (169)	
Community Hospital	51 (30.2)
Regional Hospital	35 (20.7)
Tertiary referral center	76 (45.0)
Military hospital	3 (1.8)
Others	4 (2.4)
Time Working at the NICU (169)	
≥ 5 years but ≤10 years	5 (3.0)
>10 years but ≤ 20 years	40 (23.7)
> 20 years	124 (73.4)

Current Practices

An overview of responses from Survey 1, related to current practices of probiotics in Canada and the U.S. are shown in Table 8. This survey is answering the research question, "What are the current practices related to the use of probiotics in Canada and the United States?" Survey 1 reported that from the 197 Medical Directors of NICUs surveyed, 47 (23.9%) NICUs prescribe probiotics for premature infants. However, only 41 Medical Directors shared their probiotic protocol. The results showed that from the total of participants in Canada, 8 (40%) prescribed probiotics whereas from the total of the participants in the U.S., 39 (22%) prescribed probiotics.

Details of the probiotic formulation administered (product, country, doses, indication and time of practice) are presented in Table 8. The probiotic products that are given the most in U.S are Culturelle, and VSL #3 and in Canada is FloraBaby. Regarding time of use of the product in the NICU, the longest time of use was 10 years and the shortest time of use was < 1 month.
The participants did not report that the NICUs are prescribe more than one probiotic product.

Table 8

Current Practices of Probiotics Formulations for Premature Infants

Country	Product	Indication	Doses	Length of use
U.S.	ABC Acidhophilus[1]	<1500 grams	0.5 teaspoon (2.5 ml)	6 months
U.S.	ABC Acidhophilus	Infants <35 weeks or SGA	1.5 gm/day	15 months
U.S.	ABC Acidhophilus	for patients with prolonged antibiotic courses, not routine use	Determined by dietetics, half a scoop is what I recall	I do not know
U.S	Align (Bifidobacterium)	<32 weeks at birth	2 mg per day	5 years
U.S.	Bifidobacterium,lactobacillus	Based on weight and use it in all infants < 36 weeks	capsules in 125,250 and 375 mg	3 years
U.S	Biogaia Drops	<34 0/7 weeks, <=1500g	0.2ml	<1 month
U.S	Biogaia Drops	Exposure to antibiotics.	5 drops.	5 years
U.S.	Biogaia Drops	Less than 32 weeks	5 drops daily	3 years
U.S	Biogaia Drops	< 34 weeks	0.2 ml daily	6 years
Canada	Biogaia® Drops[2]	Case by case basis at present	5 drops per day	1 year
U.S	Culturelle[3]	< 34 weeks or at risk for NEC	0.5 capsule daily	5 years
U.S.	Culturelle	1000 < bwgt < 1500	Mix one capsule with 2 ml sterile water. Give 1 ml of this mixture, once daily, PO or OG.	2 years
U.S.	Culturelle[4]	<34 weeks	Half capsule	5 years
U.S.	Culturelle	at risk for NEC	0.5 capsule daily	7 years
U.S.	Culturelle	Antibiotic therapy	1 packet/day	10 years
U.S	Culturelle	Varies: antibiotic induced diarrhea, malabsorption, not routinely prescribed	1/2 capsule b.i.d	I do not know
U.S	DBS	<1500gr	1 capsule/day	5 years
U.S.	Flora Q2[5]	< 1500 grams	1/8 capsule mixed with feeding	7 years
U.S.	Flora Q2	< 1500 grams	1/8 capsule	7 years
U.S	Flora Tummys[6]	< 32 weeks,< 1500 gr	1/2 Packet daily	5 months
Canada	FloraBaby Powder	<32 weeks at birth	0.5 g or half scoop daily	18 months
Canada	FloraBaby Powder	< 1500 grams; major gut anomolies (gastroschsis, and post op major bowel re-section)	0.5 grams once daily	1 year

Canada	FloraBaby Powder[7]	<33 weeks gestation at birth	0.5 grams powder in 1-2 ml sterile water	4 months
Canada	FloraBaby Powder	<32 weeks	0.5 g daily	1 year
U.S	FloraBaby Powder	< 34 weeks, < 1500 gr	Half a scoop daily	6 months
Canada	FloraBaby Powder	< 33 weeks or < 1500gr	0.5 g daily	1 year
U.S	Gerber Soothe Drops	<33 weeks, < 1500 g	0.2 ml once daily	4 months
U.S.	Gerber Soothe Drops (new Biogaia)	<= 35 weeks or on antibiotics	<= 1500g: 3 drops; >1500g: 5 drops	5 years
U.S	Jarro-Dophilis Original	<1500 gr	1 capsule - 3.4 billion CFU	4 months
U.S	Jarro-Dophilus Original	<1800 gr	1 capsule	7 months
U.S.	Lactobacillus	< 1000 gr	1/2 cap b.i.d	4 years
U.S.	Risaquad	All admitted NICU patients receiving any enteral feeds	One half capsule per day with feeding	6 months
U.S	Risaquad	<34 weeks, <1500g	1/8 capsule daily	1 year
U.S	Risaquad[8]	All patients admitted to the NICU	1/2 package	6 months
U.S.	Udo's choice[9]	<1350gr or <30 weeks	1 gram daily	3 years
U.S	VSL#3[10] (Sigma-Tau Pharmaceuticals)	All infants	0.5 mL (1.5 billion CFUs)	3-5 years
U.S.	VSL#3	< 34 weeks, <1800 grams	1/4 capsule	6 years
U.S	VSL#3[11]	<34 weeks	1/2 capsule	2 years
U.S	VSL#3	<1500 gr or less than 32 weeks	1/2 capsule (powder) daily	2 yrs ago
U.S.	VSL#3	less than 32 weeks	1/4 capsule	6 months
U.S.	VSL#3[11]	<34 weeks	1/2 capsule	3 years

1. This was the formulation we were using prior to the recall; as of this time, we are pursuing other options
2. We have to use this product because our infection control practitioner would not allow the use of powder formulation
3. Recently increased doses from 0.5 capsule MWF to 0.5 capsule daily. In previous unit used 3d 0.5 capsule b.i.d
4. This is available from hospital distributors, we are working to bring in FloraBaby®
5. We have used this product for 7 years with thousands of patient days. Our NEC rate is very low
6. Individuals packets. Less chance of contamination
7. N0 formulary at present. Application for formulary in process. Informed consent documented. Standard information sheet in development
8. We have chosen because it was already on formulary at the hospital
9. Mixed in 1st feed of the day- minimum 3ml
10. Pharmacy mixes; nurses does 0.5 via sterile syringe
11. Contains 8 species of probiotics

Other details about the formulation (means of administration, contraindications, and discontinuity of administration) are shown in Table 9. Over half of the participants (n = 24 [51.1%]) whose NICU uses probiotics reported that probiotics are mixed with ordered feeding and given during regular feeding, while 7 (14.9%) reported that probiotics are mixed with water during regular feeds. In NICUs where probiotics are prescribed, 22 (47.8%) of the participants responded that probiotics are not given when there are symptoms of suspected or definitive Necrotizing Enterecolitis. Several participants (n= 18 [38.3%]) mentioned that there are not specific contraindications for administering probiotics. Less than half of the participants (n=18 [38.3%]) reported that probiotics were discontinued when the infant is discharged at home or transferred to another facility. Several participants (n= 11 [18%]) reported that probiotics are discontinued when the infants reaches a gestational age of 36 weeks.

Table 9

Formulation Details

Characteristic	*n* (%)
Administration (42)	
Probiotics are mixed with the ordered feeding and given during regular feeding	24 (51.1)
Probiotics are mixed with the ordered feeding and given separate from regular feeding	3 (6.4)
Probiotics are mixed with water and given during regular feeds	7 (14.9)
Probiotics are mixed with water and given separate from regular feeds	3 (6.4)
Other, please specify[1,2,3]	3 (6.4)
I do not know	2 (4.3)
Contraindications (42)	
There is not specified contraindications	18 (38.3)
Infant with surgically-transected gut/short gut	7 (14.9)
Infant receiving inotropic support (Dopamine, Dobutamine, Epinephrine)	11 (23.4)
Infants on continue gastric suctioning	14 (29.8)
Extremely low birth weight infants	1 (2.1)
Active gastric lesion and/or gastrointestinal bleeding	12 (25.5)
Symptoms of suspected or definitive NEC	22 (46.8)
I do not know	0 (0.0)
Others	
Cardiovascular instability	1 (2.1)
NPO	6 (12.7)
feeds held for any reason	1 (2.1)
Immunocompromised infants such as neutropenic	1 (2.1)
Infant with gastrointestinal malformation,	1 (2.1)
Low absolute neutrophil count	2 (4.2)
Suspended when infant is NPO and started whenever an infant is tolerating at	1 (2.1)
Sepsis	1 (2.1)
Only used in infants that are feeding	1 (2.1)
Discontinuation of probiotics (42)	
When the infant is discharged home or transferred to another facility	18 (38.3)
When the infants reaches a particular gestational age. Specify _____ age	
36 weeks	11 (23.4)
35 weeks	3 (6.38)
34 weeks	6 (12.7)
When infants reaches a particular weight. Specify _____ weight	0 (0.0)
I do not know	1 (2.1)
Other:	
3 months of age is recommended, although the parents may discontinue when they	1 (2.1)
6 weeks of rx	1 (2.1)
Most will continue the probiotic after discharge	1 (2.1)

No specific end point	1 (2.1)
No specified in our guideline, however, majority stop it at 34-term corrected GA or two weeks old, whichever comes last	1 (2.1)
Two weeks after discharge	1 (2.1)
When no longer tube fed	1 (2.1)
When we think the bowel is adequate colonized	1 (2.1)

* Some participants selected two items in this question.
1. 1/8 capsule mixed with feeding,
2. Mixed into 1st feed of the day- minimum 3 ml.
3. Pharmacy mixes; a nurse does 0.5 ml via sterile Syringe.

Medical Directors were asked to what extent a variety of factors (organized according to the TDF: knowledge, skills, professional, role and identity, optimism, beliefs about consequences, intention, decision making process, feelings, environmental process and resources, and social context) have influenced their unit to start administering probiotics (Table 10). Important aspects or situations evaluated in each TDF domain that influenced implementation of probiotics to "a great extent" were the following:

- Looking into the evidence related to use of probiotics for premature infants (n=34 [87.2%]).
- Confidence about the benefit of probiotics for premature infants (n=32 [82.1%]).
- Knowledge about the evidence related to the use of probiotics for premature infants (n=32 [80%]).
- Belief that there is sufficient evidence about the benefits of probiotics for premature infants (n=28 [71.8%]).
- The health care team believes that administering probiotics to premature infants is a safe practice (n=27 [69.2%])

Table 10

Responses of Medical Directors regarding the Extent to which Various Factors Influenced their Neonatal Intensive Care Unit to start Prescribing Probiotics

Domains (n)	No extent n (%)	Little extent n (%)	Some extent n (%)	Great extent n (%)
Knowledge				
Participation in educational activities related to probiotic supplementation in premature infants (40)	6 (15.0)	6 (15.0)	15 (37.5)	13 (32.5)
Knowledge about a safe probiotic product to be used for premature infants (40)	1 (2.5)	7 (17.5)	14 (35.0)	18 (45.0)
Knowledge about the evidence related to use of probiotics for premature infants (39)	0 (0.0)	1 (2.5)	7 (17.5)	32 (80.0)
Skills				
Familiarity about how to prescribe probiotics (40)	1 (2.5)	8 (20.0)	24 (60.0)	7 (17.5)
Past experience with prescribing probiotics to premature infants in the NICU (39)	23 (59.0)	8 (25.0)	5 (12.8)	3 (7.7)
Professional Role and Identity				
Most of my colleagues believe that the evidence to support the use of probiotics is strong (40)	1 (2.5)	2 (5.0)	15 (37.5)	22 (55.0)
Optimism				
There is sufficient evidence about the benefits of probiotics for the premature infant (39)	1 (2.6)	3 (7.7)	7 (17.9)	28 (71.8)
Beliefs about consequences				
The health care team believes that administering probiotics to premature infants is a safe practice (39)	0 (0.0)	1 (2.6)	11 (28.2)	27 (69.2)
The lack of adverse events related to probiotic supplementation in premature infants (39)	1 (2.6)	2 (5.1)	15 (38.5)	21 (53.8)
Intention				

We looked into the evidence related to use of probiotics for premature infants (39)	0 (0.0)	0 (0.0)	5 (12.8)	34 (87.2)
Decision making process				
The health care team helped with the decision making process (39)	1 (2.6)	0 (0.0)	12 (30.8)	26 (66.7)
Feelings				
I am confident about the benefit of probiotics for premature infants (39)	0 (0.0)	3 (7.7)	4 (10.3)	32 (82.1)
Environmental context and resources				
Pharmacy supported the use of probiotics for premature infants (37)	2 (5.4)	5 (13.5)	13 (35.1)	17 (45.9)
Therapeutics committee supported the use of probiotics for premature infants (37)	10 (27.0)	5 (13.5)	10 (27.0)	12 (32.4)
Infection control committee supported the use of probiotics for premature infants (37)	11 (29.7)	10 (27.0)	7 (18.9)	9 (24.3)
Awareness that probiotics are used in other nurseries in my country (37)	1 (2.7)	6 (16.2)	16 (43.2)	14 (37.8)
The knowledge of protocols/polices about the use of probiotics that are used in other nurseries (36)	3 (8.1)	9 (24.3)	20 (54.1)	5 (13.5)
The awareness of a safe probiotic product that could administer to the premature infants (37)	1 (2.7)	4 (10.8)	20 (54.1)	12 (32.4)
Social Influences				
Positive feedback from other health care professionals in the NICU about implementing the use of probiotics for premature infants (37)	7 (18.9)	4 (10.8)	22 (59.5)	4 (10.8)
Parents have requested the use of probiotics for their infants (36)	24 (66.7)	10 (27.8)	1 (2.8)	1 (2.8)
The awareness that other NICUs in my country are administering probiotics for premature infants (37)	6 (16.2)	11 (29.7)	12 (32.4)	8 (21.6)
The awareness that other NICUs in other countries are administering probiotics for premature infants (37)	5 (13.5)	8 (21.6)	19 (51.4)	5 (13.5)

Medical Directors were asked to what extent they believed different barriers, which where framed using the TDF (knowledge, skills, beliefs about consequences, decision making process, environmental process and resources, and social context) have interfered with the use of probiotics in others NICUs across their country (Table 11). There were no responses with more than 50% representing barriers that have interfered to a great extent the use of probiotics. However, there were barriers which several participants believed have interfered to "some extent" with the use of probiotics in other NICUs. These barriers are the following:

- Lack of experience prescribing probiotics to premature infants (n=24 [63.2%]).
- Belief that use of probiotics for premature infants might have negative outcomes (n=24 [63.2%]).
- Lack of knowledge about how to prescribe probiotics (n=22 [59.5%]).
- Lack of awareness of safe probiotic products to administer to premature infants (n=22 [59.5%]).

Table 11

Barriers that Medical Directors Believe have Interfered with the Use of Probiotics in other NICUs across their Country.

Domains	No extent *n* (%)	Little extent *n* (%)	Some extent *n* (%)	Great extent *n* (%)
Knowledge				
Lack of participation in educational activities related to probiotic supplementation in premature infants (38)	5 (13.2)	10 (26.3)	18 (47.4)	5 (13.2)
Lack of knowledge about a safe probiotic product to be used in premature infants (38)	2 (5.3)	3 (7.9)	23 (60.5)	10 (26.3)
Lack of knowledge about the evidence related to use of probiotics for premature infants (38)	4 (10.5)	10 (26.3)	20 (52.6)	4 (10.5)
Skills				
Lack of knowledge about how to prescribe probiotics (37)	2 (5.4)	7 (18.9)	22 (59.5)	6 (16.2)
Lack of experience prescribing probiotics to premature infants (38)	2 (5.3)	3 (7.9)	24 (63.2)	9 (23.7)
Professional Role and Identity				
The belief of health care professionals that the evidence related to use of probiotics is weak (38)	3 (7.9)	10 (26.3)	21 (55.3)	4 (10.5)
Optimism				
The belief that use of probiotics for premature infants might have negative outcomes (38)	4 (10.5)	4 (10.5)	24 (63.2)	6 (15.8)
Beliefs about consequences				
The belief that use of probiotics for premature infants is not a safe practice (37)	1 (2.7)	10 (27.0)	21 (56.8)	5 (13.5)
Decision making process				
Difficulties in the health care team with the decision making process (37)	3 (8.1)	10 (27.0)	20 (54.1)	4 (10.8)
Environmental context and resources				
Lack of institutional support (37)	8 (21.6)	7 (18.9)	16 (43.2)	6 (16.2)

Lack of awareness of safe probiotic products to administer to premature infants (37)	3 (8.1)	3 (8.1)	22 (59.5)	9 (24.3)
Social Influences				
Negative feedback from other health care professionals about implementing the use of probiotics for premature infants (37)	10 (27.0)	11 (29.7)	13 (35.9)	3 (8.1)

Factors Affecting the Implementation of Probiotics (Survey 1)

Survey 1 reported from the 197 Medical Directors of NICUs surveyed, 150 (76.1%) NICUS do not prescribe probiotics for premature infants. From the NICUs that did not prescribe probiotics, 12 (8%) were from Canada and 138 (83%) were from the U.S. The participants who reported that they were not giving probiotics were asked questions (in the form of statements) about factors that might affect the implementation of this practice (survey 2, version 1). The participants' answers to this survey helped to address the second research question, "What are the most significant factors that influence the willingness of health care professionals to support the use of probiotics?" Only Medical Directors' answers are described in this section. To answer the research question, an outcome variable was used that asked about participant's opinion regarding probiotics practice (Table 12). This opinion indirectly gave an account about their willingness to use probiotics. Descriptive statistics about statements that assessed factors affecting the implementation of probiotics are presented. The results of the test of independence (chi-square and fisher's exact test) between the outcome variable and factors affecting the implementation of probiotics are shown below. Tests of independence between the outcome variable and demographics are presented. These test of independence between the outcome variable and factors affecting the implementation of probiotics help show which factors are most significant in affecting the implementation of probiotics for Medical Directors.

Table 12

Medical Directors' Opinions about Probiotics Practice

Statement (n)	Strongly Disagree n (%)	Disagree n (%)	Unsure/ Uncertain (%)	Agree n (%)	Strongly Agree n (%)
Probiotics should be routinely administered to premature infants who meet selected criteria (136)	16 (10.7)	31 (20.7)	49 (32.7)	31 (20.7)	9 (6)

Factors from the TDF that might affect the implementation of probiotics are presented in Table 13. The most frequent responses in this questionnaire to statements that reflect aspects that might negatively affect the implementation of probiotics are the following:

- Lack of certainty regarding optimal products, dosages, and formulations of probiotics for premature infants (n=132 [97.2%]).
- Lack of experience prescribing probiotics (n=122 [89.7%]).
- The belief from colleagues that more evidence is required to support the use of probiotics (n=116 [84.3%]).
- There is difficulty about deciding what specific probiotics products and doses to use (n=112 [83.6%]).
- The belief that the evidence regarding the use of probiotics has flaws (n=111 [81.6%]).
- Concerns about the quality of probiotic products (n=105 [80.2%]).

Table 13

Responses from Medical Directors Survey about Factors affecting the Implementation of Probiotics

	Factors affecting the implementation of probiotics				
Domain	Strongly Disagree n (%)	Disagree n (%)	Unsure/ Uncertain n (%)	Agree n (%)	Strongly Agree n (%)
Knowledge (n)					
I am up-to-date on the scientific evidence supporting the use of probiotics for premature infants (136)	2 (1.5)	21 (15.4)	27 (19.9)	65 (47.8)	21 (15.4)
There is strong evidence supporting the use of probiotics for premature infants (136)	3 (2.2)	41 (30.1)	35 (25.7)	49 (36.0)	8 (5.9)
More evidence is required to support the routine use of probiotics in premature infants (136)	2 (1.5)	13 (9.6)	10 (7.4)	76 (55.9)	35 (25.7)
The evidence regarding the use of probiotics for premature infants has flaws (136)	1 (0.7)	19 (14.0)	40 (29.4)	65 (47.8)	11 (8.1)
In spite of the evidence, many questions still remain about optimal products, dosages, and formulations of probiotics that can be given to preterm infants (136)	1 (0.7)	0 (0.0)	3 (2.2)	59 (43.4)	73 (53.7)
I can name at least one probiotic product that can be given to premature infants (136)	13 (9.6)	27 (19.9)	17 (12.5)	61 (44.9)	18 (13.2)
I am aware of contraindications for giving probiotic supplements to premature infants (136)	1 (0.7)	22 (16.2)	43 (31.6)	59 (43.4)	11 (8.1)
Skills					
I have adequate skills to evaluate the results of the evidence (e.g., randomized control trials, meta-analyses) regarding probiotic use for premature infants (136)	1 (0.7)	2 (1.5)	8 (5.9)	85 (62.5)	40 (29.4)
I know the formulations and dosages of probiotics to prescribe to premature infants (136)	24 (17.6)	64 (47.1)	30 (22.1)	15 (11.0)	3 (2.2)
I have experience prescribing probiotics for premature infants (136)	65 (47.8)	57 (41.9)	4 (2.9)	9 (6.6)	1 (0.7)

Professional role and identity					
Most of my colleagues believe that more evidence is required to support the use of probiotics for premature infants (136)	0 (0.0)	11 (8.1)	9 (6.6)	80 (58.8)	36 (26.5)
Prescribing probiotics is not supported by current clinical practice guidelines in Canada or U.S. (136)	1 (0.7)	19 (14.0)	35 (25.7)	59 (43.4)	22 (16.2)
Beliefs					
I am confident in my ability to prescribe the appropriate dosage of probiotics for premature infants (134)	21 (15.7)	67 (50.0)	24 (17.9)	21 (15.7)	1 (0.7)
Prescribing probiotics would make me feel uncomfortable (134)	3 (2.2)	31 (23.1)	31 (23.1)	56 (41.8)	13 (9.7)
I am concerned about the safety of administering probiotics to premature infants (132)	1 (0.8)	14 (10.6)	15 (11.4)	68 (51.5)	34 (25.8)
Prescribing probiotics might put me at risk of a malpractice suit (132)	9 (6.8)	30 (22.7)	52 (39.4)	31 (23.5)	10 (7.6)
Opinions					
Probiotics are associated with positive outcomes in the health of premature infants (134)	1 (0.7)	6 (4.5)	40 (29.9)	81 (60.4)	6 (4.5)
Prescribing probiotics is one of the best recent medical advances in neonatology (134)	11 (8.2)	37 (27.6)	55 (41.0)	29 (21.6)	2 (1.5)
Prescribing probiotics for premature infants is risky (134)	0 (0.0)	22 (16.4)	62 (46.3)	42 (31.3)	8 (6.0)
Intention					
I am actively looking into the evidence supporting the use of probiotics for premature infants because I would like to have this practice implemented at my health care facility (135)	10 (7.4)	40 (29.6)	16 (11.9)	54 (40.0)	15 (11.1)
I have no interest in prescribing probiotics to premature infants (135)	24 (17.8)	70 (51.9)	21 (15.6)	17 (12.6)	3 (2.2)
I am contemplating prescribing probiotics to premature infants (135)	5 (3.7)	32 (23.7)	24 (17.8)	67 (49.6)	7 (5.2)
There is enough evidence supporting the prescription of probiotics for premature infants (135)	8 (5.9)	47 (34.8)	47 (34.8)	30 (22.2)	3(2.2)
Decision process					
It is difficult to decide whether or not I support the use of probiotics for premature infants (134)	7 (5.2)	53 (39.6)	25 (18.7)	48 (35.8)	1 (0.7)

Deciding whether or not to prescribe probiotics for premature infants is difficult for me (133)	9 (6.8)	51 (38.3)	23 (17.3)	48 (36.1)	2 (1.5)
Deciding whether or not to prescribe probiotics for premature infants generates conflict within the health care team (133)	8 (6.0)	48 (36.1)	29 (21.8)	44 (33.1)	4 (3.0)
The evidence regarding the use of probiotics is confusing (134)	3 (2.2)	41 (30.6)	31 (23.1)	55 (41.0)	4 (3.0)
It is difficult to decide what specific probiotic products and doses to use in premature infants (134)	1 (0.7)	8 (6.0)	13 (9.7)	58 (43.3)	54 (40.3)
Feelings					
Fears about causing harm prevents me from prescribing probiotics for premature infants (135)	4 (3.0)	30 (22.2)	21 (15.6)	61 (45.2)	19 (14.1)
Environmental context and resources					
I am knowledgeable about the Health Canada regulations on the safety and quality of probiotic products in Canada (13)	2 (15.4)	6 (46.2)	3 (23.1)	2 (15.4)	0 (0.0)
I am confident that the Health Canada regulations ensure that probiotics products are safe to be given to premature infants (13)	0 (0.0)	2 (15.4)	9 (69.2)	2 (15.4)	0 (0.0)
I do not prescribe probiotics for premature infants due to the lack of regulations related to of the quality and safety of probiotic products in The United States (124)	0 (0.0)	15 (12.1)	12 (9.7)	52 (41.9)	44 (35.5)
I am knowledgeable about how probiotics are regulated in The United States (124)	6 (4.8)	37 (29.8)	28 (22.6)	47 (37.9)	5 (4.0)
Sufficient opportunities are available to learn about probiotics for premature infants (132)	2 (1.5)	27 (20.5)	34 (25.8)	63 (47.7)	6 (4.5)
I do not have online access to the scientific evidence about use of probiotics for premature infants (131)	45 (34.4)	72 (55.0)	3 (2.3)	9 (6.9)	2 (1.5)
Lack of time prevents me from accessing evidence regarding the efficacy of probiotics for premature infants (131)	27 (20.7)	72 (55.0)	19 (14.5)	12 (9.2)	1 (0.8)
I do not have enough time to help establish a guideline for the use of probiotics for premature infants (131)	23 (17.6)	71 (54.2)	15 (11.5)	18 (13.7)	4 (3.1)
I do not have adequate time to discuss the use of probiotics with my colleagues (131)	26 (19.8)	86 (65.6)	10 (7.6)	9 (6.9)	0 (0.0)
I am concerned about the quality of the currently available probiotic products	2 (1.5)	8 (6.1)	16 (12.2)	64 (48.9)	41 (31.3)

which may be given to premature infants (131)					
I do not have institutional support for establishing the use of probiotics as a standardized practice in my unit (131)	6 (4.6)	47 (35.9)	38 (29.0)	32 (24.4)	8 (6.1)
Lack of standardized guidelines in Canada or U.S. prevent me from prescribing probiotics for premature infants (132)	3 (2.3)	14 (10.6)	23 (17.4)	62 (47.0)	30 (22.7)
Social Influences					
I have received mostly negative feedback from other health care professional about giving probiotics to premature infants (131)	4 (3.1)	89 (68.5)	18 (13.8)	15 (11.5)	4 (3.1)
My colleagues do not support the use of probiotics for premature infants (130)	1 (0.8)	53 (40.8)	29 (22.3)	39 (30.0)	8 (6.2)
Parents have expressed to me that they want me to prescribe probiotics for their premature infants (130)	25 (19.2)	74 (56.9)	19 (14.6)	11 (8.5)	1 (0.8)
Parental request to prescribe probiotics has influenced medical practice (130)	23 (11.7)	71 (54.6)	22 (16.9)	13 (10.0)	1 (0.8)
The administration of probiotics in some health care facilities in the U.S. and Canada motivates me to prescribe them to premature infants (130)	17 (13.1)	48 (36.9)	29 (22.3)	34 (26.2)	2 (1.5)

Responses to questions that assessed knowledge about probiotics are summarized in Table 14. In total, 15 questions were asked. The mean knowledge score was 10.9 out of 15 (72%). This result demonstrates that the participants have a fair knowledge about probiotics.

Table 14

Responses from Medical Directors Survey to Knowledge Questions about Probiotics

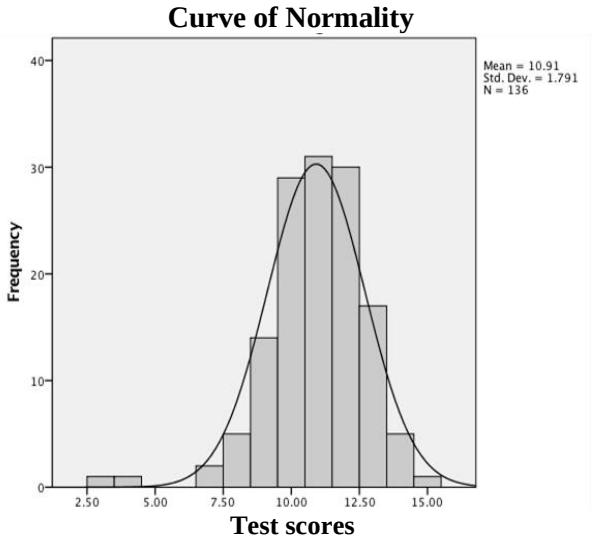
Knowledge Domain (n)	TRUE *n* (%)	FALSE *n* (%)	UNSURE *n* (%)
Probiotics are the same as prebiotics (138)	0 (0.0)	135 (97.8)*	3 (2.2)
To be probiotic, a bacteria must confer a health benefit (139)	83 (59.7)*	40 (28.8)	16 (11.5)
Probiotic can be live, dead, or pasteurized bacteria (138)	38 (27.5)	76 (55.1)*	24 (17.4)
Probiotics may be found in:			
Soy beans (135)	24 (17.8)	55 (40.7)*	56 (41.5)
Cheese (136)	92 (67.6)*	15 (11)	29 (21.3)
Breast Milk (136)	113 (83.1)*	13 (9.6)	10 (7.4)
Green Tea (133)	5 (3.8)	81 (60.9)*	47 (35.3)
Yogurt (137)	131 (95.6)*	0 (0.0)	6 (4.4)
Examples of probiotics strains include:			
Streptococcus thermophiles (137)	35 (25.5)*	40 (29.2)	62 (45.3)
Lactobacillus reuteri (138)	124 (89.9)*	2 (1.4)	12 (8.7)
Bifidobacterium bifidum (139)	132 (95)*	1 (0.7)	6 (4.3)
Staphylococcus pneumonia (136)	0 (0.0)	129 (94.9)*	7 (5.1)
Probiotics are being given to premature infants in some hospitals in Canada or U.S. (135)	131 (97)*	0 (0.0)	4 (3.0)
There is a standardized guideline in with dosage and formulation for probiotic use for premature infants (135)	1 (0.7)	129 (95.6)*	5 (3.7)
In the U.S. manufactures and distributors of probiotics are responsible for insuring the safety and quality of their products (126)	50 (39.4)*	59 (46.5)	17 (13.4)
A Health Canada Product license indicates that probiotic products are safe, effective and of high quality under recommended conditions of use (13)	4 (30.8)*	4 (30.8)	5 (38.5)

* Correct answer

One-way ANOVA and non-parametric test among knowledge score groups. The participants' response to the outcome variable "Probiotics should be routinely administered to premature infants who meet selected criteria", was divided into three groups (the responses obtained from strongly disagree and disagree were condensed to disagree and formed one group, the responses obtained

from strongly agree to agree were condensed to agree and formed the second group, the third group was the uncertain/unsure responses). One-way-ANOVA and a non-parametric (Kruskall Wallis) test were performed to determine if the mean knowledge scores were statistically different among the groups.

Different approaches were used to evaluate normality in the knowledge scores. Normality is an assumption required to perform one-way ANOVA test. First**,** a curve of normality was performed on the scores of the knowledge questionnaire. The curve of normality was normally distributed with slight skewedness to the left (skewedness: -1.020).



Secondly, the Kolmogorov – Smirnov test was performed to test normality in the knowledge scores and it was reported as $p < 0.001$, indicating the distribution was not normal. Normal distributions have a p value > 0.05 (Elliot & Woodward, 2007). Although this test showed that the distribution of knowledge scores is not normal, a one-way ANOVA test was performed (Table 15-Descriptives and Table-16-ANOVA) because in sample sizes larger than 30, the violation of the normality assumption should not pose problems with parametric testing as long as the data is not severely departed from a normal curve (Elliot & Woodward, 2007,

Ghasemi & Zahediasl, 2012, Pallant, 2007).

Table 15

Summary of the Descriptive for Knowledge Scores of Medical Directors Survey

Groups (n)	M	SD	SE	95% Confidence Interval for Mean		Min	Max
				Lower Bound	Upper Bound		
Disagree (47)	10.31	2.01	0.29	9.72	10.90	3.00	13.00
Uncertain/unsure (49)	11.1	1.66	0.23	10.64	11.60	8.00	14.00
Agree (40)	11.35	1.49	0.23	10.87	11.82	8.00	15.00
Total	10.9	1.79	0.15	10.60	11.21	3.00	15.00

Table 16

One-way ANOVA for Knowledge Scores of Medical Directors Survey

	SS	DF	MS	F	P
Between groups	26.363	2	13.18	4.31	.015
Within groups	406.578	133	3.05		
Total	432.941	135			

*p <0.05

The one way-ANOVA test indicated a significant difference among the mean knowledge score between groups because (p=0.015). The post hoc tests Tukey HSD and Bonferroni were performed to identify what mean groups were statistically different. These tests revealed that the mean knowledge score of the group “disagree” was significantly lower compared to the mean score of the “agree” group (Tukey HSD p= 0.019, Bonferroni p = 0.021). There were no significant differences between the mean scores of agree and uncertain/unsure group (Tukey HSD p= 0.815, Bonferroni p=1.000) and disagree and uncertain/unsure group (Turkey HSD p= 0.67, Bonferroni p=0.78). Participants who disagreed with the statement “Probiotics should be routinely administered to premature infants who meet selected criteria” had a lower mean knowledge score than participants who agreed with the same statement. In contrast, the Kruskall Wallis test revealed no significant

difference in mean knowledge scores among the three groups ($p = 0.06$), although the result approached statistical significance. The Kruskall Wallis test is recommended when the assumption of normality is violated (Lund & Lund, 2014). In this study, the Kruskal Wallis test was performed because the knowledge score distribution was not normal in the Kolmogorov – Smirnov test.

Factors affecting the implementation of probiotics and the outcome variable in survey 1. The tests of independence (chi-square and fisher's exact test) between each of the questions related to factors affecting the implementation of probiotics and the outcome variable were performed (Table 17).

The results revealed that participants who disagreed with the statement, "Probiotics should be routinely administered to premature infants who meet selected criteria", were more likely to agree with the following statements (only results with $p < 0.0001$ are presented below):

- More evidence is required to support the routine use of probiotics in premature infants.
- The evidence regarding the use of probiotics for premature infants has flaws.
- Most of my colleagues believe that more evidence is required to support the use of probiotics for premature infants.
- Prescribing probiotics is not supported by current clinical practice guidelines in Canada or U.S.
- Prescribing probiotics would make me feel uncomfortable.
- I am concerned about the safety of administering probiotics to premature infants.
- Prescribing probiotics for premature infants is risky.
- The evidence regarding the use of probiotics is confusing.
- I have no interest in prescribing probiotics to premature infants.
- Fears about causing harm prevents me from prescribing probiotics for premature infants.

The results revealed that the participants who disagreed with the statement "Probiotics should be routinely administered to premature infants who meet selected criteria" were more likely to disagree with the following statements (only results with $p < 0.0001$ are presented below):

- There is strong evidence supporting the use of probiotics for premature infants.
- Probiotics are associated with positive outcomes in the health of premature infants.
- Prescribing probiotics is one of the best recent medical advances in neonatology.
- I am contemplating prescribing probiotics to premature infants.
- I am actively looking into the evidence supporting the use of probiotics for premature infants because I would like to have this practice implemented at my health care facility.
- There is enough evidence supporting the prescription of probiotics for premature infants.
- Parents have expressed to me that they want me to prescribe probiotics for their premature infants.
- The administration of probiotics in some health care facilities in the U.S. and Canada motivates me to prescribe them to premature infants.

Table 17

Responses from Medical Directors Survey about Factors Affecting the Implementation of Probiotics and the outcome variable

Factors affecting the implementation of probiotics		Probiotics should be routinely administered to premature infants who meet selected criteria			
Domain (n)	Values	Disagree n (%)	Unsure/ Uncertain n (%)	Agree n (%)	Chi-square P value
Knowledge					
I am up-to-date on the scientific evidence supporting the use of probiotics for premature infants (136)	Disagree	8 (34.8)	10 (43.5)	5 (21.7)	0.400
	Uncertain/ Unsure	13 (48.1)	8 (29.6)	6 (22.2)	
	Agree	26 (30.2)	31 (36.0)	29 (33.7)	
There is strong evidence supporting the use of probiotics for premature infants (136)	Disagree	29 (65.9)	12 (27.3)	3 (6.8)	<0.0001
	Uncertain/ Unsure	9 (25.7)	19 (54.3)	7 (20.0)	
	Agree	9 (15.8)	18 (31.6)	30 (52.6)	
More evidence is required to support the routine use of probiotics in premature infants (136)	Disagree	1 (6.7)	2 (13.3)	12 (80.0)	*<0.0001
	Uncertain/ Unsure	1 (10.0)	6 (60.0)	3 (30.0)	
	Agree	45 (40.5)	41 (36.9)	25 (22.5)	
The evidence regarding the use of probiotics for premature infants has flaws (136)	Disagree	3 (15.0)	3 (15.0)	14(70.0)	<0.0001
	Uncertain/ Unsure	11(27.5)	20 (50.0)	9 (22.5)	
	Agree	33 (43.4)	26 (34.2)	17 (22.4)	
In spite of the evidence, many questions still remain about optimal products, dosages, and formulations of probiotics that can be given to preterm infants (132)	Disagree	1 (100)	0 (0.0)	0 (0.0)	*0.303
	Uncertain/ Unsure	0 (0.0)	2 (66.7)	1 (33.3)	
	Agree	46 (34.8)	47 (35.6)	39 (29.5)	
I can name at least one probiotic product that can be given to premature infants (136)	Disagree	23 (57.5)	12 (30.0)	5 (12.5)	0.001
	Uncertain/ Unsure	8 (47.1)	5 (29.4)	4 (23.5)	
	Agree	16 (20.3)	32 (40.5)	31 (39.2)	
I am aware of contraindications for giving probiotic supplements to premature infants (136)	Disagree	11 (47.8)	7 (30.4)	5 (21.7)	0.528
	Uncertain/ Unsure	15 (34.9)	17 (39.5)	11 (25.6)	
	Agree	21 (30.0)	25 (35.7)	24 (34.3)	
Skills					
I have adequate skills to evaluate the results of the evidence (e.g., randomized control trials, meta-	Disagree	2 (66.7)	0 (0.0)	1 (33.3)	*0.417
	Uncertain/ Unsure	4 (50.0)	2 (25.0)	2 (25.0)	

analyses) regarding probiotic use for premature infants (136)	Agree	41 (32.8)	47 (37.6)	37 (29.6)	
I know the formulations and dosages of probiotics to prescribe to premature infants (136)	Disagree	36 (40.9)	32 (36.4)	20 (22.7)	0.101
	Uncertain/ Unsure	8 (26.7)	11 (36.7)	11 (36.7)	
	Agree	3 (16.7)	6 (33.3)	9 (50.0)	
I have experience prescribing probiotics for premature infants (136)	Disagree	46 (37.7)	44 (36.1)	32 (26.2)	*0.54
	Uncertain/ Unsure	0 (0.0)	1 (25.0)	3 (75.0)	
	Agree	1 (10.0)	4 (40.0)	5 (50.0)	
Professional role and identity					
Most of my colleagues believe that more evidence is required to support the use of probiotics for premature infants (136)	Disagree	0 (0.0)	2 (18.2)	9 (81.8)	*<0.001
	Uncertain/ Unsure	1 (11.1)	4 (44.4)	4 (44.4)	
	Agree	46 (39.7)	43 (37.1)	27 (23.3)	
Prescribing probiotics is not supported by current clinical practice guidelines in Canada or U.S. (136)	Disagree	2 (10.0)	4 (20.0)	14 (70.0)	<0.001
	Uncertain/ Unsure	8 (22.9)	17 (48.6)	10 (28.6)	
	Agree	37 (45.7)	28 (34.6)	16 (19.8)	
Beliefs					
I am confident in my ability to prescribe the appropriate dosage of probiotics for premature infants (134)	Disagree	37 (42.0)	30 (34.1)	21 (23.9)	0.085
	Uncertain/ Unsure	5 (20.8)	11 (45.8)	8 (33.3)	
	Agree	4 (18.2)	8 (36.4)	10 (45.5)	
Prescribing probiotics would make me feel uncomfortable (134)	Disagree	5 (14.7)	10 (29.4)	19 (55.9)	<0.0001
	Uncertain/ Unsure	5 (16.1)	16 (51.6)	10 (32.3)	
	Agree	36 (52.2)	23 (33.3)	10 (14.5)	
I am concerned about the safety of administering probiotics to premature infants (132)	Disagree	0 (0.0)	5 (33.3)	10 (66.7)	*<0.0001
	Uncertain/ Unsure	1 (6.7)	8 (53.3)	6 (40.0)	
	Agree	44 (43.1)	35 (34.3)	23 (22.5)	
Prescribing probiotics might put me at risk of a malpractice suit (132)	Disagree	10 (25.6)	12 (30.8)	17 (43.6)	0.127
	Uncertain/ Unsure	17 (32.7)	23 (44.2)	12 (23.1)	
	Agree	18 (43.9)	13 (31.7)	10 (24.4)	
Opinions					
Probiotics are associated with positive outcomes in the health of premature infants (134)	Disagree	7 (100.0)	0 (0.0)	0 (0.0)	*<0.0001
	Uncertain/ Unsure	18 (45.0)	17 (42.5)	5 (12.5)	
	Agree	21 (24.1)	32 (36.8)	34 (39.1)	
Prescribing probiotics is one of the best recent medical advances in neonatology (134)	Disagree	27 (56.3)	16 (33.3)	5 (10.4)	<0.0001
	Uncertain/ Unsure	16 (29.1)	23 (41.8)	16 (29.1)	
	Agree	3 (9.7)	10 (32.3)	18 (58.1)	
Prescribing probiotics for premature infants is risky (134)	Disagree	2 (9.1)	3 (13.6)	17 (77.3)	<0.0001
	Uncertain/ Unsure	13 (21.0)	33 (53.2)	16 (25.8)	

	Agree	31 (62.0)	13 (26.0)	6 (12.0)	
Intention					
I am actively looking into the evidence supporting the use of probiotics for premature infants because I would like to have this practice implemented at my health care facility (135)	Disagree	30 (60.0)	16 (32.0)	4 (8.0)	<0.0001
	Uncertain/ Unsure	6 (37.5)	7 (43.8)	3 (18.8)	
	Agree	10 (14.5)	26 (37.7)	33 (47.8)	
I have no interest in prescribing probiotics to premature infants (135)	Disagree	19 (20.2)	36 (38.3)	39 (41.5)	<0.0001
	Uncertain/ Unsure	12 (57.1)	8 (38.1)	1 (4.8)	
	Agree	15 (75.0)	5 (25.0)	0 (0.0)	
I am contemplating prescribing probiotics to premature infants (135)	Disagree	25 (67.6)	9 (24.3)	3 (8.1)	<0.0001
	Uncertain/ Unsure	11 (45.8)	11 (45.8)	2 (8.3)	
	Agree	10 (13.5)	29 (39.2)	35 (47.3)	
There is enough evidence supporting the prescription of probiotics for premature infants (135)	Disagree	34 (61.8)	18 (32.7)	3 (5.5)	<0.0001
	Uncertain/ Unsure	10 (21.3)	24 (51.1)	13 (27.7)	
	Agree	2 (6.1)	7 (21.2)	24 (72.7)	
Decision process					
It is difficult to decide whether or not I support the use of probiotics for premature infants (134)	Disagree	20 (33.3)	14 (23.3)	26 (43.3)	0.005
	Uncertain/ Unsure	7 (28.0)	10 (40.0)	8 (32.0)	
	Agree	18 (36.7)	25 (51.0)	6 (12.2)	
Deciding whether or not to prescribe probiotics for premature infants is difficult for me (133)	Disagree	24 (40.0)	15 (25.0)	21 (35.0)	0.030
	Uncertain/ Unsure	5 (21.7)	8 (34.8)	10 (43.5)	
	Agree	16 (32.0)	25 (50.0)	9 (18.0)	
Deciding whether or not to prescribe probiotics for premature infants generates conflict within the health care team (133)	Disagree	21 (37.5)	22 (39.3)	13 (23.2)	0.502
	Uncertain/ Unsure	8 (27.6)	12 (41.4)	9 (31.0)	
	Agree	16 (33.3)	14 (29.2)	18 (37.5)	
The evidence regarding the use of probiotics is confusing (134)	Disagree	11 (25.0)	13 (29.5)	20 (45.5)	<0.0001
	Uncertain/ Unsure	4 (12.9)	13 (41.9)	14 (45.2)	
	Agree	30 (50.8)	23 (39.0)	6 (10.2)	
It is difficult to decide what specific probiotic products and doses to use in premature infants (134)	Disagree	4 (44.4)	2 (22.2)	3 (33.3)	*0.188
	Uncertain/ Unsure	1 (7.7)	7 (53.8)	5 (38.5)	
	Agree	40 (35.7)	40 (35.7)	32 (28.6)	
Feelings					
Fears about causing harm prevents me from prescribing probiotics for premature infants (135)	Disagree	7 (20.6)	8 (23.5)	19 (55.9)	<0.0001
	Uncertain/ Unsure	4 (19.0)	12 (57.1)	5 (23.8)	
	Agree	35 (43.8)	29 (36.3)	16 (20.0)	
Environmental context and resources					
	Disagree	2 (25.0)	2 (25.0)	4 (50.0)	*0.463

I am knowledgeable about the Health Canada regulations on the safety and quality of probiotic products in Canada (13)	Uncertain/ Unsure	1 (33.3)	0 (0.0)	2 (66.7)	
	Agree	0 (0.00	0 (0.0)	2 (100.0)	
I am confident that the Health Canada regulations ensure that probiotics products are safe to be given to premature infants (13)	Disagree	0 (0.0)	0 (0.0)	2 (100.0)	*0.498
	Uncertain/ Unsure	2 (22.2)	2 (22.2)	5 (55.6)	
	Agree	1 (50.0)	0 (0.0)	1 (50.0)	
I do not prescribe probiotics for premature infants due to the lack of regulations related to of the quality and safety of probiotic products in The United States (123)	Disagree	4 (26.7)	6 (40.0)	5 (33.3)	*0.832
	Uncertain/ Unsure	4 (33.3)	6 (50.0)	2 (16.7)	
	Agree	34 (35.4)	36 (37.5)	26 (27.1)	
I am knowledgeable about how probiotics are regulated in The United States (123)	Disagree	15 (34.9)	16 (37.2)	12 (27.9)	0.922
	Uncertain/ Unsure	8 (28.6)	13 (46.4)	7 (25.0)	
	Agree	19 (36.5)	19 (36.5)	14 (26.9)	
Sufficient opportunities are available to learn about probiotics for premature infants (132)	Disagree	13 (44.8)	11 (37.9)	5 (17.2)	0.094
	Uncertain/ Unsure	8 (23.5)	10 (29.4)	16 (47.1)	
	Agree	22 (31.9)	28 (40.6)	19 (27.5)	
I do not have online access to the scientific evidence about use of probiotics for premature infants (131)	Disagree	39 (33.3)	42 (35.9)	36 (30.8)	*0.311
	Uncertain/ Unsure	1 (33.3)	0 (0.0)	2 (66.7)	
	Agree	3 (27.3)	6 (54.5)	2 (18.2)	
Lack of time prevents me from accessing evidence regarding the efficacy of probiotics for premature infants (131)	Disagree	32 (32.3)	38 (38.4)	29(29.3)	*0.552
	Uncertain/ Unsure	7 (36.8)	4 (21.1)	8 (42.1)	
	Agree	4 (30.8)	6 (46.2)	3 (23.1)	
I do not have enough time to help establish a guideline for the use of probiotics for premature infants (131)	Disagree	32 (34.0)	33 (35.1)	29 (30.9)	*0.967
	Uncertain/ Unsure	5 (33.3)	6 (40.0)	4 (26.7)	
	Agree	6 (27.3)	9 (40.9)	7 (31.8)	
I do not have adequate time to discuss the use of probiotics with my colleagues (131)	Disagree	34 (30.4)	41 (36.6)	37 (33.0)	*0.448
	Uncertain/ Unsure	5 (50.0)	3 (30.0)	2 (20.0)	
	Agree	4 (44.4)	4 (44.4)	1 (11.1)	
I am concerned about the quality of the currently available probiotic products which may be given to premature infants (131)	Disagree	2 (20.0)	3 (30.0)	5 (50.0)	*0.435
	Uncertain/ Unsure	4 (25.0)	5 (31.3)	7 (43.8)	
	Agree	37 (35.2)	40 (38.1)	28 (26.7)	
I do not have institutional support for establishing the use of probiotics as a standardized practice in my unit (131)	Disagree	17 (32.1)	22 (41.5)	14 (26.4)	0.277
	Uncertain/ Unsure	16 (42.1)	13 (34.2)	9 (23.7)	
	Agree	10 (25.0)	13 (32.5)	17 (42.5)	
Lack of standardized guidelines in Canada or U.S. prevent me from	Disagree	4 (23.5)	4 (23.5)	9 (52.9)	0.144
	Uncertain/ Unsure	6 (26.1)	8 (34.8)	9 (39.1)	

prescribing probiotics for premature infants (132)	Agree	33 (35.9)	37 (40.2)	22 (23.9)	
Social Influences					
I have received mostly negative feedback from other health care professionals about giving probiotics to premature infants (130)	Disagree	26 (28.0)	38 (40.9)	29 (31.2)	0.159
	Uncertain/ Unsure	8 (44.4)	7 (38.9)	3 (16.7)	
	Agree	8 (42.1)	3 (15.8)	8 (42.1)	
My colleagues do not support the use of probiotics for premature infants (130)	Disagree	8 (14.8)	24 (44.4)	22 (40.7)	0.006
	Uncertain/ Unsure	11 (37.9)	11 (37.9)	7 (24.1)	
	Agree	23 (48.9)	13 (27.7)	11 (23.4)	
Parents have expressed to me that they want me to prescribe probiotics for their premature infants (130)	Disagree	40 (40.4)	31 (31.3)	28 (28.3)	*<0.0001
	Uncertain/ Unsure	0 (0.0)	10 (52.6)	9 (47.4)	
	Agree	2 (16.7)	7 (58.3)	3 (25.0)	
Parental request to prescribe probiotics has influenced medical practice (130)	Disagree	36 (38.3)	32 (34.0)	26 (27.7)	*0.103
	Uncertain/ Unsure	5 (22.7)	9 (40.9)	8 (36.4)	
	Agree	1 (7.1)	7 (50.0)	6 (42.9)	
The administration of probiotics in some health care facilities in the United States and Canada motivates me to prescribe them to premature infants (130)	Disagree	34 (52.3)	22 (33.8)	9 (13.8)	<0.0001
	Uncertain/ Unsure	8 (27.6)	12 (41.4)	9 (31.0)	
	Agree	0 (0.0)	14 (38.9)	22 61. 1)	

* Fisher's exact test

Demographics and the Outcome Variable in Survey 1. The association between demographics and the outcome variable are shown in Table 18. Using fisher's exact test, there was no relationship between the outcome variable and sex, age, time of working in NICUs, current position, type of hospital and geographic location ($p>0.05$).

Table 18

Demographics Characteristics and the Outcome Variable from Medical Directors' Survey

Variable	Probiotics should be routinely administered to premature infants who meet selected criteria			
Demographics (n)	Disagree *n* (%)	Unsure/ Uncertain *n* (%)	Agree *n* (%)	Fisher's exact test P value
Sex (130)				
Female	12 (37.5)	10 (31.3)	10 (31.3)	0.622
Male	29 (29.6)	39 (39.8)	30 (30.6)	
Age (129)				
25-44 years	2 (20.0)	2 (20.0)	6 (60.0)	0.363
45-54 years	11 (34.4)	13 (40.6)	8 (25.0)	
>54 years	28 (32.2)	34 (39.1)	25 (28.7)	
Time working in NICU (131)				
>5 years to ≤ 10 years	0 (0.0)	1 (33.3)	2 (66.7)	
> 10 years to ≤ 20 years	10 (32.3)	12 (38.7)	9 (29.0)	0.563
> 20 years	32 (33.0)	36 (37.1)	29 (29.9)	
Current position (129)				
Medical Director of NICU	40 (33.3)	48 (39.2)	33 (27.5)	0.058
Other leadership positions	1 (11.1)	2 (22.2)	6 (66.7)	
Type of hospital (131)				
Community hospital	16 (38.1)	20 (47.6)	6 (14.3)	0.170
Regional Hospital	7 (26.9)	9 (34.6)	10 (38.5)	
Tertiary referral center	19 (32.2)	18 (30.5)	22 (37.3)	
Military hospital	0 (0.0)	1 (50.0)	1 (50.0)	
Others	0 (0.0)	1 (50.0)	1 (50.0)	
Location in Canada (9)				
Western Canada	1 (25.0)	0 (0.0)	3 (75.0)	0.407
Eastern Canada	0 (0.0)	0 (0.0)	2 (100.0)	
Central Canada	0 (0.0)	1 (33.3)	2 (66.7)	
Location in U.S. (121)				
Midwest	5 (14.3)	18 (51.4)	12 (34.3)	0.078
Northeast	15 (53.6)	7 (25.0)	6 (21.4)	
South	13 (38.2)	13 (38.2)	8 (23.5)	
West	8 (33.3)	10 (41.7)	6 (25.0	

Demographics and Probiotics Prescription in NICUs. A contingency table between demographics (sex, age, time of working in NCIU, type of hospital, location) and whether or not probiotics are prescribed in the NICU are shown in Table 19. Using chi-square test or fisher's exact's test, there was no relationship between whether or not probiotics re prescribed and sex, age, time of working in NICUs, probiotics prescription or location ($p > 0.05$).

Table 19

Demographic Variables and Probiotics Prescription

Variable (n)	Unit prescribing probiotics		Chi-square P value
	Yes	No	
Sex (168)	n (%)	n (%)	
Female	5(13.2)	32 (24.6)	0.134
Male	33(86.8)	98(75.4)	
Age (167)			
25-44 years	6(15.8)	10(7.8)	0.327
45-54 years	8(21.1)	32(24.8)	
>55 yeard	24(63.2)	87(67.4)	
Time working in NICU (169)			
>10 years but ≤ 20 years	11(28.9)	34(26)	0.135
>20 years	27(71.1)	97(74)	
Type of hospital (169)			
Community hospital	9 (17.6)	42 (82.4)	*0.635
Regional Hospital	9 (25.7)	26 (21.4)	
Tertiary referral center	17 (22.4)	59 (77.6)	
Military hospital	1 (33.3)	2(66.7)	
Others	2 (50.0)	2 (50.0)	
Canada Location (14)			
Western Canada	1 (20)	4(44.4)	*6.16
Eastern Canada	2(40)	2(22.2)	
Central Canada	2(40)	3(33.3)	
U.S location (154)			
Midwest	12(36.4)	35 (28.9)	0.424
Northeast	4(12.1)	28(23.1)	
South	8(24.2)	34(28.1)	
West	9(27.3)	24(19.8)	

*Fisher's exact test

Survey 2 (version 1): Neonatologists and Nurse Practitioners

In this section about the results of survey 2 (version 1), I present an overview of the response rates by providing details of the different communication approaches used with the participants. Also, the demographic characteristics of the participants of this survey are presented. Then, a description about factors affecting the implementation of probiotics is presented.

Overview of Responses Rates

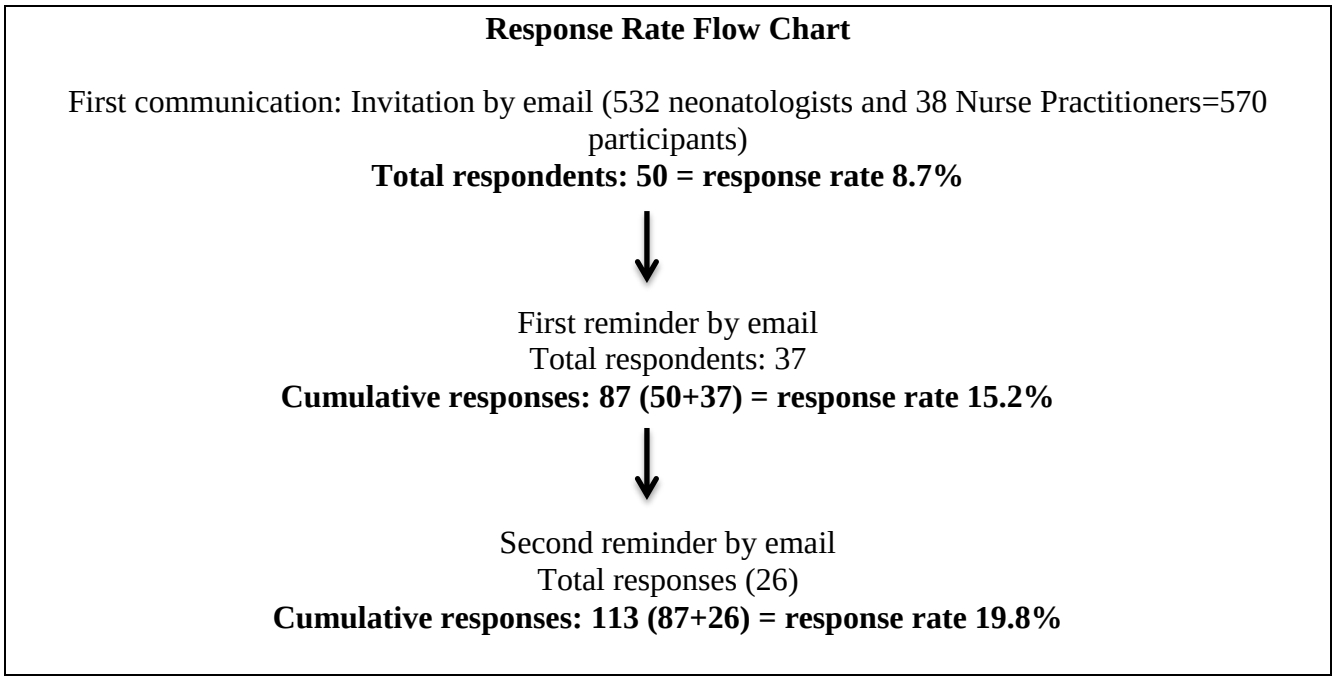
This survey had a response rate of 113 participants (19.8%), from which 59.3 % (67) participants were from Canada and 40.7% (46) participants were from the U.S. The response rate in Canada was 25.8% (46 out of 178 participants contacted) and U.S. was 17.1% (67 out of 392 participants contacted). Figure 2 presents a flow chart of the response rate. A three contact strategy (Dillman et al., 2009) was used to maximize response rates in this study. Communications with the participants were the following:

1. An invitation was emailed on January 21, 2015 to U.S. and Canadian Neonatologists. The survey was designed in English and French language. The invitation was personalized, included a university logo, had the pictures of the principal investigator, supervisors and committee (see Appendix K). Also, an invitation was sent on January 23, 2015to 38 Nurse Practitioners by the CANN (see Appendix L). This invitation was not sent using FluidSurvey™ Software because it was sent by the CANN. Thus, the logo of the university and photographs of the committee members were not included.
2. A First reminder was emailed on January 28, 2015 to Neonatologist using the same format of invitation mentioned in the first communication (see Appendix M). Also, a reminder was emailed by the CANN on February 2 to Nurse Practitioners including the same specifications mentioned in the first communication (see Appendix N).

3. A Final reminder was emailed on February 4, 2015 to Neonatologist using the same format of invitation mentioned in the first communication (see Appendix O). Also, a reminder was emailed by the CANN on February 9, 2015 to Nurse Practitioners including the same specifications mentioned in the first communication (see Appendix P).

Figure 2

Response Rate Flow Chart Survey 2 (version 1)



Demographic Characteristics for Survey 2 (Version 1)

The demographic characteristic of the participants for survey 2, version 1 (sex, age, country, current position, type of hospital, type of unit, and time working in NICU) are presented in Table 20. There were 113 participants in this study. The most prevalent age range was 36-45 (n= 34 [35.8%]), followed by 46-55(n= 29 [30.5%]). In Canada, over half (n=32 [57.1%]) of the participants were from Central Canada. U.S. participants were mostly located in the Midwest 16 (41%) and Northeast (n=9 [23.1%]. Over half of the participants (*n*=60 [63.2] worked as academic neonatologists. Most

of the participants worked in a tertiary referral center (n=68 [71.6%] and community hospitals (n= 17 [17.9%]). The majority of the participants worked in NICUs Level III (*n*=86 [90.5]). Several participants had worked in NICUs more than 10 years but less than or equal to 20 years (n=42 [44.2%]).

Table 20

Demographics Characteristics of Neonatologist and Nurse Practitioners

Characteristic (n)	*n* (%)
Sex (95)	
Female	49 (51.6)
Male	46 (48.7)
Age range (95)	
< 26 years	1(1.1)
26-35 years	3(3.2)
36-45 years	34(35.8)
46-55 years	29(30.5)
56-65 years	19(20)
> 65 years	9(9.5)
Current Position in the NICU (95)	
Academic Neonatologist	60 (63.2)
Non- academic Neonatologist	20(21.1)
Neonatal or Pediatric Nurse Practitioner	13 (13.7)
Other	2(2.1)
Types of unit (95)	
Specialty neonatal care level II	5 (5.2)
Neonatal Intensive care Level II and level III	18 (18.9)
Neonatal Intensive Care Level III	50 (52.6)
Others	4 (4.2)
I do not know	18 (18.9)
Type of Hospital (95)	
Community Hospital	17 (17.8)
Regional Hospital	8 (8.4)
Tertiary referral center	68 (71.5)
Military hospital	1 (1.0)
Others	1 (1.0)
Time Working at the NICU (95)	
>1 years but ≤ 5 years	2 (2.1)
>5 years but ≤10 years	14 (14.7)
>10 years but ≤ 20 years	42 (44.2)
> 20 years	37 (38.9)
Locations	
Canada (56)	
Western	21 (37.5)
Central	32 (57.1)
Eastern	3 (5.4)

U.S. (39)	
Midwest	16 (41)
Northeast	9 (23.1)
South	7 (17.9)
West	7 (17.9)

Factors Affecting the Implementation of Probiotics (survey 2, version 1)

Descriptive statistics about statements assessing factors affecting the implementation of probiotics are presented. The results of the test of independence (chi-square and fisher's exact test) between the outcome variable and factors affecting the implementation of probiotics are described next. The results of the test of independence indicated the most significant factors affecting the implementation of probiotics for neonatologists and nurse practitioners.

Table 21

Neonatologists and Nurse practitioners' Opinions about Probiotics Practice

Statement (n)	Strongly Disagree n (%)	Disagree n (%)	Unsure/ uncertain n (%)	Agree n (%)	Strongly Agree n (%)
Probiotics should be routinely administered to premature infants who meet selected criteria (102)	3 (2.9)	13 (12.7)	27 (26.5)	39 (38.2)	20 (19.6)

The factors from the TDF that might affect the implementation of probiotics are presented in table 22. The most frequent responses in this questionnaire that reflect aspects that might negatively affect the implementation of probiotics are the following:

- Lack of certainty regarding optimal products, dosages, and formulations of probiotics for premature infants (n=95 [93.1%]).

- There is difficulty about deciding what specific probiotics products and doses to use (n=75 [75.8]).
- Lack of experience prescribing probiotics (n=74 [72.5%]).
- Concerns about the quality of probiotic products (n=61 [64.2%]).
- They believe that more evidence is required to support the routine use of probiotics in premature infants (n= 65 ([63.7]).

Table 22

Responses from Neonatologists and Nurse Practitioners about Factors Affecting the Implementation of Probiotics

	Factors affecting the implementation of probiotics				
Domain	Strongly Disagree *n* (%)	Disagree *n* (%)	Unsure/ Uncertain *n* (%)	Agree *n* (%)	Strongly Agree *n* (%)
Knowledge					
I am up-to-date on the scientific evidence supporting the use of probiotic for premature infants (102)	2 (2.0)	17 (16.7)	22 (21.6)	50 (49.0)	11 (10.8)
There is strong evidence supporting the use of probiotics for premature infants (102)	1 (1.0)	11 (10.8)	30 (29.4)	47 (46.1)	13 (12.7)
More evidence is required to support the routine use of probiotics in premature infants (102)	3 (2.9)	24 (23.5)	10 (9.8)	39 (38.2)	26 (25.8)
The evidence regarding the use of probiotics for premature infants has flaws (102)	0 (0.0)	17 (16.7)	38 (37.3)	38 (37.3)	9 (8.8)
In spite of the evidence, many questions still remain about optimal products, dosages, and formulations of probiotics that can be given to preterm infants (102)	0 (0.0)	0 (0.0)	7 (6.9)	45 (44.1)	50 (49.0)
I can name at least one probiotic product that can be given to premature infants (102)	6 (5.9)	14 (13.7)	14 (13.7)	49 (48.0)	19 (18.6)
I am aware of contraindications for giving probiotic supplements to premature infants (102)	2 (2.0)	7 (6.9)	26 (25.5)	59 (57.8)	8 (7.8)
Skills					
I have enough skills to evaluate the results of the evidence (e.g., randomized control trials, meta-analyses) regarding probiotic use for premature infants (102)	1 (1.0)	3 (2.9)	10 (9.8)	62 (60.8)	26 (25.8)
I know the formulations and dosages of probiotics to prescribe to premature infants (102)	14 (13.7)	38 (37.3)	26 (25.5)	22 (21.6)	2 (2.0)
I have experience prescribing probiotics for premature infants (102)	30 (29.4)	44 (43.1)	5 (4.9)	18 (17.6)	5 (4.9)

Professional role and identity					
Most of my colleagues believe that more evidence is required to support the use of probiotics for premature infants (102)	3 (2.9)	20 (19.6)	21 (20.6)	39 (38.2)	19 (18.6)
Prescribing probiotics is not supported by current clinical practice guidelines in U.S. (43)	1 (2.3)	3 (7.0)	13 (30.2)	21 (48.8)	5 (11.6)
Prescribing probiotics is not supported by current clinical practice guidelines in Canada (59)	0 (0.0)	13 (22.0)	21 (35.6)	23 (39.0)	2 (3.4)
Beliefs					
I am confident in my ability to prescribe the appropriate dosage of probiotics for premature infants (102)	9 (8.8)	33 (32.4)	31 (30.4)	25 (24.5)	4 (3.9)
Prescribing probiotics would make me feel uncomfortable (102)	16 (15.8)	33 (32.7)	27 (26.7)	22 (21.8)	3 (3.0)
I am concerned about the safety of administering probiotics to premature infants (102)	3 (2.9)	24 (23.5)	16 (15.7)	44 (43.1)	15 (14.7)
Prescribing probiotics might put me at risk of a malpractice suit (102)	7 (6.9)	41 (41.2)	34 (33.3)	16 (15.7)	4 (3.9)
Opinions					
Probiotics are associated with positive outcomes in the health of premature infants (102)	0 (0.0)	3(2.9)	29 (28.4)	58 (56.9)	12 (11.8)
Prescribing probiotics is one of the best recent medical advances in neonatology (102)	2 (2.0)	23 (22.5)	42 (41.2)	33 (32.4)	2 (2.0)
Prescribing probiotics for premature infants is risky (102)	4 (3.9)	36 (35.3)	42 (41.2)	17 (16.7)	3 (2.9)
Intention					
I am actively looking into the evidence supporting the use of probiotics for premature infants because I would like to have this practice implemented at my health care facility (101)	6 (5.9)	20 (19.8)	23 (22.8)	41 (40.6)	11 (19.9)
I have no interest in prescribing probiotics to premature infants (101)	28 (27.7)	50 (49.7)	18 (17.8)	5 (5.0)	0 (0.0)
I am contemplating prescribing probiotics to premature infants (101)	2 (2.0)	16 (15.8)	24 (23.8)	48 (47.5)	11 (10.9)
There is enough evidence supporting the prescription of probiotics for premature infants (102)	5 (4.9)	21 (20.6)	31 (30.4)	36 (35.3)	9 (8.8)

Decision process					
It is difficult to decide whether or not I support the use of probiotics for premature infants (99)	11 (11.1)	39 (39.4)	10 (10.1)	36 (36.4)	3 (3.0)
Deciding whether or not to prescribe probiotics for premature infants is difficult for me (99)	10 (10.1)	45 (45.5)	10 (10.1)	30 (30.3)	4 (4.0)
Deciding whether or not to prescribe probiotics for premature infants generates conflict within the health care team (99)	6 (6.1)	31 (31.3)	12 (12.1)	44 (44.4)	6 (6.1)
The evidence regarding the use of probiotics is confusing (99)	6 (6.1)	31 (31.3)	21 (21.2)	36 (36.4)	5 (5.1)
It is difficult to decide what specific probiotic products and doses to use in premature infants (99)	2 (2.0)	8 (8.1)	14 (14.1)	47 (47.5)	28 (28.3)
Feelings					
Fears about causing harm prevents me from prescribing probiotics for premature infants (98)	9 (9.2)	41 (41.8)	12 (12.2)	29 (29.6)	7 (7.1)
Environmental context and resources					
I am knowledgeable about the Health Canada regulations on the safety and quality of probiotic products in Canada (59)	4 (6.8)	21 (35.6)	22 (37.3)	11 (18.6)	1 (1.7)
I am confident that the Health Canada regulations ensure that probiotics products are safe to be given to premature infants (59)	3 (5.1)	16 (27.1)	26 (44.1)	14 (23.7)	0 (0.0)
I do not prescribe probiotics for premature infants due to the lack of regulations related to of the quality and safety of probiotic products in the U.S. (40)	1 (2.5)	7 (17.5)	5 (12.5)	14 (35.0)	13 (32.5)
I am knowledgeable about how probiotics are regulated in the U.S. (40)	4 (10.0)	11 (27.5)	14 (35.0)	10 (25.0)	1 (2.5)
Sufficient opportunities are available to learn about probiotics for premature infants (99)	2 (2.0)	19 (19.2)	15 (15.2)	56 (56.6)	7 (7.1)
I do not have online access to the scientific evidence about use of probiotics for premature infants (99)	34 (34.3)	53 (53.5)	5 (5.1)	6 (6.1)	1 (1.0)
Lack of time prevents me from accessing evidence regarding the efficacy of probiotics for premature infants (95)	14 (14.7)	52 (54.7)	7 (7.4)	19 (20.0)	3 (3.2)

I do not have enough time to help establish a guideline for the use of probiotics for premature infants (95)	11 (11.6)	35 (36.8)	12 (12.6)	31 (32.6)	6 (6.3)
I do not have adequate time to discuss the use of probiotics with my colleagues (95)	14 (14.7)	55 (57.9)	8 (8.4)	16 (16.8)	2 (2.1)
I am concerned about the quality of the currently available probiotic products which may be given to premature infants (95)	0 (0.0)	14 (14.7)	20 (21.1)	42 (44.2)	19 (20.0)
I do not have institutional support for establishing the use of probiotics as a standardized practice in my unit (95)	2 (2.1)	31 (32.6)	24 (25.3)	29 (30.5)	9 (9.5)
Lack of standardized guidelines in U.S. prevents me from prescribing probiotics for premature infants (39)	0 (0.0)	7 (17.9)	6 (15.4.)	11 (28.2)	15 (38.5)
Lack of standardized guidelines in Canada prevents me from prescribing probiotics for premature infants (56)	6 (10.7)	11 (19.6)	16 (28.6)	22 (39.3)	1 (1.8)
Social Influences					
I have received mostly negative feedback from other health care professionals about giving probiotics to premature infants (95)	11 (11.6)	54 (56.8)	15 (15.8)	15 (15.8)	0 (0.0)
My colleagues do not support the use of probiotics for premature infants (95)	9 (9.5)	34 (35.8)	24 (25.3)	25 (26.3)	3 (3.2)
Parents have expressed to me that they want me to prescribe probiotics for their premature infants (95)	11 (11.6)	35 (36.8)	11 (11.6)	31 (32.6)	7 (7.4)
Parental request to prescribe probiotics has influenced medical practice (95)	11 (11.6)	34 (35.8)	22 (23.2)	21 (22.1)	7 (7.4)
The administration of probiotics in some health care facilities in the United States and Canada motivates me to prescribe them to premature infants (95)	10 (10.5)	21 (22.1)	27 (28.4)	32 (33.7)	5 (5.3)

Responses to questions that assessed knowledge about probiotics are summarized in Table 23. In total 15 questions were asked. The mean knowledge score was 10.7 out of 15 (71.3%). This result demonstrates that the participants have a fair knowledge about probiotics.

Table 23

Responses from Neonatologists and Nurse practitioners' Survey to Knowledge Questions about Probiotics

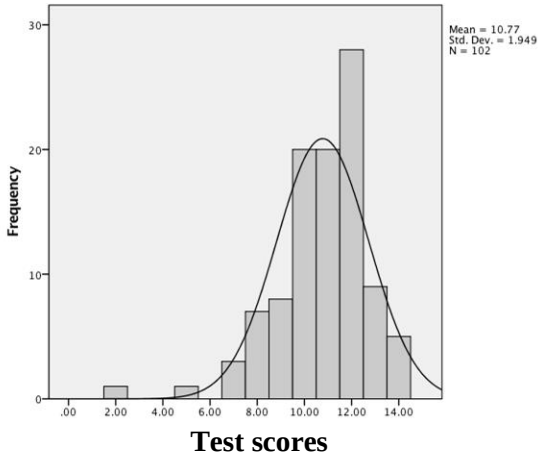
Knowledge Domain (n)	TRUE n (%)	FALSE n (%)	UNSURE n (%)
Probiotics are the same as prebiotics (112)	0 (0.0)	103 (92)*	9 (7.5)
To be probiotic, a bacteria must confer a health benefit (112)	70 (62.5)*	29 (25.9)	13 (10.8)
Probiotic can be live, dead, or pasteurized bacteria (112)	30 (26.8)	58 (51.8)*	24 (21.4)
Probiotics may be found in:			
Soy beans (103)	13 (12.6)	41 (39.8)*	49 (47.6)
Cheese (103)	66 (64.1)*	11 (10.7)	26 (25.2)
Breast Milk (103)	81 (78.6)*	12 (11.2)	10 (9.7)
Green Tea (103)	6 (5.8)	54 (52.4)*	43 (41.7)
Yogurt (103)	101 (98.1)*	0 (0.0)	2 (1.9)
Examples of probiotics strains include:			
Streptococcus thermophiles (103)	29 (28.2)*	43 (41.7)	31 (30.1)
Lactobacillus reuteri (103)	96 (93.2)*	1 (1.0)	6 (5.8)
Bifidobacterium bifidum (103)	101 (98.1)*	0 (0.0)	2 (1.9)
Staphylococcus pneumonia (103)	1 (1.0)	96 (93.2)*	6 (5.8)
Probiotics are being given to premature infants in some hospitals in Canada or U.S.(105)	98 (93.3)*	2 (1.9)	5 (4.8)
There is a standardized North American guideline in with dosage and formulation for probiotic use for premature infants (103)	4 (3.9)	92 (89.3)*	7 (6.8)
In the United States manufacturers and distributors of probiotics are responsible for insuring the safety and quality of their products (43)	17 (39.5)*	18 (41.9)	8 (18.6)
A Health Canada Product license indicates that probiotic products are safe, effective and of high quality under recommended conditions of use (62)	21 (33.9)*	19 (30.6)	22 (35.5)

* Correct answer

One-way ANOVA and non-parametric test among knowledge score groups. The participants' response to the outcome variable "Probiotics should be routinely administered to premature infants who meet selected criteria" was divided in three groups (the responses obtained from strongly disagree and disagree were condensed to disagree and formed one group, the responses obtained from strongly agree to agree were condensed to agree and formed the second group, the third group was the uncertain/unsure responses.). One-way ANOVA and a non-parametric (Kruskall Wallis) test were performed to determine if the mean knowledge scores were statistically different among the groups.

First, a curve of normality was performed on the scores of the knowledge questionnaire. The curve of normality was normally distributed with skewedness to the left (skewedness: -1.24).

Curve of Normality



Secondly, the Kolmogorov-Smirnov test reported a $p < 0.001$. Thus, this results showed that the distribution is not normal. Although this test showed that the distribution of knowledge scores is not normal, a one-way ANOVA test was performed (Table 24-Descriptive, Table 25- ANOVA).

Table 24

Summary of the Descriptive for Knowledge Scores of Neonatologists and Nurse Practitioners' Survey

Groups (n)	M	SD	SE	95% Confidence Interval for Mean		Min	Max
				Lower Bound	Upper Bound		
Disagree (16)	10.81	1.22	.030	10.16	11.46	8.00	13.00
Uncertain/unsure (27)	9.59	2.51	0.48	8.59	10.58	2.00	13.00
Agree (59)	11.30	1.56	0.20	10.89	11.71	8.00	14.00
Total (102)	10.77	1.94	0.19	10.39	11.15	2.00	14.00

Table 25

ANOVA for knowledge Scores of Neonatologists and Nurse Practitioners' Survey

	SS	DF	MS	F	P
Between groups	54.349	2	27.175	8.166	.001
Within groups	329.464	99	3.328		
Total	383.814	101			

*p <0.05

The one-way ANOVA test indicated a statically significant difference among the mean knowledge scores between groups (p=0.001). The post hoc tests Tukey HSD and Bonferroni revealed that the mean knowledge score of the group "uncertain/unsure" was significantly lower compared to the mean score of the "agree" group (Tukey HSD p=< 0.0001, Bonferroni p = 0.0001). No statically significant differences between the mean scores of disagree and uncertain/unsure group (Tukey HSD p= 0.091, Bonferroni p=0.110) and disagree and agree group (Turkey HSD p= 0.605, Bonferroni p=1.000) were found. Participants who were unsure/uncertain with the statement "Probiotics should be routinely administered to premature infants who meet selected criteria" had a lower mean knowledge score than participants who agree with the same statement. In addition, the Kruskall Wallis test revealed a significant difference among the mean groups (p = 0.006).

Factors affecting the implementation of probiotic and the outcome variable in survey 2 (version 1). Test of independence (fisher's exact test) between each of the questions related to factors affecting the implementation of probiotics and the outcome variable were performed (Table 26). The results of the tests showed factors affecting implementation of probiotics that were significantly associated with the outcome variable.

The tests results revealed that the participants who disagreed with the statement "Probiotics should be routinely administered to premature infants who meet selected criteria" were more likely to disagree with the following statements (only results with $p < 0.0001$ are presented below):

- There is strong evidence supporting the use of probiotics for premature infants.
- Probiotics are associated with positive outcomes in the health of premature infants.
- Prescribing probiotics is one of the best recent medical advances in neonatology.
- I know the formulations and dosages of probiotics to prescribe to premature infants.
- I am contemplating prescribing probiotics to premature infants.
- I am actively looking into the evidence supporting the use of probiotics for premature infants because I would like to have this practice implemented at my health care facility.
- There is enough evidence supporting the prescription of probiotics for premature infants.

- The administration of probiotics in some health care facilities in the United States and Canada motivates me to prescribe them to premature infants.

The tests results revealed that the participants who disagreed with the statements "Probiotics should be routinely administered to premature infants who meet selected criteria" were more likely to agree with the following statements (only results with $p < 0.0001$ are presented below):

- Prescribing probiotics would make me feel uncomfortable.
- I am concerned about the safety of administering probiotics to premature infants.
- I am concerned about the quality of the currently available probiotic products which may be given to premature infants.
- Prescribing probiotics for premature infants is risky.
- The evidence regarding the use of probiotics is confusing.
- I have no interest in prescribing probiotics to premature infants.
- Fears about causing harm prevents me from prescribing probiotics for premature infants.
- It is difficult to decide whether or not I support the use of probiotics for premature infants.

Table 26

Responses from Neonatologists and Nurse Practitioners about Factors Affecting the Implementation of Probiotics and the Outcome Variable

Factors affecting the implementation of probiotics		Factors affecting the implementation of probiotics			
Domain (n)	Values	Disagree *n* (%)	Unsure/ Uncertain *n* (%)	Agree *n* (%)	Fisher's exact test P value
Knowledge					
I am up-to-date on the scientific evidence supporting the use of probiotics for premature infants (102)	Disagree	2 (10.5)	13 (68.4)	4 (21.1)	<0.0001
	Uncertain/ Unsure	4 (18.2)	7 (31.8)	11 (50.0)	
	Agree	10 (16.4)	7 (11.5)	44 (72.1)	
There is strong evidence supporting the use of probiotics for premature infants (102)	Disagree	6 (50.0)	3 (25.0)	3 (25.0)	<0.0001
	Uncertain/ Unsure	4 (13.3)	17 (56.7)	9 (30.0)	
	Agree	6 (10.0)	7 (11.7)	47 (78.3)	
More evidence is required to support the routine use of probiotics in premature infants (102)	Disagree	2 (7.4)	1 (3.7)	24 (88.9)	0.001
	Uncertain/ Unsure	2 (20.0)	4 (40.0)	4 (40.0)	
	Agree	12 (18.5)	22 (33.8)	31 (47.7)	
The evidence regarding the use of probiotics for premature infants has flaws (102)	Disagree	1 (5.9)	1 (5.9)	15 (88.2)	0.007
	Uncertain/ Unsure	3 (7.9)	12 (31.6)	23 (60.5)	
	Agree	12 (25.5)	14 (29.8)	21 (44.7)	
In spite of the evidence, many questions still remain about optimal products, dosages, and formulations of probiotics that can be given to preterm infants (102)	Disagree	0 (0.0)	3 (42.9)	4 (57.1)	0.232
	Uncertain/ Unsure	16 (16.8)	24 (25.3)	55 (57.9)	
	Agree	16 (57.7)	27 (26.5)	59 (57.8)	
I can name at least one probiotic product that can be given to premature infants (102)	Disagree	7 (35.0)	8 (40.0)	5 (25.0)	0.008
	Uncertain/ Unsure	2 (14.3)	5 (35.7)	7 (50.0)	
	Agree	7 (10.3)	14 (20.6)	47 (69.1)	
I am aware of contraindications for giving probiotic supplements to premature infants (102)	Disagree	1 (11.1)	4 (44.4)	4 (44.4)	0.115
	Uncertain/ Unsure	4 (15.4)	11 (42.3)	11 (42.3)	
	Agree	11 (16.4)	12 (17.9)	44 (65.7)	
Skills					
	Disagree	1 (25.0)	3 (75.0)	0 (0.0)	0.094

I have adequate skills to evaluate the results of the evidence (e.g., randomized control trials, meta-analyses) regarding probiotic use for premature infants (102)	Uncertain/ Unsure	1 (10.0)	2 (20.0)	7 (70.0)	
	Agree	14 (15.9)	22 (25.0)	52 (59.1)	
I know the formulations and dosages of probiotics to prescribe to premature infants (102)	Disagree	12 (23.1)	22 (42.3)	18 (34.6)	<0.0001
	Uncertain/ Unsure	2 (7.7)	2 (7.7)	22 (84.6)	
	Agree	2 (8.3)	3 (12.5)	19 (79.2)	
I have experience prescribing probiotics for premature infants (102)	Disagree	14 (18.9)	25 (33.8)	35 (47.3)	0.003
	Uncertain/ Unsure	0 (0.0)	1 (20.0)	4 (80.0)	
	Agree	2 (8.7)	1 (4.3)	20 (87.0)	
Professional role and identity					
Most of my colleagues believe that more evidence is required to support the use of probiotics for premature infants (102)	Disagree	2 (8.7)	1 (4.3)	20 (87.0)	0.011
	Uncertain/ Unsure	3 (14.3)	7 (43.3)	11 (52.4)	
	Agree	11 (19.0)	19 (32.8)	28 (48.3)	
Prescribing probiotics is not supported by current clinical practice guidelines in USA (43)	Disagree	0 (0.0)	0 (0.0)	4 (100.0)	0.041
	Uncertain/ Unsure	3 (23.1)	7 (53.8)	3 (23.1)	
	Agree	6 (23.1)	7 (26.9)	13 (50.0)	
Prescribing probiotics is not supported by current clinical practice guidelines in Canada (59)	Disagree	2 (15.4)	1 (7.7)	10 (76.9)	0.576
	Uncertain/ Unsure	3 (14.3)	5 (23.8)	13 (61.9)	
	Agree	2 (8.0)	7 (28.0)	16 (64.0)	
Beliefs					
I am confident in my ability to prescribe the appropriate dosage of probiotics for premature infants (102)	Disagree	13 (31.0)	13 (31.0)	16 (38.1)	0.001
	Uncertain/ Unsure	2 (60.5)	9 (29.0)	20 (64.5)	
	Agree	1 (3.4)	5 (17.2)	23 (79.3)	
Prescribing probiotics would make me feel uncomfortable (101)	Disagree	2 (4.1)	6 (12.2)	41 (83.7)	<0.0001
	Uncertain/ Unsure	1 (3.7)	13 (48.1)	13 (48.1)	
	Agree	13 (52.0)	7 (28.0)	5 (20.0)	
I am concerned about the safety of administering probiotics to premature infants (102)	Disagree	1 (3.7)	1 (3.7)	25 (92.6)	<0.0001
	Uncertain/ Unsure	1 (6.3)	7 (43.8)	8 (50.0)	
	Agree	14 (23.7)	19 (32.2)	26 (44.1)	
Prescribing probiotics might put me at risk of a malpractice suit (102)	Disagree	3 (6.3)	10 (20.8)	35 (72.9)	0.020
	Uncertain/ Unsure	9 (26.5)	12 (35.3)	13 (38.2)	
	Agree	4 (20.0)	5 (25.0)	11 (55.0)	
Opinions					
Probiotics are associated with positive outcomes in the health of premature infants (102)	Disagree	3 (100.0)	0 (0.0)	0(0.0)	<0.0001
	Uncertain/ Unsure	8 (27.6)	18 (62.1)	3 (10.3)	
	Agree	5 (7.1)	9 (12.9)	56 (80.0)	

Prescribing probiotics is one of the best recent medical advances in neonatology (102)	Disagree	10 (40.0)	10 (40.0)	5 (20.0)	<0.0001
	Uncertain/ Unsure	4 (9.5)	15 (35.7)	23 (53.8)	
	Agree	2 (5.7)	2 (5.7)	31 (88.6)	
Prescribing probiotics for premature infants is risky (102)	Disagree	1 (2.5)	1 (2.5)	38 (95.0)	<0.0001
	Uncertain/ Unsure	8 (19.0)	22 (52.4)	12 (28.6)	
	Agree	7 (35.0)	4 (20.0)	9 (45.0)	
Intention					
I am actively looking into the evidence supporting the use of probiotics for premature infants because I would like to have this practice implemented at my health care facility (101)	Disagree	10 (38.5)	10 (38.5)	6 (23.1)	<0.0001
	Uncertain/ Unsure	2 (8.7)	10 (53.5)	11 (47.8)	
	Agree	3 (5.8)	7 (13.5)	42 (80.0)	
I have no interest in prescribing probiotics to premature infants (101)	Disagree	7 (9.0)	17 (21.8)	54 (69.2)	<0.0001
	Uncertain/ Unsure	6 (33.3)	8 (44.4)	4 (22.2)	
	Agree	3 (60.0)	1 (20.0)	1 (20.0)	
I am contemplating prescribing probiotics to premature infants (101)	Disagree	9 (50.0)	4 (22.2)	5 (27.8)	<0.0001
	Uncertain/ Unsure	3 (4.5)	12 (50.0)	9 (37.5)	
	Agree	3 (5.1)	11 (18.6)	45 (76.3)	
There is enough evidence supporting the prescription of probiotics for premature infants (102)	Disagree	12 (46.2)	10 (38.5)	4 (15.4)	<0.0001
	Uncertain/ Unsure	3 (9.7)	15 (48.4)	13 (41.9)	
	Agree	1 (2.2)	2 (4.4)	42 (93.3)	
Decision process					
It is difficult to decide whether or not I support the use of probiotics for premature infants (99)	Disagree	5 (10.0)	5 (10.0)	40 (80.0)	<0.0001
	Uncertain/ Unsure	2 (20.0)	1 (10.0)	7 (70.0)	
	Agree	8 (20.5)	20 (51.3)	11 (28.2)	
Deciding whether or not to prescribe probiotics for premature infants is difficult for me (99)	Disagree	9 (16.4)	6 (10.9)	40 (72.7)	0.003
	Uncertain/ Unsure	1 (10.0)	4 (40.0)	5 (50.0)	
	Agree	5 (14.7)	16 (47.1)	13 (38.2)	
Deciding whether or not to prescribe probiotics for premature infants generates conflict within the health care team (99)	Disagree	5 (13.5)	7 (18.9)	25 (67.6)	0.568
	Uncertain/ Unsure	1 (8.3)	4 (33.3)	7 (58.3)	
	Agree	9 (18.0)	15 (30.0)	26 (52.0)	
The evidence regarding the use of probiotics is confusing (99)	Disagree	2 (5.4)	2 (5.4)	33 (89.2)	<0.0001
	Uncertain/ Unsure	2 (9.5)	9 (42.9)	10 (47.6)	
	Agree	11 (26.8)	15 (36.6)	15 (36.6)	
It is difficult to decide what specific probiotic products and doses to use in premature infants (99)	Disagree	0 (0.0)	0 (0.0)	10 (100.0)	0.020
	Uncertain/ Unsure	3 (21.4)	4 (28.6)	7 (50.0)	
	Agree	12 (16.0)	22 (29.3)	41 (54.7)	

Feelings					
Fears about causing harm prevents me from prescribing probiotics for premature infants (98)	Disagree	3 (6.0)	8 (16.0)	39 (78.0)	<0.0001
	Uncertain/ Unsure	1 (8.3)	2 (16.7)	9 (75.0)	
	Agree	11 (30.6)	15 (41.7)	10 (27.8)	
Environmental context and resources					
I am knowledgeable about the Health Canada regulations on the safety and quality of probiotic products in Canada (59)	Disagree	2 (8.0)	9 (36.0)	14 (56.0)	0.199
	Uncertain/ Unsure	4 (18.2)	2 (9.1)	16 (72.7)	
	Agree	1 (8.3)	2 (16.7)	9 (75.0)	
I am confident that the Health Canada regulations ensure that probiotics products are safe to be given to premature infants (59)	Disagree	6 (31.6)	5 (26.3)	8 (42.1)	0.010
	Uncertain/ Unsure	1 (3.8)	4 (15.4)	21 (80.8)	
	Agree	0 (0.0)	4 (28.6)	10 (71.4)	
I do not prescribe probiotics for premature infants due to the lack of regulations related to of the quality and safety of probiotic products in The United States (40)	Disagree	0 (0.0)	3 (37.5)	5 (62.5)	0.122
	Uncertain/ Unsure	0 (0.0)	2 (40.0)	3 (60.0)	
	Agree	8 (29.6)	8 (29.6)	11 (40.7)	
I am knowledgeable about how probiotics are regulated in The United States (40)	Disagree	1 (6.7)	9 (60.0)	5 (43.3)	0.016
	Uncertain/ Unsure	2 (14.3)	3 (21.4)	9 (64.3)	
	Agree	5 (45.5)	1 (9.1)	5 (45.5)	
Sufficient opportunities are available to learn about probiotics for premature infants (99)	Disagree	2 (9.5)	9 (42.9)	10 (46.6)	0.124
	Uncertain/ Unsure	4 (26.7)	5 (33.3)	6 (40.0)	
	Agree	9 (14.3)	12 (19.0)	42 (66.7)	
I do not have online access to the scientific evidence about use of probiotics for premature infants (99)	Disagree	15 (17.2)	23 (26.4)	49 (56.3)	0.333
	Uncertain/ Unsure	0 (0.0)	1 (20.0)	4 (80.0)	
	Agree	0 (0.0)	2 (28.6)	5 (71.4)	
Lack of time prevents me from accessing evidence regarding the efficacy of probiotics for premature infants (95)	Disagree	10 (15.2)	12 (18.2)	44 (66.7)	0.005
	Uncertain/ Unsure	3 (42.9)	2 (28.6)	2 (28.6)	
	Agree	1 (4.5)	12 (54.5)	9 (40.9)	
I do not have enough time to help establish a guideline for the use of probiotics for premature infants (95)	Disagree	9 (19.6)	8 (17.4)	29 (63.0)	0.071
	Uncertain/ Unsure	1 (8.3)	2 (16.7)	9 (75.0)	
	Agree	4 (10.8)	16 (43.2)	17 (45.9)	
I do not have adequate time to discuss the use of probiotics with my colleagues (95)	Disagree	12 (17.4)	12 (17.4)	45 (65.2)	0.002
	Uncertain/ Unsure	2 (25.0)	4 (50.0)	2 (25.0)	
	Agree	0 (0.0)	10 (55.6)	8 (44.4)	
I am concerned about the quality of the currently available probiotic products which may be given to premature infants (95)	Disagree	1 (7.1)	0 (0.0)	13 (92.9)	<0.0001
	Uncertain/ Unsure	0 (0.0)	8 (40.0)	12 (60.0)	
	Agree	13 (21.3)	18 (29.5)	30 (49.2)	

I do not have institutional support for establishing the use of probiotics as a standardized practice in my unit (95)	Disagree	3 (9.1)	5 (15.2)	25 (75.8)	0.049
	Uncertain/ Unsure	4 (16.7)	11 (45.8)	9 (37.5)	
	Agree	7 (18.4)	10 (26.3)	21 (55.3)	
Lack of standardized guidelines in U.S. prevents me from prescribing probiotics for premature infants (39)	Disagree	2 (28.6)	1 (14.3)	4 (57.1)	0.351
	Uncertain/ Unsure	0 (0.0)	3 (50.0)	3 (50.0)	
	Agree	6 (23.1)	9 (34.6)	11 (42.3)	
Lack of standardized guidelines in Canada prevents me from prescribing probiotics for premature infants (56)	Disagree	1 (5.9)	2 (11.5)	14 (82.4)	0.521
	Uncertain/ Unsure	2 (12.5)	5 (31.3)	9 (56.3)	
	Agree	3 (15.0)	6 (26.1)	14 (60.9)	
Social Influences					
I have received mostly negative feedback from other health care professionals about giving probiotics to premature infants (95)	Disagree	8 (12.3)	17 (26.2)	40 (61.5)	0.534
	Uncertain/ Unsure	4 (26.7)	3 (20.0)	8 (53.3)	
	Agree	2 (13.3)	6 (40.0)	7 (46.7)	
My colleagues do not support the use of probiotics for premature infants (95)	Disagree	4 (9.3)	6 (14.0)	43 (76.7)	0.017
	Uncertain/ Unsure	5 (20.8)	9 (37.5)	10 (41.7)	
	Agree	5 (17.9)	11 (23.3)	12 (42.9)	
Parents have expressed to me that they want me to prescribe probiotics for their premature infants (95)	Disagree	10 (21.7)	19 (41.3)	17 (37.0)	0.001
	Uncertain/ Unsure	1 (9.1)	3 (27.3)	7 (63.6)	
	Agree	3 (7.9)	4 (10.5)	31 (81.6)	
Parental request to prescribe probiotics has influenced medical practice (95)	Disagree	8 (17.8)	18 (40.0)	19 (42.2)	0.013
	Uncertain/ Unsure	4 (18.2)	5 (22.7)	13 (59.1)	
	Agree	2 (7.1)	3 (10.7)	23 (82.1)	
The administration of probiotics in some health care facilities in the United States and Canada motivates me to prescribe them to premature infants (95)	Disagree	11 (35.5)	12 (38.7)	8 (25.8)	<0.0001
	Uncertain/ Unsure	2 (7.4)	10 (37.0)	15 (55.6)	
	Agree	1 (2.7)	4 (10.8)	32 (86.5)	

Outcome variable and demographics of survey 2 (version 1). The association between demographics and the outcome variable are shown in Table 27. Using fisher's exact test, there was not relation between the outcome variable and sex, age, time of working in NICUs, current position, type of hospital and geographic location ($p>0.05$).

Table 27

Demographics and the Outcome Variable of Neonatologists and Nurse Practitioners

Variable	Probiotics should be routinely administered to premature infants who meet selected criteria			
Demographics (n)	Disagree *n* (%)	Unsure/ Uncertain *n* (%)	Agree *n* (%)	Fisher's exact test P value
Sex (95)				
Female	9 (18.4)	16 (32.7)	24 (49.0)	0.189
Masculine	5 (10.9)	10 (21.7)	31 (67.4)	
Age (95)				
≤ 45 years	3 (7.9)	10 (26.3)	25 (65.8)	0.770
46-55 years	6 (20.7)	8 (27.6)	15 (51.7)	
56-65 years	3 (15.8)	6 (31.6)	10 (52.6)	
>65 years	2 (22.2)	2 (22.2)	5 (55.6)	
Time working in NICU (95)				
≤ 10 years	2 (12.5)	5 (31.3)	9 (56.3)	
11 years to 20 years	6 (14.3)	9 (21.4)	27 (64.3)	0.792
> 20 years	6 (16.2)	12 (32.4)	19 (51.4)	
Profession (95)				
Academic Neonatologist	11 (18.3)	15 (25.0)	34 (56.7)	0.425
Non-Academic neonatologist	3 (15.0)	5 (25.0)	12 (60.0)	
Nurse Practitioner	0 (0.0)	5 (38.5)	8 (61.5)	
Other	0 (0.0)	1 (50.0)	1 (50.0)	
Type of hospital (95)				
Community hospital	2 (11.8)	5 (294)	10 (58.8)	0.960
Regional Hospital	1 (12.5)	2 (25.0)	5 (62.5)	
Tertiary referral center	11 (16.2)	19 (27.9)	38 (55.9)	
Military hospital	0 (0.0)	0 (00.0)	1 (100.0)	
Others	0 (0.0)	0 (0.0)	1 (100.0)	
Location in Canada (56)				
Western Canada	2 (9.5)	4 (19.0)	15 (71.4)	0.871
Eastern Canada	0 (0.0)	1 (33.3)	2 (66.7)	
Central Canada	4 (12.5)	8 (25.0)	20 (62.5)	
Location in U.S. (39)				
Midwest	3 (18.8)	6 (37.5)	7 (43.8)	0.531
Northeast	3 (33.3)	3 (33.3)	3 (33.3)	
South	2 (28.6)	2(28.6)	3 (42.9)	
West	0 (0.0)	2 (28.6)	5 (71.4)	

Survey 2 (version 2): Nurses

In this section about the results of survey 2 (version 2), I present an overview of the response rates by providing details of the different communication approaches used with the participants. Also, the demographics characteristics of the participants of this survey are presented. Then, the results of the questionnaire about factors affecting the implementation of probiotics will be described.

Overview of Responses Rates

This survey had a response rate of 30% (75 participants out of 250 nurses contacted), of whom 100% were from Canada. Figure 3 presents a flow chart of the response rates. A three contact strategy (Dillman et al., 2009) was used to maximize response rates in this study.

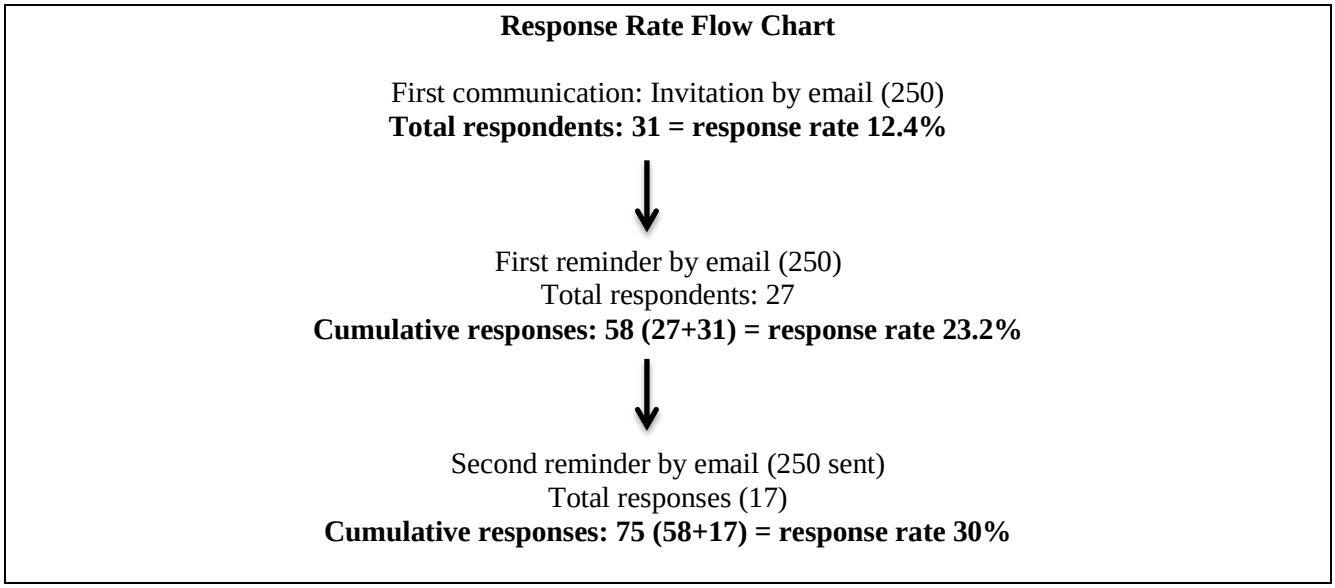
Communications with the participants were the following:

1. An invitation was emailed on January 23, 2015 to 232 Canadian neonatal nurses. The survey was designed in English and French language. The invitation was addressed to CANN members and given that was sent it by the CANN organization and not directly from FluidSurvey™ software, it was not possible to add the logo of the university and photographs of the committee members (see Appendix L). Also, an invitation was sent on January 21, 2015 to Neonatal nurses from Canada (18 neonatal nurses) that the investigator met in three different neonatal nurses conferences from 2012 to 2014 (see Appendix R). These neonatal nurses voluntary shared their email during the conferences and approval to be contacted in the future.
2. A reminder was sent on February 2, 2015 to the members of the CANN (see Appendix N). Also, a reminder was sent by the investigator on January 28, 2015 to the neonatal nurses from conferences (see Appendix S).

3. A final reminder was sent by email on Feb 9, 2015 to the members of the CANN (see Appendix P). Also the investigator sent a reminder on February 11, 2015 to the neonatal nurses from conferences (see Appendix T).

Figure 3

Response Rate Flow Chart Survey 2 version 2



Demographic Characteristics for survey 2 version 2

The demographic characteristic of the participants for survey 2, version 2 (sex, age, country, level of education, current position, type of unit, type of hospital and time working in NICU) are presented in Table 28. There were 75 participants in this study. The majority of the participants (n= 58 [98.3%]) were female. The most prevalent age range was 46-55 years (*n*= 18 [30.0%]), followed by 56-65 years (*n*= 13 [21.7%]). Several participants (n = 26 [46.4.1%]) were from Western Canada. The most prevalent level of education among the participants was Bachelor of Nursing or Bachelor of Nursing Science (n=35 [59.3%]). The majority of the participants (n=43 [74.1%] worked as a staff nurse. Over half of the participants worked in a tertiary referral center (n=31

[51.7%] and regional hospitals (n= 15 [25.0%]). The majority of the participants (n=30 [53.6%]) work in NICUs Level III. Several participants had worked in NICUs more than 20 years (*n*=28 [46.7%]).

Table 28

Demographics Characteristics of Nurses

Characteristic (n)	*n* (%)
Sex (59)	
Female	58 (98.3)
Male	1 (1.7)
Age range (60)	
< 26 years	9 (15.0)
26-35 years	11 (18.3)
36-45 years	8 (13.3)
46-55 years	18 (30.0)
56-65 years	13 (21.7)
> 65 years	1 (1.7)
Location (56)	
Western Canada	26 (46.4)
Central Canada	22 (39.3)
Eastern Canada	8 (14.3)
Levels of Education (59)	
Bachelor of Nursing or Bachelor of Nursing Science	35 (59.3)
Master of Nursing	9 (15.3)
Doctoral Degree (Ph.D)	1 (1.7)
Other	14 (23.7)
Current Position in the NICU (58)	
Staff Nurse	43 (74.1)
Clinical Nurse Specialist	4 (6.9)
Nurse Educators	6 (10.3)
Nurse Manager	1 (1.7)
Others positions at the NICU	4 (6.9)
Types of unit (s) (56)	
Specialty neonatal care level II	16 (28.6)
Neonatal Intensive care level II and level III	5 (8.9)
Neonatal intensive Care level III	30 (53.6)
Others	5 (8.9)
Type of Hospital (60)	
Community Hospital	10 (16.7)

Regional Hospital	15 (25.0)
Tertiary referral center	31 (51.7)
Others	1 (1.7)
I do not know	3 (5.0)
Time Working at the NICU (60)	
< 1 year	3 (5.0)
>1 years but ≤ 5 years	11 (18.3)
>5 years but ≤10 years	8 (13.3)
>10 years but ≤ 20 years	10 (16.7)
> 20 years	28 (46.7)

Descriptive statistics about statements assessing factors affecting the implementation of probiotics are presented. Next, the results of test of independence (chi-square and fisher's exact test) between the outcome variable and these factors affecting the implementation of probiotics are presented. The responses of the outcome variable are shown in Table 31.

Table 29

Nurses' Opinion of Probiotic Use

Statement	Strongly Disagree *n* (%)	Disagree *n* (%)	Unsure/ uncertain *n* (%)	Agree *n* (%)	Strongly Agree *n* (%)
Probiotics should be routinely administered to premature infants who meet selected criteria (62)	0 (0.0)	1 (1.6)	17 (27.4)	31 (50.0)	13 (21.0)

The factors from the TDF that might affect the implementation of probiotics are presented in Table 30. The most frequent responses in this questionnaire to statements that reflect aspects that might negatively affect the implementation of probiotics are the following:

- Lack of certainty regarding optimal products, dosages, and formulations of probiotics for premature infants (*n*=44[66.7%]).
- They believe that more evidence is required to support the routine use of probiotics in premature infants (*n*=40 [60.6]).
- Lack of experience prescribing probiotics (*n*=48 [72.7%]).
- They are not up to date on the scientific evidence supporting the use of probiotics for premature infants (*n*= 37([56.9].

Table 30

Responses from Nurses about Factors Affecting the Implementation of Probiotics

Factors affecting the implementation of probiotics					
Chapter Domain (n)	Strongly Disagree *n* (%)	Disagree *n* (%)	Unsure/ uncertain *n* (%)	Agree *n* (%)	Strongly Agree *n* (%)
Knowledge					
I am up-to-date on the scientific evidence supporting the use of probiotics for premature infants (61)	10 (13.4)	26 (42.6)	16 (26.2)	9 (14.8)	0 (0.0)
There is strong evidence supporting the use of probiotics for premature infants (62)	0 (0.0)	6 (9.7)	35 (56.5)	21 (33.9)	0 (0.0)
More evidence is required to support the routine use of probiotics in premature infants (62)	0 (0.0)	4 (6.5)	20 (32.3)	29 (46.8)	9 (14.5)
The evidence regarding the use of probiotics for premature infants has flaws (61)	0 (0.0)	2 (3.3)	50 (82.0)	9 (14.8)	0 (0.0)
In spite of the evidence, many questions still remain about optimal products, dosages, and formulations of probiotics that can be given to preterm infants (62)	0 (0.0)	1 (1.6)	20 (32.3)	34 (54.8)	7 (11.3)
I can name at least one probiotic product that can be given to premature infants (62)	5 (8.1)	16 (25.8)	11 (17.7)	21 (33.9)	9 (14.5)
I am aware of contraindications for giving probiotic supplements to premature infants (61)	6 (9.8)	24 (39.3)	19 (31.1)	12 (19.7)	0 (0.0)
Skills					
I have enough skills to evaluate the results of the evidence (e.g., randomized control trials, meta-analyses) regarding probiotic use for premature infants (62)	4 (6.5)	12 (19.4)	19 (30.6)	25 (40.3)	2 (3.2)
I know how to administer probiotics to premature infants (62)	5 (8.1)	21 (33.9)	11 (17.7)	20 (32.3)	5 (8.1)
I have experience administering probiotics for premature infants (62)	18 (29.0)	26 (41.9)	4 (6.5)	12 (19.4)	2 (3.2)
Professional role and identity					

Most of my colleagues believe that more evidence is required to support the use of probiotics for premature infants (61)	1 (1.6)	7 (11.5)	32 (52.5)	20 (32.8)	1 (1.6)
Administration of probiotics is not supported by current clinical practice guidelines in Canada (61)	1 (1.6)	13 (21.3)	38 (62.3)	8 (13.1)	1 (1.6)
Beliefs					
I am confident in my ability to administer probiotics for premature infants (61)	3 (4.9)	10 (16.4)	20 (32.8)	26 (42.6)	2 (3.3)
Administering probiotics would make me feel uncomfortable (62)	9 (14.5)	36 (58.1)	13 (21.0)	4 (6.5)	0 (0.0)
I am concerned about the safety of administering probiotics to premature infants (62)	2 (3.2)	21 (33.9)	17 (27.4))	20 (32.3)	2 (3.2)
Administering probiotics might put me at risk of a malpractice suit (61)	5 (8.2)	32 (52.5)	22 (36.1)	1 (1.6)	1 (1.6)
Opinions					
Probiotics are associated with positive outcomes in the health of premature infants (59)	1(1.6)	0 (0.0)	25 (42.4)	13 (50.8)	3 (5.1)
Administering probiotics is one of the best recent medical advances in neonatology (59)	1 (1.7)	5 (8.5)	35 (59.3)	16 (27.1)	2 (3.4)
Giving probiotics for premature infants is risky (59)	1 (1.7)	19 (32.2)	31 (52.5)	8 (13.6)	0 (0.0)
Intention					
I am actively looking into the evidence supporting the use of probiotics for premature infants because I would like to have this practice implemented at my health care facility (59)	1 (1.7)	24 (40.7)	12 (20.3)	20 (33.9)	2 (3.4)
I have no interest in recommending the use of probiotics to premature infants to the neonatal health care team (60)	8 (13.3)	34 (56.7)	16 (26.7)	2 (3.3)	0 (0.0)
My colleagues are contemplating prescribing probiotics to premature infants (59)	2 (3.4)	11 (18.6)	21 (35.6)	18 (30.5)	7 (11.9)
There is enough evidence supporting the use of probiotics for premature infants for me to recommend their use to my colleagues (59)	2 (3.4)	7 (11.9)	36 (61.0)	13 (22.0)	1 (1.7)
Decision process					
It is difficult to decide whether or not I support the use of probiotics for premature infants (55)	3 (5.5)	20 (36.4)	8 (14.5)	22 (40.0)	2 (3.6)
Deciding whether or not to prescribe probiotics is difficult for the health care team (56)	1 (1.8)	10 (17.9)	21 (37.5)	23 (41.1)	1 (1.8)

Deciding whether or not to prescribe probiotics for premature infants generates conflict within the health care team (56)	1 (1.8)	14 (25.0)	20 (35.7)	19 (33.9)	2 (3.6)
The evidence regarding the use of probiotics is confusing (55)	1 (1.8)	9 (16.4)	31 (56.4)	13 (23.6)	1 (1.8)
It is difficult to recommend specific probiotic products and formulation to my colleagues (55)	1 (1.8)	6 (10.9)	22 (40.0)	21 (38.2)	5 (9.1)
Feelings					
Fears about causing harm prevents me from recommending to my colleagues the use of probiotics for premature infants (55)	2 (3.6)	24 (43.6)	22 (40.0)	6 (10.9)	1 (1.8)
Environmental context and resources					
I am knowledgeable about the Health Canada regulations on the safety and quality of probiotic products in Canada (56)	8 (14.3)	32 (57.1)	9 (16.1)	7 (12.5)	0 (0.0)
I am confident that the Health Canada regulations ensure that probiotics products are safe to be given to premature infants (56)	2 (3.60	5 (8.9)	29 (51.8)	18 (32.1)	2 (3.6)
Sufficient opportunities are available to learn about probiotics for premature infants (56)	5 (8.9)	18 (32.1)	19 (33.9)	14 (25.0)	0 (0.0)
I do not have online access to the scientific evidence about use of probiotics for premature infants (56)	10 (17.9)	28 (50.0)	10(17.9)	8 (14.3)	0 (0.0)
Lack of time prevents me from accessing evidence regarding the efficacy of probiotics for premature infants (56)	1 (1.8)	21 (37.5)	10 (17.9)	23 (41.1)	1 (1.8)
I do not have enough time to help establish a guideline for the use of probiotics for premature infants (55)	2 (3.6)	11 (20.0)	16 (29.1)	26 (47.3)	0 (0.0)
I do not have adequate time to discuss the use of probiotics with my colleagues (56)	1 (1.8)	27 (48.2)	12 (21.4)	16 (28.6)	0 (0.0)
I am concerned about the quality of the currently available probiotic products which may be given to premature infants (54)	1 (1.9)	12 (22.2)	28 (51.9)	10 (18.5)	3 (5.6)
I do not have institutional support for establishing the use of probiotics as a standardized practice in my unit (56)	4 (7.1)	11 (19.6)	19 (33.9)	18 (32.1)	4 (7.1)
Lack of standardized guidelines in Canada prevents me to recommend the use of probiotics for premature infants (55)	1 (1.8)	4 (7.3)	33 (60.0)	16 (29.1)	1 (1.8)
Social Influences					
I have received mostly negative feedback from other health care professionals about giving probiotics to premature infants (56)	6 (10.7)	36 (64.3)	9 (16.1)	4 (7.1)	1 (1.8)
My colleagues do not support the use of probiotics for premature infants (55)	3 (5.5)	20 (36.4)	26 (47.3)	6 (10.9)	0 (0.0)

Parents have expressed to me that they want probiotics to be prescribe for their premature infants (55)	7 (12.7)	19 (34.5)	11 (20.0)	15 (27.3)	3 (5.5)
Parental request to prescribe probiotics has influenced medical practice (56)	3 (5.4)	19 (33.9)	19 (33.9)	14 (25.0)	1 (1.8)
The administration of probiotics in some health care facilities in the U.S. and Canada motivates me to recommend their use to my colleagues (56)	2 (3.6)	12 (21.4)	22 (39.3)	19 (33.9)	1 (1.8)

Responses to questions that assessed knowledge about probiotics are summarized in Table 31. In total 15 knowledge questions were asked. The mean knowledge score was 8.52 out of 15 (56.8%). This result demonstrates that participants have a low knowledge about probiotics.

Table 31

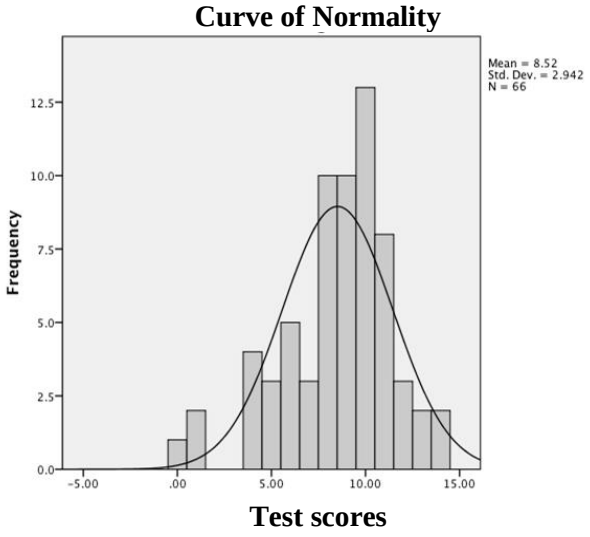
Responses from Nurses' Survey to Knowledge Questions about Probiotics

Knowledge Domain (n)	TRUE *n* (%)	FALSE *n* (%)	UNSURE *n* (%)
Probiotics are the same as prebiotics (76)	1 (1.3)	54 (71.1)*	21 (27.6)
To be probiotic, a bacteria must confer a health benefit (77)	44 (57.1)*	11 (14.3)	22 (28.6)
Probiotic can be live, dead, or pasteurized bacteria (76)	21 (27.6)	24 (31.6)*	31 (40.8)
Probiotics may be found in:			
Soy beans (72)	17 (23.6)	16 (22.2)	39 (54.2)
Cheese (72)	41(56.1)*	11 (15.3)	20 (27.8)
Breast Milk (72)	50 (69.4)*	7 (9.7)	15 (20.8)
Green Tea (72)	11(15.3)	30 (41.7)*	31 (43.1)
Yogurt (71)	64 (90.1)*	2 (2.8)	5 (7)
Examples of probiotics strains include:			
Streptococcus thermophiles (71)	2 (2.8)*	37 (52.1)	32 (45.1)
Lactobacillus reuteri (71)	51 (71.8)*	0 (0)	20 (28.2)
Bifidobacterium bifidum (72)	50 (69.4)*	1 (1.4)	21(21.2)
Staphylococcus pneumonia (71)	0 (0.0)	54 (76.1)*	17 (23.9)
Probiotics are being given to premature infants in some hospitals in Canada or U.S.(72)	56 (77.8)*	0(0)	16 (22.2)
There is a standardized North American guideline in with dosage and formulation for probiotic use for premature infants (72)	9 (12.5)	35 (48.6)*	28 (38.9)
A Health Canada Product license indicates that probiotic products are safe, effective and of high quality under recommended conditions of use (68)	36 (52.9)*	2 (2.9)	30 (44.1)

Correct answer *

T- test and non-parametric test among knowledge score groups. The participant's response to the outcome variable "Probiotics should be routinely administered to premature infants who meet selected criteria" was divided into two groups (the responses obtained from strongly disagree, disagree, uncertain/unsure formed one group, the responses obtained from strongly agree to agree formed the second group). T test and a non-parametric test were performed to determine if the mean knowledge scores were statistically different among the groups.

Normality is a requirement to perform t- test. A curve of normality was performed on the scores of the knowledge questionnaire. The curve of normality showed skewedness to the left (skewedness: -0.78).



The Kolmogorov-Smirnov test was performed to test normality in the distribution of the knowledge scores and it reported a p = 0.001. This result showed that the distribution is not normal because normal distributions have a p value > 0.05 (Elliot & Woodward, 2007). Although this test showed that the distribution of knowledge scores is not normal, t-test was performed (Table 32). Abnormal distribution do not have large effect in the t-test (Lund & Lund, 2014).

Table 32.

T-test of knowledge Scores between 2 Groups

Groups (n)	M	SD	DF	T	F	P
Disagree/unsure (18)	7.3	3.82	0.90076	-1.64	6.34	0.11
Agree (44)	9	2.51	0.37916			

*p<0.05

The t-test failed to reveal a statistically difference among the mean groups (p=0.11). In addition, the non-parametric test Mann Whitney U test revealed that the group "agree" was not statistically significantly higher than the "disagree/uncertain/ unsure" group (p = 0.096). The Mann Whitney U test was used because the Kolmogorov-Smirnov test reported that the knowledge scores are not normally distributed (Everitt & Skrondal, 2010).

Factors affecting the implementation of probiotics and the outcome variable in survey 2, version 2. Independent tests (fisher's exact test and chi-square test) between each of the questions related to factors affecting the implementation of probiotics and the outcome variable were performed (Table 33). It is important to note that only one participant answered disagree in the outcome variable. Thus, the group disagree, strongly disagree, uncertain/ unsure formed one group and the group agree and strongly agree formed the second group.

The results of the tests showed factors affecting implementation of probiotics that were significantly associated with the outcome variable.

The tests results revealed that the participants who disagreed/unsure or uncertain with the statement "Probiotics should be routinely administered to premature infants who meet selected criteria" were more likely to disagree with the following statements (only results with $p < 0.01$ are presented below):

- I am confident in my ability to administer probiotics for premature
- There is enough evidence supporting the use of probiotics for premature infants for me to recommend their use to my colleagues.
- Probiotics are associated with positive outcomes in the health of premature infants
- I know how to administer probiotics to premature infants

- I am confident that the Health Canada regulations ensure that probiotics products are safe to be given to premature infants
- My colleagues do not support the use of probiotics for premature infants
- The administration of probiotics in some health care facilities in The U.S. and Canada motivates me to recommend their use to my colleagues
- Parental request to prescribe probiotics has influenced medical practice

The tests results showed that the participants who disagreed/ unsure/uncertain with the statement "Probiotics should be routinely administered to premature infants who meet selected criteria" were more likely to agree with the following statements (only results with $p < 0.01$ are presented below):

- I am concerned about the safety of administering probiotics to premature infants
- It is difficult to decide whether or not I support the use of probiotics for infants

Table 33

Responses from Nurses about Factors Affecting the Implementation of Probiotics and the Outcome Variable

		Probiotics should be routinely administered to premature infants who meet selected criteria		
Domain (n)	Values	Disagree Unsure/ Uncertain *n* (%)	Agree *n* (%)	Fisher's exact test P value
Knowledge				
I am up-to-date on the scientific evidence supporting the use of probiotics for premature infants (62)	Disagree	14 (38.9)	22 (61.1)	0.195
	Uncertain/ Unsure	3 (18.8)	13 (81.3)	
	Agree	1 (11.1)	8 (88.9)	
There is strong evidence supporting the use of probiotics for premature infants (62)	Disagree	2 (33.3)	4 (66.7)	0.065
	Uncertain/ Unsure	14 (40.0)	21 (60.0)	
	Agree	2 (9.5)	19 (90.5)	
More evidence is required to support the routine use of probiotics in premature infants (62)	Disagree	0 (0.0)	4 (100.0)	0.239
	Uncertain/ Unsure	4 (20.0)	16 (80.0)	
	Agree	14 (36.8)	24 (63.2)	
The evidence regarding the use of probiotics for premature infants has flaws (61)	Disagree	0 (0.0)	2 (100.0)	0.999
	Uncertain/ Unsure	15 (30.0)	35 (70.0)	
	Agree	3 (33.3)	6 (66.7)	
In spite of the evidence, many questions still remain about optimal products, dosages, and formulations of probiotics that can be given to preterm infants (62)	Disagree	0 (0.0)	1 (100.0)	0.120
	Uncertain/ Unsure	9 (45.0)	11 (55.0)	
	Agree	9 (22.0)	32 (78.0)	
I can name at least one probiotic product that can be given to premature infants (62)	Disagree	8 (38.1)	13 (61.9)	*0.019
	Uncertain/ Unsure	6 (54.5)	5 (45.5)	
	Agree	4 (13.3)	26 (86.7)	
I am aware of contraindications for giving probiotic supplements to premature infants (61)	Disagree	9 (30.0)	21 (70.0)	*0.485
	Uncertain/ Unsure	7 (36.8)	12 (63.2)	
	Agree	2 (16.7)	10 (83.3)	
Skills				
I have enough skills to evaluate the results of the evidence (e.g., randomized	Disagree	4 (25.0)	12 (75.0)	*0.909
	Uncertain/ Unsure	6 (31.6)	13 (68.4)	

control trials, meta-analyses) regarding probiotic use for premature infants (62)	Agree	8 (29.6)	19 (70.4)	
I know how to administer probiotics to premature infants (62)	Disagree	11(42.3)	15 (57.7)	*0.011
	Uncertain/ Unsure	5 (45.5)	6 (54.5)	
	Agree	2 (8.0)	23 (92.0)	
I have experience administering probiotics for premature infants (62)	Disagree	15 (34.1)	29 (65.9)	0.357
	Uncertain/ Unsure	1 (25.0)	3 (75.0)	
	Agree	2 (14.3)	12 (85.7)	
Professional role and identity				
Most of my colleagues believe that more evidence is required to support the use of probiotics for premature infants (61)	Disagree	2 (25.0)	6 (75.0)	*0.680
	Uncertain/ Unsure	11 (34.4)	21 (65.6)	
	Agree	5 (23.8)	16 (76.2)	
Administration of probiotics is not supported by current clinical practice guidelines in Canada (61)	Disagree	2 (14.3)	12 (85.7)	0.284
	Uncertain/ Unsure	14 (36.8)	24 (63.2)	
	Agree	2 (22.2)	7 (77.8)	
Beliefs				
I am confident in my ability to administer probiotics for premature infants (61)	Disagree	10 (76.9)	3 (23.1)	<0.0001
	Uncertain/ Unsure	5 (25.0)	15 (75.0)	
	Agree	3 (10.7)	25 (89.3)	
Administering probiotics would make me feel uncomfortable (62)	Disagree	7 (15.6)	38 (84.4)	<0.0001
	Uncertain/ Unsure	11 (84.6)	2 (15.4)	
	Agree	0 (0.0)	4 (100.0)	
I am concerned about the safety of administering probiotics to premature infants (62)	Disagree	1 (4.3)	22 (95.7)	*0.001
	Uncertain/ Unsure	5 (29.4)	12 (70.6)	
	Agree	12 (54.5)	10 (45.5)	
Administering probiotics might put me at risk of a malpractice suit (61)	Disagree	7 (18.9)	30 (81.1)	0.046
	Uncertain/ Unsure	10 (45.5)	12 (54.5)	
	Agree	1 (50.0)	1 (50.0)	
Opinions				
Probiotics are associated with positive outcomes in the health of premature infants (59)	Disagree	1 (100.0)	0 (0.0)	0.003
	Uncertain/ Unsure	12 (48.0)	13 (52.0)	
	Agree	5 (15.2)	28 (84.8)	
Administration of probiotics is one of the best recent medical advances in neonatology (59)	Disagree	4 (66.7)	2 (33.3)	0.028
	Uncertain/ Unsure	12 (34.3)	23 (65.7)	
	Agree	2 (11.1)	16 (88.9)	
Giving probiotics to premature infants is risky (59)	Disagree	1 (5.0)	19 (95.0)	*0.009
	Uncertain/ Unsure	14 (45.2)	17 (54.8)	

	Agree	3 (37.5)	5 (62.5)	
Intention				
I am actively looking into the evidence supporting the use of probiotics for premature infants because I would like to have this practice implemented at my health care facility (59)	Disagree	11 (44.0)	14 (56.0)	*0.022
	Uncertain/ Unsure	5 (41.7)	7 (58.3)	
	Agree	2 (9.1)	20 (90.9)	
I have no interest in recommending the use of probiotics for premature infants to the neonatal health care team (60)	Disagree	10 (23.8)	32 (76.2)	0.224
	Uncertain/ Unsure	7 (43.8)	9 (56.3)	
	Agree	1 (50.0)	1 (50.0)	
My colleagues are contemplating prescribing probiotics to premature infants (59)	Disagree	5 (38.5)	8 (61.5)	*0.323
	Uncertain/ Unsure	8 (38.1)	13 (36.1)	
	Agree	5 (20.0)	20 (80.0)	
There is enough evidence supporting the use of probiotics for premature infants for me to recommend their use to my colleagues (59)	Disagree	5 (55.6)	4 (44.4)	0.003
	Uncertain/ Unsure	13 (36.1)	23 (63.9)	
	Agree	0 (0.0)	14 (100.0)	
Decision process				
It is difficult to decide whether or not I support the use of probiotics for premature infants (55)	Disagree	2 (8.7)	21 (91.3)	*0.001
	Uncertain/ Unsure	2 (25.0)	6 (75.0)	
	Agree	14 (58.3)	10 (41.7)	
Deciding whether or not to prescribe probiotics is difficult for the health care team (56)	Disagree	2 (18.2)	9 (81.8)	*0.512
	Uncertain/ Unsure	8 (38.1)	13 (61.9)	
	Agree	8 (33.3)	16 (66.7)	
Deciding whether or not to prescribe probiotics for premature infants generates conflict within the health care team (56)	Disagree	3 (20.0)	12 (80.0)	*0.451
	Uncertain/ Unsure	8 (40.0)	12 (60.0)	
	Agree	7 (33.3)	14 (66.7)	
The evidence regarding the use of probiotics is confusing (56)	Disagree	3 (30.0)	7 (70.0)	0.678
	Uncertain/ Unsure	9 (29.0)	22 (71.0)	
	Agree	6 (42.1)	8 (57.1)	
It is difficult to recommend a specific probiotic products and formulations to my colleagues (55)	Disagree	1 (14.3)	6 (85.7)	0.523
	Uncertain/ Unsure	7 (31.8)	15 (68.8)	
	Agree	10 (38.5)	16 (61.5)	
Feelings				
Fears about causing harm prevents me from recommending to my colleagues the use of probiotics for premature infants (55)	Disagree	7 (26.9)	19 (73.1)	0.670
	Uncertain/ Unsure	8 (36.4)	14 (63.6)	
	Agree	3 (42.9)	4 (57.1)	
Environmental context and resources				

I am knowledgeable about the Health Canada regulations on the safety and quality of probiotic products in Canada (56)	Disagree	13 (32.5)	27 (67.5)	0.534
	Uncertain/ Unsure	4 (44.4)	5 (55.6)	
	Agree	1 (14.3)	6 (85.7)	
I am confident that the Health Canada regulations ensure that probiotics products are safe to be given to premature infants (56)	Disagree	6 (85.7)	1 (14.3)	0.008
	Uncertain/ Unsure	7 (24.1)	22 (75.9)	
	Agree	5 (25.0)	15 (75.0)	
Sufficient opportunities are available to learn about probiotics for premature infants (56)	Disagree	7 (30.4)	16 (69.6)	*0.210
	Uncertain/ Unsure	10 (52.6)	9 (47.4)	
	Agree	1 (7.1)	13 (92.9)	
I do not have online access to the scientific evidence about use of probiotics for premature infants (56)	Disagree	12 (31.6)	26 (68.4)	0.828
	Uncertain/ Unsure	4 (40.0)	6 (60.0)	
	Agree	2 (25.0)	6 (75.0)	
Lack of time prevents me from accessing evidence regarding the efficacy of probiotics for premature infants (56)	Disagree	6 (27.3)	16 (72.7)	*0.764
	Uncertain/ Unsure	4 (40.0)	6 (60.0)	
	Agree	8 (33.3)	16 (66.7)	
I do not have enough time to help establish a guideline for the use of probiotics for premature infants (55)	Disagree	5 (38.5)	8 (61.5)	*0.865
	Uncertain/ Unsure	6 (37.5)	10 (62.5)	
	Agree	7 (26.9)	19 (73.1)	
I do not have adequate time to discuss the use of probiotics with my colleagues (56)	Disagree	8 (28.6)	20 (71.4)	*0.826
	Uncertain/ Unsure	4 (33.3)	8 (66.7)	
	Agree	6 (37.5)	10 (62.5)	
I am concerned about the quality of the currently available probiotic products which may be given to premature infants (54)	Disagree	1 (7.7)	12 (92.3)	0.075
	Uncertain/ Unsure	11 (39.3)	17 (60.7)	
	Agree	6 (46.2)	7 (53.8)	
I do not have institutional support for establishing the use of probiotics as a standardized practice in my unit (56)	Disagree	3 (20.0)	12 (80.0)	*0.062
	Uncertain/ Unsure	10 (52.6)	9 (47.4)	
	Agree	5 (22.7)	17 (77.3)	
Lack of standardized guidelines in Canada prevents me to recommend the use of probiotics for premature infants (55)	Disagree	2 (40.0)	3 (60.0)	0.556
	Uncertain/ Unsure	9 (27.2)	24 (72.7)	
	Agree	7 (41.2)	10 (58.8)	
Social Influences				
I have received mostly negative feedback from other health care professionals about giving probiotics to premature infants (56)	Disagree	10 (23.8)	32 (76.2)	0.036
	Uncertain/ Unsure	6 (66.7)	3 (33.3)	
	Agree	2 (40.0)	3 (60.0)	
	Disagree	3 (13.0)	20 (87.0)	0.006

My colleagues do not support the use of probiotics for premature infants (55)	Uncertain/ Unsure	14 (53.8)	12 (46.2)	
	Agree	1 (16.7)	5 (83.3)	
Parents have expressed to me that they want me to prescribe probiotics for their premature infants (55)	Disagree	12 (46.2)	14 (53.8)	*0.112
	Uncertain/ Unsure	3 (27.8)	8 (72.7)	
	Agree	3 (16.7)	15 (83.3)	
Parental request to prescribe probiotics has influenced medical practice (56)	Disagree	10 (45.5)	12 (54.5)	0.008
	Uncertain/ Unsure	8 (42.1)	11 (57.9)	
	Agree	0 (0.0)	15 (100.0)	
The administration of probiotics in some health care facilities in the United States and Canada motivates me to recommend them to premature infants (56)	Disagree	7 (50.0)	7 (50.0)	0.005
	Uncertain/ Unsure	10 (45.5)	12 (54.5)	
	Agree	1 (5.0)	19 (95.0)	

* Chi-Square

Demographics and the Outcome Variable. A contingency table of demographics (sex, age, time of working in NCIU, level of education, current position, type of hospital and locations) and the outcome variable are shown in Table 34. The fisher's exact test or chi-square test reported that there is not a significant relation between the outcome variable and sex, age, type of hospital, time of working in NICUs and geographic location ($p>0.05$).

Table 34

Demographics Characteristics of Nurses and Outcome Variable

	Probiotics should be routinely administered to premature infants who meet selected criteria		
Demographics (n)	Unsure/ Uncertain *n* (%)	Agree *n* (%)	Chi Square test P value
Sex (55)			
Female	17 (31.5)	37 (68.5)	*0.32
Male	1 (100.0)	0 (0.0)	
Age (56)			
<35 years	5 (25.0)	15 (75.0)	0.09
36-55 years	6 (25.0)	18 (75.0)	
>56 years	7 (58.3)	5 (41.7)	
Time working in NICU (56)			

≤ 20years	6 (20.0)	24 (80.0)	**0.07
>20 years	12 (46.2)	14 (53.8)	
Level of Education			
Bachelor of Nursing or Bachelor of Nursing Science	8 (24.2)	25 (75.8)	*0.34
Master of Nursing	5 (62.5)	3 (37.5)	
Doctoral Degree	0 (0.0)	1 (100.0)	
Other	5 (38.5)	8 (61.5)	
Current position (54)			
Staff nurse	12 (30.0)	28 (70.0)	*0.07
Clinical nurse specialist	1 (25.0)	3 (75.0)	
Nurse educator	3 (60.0)	2 (40.0)	
Nurse Manager	1 (100.0)	0 (0.0)	
Other	1 (100.0)	3 (75.0)	
Type of hospital (54)			
Regional Hospital	3 (20.0)	12 (80.0)	*0.47
Tertiary referral center	7 (25.0)	21 (75.0)	
Community hospital, others and I do not know	7 (63.6)	4 (36.4)	
Location (56)			
Western Canada	7 (26.9)	19 (73.1)	0.52
Eastern Canada	2 (25.0)	6 (75.0)	
Central Canada	9 (40.9)	13 (59.1)	

*****Fisher's exact test
** Continuity correction p value used because it is a 2 x2 table

Summary

Based on the results of this study, the two research questions were answered as follows:

1. What are the current practices of probiotics in premature infants in Canada and the U.S.? Survey 1 reported 41 NICUs are currently administering probiotics (3.9% of the units surveyed), from which 6 from NICUs in Canada and 35 are from NICUs in the U.S. In total, 15 different kind of products were given in the NICUs surveyed. Only one type of probiotic product is given in each of the NICUs that are using probiotics. NICUs in Canada mostly give FloraBaby™ (n=5 of the 6 units). In Canada probiotics is mostly given in the Eastern Canada (n =2 unit of the 6 units) and Central Canada (n =2 unit of the 6 units).Regarding the time of use in the NICU, in Canada they have been giving them since a year ago. Probiotics products mostly used in the U.S. are Culturelle® (n=6 [17.1%]), VSL #3 (n=6 [17.1%]) and Biogaia® (n=5 [14.28%]). In the U.S., probiotics has been used for the last 10 years. In U.S probiotics are mostly used in the Midwest region (n=12 units of the 35 units) and the west region (n=9 units of the 35 units). Other data regarding the details of the formulation such as how the product is administered, what are the contraindications, and when it is discontinued were also collected.

2. What are the most significant factors that influence the willingness of health care professionals to support the use of probiotics? The health care professionals that participated in this survey were Medical Directors of NICUs, neonatologists, nurse practitioners and nurses. The responses regarding the tests of independence (chi-square and fisher's exact test) between the outcome variable and statements of factors affecting the implantation of probiotics were similar among Medical Directors, neonatologists and nurse practitioners. However, lack of association were observed between the outcome viable and demographics characteristics such sex, age, type of hospital, time of working in

NICUs and geographic location. The most significant factors that are affecting the willingness of Medical Directors, neonatologists and nurse practitioners are the following:

Negative perceptions about the evidence:

- They believe that the evidence regarding probiotics is not strong, is not enough and has flaws.
- They believe that more evidence is required to support this practice.
- Most of their colleagues believe that more evidence is required to support the use of probiotics for premature infants
- They believe that probiotics is not associated with positive outcomes in the health for premature infants.
- They believe that the evidence regarding the use of probiotics is confusing.

Lack of knowledge:

- The perceived that they have lack of knowledge regarding the formulations and dosages of probiotics to prescribe to premature infants.
- Health care professionals with lower knowledge scores were disagree or unsure regarding the potential use of probiotics in the NICUs.

Difficulties in the decision process:

- They expressed that it is difficult to decide whether or not they support the use of probiotics for premature infants.

Absence of Clinical guidelines:

- Probiotics is not supported by current clinical practice guidelines in Canada or U.S.

Lack of intentions towards implementation of this practice:

- They are not contemplating the use of probiotics.
- They are not interested in looking into the evidence.
- They have no interest in prescribing probiotics to premature infants.

Concerns about the safety of probiotics

- They are concerned about the safety of administering probiotics to premature infants.
- They are concerned about the quality of the currently available probiotic products which may be given to premature infants.

Negative feelings and mindset towards this practice:

- They believe that prescribing probiotics for premature infants is risky.
- They feel that prescribing probiotics would make them feel uncomfortable.
- They believe that probiotics is not the best medical advantage in neonatology.
- The administration of probiotics in some health care facilities in the U.S. and Canada do not motivates them to prescribe.
- Fears about causing harm prevents them from prescribing probiotics to premature infants.

The statistical test performed between the outcome variable and statements of factors affecting the implantation of probiotics among nurses reflect the most significant factors that negatively affect the willingness of nurses to support the use of probiotics. These factors are the following:

Lack of knowledge and skills

- They do not feel confident in the ability to administer probiotics for premature infants
- They perceive, they do not know how to administer of probiotics
- They scored low in the knowledge questions about probiotics.

Negative perceptions about the evidence:

- They believe that probiotics is not associated with positive outcomes in the health for

Premature infants.

Concerns about the safety of probiotics

- They are concerned about the safety of administering probiotics to premature infants

Difficulties in the decision making process:

- They perceived difficult to decide whether or not they support the use of probiotics for infants

Negative feelings regarding regulations

- They think that the Health Canada regulations do not ensure that probiotics products are safe to be given to premature infants

Lack of a supportive environment

- My colleagues do not support the use of probiotics for premature infants

The multiples domains of the TDF help to assess different factor that are possible affecting the implementation of probiotics. The results of the surveys that were administered to health care professional pointed up that the domains more affected were knowledge, optimism (labeled opinions in the survey), beliefs about consequences (labeled beliefs in the survey) , decision process, environmental process and resources, and social influences. In average 2 to 4 items of these domains were related to factors affecting the implementations of probiotics among health care professionals.

Chapter Six: Discussion

In this chapter, I begin with a discussion of the study's major findings, within the context of recent publications. The appropriateness of the framework that guided this study is critiqued, followed by sections on strengths and limitations. Finally, I present recommendations for future research, practice, and policy.

Given the pronounced lack of studies on current practices and factors affecting the implementation of probiotics in NICUs, my study serves to highlight important aspects and controversies relating to this clinical practice. It is my hope that the findings here will guide future research and reduce barriers to implementation of this practice.

Current practices

Of the 197 NICU medical directors in the U.S. and Canada who responded to the survey, only a quarter of NICUs (47 [23.9%]), represented by 39 in the U.S. and 8 in Canada, prescribed probiotics. The prevalence of prescribing probiotics in NICUs in the U.S. and Canada is relatively low compared to other countries. Although no similar studies related to prescribing practices in other countries exist, there are some publications that provide insight into the widespread use of probiotics. In Australia, 80% (16 out of 20) of tertiary hospitals routinely administer probiotics to premature infants (Deshpande, Shingde, Leroi, & Xiao, 2013). Similarly, in Germany, 74% (34 out of 46) of the NICUs that are members of the German Neonatal Network use probiotics on premature infants (Härtel et al., 2014). However, the results of this study cannot be generalized due to the low response rate in the medical director's survey (18.8%). It is possible that more NICUs are routinely administering probiotics. Alternately, this prevalence rate may be overestimated, because MDs in NICUs who have administered probiotics may have been more likely to respond to this survey than those MDs who do not routinely use probiotics. Use of probiotics was most frequently reported by

medical directors in the Midwest U.S. (12 out of 39 participants), Central Canada (2 out of 8 participants) and Eastern Canada (2 out of 8 participants). The reason(s) why reporting of probiotics use is more prevalent in these regions is/are unknown, as there are no previous reports in the literature.

A total of 41 medical directors provided details of their protocols and reported the variability in the probiotics formulations used across Canada and the U.S. Such variations could be due to the absence of national guidelines on probiotics, their availability, and familiarity with probiotics products in these countries. The probiotics products that are given most frequently in the U.S. included Culturelle (*Lactobacillus* GG, 6 participants), VSL #3 (1 strain of *Streptococcus*, 3 strains of *Bifidobacterium,* and 4 strains of *Lactobacillus*, 6 participants), while in Canada they comprise FloraBaby (*L. rhamnosus, B. breve, B. bifidum, B. infantis, B. longum, and* Fructooligosaccharide, 5 participants). In contrast, some differences were observed in products used in other countries. For example, NICUs in Italy commonly use *Lactobacillus* GG (Manzoni et al., 2011b), while a NICU in Finland uses *Lactobacillus* GG (Luoto, Isolauri, & Lehtonen, 2010b). In addition, routine use of Infloran (*Lactobacillus acidophilus* and *Bifidobacterium infantis*) was documented in a NICU in Austria (Repa et al., 2015) and also in several (34) NICUs in Germany (Härtel et al., 2014). Similarly, most of the Australian tertiary hospitals routinely use *Lactobacillus acidophilus and Bifidobacterium bifidum* (Deshpande et al., 2013). *Bifidobacterium breve* has been routinely administered in a Japanese NICU (Yamashiro & Nagata, 2013). Furthermore, NICUs in France routinely provide Lactobacillus *rhamnosus Lcr35*. In Canada and the U. S., there is a prevalent use of multistrain products (e.g., Florababy, VSL #3). In contrast, in other countries, single strains (e.g., *Lactobacillus* GG) or two strains (combinations of *Lactobacillus* and *Bifidobacterium* spp.) are predominant. This trend of using multistrain probiotics containing *Lactobacillus* and

Bifidobacterium products in both American and Canadian NICUs might be explained by availability of these products in these countries, in addition to the evidence of the effectiveness of products with *Lactobacillus* and mixture of probiotics in reducing the incidence of NEC (AlFaleh & Anabrees, 2014).

In this research, I found that probiotics are mostly prescribed for infants who weigh less than 1500 grams, and/or are fewer than 34 weeks at birth (18 out of 41 participants). Similarly in other countries, such as Australia, Finland, and Austria, probiotics are usually prescribed for infants who weigh less than 1500 grams, and/or are less than 34 weeks at birth (Girish Deshpande, Rao, & Patole, 2015, (Luoto et al., 2010b; Repa et al., 2015). Moreover, in this study (18 out of 41 participants) and in other countries, such as Austria (Repa et al., 2015), France (Bonsante, Iacobelli, & Gouyon, 2013), Finland (Luoto et al., 2010b), and Japan (Yamashiro & Nagata, 2013), probiotics are discontinued when the infant is discharged from the hospital to home or is transferred to another facility.

Giving probiotics to premature infants < 1500 grams has been supported in recent meta-analyses (Aceti et al., 2015; AlFaleh & Anabrees, 2014). The authors of these meta-analyses concluded that probiotics decrease the incidence of NEC in premature infants weighing < 1500 grams. However, there are insufficient data regarding the benefits and effects in infants weighing < 1000 grams at birth (Aceti et al., 2015; AlFaleh & Anabrees, 2014). In addition, because the population of premature infants weighing < 1500 grams (Kosloske, 1994; Sankaran et al., 2004; Uauy et al., 1991) is the most vulnerable to NEC, probiotics are targeted to this population.

Factors Affecting the Implementation of Probiotics

In this study, I identified several factors that influenced the implementation of probiotics. Some of these factors have both positive and negative influence on the willingness of Health Care

Professionals (HCPs) to support the use of probiotics. First, I discuss the results from medical directors, neonatologists, and nurse practitioners' surveys due to the similarity in the results. Thereafter, I present the results from the nurses' survey.

Medical Directors, Neonatologists and Nurse Practitioners' Surveys

Perceptions about the evidence. From the survey of medical directors, neonatologists, and nurse practitioners who do not administer probiotics routinely, one of the most influential factors that affected their willingness to use probiotics was the negative perception regarding the current evidence. These HCPs perceived that the evidence was flawed. In contrast, those medical directors who did use probiotics indicated that the factors that positively influenced their implementation of this therapy to a great extent were having knowledge about the evidence and the belief that there is sufficient evidence showing the benefits of probiotics for premature infants. Perceptions about the evidence played an important role in the use of this therapy. Professionals looking at the same evidence may draw different conclusions. These differing attitudes about the evidence are seen in the literature.

Some professionals believe the evidence about probiotics use is not convincing (Oncel, Erdeve, & Dilmen, 2014). For instance, these authors suggested that the positive benefits of probiotics are controversial because of the contradictory results in the evidence. Some studies provided evidence that *Bifidobacterium* and *Lactobacillus* reduce the incidence of NEC, while others did not report any benefit (Oncel et al., 2014). Oncel et al., (2014) mentioned two studies in particular that did not seem to affect the rate of NEC. One study was designed to evaluate the effect of oral *Lactobacillus reuteri* on the incidence and severity of NEC, and another study evaluated supplementation of *Lactobacillus sporogenes* for the prevention of NEC. In contrast, Barrington (2014) gave a different interpretation of the evidence from these two studies. He believed that both studies are consistent with the

published data regarding the efficacy of probiotics. It is common for physicians who observe the same detail to disagree on multiple aspects of medical practice. They may disagree about anything from taking a medical history to performing a physical exam, interpreting a laboratory test, and recommending a treatment (Kumar & Nash, 2010).

In addition to differences in interpretation of the evidence, there are other issues affecting the perception the evidence. Some investigators criticized past meta-analyses on probiotics for premature infants for such issues as the presence of confounders, and the diversity of studies included (Alfaleh et al., 2011, Alfaleh & Bassler, 2008). Others authors highlighted the cofounding effect on the feeding regimen (Soll, 2010). Feeding regimen is an important confounder because breast milk and donor milk have significantly lowered the incidence of NEC (Boyd, Quigley, & Brocklehurst, 2007b). The diversity of studies included in meta-analyses have also been criticized because the benefits of probiotics appear to be strain-specific, so including data from different strains may lead to distorted conclusions (Szajewska, 2010).

In the results of this study, it was clear that another barrier affecting HCPs' willingness to use probiotics was their perception of the evidence as "confusing". This negative connotation about the evidence could be due to the diversity of studies found in the literature varying in strain(s) of probiotics uses, dosing regimen, and duration of treatment adversely affecting the ideal formulation (Luedtke et al., 2012, Patel & Denning, 2013). Similarly, some professionals such as neonatologists and nurse practitioners believe more studies are necessary in order to discover the most effective strain(s) of probiotics in preventing NEC (Anderson, 2015; Huda, Chaudhery, Ibrahim, & Pramanik, 2014; Luedtke, Yang, & Wild, 2012).

The confusion around the evidence regarding probiotics has led to a belief that more large scale control trials are needed. For example, one author recently mentioned a need for large-scale trials to

better evaluate the role of probiotics in preventing NEC in premature low birth weight infants (Gritz & Bhandari, 2015). Similarly, another author called for larger studies (Neu, 2014). According to Neu (2014), when calculating a sample size based on a 5% baseline necrotizing enterocolitis rate and a 30% reduction of necrotizing enterocolitis after the intervention, the sample size needed would be nearly 2,000 in each arm of the study. Currently, there are no studies of this magnitude. Also, other authors have stressed the need for a national multi-center trial in order to justify the use of probiotics in premature infants in North America (Qasem, Alnaqui, Jorgensen, & Friel, 2014). In contrast, authors who support the use of probiotics believe that only studies comparing strains, premature infants populations and length of therapy are necessary (Janvier, Malo, & Barrington, 2014). These comparative studies will benefit at risk neonates (Shane, Deshpande, & Merenstein, 2013). Other authors agreed that conducting placebo control trials group present ethical challenges as the placebo group would be deprived of an active treatment with the potential to prevent NEC (Girish Deshpande et al., 2010b).

Knowledge. HCPs' knowledge about probiotics and probiotics formulations influenced their willingness to use this therapy in NICUs. Medical directors who agreed with the routine use of probiotics had a significantly higher mean score on knowledge of probiotics (11.3 out of 15) than did medical directors who disagreed (10.3 out of 15). Similarly, those medical directors whose NICUs prescribe probiotics currently reported that two positive factors that influenced their implementation of probiotics to some extent were knowledge about which probiotics products were safe for use in premature infants and familiarity with prescribing probiotics. In contrast, HCPs whose NICUs currently do not prescribe probiotics reported that they do not know the formulations and dosages of probiotics to that should be prescribed to premature infants. Although I found no extant studies which reported that HCPs lack knowledge about probiotics formulations, there were some

suggestions regarding possible differences in their levels of knowledge. One possible cause is that they are not up-to-date on the evidence on about probiotics. For example, in this study, only 63.2% (89) of medical directors whose NICUs do not prescribe probiotics reported that they familiar with current scientific evidence about probiotic use. In contrast, 80% (32) of medical director whose NICUs do prescribe probiotics stated that their knowledge of the evidence influenced their use of probiotics in their NICUs greatly. Ignorance concerning current evidence may have influenced the former's low scores on the knowledge test. This is because the test of knowledge in this study evaluated the participants' knowledge of strains used currently in neonatal research, as well as their general knowledge about probiotics.

Another factor that could affect physicians' lack of knowledge regarding probiotics is the lack of education on nutrition. Probiotics are considered a nutritional supplement. A survey conducted in medical schools revealed that students received, on average, less than 20 hours of education on nutrition over their 4 years of training. Most nutrition courses are taught during the early years of medical school and are not presented in the context of diseases (Adams, Kohlmeier, & Zeisel, 2010).

The results of the knowledge scores of HCPs who did not support routine use of probiotics suggest that these providers have not taken the initiative to acquire knowledge about probiotics, and may lack the opportunity to do so as well. Acquiring knowledge is part of the knowledge translation process of any clinical practice, specifically the "action cycle" step of knowledge translation in the map proposed by Graham et al., (2006). The action cycle step leads to the implementation of knowledge (Graham et al., 2006). Therefore, knowledge has been linked to HCPs' behavior in clinical practice. Having more knowledge can positively improve clinical practice and vice versa. For instance, a large study done in 24 Oklahoma hospitals that targeted HCPs who provide perinatal care reported an increase in levels of knowledge after completing a perinatal continued-education

program. One year after completion of this education program, there were statistically significant changes in health practices (Harris, Yates, & Crosby, 1995). Similar studies have also reached the conclusion that knowledge affects practice (Bernaix, Schmidt, Arrizola, Iovinelli, & Medina-Poelinez, 2008, Senarath, Fernando, & Rodrigo, 2007).

Decision process. According to the TDF, the decision process is the ability to choose between two or more alternatives (Cane et al., 2012a). In this study, the decision process domain was assessed by asking whether or not deciding to use probiotics is difficult, whether the evidence is confusing, if the decision generates conflict within the health care team and if it is difficult to decide what to prescribe. In this study, medical directors reported that one of the factors that strongly influenced the use of probiotics in their NICUs was the support of the health care team in the decision-making process; however, NICUs who are not currently offering this therapy face the opposite situation. One factor affecting the willingness of medical directors, neonatologists and nurse practitioners (NPs) to use probiotics is the difficulty of deciding whether or not to support probiotics use in premature infants. In addition, neonatologists and NPs who were not willing to support routinely use of probiotics reported that the evidence is confusing. Difficulties in the deciding-making process are consistent with the literature. Neu (2014) stated, "One of the most controversial areas in neonatology over the past few years is whether probiotics should be provided routinely to preterm infants for prevention of necrotizing enterocolitis" (p. 167). The findings about aspects that affect the decision process leads one to think that they are related to the perception on the evidence. Besides clinical experience and judgment, scientific evidence is considered vital to guide clinical decision process (Clancy & Cronin, 2005); however, quality and characteristics of the evidence might affect it use in clinical practice (Grol & Grimshaw, 2003). Therefore, the issues with

the evidence mentioned earlier about the evidence being flawed, confusing, and the diverse interpretation on the evidence are likely affecting the clinical decision process.

Absence of clinical guidelines. In this research, one factor affecting the willingness of medical directors, neonatologists and nurse practitioners to use probiotics was the lack of clinical guidelines in the U.S. and Canada. Creation of clinical guidelines is one of the first steps of knowledge translation in any clinical practice, since guidelines present knowledge in concise and clear formats (Graham et al., 2006; Hayward, Wilson, Tunis, Bass, & Guyatt, 1995). Furthermore, "clinical guidelines from responsible organizations provide a framework for determining acceptable care" (Polin & Lorenz, 2015, p.7). Currently there is a probiotics clinical guideline in U.S published by a neonatal nurse practitioner (Parker, 2014) and also there are clinical guidelines in Australia (Girish Deshpande et al., 2015) and Spain (Espinosa-Fernández et al., 2014, Narbona López et al., 2014). However, there are not clinical guidelines from professional organizations in U.S. and Canada.

Professional organizations in the U.S. and Canada had only issued position statements about probiotics which are only a published stance about a medical practice ("Medical Dictionary," n.d.). Nutrition and Gastroenterology Committee of the Canadian Pediatric Society's position statement pointed out, "physicians should consider recommending probiotics to prevent necrotizing enterocolitis in preterm infants who are at risk of necrotizing enterocolitis…and physicians should promote research to outline which strains and dose of probiotics should be used in specific conditions" (Marchand, 2012, p.575). In contrast, the American Academy of Pediatrics did not seem convinced of the evidence; they stated that "there is some evidence that probiotics prevent necrotizing enterocolitis in very low birth weight infants (birth weight between 1000 and 1500 g), but more studies are needed" (D. W. Thomas & Greer, 2010, p. 1217). Furthermore, the American Society for Parenteral and Enteral Nutrition recommendations regarding nutritional support of

neonatal patients at risk of NEC suggested that " further research is needed" and " there is insufficient data to recommend probiotics"(Fallon et al., 2012. p. 509).In conclusion, the position statements from these organizations emphasised the need for more research, and were not ready to issue clinical guidelines.

Safety of probiotics. The research results also uncovered that one of the factors that had a positive influence on the use of probiotics was the health care team's belief that administering probiotics to premature infants was a safe practice. In contrast, one factor affecting the willingness of medical directors, neonatologists and nurse practitioners to use probiotics was their negative perception of the safety of probiotics administration and the probiotics products available. The risk of septicemia was documented in the literature as an important safety concern. Some physicians have pointed out that probiotics prematurely expose the premature infant intestine, which is sensitive to inflammation in a microbial encounter, causing inflammation or sepsis (Patel & Denning, 2013)**.**

Recently in Switzerland, *Bifidbacterium longum* bacteremia occurred in two premature infants receiving probiotics. Both premature infants were successfully treated with antibiotics (Bertelli et al., 2015). In addition, three other cases of *Bifidobacterium longum* bacteremia were reported in three premature infants in Switzerland. Two had a transient bacteremia that did not require antibiotics, while the third infant was treated with antibiotics (Zbinden, Zbinden, Berger, & Arlettaz, 2015). However, some physicians did not seem to be concerned about this complication because sepsis is easy to treat (Ofek Shlomai et al., 2014). Other authors had concerns regarding both short-term and long-term safety and agreed it is important to perform long-term outcome assessments to determine short-term and long-term safety before administering probiotics (Anderson, 2014, Szajewska, 2011).

Some authors expressed concern about the safety of probiotics due to the lack of regulations of probiotics products in the U.S. (Chan et al., 2015, Luedtke et al., 2012) and Canada (Chan et al.,

2015). It has been stressed that the lack of regulations and the concerns about the manufacturing and safety of these products must be addressed (Anderson, 2015). Safety of the product is an important issue that prevents the implementation of this practice. For instance, Chan et al., (2005) stated, "the argument against the routine use of probiotics is not about efficacy. Rather, it is a safety and ethical issue—are we providing a product that is not contaminated, adulterated, or inconsistent with what we intend to prescribe?" (Chan, Soltani, & Hazlet, 2015, p. 502). These same authors believe that probiotics product regulations are quite different from the regulations that pharmaceutical products undergo (Chan et al., 2015). In the U.S., probiotics are considered a dietary supplement (Chan et al., 2015, Luedtke et al., 2012). The manufacturers of probiotics products in the U.S. are not required to comply with safety measures that evaluate the purity of the product or test whether contamination has occurred (Chan et al., 2015). The regulations in Canada for health products are different from the U.S., as Health Canada evaluates the quality of the product. However, Canadian regulations for probiotics are not as rigorous when compared to the regulations for pharmaceuticals (Chan et al., 2015). In response to the issues surrounding the regulations of probiotics products, the Nutrition and Gastroenterology Committee of the Canadian Pediatric Society (Marchand, 2012) recommended, "the federal government should require manufacturers of probiotics and products containing probiotics to provide high quality products with precise and informative labeling" (p.575). Similarly, other authors stressed a need for stricter regulations, in order to create probiotics standards similar to pharmaceutical products (Chan et al., 2015).

The regulatory issues about product quality are important given the past contaminations of probiotics products in the U.S. In 2012, two probiotics products (i.e., iFlora® Kids Multi-Probiotics and iFlora™ 4-Kids Powder) were recalled due to possible contamination with Salmonella (FDA, 2012). In 2014, a probiotics product named ABC Dophillus powder was recalled due to

contamination with the mold *Rhizopus oryzae*, which could cause a fatal fungal infection known as gastrointestinal mucormycosis (Bethesda, 2014). The contamination was known to the public after an infant in Connecticut died due to mucormycosis, caused by the contaminated product. As a response to this contamination, an expert from the FDA said, "Though probiotics are cultured organism, they are no more of a risk for this type of contamination than any other ingredient category" (Schultz, 2015, p.1). A physician responded to this contamination by saying, "Avoidable risks such as this one should of course be avoided. It would be a great mistake to suggest that this is a valid reason to avoid introducing probiotics" (Barrington, 2015, para. 3).

Another concern regarding probiotics products is the lack of studies evaluating commercial products available in the U.S. (Luedtke et al., 2012). However, the majority of the products evaluated in premature infants are not sold in the U.S. (Thomas, Greer, American Academy of Pediatrics Committee on Nutrition, & American Academy of Pediatrics Section on Gastroenterology, Hepatology, and Nutrition, 2010).

Intentions to implement this practice. Intention was a domain of the TDF that was used in this study to evaluate the conscious decision to perform an action (Cane, O'Connor, & Michie, 2012b). The intention domain in the TDF has constructs of the Transtheoretical Model (TTM). The TTM is a model that analyzes behavior change (Prochaska & Velicer, 1997). In this model, behavior change includes five stages: precontemplation (not ready), contemplation (getting ready), preparation (ready), action and maintenance (Prochaska & Velicer, 1997). From the results of this project, I noted that one of the most influential factors affecting the willingness of medical directors, neonatologists and nurse practitioners to prescribe probiotics is a lack of intention towards the implementation of this practice (not ready). They are not contemplating the use of probiotics, actively looking at the evidence, or interested in prescribing probiotics to premature infants. This

indicates that these HCPs are not ready to change, which constitutes an important factor that limits the implementation of probiotics in NICUs. In contrast, this study found that one of the factors strongly influencing medical directors whose NICUs are utilizing probiotics was having the intention to implement this practice. They looked into the evidence related to use of probiotics for premature infant, which means that they pursued the actions necessary to start a practice change.

The literature covered several possible reasons for not being ready to implement this clinical change. For instance, the perception of unanswered questions regarding probiotics therapy and the concern about the safety of probiotics products are both possible reasons affecting the intention of using probiotics. There are concerns regarding safety of the therapy, optimum species and combinations, length of therapy (Patel & Denning, 2013), and regulation and safety of products available (Anderson, 2015). It can be assumed that HCPs would not be ready to start implementing probiotics therapy until they had clear details about the formulations (clinical guidelines) and the safety issues regarding the regulation of probiotics products.

Mindset towards the practice. In this study, I discovered that one of the factors that positively influenced, to some and/or a great extent, the use of probiotics in premature infants was the belief that probiotics for premature infants were beneficial and safe. In contrast, one of the most influential factors that negatively affected the willingness of medical directors, neonatologists and nurse practitioners to avoid the use of probiotics was having pre-existing negative beliefs toward this practice. These HCPs perceived that prescribing probiotics for premature infants was risky, made them feel uncomfortable, and could cause harm. Moreover, they perceived that probiotics were not one of the best advances in neonatology, and, in spite of probiotics therapy being provided in other NICUs, they were not motivated to use them.

The negative feelings about this practice were closely related to the precept that clinicians follow: "First, do no harm." (Hayward et al., 1995, p.4). Offering a therapy that many clinicians perceive can cause harm, possibly because of the safety concerns mentioned before, is against health professionals' personal conviction to avoid harm. In contrast, medical directors whose NICUs prescribe probiotics may not believe that probiotics therapy causes harm, but rather, is a beneficial [32 (82.1%0] and safe [27 (69.1%)] practice, and this attitude has a considerable influence on its use in NICUs.

Nurses' Survey

While the responses of the medical directors, neonatologists, and nurse practitioners yielded similar results in the inferential statistics tests regarding factors affecting the implementation of probiotics, the responses of the nurses were somewhat different. Interestingly, in the literature review, only two articles were found to be written by nurses about probiotics for premature infants (Asmerom, Crowe, & Marin, 2015,Yowell, 2014). These articles addressed concerns about probiotics use in premature infants.

Perceptions about the evidence. Neonatal nurses perceived that more evidence is needed concerning the use of probiotics in premature infants and believed that probiotics were not associated with positive outcomes in the health for premature infants. These results were consistent with the literature finding that nurses perceived that the evidence was insufficient. A staff nurse mentioned a need for more uniformity between the studies in the type of strain used, as well as doses and schedules. She also added that probiotics should not be implemented until more research is available (Yowell, 2014). Similarly, other nurses pointed out that appropriate evidence is necessary to define optimal doses and preparations (Asmerom et al., 2015).

Lack of knowledge and skills. From the results of this study, I noted that one of the most influential factors affecting nursing support of probiotics use is the lack of skills regarding probiotics administration. In this study, nurses perceived that they did not know how to administer probiotics or feel confident in their ability to administer probiotics for premature infants. In addition, another factor that could affect nursing support of probiotics was the low knowledge scores among nurses. Nurses scored low on the knowledge test about probiotics. The mean knowledge score was 8.2 out 15, which is equivalent to only 56.8% correct answers. One possible reason for the low score could be due to the lack of reading literature about probiotics. For instance in this study, over half of the nurses (36 [56%] reported that they are not up to date on the scientific evidence about probiotics for premature infants. In studies among nurses, the reason for not accessing literature are lack of skill on appraising evidence and lack of time to review literature on regular basis (Malik, McKenna, & Plummer, 2015). In addition, the high dropout rates of the nurses' survey (13 out of 75 [17%]) during the first section that included knowledge questions about probiotics, could be an indication that nurses felt uncomfortable answering questions that tested probiotics knowledge.

These results, which indicated that nurses lack skills and knowledge about probiotics use, may indicate that they have few opportunities to acquire knowledge and experience in administering probiotics in their workplaces. It is possible that is a not a priority for health institutions to facilitate educational activities about probiotics therapy. The lack of knowledge and skills on probiotics by nurses negatively affected their willingness to support the use of probiotics, which may potentially cause them not to recommend probiotics to their health care team. Several nurses (46 [70%]) reported that they had no interest in recommending probiotics to their health care team. Thus, a lack of skills concerning probiotics administration seems to affect their actions, which is supported by the framework used in this study. According to the TDF, skills are abilities learned by practice that

affect behaviors (Cane et al., 2012b). Similarly, other studies among nurses have reported that experience is an important source of knowledge and plays a significant role in clinical practice (Malik et al., 2015), Slyne, Phillips, & Parkes, 2012).

Concerns about the safety of probiotics. In this research, an influential factor affecting nurses' support of probiotics use were concerns about the safety of probiotics. Some nurses were concerned about the safety of administering probiotics to premature infants and they perceived the Health Canada regulations as insufficient for ensuring that probiotics products are safe for premature infants. These safety concerns are consistent with the literature review.

In the literature review, no articles were found stating nurses' concerns about Health Canada regulations on probiotics. Therefore, it was not possible to support the results of this study regarding those concerns. However, nurses in the U.S. have indicated concern about the U.S. Food and Drug Administration's (FDA) lack of probiotics regulation. They stressed that the lack of regulation of food supplements, such as probiotics, increase the risk of contamination or incorrect dosage advertisement (Asmerom et al., 2015). In addition, nurses have safety concerns regarding probiotics administration. They expressed this safety concern because of the publications of septicemia cases related to probiotics therapy in premature infants and the risk of cross contamination. They believe that contamination can occur during administration. For instance, if a person uses the same place to prepare intravenous drugs and probiotics, live bacteria can contaminate the intravenous preparation and be injected in the infant, potentially causing bacteremia (Asmerom et al., 2015).

Decision process. In this study, I found that the difficulty of making the decision is one factor affecting the willingness of nurses to support the use of probiotics. This finding is consistent with the literature. One nurse mentioned existing controversy over routine use of probiotics in premature infants, stating that one of the main reasons for this controversy is the lack of regulation of probiotics

products (Asmerom et al., 2015). The same author acknowledged that, in spite of the existence of studies suggesting the potential benefits of probiotics, the evidence is still inadequate, and more data is needed to establish optimal preparations and clinical guidelines (Asmerom et al., 2015). It appears that the perception of inconclusive evidence is causing difficulties in the decision-making process.

Lack of a supportive environment. One influential factor revealed during research that affected the willingness of nurses to support probiotics was the lack of a supportive environment. Some nurses perceived that their colleagues did not support the use of probiotics for premature infants. According to the TDF, environment can encourage or discourage behavior (Cane et al., 2012b). In this study, nurses' willingness to support the use of probiotics was influenced negatively by the physicians' lack of support for this practice. It has been demonstrated that physicians have an important impact in nursing behavior. For instance, in a study that targeted nurses working in acute critical care settings, it was reported that if a physician supported the introduction of protocols, nurses seemed to use them. In the same study, nurses reported that a common and very accessible source of information for resolving uncertainties with clinical decisions were peers and physicians with extensive clinical experience (Thompson et al., 2001).

The Theoretical Domains Framework

This is the first study that implements the TDF framework in order to explore behavior related to the implementation of probiotics in NICUs. The TDF linked the findings to a framework and subsequently identified the most influential factors in HCPs behavior. Rather than narrowing the assessment by using a particular health behavior theory, the framework permitted a comprehensive assessment of areas related to behavior among HCPs (Michie et al., 2005). Although the creation of questions for the survey that utilized the framework was a time-consuming procedure, it was a straightforward process. The authors of the TDF provided examples for questions created from each

domain (Michie et al., 2005), and other studies have published their questionnaires. Therefore, there were existing questionnaire formats and question samples that facilitated the use of the framework (Amemori, Korhonen, et al., 2011; Brotherton et al., 2010). Although the TDF was a useful framework for this study, some disadvantages were found. The TDF is a descriptive framework that includes different domains, rather than an explanatory theory with relationships among the domains. Thus, an elaborate explanation of a particular behavior is limited (Michie et al., 2005). However, the results of this study suggest some relationship among domains; therefore, consideration of the links between domains will help to give explanations for behavior change, which could be beneficial for targeting the most important issues for implementing any practice.

Although many aspects of the TDF appear to influence HCPs' behavior in clinical practice, six domains emerged as the most influential: knowledge, optimism, beliefs about consequences, decision process, environmental context and resources, and social influences.

The results revealed that the domain goal of the TDF (dependent variable) was negatively related to the other domains, especially those that were the most influential in health care professionals' behavior towards probiotics use.

Although many of the findings of this study are consistent with the literature, the knowledge deficit among HCPs regarding probiotics was a novel finding. Similarities and differences from the results on the influential domains were found in other studies that used the TDF framework. For instance, knowledge, beliefs about consequences, and the social influence domains were reported as influential in transfusion behavior of intensive care unit physicians (Islam et al., 2012), primary care practitioners' clinical behaviors in relation to HPV (McSherry, Dombrowski, Francis, Murphy, Martin, O'Leary, et al., 2012) and compliance of chiropractors with diagnostic imaging guideline recommendations for spine disorders (BussiŠres, Patey, Francis, Sales, & Grimshaw, 2012). In

contrast, other domains were found to be influential in other studies, such as social/professional role and identify, beliefs about capabilities (BussiŠres et al., 2012; Islam et al., 2012) and emotion (McSherry, Dombrowski, Francis, Murphy, Martin, O?Leary, et al., 2012), which were not found to be influential in this study. These differences between this study and other studies were expected given the complexity of human behavior and differences in the clinical practices assessed using the TDF. For example, the emotion domain was influential in the behaviors of primary health care practitioners, given that talking about HPV infection and having smears were found to be sensitive topics to discuss with patients (McSherry, et al., 2012)., but was not influential in this study of probiotics use.

Relationships among the Factors Affecting the Implementation of Probiotics

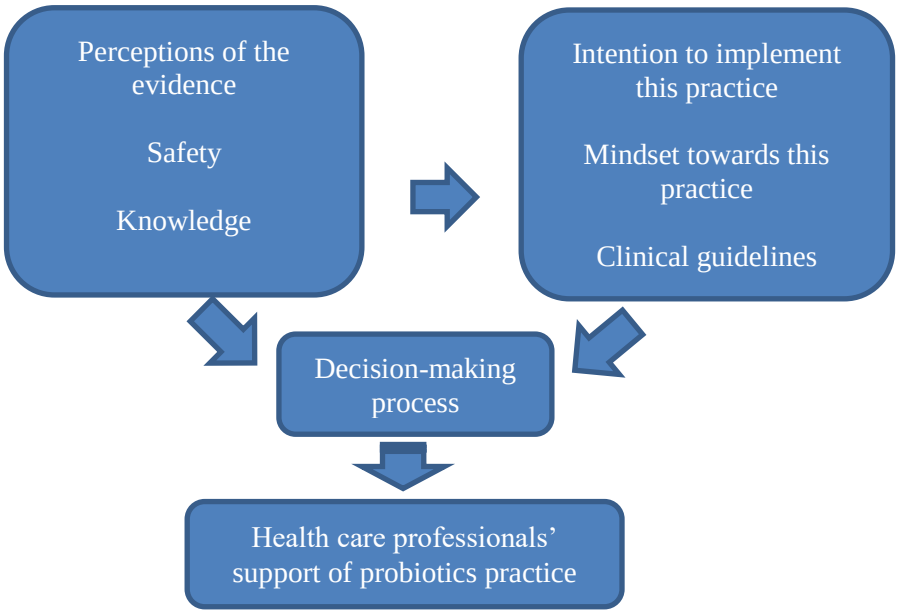
This descriptive study identified the most significant factors currently affecting the willingness of HCPs in supporting probiotics use. In addition, the survey results revealed relationships among the factors affecting the implementation of probiotics. The TDF was instrumental in the identification of influential factors affecting HCPs' behavior. However, the structure of TDF does not allow for explanation of potential relationships between factors. Ideas about these relationships were elucidated from data obtained in the surveys and supported by a review of the literature.

While the medical directors, neonatologists and nurse practitioners surveyed differed in the factors that influence their use of probiotics, they also shared similar influences. These similarities are likely the main influences for HCP's behavior. Similarities were found in perceptions concerning evidence, safety of probiotics, knowledge of probiotics and the evidence, and decision-making processes. Other factors, such as mindset towards this practice, and intention were also relevant.

First, in the results of this study, *perceptions about the evidence, safety of probiotics and knowledge about probiotics* were clearly the main influences in the HCPs' *decision-making* process. These influences are reflected in HCPs' support of the use of probiotics for premature infants. Subsequently, *perceptions about the evidence, safety of probiotics*, and *knowledge about probiotics and evidence* possibly results in either *negative or positive mindsets towards this practice*, affecting both the *intention* to execute this practice and the design of *clinical guidelines.* The negative or positive *mindsets towards this practice*, as well as *intentions* to execute, may have repercussions in the *decision-making process* (Figure 4).

Figure 4.

Relationships among factors influencing health care professionals support of probiotics practice.



Medical directors whose NICUs currently supplement preterm infant feedings with probiotics reported several key factors that greatly influenced the use of probiotics in their NICU: having knowledge of the evidence (82.1% [32]), perceiving that the evidence was sufficient (71.8% [28]),

and believing that probiotics are beneficial (82.1[32]). In addition, their health care team perceived that probiotics were safe in practice (69.2% [27]) and helped in the decision-making process [66.7% [26]). These key influences illustrate that the participants read the evidence, believed it, and thought it was a safe practice; therefore, they subsequently implemented it. By observing the positive *perception about the evidence* and the *safety* of this practice, we can conclude that the *decision-making process* was achieved and supported by the healthcare team. In contrast, the same three factors that positively influenced HCPs to support the use of probiotics (perception of the evidence, safety of probiotics, and knowledge) are simultaneously causing a negative influence among those who do not support the practice. The results of this study for both physicians and nurses illustrate that the most influential factors affecting the support of probiotics are the *perceptions of the evidence* as flawed and insufficient, as well as concerns about the *safety* of the practice and available products. Regarding *knowledge* about probiotics, the physician surveys (Survey #1 and Survey #2) reported that participants who are unsure or unsupportive of the use of probiotics had lower mean knowledge scores than those who supported the use of probiotics. In addition, the mean knowledge score in the nurses' survey was low (8.52/15). HCPs likely face difficulties or lack a *decision-making* process due to an absence of knowledge concerning probiotics, failure to believe in the evidence, and concerns over the safety of this practice. In fact, this survey reported that HCPs who do not support probiotics use also had difficulty deciding whether or not to support probiotics use in premature infants. This difficulty was one of the most influential factors in the decision-making process. In conclusion, the results of this study suggest that the perception of the evidence, perception of safety of probiotics, and amount of previous knowledge all play important roles in the *decision-making* process.

These findings about the relationships between *perception of the evidence*, existing *knowledge*, and *safety* concerns are consistent with literature on knowledge translation. First, taking knowledge available (e.g., primary studies), synthesizing it (e.g., meta-analyses), and making it clear (e.g., practice guidelines, decision aids) so it can be used (Graham et al., 2006) are some of the first steps that should take place for knowledge translation of a practice. However, it is important to remember that these activities of knowledge translation are simultaneously being affected by both negative and positive perceptions of the evidence and existing knowledge about probiotics. Second, any knowledge translation activity for improved health needs to be "ethically sound." This means that the activities must be "consistent with ethical principles, and norms, values, as well as legal and other regulatory frameworks" (Canadian Institute of Health Research, 2005, Four Elements of Knowledge Translation, para. 4). Therefore, the *safety* concerns regarding probiotics influence *decision making-processes* because of the existing principles of HCPs, such as do no harm (Graham et al., 2006).

The results of this study revealed evidence that HCPs who do not support the use of probiotics have no *intention* to implement this practice. For instance, these HCPs are not contemplating prescribing probiotics, and they have no interest in prescribing probiotics. In addition, they have a *negative mindset* towards this practice (e.g., they believe that probiotics practice is not the best advance of neonatology and that the practice is risky). Their negative mindset and lack of interest concerning this practice could be due to the negative *perceptions about the evidence*, lack of *knowledge* about probiotics evidence, and *safe*ty concerns about this practice.

In addition, it was reported in this study that the *lack of clinical guidelines* also negatively affect the willingness of HCPs to support this practice. Furthermore, *the lack of clinical guidelines* within professional organizations could also be attributed to the negative *perceptions of the evidence*,

the *safety* concerns about this practice, negative *mindset about the practice***,** and lack of *intention* to implement this practice. Ultimately, the lack of *clinical guidelines* affects the *decision-making* process.

In contrast, HCPs that currently utilize probiotics might have experienced a different situation. The survey results revealed evidence that those HCPs were *intentional* about into putting research into practice**.** For instance, HCPs reported that research into probiotics use for premature infants was one of the key influences for starting probiotics at their NICU (87.2% [34]). In addition, the results of this study revealed that having a positive *mindset* towards probiotics use was an important influence for HCPs deciding to support the use of probiotics. These HCPs believe that probiotics were beneficial (28 [71.8 %]). Moreover, HCPs supporting the use of probiotics reported that awareness of protocols and polices positively influenced their use of probiotics (25 [67.6%)]). Therefore, practice guidelines may positively influence the support of probiotics supplements in premature infants.

We can speculate that the HCPs who supported the use of probiotics faced an unproblematic *decision-making* process. They were knowledgeable about the evidence and believed that probiotics are beneficial and safe. In addition, awareness of a protocol or clinical guidelines might have helped facilitate the process of implementing probiotics in the NICU. Due to these factors, these HCPs had a positive *mindset* about the implementation of probiotics and were *intentional* about putting them into practice.

In conclusion, perceptions about the evidence, knowledge about probiotics and the evidence, perceptions about probiotics safety, intention and mindset towards this practice, and clinical guidelines likely influence the decision-making process and consequently HCPs' support of probiotics use for premature infants.

Given that the TDF does not explain relationships among domains, it was not possible to support the relationships mentioned above using the TDF. Currently, there is no behavioral change theory that supports potential relationships among factors found in this study, because the domains used were drawn specifically from the TDF. However, some of the potential relationships among factors that affected the implementation of probiotics can be explained with the theory of planned behavior (TPB).

Factors Affecting the Implementation of Probiotics in the Context of the Theory of Planned Behavior

The TPB also may help explain and support the results of this study. It is impossible to explain all of the results of this study fully, using the TPB, given that the study was not designed using this theory, but the TDF instead, which includes more domains than does the TPB. However, the TPB may be instrumental in explaining the effects of the intention to give probiotics, using as a reference some of the main results of this study.

The TPB is a behavioral change theory that attempts to explain and predict behavior in different scenarios (Ajzen, 1991), and it is one of the applicable models of human behaviour used most widely (Rush, 2014). The TPB describes how the *intentions* to perform a behavior are determined by *attitudes towards that behavior*, *subjective norms*, and *perceived behavioral control*, which are influenced by behavioral, normative, and control beliefs, respectively (Ajzen, 1991). These three major determinants of behavior can predict between 27% and 39% of the variance in behavior and intentions, respectively (Armitage & Conner, 2001). *Attitudes towards the behavior* refer to unfavorable or favorable assessments of the behavior and take into account the outcomes of performing the behavior (Ajzen, 1991). This study demonstrated that a negative or positive attitude towards probiotics therapy was one of the most influential factors that affected the willingness to use

probiotics. For example, HCPs whose NICUs do not administer probiotics demonstrated a negative mindset towards the practice, while those with positive attitudes do use probiotics. Therefore, according to the TPB, we can speculate that attitudes towards the use of probiotics affect the intention to engage in the practice and, as a consequence, the behavior itself. *Subjective norms* are the perceived social pressure from peers or groups that affect engaging in a particular behavior (Ajzen, 1991). In this study, the social influences domain might help evaluate how peers influence the behavior negatively or positively. However, the results of the study across the participants whose NICUs prescribe probiotics were not uniform regarding subjective norms. For those NICUs that do administer probiotics, one of the factors that affected its use was positive feedback from colleagues (59.5% [22]). In contrast, in those NICUs that do not give probiotics, medical directors, neonatologists, and nurse practitioners reported that feedback from colleagues was not an influential factor that affected their willingness to use probiotics. However, the nurses' survey showed that nurses' willingness to support the use of probiotics was influenced negatively by physicians' who did not support the practice. In conclusion, subjective norms appeared to have some influence on HCPs' use of probiotics, but it was not among the most influential factors that affected behavior change in HCPs. *Perceived behavioral control* is the perceived ease or difficulty of engaging in a behavior and is influenced by the impediments anticipated (Ajzen, 1991). People's perceptions of their ability to perform a behavior are determined by the skills, resources, and other requirements needed to perform the behavior (Ajzen, n.d.). This study revealed that HCPs perceived a range of obstacles to implementing the use of probiotics. For example, some HCPs perceived that evidence that supports the use of probiotics is insufficient, and that their administration, and the products themselves, are unsafe. Further, HCPs perceived that the lack of clinical guidelines affected their willingness to perform this practice. Therefore, perceptions of these multiple obstacles affected

HCPs' intention to use probiotics in their NICUs. According to the TPB, "a person's *intention* to perform (or not to perform) a behavior is the most important determinant to action" (Fishbein & Ajzen, 1975, p. 118). In this study, HCPs who did not support the use of probiotics stated that they did not intend to engage in the practice, while those who currently prescribe probiotics were intentional in implementing the practice. Therefore, this study indicated that *intention* seemed to predict probiotics use, as proposed in the TPB.

The more positive the attitude and subjective norms towards a behavior and the greater the perceived behavioral control, the more probable it is that a person will intend to engage in a behavior (Ajzen, 1991). The significance of attitudes, subjective norms, and perceived behavioral control varies across behaviors. For example, it has been shown with respect to some behaviors that *attitudes* have a significant effect on *intentions*, that for others, *attitudes* and *perceived behavioral control* influenced intentions greatly, while for yet other behaviors, all three predictors influenced the *intentions* to engage in a specific behavior (Ajzen, 1991). For example, after considering the results of this study in the context of the TPB, I concluded that the major determinants of HCPs' intentions to use probiotics and their actual behavior (probiotics use) included their individual *attitudes towards the behavior*, as well as *perceived behavioral control*, while *subjective norms* were less influential. These main results were discussed previously and are supported by the literature review. However, another study guided by the TPB would be required to explain the proportion of the variance in intention and behavior with respect to probiotics use that is contributed by each of the three components of the TPB.

Thus, although some of the main results of this study can be explained by the TPB, the theory itself may have some drawbacks, given that other determinants that affect intentions and behavior may be missing. Theoretical domains, such as knowledge and the decision making process,

are not considered and were relevant in this study. The theory requires constructs that include affective antecedents (e.g., emotional and motivational) (Bilic, 2005), as well as moral norms (Rush, 2014). The absence of such constructs may be one of the reasons why the TPB cannot explain a large proportion of the variance in intentions and behavior (Bilic, 2005). Based on past studies that have used prediction models, the TPB indicates that attitudes, normative beliefs, and perceived behavioral control affect intention; however, the particular form of the relationships among these 3 components is uncertain (Ajzen, 1991).

Optimal Target for Oxygenation in Newborn

Oxygen is normally used as a therapy in NICUs and is an essential part of respiratory therapy (Manja, Lakshminrusimha, & Cook, 2015; Tin & Gupta, 2007). The purpose of oxygen therapy is to reach satisfactory oxygen tensions in the body without producing oxygen toxicity (Tin & Gupta, 2007). Oxygen therapy as a medicinal treatment has a lengthy history (Tin & Hey, 2003). The routine use of oxygen in preterm infants started from observations in the 1940s by Wilson, Brockett, & Howard (1942). They showed that the irregularity of breathing patterns seen on short gestation infants was resolved when they were supplemented more than 70% of oxygen to breath. This observation encouraged the practice of unrestricted oxygen supplementation for premature infants in the 1940s. The epidemic of retrolental fibroplasia (currently called retinopathy of prematurity) and blindness was well known in the 1940s and 1950s (Appelbaum, 1952). Studies done in the early 1950s reported that a reduced incidence of retrolental fibroplasia was related to a reduction in the amount of supplemental oxygen (Kinsey, 1956; Parmelee, Pilger, & Austin, 1956; Patz, Hoeck, & De La Cruz, 1952). However, years later it was also noticed that decreasing the quantity oxygen therapy increased mortality (Bolton & Cross, 1974). In spite of more than 50 years of continuous research on ideal saturation by pulse oximetry (Sp02) in premature infants receiving oxygen, this

topic has remained controversial (Tin, 2002). Factors that have contributed to this controversy will be described using the TDF, and will be further analysed with respect to the use of probiotics.

The knowledge domain of the TDF, which includes acquisition of knowledge as well as interpretation of the evidence (Cane et al., 2012a), is the key domain affecting the issues regarding optimal ranges of oxigenotherapy, because the evidence is contradictory and may be flawed. For example, in three international RCTs in which a total of 2448 infants were enrolled (973 in the United Kingdom, 1135 in Australia, and 340 in New Zealand), it was reported that "targeting an oxygen saturation below 90% (85-90%) with the use of current oximeters in extremely preterm infants was associated with an increased risk of death" (The BOOST II United Kingdom, Australia, and New Zealand Collaborative Groups, 2013, p. 2094). The study concluded that targeting a saturation by oximetry between 91% and 95% is safer. In contrast, a second study that randomized 1201 infants from hospitals in Canada, U.S, Argentina, Finland, Germany and Israel indicated that there was not a difference in death and disability between the oxygen groups targeting oxygen saturations of 85% to 91% and 91% to 95% (Schmidt et al., 2013). Also, both studies were criticized because the pulse oximeter location was not specified and the variation related to the accuracy of pulse oximeters (Lakshminrusimha, Manja, Mathew, & Suresh, 2015). In addition, a recent meta-analyses regarding the oxygen saturation target range for extremely preterm infants reported that there is still uncertainty to make a recommendation because of the low quality of evidence (Manja et al., 2015). Health care professionals have argued that further studies that focus on better methods for assessing oxygenation are needed as well as strategies to prevent hypoxemia (<85% SpO_2) and hyperoxemia (>95% SpO_2) (Lakshminrusimha et al., 2015).

Based on the current analysis of factors affecting the implementation of probiotics, it is apparent that as with factors affecting the decisions regarding optimal oxygen saturation in premature infants,

the quality of evidence affects implementation of practices. High quality evidence is important in making clinical decisions; therefore, further studies are needed to resolve these clinical controversies.

Factors that Affected the Use of Antenatal Steroids

In addition to the controversy over the use of probiotics with premature infants, another controversial medical treatment, that of the use of antenatal steroids, shares some of the issues that affect the routine use of probiotics. Antenatal steroids have long provoked considerable controversy in perinatology (Stokowski, 2004), and approximately 30 years of ongoing research was required before the medical community accepted the therapy. Animal studies in the 1960s revealed that glucocorticoids accelerated the development of organs, particularly the lungs. Similarly, a study conducted by Liggins and Howie in 1972 found that glucocorticoids decreased the incidence of respiratory distress syndrome (RDS) in infants born before 32 weeks and reduced mortality as well; many other studies have been performed since. This situation prevailed until 1990, when a meta-analysis of 12 RCTs that involved the use of corticosteroids was conducted with approximately 3000 patients. This analysis showed that the use of antenatal corticosteroids reduced the incidence of respiratory distress syndrome by 50% and neonatal mortality by 40%, and reduced NEC enterocolitis and periventricular hemorrhage (PVH) as well (Crowley, Chalmers, & Keirse, 1990). Despite this evidence, the use of corticosteroids remained low in the early 1990s (Crowley et al., 1990), and several factors affected their widespread use. The factors that affected the use of antenatal steroids will be described using the TDF to show how this treatment shares some of the problems that affect the use of probiotics in preterm infants.

The knowledge domain of the TDF includes being not only aware of the evidence, but also its scientific rationale and interpretation of the evidence (Cane et al., 2012a). One factor related to the

infrequent use of antenatal corticosteroids is the different interpretations of the current evidence, which has not been considered sufficient to promote routine use, because the medical community remains uncertain of their potential benefits (Bronstein & Goldenberg, 1995). Robertson (1982) suggested that the benefits of corticosteroid therapy are limited primarily to white males between 30 to 32 weeks of gestation. However, Avery (1984) expressed his disproval of the medical community's resistance to the therapy, which he believed was crucial in preventing respiratory distress syndrome. Similarly, other authors stated that the benefits of antenatal corticosteroids were unquestionable (Crowley et al., 1990, Tchobroutskyr, 1996). Sinclair (1995) suggested that the low implementation of antenatal steroids may be due to the lack of opportunities to evaluate the evidence, and physicians' incompetence in identifying valid evidence (Sinclair, 1995). Similar to the past status of the use of antenatal corticosteroids, probiotics use in premature infants also has been affected by conflicting interpretations of the evidence and the possible lack of opportunities to gain knowledge on the subject.

In the belief about the consequences domain of the TDF, it was evident that safety issues regarding probiotics therapy were influential factors that affected the support of its use in NICUs. Similarly, safety issues regarding the fetus and mother after exposure to antenatal corticosteroids created concerns in the medical community that affected the acceptance of this practice. One author mentioned that the lack of implementation of antenatal steroids are the result of different assessments of the evidence regarding concerns such as maternal or fetal infection, and maternal diabetes and hypertension (Sinclair, 1995).

Some studies have reported that antenatal steroids were beneficial in the prevention of respiratory distress syndrome, but mothers who received antenatal steroids had increased rates of infection after premature rupture of membranes; therefore, the medical community was advised to look for safer therapies (Taeusch et al., 1979). Concerns were raised that corticosteroids could suppress long-term

central nervous system development, as it was reported that suppression of brain development occurred in rhesus monkeys, especially in the cerebellum (Uno et al., 1990). In order to address some of these safety concerns, longitudinal studies were conducted in the 1990s of children whose mothers received antenatal corticosteroids (Schmand et al., 1990, Smolders-de Haas et al., 1990). These studies reported that antenatal steroids had no physical or neurological effects on the children. Although there was an increase in hospital admissions in the steroids group, none were for serious infectious diseases (Smolders-de Haas et al., 1990).

In the TDF, social influences that can affect change include those from professional organizations. One of the factors that affects the implementation of probiotics adversely is the lack of clinical guidelines from such organizations. It is possible that the use of antenatal steroids remained low in the U.S. for the same reason. In 1990, only 12% of the infants who took part in the Vermont-Oxford Trial received a complete course of antenatal steroids (The Vermont-Oxford Trials Network, 1993). Because of the meta-analysis performed in 1990 on the ability of antenatal corticosteroids to produce large reductions in respiratory distress syndrome, mortality, intraventricular hemorrhage, and NEC, and the infrequent use of this therapy in women who delivered premature infants, the U.S. National Institutes of Health (NIH) organised a consensus conference to bring together several specialists in perinatology. This consensus was conducted to encourage the use of antenatal steroids in medical practice. The consensus advocated the use of antenatal corticosteroids and issued practical recommendations for the therapy that included indications, drugs, doses, and timing, all of which were supported by scientific evidence (Gilstrap et al., 1995). Yet, although the NIH consensus endorsed antenatal use of corticosteroids, and their use increased, they still remained underutilized. In 1995, Bronstein and Goldenberg reported that only 26% of infants from the Vermont-Oxford Network Trial received antenatal corticosteroids. Due to

their continued infrequent use, the NIH then executed a quality improvement campaign (Leviton, Goldenberg, Baker, & et al, 1999). In order to evaluate the effect of the campaign, 27 randomized tertiary hospitals in the U.S. received either the usual dissemination of practice recommendations—which consists of publication of the NIH recommendations and endorsement by the American College of obstetricians and Gynecologists—or this usual practice plus active dissemination. In the latter condition, focus groups were conducted before the intervention with neonatologists, obstetricians, and maternal-fetal medicine specialists in the U.S. to understand the barriers that were preventing the implementation of this therapy. They concluded that clinicians overestimated the negative outcomes and underestimated its benefits (Leviton, Baker, Hassol, & Goldenberg, 1995). Therefore, the NIH recommendation included the statement, "The benefits of antenatal administration of corticosteroids to fetuses at risk of preterm delivery vastly outweigh the potential risks. These benefits include not only a reduction in the risk of RDS, but also a substantial reduction in mortality and IVH" (Gilstrap et al., 1995, p. 417).

The hospitals that received active dissemination were exposed to a campaign that included recruiting local medical leaders to encourage physicians to prescribe corticosteroids, a charts reminder system, and discussion with doctors about clinical cases in which corticosteroids can be administered. The educational intervention was successful, in that it increased the use of antenatal steroids in the U.S. from 33% to 68.3% (108% increase). Hospitals that were exposed to the usual dissemination also increased their use of antenatal steroids from 32.9% to 57.6% (78% increase).

In analyzing the factors that affect the implementation of probiotics currently, and the factors that affected the use of antenatal steroids, it is clear that interpretation of the evidence, safety issues, and lack of clinical guidelines from professional organizations play important roles in HCPs willingness to support these treatments. I found it particularly thought provoking that the results of

the qualitative study of factors that affect the implementation of antenatal steroids concluded that the reason why physicians did not use the evidence in their practices was because they underestimated the benefits and overestimated the risks of the therapy. It is possible that those HCPs who do not support the use of probiotics hold this interpretation bias as well. My question is, are HCPs so concerned about the safety issues related to probiotics use (e.g., infections, product quality) that they overlook their benefits in preventing NEC and mortality in premature infants?. Scientists who study human decision making have found constant bias in humans' judgment of probabilities, such that people have a tendency to assess that very low probability outcomes are higher than they are (Fischhoff, Bostrom, & Quadrel, 1993; Slovic, 1987). Thus, dreaded adverse events are avoided even when the risk is very low (Slovic, 1987). In addition, after analysing the factors that affected the widespread use of antenatal steroids, it is clear that endorsements, recommendations, and educational campaigns on the part of professional organizations had significant positive influences on HCPs' behavior. Similarly, it is likely that probiotics therapy would benefit from educational activities campaigns and endorsements from professional organizations.

Study Strengths and Limitations

Strengths of the Study

This is the first study to report on current practices involving the administration of probiotics for premature infants in Canada and the U.S. NICUs. The data collected regarding current clinical protocols includes products used, indications, dosages, contraindications, when discontinued and time of use. This clinical information adds new knowledge to the area of probiotics. Also, this is the first study to investigate factors affecting the implementation of probiotics. Knowledge deficit among HCPs was a novel finding regarding factors affecting implantation of probiotics.

A strength of this study was the use of an online survey which allowed collection of information about a large population in an efficient, cost effective, easy and creative manner. The response time for answering the survey was up to 7 days, which is similar to what is reported in the literature for online surveys (Hoonakker & Carayon, 2009). Overall, the data collection time was short and efficient. Given that I used Dillman's method (Dillman et al., 2009) to increase response rate by using follow up reminders, the data collection process took 4 weeks for the neonatologists and nurse practitioners' survey and the nurses' survey. The data collection for the medical directors' survey took 2.5 months because another reminder was sent one month after the planned 4 week data collection. The use of the Dillman's method (Dillman et al., 2009) in this study increased the survey response rate up to 3 times the initial response. This online survey was cost- effective as it did not require telephone, interviewer, or data entry fees. The results were recorded directly into FluidSurvey™ software and were downloaded once the data collection period had finished, thus saving time and money. The online survey was easy to administer, because the FluidSurvey™ software allowed me to keep track of who had and who had not responded, so follow up reminders were only sent to the non-respondents. Also, the software permitted the incorporation of skip patterns, logos, images, and fonts, which made the survey visually appealing.

Another strength of this study was the sample frame used for the medical directors' survey, because it allowed me to sample from approximately 95% of the population. Using the largest sample size possible was advantageous because it is more representative of the target population and the sampling error is smaller (Polit & Beck, 2012). It has been documented that "response representativeness is more important than response rate in survey research" (Cook, Heath, & Thompson, 2000, p. 821). The Directory of Newborn Intensive Care and Neonatology of the USA and Canada was instrumental in getting the contact information (address and email) of medical

directors in the U.S. and Canada, because only 5% of the invitation letters were returned. One strength in the medical directors' survey was the use of a dual invitation. The first invitation to participate in the study was mailed. After the first outreach, another invitation was sent by email, which doubled the initial response rate. The response rate increased from 6% (63 participants) to 12.8% (134 participants). This increase in response rate after the second contact with the participants, was not observed in the other surveys of this study.

An additional strength of this study was the use of the TDF as a guide in the development of the questionnaire for this study. This framework allowed for the comprehensive assessment of multiple factors that might trigger behavior change. Although each domain evaluated different issues potentially affecting behavior change, the causal processes linking domains were not part of this framework. In spite of this limitation, this is the first study using the TDF that assessed association between the "goal" domain with the other domains of the framework (knowledge, skills, professional role and identity, beliefs about capabilities, beliefs about consequences, optimism, intention, decision making process, environmental context and resources, social influences, and emotions). The new use of this framework suggest that there are relations between the domain goal and the other domains. This different use of the TDF can be tested and transferred to other studies that are examining factors affecting the implementation of a clinical practice. In addition, I identified relationships among the most influential factors affecting the implementation of probiotics.

Limitations of the Study

A major limitation of this study was the low survey response rate of medical directors, neonatologists and nurse practitioners, which was 19.8% and 18.8% respectively. However, when compared with similar studies among perinatal physicians, the response rate obtained was congruent at the low end, but within range of the 15%-44% response rates of these types of studies. For

example, a survey of perinatal physicians about ethics of resuscitation had a response rate of 15%, (Laventhal et al., 2011), a survey of neonatologists' attitudes toward life-sustaining treatments in the NICU had a response rate of 17%, (Feltman, Du, & Leuthner, 2012) , a survey of U.S. NICU directors about variability of criteria for donated pasteurized human milk use had a 33% response rate (Hagadorn et al., 2014), and a survey of U.S. medical directors about the prevalence of and attitudes toward neonatal functional echocardiography use and training had a response rate of 43.7% (Schachinger et al., 2014). One possible reason for this low response rate was the topic of the survey. When a topic is of high salience (e.g. high interest to surveyees), respondents are more likely to participate in the survey (Dillman, 2007). It is possible that several HCPs were not interested in supplementing probiotics to premature infants; therefore, they were not interested in answering the survey. Several studies have documented that the salience of a topic is one of the most significant aspects in impacting survey response rates in surveys (Cook et al., 2000; Edwards et al., 2002; Fan & Yan, 2010; Sheehan & McMillan, 1999).

Having a low response can lead to a non-response bias which means there was difference between the characteristics of the respondents and non-respondents (Sedgwick, 2014). Low response rates affect the ability to generalize findings (Pinsonneault & Kraemer, 1993). However, the response rate by itself does not indicate a definite bias (Sax, Gilmartin, & Bryant, 2003). Dillman (1991) and Krosnick (1999) stated that when the sample is representative of the population, low response rates do not cause bias. In this study, the sample of medical directors was representative, so it is possible that there was no response bias in the sample population. However, the samples of neonatologists, nurse practitioners, and nurses were not representative of the populations of these practitioners. The Directory of Newborn Intensive Care and Neonatology of the U.S. and Canada only published the emails and addresses of some neonatologists; therefore, only those whose email

addresses were available were invited to participate. Further, it was only possible to access a partial population of nurses and NPs in Canada thorough a professional organization. In addition, the population of nurses in the U.S. was not representative, as it was not possible to gain access to this population through a professional association. Given that there was inadequate representation in the survey of neonatologists, NPs, and nurses, it is likely that the survey results showed some degree of non-response bias; therefore, caution needs to be used in generalizing the results from these populations. It is problematic to quantify the extent of the non-response bias in these surveys, as there is limited information about the attitudes of non-respondents (Sedgwick, 2014).

Another limitation was that the response rate of participants from U.S. was slightly lower than participants from Canada (17.1% vs. 25.8%, respectively). It could have been that Canadian respondents were more willing to participate in the survey given that the principal investigator and her committee are affiliated with a Canadian university. Given that the overrepresentation of Canadians participants was not very high, this non-response bias likely occurred in a negligible level (Lavrakas, 2008).

Limitations of this study also included the lack of published articles authored by nurses about probiotics which constrained the analysis of the nurses' survey. Another limitation is that the nurses' survey had a high dropout rate (13 out of 75 [17%]) during the first part of the survey that corresponded to the knowledge questionnaire, which could also limit the generalization of the survey results. This high dropout rate could have possibly been avoided by asking knowledge questions near the end of the survey. It has been documented that the beginning of the survey should start with easy questions in order to help decrease dropout rates (Renwarden, 2014).

Another limitation in this study was that the questionnaires given had not been previously tested; therefore, this study had increased risk of measurement errors, given that some questions

might not measure what they were expected to measure. Instrument (questionnaire) measurement errors can occur leading to inaccurate results (Biemer, Groves, Lyberg, Mathiowetz, & Sudman, 1991). To minimize this error, content validity was assessed by a panel of experts. In addition, the surveys were pilot tested.

The TDF was a good fit for this study, as it assessed a wide range of possible factors affecting the behavior of HCPs towards the implementation of probiotics. However, it also had some limitations. For example, the domains of the framework were not linked; therefore, relationships among the domains were not supported in the framework. In spite of this limitation, some relationships among the domains were observed in the discussion section and supported by the literature, and results of this study. Although this study utilized inferential statistics to test association among some domains, future research is needed to test for relationships among the framework domains.

Recommendations for Future Research

From the respondents of the survey, few NICUs in the U.S. and Canada utilize probiotics. The lack of implementation of this practice was related to the negative perception of the evidence and this practice. The study results revealed the need for more research on probiotics and its safety, but it did not provide information about what specific research is needed. Qualitative studies that incorporate interviews and focus groups with HCPs in the NICU are recommended in order to have a better understanding of what specific research is needed in the area of probiotics. Nevertheless, the literature review provided specifics types of research that HCPs require in order to be convinced about the benefits and safety of this practice. Some professionals requested larger RCTs in premature infants in order to observe the benefits (Gritz & Bhandari, 2015; Neu, 2014). Controversy exists over whether more randomized control trials are required prior to widespread implementation

of this practice. However, larger studies are needed so those HCPS who have negative perception about the current evidence can make a decision concerning this practice, therefore resolving the controversy. HCPs, whether or not they support the use of probiotics have requested studies that tested different regimens of administration so that information about optimal products, dosages and timing of administration, and length of therapy would be identified.

Other relevant studies that need to be conducted are those regarding long-term outcomes of probiotics use in premature infants. In addition, safety studies testing the quality of products suitable for premature infants are recommended, given the lack of previous studies and the existing cases of contamination. Other future research could include studies to determine the effectiveness of continuing education on the use of probiotics in changing decisions about the implementation of the practice. For instance, in the case of antenatal steroids, it was demonstrated that educative campaigns facilitated the implementation of this practice.

Recommendations for Practice

A general lack of knowledge about probiotics is likely affecting the willingness of HCPs to use probiotics. It is important that NICUs perform educational activities regarding probiotics and that HCPs are provided with the latest research about benefits, risks and contraindications. The educational activities should involve the multidisciplinary teams that work in the NICU, such as medical directors, neonatologists, nurse practitioners, nurses, and nutritionists. Thus, they can learn more about probiotics, be updated about the evidence and properly inform parents about this practice.

HCPs have an ethical responsibility to inform parents about the evidence regarding the benefits of probiotics and the risks of administration in order to help them make informed decisions. A survey about parental views on probiotics in preterm infants reported that 96% (51 out of 53) of the

participants considered that parents of high risk premature infants hospitalized in institutions that do not administer probiotics should be educated about the potential benefits (Sesham, Oddie, Embleton, & Clarke, 2014). This study should have also included parental view questions about being educated on the risks of this therapy.

In NICUs planning to start implementing probiotics, it is important to ensure that the probiotics product is not contaminated. It is necessary, therefore, that laboratories confirm taxonomy, number of colonies and exclusion of contaminates in the probiotics product, in order to prevent premature infants from receiving pathogenic organisms (Deshpande, Rao, Keil, & Patole, 2011; Janvier et al., 2014).

In this study, I reported that 38% (18 out of 42) of the NICUs using probiotics do not have any contraindications in their protocol. It is important that NICUs wanting to give probiotics should develop strict inclusion and exclusion criteria based on the available evidence, their patient population, and the shared decision making with the family and other HCPs.

Policy Recommendations

It was evident in this study that probiotics are given in some neonatal intensive care units. The development of clinical practice guidelines by professional associations in the U.S. and Canada is strongly recommended. Professional associations in the U.S. and Canada should publish guidelines using products that that have *Lactobacillus* and mixture of probiotics. The authors of the latest meta-analysis on probiotics reported that both *Lactobacillus* and mixture of probiotics strains significantly reduce the incidence of NEC (AlFaleh & Anabrees, 2014).

The establishment of guidelines would encourage the safe implementation of probiotics, such as incorporating contradictions with their use and giving the right dosages. In addition, the current overview of practices presented in this study could provide probiotics formulation information that

may be useful to create national guidelines in the U.S. and Canada. However, as mentioned before, the design of the guidelines from professional organizations is being hindered by the negative perception of the evidence so it is likely that more studies need to be performed before the publications of guidelines.

The U.S. FDA should oversee quality control for dietary supplements containing probiotics, given that the FDA's premarket assessment or approval for safety and effectiveness are not currently required for dietary supplements (Marks & Michael, 2014). Quality control standards, similar to those used in Canada for health products are needed in the U.S., due to the risk of contamination and to ensure that the product content is what is advertised on the label. Implementing new standards would potentially make probiotics more effective, ensure that infants are receiving a safe product, and help prevent morbidity related to product contamination. Also, physicians may feel more comfortable prescribing probiotics if the FDA oversaw the quality control. In Canada, probiotics are considered a health product when they have a therapeutic use (e.g., claims about illness risk reduction). Health products undergo quality control measures that validate that the product contains what the label claims (Health Canada, 2012). When verifying new health claims, Health Canada inquiries about the manufacturer's supplementary scientific evidence supporting the health product's quality, efficacy, and safety (Health Canada, 2009). Once Health Canada has assessed the product, it issues a product license.

Conclusions

This study is the first to identify current practices in probiotics supplementation for premature infants across Canada and the U.S. It provides valuable information about probiotic products available in Canada and the U.S., and details concerning formulations and contraindications in current protocols. Moreover, this study identified the most influential factors that affect HCPs'

willingness to use probiotics, thereby providing relevant information concerning issues that need to be addressed.

The majority of the study findings with respect to factors that affect probiotics use are consistent with the literature review. The TDF proved useful in describing issues that influenced behavior change and, therefore, the implementation of a practice. The implications for future research concerning the need for more studies about probiotics use, and its safety, as well as the need for clinical guidelines from professional organizations were presented. It is essential to regulate probiotics products better, especially in the U.S. Based on prior experiences that showed the benefits of educational programs on antenatal steroid use, similar programs on probiotics were recommended.

In this study was evident that more research on probiotics, better product regulations, and endorsements from professional organizations are required. Such efforts will address barriers about probiotics use within health care professionals, and thereby help the medical community to decide whether or not probiotics should be embraced in clinical settings.

References

Abrahamsson, T. R., Rautava, S., Moore, A. M., Neu, J., & Sherman, P. M. (2014). The Time for a Confirmative Necrotizing Enterocolitis Probiotics Prevention Trial in the Extremely Low Birth Weight Infant in North America Is Now! *The Journal of Pediatrics*, *165*(2), 389–394. http://doi.org/10.1016/j.jpeds.2014.05.012

Aceti, A., Gori, D., Barone, G., Callegari, M. L., Mauro, A. D., Fantini, M. P., … $author.lastName, $author firstName. (2015). Probiotics for prevention of necrotizing enterocolitis in preterm infants: systematic review and meta-analysis. *Italian Journal of Pediatrics*, *41*(1), 89. http://doi.org/10.1186/s13052-015-0199-2

Adams, J. B., Johansen, L. J., Powell, L. D., Quig, D., & Rubin, R. A. (2011). Gastrointestinal flora and gastrointestinal status in children with autism -- comparisons to typical children and correlation with autism severity. *BMC Gastroenterology*, *11*, 22. http://doi.org/10.1186/1471-230X-11-22

Adams, K. M., Kohlmeier, M., & Zeisel, S. H. (2010). Nutrition education in U.S. medical schools: latest update of a national survey. *Academic Medicine: Journal of the Association of American Medical Colleges*, *85*(9), 1537–1542. http://doi.org/10.1097/ACM.0b013e3181eab71b

Agostoni, C., Buonocore, G., Carnielli, V., De Curtis, M., Darmaun, D., Decsi, T., … Ziegler, E. (2010). Enteral Nutrient Supply for Preterm Infants: Commentary From the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. *Journal of Pediatric Gastroenterology and Nutrition*, *50*, 85–91. http://doi.org/10.1097/MPG.0b013e3181adaee0

Ajzen, I. (1991). The theory of planned behavior. *Organizational Behavior and Human Decision Processes*, *50*(2), 179–211. http://doi.org/http://dx.doi.org.proxy1.lib.umanitoba.ca/10.1016/0749-5978(91)90020-T

Ajzen, I. (n.d.). Theory of Planned Behavior. Retrieved January 5, 2016, from http://people.umass.edu/aizen/tpb.html

Akira, S., Uematsu, S., & Takeuchi, O. (2006). Pathogen Recognition and Innate Immunity. *Cell*, *124*(4), 783–801. http://doi.org/10.1016/j.cell.2006.02.015

AlFaleh, K., & Anabrees, J. (2014). Probiotics for prevention of necrotizing enterocolitis in preterm infants. *Evidence-Based Child Health: A Cochrane Review Journal*, *9*(3), 584–671. http://doi.org/10.1002/ebch.1976

Alfaleh, K., Anabrees, J., & Bassler, D. (2010). Probiotics reduce the risk of necrotizing enterocolitis in preterm infants: a meta-analysis. *Neonatology*, *97*(2), 93–99. http://doi.org/10.1159/000235684

Alfaleh, K., Anabrees, J., Bassler, D., & Al-Kharfi, T. (2011). Probiotics for prevention of necrotizing enterocolitis in preterm infants. *Cochrane Database of Systematic Reviews (Online)*, (3), CD005496. http://doi.org/10.1002/14651858.CD005496.pub3

Alfaleh, K., & Bassler, D. (2008). Probiotics for prevention of necrotizing enterocolitis in preterm infants. *The Cochrane Database of Systematic Reviews*, (1), CD005496. http://doi.org/10.1002/14651858.CD005496.pub2

Amemori, M., Korhonen, T., Kinnunen, T., Michie, S., & Murtomaa, H. (2011). Enhancing implementation of tobacco use prevention and cessation counselling guideline among dental providers: a cluster randomised controlled trial. *Implementation Science*, *6*(1), 13. http://doi.org/10.1186/1748-5908-6-13

Amemori, M., Michie, S., Korhonen, T., Murtomaa, H., & Kinnunen, T. H. (2011). Assessing implementation difficulties in tobacco use prevention and cessation counselling among dental providers. *Implementation Science*, *6*(1), 50. http://doi.org/10.1186/1748-5908-6-50

Anand, R. J., Leaphart, C. L., Mollen, K. P., & Hackam, D. J. (2007). The role of the intestinal barrier in the pathogenesis of necrotizing enterocolitis. *Shock (Augusta, Ga.)*, *27*(2), 124–133. http://doi.org/10.1097/01.shk.0000239774.02904.65

Anderson, S. (2015). Probiotics for Preterm Infants: A Premature or Overdue Necrotizing Enterocolitis Prevention Strategy? *Neonatal Network*, *34*(2), 83–101. http://doi.org/10.1891/0730-0832.34.2.83

Appelbaum, A. (1952). Retrolental fibroplasia; blindness in infants of low weight at birth. *California Medicine*, *77*(4), 259–265.

Armitage, C. J., & Conner, M. (2001). Efficacy of the Theory of Planned Behaviour: A meta-analytic review. *British Journal of Social Psychology*, *40*(4), 471–499. http://doi.org/10.1348/014466601164939

Arslan, F., de Kleijn, D. P. V., Timmers, L., Doevendans, P. A., & Pasterkamp, G. (2008). Bridging innate immunity and myocardial ischemia/reperfusion injury: the search for therapeutic targets. *Current Pharmaceutical Design*, *14*(12), 1205–1216.

Arvola, T., Laiho, K., Torkkeli, S., Mykkänen, H., Salminen, S., Maunula, L., & Isolauri, E. (1999). Prophylactic Lactobacillus GG reduces antibiotic-associated diarrhea in children with respiratory infections: a randomized study. *Pediatrics*, *104*(5), e64.

Asmerom, M., Crowe, L., & Marin, T. (2015). Understanding the Biologic Therapies of Probiotics, Prebiotics, and Synbiotics: Exploring Current Evidence for Use in Premature Infants for the Prevention of Necrotizing Enterocolitis. *The Journal of Perinatal & Neonatal Nursing*, *29*(3), 240–247. http://doi.org/10.1097/JPN.0000000000000120

Avery, M. E. (1984). The argument for prenatal administration of dexamethasone to prevent respiratory distress syndrome. *The Journal of Pediatrics*, *104*(2), 240.

Awad, H., Mokhtar, G., Imam, S. S., Gad, G. I., Hafez, H., & Aboushady, N. (2010). Comparison Between Killed and Living Probiotic Usage Versus Placebo for the Prevention of Necrotizing Enterocolitis and Sepsis in Neonates. *Pakistan Journal of Biological Sciences*, *13*(6), 253–262.

Bachmann, D., Elfrink, J., & Vazzana, G. (1996). Tracking the progress of E-mail vs. snail-mail. *Marketing Research*, *8*(2), 30.

Bailey, J. L., & Yeung, S. Y. (2011). Probiotics for disease prevention: a focus on ventilator-associated pneumonia. *The Annals of Pharmacotherapy*, *45*(11), 1425–1432. http://doi.org/10.1345/aph.1Q241

Bandura, A. (1986). *Social foundations of thought and action: a social cognitive theory*. Englewood Cliffs, N.J: Prentice-Hall.

Bandura, A. (2004). Health Promotion by Social Cognitive Means. *Health Education & Behavior*, *31*(2), 143–164. http://doi.org/10.1177/1090198104263660

Bandura, A., & Walters, R. H. (1963). *Social learning and personality development*. New York: Holt, Rinehart and Winston.

Barrington, K. (2013). Probiotics in the NICU: a "how-to" guide | Neonatal Research. Retrieved November 29, 2013, from http://neonatalresearch.org/2013/05/22/probiotics-in-the-nicu-a-how-to-guide/

Barrington, K. J. (2015). What is the news about probiotics? Retrieved from http://neonatalresearch.org/2015/03/09/what-is-the-news-about-probiotics/

Barrington, K., & Janvier, A. (2013, October). *Probiotics and Prebiotics*. Presented at the COCHRANE NEONATAL REVIEW GROUP WEB SEMINAR, webinar.

Basith, S., Manavalan, B., Lee, G., Kim, S. G., & Choi, S. (2011). Toll-like receptor modulators: a patent review (2006 – 2010). *Expert Opinion on Therapeutic Patents*, *21*(6), 927–944. http://doi.org/10.1517/13543776.2011.569494

Basu, S., Chatterjee, M., Ganguly, S., & Chandra, P. K. (2007). Efficacy of Lactobacillus rhamnosus GG in acute watery diarrhoea of Indian children: a randomised controlled trial. *Journal of Paediatrics and Child Health*, *43*(12), 837–842. http://doi.org/10.1111/j.1440-1754.2007.01201.x

Basu, S., Paul, D. K., Ganguly, S., Chatterjee, M., & Chandra, P. K. (2009). Efficacy of high-dose Lactobacillus rhamnosus GG in controlling acute watery diarrhea in Indian children: a randomized controlled trial.

Journal of Clinical Gastroenterology, *43*(3), 208–213. http://doi.org/10.1097/MCG.0b013e31815a5780

Beattie, L. M., Hansen, R., & Barclay, A. R. (2010). Probiotics for preterm infants: confounding features warrant caution. *Pediatrics*, *126*(3), e742-743-745. http://doi.org/10.1542/peds.2010-1949C

Bernaix, L. W., Schmidt, C. A., Arrizola, M., Iovinelli, D., & Medina-Poelinez, C. (2008). Success of a Lactation Education Program on NICU Nurses' Knowledge and Attitudes. *Journal of Obstetric, Gynecologic, & Neonatal Nursing*, *37*(4), 436–445. http://doi.org/10.1111/j.1552-6909.2008.00261.x

Bernardo, W. M., Aires, F. T., Carneiro, R. M., Sá, F. P. de, Rullo, V. E. V., & Burns, D. A. (2013). Effectiveness of probiotics in the prophylaxis of necrotizing enterocolitis in preterm neonates: a systematic review and meta-analysis. *Jornal de Pediatria*, *89*(1), 18–24. http://doi.org/10.1016/j.jped.2013.02.004

Bertelli, C., Pillonel, T., Torregrossa, A., Prod'hom, G., Fischer, C. J., Greub, G., & Giannoni, E. (2015). Bifidobacterium longum Bacteremia in Preterm Infants Receiving Probiotics. *Clinical Infectious Diseases*, *60*(6), 924–927. http://doi.org/10.1093/cid/ciu946

Besselink, M. G. H., van Santvoort, H. C., Buskens, E., Boermeester, M. A., van Goor, H., Timmerman, H. M., … Acute Pancreatitis Werkgroep Nederland. (2008). [Probiotic prophylaxis in patients with predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial]. *Nederlands tijdschrift voor geneeskunde*, *152*(12), 685–696.

Bethesda, C. F. F. 6931 A. R. 2nd floor. (2014). Recall of Probiotic ABC Dophilus Powder Due to Mold Contamination | CF Foundation. Retrieved July 31, 2015, from https://www.cff.org/News/News-Archive/2014/Recall-of-Probiotic-ABC-Dophilus-Powder-Due-to-Mold-Contamination/

Bezirtzoglou, E., Tsiotsias, A., & Welling, G. W. (n.d.). Microbiota profile in feces of breast- and formula-fed newborns by using fluorescence in situ hybridization (FISH). *Anaerobe*. http://doi.org/10.1016/j.anaerobe.2011.03.009

Bhandari, M., Montori, V., Devereaux, P. J., Dosanjh, S., Sprague, S., & Guyatt, G. H. (2003). Challenges to the practice of evidence-based medicine during residents' surgical training: a qualitative study using grounded theory. *Academic Medicine: Journal of the Association of American Medical Colleges*, *78*(11), 1183–1190.

Biasucci, G., Benenati, B., Morelli, L., Bessi, E., & Boehm, G. (2008). Cesarean Delivery May Affect the Early Biodiversity of Intestinal Bacteria. *The Journal of Nutrition*, *138*(9), 1796S–1800S.

Biasucci, G., Rubini, M., Riboni, S., Morelli, L., Bessi, E., & Retetangos, C. (2010). Mode of delivery affects the bacterial community in the newborn gut. *Early Human Development*, *86*(1, Supplement), 13–15. http://doi.org/10.1016/j.earlhumdev.2010.01.004

Biemer, P. P., Groves, R., Lyberg, L., Mathiowetz, N., & Sudman, S. (Eds.). (1991). *Measurement errors in surveys*. New York: Wiley.

Bilic, B. (2005). The theory of planned behaviour and health behaviours: critical analysis of methodological and theoretical issues, *2*, 243–259.

Bin-Nun, A., Bromiker, R., Wilschanski, M., Kaplan, M., Rudensky, B., Caplan, M., & Hammerman, C. (2005). Oral Probiotics Prevent Necrotizing Enterocolitis in Very Low Birth Weight Neonates. *The Journal of Pediatrics*, *147*(2), 192–196. http://doi.org/10.1016/j.jpeds.2005.03.054

Blümer, N., Pfefferle, P. I., & Renz, H. (2007). Development of mucosal immune function in the intrauterine and early postnatal environment. *Current Opinion in Gastroenterology*, *23*, 655–660. http://doi.org/10.1097/MOG.0b013e3282eeb428

Bolton, D. P. G., & Cross, K. W. (1974). Further observations on cost of preventing retrolental fibroplasia. *The Lancet*, *303*(7855), 445–448. http://doi.org/10.1016/S0140-6736(74)92395-2

Bonsante, F., Iacobelli, S., & Gouyon, J.-B. (2012). Routine Probiotic Use in Very Preterm Infants: Retrospective Comparison of Two Cohorts. *American Journal of Perinatology*. http://doi.org/10.1055/s-0032-1321498

Bonsante, F., Iacobelli, S., & Gouyon, J.-B. (2013). Routine probiotic use in very preterm infants: retrospective comparison of two cohorts. *American Journal of Perinatology*, *30*(1), 41–46. http://doi.org/10.1055/s-0032-1321498

Boyd, C. A., Quigley, M. A., & Brocklehurst, P. (2007a). Donor breast milk versus infant formula for preterm infants: systematic review and meta-analysis. *Archives of Disease in Childhood. Fetal and Neonatal Edition*, *92*(3), F169-175. http://doi.org/10.1136/adc.2005.089490

Boyd, C. A., Quigley, M. A., & Brocklehurst, P. (2007b). Donor breast milk versus infant formula for preterm infants: systematic review and meta-analysis. *Archives of Disease in Childhood. Fetal and Neonatal Edition*, *92*(3), F169-175. http://doi.org/10.1136/adc.2005.089490

Braga, T. D., da Silva, G. A. P., de Lira, P. I. C., & de Carvalho Lima, M. (2011). Efficacy of Bifidobacterium breve and Lactobacillus casei oral supplementation on necrotizing enterocolitis in very-low-birth-weight preterm infants: a double-blind, randomized, controlled trial. *The American Journal of Clinical Nutrition*, *93*(1), 81–86. http://doi.org/10.3945/ajcn.2010.29799

Braithwaite, D., Emery, J., De Lusignan, S., & Sutton, S. (2003). Using the Internet to conduct surveys of health professionals: a valid alternative? *Family Practice*, *20*(5), 545–551.

Bronstein, J. M., & Goldenberg, R. L. (1995). Practice variation in the use of corticosteroids: A comparison of eight data sets. *American Journal of Obstetrics and Gynecology*, *173*(1), 296–298. http://doi.org/10.1016/0002-9378(95)90217-1

Brotherton, J. M. L., Leask, J., Jackson, C., McCaffery, K., & Trevena, L. J. (2010). National survey of general practitioners' experience of delivering the National Human Papillomavirus Vaccination Program. *Sexual Health*, *7*(3), 291–298. http://doi.org/10.1071/SH09135

Bussières, A. E., Patey, A. M., Francis, J. J., Sales, A. E., Grimshaw, J. M., & the Canada PRIme Plus Team. (2012). Identifying factors likely to influence compliance with diagnostic imaging guideline recommendations for spine disorders among chiropractors in North America: a focus group study

using the Theoretical Domains Framework. *Implementation Science*, *7*(1), 82. http://doi.org/10.1186/1748-5908-7-82

BussiŠres, A. E., Patey, A. M., Francis, J. J., Sales, A. E., & Grimshaw, J. M. (2012). Identifying factors likely to influence compliance with diagnostic imaging guideline recommendations for spine disorders among chiropractors in North America: a focus group study using the Theoretical Domains Framework. *Implementation Science*, *7*(1), 82–92. http://doi.org/10.1186/1748-5908-7-82

Calder, P. C., Krauss-Etschmann, S., de Jong, E. C., Dupont, C., Frick, J.-S., Frokiaer, H., … Koletzko, B. (2006). Early Nutrition and Immunity – Progress and Perspectives. *British Journal of Nutrition*, *96*(4), 774–790. http://doi.org/10.1079/BJN20061917

Canadian Institute of Health Research. (2005, October 25). Knowledge Translation at CIHR. Retrieved November 24, 2015, from http://www.cihr-irsc.gc.ca/e/29418.html

Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, & Social Sciences and Humanities Research Council of Canada. (2010). Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. Retrieved from http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/Default/

Canani, R. B., Cirillo, P., Terrin, G., Cesarano, L., Spagnuolo, M. I., Vincenzo, A. D., … Guarino, A. (2007). Probiotics for treatment of acute diarrhoea in children: randomised clinical trial of five different preparations. *BMJ*, *335*(7615), 340. http://doi.org/10.1136/bmj.39272.581736.55

Cane, J., O'Connor, D., & Michie, S. (2012a). Validation of the theoretical domains framework for use in behaviour change and implementation research. *Implementation Science*, *7*(1), 37. http://doi.org/10.1186/1748-5908-7-37

Cane, J., O'Connor, D., & Michie, S. (2012b). Validation of the theoretical domains framework for use in behaviour change and implementation research. *Implementation Science*, *7*(1), 37–53. http://doi.org/10.1186/1748-5908-7-37

Caplan, M. S., Miller-Catchpole, R., Kaup, S., Russell, T., Lickerman, M., Amer, M., … Thomson, R. J. (1999). Bifidobacterial supplementation reduces the incidence of necrotizing enterocolitis in a neonatal rat model. *Gastroenterology*, *117*(3), 577–583.

Cardwell, C. R., Stene, L. C., Joner, G., Cinek, O., Svensson, J., Goldacre, M. J., … Patterson, C. C. (2008). Caesarean section is associated with an increased risk of childhood-onset type 1 diabetes mellitus: a meta-analysis of observational studies. *Diabetologia*, *51*(5), 726–735. http://doi.org/10.1007/s00125-008-0941-z

Center for Disease Control and Prevention. (2006). Community-associated methicillin-resistant Staphylococcus aureus infection among healthy newborns--Chicago and Los Angeles County, 2004. *MMWR. Morbidity and Mortality Weekly Report*, *55*(12), 329–332.

Chan, L.-N., Soltani, H., & Hazlet, T. K. (2015). Probiotics for Neonates: Safety for Prime Time Questioned without Regulatory Changes. *The Journal of Pediatrics*, *166*(2), 502. http://doi.org/10.1016/j.jpeds.2014.10.041

Cho, Y. I., Johnson, T. P., & VanGeest, J. B. (2013). Enhancing Surveys of Health Care Professionals A Meta-Analysis of Techniques to Improve Response. *Evaluation & the Health Professions*, *36*(3), 382–407. http://doi.org/10.1177/0163278713496425

Chou, I.-C., Kuo, H.-T., Chang, J.-S., Wu, S.-F., Chiu, H.-Y., Su, B.-H., & Lin, H.-C. (2010). Lack of Effects of Oral Probiotics on Growth and Neurodevelopmental Outcomes in Preterm Very Low Birth Weight Infants. *The Journal of Pediatrics*, *156*(3), 393–396. http://doi.org/10.1016/j.jpeds.2009.09.051

Clancy, C. M., & Cronin, K. (2005). Evidence-Based Decision Making: Global Evidence, Local Decisions. *Health Affairs*, *24*(1), 151–162. http://doi.org/10.1377/hlthaff.24.1.151

CLAUD, E. C., & WALKER, W. A. (2001). Hypothesis: inappropriate colonization of the premature intestine can cause neonatal necrotizing enterocolitis. *The FASEB Journal*, *15*(8), 1398–1403. http://doi.org/10.1096/fj.00-0833hyp

Conroy, M. E., Shi, H. N., & Walker, W. A. (2009). The long-term health effects of neonatal microbial flora. *Current Opinion in Allergy and Clinical Immunology*, *9*, 197–201. http://doi.org/10.1097/ACI.0b013e32832b3f1d

Cook, C., Heath, F., & Thompson, R. L. (2000a). A Meta-Analysis of Response Rates in Web- or Internet-Based Surveys. *Educational and Psychological Measurement*, *60*(6), 821–836. http://doi.org/10.1177/00131640021970934

Cook, C., Heath, F., & Thompson, R. L. (2000b). A Meta-Analysis of Response Rates in Web- or Internet-Based Surveys. *Educational and Psychological Measurement*, *60*(6), 821–836. http://doi.org/10.1177/00131640021970934

Cooke, G., Behan, J., & Costello, M. (2006). Newly identified vitamin K-producing bacteria isolated from the neonatal faecal flora. *Microbial Ecology in Health and Disease*, *18*(3–4), 133–138. http://doi.org/10.1080/08910600601048894

Costalos C, Skouteri V, & Gounaris A. (2003). Enteral feeding of premature neonates with Saccharomyces boulardii. *Early Hum Dev*, *74*, 89–96. http://doi.org/10.1016/S0378-3782(03)00090-2

Costeloe, K. (2012). PiPS: Trial of probiotic administered early to prevent infection and necrotizing enterocolitis. Retrieved from http://www.hta.ac.uk/protocols/200505010004.pdf

Crowley, P., Chalmers, I., & Keirse, M. (1990). The effects of corticosteroid administration before preterm delivery: an overview of the evidence from controlled trials. *BJOG: An International Journal of Obstetrics & Gynaecology*, *97*(1), 11–25. http://doi.org/10.1111/j.1471-0528.1990.tb01711.x

Cukrowska, B., LodInová-ZádnIková, R., Enders, C., Sonnenborn, U., Schulze, J., & Tlaskalová-Hogenová, H. (2002). Specific proliferative and antibody responses of premature infants to intestinal colonization with nonpathogenic probiotic E. coli strain Nissle 1917. *Scandinavian Journal of Immunology*, *55*(2), 204–209.

Curran, J. A., Brehaut, J., Patey, A. M., Osmond, M., Stiell, I., & Grimshaw, J. M. (2013). Understanding the Canadian adult CT head rule trial: use of the theoretical domains framework for process evaluation. *Implementation Science*, *8*(1), 25. http://doi.org/10.1186/1748-5908-8-25

Dai, D., & Walker, W. A. (1998). Role of bacterial colonization in neonatal necrotizing enterocolitis and its prevention. *Zhonghua Minguo Xiao Er Ke Yi Xue Hui Za Zhi [Journal]. Zhonghua Minguo Xiao Er Ke Yi Xue Hui*, *39*(6), 357–365.

D'Aimmo, M. R., Mattarelli, P., Biavati, B., Carlsson, N. G., & Andlid, T. (2012). The potential of bifidobacteria as a source of natural folate. *Journal of Applied Microbiology*, *112*(5), 975–984. http://doi.org/10.1111/j.1365-2672.2012.05261.x

Davidson, R. (1992). Prochaska and DiClemente's model of change: a case study? *British Journal of Addiction*, *87*(6), 821–822. http://doi.org/10.1111/j.1360-0443.1992.tb01971.x

De Groote, M. A., Frank, D. N., Dowell, E., Glode, M. P., & Pace, N. R. (2005). Lactobacillus rhamnosus GG bacteremia associated with probiotic use in a child with short gut syndrome. *The Pediatric Infectious Disease Journal*, *24*(3), 278–280.

De Leeuw, E. D., Dillman, D. A., & Hox, J. J. (2008). *International handbook of survey methodology*. New York [u.a.]: Lawrence Erlbaum Ass.

de Moreno de LeBlanc, A., & Perdigón, G. (2010). The application of probiotic fermented milks in cancer and intestinal inflammation. *Proceedings of the Nutrition Society*, *69*(3), 421–428. http://doi.org/10.1017/S002966511000159X

Deshpande, G., Rao, S., Keil, A., & Patole, S. (2011). Evidence-based guidelines for use of probiotics in preterm neonates. *BMC Medicine*, *9*, 92. http://doi.org/10.1186/1741-7015-9-92

Deshpande, G., Rao, S., & Patole, S. (2015). Probiotics in neonatal intensive care – Back to the future. *Australian and New Zealand Journal of Obstetrics and Gynaecology*, *55*(3), 210–217. http://doi.org/10.1111/ajo.12328

Deshpande, G., Rao, S., Patole, S., & Bulsara, M. (2010a). Probiotics for preterm neonates, time to acknowledge the elephant in the room and call the parents. *Pediatrics*, *126*(3), e744–e745. http://doi.org/10.1542/peds.2010-1949E

Deshpande, G., Rao, S., Patole, S., & Bulsara, M. (2010b). Updated Meta-analysis of Probiotics for Preventing Necrotizing Enterocolitis in Preterm Neonates. *Pediatrics*, *125*(5), 921–930. http://doi.org/10.1542/peds.2009-1301

Deshpande, G., Shingde, V., Leroi, M., & Xiao, J. (2013). Routine probiotics for preterm neonates: experience in a tertiary Australian neonatal intensive care unit. *Journal of Paediatrics and Child Health*, *49*(S2), 10–58. http://doi.org/10.1111/jpc.12132

Dillman, D. A. (1991). The Design and Administration of Mail Surveys. *Annual Review of Sociology*, *17*, 225–249.

Dillman, D. A. (2007). *Mail and internet surveys: the tailored design method* (2nd ed., 2007 update with new internet, visual, and mixed-mode guide). Hoboken, N.J: Wiley.

Dillman, D. A., Smyth, J. D., & Christian, L. M. (2009). *Internet, mail, and mixed-mode surveys : the tailored design method*. Hoboken: John Wiley & Sons.

Dishman, R. K., Thom, N. J., Rooks, C. R., Motl, R. W., Horwath, C., & Nigg, C. R. (2009). Failure of Post-Action Stages of the Transtheoretical Model to Predict Change in Regular Physical Activity: A Multiethnic Cohort Study. *Annals of Behavioral Medicine*, *37*(3), 280–293. http://doi.org/10.1007/s12160-009-9113-8

Dogherty, E. J., Harrison, M. B., Graham, I. D., Vandyk, A. D., & Keeping-Burke, L. (2013). Turning knowledge into action at the point-of-care: the collective experience of nurses facilitating the implementation of evidence-based practice. *Worldviews on Evidence-Based Nursing / Sigma Theta Tau International, Honor Society of Nursing*, *10*(3), 129–139. http://doi.org/10.1111/wvn.12009

Dominguez-Bello, M. G., Blaser, M. J., Ley, R. E., & Knight, R. (2011). Development of the Human Gastrointestinal Microbiota and Insights From High-Throughput Sequencing. *Gastroenterology*, *140*(6), 1713–1719. http://doi.org/10.1053/j.gastro.2011.02.011

Drago, L., Rodighiero, V., Celeste, T., Rovetto, L., & De Vecchi, E. (2010). Microbiological evaluation of commercial probiotic products available in the USA in 2009. *Journal of Chemotherapy (Florence, Italy)*, *22*(6), 373–377.

Duncan, E. M., Francis, J. J., Johnston, M., Davey, P., Maxwell, S., McKay, G. A., … on behalf of the PROTECT Study Group. (2012). Learning curves, taking instructions, and patient safety: using a theoretical domains framework in an interview study to investigate prescribing errors among trainee doctors. *Implementation Science*, *7*(1), 86. http://doi.org/10.1186/1748-5908-7-86

Dutta-Bergman, M. J. (2003). The Linear Interaction Model of Personality Effects in Health Communication. *Health Communication*, *15*(1), 101–116. http://doi.org/10.1207/S15327027HC1501_5

Eaton, S., & Hall, N. J. (2013). The potential of probiotics in the fight against necrotizing enterocolitis. *Expert Review of Gastroenterology & Hepatology*, *7*(7), 581–583. http://doi.org/10.1586/17474124.2013.827480

Edwards, P., Roberts, I., Clarke, M., DiGuiseppi, C., Pratap, S., Wentz, R., & Kwan, I. (2002). Increasing response rates to postal questionnaires: systematic review. *BMJ (Clinical Research Ed.)*, *324*(7347), 1183.

Elazab, N., Mendy, A., Gasana, J., Vieira, E. R., Quizon, A., & Forno, E. (2013). Probiotic administration in early life, atopy, and asthma: a meta-analysis of clinical trials. *Pediatrics*, *132*(3), e666-676. http://doi.org/10.1542/peds.2013-0246

Elliot, A., & Woodward, W. (2007). *Statistical Analysis Quick Reference Guidebook*. 2455 Teller Road, Thousand Oaks California 91320 United States of America: SAGE Publications, Inc. Retrieved from http://srmo.sagepub.com/view/statistical-analysis-quick-reference-guidebook/SAGE.xml

Espinosa Fernández, M. G., Sánchez-Tamayo, T., Moreno Algarra, M. C., Fernández Romero, V., Vallejo Triano, J., Tapia Moreno, E., & Salguero García, E. (2014). New clinical practice guideline on enteral feeding in very low birth weight infants; second part. *NUEVA GUÍA DE PRÁCTICA CLÍNICA SOBRE NUTRICIÓN ENTERAL DEL RECIÉN NACIDO DE MUY BAJO PESO AL NACIMIENTO; SEGUNDA PARTE.*, *30*(2), 329–337. http://doi.org/10.3305/nh.2014.30.2.7590

Everitt, B., & Skrondal, A. (2010). *The Cambridge dictionary of statistics*. Cambridge; New York: Cambridge University Press. Retrieved from http://www.books24x7.com/marc.asp?bookid=36106

Fabian, E., Majchrzak, D., Dieminger, B., Meyer, E., & Elmadfa, I. (2008). Influence of probiotic and conventional yoghurt on the status of vitamins B1, B2 and B6 in young healthy women. *Annals of Nutrition & Metabolism*, *52*(1), 29–36. http://doi.org/10.1159/000114408

Falk, M., & Anderson, C. (2008). Prevention of skin cancer in primary healthcare: an evaluation of three different prevention effort levels and the applicability of a phototest. *The European Journal of General Practice*, *14*(2), 68–75. http://doi.org/10.1080/13814780802423430

Fallon, E. M., Nehra, D., Potemkin, A. K., Gura, K. M., Simpser, E., Compher, C., … Worthington. (2012). A.S.P.E.N. Clinical Guidelines: Nutrition Support of Neonatal Patients at Risk for Necrotizing Enterocolitis. *Journal of Parenteral and Enteral Nutrition*, *36*(5), 506–523. http://doi.org/10.1177/0148607112449651

Fan, W., & Yan, Z. (2010). Factors affecting response rates of the web survey: A systematic review. *Computers in Human Behavior*, *26*(2), 132–139. http://doi.org/10.1016/j.chb.2009.10.015

Fanaro, S., Chierici, R., Guerrini, P., & Vigi, V. (2003). Intestinal microflora in early infancy: composition and development. *Acta Paediatrica (Oslo, Norway: 1992). Supplement*, *91*(441), 48–55.

FDA. (2010). FDA Basics > Are dietary supplements approved by FDA? Retrieved November 19, 2013, from http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194344.htm

FDA. (2012). Safety Alerts for Human Medical Products > iFlora Kids Multi-Probiotic and iFlora 4-Kids Powder Dietary Supplements: Recall - Possible Salmonella Contamination. Retrieved November 19, 2013, from http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm311077.htm

FDA. (2013). Orphan Drug Act. Retrieved November 19, 2013, from http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcact/significantamendmentstothefdcact/orphandrugact/default.htm

Feltman, D. M., Du, H., & Leuthner, S. R. (2012). Survey of neonatologists' attitudes toward limiting life-sustaining treatments in the neonatal intensive care unit. *Journal of Perinatology*, *32*(11), 886–892.

Finer, N., & Barrington, K. J. (1996). Nitric oxide for respiratory failure in infants born at or near term. In *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd. Retrieved from http://onlinelibrary.wiley.com.proxy2.lib.umanitoba.ca/doi/10.1002/14651858.CD000399.pub2/abstract

Fink, A. (2003). *The survey kit* (2nd ed). Thousand Oaks, Calif: Sage Publications.

Fischhoff, B., Bostrom, A., & Quadrel, M. J. (1993). Risk perception and communication. *Annual Review of Public Health*, *14*, 183–203. http://doi.org/10.1146/annurev.pu.14.050193.001151

Fishbein, M., & Ajzen, I. (1975). *Belief, attitude, intention, and behavior: an introduction to theory and research*. Reading, Mass: Addison-Wesley Pub. Co.

Fowler, F. J. (1995). *Improving survey questions : design and evaluation.* Thousand Oaks: Sage.

Francis, J. J., Tinmouth, A., Stanworth, S. J., Grimshaw, J. M., Johnston, M., Hyde, C., … Eccles, M. P. (2009). Using theories of behaviour to understand transfusion prescribing in three clinical contexts in two countries: Development work for an implementation trial. *Implementation Science*, *4*(1), 70. http://doi.org/10.1186/1748-5908-4-70

French, S. D., Green, S. E., O'Connor, D. A., McKenzie, J. E., Francis, J. J., Michie, S., … Grimshaw, J. M. (2012). Developing theory-informed behaviour change interventions to implement evidence into practice: a systematic approach using the Theoretical Domains Framework. *Implementation Science*, *7*(1), 38. http://doi.org/10.1186/1748-5908-7-38

Freyer, J., Bott, K., Riedel, J., Wedler, B., Meyer, C., Rumpf, H.-J., … Hapke, U. (2006). Psychometric properties of the "Processes of Change" scale for alcohol misuse and its short form (POC-20). *Addictive Behaviors*, *31*(5), 821–832. http://doi.org/10.1016/j.addbeh.2005.06.007

Frost, B. L., & Caplan, M. S. (2013). Necrotizing enterocolitis: Pathophysiology, platelet-activating factor, and probiotics. *Seminars in Pediatric Surgery*, *22*(2), 88–93. http://doi.org/10.1053/j.sempedsurg.2013.01.005

Fukata, M., Chen, A., Vamadevan, A. S., Cohen, J., Breglio, K., Krishnareddy, S., … Abreu, M. T. (2007). Toll-Like Receptor-4 Promotes the Development of Colitis-Associated Colorectal Tumors. *Gastroenterology*, *133*(6), 1869–1869.e14. http://doi.org/10.1053/j.gastro.2007.09.008

Garland, S. M., Jacobs, S. E., & Tobin, J. M. (2010). A cautionary note on instituting probiotics into routine clinical care for premature infants.

Garlanda, C., Riva, F., Veliz, T., Polentarutti, N., Pasqualini, F., Radaelli, E., … Mantovani, A. (2007). Increased susceptibility to colitis-associated cancer of mice lacking TIR8, an inhibitory member of the interleukin-1 receptor family. *Cancer Research*, *67*(13), 6017–6021. http://doi.org/10.1158/0008-5472.CAN-07-0560

Garrido, D., Dallas, D. C., & Mills, D. A. (2013). Consumption of human milk glycoconjugates by infant-associated bifidobacteria: mechanisms and implications. *Microbiology (Reading, England)*. http://doi.org/10.1099/mic.0.064113-0

Gewirtz, A. (2011). Physiological Interactions Between Toll-Like Receptors and the Microbiome. *Annual Review of Physiology*, *74*, 110301101907077. http://doi.org/10.1146/annurev-physiol-020911-153330

Ghasemi, A., & Zahediasl, S. (2012). Normality Tests for Statistical Analysis: A Guide for Non-Statisticians. *International Journal of Endocrinology and Metabolism*, *10*(2), 486–489. http://doi.org/10.5812/ijem.3505

Gilstrap, L., Christensen, R., Clewell, W., D'Alton, M., Davidsosn, E., Escobedo, M., … Goddard-Finegold, J. (1995). Effect of corticosteroids for fetal maturation on perinatal outcomes: NIH consensus development panel on the effect of corticosteroids for fetal maturation on perinatal outcomes. *JAMA*, *273*(5), 413–418. http://doi.org/10.1001/jama.1995.03520290065031

Gleason, C., & Sherin, D. (2012). *Avery's diseases of the newborn.* (9th ed. /). Philadelphia PA: Elsevier/Saunders.

Graham, I. D., Logan, J., Harrison, M. B., Straus, S. E., Tetroe, J., Caswell, W., & Robinson, N. (2006). Lost in knowledge translation: Time for a map? *Journal of Continuing Education in the Health Professions*, *26*(1), 13–24. http://doi.org/10.1002/chp.47

Greenlaw, C., & Brown-Welty, S. (2009). A Comparison of Web-Based and Paper-Based Survey Methods Testing Assumptions of Survey Mode and Response Cost. *Evaluation Review*, *33*(5), 464–480. http://doi.org/10.1177/0193841X09340214

Gritz, E. C., & Bhandari, V. (2015). The human neonatal gut microbiome: a brief review. *Neonatology*, *3*, 17. http://doi.org/10.3389/fped.2015.00017

Grol, R., & Grimshaw, J. (2003). From best evidence to best practice: effective implementation of change in patients' care. *The Lancet*, *362*(9391), 1225–1230. http://doi.org/10.1016/S0140-6736(03)14546-1

Guandalini, S., Magazzù, G., Chiaro, A., La Balestra, V., Di Nardo, G., Gopalan, S., … Setty, M. (2010). VSL#3 Improves Symptoms in Children With Irritable Bowel Syndrome: A Multicenter, Randomized,

Placebo-Controlled, Double-Blind, Crossover Study. *Journal of Pediatric Gastroenterology and Nutrition*, *51*(1), 24–30. http://doi.org/10.1097/MPG.0b013e3181ca4d95

Guarner, F., & Malagelada, J.-R. (2003). Gut flora in health and disease. *Lancet*, *361*(9356), 512.

Guarner, F., & Schaafsma, G. . (1998a). Probiotics. *International Journal of Food Microbiology*, *39*(3), 237–238. http://doi.org/10.1016/S0168-1605(97)00136-0

Guarner, F., & Schaafsma, G. J. (1998b). Probiotics. *International Journal of Food Microbiology*, *39*(3), 237–238.

Gueimonde, M., Laitinen, K., Salminen, S., & Isolauri, E. (2007). Breast milk: a source of bifidobacteria for infant gut development and maturation? *Neonatology*, *92*(1), 64–66. http://doi.org/10.1159/000100088

Hagadorn, J. I., Brownell, E. A., Lussier, M. M., Parker, M. G. K., & Herson, V. C. (2014). Variability of Criteria for Pasteurized Donor Human Milk Use A Survey of U.S. Neonatal ICU Medical Directors. *Journal of Parenteral and Enteral Nutrition*, 148607114550832. http://doi.org/10.1177/0148607114550832

Hamilton-Miller, J. M. T., Gibson, G. R., & Bruck, W. (2003). Some insights into the derivation and early uses of the word “probiotic.” *British Journal of Nutrition*, *90*(4), 845–845. http://doi.org/10.1079/BJN2003954

Harris, J. K., Yates, B., & Crosby, W. M. (1995). A Perinatal Continuing Education Program: Its Effects on the Knowledge and Practices of Health Professionals. *Journal of Obstetric, Gynecologic, & Neonatal Nursing*, *24*(9), 829–835. http://doi.org/10.1111/j.1552-6909.1995.tb02567.x

Härtel, C., Pagel, J., Rupp, J., Bendiks, M., Guthmann, F., Rieger-Fackeldey, E., … Göpel, W. (2014). Prophylactic Use of Lactobacillus acidophilus/Bifidobacterium infantis Probiotics and Outcome in Very Low Birth Weight Infants. *The Journal of Pediatrics*, *165*(2), 285–289.e1. http://doi.org/10.1016/j.jpeds.2014.04.029

Hayward, R., Wilson, M., Tunis, S., Bass, E., & Guyatt, G. (1995). Users' guides to the medical literature: Viii. how to use clinical practice guidelines a. are the recommendations valid? *JAMA*, *274*(7), 570–574. http://doi.org/10.1001/jama.1995.03530070068032

Health Canada. (2009, April 16). [frequently asked questions]. Retrieved October 27, 2015, from http://www.hc-sc.gc.ca/fn-an/label-etiquet/claims-reclam/probiotics_qa-qr_probiotiques-eng.php#a4

Health Canada. (2012). Natural Health Products - Drugs and Health Products - Main Page - Health Canada. Retrieved June 19, 2012, from http://www.hc-sc.gc.ca/dhp-mps/prodnatur/index-eng.php

Honda, K., & Gorin, S. S. (2006). A model of stage of change to recommend colonoscopy among urban primary care physicians. *Health Psychology: Official Journal of the Division of Health Psychology, American Psychological Association*, *25*(1), 65–73. http://doi.org/10.1037/0278-6133.25.1.65

Hoonakker, P., & Carayon, P. (2009). Questionnaire Survey Nonresponse: A Comparison of Postal Mail and Internet Surveys. *International Journal of Human-Computer Interaction*, *25*(5), 348–373. http://doi.org/10.1080/10447310902864951

Hopkins, M. J., Macfarlane, G. T., Furrie, E., Fite, A., & Macfarlane, S. (2005). Characterisation of intestinal bacteria in infant stools using real-time PCR and northern hybridisation analyses. *FEMS Microbiology Ecology*, *54*(1), 77–85. http://doi.org/10.1016/j.femsec.2005.03.001

Hoyos, A. B. (1999). Reduced incidence of necrotizing enterocolitis associated with enteral administration of Lactobacillus acidophilus and Bifidobacterium infantis to neonates in an intensive care unit. *International Journal of Infectious Diseases: IJID: Official Publication of the International Society for Infectious Diseases*, *3*(4), 197–202.

Hu, X.-Y., Zhou, Y.-X., Xu, S.-Z., & Lin, Y.-Y. (2010). [Effects of probiotics on feeding intolerance in low birth weight premature infants]. *Zhongguo Dang Dai Er Ke Za Zhi = Chinese Journal of Contemporary Pediatrics*, *12*(9), 693–695.

Huang, Y., Wang, J., Cheng, Y., & Zheng, Y. (2010). The hypocholesterolaemic effects of Lactobacillus acidophilus American Type Culture Collection 4356 in rats are mediated by the down-regulation of Niemann-Pick C1-Like 1. *British Journal of Nutrition*, *104*(6), 807–812. http://doi.org/10.1017/S0007114510001285

Huda, S., Chaudhery, S., Ibrahim, H., & Pramanik, A. (2014). Neonatal necrotizing enterocolitis: Clinical challenges, pathophysiology and management. *Pathophysiology*, *21*(1), 3–12. http://doi.org/10.1016/j.pathophys.2013.11.009

Hunter, C., Dimaguila, M. A. V. T., Gal, P., Wimmer, J. E. J., Ransom, J. L., Carlos, R. Q., … Davanzo, C. C. (2012). Effect of routine probiotic, Lactobacillus reuteri DSM 17938, use on rates of necrotizing enterocolitis in neonates with birthweight < 1000 grams: a sequential analysis. *BMC Pediatrics*, *12*, 142. http://doi.org/10.1186/1471-2431-12-142

Hunter, C. J., Upperman, J. S., Ford, H. R., & Camerini, V. (2008). Understanding the Susceptibility of the Premature Infant to Necrotizing Enterocolitis (NEC). *Pediatric Research*, *63*(2), 117–123. http://doi.org/10.1203/PDR.0b013e31815ed64c

Indrio, F., Riezzo, G., Raimondi, F., Bisceglia, M., Cavallo, L., & Francavilla, R. (2008). The effects of probiotics on feeding tolerance, bowel habits, and gastrointestinal motility in preterm newborns. *The Journal of Pediatrics*, *152*(6), 801–806. http://doi.org/10.1016/j.jpeds.2007.11.005

Indrio, F., Riezzo, G., Raimondi, F., Bisceglia, M., Cavallo, L., & Francavilla, R. (2009). Effects of probiotic and prebiotic on gastrointestinal motility in newborns. *Journal of Physiology and Pharmacology: An Official Journal of the Polish Physiological Society*, *60 Suppl 6*, 27–31.

Ioannidis, J. P. A., & Lau, J. (2001). Evolution of treatment effects over time: Empirical insight from recursive cumulative metaanalyses. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(3), 831–836.

Islam, R., Tinmouth, A. T., Francis, J. J., Brehaut, J. C., Born, J., Stockton, C., … Grimshaw, J. M. (2012). A cross-country comparison of intensive care physicians' beliefs about their transfusion behaviour: A qualitative study using the theoretical domains framework. *Implementation Science*, *7*(1), 93–108. http://doi.org/10.1186/1748-5908-7-93

Jacobs, S. E., Hunt, R., Tarnow-Mordi, W. O., Inder, T. E., & Davis, P. G. (2008). Cochrane Review: Cooling for newborns with hypoxic ischaemic encephalopathy. *Evidence-Based Child Health: A Cochrane Review Journal*, *3*(4), 1049–1115. http://doi.org/10.1002/ebch.293

Jacobs, S. E., Tobin, J. M., Opie, G. F., Donath, S., Tabrizi, S. N., Pirotta, M., … for the ProPrems Study Group. (2013). Probiotic Effects on Late-onset Sepsis in Very Preterm Infants: A Randomized Controlled Trial. *Pediatrics*. http://doi.org/10.1542/peds.2013-1339

Jacquot, A., Neveu, D., Aujoulat, F., Mercier, G., Marchandin, H., Jumas-Bilak, E., & Picaud, J.-C. (2011a). Dynamics and Clinical Evolution of Bacterial Gut Microflora in Extremely Premature Patients. *The Journal of Pediatrics*, *158*(3), 390–396. http://doi.org/10.1016/j.jpeds.2010.09.007

Jacquot, A., Neveu, D., Aujoulat, F., Mercier, G., Marchandin, H., Jumas-Bilak, E., & Picaud, J.-C. (2011b). Dynamics and Clinical Evolution of Bacterial Gut Microflora in Extremely Premature Patients. *The Journal of Pediatrics*, *158*(3), 390–396. http://doi.org/10.1016/j.jpeds.2010.09.007

Jahan, S., & Henary, B. (2013). Attitudes of primary health care physician managers toward research: a pre-experimental study. *Australian Journal of Primary Health*, *19*(2), 171–176. http://doi.org/10.1071/PY11146

Janvier, A., & Barrington, K. J. (2005). The Ethics of Neonatal Resuscitation at the Margins of Viability: Informed Consent and Outcomes. *The Journal of Pediatrics*, *147*(5), 579–585. http://doi.org/10.1016/j.jpeds.2005.06.002

Janvier, A., Lantos, J., & Barrington, K. (2013). The politics of probiotics: probiotics, necrotizing enterocolitis and the ethics of neonatal research. *Acta Paediatrica (Oslo, Norway: 1992)*, *102*(2), 116–118. http://doi.org/10.1111/apa.12083

Janvier, A., Malo, J., & Barrington, K. J. (2014). Cohort Study of Probiotics in a North American Neonatal Intensive Care Unit. *The Journal of Pediatrics*, *164*(5), 980–985. http://doi.org/10.1016/j.jpeds.2013.11.025

Jenke, A., Ruf, E.-M., Hoppe, T., Heldmann, M., & Wirth, S. (2011). Bifidobacterium septicaemia in an extremely low-birthweight infant under probiotic therapy. *Archives of Disease in Childhood - Fetal and Neonatal Edition*, *97*(3), F217–F218. http://doi.org/10.1136/archdischild-2011-300838

Kale-Pradhan, P. B., Jassal, H. K., & Wilhelm, S. M. (2010). Role of Lactobacillus in the Prevention of Antibiotic-Associated Diarrhea: A Meta-analysis. *Pharmacotherapy*, *30*, 119–126. http://doi.org/10.1592/phco.30.2.119

Kalliomäki, M., Salminen, S., Poussa, T., & Isolauri, E. (2007). Probiotics during the first 7 years of life: A cumulative risk reduction of eczema in a randomized, placebo-controlled trial. *Journal of Allergy and Clinical Immunology*, *119*(4), 1019–1021. http://doi.org/10.1016/j.jaci.2006.12.608

Kelly, D., King, T., & Aminov, R. (2007). Importance of microbial colonization of the gut in early life to the development of immunity. *Mutation Research*, *622*(1–2), 58–69. http://doi.org/10.1016/j.mrfmmm.2007.03.011

Kim, J. Y., Kwon, J. H., Ahn, S. H., Lee, S. I., Han, Y. S., Choi, Y. O., … Ji, G. E. (2009). Effect of probiotic mix (Bifidobacterium bifidum, Bifidobacterium lactis, Lactobacillus acidophilus) in the primary prevention of eczema: a double-blind, randomized, placebo-controlled trial. *Pediatric Allergy and Immunology*, *21*(2p2), e386–e393. http://doi.org/10.1111/j.1399-3038.2009.00958.x

Kim, S. S. (2008). Predictors of short-term smoking cessation among Korean American men. *Public Health Nursing (Boston, Mass.)*, *25*(6), 516–525. http://doi.org/10.1111/j.1525-1446.2008.00738.x

Kinsey, V. E. (1956). Retrolental fibroplasia; cooperative study of retrolental fibroplasia and the use of oxygen. *A.M.A. Archives of Ophthalmology*, *56*(4), 481–543.

Kitajima, H., Sumida, Y., Tanaka, R., Yuki, N., Takayama, H., & Fujimura, M. (1997). Early administration of Bifidobacterium breve to preterm infants: randomised controlled trial. *Archives of Disease in Childhood Fetal and Neonatal Edition*, *76*(2), F101–F107.

Koniak-Griffin, D., & Stein, J. A. (2006). Predictors of sexual risk behaviors among adolescent mothers in a human immunodeficiency virus prevention program. *The Journal of Adolescent Health: Official Publication of the Society for Adolescent Medicine*, *38*(3), 297.e1-11. http://doi.org/10.1016/j.jadohealth.2004.12.008

Kopp, M. V., Hennemuth, I., Heinzmann, A., & Urbanek, R. (2008). Randomized, Double-Blind, Placebo-Controlled Trial of Probiotics for Primary Prevention: No Clinical Effects of Lactobacillus GG Supplementation. *Pediatrics*, *121*(4), e850–e856. http://doi.org/10.1542/peds.2007-1492

Kosloske, A. M. (1994). Epidemiology of necrotizing enterocolitis. *Acta Paediatrica (Oslo, Norway: 1992). Supplement*, *396*, 2–7.

Krahn M, & Naglie G. (2008). The next step in guideline development: Incorporating patient preferences. *JAMA*, *300*(4), 436–438. http://doi.org/10.1001/jama.300.4.436

Krosnick, J. A. (1999). Survey Research. *Annual Review of Psychology*, *50*(1), 537–567. http://doi.org/10.1146/annurev.psych.50.1.537

Kumar, S., & Nash, D. (2010). *Demand better!: revive our broken healthcare system* (1st ed). Bozeman, MT: Second River Healthcare Press.

Kunz, A. N., Noel, J. M., & Fairchok, M. P. (2004). Two cases of Lactobacillus bacteremia during probiotic treatment of short gut syndrome. *Journal of Pediatric Gastroenterology and Nutrition*, *38*(4), 457–458.

Lakshminrusimha, S., Manja, V., Mathew, B., & Suresh, G. K. (2015). Oxygen targeting in preterm infants: a physiological interpretation. *Journal of Perinatology*, *35*(1), 8–15. http://doi.org/10.1038/jp.2014.199

Land, M., Rouster-Stevens, K., Woods, C., Cannon, M., Cnota, J., & Shetty, A. (2005). Lactobacillus sepsis associated with probiotic therapy. *Pediatrics*, *115*(1), 178–181.

Laventhal, N., Spelke, M. B., Andrews, B., Larkin, L. K., Meadow, W., & Janvier, A. (2011). Ethics of resuscitation at different stages of life: a survey of perinatal physicians. *Pediatrics*, *127*(5), e1221-1229. http://doi.org/10.1542/peds.2010-1031

Leviton, L., Baker, S., Hassol, A., & Goldenberg, R. L. (1995). An exploration of opinion and practice patterns affecting low use of antenatal corticosteroids. *American Journal of Obstetrics and Gynecology*, *173*(1), 312–316.

Leviton, L., Goldenberg, R., Baker, S., & et al. (1999). Methods to encourage the use of antenatal corticosteroid therapy for fetal maturation: A randomized controlled trial. *JAMA*, *281*(1), 46–52. http://doi.org/10.1001/jama.281.1.46

Li, D., Rosito, G., & Slagle, T. (2013). Probiotics for the prevention of necrotizing enterocolitis in neonates: an 8-year retrospective cohort study. *Journal of Clinical Pharmacy and Therapeutics*, n/a–n/a. http://doi.org/10.1111/jcpt.12084

Liao, W. (2010, May 27). Probiotics and Necrotizing Enterocolitis. Letter to the editor.

Liggins, G. C., & Howie, R. N. (1972). A Controlled Trial of Antepartum Glucocorticoid Treatment for Prevention of the Respiratory Distress Syndrome in Premature Infants. *Pediatrics*, *50*(4), 515–525.

Lin, H.-C., Hsu, C.-H., Chen, H.-L., Chung, M.-Y., Hsu, J.-F., Lien, R., … Su, B.-H. (2008). Oral Probiotics Prevent Necrotizing Enterocolitis in Very Low Birth Weight Preterm Infants: A Multicenter, Randomized, Controlled Trial. *Pediatrics*, *122*(4), 693–700. http://doi.org/10.1542/peds.2007-3007

Lin HC, Hsu CH, Chen HL, Chung MY, Hsu JF, & Lien RI. (2008). Oral robiotics prevent necrotizing enterocolitis in very low birth weight preterm infants: A multicenter randomized controlled trial. *Pediatrics*, *122*, 693–700. http://doi.org/10.1542/peds.2007-3007

Lin HC, Su BH, & Chen AC. (2005). Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants. *Pediatrics*, *115*, 1–4. http://doi.org/10.1542/peds.2005-0245

Littell, J. H., & Girvin, H. (2002). Stages of Change A Critique. *Behavior Modification*, *26*(2), 223–273. http://doi.org/10.1177/0145445502026002006

Luedtke, S. A., Yang, J. T., & Wild, H. E. (2012). Probiotics and Necrotizing Enterocolitis: Finding the Missing Pieces of the Probiotic Puzzle. *The Journal of Pediatric Pharmacology and Therapeutics*, *17*(4), 308–328. http://doi.org/10.5863/1551-6776-17.4.308

Lund, A., & Lund, M. (2014). Laerd Statistics [Educational]. Retrieved September 10, 2015, from https://statistics.laerd.com/

Luoto, R., Isolauri, E., & Lehtonen, L. (2010a). Safety of Lactobacillus GG Probiotic in Infants with Very Low Birth Weight: Twelve Years of Experience. *Clinical Infectious Diseases*, *50*(9), 1327–1328. http://doi.org/10.1086/651694

Luoto, R., Isolauri, E., & Lehtonen, L. (2010b). Safety of Lactobacillus GG probiotic in infants with very low birth weight: twelve years of experience. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, *50*(9), 1327–1328. http://doi.org/10.1086/651694

Lye, H.-S., Rusul, G., & Liong, M.-T. (2010). Removal of cholesterol by lactobacilli via incorporation and conversion to coprostanol. *Journal of Dairy Science*, *93*(4), 1383–1392. http://doi.org/10.3168/jds.2009-2574

Mack, D. R., Michail, S., Wei, S., McDougall, L., & Hollingsworth, M. A. (1999). Probiotics inhibit enteropathogenic E. coliadherence in vitro by inducing intestinal mucin gene expression. *American Journal of Physiology - Gastrointestinal and Liver Physiology*, *276*(4), G941–G950.

Magne, F., Suau, A., Pochart, P., & Desjeux, J.-F. (2005). Fecal microbial community in preterm infants. *Journal of Pediatric Gastroenterology and Nutrition*, *41*(4), 386–392.

Maheux, B. C. J. (1989). Increasing Response Rates in Physicians' Mail Surveys: An Experimental Study. *American Journal of Public Health*, *79*(5), 638.

Malik, G., McKenna, L., & Plummer, V. (2015). Perceived knowledge, skills, attitude and contextual factors affecting evidence-based practice among nurse educators, clinical coaches and nurse specialists. *International Journal of Nursing Practice*, *21*, 46–57. http://doi.org/10.1111/ijn.12366

Manfreda, K. L., Bosnjak, M., Berzelak, J., Haas, I., & Vehovar, V. (2008). Web surveys versus other survey modes. *International Journal of Market Research*, *50*(1), 79–104.

Manja, V., Lakshminrusimha, S., & Cook, D. (2015). Oxygen saturation target range for extremely preterm infants: A systematic review and meta-analysis. *JAMA Pediatrics*, *169*(4), 332–340. http://doi.org/10.1001/jamapediatrics.2014.3307

Manzoni, P., Lista, G., Gallo, E., Marangione, P., Priolo, C., Fontana, P., … Farina, D. (2011a). Routine Lactobacillus rhamnosus GG administration in VLBW infants: A retrospective, 6-year cohort study. *Early Human Development*, *87*, *Supplement*, S35–S38. http://doi.org/10.1016/j.earlhumdev.2011.01.036

Manzoni, P., Lista, G., Gallo, E., Marangione, P., Priolo, C., Fontana, P., … Farina, D. (2011b). Routine Lactobacillus rhamnosus GG administration in VLBW infants: a retrospective, 6-year cohort study. *Early Human Development*, *87 Suppl 1*, S35-38. http://doi.org/10.1016/j.earlhumdev.2011.01.036

Marchand, V. (2012). Using probiotics in the paediatric population. *Paediatrics & Child Health*, *17*(10), 575.

Marks, P., & Michael, L. (2014, December). Drug warning regarding the use of dietary supplements in inmmunocompromised persons. Retrieved from http://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/UCM426233.pdf

Marques, T. M., Wall, R., Ross, R. P., Fitzgerald, G. F., Ryan, C. A., & Stanton, C. (2010). Programming infant gut microbiota: influence of dietary and environmental factors. *Current Opinion in Biotechnology*, *21*(2), 149–156. http://doi.org/10.1016/j.copbio.2010.03.020

Martin, C. R., & Walker, W. A. (2008). Probiotics: Role in Pathophysiology and Prevention in Necrotizing Enterocolitis. *Seminars in Perinatology*, *32*(2), 127–137. http://doi.org/10.1053/j.semperi.2008.01.006

Martin CR, & Walker WA. (2008). Probiotics: role in pathophysiology and prevention in necrotizing enterocolitis. *Semin Perinatol*, *32*, 127–137. http://doi.org/10.1053/j.semperi.2008.01.006

Martis, R., Ho, J. J., Crowther, C. A., & SEA-ORCHID Study Group. (2008). Survey of knowledge and perception on the access to evidence-based practice and clinical practice change among maternal and infant health practitioners in South East Asia. *BMC Pregnancy and Childbirth*, *8*, 34. http://doi.org/10.1186/1471-2393-8-34

Masuda, M., Ide, M., Utsumi, H., Niiro, T., Shimamura, Y., & Murata, M. (2012). Production potency of folate, vitamin B(12), and thiamine by lactic acid bacteria isolated from Japanese pickles. *Bioscience, Biotechnology, and Biochemistry*, *76*(11), 2061–2067.

McKenzie, J. E., French, S. D., O'Connor, D. A., Grimshaw, J. M., Mortimer, D., Michie, S., … Green, S. E. (2008). IMPLEmenting a clinical practice guideline for acute low back pain evidence-based manageMENT in general practice (IMPLEMENT): Cluster randomised controlled trial study protocol. *Implementation Science*, *3*(1), 11. http://doi.org/10.1186/1748-5908-3-11

McKenzie, J. E., O'Connor, D. A., Page, M. J., Mortimer, D. S., French, S. D., Walker, B. F., … Green, S. E. (2010). Improving the care for people with acute low-back pain by allied health professionals (the

ALIGN trial): A cluster randomised trial protocol. *Implementation Science*, *5*(1), 86. http://doi.org/10.1186/1748-5908-5-86

McLaws, M.-L., Maharlouei, N., Yousefi, F., & Askarian, M. (2012). Predicting hand hygiene among Iranian health care workers using the theory of planned behavior. *American Journal of Infection Control*, *40*(4), 336–339. http://doi.org/10.1016/j.ajic.2011.04.004

McSherry, L. A., Dombrowski, S. U., Francis, J. J., Murphy, J., Martin, C. M., O'Leary, J. J., … ATHENS Group. (2012). "It"s a can of worms': understanding primary care practitioners' behaviours in relation to HPV using the theoretical domains framework. *Implementation Science*, *7*(1), 73. http://doi.org/10.1186/1748-5908-7-73

McSherry, L. A., Dombrowski, S. U., Francis, J. J., Murphy, J., Martin, C. M., O?Leary, J. J., & Sharp, L. (2012). "It"s a can of worms': understanding primary care practitioners' behaviours in relation to HPV using the theoretical domains framework. *Implementation Science*, *7*, 73.

Medical Dictionary. (n.d.). Retrieved October 25, 2015, from http://medical-dictionary.thefreedictionary.com/position+statement

Michie, S. (2005). Making psychological theory useful for implementing evidence based practice: a consensus approach. *Quality and Safety in Health Care*, *14*(1), 26–33. http://doi.org/10.1136/qshc.2004.011155

Mihatsch, W. A., Braegger, C. P., Decsi, T., Kolacek, S., Lanzinger, H., Mayer, B., … van Goudoever, J. B. (2012). Critical systematic review of the level of evidence for routine use of probiotics for reduction of mortality and prevention of necrotizing enterocolitis and sepsis in preterm infants. *Clinical Nutrition*, *31*(1), 6–15. http://doi.org/10.1016/j.clnu.2011.09.004

Millar, M., Wilks, M., & Costeloe, K. (2003). Probiotics for preterm infants? *Archives of Disease in Childhood Fetal and Neonatal Edition*, *88*(5), F354–F358. http://doi.org/10.1136/fn.88.5.F354

Millar, M., Wilks, M., Fleming, P., & Costeloe, K. (2012). Should the use of probiotics in the preterm be routine? *Archives of Disease in Childhood - Fetal and Neonatal Edition*, *97*(1), F70–F74. http://doi.org/10.1136/adc.2009.178939

Misra, S., Sabui, T. K., & Pal, N. K. (2009). A randomized controlled trial to evaluate the efficacy of lactobacillus GG in infantile diarrhea. *The Journal of Pediatrics*, *155*(1), 129–132. http://doi.org/10.1016/j.jpeds.2009.01.060

Mittman, B. S., Tonesk, X., & Jacobson, P. D. (1992). Implementing clinical practice guidelines: social influence strategies and practitioner behavior change. *QRB. Quality Review Bulletin*, *18*(12), 413–422.

Moayyedi, P., Ford, A. C., Talley, N. J., Cremonini, F., Foxx-Orenstein, A. E., Brandt, L. J., & Quigley, E. M. M. (2010). The Efficacy of Probiotics in the Treatment of Irritable Bowel Syndrome: A Systematic Review. *Gut*, *59*(3), 325–332. http://doi.org/10.1136/gut.2008.167270

Mohan, R., Koebnick, C., Schildt, J., Schmidt, S., Mueller, M., Possner, M., … Blaut, M. (2006). Effects of Bifidobacterium lactis Bb12 Supplementation on Intestinal Microbiota of Preterm Infants: a Double-Blind, Placebo-Controlled, Randomized Study. *Journal of Clinical Microbiology*, *44*(11), 4025–4031. http://doi.org/10.1128/JCM.00767-06

Mohan R, Koebnick C, & Schildt J. (2006). Effect of Bifidobacterium lactis Bb12 supplementation on intestinal microbiota of preterm neonates: a double placebo controlled, randomized study. *J Clin Microbiol*, *44*, 4025–4031. http://doi.org/10.1128/JCM.00767-06

Morishita, T., Tamura, N., Makino, T., & Kudo, S. (1999). Production of menaquinones by lactic acid bacteria. *Journal of Dairy Science*, *82*(9), 1897–1903. http://doi.org/10.3168/jds.S0022-0302(99)75424-X

Mshvildadze, M. (2008). Intestinal microbiota development in the premature neonate: establishment of a lasting commensal relationship? *Nutrition Reviews*, *66*(11), 658–663. http://doi.org/10.1111/j.1753-4887.2008.00119.x

Narbona López, E., Uberos Fernández, J., Armadá Maresca, M. I., Couce Pico, M. L., Rodríguez Martínez, G., & Saenz de Pipaon, M. (2014). Grupo de Nutrición y Metabolismo Neonatal, Sociedad Española de Neonatología: recomendaciones y evidencias para la suplementación dietética con probióticos en recién nacidos de muy bajo peso al nacer. *Anales de Pediatría*, *81*(6), 397.e1-397.e8. http://doi.org/10.1016/j.anpedi.2014.06.020

Neu, J. (2011). Routine Probiotics for Premature Infants: Let's Be Careful! *The Journal of Pediatrics*, *158*(4), 672–674. http://doi.org/10.1016/j.jpeds.2010.11.028

Neu, J. (2014). The developing intestinal microbiome: probiotics and prebiotics. *World Review of Nutrition and Dietetics*, *110*, 167–176. http://doi.org/10.1159/000358465

Neu, J., & Shuster, J. (2010). Nonadministration of Routine Probiotics Unethical—Really? *Pediatrics*, *126*(3), e740–e741. http://doi.org/10.1542/peds.2010-1949A

Norman, P. (2011). The theory of planned behavior and binge drinking among undergraduate students: assessing the impact of habit strength. *Addictive Behaviors*, *36*(5), 502–507. http://doi.org/10.1016/j.addbeh.2011.01.025

Ofek Shlomai, N., Deshpande, G., Rao, S., & Patole, S. (2014). Probiotics for preterm neonates: what will it take to change clinical practice? *Neonatology*, *105*(1), 64–70. http://doi.org/10.1159/000354891

Ohishi, A., Takahashi, S., Ito, Y., Ohishi, Y., Tsukamoto, K., Nanba, Y., … Nakamura, T. (2010). Bifidobacterium Septicemia Associated with Postoperative Probiotic Therapy in a Neonate with Omphalocele. *The Journal of Pediatrics*, *156*(4), 679–681. http://doi.org/10.1016/j.jpeds.2009.11.041

O'Mahony, L., McCarthy, J., Kelly, P., Hurley, G., Luo, F., Chen, K., … Quigley, E. M. M. (2005). Lactobacillus and bifidobacterium in irritable bowel syndrome: Symptom responses and relationship to cytokine profiles. *Gastroenterology*, *128*(3), 541–551. http://doi.org/10.1053/j.gastro.2004.11.050

Oncel, M. Y., Erdeve, O., & Dilmen, U. (2014). Probiotics for necrotizing enterocolitis: not always a success story. *The Journal of Pediatrics*, *165*(2), 417. http://doi.org/10.1016/j.jpeds.2014.04.035

Pallant, J. (2007). *SPSS survival manual : a step by step guide to data analysis using SPSS for Windows* (3rd ed. .). Maidenhead, England ; New York: McGraw Hill/Open University Press.

Paolo, A. M., Bonaminio, G. A., Gibson, C., Partridge, T., & Kallail, K. (2000). Response Rate Comparisons of E-Mail- and Mail-Distributed Student Evaluations. *Teaching and Learning in Medicine*, *12*(2), 81–84. http://doi.org/10.1207/S15328015TLM1202_4

Parker, R. (2014). Probiotic guideline for necrotizing enterocolitis prevention in very low-birth-weight neonates. *Advances in Neonatal Care: Official Journal of the National Association of Neonatal Nurses*, *14*(2), 88–95. http://doi.org/10.1097/ANC.0000000000000043

Parmelee, A. H., Pilger, I. S., & Austin, W. O. (1956). Retrolenta fibroplasia—A Reduction in Incidence Following a Decrease in Use of Oxygen Therapy for Premature Infants. *California Medicine*, *84*(6), 424–426.

Patel, R. M., & Denning, P. W. (2013). Therapeutic Use of Prebiotics, Probiotics, and Postbiotics to Prevent Necrotizing Enterocolitis. *Clinics in Perinatology*, *40*(1), 11–25. http://doi.org/10.1016/j.clp.2012.12.002

Patz, A., Hoeck, L. E., & De La Cruz, E. (1952). Studies on the effect of high oxygen administration in retrolental fibroplasia. I. Nursery observations. *American Journal of Ophthalmology*, *35*(9), 1248–1253.

Pawlak, R., Connell, C., Brown, D., Meyer, M. K., & Yadrick, K. (2005). Predictors of multivitamin supplement use among African-American female students: a prospective study utilizing the theory of planned behavior. *Ethnicity & Disease*, *15*(4), 540–547.

Penders, J., Thijs, C., Vink, C., Stelma, F. F., Snijders, B., Kummeling, I., … Stobberingh, E. E. (2006). Factors Influencing the Composition of the Intestinal Microbiota in Early Infancy. *Pediatrics*, *118*(2), 511–521. http://doi.org/10.1542/peds.2005-2824

Penn, L., Dombrowski, S. U., Sniehotta, F. F., & White, M. (2013). Participants' perspectives on making and maintaining behavioural changes in a lifestyle intervention for type 2 diabetes prevention: a qualitative study using the theory domain framework. *BMJ Open*, *3*(6), e002949–e002949. http://doi.org/10.1136/bmjopen-2013-002949

Peterson, D. A., Frank, D. N., Pace, N. R., & Gordon, J. I. (2008). Metagenomic Approaches for Defining the Pathogenesis of Inflammatory Bowel Diseases. *Cell Host & Microbe*, *3*(6), 417–427. http://doi.org/10.1016/j.chom.2008.05.001

Pinsonneault, A., & Kraemer, K. L. (1993). Survey Research Methodology in Management Information Systems: An Assessment. *Journal of Management Information Systems*, *10*(2), 75–105.

Plaut, A. G. (1997). Trefoil peptides in the defense of the gastrointestinal tract. *The New England Journal of Medicine*, *336*(7), 506–507. http://doi.org/10.1056/NEJM199702133360712

Podolsky, D. K., Gerken, G., Eyking, A., & Cario, E. (2009). Colitis-Associated Variant of TLR2 Causes Impaired Mucosal Repair Because of TFF3 Deficiency. *Gastroenterology*, *137*(1), 209–220. http://doi.org/10.1053/j.gastro.2009.03.007

Polin, R. A., & Lorenz, J. M. (2015). Value and limitations of clinical practice guidelines in neonatology. *Seminars in Fetal and Neonatal Medicine*. http://doi.org/10.1016/j.siny.2015.09.004

Polit, D. F., & Beck, C. T. (2012). *Nursing research : generating and assessing evidence for nursing practice*. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins.

Ponnet, K., Wouters, E., Van Hal, G., Heirman, W., & Walrave, M. (2013). Determinants of physicians' prescribing behaviour of methylphenidate for cognitive enhancement. *Psychology, Health & Medicine*. http://doi.org/10.1080/13548506.2013.802361

Presseau, J., Johnston, M., Francis, J. J., Hrisos, S., Stamp, E., Steen, N., … Eccles, M. P. (2013). Theory-based predictors of multiple clinician behaviors in the management of diabetes. *Journal of Behavioral Medicine*. http://doi.org/10.1007/s10865-013-9513-x

Prochaska, J. O. (2000). Change at different Stages. In *Handbook of psychological change: psychotherapy processes & practices for the 21st century*. New York: Wiley.

Prochaska, J. O. (2006). Is social cognitive theory becoming a transtheoretical model? A comment on Dijkstra et al. (2006). *Addiction (Abingdon, England)*, *101*(7), 916–917. http://doi.org/10.1111/j.1360-0443.2006.01500.x

Prochaska, J. O., DiClemente, C. C., & Norcross, J. C. (1992). In Search of How People Change: Applications to Addictive Behaviors. *American Psychologist September 1992*, *47*(9), 1102–1114.

Prochaska, J. O., & Norcross, J. C. (1979). *Systems of psychotherapy: a transtheoretical analysis*. Dorsey Press: Dorsey Press.

Prochaska, J. O., & Velicer, W. F. (1997). The transtheoretical model of health behavior change. *American Journal of Health Promotion: AJHP*, *12*(1), 38–48.

Qasem, W., Alnaqui, A., Jorgensen, S., & Friel, J. (2014). Probiotics and Synbiotics in Necrotizing Enterocolitis: Where Are We? *Journal of Pediatrics & Neonatal Care*, *1*(1). http://doi.org/10.15406/jpnc.2014.01.00007

Quigley, M., Henderson, G., Anthony, M. Y., & McGuire, W. (2007). Formula milk versus donor breast milk for feeding preterm or low birth weight infants. *Cochrane Database of Syst Rev*, (4). Retrieved from http://onlinelibrary.wiley.com.proxy1.lib.umanitoba.ca/doi/10.1002/14651858.CD002971.pub2/abstract

Ramasamy, K., Abdullah, N., Wong, M. C., Karuthan, C., & Ho, Y. W. (2009). Bile salt deconjugation and cholesterol removal from media by Lactobacillus strains used as probiotics in chickens. *Journal of the Science of Food and Agriculture*, *90*(1), 65–69. http://doi.org/10.1002/jsfa.3780

Renwarden, R. (2014). Maximize Response Rates and Minimize Bias with the Proper Survey Structure. Retrieved August 4, 2015, from http://fluidsurveys.com/university/maximize-response-rates-minimize-bias-proper-survey-structure/

Repa, A., Thanhaeuser, M., Endress, D., Weber, M., Kreissl, A., Binder, C., … Haiden, N. (2015). Probiotics (Lactobacillus acidophilus and Bifidobacterium bifidum) prevent NEC in VLBW infants fed breast milk but not formula. *Pediatric Research*, *77*(2), 381–388. http://doi.org/10.1038/pr.2014.192

Roberts, D., & Dalziel, S. (2006). Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *The Cochrane Database of Systematic Reviews*, (3), CD004454. http://doi.org/10.1002/14651858.CD004454.pub2

Robertson, N. R. (1982). Advances in respiratory distress syndrome. *British Medical Journal (Clinical Research Ed.)*, *284*(6320), 917–918.

Rojas, M. A., Lozano, J. M., Rojas, M. X., Rodriguez, V. A., Rondon, M. A., Bastidas, J. A., … Arevalo, M. (2012). Prophylactic probiotics to prevent death and nosocomial infection in preterm infants. *Pediatrics*, *130*(5), e1113-1120. http://doi.org/10.1542/peds.2011-3584

Romeo, M. G., Romeo, D. M., Trovato, L., Oliveri, S., Palermo, F., Cota, F., & Betta, P. (2011). Role of probiotics in the prevention of the enteric colonization by Candida in preterm newborns: incidence of late-onset sepsis and neurological outcome. *J Perinatol*, *31*(1), 63–69.

Rouge C, Piloquet H, Butel M, Rochat F, & Ferraris L. (2009). Oral supplementation with probiotics in very low birth weight preterm infants: a randomized, double-blind, placebo-controlled trial. *Am J Clin Nutr*, *89*, 1828–1835. http://doi.org/10.3945/ajcn.2008.26919

Rush, V. (Ed.). (2014). *Planned Behavior : Theory, Applications and Perspectives*. New York: Nova Science Publishers. Retrieved from http://web.a.ebscohost.com.uml.idm.oclc.org/ehost/ebookviewer/ebook/bmxlYmtfXzc1NDg3M19fQU41?sid=3c03664b-dcec-4fb6-b991-69e17f601d2a@sessionmgr4005&vid=0&format=EB&rid=1

Sable, M. R., Schwartz, L. R., Kelly, P. J., Lisbon, E., & Hall, M. A. (2006). Using the theory of reasoned action to explain physician intention to prescribe emergency contraception. *Perspectives on Sexual and Reproductive Health*, *38*(1), 20–27. http://doi.org/10.1363/psrh.38.020.06

Sackett, D. L., Rosenberg, W. M. C., Gray, J. A. M., Haynes, R. B., & Richardson, W. S. (1996). Evidence based medicine: what it is and what it isn't. *BMJ*, *312*(7023), 71–72. http://doi.org/10.1136/bmj.312.7023.71

Samanta, M., Sarkar, M., Ghosh, P., Ghosh, J. kr, Sinha, M. kr, & Chatterjee, S. (2009). Prophylactic Probiotics for Prevention of Necrotizing Enterocolitis in Very Low Birth Weight Newborns. *Journal of Tropical Pediatrics*, *55*(2), 128–131. http://doi.org/10.1093/tropej/fmn091

Sampath, V., Menden, H., Helbling, D., Li, K., Gastonguay, A., Ramchandran, R., & Dimmock, D. P. (2015). SIGIRR Genetic Variants in Premature Infants With Necrotizing Enterocolitis. *Pediatrics*, *135*(6), e1530–e1534. http://doi.org/10.1542/peds.2014-3386

Sanders, M. E. (2009). How Do We Know When Something Called "Probiotic" Is Really a Probiotic? A Guideline for Consumers and Health Care Professionals, *1*(1), 3–12.

Sankaran, K., Puckett, B., Lee, D. S. C., Seshia, M., Boulton, J., Qiu, Z., … Canadian Neonatal Network. (2004). Variations in incidence of necrotizing enterocolitis in Canadian neonatal intensive care units. *Journal of Pediatric Gastroenterology and Nutrition*, *39*(4), 366–372.

Sari, F. N., Dizdar, E. A., Oguz, S., Erdeve, O., Uras, N., & Dilmen, U. (2011). Oral probiotics: Lactobacillus sporogenes for prevention of necrotizing enterocolitis in very low-birth weight infants: a randomized, controlled trial. *Eur J Clin Nutr*, *65*(4), 434–439.

Sari, F. N., Eras, Z., Dizdar, E. A., Erdeve, O., Oguz, S. S., Uras, N., & Dilmen, U. (2012). Do oral probiotics affect growth and neurodevelopmental outcomes in very low-birth-weight preterm infants? *American Journal of Perinatology*, *29*(8), 579–586. http://doi.org/10.1055/s-0032-1311981

Satoh, Y., Shinohara, K., & Umezaki, H. (2007). Bifidobacteria prevents necrotising enterocolitis and infection. *Int J Probiot Prebiot*, *2*, 149–154.

Sax, L. J., Gilmartin, S. K., & Bryant, A. N. (2003). Assessing Response Rates and Nonresponse Bias in Web and Paper Surveys. *Research in Higher Education*, *44*(4), 409–432. http://doi.org/10.1023/A:1024232915870

Schachinger, S., Stansfield, R. B., Ensing, G., & Schumacher, R. (2014). The prevalence of and attitudes toward neonatal functional echocardiography use and training in the United States: a survey of neonatal intensive care unit medical directors. *Journal of Neonatal-Perinatal Medicine*, *7*(2), 125–130. http://doi.org/10.3233/NPM-1474013

Schmand, B., Neuvel, J., Smolders-de Haas, H., Hoeks, J., Treffers, P. e., & Koppe, J. g. (1990). Psychological Development of Children Who Were Treated Antenatally With Corticosteroids to Prevent Respiratory Distress Syndrome. *Pediatrics*, *86*(1), 58.

Schmidt, B., Whyte, R. K., Asztalos, E. V., Moddemann, D., Poets, C., Rabi, Y., … Canadian Oxygen Trial (COT) Group, for the. (2013). Effects of Targeting Higher vs Lower Arterial Oxygen Saturations on Death or Disability in Extremely Preterm Infants: A Randomized Clinical Trial. *JAMA*, *309*(20), 2111. http://doi.org/10.1001/jama.2013.5555

Schultz, H. (2015). FDA warning over infant's death shouldn't call safety of probiotics into question, experts say. Retrieved July 31, 2015, from http://www.nutraingredients-usa.com/Regulation/FDA-warning-over-infant-s-death-shouldn-t-call-safety-of-probiotics-into-question-experts-say

Sedgwick, P. (2014). Non-response bias versus response bias. *BMJ*, *348*, g2573. http://doi.org/10.1136/bmj.g2573

Senarath, U., Fernando, D. N., & Rodrigo, I. (2007). Effect of training for care providers on practice of essential newborn care in hospitals in Sri Lanka. *Journal of Obstetric, Gynecologic, and Neonatal Nursing: JOGNN / NAACOG*, *36*(6), 531–541. http://doi.org/10.1111/j.1552-6909.2007.00183.x

Sesham, R., Oddie, S., Embleton, N. D., & Clarke, P. (2014). Probiotics for preterm neonates: parents' perspectives and present prevalence. *Archives of Disease in Childhood - Fetal and Neonatal Edition*, *99*(4), F345–F345. http://doi.org/10.1136/archdischild-2014-306344

Shane, A., Deshpande, G., & Merenstein, D. (2013). Improved neonatal outcomes with probiotics. *JAMA Pediatrics*, *167*(10), 885–886. http://doi.org/10.1001/jamapediatrics.2013.2590

Shannon, D. M., & Bradshaw, C. C. (2002). A Comparison of Response Rate, Response Time, and Costs of Mail and Electronic Surveys. *The Journal of Experimental Education*, *70*(2), 179–192. http://doi.org/10.1080/00220970209599505

Sharma, M., & Romas, J. A. (2012). *Theoretical foundations of health education and health promotion* (2nd ed). Sudbury, MA: Jones & Bartlett Learning.

Sheehan, K. B., & McMillan, S. J. (1999). Response Variation in E-Mail Surveys: An Exploration. *Journal of Advertising Research*, *39*(4), 45–54.

Sherman, P. M., Ossa, J. C., & Johnson-Henry, K. (2009). Unraveling mechanisms of action of probiotics. *Nutrition in Clinical Practice: Official Publication of the American Society for Parenteral and Enteral Nutrition*, *24*(1), 10–14. http://doi.org/10.1177/0884533608329231

Siggers, R. H., Siggers, J., Boye, M., Thymann, T., Mølbak, L., Leser, T., … Sangild, P. T. (2008). Early Administration of Probiotics Alters Bacterial Colonization and Limits Diet-Induced Gut Dysfunction and Severity of Necrotizing Enterocolitis in Preterm Pigs. *The Journal of Nutrition*, *138*(8), 1437–1444.

Sinclair, J. C. (1995). Meta-analysis of randomized controlled trials of antenatal corticosteroid for the prevention of respiratory distress syndrome: Discussion. *American Journal of Obstetrics and Gynecology*, *173*(1), 335–344. http://doi.org/10.1016/0002-9378(95)90223-6

Singer, E. (2008). Ethical Issues in Surveys. In *International handbook of survey methodology* (p. 549). New York, NY: Psychology Press.

Slovic, P. (1987). Perception of risk. *Science*, *236*(4799), 280–285. http://doi.org/http://dx.doi.org.uml.idm.oclc.org/10.1126/science.3563507

Slyne, H., Phillips, C., & Parkes, J. (2012). Infection prevention practice: how does experience affect knowledge and application? *Journal of Infection Prevention*, *13*(3), 92–96. http://doi.org/10.1177/1757177412446855

Smolders-de Haas, H., Neuvel, J., Schmand, B., Treffers, P. E., Koppe, J. G., & Hoeks, J. (1990). Physical development and medical history of children who were treated antenatally with corticosteroids to prevent respiratory distress syndrome: a 10- to 12-year follow-up. *Pediatrics*, *86*(1), 65–70.

Soll, R. F. (2010). Probiotics: Are We Ready for Routine Use? *Pediatrics*, *125*(5), 1071–1072. http://doi.org/10.1542/peds.2010-0643

Solomons, N. M., & Spross, J. A. (2011). Evidence-based practice barriers and facilitators from a continuous quality improvement perspective: an integrative review. *Journal of Nursing Management*, *19*(1), 109–120. http://doi.org/10.1111/j.1365-2834.2010.01144.x

Spencer, S. (2004). Watch Your Language! Retrieved February 18, 2014, from http://www.netconcepts.com/watch-your-language/

Squires, J. E., Suh, K. N., Linklater, S., Bruce, N., Gartke, K., Graham, I. D., … Grimshaw, J. M. (2013). Improving physician hand hygiene compliance using behavioural theories: a study protocol. *Implementation Science*, *8*(1), 16. http://doi.org/10.1186/1748-5908-8-16

Stokowski, L. (2004). Controversies in Using Steroids: From Fetus to Newborn. Retrieved January 22, 2016, from http://www.medscape.org/viewarticle/481188

Strozzi, G. P., & Mogna, L. (2008). Quantification of folic acid in human feces after administration of Bifidobacterium probiotic strains. *Journal of Clinical Gastroenterology*, *42 Suppl 3 Pt 2*, S179-184. http://doi.org/10.1097/MCG.0b013e31818087d8

Sue, V. M., & Ritter, L. A. (2007). *Conducting online surveys*. Los Angeles: Sage Publications. Retrieved from http://site.ebrary.com/id/10333446

Szajewska, H. (2010). Probiotics and prebiotics in preterm infants: where are we? Where are we going? *Early Human Development*, *86 Suppl 1*, 81–86. http://doi.org/10.1016/j.earlhumdev.2010.01.019

Szajewska, H. (2011). Short- and Long-Term Effects of Probiotics Administered Early in Life. In H. van Goudoever, S. Guandalini, & R. E. Kleinman (Eds.), *Nestlé Nutrition Institute Workshop Series* (Vol. 68, pp. 65–82). Basel: KARGER. Retrieved from http://www.karger.com/doi/10.1159/000325665

Szajewska, H., & Shamir, R. (2010, April 29). Is a meta-analytical approach appropriate to assess the efficacy of probiotics? Retrieved from http://pediatrics.aappublications.org.proxy2.lib.umanitoba.ca/content/125/5/921/reply#pediatrics_el_50064

Taeusch, H. W., Frigoletto, F., Kitzmiller, J., Avery, M. E., Hehre, A., Fromm, B., … Neff, R. K. (1979). Risk of Respiratory Distress Syndrome After Prenatal Dexamethasone Treatment. *Pediatrics*, *63*(1), 64–72.

Tarnow-Mordi, W. O., Wilkinson, D., Trivedi, A., & Brok, J. (2010). Probiotics, mortality, transparency and parental choice: need for major changes in practice. *Pediatrics*, *126*(3), e743–e744. http://doi.org/10.1542/peds.2010-1949D

Tarnow-Mordi, W. O., Wilkinson, D., Trivedi, A., & Brok, J. (2010). Probiotics Reduce All-Cause Mortality and Necrotizing Enterocolitis: It Is Time to Change Practice. *Pediatrics*, *125*(5), 1068–1070. http://doi.org/10.1542/peds.2009-2151

Taupin, D. R., Kinoshita, K., & Podolsky, D. K. (2000). Intestinal trefoil factor confers colonic epithelial resistance to apoptosis. *Proceedings of the National Academy of Sciences of the United States of America*, *97*(2), 799–804.

Taylor, A. L., Dunstan, J. A., & Prescott, S. L. (2007). Probiotic supplementation for the first 6 months of life fails to reduce the risk of atopic dermatitis and increases the risk of allergen sensitization in high-risk

children: a randomized controlled trial. *The Journal of Allergy and Clinical Immunology*, *119*(1), 184–191. http://doi.org/10.1016/j.jaci.2006.08.036

Tchobroutskyr, C. (1996). Indication of corticotherapy for fetal pulmonary maturation. *Contraception, Fertilité, Sexualité (1992)*, *24*(5), 413–416.

Te Pas, E., van Dijk, N., Bartelink, M. E. L., & Wieringa-De Waard, M. (2013). Factors influencing the EBM behaviour of GP trainers: A mixed method study. *Medical Teacher*, *35*(3), e990–e997. http://doi.org/10.3109/0142159X.2012.733044

Thavagnanam, S., Fleming, J., Bromley, A., Shields, M. D., & Cardwell, C. R. (2008). A meta-analysis of the association between Caesarean section and childhood asthma. *Clinical & Experimental Allergy*, *38*(4), 629–633. http://doi.org/10.1111/j.1365-2222.2007.02780.x

The BOOST II United Kingdom, Australia, and New Zealand Collaborative Groups. (2013). Oxygen Saturation and Outcomes in Preterm Infants. *New England Journal of Medicine*, *368*(22), 2094–2104. http://doi.org/10.1056/NEJMoa1302298

The Vermont-Oxford Trials Network. (1993). The Vermont-Oxford Trials Network: very low birth weight outcomes for 1990. Investigators of the Vermont-Oxford Trials Network Database Project. *Pediatrics*, *91*(3), 540–545.

Thomas, D. W., & Greer, F. R. (2010). Clinical Report—Probiotics and Prebiotics in. *Pediatrics*, peds.2010-2548. http://doi.org/10.1542/peds.2010-2548

Thomas, D. W., Greer, F. R., American Academy of Pediatrics Committee on Nutrition, & American Academy of Pediatrics Section on Gastroenterology, Hepatology, and Nutrition. (2010). Probiotics and prebiotics in pediatrics. *Pediatrics*, *126*(6), 1217–1231. http://doi.org/10.1542/peds.2010-2548

Thomas, M. R., Litin, S. C., Osmon, D. R., Corr, A. P., Weaver, A. L., & Lohse, C. M. (2001). Lack of effect of Lactobacillus GG on antibiotic-associated diarrhea: a randomized, placebo-controlled trial. *Mayo Clinic Proceedings. Mayo Clinic*, *76*(9), 883–889. http://doi.org/10.4065/76.9.883

Thompson, C., McCaughan, D., Cullum, N., Sheldon, T. A., Mulhall, A., & Thompson, D. R. (2001). The accessibility of research-based knowledge for nurses in United Kingdom acute care settings. *Journal of Advanced Nursing*, *36*(1), 11–22. http://doi.org/10.1046/j.1365-2648.2001.01938.x

Tin, W. (2002). Oxygen Therapy: 50 Years of Uncertainty. *PEDIATRICS*, *110*(3), 615–616. http://doi.org/10.1542/peds.110.3.615

Tin, W., & Gupta, S. (2007). Optimum oxygen therapy in preterm babies. *Archives of Disease in Childhood - Fetal and Neonatal Edition*, *92*(2), F143–F147. http://doi.org/10.1136/adc.2005.092726

Tin, W., & Hey, E. (2003). The Medical Use of Oxygen: A Century of Research in Animals and Humans. *NeoReviews*, *4*(12), 349e–355. http://doi.org/10.1542/neo.4-12-e349

Trevena, L. J., Irwig, L., Isaacs, A., & Barratt, A. (2007). GPs want tailored, user friendly evidence summaries--a cross sectional study in New South Wales. *Australian Family Physician*, *36*(12), 1065–1069.

Uauy, R. D., Fanaroff, A. A., Korones, S. B., Phillips, E. A., Phillips, J. B., & Wright, L. L. (1991). Necrotizing enterocolitis in very low birth weight infants: biodemographic and clinical correlates. National Institute of Child Health and Human Development Neonatal Research Network. *The Journal of Pediatrics*, *119*(4), 630–638.

Uno, H., Lohmiller, L., Thieme, C., Kemnitz, J. W., Engle, M. J., Roecker, E. B., & Farrell, P. M. (1990). Brain damage induced by prenatal exposure to dexamethasone in fetal rhesus macaques. I. Hippocampus. *Developmental Brain Research*, *53*(2), 157–167. http://doi.org/10.1016/0165-3806(90)90002-G

van der Waaij, L. A., Mesander, G., Limburg, P. C., & van der Waaij, D. (1994). Direct flow cytometry of anaerobic bacteria in human feces. *Cytometry*, *16*(3), 270–279. http://doi.org/10.1002/cyto.990160312

van Dijk, N., Hooft, L., & Wieringa-de Waard, M. (2010). What are the barriers to residents' practicing evidence-based medicine? A systematic review. *Academic Medicine: Journal of the Association of American Medical Colleges*, *85*(7), 1163–1170. http://doi.org/10.1097/ACM.0b013e3181d4152f

Vanderhoof, J. A., Whitney, D. B., Antonson, D. L., Hanner, T. L., Lupo, J. V., & Young, R. J. (1999). Lactobacillus GG in the prevention of antibiotic-associated diarrhea in children. *The Journal of Pediatrics*, *135*(5), 564–568.

VanGeest, J. B., Johnson, T. P., & Welch, V. L. (2007). Methodologies for Improving Response Rates in Surveys of Physicians A Systematic Review. *Evaluation & the Health Professions*, *30*(4), 303–321. http://doi.org/10.1177/0163278707307899

Vijay-Kumar, M., Wu, H., Jones, R., Grant, G., Babbin, B., King, T. P., … Neish, A. S. (2006). Flagellin Suppresses Epithelial Apoptosis and Limits Disease during Enteric Infection. *The American Journal of Pathology*, *169*(5), 1686–1700. http://doi.org/10.2353/ajpath.2006.060345

Viljanen, M., Kuitunen, M., Haahtela, T., Juntunen-Backman, K., Korpela, R., & Savilahti, E. (2005). Probiotic effects on faecal inflammatory markers and on faecal IgA in food allergic atopic eczema/dermatitis syndrome infants. *Pediatric Allergy and Immunology*, *16*(1), 65–71. http://doi.org/10.1111/j.1399-3038.2005.00224.x

Vogt, W. P. (2005). *Dictionary of statistics & methodology a nontechnical guide for the social sciences*. Thousand Oaks, Calif.: Sage Publications. Retrieved from http://site.ebrary.com/id/10387928

Waltz, C. F., Strickland, O., & Lenz, E. R. (2010). *Measurement in nursing and health research*. New York, NY: Springer Pub.

Wang, Q., Dong, J., & Zhu, Y. (2012). Probiotic supplement reduces risk of necrotizing enterocolitis and mortality in preterm very low-birth-weight infants: an updated meta-analysis of 20 randomized, controlled trials. *Journal of Pediatric Surgery*, *47*(1), 241–248. http://doi.org/10.1016/j.jpedsurg.2011.09.064

Wang, Y., Gao, L., Zhang, Y., Shi, C., & Ren, C. (2014). Efficacy of probiotic therapy in full-term infants with critical illness. *Asia Pacific Journal of Clinical Nutrition*, *23*(4), 575–580.

Wang, Y., Hoenig, J. D., Malin, K. J., Qamar, S., Petrof, E. O., Sun, J., … Claud, E. C. (2009). 16S rRNA gene-based analysis of fecal microbiota from preterm infants with and without necrotizing enterocolitis. *The ISME Journal*, *3*(8), 944–954. http://doi.org/10.1038/ismej.2009.37

Warner, P. (2013). Testing association with Fisher's Exact test. *Journal of Family Planning and Reproductive Health Care*, *39*(4), 281–284. http://doi.org/10.1136/jfprhc-2013-100747

Westerbeek, E. A. M., van den Berg, A., Lafeber, H. N., Knol, J., Fetter, W. P. F., & van Elburg, R. M. (2006). The intestinal bacterial colonisation in preterm infants: A review of the literature. *Clinical Nutrition*, *25*(3), 361–368. http://doi.org/10.1016/j.clnu.2006.03.002

Westra, A. E., Wit, J. M., Sukhai, R. N., & de Beaufort, I. D. (2011). How Best to Define the Concept of Minimal Risk. *The Journal of Pediatrics*, *159*(3), 496–500. http://doi.org/10.1016/j.jpeds.2011.05.034

Whitelaw, S., Baldwin, S., Bunton, R., & Flynn, D. (2000). The status of evidence and outcomes in Stages of Change research. *Health Education Research*, *15*(6), 707–718. http://doi.org/10.1093/her/15.6.707

Whorwell, P. J., Altringer, L., Morel, J., Bond, Y., Charbonneau, D., O'Mahony, L., … Quigley, E. M. M. (2006). Efficacy of an encapsulated probiotic Bifidobacterium infantis 35624 in women with irritable bowel syndrome. *The American Journal of Gastroenterology*, *101*(7), 1581–1590. http://doi.org/10.1111/j.1572-0241.2006.00734.x

Wickens, K., Black, P. N., Stanley, T. V., Mitchell, E., Fitzharris, P., Tannock, G. W., … Crane, J. (2008). A differential effect of 2 probiotics in the prevention of eczema and atopy: A double-blind, randomized, placebo-controlled trial. *Journal of Allergy and Clinical Immunology*, *122*(4), 788–794. http://doi.org/10.1016/j.jaci.2008.07.011

Wilson, J. L., Brockett, S., & Howard, P. (1942). Respiration of premature infants: Response to variations of oxygen and to increased carbon dioxide in inspired air. *American Journal of Diseases of Children*, *63*(6), 1080. http://doi.org/10.1001/archpedi.1942.02010060064002

Wu, W., Li, R., Malladi, S. S., Warshakoon, H. J., Kimbrell, M. R., Amolins, M. W., … David, S. A. (2010). Structure−Activity Relationships in Toll-like Receptor-2 Agonistic Diacylthioglycerol Lipopeptides. *J. Med. Chem.*, *53*(8), 3198–3213. http://doi.org/10.1021/jm901839g

Wu, X.-L., Li, Y.-F., Zhou, B.-Y., Wu, L.-J., & Wu, Z.-J. (2011). [Effects of bifidobacteria on respiratory and gastrointestinal tracts in neonates receiving mechanical ventilation]. *Zhongguo dang dai er ke za zhi = Chinese journal of contemporary pediatrics*, *13*(9), 704–707.

Xiao, H., Gulen, M. F., Qin, J., Yao, J., Bulek, K., Kish, D., … Li, X. (2007). The Toll–Interleukin-1 Receptor Member SIGIRR Regulates Colonic Epithelial Homeostasis, Inflammation, and Tumorigenesis. *Immunity*, *26*(4), 461–475. http://doi.org/10.1016/j.immuni.2007.02.012

Yamashiro, Y., & Nagata, S. (2013). Application of Probiotics to Ameliorate Ill Conditions from, Preterm Infants to the Elderly People. *Journal of Probiotics & Health*, *1*(3). http://doi.org/10.4172/2329-8901.1000112

Yee, W. H., Soraisham, A. S., Shah, V. S., Aziz, K., Yoon, W., & Lee, S. K. (2012). Incidence and timing of presentation of necrotizing enterocolitis in preterm infants. *Pediatrics*, *129*(2), e298-304. http://doi.org/10.1542/peds.2011-2022

Yoon, H. S. (2010). Neonatal innate immunity and Toll-like receptor. *Korean Journal of Pediatrics*, *53*, 985. http://doi.org/10.3345/kjp.2010.53.12.985

Yowell, M. (2014). Using probiotics to prevent necrotizing enterocolitis: Why have we not changed practice? *Journal of Neonatal Nursing*, *20*(5), 214–217. http://doi.org/10.1016/j.jnn.2014.03.003

Zbinden, A., Zbinden, R., Berger, C., & Arlettaz, R. (2015). Bacteremia in Three Preterm Infants on Probiotic Therapy. *Neonatology*, *107*(1), 56–59. http://doi.org/10.1159/000367985

Zeng, H., Wu, H., Sloane, V., Jones, R., Yu, Y., Lin, P., … Neish, A. S. (2006). Flagellin/TLR5 responses in epithelia reveal intertwined activation of inflammatory and apoptotic pathways. *American Journal of*

Physiology - Gastrointestinal and Liver Physiology, *290*(1), G96–G108. http://doi.org/10.1152/ajpgi.00273.2005

Zwolsman, S., te Pas, E., Hooft, L., Wieringa-de Waard, M., & van Dijk, N. (2012). Barriers to GPs' use of evidence-based medicine: a systematic review. *The British Journal of General Practice: The Journal of the Royal College of General Practitioners*, *62*(600), e511-521. http://doi.org/10.3399/bjgp12X652382

Appendices

Appendix A

Table 1

Type of Bacteria

Type of bacteria	**Examples**	**Functions**
Beneficial	*Lactobacillus, Bifidobacteria*	Inhibition of pathogenic bacterial growth; production of essential vitamins; degradation and fermentation of food substrates; promotion of feeding tolerance; and stimulation of immune functions
Potentially Pathogenic	*Enterobacteria*, Enterococci, *Escheria coli*, *Streptococci* and *Bacteroides*	The pathogenic effects of these bacteria include feeding intolerances, and inflammation and infection. In the context of the preterm infant, bacterial infection or over-colonization are associated with NEC
Pathogenic	bacteria-like Proteus, *Staphylococci*, *Clostridia*, *Pseudomonas* and *Klebsiellae*.	

*This Table summarize findings of the literature done by (Westerbeek et al., 2006).

Appendix B

Table 2.
Summary of probiotics used in Canada and the United States

Country	Probiotic	Doses	Indications	Discontinuation	Contraindications
Canada[1]	**FloraBaby**[MD] *(L. rhamnosus, B breve, B. bifidum*, *B. infantis*, and *B longum*)	2 x 10^9 UFC/day	<33 weeks or <1500 gr	34 weeks postconceptional age if patient is receiving all nutrition orally or transferred to another health care unit	Patient NPO, congenital abnormalities pathologies gastro-intestinal pathologies (eg. NEC, digestive perforation,recent gastro-intestinal surgery, short intestine), and innate immune deficits. Relative contraindications: Neonatal asphyxia, NEC grade III antecedents, acquired immunosuppression*. Any other medical condition where the integrity of the digestive tract is compromised (eg: allergy to bovine proteins suspected or proven) *(eg: more than 2 weeks of dexamethasone 0.3 mg/kg/hr or hydrocortisone 8 mg/kg/hr)
United States[2]	**BioGaia®** Probiotic Drops *(Lactobacillus reuteri Protectis) (li, Ro*	0.17ml= 5 drops /day	<34 weeks and <1500 gr Prolonged Antibiotic treatment	When the infant reaches a CGA of 36 weeks, or is discharged home or transferred to another facility	Inotropic support (Dopamine, Dobutamine, Epinephrine); continuous gastric suctioning gastric lesion and/or GI bleeding; surgical transection and NEC.
United States[3]	**BioGaia®** Probiotic Drops *(Lactobacillus reuteri Protectis)*	0.2 mL daily	<1500gr and Prolonged use of Antibiotics	Until 34 weeks or close to discharge home	Information not provided.
United States[2]	**ABC Dophilus®** (*S.thermophilus, B.infantis, B. bifidium)*	VLBW 1000gm-1500gm: Dose is 1.05 x 10^9 CFUs/day ELBW < 1000gm: Dose is 0.5 x 10^9 CFUs/day	<34 weeks and <1500 gr	When the infant reaches a CGA of 36 weeks, or is discharged home or transferred to another facility	Inotropic support (Dopamine, Dobutamine, Epinephrine); continuous gastric suctioning gastric lesion and/or GI bleeding; surgical transection and NEC.

1 (K, Barrington, personal communication, February 2, 2013)

2 (N. Nabovsky, personal communication , April 19, 2012)

3. (Hunter et al., 2012)

Appendix C

A Probiotic Survey for Medical Directors

Thank you for your willingness to complete this survey and be part of a very important dissertation study on the use of probiotics in premature infants. Please enter the access code if provided:

[ ]

Section 1: Current Practices or Factors Affecting the Implementation of ProbioticsS1Q01. Does your clinical unit prescribe probiotics for preterm infants?

- ○ Yes
- ○ No

Given that you indicated that your clinical unit is NOT using probiotics you will be asked questions to indentify the factors that are affecting the implementation of this practice.

Factors that Affect Routine Use of Probiotics for Premature Infants
Section 1: Factors affecting routine implementation of probiotics in neonatal practiceSection 2: Demographics
SECTION 1: Factors affecting routine implementation of probiotics in neonatal practice

This section begins with questions about general knowledge of probiotics, followed by questions about other relevant factors (e.g., skills, professional role, and environmental context). Some questions may seem repetitive but it is important to answer each one.

S1Q2. Please indicate whether each statement is TRUE or FALSE. Choose UNSURE if appropriate.

	TRUE	FALSE	UNSURE
Probiotics are the same as prebiotics	○	○	○
To be probiotic, a bacteria must confer a health benefit	○	○	○
Probiotic can be live, dead, or pasteurized bacteria	○	○	○

Probiotics may be found in:

	TRUE	FALSE	UNSURE
Soy beans	○	○	○
Cheese	○	○	○
Breast milk	○	○	○
Green tea	○	○	○

Yogourt ○ ○ ○

Examples of probiotics strains include:

	TRUE	FALSE	UNSURE
Streptococcus thermophilus	○	○	○
Lactobacillus reuteri	○	○	○
Bifidobacterium bifidum	○	○	○
Staphylococcus pneumonia	○	○	○

Please indicate whether each statement is TRUE or FALSE. Choose UNSURE if appropiate.

	TRUE	FALSE	UNSURE
Probiotics are being given to premature infants in some hospitals in	○	○	○
There is a standardized guideline in with dosage and formulation for probiotic use for premature infants	○	○	○
In the United States manufactures and distributores of probiotics are responsible for insuring the safety and quality of their products	○	○	○
A Health Canada Product license indicates that probiotic products are safe, effective and of high quality under recommended conditions of use	○	○	○

S1Q02. Please complete the information regarding the formulation you prescribe to premature infants:

a) Commercial name

○ FloraBaby™ Powder
○ Biogaia® Drops
○ ABC Acidhophilus®
○ other, specify: _____

b) Indication (e.g., infants

c) Dosage (e.g., 3 drops, half a scoop)

d) Is your formulation routinely prescribed to infants with the above indication?

○ Yes
○ No

Would you like to comment about this formulation?

○ Yes
○ No

Please type your comment below:

Would you like to add another probiotic formulation?

○ Yes
○ No

S1Q02A. Please complete the information regarding another formulation you prescribe to premature infant:

a) Commercial name

○ FloraBaby™ Powder
○ Biogaia® Drops
○ ABC Acidhophilus®
○ other, specify: _____

b) Indication (e.g., infants

c) Dosage (e.g., 3 drops, half a scoop)

d) Is your formulation routinely prescribed to infants with the above indication?
- ○ Yes
- ○ No

Would you like to comment about this formulation?
- ○ Yes
- ○ No

Please type your comment below:

S1Q3. How are probiotics administered in your unit? (Check all that apply)
- ☐ Probiotics are mixed with the ordered feeding and given during regular feeding
- ☐ Probiotics are mixed with the ordered feeding and given separate from regular feeding
- ☐ Probiotics are mixed with water and given during regular feeds
- ☐ Probiotics are mixed with water and given separate from regular feeds
- ☐ Other, please specify... _____
- ☐ I do not know

S1Q4. In what medical conditions are probiotics contraindicated in your unit? (Check all that apply)
- ☐ There are no specified contraindications
- ☐ Infants with a surgically-transected gut/short gut
- ☐ Infant receiving inotropic support (Dopamine, Dobutamine, Epinephrine)
- ☐ Infants on continuous gastric suctioning
- ☐ Extremely low birth weight infants
- ☐ Active gastric lesion and/or gastro intestinal bleeding
- ☐ Symptoms of suspected or definitive NEC such as abdominal distension, abdominal peritonitis, pneumoperitoneum or pneumotosis on xray and/or bilious residuals
- ☐ Other, please specify... _____
- ☐ I do not know

S1Q5. When does your unit discontinue the use of probiotics for the premature infant? (Check all that apply)
- ☐ When the infant is discharged home or transferred to another facility
- ☐ When the infant reaches a particular corrected gestational age. Specify age: _____
- ☐ When an infant reaches a particular weight. Specify weight: _____
- ☐ I do not know
- ☐ Other, please specify... _____

S1Q6. Approximately how long ago did your unit routinely start prescribing probiotics for premature infants? (Choose one response)
- ○ Approximately (years) _____
- ○ Approximately (months) _____
- ○ I do not know

S1Q7. To what extent did the following factors influence your unit to start prescribing probiotics?

Knowledge

	No extent	Little extent	Some extent	Great extent
Participation in educational activities related to probiotic supplementation in premature infants	○	○	○	○

Knowledge about a safe probiotic product to be used for premature infants	○	○	○	○
knowledge about the evidence related to use of probiotics for premature infants	○	○	○	○

Skills

	No extent	Little extent	Some extent	Great extent
Familiarity about how to prescribe probiotics	○	○	○	○
Past experience with prescribing probiotics to premature infants in the NICU	○	○	○	○

Professional role and identity

	No extent	Little extent	Some extent	Great extent
Most of my colleagues believe that the evidence to support the use of probiotics is strong	○	○	○	○

Optimism

	No extent	Little extent	Some extent	Great extent
There is sufficient evidence about the benefits of probiotics for the premature infant population	○	○	○	○

Intention

	No extent	Little extent	Some extent	Great extent
We looked into the evidence related to use of probiotics for premature infants	○	○	○	○

S1Q8. To what extent do you believe the following barriers interfere with the use of probiotics in other NICUs across your country?

Skills

	No extent	Little extent	Some extent	Great extent
Lack of knowledge about how to prescribe probiotics	○	○	○	○
Lack of experience prescribing probiotics to premature infants	○	○	○	○

Professional role and identity

	No extent	Little extent	Some extent	Great extent
The belief of health care professionals that the evidence related to use of probiotics is weak	○	○	○	○

Optimism

	No extent	Little extent	Some extent	Great extent
The belief that use of probiotics for premature infants might have negative outcomes	○	○	○	○

S1Q8. To what extent do you believe the following barriers interfere with the use of probiotics in other NICUs across your country?

Beliefs about consequences

	No extent	Little extent	Some extent	Great extent
The belief that use of probiotics for premature infants is not a safe practice	○	○	○	○

Decision making process

	No extent	Little extent	Some extent	Great extent
Difficulties in the health care team with the decision making process	○	○	○	○

Environmental context and resources

	No extent	Little extent	Some extent	Great extent
Lack of institutional support	○	○	○	○
Lack of awareness of safe probiotic products to administer to premature infants	○	○	○	○

Social influences

	No extent	Little extent	Some extent	Great extent
Negative feedback from other health care professionals about implementing the use of probiotics for premature infants	○	○	○	○

Section 2: Demographics

S2Q1. What is your sex?

- ○ **Female**
- ○ **Male**

Chapter S2Q2. What is your age in years?

- ○ Less than 25 years
- ○ 25-34
- ○ 35-44
- ○ 45-54
- ○ 55-64
- ○ Greater than 64 years

Chapter S2Q3. Check the location of the unit where you currently work?

- ○ **Western Canada** (British Columbia, Alberta, Manitoba, and Saskatchewan)
- ○ **Eastern Canada** (New Brunswick, Prince Edward Island, Nova scotia, Newfoundland and Labrador)
- ○ **Central Canada** (Ontario, Quebec)
- ○ **Northern Canada** (Yukon, Northern Territories and Nunavut)

Chapter S2Q3. Check the location of the unit where you currently work?

- ○ **Midwest** (Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri , Nebraska, North Dakota, South Dakota, Ohio, Wisconsin)
- ○ **Northeast** (Connecticut, Delaware, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont)
- ○ **South** (Alabama, Arkansas, Florida, Kentucky, Georgia, Louisiana, Mississippi, Oklahoma, North Carolina, South Carolina, Tennessee, Texas, Virginia, West Virginia)
- ○ **West** (Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada , New Mexico, Oregon , Utah, Wyoming, Washington)

S2Q4. What is your current position in the NICU? (Check one)

- ○ Medical Director of the Neonatal Intensive Care Unit (NICU)
- ○ Other, please specify... _____

S2Q5. In what type of hospital do you work?

- ○ Community Hospital
- ○ Regional Hospital
- ○ Tertiary referral center
- ○ Military hospital
- ○ I do not know
- ○ Other, please specify... _____

S2Q6. For how long have you worked with premature infants? (Check one)

- ○ Less than a year
- ○ More than 1 year but less than or equal to 5 years
- ○ More than 5 years but less than or equal to 10 years
- ○ More than 10 years but less than or equal to 20 years
- ○ More than 20 years

Appendix D

A probiotic Survey for Neonatologists and Nurse Practitioners

Please select the language in which you would like to complete the survey (English or French).Veuillez choisir la langue dans laquelle vous préfériez répondre au sondage (français ou anglais).

A Probiotic Survey for Neonatologists and Nurse Practitioners

Thank you for your willingness to participate in this internet survey and be part of a very important dissertation study. The survey is divided into TWO sections: Section 1: Factors affecting the use of probiotics for premature infants Section 2: Demographics

In which country do you practice?

- ○ **Canada**
- ○ **United States**

SECTION 1: Factors Affecting the Use of Probiotics for Premature Infants

This section begins with questions about general knowledge of probiotics, followed by questions about other relevant factors (e.g., skills, professional role, and environmental context).Some questions may seem repetitive but it is important to answer each one.

S1Q1. Please Indicate whether each statement is TRUE or False. Choose UNSURE if appropriate.

	TRUE	FALSE	UNSURE
Probiotics are the same as prebiotics	○	○	○
To be probiotic, a bacteria must confer a health benefit	○	○	○
Probiotic can be live, dead, or pasteurized bacteria	○	○	○

Probiotics may be found in:

	TRUE	FALSE	UNSURE
Soy beans	○	○	○
Cheese	○	○	○
Breast milk	○	○	○
Green tea	○	○	○

Yogurt	○	○	○

Examples of probiotics strains include:

	TRUE	FALSE	UNSURE
Streptococcus thermophilus	○	○	○
Lactobacillus reuteri	○	○	○
Bifidobacterium bifidum	○	○	○
Staphylococcus pneumonia	○	○	○

Please indicate whether each statement is TRUE or False. Choose UNSURE if appropriate.

	TRUE	FALSE	UNSURE
There is a standardized North American guideline with dosage and formulation for probiotic use for premature infants	○	○	○
Probiotics are being given to premature infants in some hospitals in Canada	○	○	○
Probiotics are being given to premature infants in some hospitals in The United States	○	○	○
In The United States manufactures and distributers of probiotics are responsible for insuring the safety and quality of their probiotics products	○	○	○
A Health Canada Product license indicates that probiotic products are safe, effective, and of high quality under recommended conditions of use	○	○	○

We would like to know your current opinion about use of probiotics for premature infants.

S1Q3. Please rate the extent to which you disagree or agree with the following statement:

Statement

	Strongly disagree	Disagree	Uncertain/Unsure	Agree	Strongly agree
Probiotics should be routinely administered to premature infants who meet selected criteria	○	○	○	○	○

S1Q4. Please rate the extent to which you disagree or agree with the following statements:

Knowledge

	Strongly disagree	Disagree	Uncertain/Unsure	Agree	Strongly agree
I am up-to-date on the scientific evidence supporting the use of probiotics for premature infants	○	○	○	○	○
There is strong evidence supporting the use of probiotics for premature infants	○	○	○	○	○
More evidence is required to support the routine use of probiotics in premature infants	○	○	○	○	○
The evidence regarding the use of probiotics for premature infants has flaws	○	○	○	○	○
In spite of the evidence, many questions still remain about optimal products, dosages, and formulations of probiotics that can be given to preterm infants	○	○	○	○	○

I can name at least one probiotic product that can be given to premature infants	○	○	○	○	○
I am aware of contraindications for probiotic supplements given to premature infants	○	○	○	○	○

Skills

	Strongly disagree	**Disagree**	**Uncertain/Unsure**	**Agree**	**Strongly agree**
I have enough skill to appraise the results of the evidence (e.g., randomized control trials, meta-analyses) regarding probiotic use for premature infants	○	○	○	○	○
I know the formulations and dosages to prescribe probiotics for premature infants	○	○	○	○	○
I have experience prescribing probiotics for premature infants	○	○	○	○	○

Profesional role and identity

	Strongly disagree	**Disagree**	**Uncertain/Unsure**	**Agree**	**Strongly agree**
Most of my colleagues believe that more evidence is required to support the use of probiotics for premature infants	○	○	○	○	○
Prescribing probiotics is not supported by current clinical practice guidelines in The United States	○	○	○	○	○
Prescribing probiotics is not supported by current clinical practice guidelines in Canada	○	○	○	○	○

Beliefs

	Strongly disagree	**Disagree**	**Uncertain/Unsure**	**Agree**	**Strongly agree**
I am concerned about the safety of administering probiotics to premature infants	○	○	○	○	○
Prescribing probiotics might put me at risk of a malpractice suit	○	○	○	○	○
I am confident in my ability to prescribe the appropriate dosage of probiotics for premature infants	○	○	○	○	○
Prescribing probiotics would make me feel uncomfortable	○	○	○	○	○

Opinions

	Strongly disagree	**Disagree**	**Uncertain/Unsure**	**Agree**	**Strongly agree**
Probiotics are associated with positive outcomes in the health of premature infants	○	○	○	○	○
Prescribing probiotics is one of the best recent medical advances in neonatology	○	○	○	○	○
Prescribing probiotics for premature infants is risky	○	○	○	○	○

Intention

	Strongly disagree	**Disagree**	**Uncertain/Unsure**	**Agree**	**Strongly agree**
I am actively looking into the evidence supporting the use of probiotics for premature infants because I would like to have this practice implemented at my health care facility	○	○	○	○	○
I have no interest in prescribing probiotics to premature infants	○	○	○	○	○
I am contemplating prescribing probiotics to premature infants	○	○	○	○	○
There is enough evidence supporting the prescription of probiotics for premature infants	○	○	○	○	○

Decision process

	Strongly disagree	Disagree	Uncertain/Unsure	Agree	Strongly agree
It is difficult to decide whether or not I support the use of probiotics for premature infants	○	○	○	○	○
Deciding whether or not to prescribe probiotics for premature infants is difficult for me	○	○	○	○	○
Deciding whether or not to prescribe probiotics for premature infants generates conflict within the health care team	○	○	○	○	○
The evidence regarding the use of probiotics is confusing	○	○	○	○	○
It is difficult to decide what specific probiotic products and doses to use in premature infants	○	○	○	○	○

Feelings

	Strongly disagree	Disagree	Uncertain/Unsure	Agree	Strongly agree
Fears about causing harm prevents me from prescribing probiotics for premature infants	○	○	○	○	○

Environmental context and resources

	Strongly disagree	Disagree	Uncertain/Unsure	Agree	Strongly agree
I am knowledgeable about the Health Canada regulations on the safety and quality of probiotic products in Canada	○	○	○	○	○
I am confident that the Health Canada regulations ensure that probiotic products are safe to be given to premature infants	○	○	○	○	○
I do not prescribe probiotics for premature infants due to the lack of regulations related to the quality and safety of probiotic products in The United States	○	○	○	○	○
I am knowledgeable about how probiotics are regulated in The United States	○	○	○	○	○
Sufficient opportunities are available to learn about probiotics for premature infants	○	○	○	○	○
I do not have online access to the scientific evidence about use of probiotics for premature infants	○	○	○	○	○

Environmental context and resources

	Strongly disagree	Disagree	Uncertain/Unsure	Agree	Strongly agree
Lack of time prevents me from accessing evidence regarding the efficacy of probiotics for premature infants	○	○	○	○	○
I do not have enough time to help establish a guideline for the use of probiotics for premature infants	○	○	○	○	○
I do not have adequate time to discuss the use of probiotics with my colleagues	○	○	○	○	○
I am concerned about the quality of the currently available probiotic products which may be given to premature infants	○	○	○	○	○
I do not have institutional support for establishing the use of probiotics as a standardized practice in my unit	○	○	○	○	○
Lack of standardized guidelines in The United States prevent me from prescribing probiotics for premature infants	○	○	○	○	○
Lack of standardized guidelines in Canada prevent me from prescribing probiotics for premature infants	○	○	○	○	○

Social influences

	Strongly disagree	Disagree	Uncertain/Unsure	Agree	Strongly agree

I have received mostly negative feedback from other health care professionals about giving probiotics to premature infants	○	○	○	○	○
My colleagues do not support the use of probiotics for premature infants	○	○	○	○	○
Parents have expressed to me that they want me to prescribe probiotics for their premature infants	○	○	○	○	○
Parental requests to prescribe probiotics have influenced medical practice	○	○	○	○	○
The administration of probiotics in some health care facilities in The United States and Canada motivates me to prescribe them to premature infants	○	○	○	○	○

SECTION 2: DEMOGRAPHICS

S2Q1. What is your sex?

- ○ Female
- ○ Male

S2Q2. Please indicate your age range?

- ○ Less than 26
- ○ 26-35
- ○ 36-45
- ○ 46-55
- ○ 56-65
- ○ Greater than 65

S2Q3. Check the location of the unit where you currently work?

- ○ **Western Canada** (British Columbia, Alberta, Manitoba, and Saskatchewan)
- ○ **Eastern Canada** (New Brunswick, Prince Edward Island, Nova scotia, Newfoundland, and Labrador)
- ○ **Central Canada** (Ontario and Quebec)
- ○ **Northern Canada** (Yukon, Northern Territories, and Nunavut)

S2Q3. Check the location of the unit where you currently work?

- ○ **Midwest** (Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri , Nebraska, North Dakota, South Dakota, Ohio, Wisconsin)
- ○ **Northeast** (Connecticut, Delaware, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont)
- ○ **South** (Alabama, Arkansas, Florida, Kentucky, Georgia, Louisiana, Mississippi, Oklahoma, North Carolina, South Carolina, Tennessee, Texas, Virginia, West Virginia)
- ○ **West** (Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada , New Mexico, Oregon, Utah, Wyoming, Washington)

S2Q04. What is your current profession? (Check one)

- ○ Academic Neonatologist (practice in a university-affiliated neonatal intensive care unit and/or practice involves teaching of pediatric/neonatal residents or neonatal fellows)
- ○ Non-academic Neonatologist (practice in a setting that is not affiliated with a university, and no involvement in pediatric/neonatal resident or neonatal fellow teaching)
- ○ Neonatal Fellow (part of training program BUT not recognized by American Board of Pediatrics or Royal College of Physicians and Surgeons of Canada)
- ○ Neonatal Subspecialty Resident (undergoing training and is recognized by the American Board of Pediatrics or Royal College of Physicians and Surgeons of Canada)
- ○ Neonatal or Pediatric Nurse Practitioner
- ○ Other, please specify... _____

S2Q5. In which type of unit(s) do you work? (Check all that apply)

- ☐ SPECIALITY NEONATAL CARE (level II): care for preterm infants ≥ 1500gr, offers resuscitation and stabilization before transfer to other facility
- ☐ NEONATAL INTENSIVE CARE (level III): Neonatal Intensive care is provided (eg, mechanical ventilation and/ or major surgeries such as bowel resection, omphalocele repair, esophageal atresia repair, myelomeningocele repair, among others).
- ☐ Other, please specify... _____
- ☐ I do not know

S2Q6. In what type of hospital do you work?

- ○ Community
- ○ Regional
- ○ Tertiary referral center
- ○ Military hospital
- ○ Other
- ○ I do not know

S2Q7. For how long have you worked with premature infants? (Check one)

- ○ Less than a year
- ○ More than 1 year but less than or equal to 5 years
- ○ More than 5 years but less than or equal to 10 years
- ○ More than 10 year but less than or equal to 20 years
- ○ More than 20 years

Free Draw Survey Thank you for participating in the survey.You are eligible to participate in a free draw for a 16GB iPad mini. If you wish to participate in the free draw, we need some personal information in order for us to ship your prize to you.This information will only be used for the purpose of the free draw and will be administered by The Manitoba Center for Nursing and Health Research. Once the free draw is done your contact information will be deleted.

Please click on the following link to be taken to the draw entry page:http://FluidSurvey™s.com/s/MHRC_Draw/

Appendix E

A Probiotic Survey of Nurses in NICUs

Please select the language in which you would like to complete the survey (English or French).Veuillez choisir la langue dans laquelle vous préfériez répondre au sondage (français ou anglais).

Thank you for your willingness to participate in this internet survey and be part of a very important dissertation study. The survey is divided into TWO sections: Section 1: Factors affecting the use of probiotics for premature infantsSection 2: Demographics

In order to direct you to your appropriate questions, please answer this question:Are you a nurse practitioner working in the NICU?

- ○ **Yes**
- ○ **No**

In which country do you practice?

- ○ **Canada**
- ○ **United States**

SECTION 1: Factors Affecting the Use of Probiotics for Premature Infants

This section begins with questions about general knowledge of probiotics, followed by questions about other relevant factors (e.g., skills, professional role, and environmental context).Some questions may seem repetitive but it is important to answer each one.

S1Q1. Please Indicate whether each statement is TRUE or False. Choose UNSURE if appropriate.

	TRUE	FALSE	UNSURE
Probiotics are the same as prebiotics	○	○	○
To be probiotic, a bacteria must confer a health benefit	○	○	○
Probiotic can be live, dead, or pasteurized bacteria	○	○	○

Probiotics may be found in:

	TRUE	FALSE	UNSURE
Soy beans	○	○	○

Cheese	○	○	○
Breast milk	○	○	○
Green tea	○	○	○
Yogurt	○	○	○

Examples of probiotics strains include:

	TRUE	FALSE	UNSURE
Streptococcus thermophilus	○	○	○
Lactobacillus reuteri	○	○	○
Bifidobacterium bifidum	○	○	○
Staphylococcus pneumonia	○	○	○

Please indicate whether each statement is TRUE or False. Choose UNSURE if appropriate.

	TRUE	FALSE	UNSURE
There is a standardized North American guideline with dosage and formulation for probiotic use for premature infants	○	○	○
Probiotics are being given to premature infants in some hospitals in Canada	○	○	○
Probiotics are being given to premature infants in some hospitals in The United States	○	○	○
In The United States manufactures and distributers of probiotics are responsible for insuring the safety and quality of their probiotics products	○	○	○
A Health Canada Product license indicates that probiotic products are safe, effective, and of high quality under recommended conditions of use	○	○	○

We would like to know your current opinion about use of probiotics for premature infants.

S1Q3. Please rate the extent to which you disagree or agree with the following statement:

Statement

	Strongly disagree	Disagree	Uncertain/Unsure	Agree	Strongly agree
Probiotics should be routinely administered to premature infants who meet selected criteria	○	○	○	○	○

S1Q4. Please rate the extent to which you disagree or agree with the following statements:

Knowledge

	Strongly disagree	Disagree	Uncertain/Unsure	Agree	Strongly agree
I am up-to-date on the scientific evidence supporting the use of probiotics for premature infants	○	○	○	○	○
There is strong evidence supporting the use of probiotics for premature infants	○	○	○	○	○
More evidence is required to support the routine use of probiotics in premature infants	○	○	○	○	○
The evidence regarding the use of probiotics for premature infants has flaws	○	○	○	○	○

In spite of the evidence, many questions still remain about optimal products, dosages, and formulations of probiotics that can be given to preterm infants	○	○	○	○	○
I can name at least one probiotic product that can be given to premature infants	○	○	○	○	○
I am aware of contraindications for probiotic supplements given to premature infants	○	○	○	○	○

Skills

	Strongly disagree	**Disagree**	**Uncertain/Unsure**	**Agree**	**Strongly agree**
I have enough skill to appraise the results of the evidence (e.g., randomized control trials, meta-analyses) regarding probiotic use for premature infants	○	○	○	○	○
I know how to administer probiotics for premature infants	○	○	○	○	○
I have experience administering probiotics for premature infants	○	○	○	○	○

Profesional role and identity

	Strongly disagree	**Disagree**	**Uncertain/Unsure**	**Agree**	**Strongly agree**
Most of my colleagues believe that more evidence is required to support the use of probiotics for premature infants	○	○	○	○	○
Adminsitration of probiotics is not supported by current clinical practice guidelines in The United States	○	○	○	○	○
Administration of probiotics is not supported by current clinical practice guidelines in Canada	○	○	○	○	○

Beliefs

	Strongly disagree	**Disagree**	**Uncertain/Unsure**	**Agree**	**Strongly agree**
I am concerned about the safety of administering probiotics to premature infants	○	○	○	○	○
Administering probiotics might put me at risk of a malpractice suit	○	○	○	○	○
I am confident in my ability to administer probiotics for premature infants	○	○	○	○	○
Administering probiotics would make me feel uncomfortable	○	○	○	○	○

Opinions

	Strongly disagree	**Disagree**	**Uncertain/Unsure**	**Agree**	**Strongly agree**
Probiotics are associated with positive outcomes in the health of premature infants	○	○	○	○	○
Administration of probiotics is one of the best recent medical advances in neonatology	○	○	○	○	○
Giving probiotics for premature infants is risky	○	○	○	○	○

Intention

	Strongly disagree	**Disagree**	**Uncertain/Unsure**	**Agree**	**Strongly agree**
I am actively looking into the evidence supporting the use of probiotics for premature infants because I would like to have this practice implemented at my health care facility	○	○	○	○	○
I have no interest in recommending the use of probiotics to premature infants to the neonatal health care team	○	○	○	○	○

My colleges are contemplating prescribing probiotics to premature infants	○	○	○	○	○
There is enough evidence supporting the use of probiotics for premature infants for me to recommend their use to my colleagues	○	○	○	○	○

Decision process

	Strongly disagree	Disagree	Uncertain/Unsure	Agree	Strongly agree
It is difficult to decide whether or not I support the use of probiotics for premature infants	○	○	○	○	○
Deciding whether or not to prescribe probiotics is difficult for the health care team	○	○	○	○	○
Deciding whether or not to prescribe probiotics for premature infants generates conflict within the health care team	○	○	○	○	○
The evidence regarding the use of probiotics is confusing	○	○	○	○	○
It is difficult to reccommend specific probiotic products and formulations to my colleagues	○	○	○	○	○

Feelings

	Strongly disagree	Disagree	Uncertain/Unsure	Agree	Strongly agree
Fears about causing harm prevents me from recommending to my colleagues the use of probiotics for premature infants	○	○	○	○	○

Environmental context and resources

	Strongly disagree	Disagree	Uncertain/Unsure	Agree	Strongly agree
I am knowledgeable about the Health Canada regulations on the safety and quality of probiotic products in Canada	○	○	○	○	○
I am confident that the Health Canada regulations ensure that probiotic products are safe to be given to premature infants	○	○	○	○	○
I do not advocate for the administration of probiotics to premature infants due to the lack of regulation on the quality and safety of probiotic products in the United States	○	○	○	○	○
I am knowledgeable about how probiotics are regulated in The United States	○	○	○	○	○
Sufficient opportunities are available to learn about probiotics for premature infants	○	○	○	○	○
I do not have online access to the scientific evidence about use of probiotics for premature infants	○	○	○	○	○

Environmental context and resources

	Strongly disagree	Disagree	Uncertain/Unsure	Agree	Strongly agree
Lack of time prevents me from accessing evidence regarding the efficacy of probiotics for premature infants	○	○	○	○	○
I do not have enough time to help establish a guideline for the use of probiotics for premature infants	○	○	○	○	○
I do not have adequate time to discuss the use of probiotics with my colleagues	○	○	○	○	○
I am concerned about the quality of the currently available probiotic products which may be given to premature infants	○	○	○	○	○
I do not have institutional support for establishing the use of probiotics as a standardized practice in my unit	○	○	○	○	○
Lack of standardized guidelines in The United States prevent me to recommend the use of probiotics for premature infants	○	○	○	○	○

Lack of standardized guidelines in Canada prevent me to recommend the use of probiotics for premature infants	○	○	○	○	○

Social influences

	Strongly disagree	Disagree	Uncertain/Unsure	Agree	Strongly agree
I have received mostly negative feedback from other health care professionals about giving probiotics to premature infants	○	○	○	○	○
My colleagues do not support the use of probiotics for premature infants	○	○	○	○	○
Parents have expressed to me that they want probiotics to be prescribed for their premature infants	○	○	○	○	○
Parental requests to prescribe probiotics have influenced medical practice	○	○	○	○	○
The administration of probiotics in some health care facilities in The United States and Canada motivates me to recommend their use to my colleagues	○	○	○	○	○

SECTION 2: DEMOGRAPHICS

S2Q1. What is your sex?

- ○ Female
- ○ Male

S2Q2. Please indicate your age range?

- ○ Less than 26
- ○ 26-35
- ○ 36-45
- ○ 46-55
- ○ 56-65
- ○ Greater than 65

S2Q3. Check the location of the unit where you currently work?

- ○ **Western Canada** (British Columbia, Alberta, Manitoba, and Saskatchewan)
- ○ **Eastern Canada** (New Brunswick, Prince Edward Island, Nova scotia, Newfoundland, and Labrador)
- ○ **Central Canada** (Ontario and Quebec)
- ○ **Northern Canada** (Yukon, Northern Territories, and Nunavut)

S2Q3. Check the location of the unit where you currently work?

- ○ **Midwest** (Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri , Nebraska, North Dakota, South Dakota, Ohio, Wisconsin)
- ○ **Northeast** (Connecticut, Delaware, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont)
- ○ **South** (Alabama, Arkansas, Florida, Kentucky, Georgia, Louisiana, Mississippi, Oklahoma, North Carolina, South Carolina, Tennessee, Texas, Virginia, West Virginia)
- ○ **West** (Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada , New Mexico, Oregon, Utah, Wyoming, Washington)

Free Draw Survey Thank you for participating in the survey.You are eligible to participate in a free draw for a 16GB iPad mini. If you wish to participate in the free draw, we need some personal information in order for us to ship your prize to you.This information will only be used for the purpose of the free draw and will be administered by The Manitoba Center for Nursing and Health Research. Once the free draw is done your contact information will be deleted.

Please click on the following link to be taken to the draw entry page:http://FluidSurvey™s.com/s/MHRC_Draw/

Applied Health Sciences
Yenly Londoño, RN, MNsc, PhD(c)
268 Helen Class Centre for Nursing
Winnipeg, Manitoba
Canada R3T 2N2
Telephone: XXX XXX XXXX
Fax: XXX XXX XXXX

Appendix F

Faculty of Graduate Studies

January 1, 2015

Dear Dr. XXXX XXXX

Re: **A Survey of Medical Directors of NICUs about Current Practices and Factors Associated with Use of Probiotics for Premature Infants**

Your input is appreciated!

You have been contacted because you are a Medical Director of a Neonatal Intensive Care Unit (NICU) listed in the *2011 Directory of Newborn Intensive Care Units and Neonatologists of the USA and Canada*, published by the American Academy of Pediatrics.

I am a graduate student in the PhD program in Applied Health Sciences at the University of Manitoba, Canada. I am currently collecting data for my dissertation entitled **A Survey of Current Practices and Factors Associated with Health Care Professionals' Use of Probiotics**. I am inviting all Medical Directors of NICUs in Canada and The United States to participate in this survey. **Whether or NOT your NICU is using probiotics, your input in this survey is very important.**

Probiotics are routinely administered to premature infants in some NICUs in North America, but we do not know the prevalence and variations of this practice, nor do we know much about factors that affect the use or non-use of probiotics. Although there are no direct benefits to you in participating in this survey, your input in this study will help to provide important information about use of probiotics. This study does not pose any risk to the participants.

This survey will take approximately 8 to 10 minutes to complete. If you decide to participate, you will be asked some demographic questions, as well as questions that pertain to whether or not probiotics are being used in your NICU, the probiotic formulation used (if applicable), and factors influencing use or non-use of probiotics. Please visit the following website address to access the survey:

Survey Link: **www.probiodirectors.com**
Access code:
This research had been approved by the Education/Nursing Research Ethics Board at the University of Manitoba. If you have any concerns or complaints, you may contact the

Human Ethics Coordinator at XXX XXX XXXXor by email at XXX XXX XXX XXX XXX XXXX.

The survey is accessible through FluidSurvey™™, and any identifying information will be removed by a research technician at the Manitoba Center for Nursing and Health Research Center (MCNHR), and data will remain anonymous. FluidSurvey™™ will not use the information collected in this survey in any way, shape, or form, nor will they make the email address of respondents available to third parties.

For any further questions or comments, do not hesitate to contact me at XXX XXX XXX XXX XXX XXXX or by phone at XXX XXX XXXX. My doctoral co-supervisor is Dr. William Diehl-Jones, who is a scientist at the Manitoba Institute for Child Health. He can be reached at XXX XXX XXX XXX XXX XXXX or at XXX XXX XXXX.

The data from the surveys will be downloaded by the MCNHR, transferred to the principal investigator and stored in a secure password-protected computer in room 268 Helen Glass Center for Nursing at the University of Manitoba. The data collected will be destroyed from the hard drive of the computer after 5 years (06/2019). The findings of this survey will be published in a peer reviewed journal, presented at academic meetings and used for educational purposes. A brief summary of the findings can be found after June 2015 in the following website: http://umanitoba.ca/faculties/nursing/academic_staff/diehl_jones.html

You are under no obligation to participate in the survey or to respond to any questions you do not wish to answer. Your submission of a completed survey will be taken as evidence of your consent to participate.

If you begin to answer the survey questions and change your mind about taking part, you can log off by simply closing the browser. If you opt to withdraw from the survey, your data will not be used in the study. Only data from completed surveys will be analyzed. Once the survey is submitted, the data can no longer be removed because it is submitted anonymously.

We thank you in advance for your participation.

Sincerely,

Yenly Catherine Londoño MNSc, RN, PhD(c)
Principal Investigator
Applied Health Sciences, University of Manitoba

William Diehl-Jones PhD, RN
Thesis co-supervisor
Scientist, Manitoba Institute for Child Health

Dr. Maureen Heaman, RN, PhD
Thesis co-supervisor
Professor, College of Nursing
University of Manitoba

Dr. Aaron Chiu, MD, FRCPC, FAAP
Committee Member
Associate Professor, Section of Neonatology
University of Manitoba

Dr. James Friel, PhD,
Committee Member
Professor, Department of Nutritional Sciences
University of Man

Appendix G

Emai invitation to Medical Directors

From: Yenly Catherine Londono Calle
Subject: A Survey of Medical Directors of NICUs about Current Practices and Factors Associated with Use of Probiotics for Premature Infants

UNIVERSITY OF MANITOBA

A Survey of Medical Directors of NICUs about Current Practices and Factors Associated with Use of Probiotics for Premature Infants

Dr. XXXX XXXX

Your input is appreciated!

You have been contacted because you are a Medical Director of a Neonatal Intensive Care Unit (NICU) listed in the *2011 Directory of Newborn Intensive Care Units and Neonatologists of the USA and Canada*, published by the American Academy of Pediatrics.

I am a graduate student in the PhD program in Applied Health Sciences at the University of Manitoba, Canada. I am currently collecting data for my dissertation entitled **A Survey of Current Practices and Factors Associated with Health Care Professionals' Use of Probiotics**.

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This survey will take approximately 8 to 10 minutes to complete. If you decide to participate, you will be asked some demographic questions, as well as questions that pertain to whether or not probiotics are being used in your NICU, the probiotic formulation used (if applicable), and factors influencing use or non-use of probiotics. Please visit the following website address to access the survey:

Survey link : **http://FluidSurvey™s.com/surveys/yen-9Nz/copy-current-practices/?code=**

This research had been approved by the Education/Nursing Research Ethics Board at the University of Manitoba. If you have any concerns or complaints, you may contact the Human Ethics Coordinator at XXX XXX XXXX or by email at XXX XXX XXX XXX XXX XXXX.
The survey is accessible through FluidSurvey™, and any identifying information will be removed by a research technician at the Manitoba Center for Nursing and Health Research Center (MCNHR), and data will remain anonymous. FluidSurvey™ will not use the information collected in this survey in any way, shape, or form, nor will they make the email address of respondents available XXX XXX XXX XXX XXX XXXX XXX XXX XXX XXX XXX XXXX to third parties.

For any further questions or comments, do not hesitate to contact me at XXX XXX XXX or by phone at XXX XXX XXXX. My doctoral co-supervisor is Dr. William Diehl-Jones, who is a scientist at the Manitoba Institute for Child Health. He can be reached at XXX XXX XXX or at XXX XXX XXXX.

The data from the surveys will be downloaded by the MCNHR, transferred to the principal investigator and stored in a secure password-protected computer in room 268 Helen Glass Center for Nursing at the University of Manitoba. The data collected will be destroyed from the hard drive of the computer after 5 years (05/2019). The findings of this survey will be published in a peer reviewed journal, presented at academic meetings and used for educational purposes. A brief summary of the findings can be found after June 2015 in the following website:
http://umanitoba.ca/faculties/nursing/academic_staff/diehl_jones.html
You are under no obligation to participate in the survey or to respond to any questions you do not wish to answer. Your submission of a completed survey will be taken as evidence of your consent to participate.

If you begin to answer the survey questions and change your mind about taking part, you can log off by simply closing the browser. If you opt to withdraw from the survey, your data will not be used in the study. Only data from completed surveys will be analyzed. Once the survey is submitted, the data can no longer be removed because it is submitted anonymously.
We appreciate your time and consideration in completing this survey. Should you wish to take part in the survey, please go to the survey website **http://FluidSurvey™s.com/surveys/yen-9Nz/copy-current-practices/?code=**

We thank you in advance for your participation!

Yenly Catherine Londoño MNSc, RN, PhD (c)
Principal Investigator
Applied Health Sciences, University of Manitoba

William Diehl-Jones PhD, RN
Thesis co-supervisor
Scientist, Manitoba Institute for Child Health

Dr. Maureen Heaman, RN, PhD
Thesis co-supervisor
Professor, College of Nursing
University of Manitoba

Dr. Aaron Chiu, MD, FRCPC, FAAP
Committee Member
Associate Professor, Section of Neonatology
University of Manitoba

Dr. James Friel, PhD,
Committee Member
Professor, Department of Nutritional Sciences
University of Manitoba

Appendix H

Postcard Reminder to Medical Directors

Yenly Catherine Londoño
University of Manitoba
268 Helen Glass Center for Nursing,
Winnipeg, CANADA MB R3T 2N2

UNIVERSITY OF MANITOBA

January 28, 2015

A Probiotic Survey for Medical Directors of NICUs

Dr. XXX XXX

Your input is appreciated it!

This is a reminder.

In the past, I contacted you to participate in a brief survey of *Medical Directors about **Current Practices and Factors Associated with the Use of Probiotics for Preterm Infants Feeds.***

Whether or NOT your NICU uses probiotics your input is important.

This data will further our understanding of the issues related to the use of probiotics in clinical practice.

I am sending this postcard as a reminder to participate in the survey.

I hope to conclude my data collection soon for completion of my dissertation.

The survey will take only 8-10 minutes to complete.

Your participation is anonymous and voluntary.
Please, go to this website to participate:

www.probiodirectors.com

I thank you in advance for your participation!

Best wishes,

Yenly Catherine Londoño *MNSc, RN, PhD Candidate*
Applied Health Sciences
University of Manitoba
[redacted]

Appendix I

Email Reminder to Medical Directors

From: Yenly Catherine Londono Calle
Subject: A Survey of Medical Directors of NICUs about Current Practices and Factors Associated with Use of Probiotics for Premature Infants

UNIVERSITY OF MANITOBA

A Survey of Medical Directors of NICUs about Current Practices and Factors Associated with Use of Probiotics for Premature Infants

Dr. XXX XXX

You have been contacted because you are a Medical Director of a Neonatal Intensive Care Unit (NICU) listed in the *2011 Directory of Newborn Intensive Care Units and Neonatologists of the USA and Canada*.

In the past, I invited you to participate in this brief online survey because **you play an important role** in helping to inform the decision-making process regarding feeding practices.**This study is part of my PhD dissertation, entitled: A Survey of Current Practices and Factors Associated with Health Care Professionals' Use of Probiotics.**
After inviting 1,045 Medical Directors, I have received a response rate of approximately 10% .
We are hoping to receive more input in this study to help provide information about factors that may be influencing probiotic use in NICUs or current probiotic's practices in North America.

Whether or NOT your NICU is using probiotics, your input in this survey is important.
The survey will take approximately 8-10 minutes. Please visit the following website to participate :http://FluidSurvey™s.com/s/MD-NICU/?code=sbtm7hapou

If you are a Medical Director who has worked within the last 6 months in NICUs across Canada and/or The United States, and your unit does not routinely administer probiotics in preterm infants feeds OR if your unit is in the process of implementing use of probiotics, we would very much like to hear from you.

Probiotics are currently an area of great clinical interest, but are seldom used in NICUs in Canada and The United States.
If you decide to participate, you will be asked some demographic questions, as well as questions that pertain to whether or not probiotics are being used in your NICU, the probiotic formulation used (if applicable), and factors influencing use or non-use of probiotics. Please visit the following website address to access the survey:http://FluidSurvey™s.com/s/MD-NICU/?code=sbtm7hapou

Your participation is anonymous and voluntary. Although there are no direct benefits to you in participating in this survey, your input in this study will help to provide important information about use of probiotics. This study does not pose any risk to the participants.
This research had been approved by the Education/Nursing Research Ethics Board at the University of Manitoba. If you have any concerns or questions, you may contact the Human Ethics Coordinator at XXXX XXX XXXX or by email at XXX XXX XXX
The survey is accessible through FluidSurvey™TM. Any identifying information will be removed by a research technician at the Manitoba Center for Nursing and Health Research Center (MCNHR), and data will remain anonymous.
The data will be downloaded by the MCNHR, transferred to the principal investigator and stored in a secure password-protected computer in room 268 Helen Glass Center for Nursing at the University of Manitoba. The data collected will be destroyed from the hard drive of the computer (06/2019)

A brief summary of the findings will be available after June 2015 at the following website: http://umanitoba.ca/faculties/nursing/academic_staff/diehl_jones.html
You are under no obligation to participate in the survey or to respond to any questions you do not wish to answer. Your submission of a completed survey will be taken as evidence of your consent to participate. Once the survey is submitted, the data can no longer be removed because the data is submitted anonymously.

If you have any question about the survey, please contact:
- Yenly Londono: XXX XXX XXXX; email: XXX XXX XXX
- Dr. William Diehl-Jones: XXX XXX XXXX; e-mail: XXX XXX XXX

We appreciate your time and consideration in completing this survey. Should you wish to take part in the survey, please go to the survey website **http://FluidSurvey™s.com/s/MD-NICU/?code=sbtm7hapou**

We thank you in advance for your participation!

Yenly Catherine Londoño MNSc, RN, PhD(c)
Principal Investigator
Applied Health Sciences, University of Manitoba

William Diehl-Jones PhD, RN
Thesis co-supervisor
Scientist, Manitoba Institute for Child Health

Dr. Maureen Heaman, RN, PhD
Thesis co-supervisor
Professor, College of Nursing
University of Manitoba

Dr. Aaron Chiu, MD, FRCPC, FAAP
Committee Member
Associate Professor, Section of Neonatology
University of Manitoba

Dr. James Friel, PhD,
Committee Member
Professor, Department of Nutritional Sciences
University of Manitoba

Appendix J

Copy of the CAAN' email

Date: Sun, 25 Nov 2012 09:35:19 -0800
From: XXX XXX XXX
Subject: Re: Information
To: XXX XXX XXX

Hi Yenly,

My sincere apologies for the delay getting back to you.

The Board of Directors is willing to support your request to distribute your survey to CANN members - as long as the survey results are collected anonymously.

When you have the survey finalized, please send it to me with an introductory email and I will send it to our Secretariat to send to our members.

Re: the conference - if would be wonderful if you were able to join us and to present a poster (the deadline for submission is Dec 3. Online registration will be available soon and although I can't recall the exact date for the early bird deadline, it will be in January 2013 ... sorry.

I look forward to meeting you too!
Debbie

Appendix K

Email invitation to Neonatologists

From: Yenly Catherine Londono Calle [XXX XXX XXX XXX XXX XXXX]
Subject: A Survey of Neonatologists about Factors Associated with Use of Probiotics for Premature Infants

UNIVERSITY OF MANITOBA

A Survey of Neonatologists about Factors Associated with Use of Probiotics for Premature Infants

Dr. XXX XXX,

Your input is appreciated!

You have been contacted because you are a neonatologist who is listed in the 2011 Directory of Newborn Intensive Care Units and Neonatologists of the USA and Canada, which was published by the American Academy of Pediatrics.

I am Yenly Catherine Londoño, a graduate student in the PhD program in Applied Health Sciences at the University of Manitoba, Canada with work experience in neonatal care. Currently, I am collecting data for my dissertation about **Factors that Affect the Use of Probiotics for Premature Infants.**

I am inviting you to participate in this study because **you play an important role** in the decision making process regarding feeding practices in Neonatal Intensive Care Units (NICUs).
Probiotics are currently an area of great clinical interest, but are seldom used in NICUs in Canada and The United States.

If you are a neonatologist who has worked within the last 6 months in NICUs across Canada and/or The United States, and your unit does not routinely administer probiotics in preterm infant feeds <u>OR</u> if your unit is in the process of implementing use of probiotics, we would very much like to hear from you.

Although there are no direct benefits to you participating in this survey, **your input will further our understanding of the issues related to the use of probiotics in clinical practice**. This study does not pose any risk to the participants.
The survey will take approximately 8-10 minutes to complete. If you decide to participate, you will be asked questions that pertain to knowledge about probiotics and factors influencing the non-use of probiotics, as well as some demographic questions. In addition, **if you complete the survey your name**

will be entered in a drawing for a chance to receive an iPad mini.
Please visit the following website to complete the survey: **http://FluidSurvey™s.com/s/neos_survey/?lang=en&code=bvwkmnlron**
Your participation is anonymous and voluntary. This research has been approved by the Education/Nursing Research Ethics Board at the University of Manitoba. If you have any concerns or questions, you may contact the Human Ethics Coordinator at XXX XXX XXXXor by email at XXX XXX XXX XXX XXX XXXX.

The survey is accessible through FluidSurvey™™. Any identifying information will be removed by a research technician at the Manitoba Center for Nursing and Health Research Center (MCNHR) and data will remain anonymous.

The data will be downloaded by the MCNHR, transferred to the principal investigator and stored in a secure password-protected computer in room 268 Helen Glass Center for Nursing at the University of Manitoba. The data will be destroyed from the computer hard drive after 5 years.
The survey findings will be published in a peer reviewed journal, presented at academic meetings and used for educational purposes. A brief summary of the findings will be availabe after June 2015 at the following website: http://umanitoba.ca/faculties/nursing/academic_staff/diehl_jones.html
For any further questions or comments, do not hesitate to contact me at XXX XXX XXX or by phone at XXX XXX XXXX. My doctoral co-supervisor is Dr. William Diehl-Jones who is a scientist at the Manitoba Institute for Child Health. He can be reached at XXX XXX XXX XXX or at XXX XXX XXXX.

You are under no obligation to participate in the survey or to respond to any questions you do not wish to answer. Your submission of a completed survey will be taken as evidence of your consent to participate. Once the survey is submitted, the data can no longer be removed because the data are submitted anonymously.

If you begin to answer the survey questions and change your mind about taking part, you can log off by simply closing the browser. If you opt to withdraw from the survey, your data will not be used in the study. Only data from completed surveys will be analyzed.
We appreciate your time and consideration in completing this survey. Should you wish to take part in the survey, please go to the survey website now:**http://FluidSurvey™s.com/s/neos_survey/?lang=en&code=bvwkmnlron**
We thank you in advance for your participation.

Best wishes,

Yenly Catherine Londoño MNSc, RN, PhD(c)
Principal Investigator
Applied Health Sciences, University of Manitoba

William Diehl-Jones PhD, RN
Thesis co-supervisor
Scientist, Manitoba Institute for Child Health

Dr. Maureen Heaman, RN, PhD
Thesis co-supervisor
Professor, College of Nursing
University of Manitoba

Dr. Aaron Chiu, MD, FRCPC, FAAP
Committee Member
Associate Professor, Section of Neonatology
University of Manitoba

Dr. James Friel, PhD,
Committee Member
Professor, Department of Nutritional Sciences
University of Manitoba

Appendix L

Email invitation to CAAN members

First Email: re: **A Survey of Nurses in NICUs about Factors Affecting the Use of Probiotics for Premature Infants**
Dear CANN member,

This email is being sent to you by the Canadian Association of Neonatal Nurses on behalf of Ms. Yenly Londoño. She was a neonatal nurse but currently a graduate student whose PhD dissertation focuses on premature infant's nutrition. *Her study targets Neonatal Nurses, Nurse Managers, Nurse Educators (NE), Clinical Nurse Specialists (CNS), and Nurse Practitioners (NP) who work in NICUs across Canada and The United States.*

A Survey of Nurses in NICUs about Factors Affecting the Use of Probiotics for Premature Infants

Your input is appreciated!

I am graduate student in the PhD program in Applied Health Sciences at the University of Manitoba, Canada with work experience in neonatal care. Currently, I am collecting data for my dissertation about **Factors that Affect Routine Use of Probiotics for Premature Infants.** I am inviting *Neonatal Nurses, Nurse Managers, NE, CNS, and NP, who work in NICUs* in Canada and/or The United States to participate in this survey.

Probiotics are currently an area of great clinical interest and are seldom used in Neonatal Intensive Care Units (NICUs) in Canada and The United States.

If you are a nurse who has worked within the last 6 months in NICUs across Canada and/or The United States, and your unit does not routinely administer probiotics in preterm infant feeds OR if your unit is in the process of implementing use of probiotics, we would very much like to hear from you.

Although there are no direct benefits to you participating in this survey, **your input will greatly help to provide information about factors that may be influencing probiotic use in NICUs**. This study does not pose any risk to the participants.

The survey will take approximately 8-10 minutes to complete. If you decide to participate, you will be asked questions that pertain to knowledge about probiotics and factors influencing the non-use of probiotics, as well as some demographic questions. In addition, **if you complete the survey your name will be entered in a drawing for a chance to receive an iPad mini.**

Please visit the following website to complete the survey: www.probionurses.com

Your participation is anonymous and voluntary. This research has been approved by the Education/Nursing Research Ethics Board at the University of Manitoba. If you have any concerns or questions, you may contact the Human Ethics Coordinator at XXX XXX XXXXor by email at XXX XXX XXX XXX XXX XXXX.

The survey is accessible through FluidSurvey™™. Any identifying information will be removed by a research technician at the Manitoba Center for Nursing and Health Research Center (MCNHR) and data will remain anonymous.

The data will be downloaded by the MCNHR, transferred to the principal investigator and stored in a secure password-protected computer in room 268 Helen Glass Center for Nursing at the University of Manitoba. The data will be destroyed from the computer hard drive after 5 years.

The survey findings will be published in a peer reviewed journal, presented at academic meetings and used for educational purposes. A brief summary of the findings will be availabe after June 2015 at the following website: http://umanitoba.ca/faculties/nursing/academic_staff/diehl_jones.html

For any further questions or comments, do not hesitate to contact me at XXX XXX XXX XXX XXX XXXX or by phone at XXX XXX XXXX. My doctoral co-supervisor is Dr. William Diehl-Jones, RN, who is a scientist at the Manitoba Institute for Child Health. He can be reached at XXX XXX XXX or at XXX XXX XXXX.

You are under no obligation to participate in the survey or to respond to any questions you do not wish to answer. Your submission of a completed survey will be taken as evidence of your consent to participate. Once the survey is submitted, the data can no longer be removed because the data are submitted anonymously.

If you begin to answer the survey questions and change your mind about taking part, you can log off by simply closing the browser. If you opt to withdraw from the survey, your data will not be used in the study. Only data from completed surveys will be analyzed.

We appreciate your time and consideration in completing this survey. Should you wish to take part in the survey, please go to the survey website now: www.probionurses.com

We thank you in advance for your participation.

Best wishes,

Yenly Catherine Londoño, RN, MNSc, PhD(c)
Principal Investigator
Applied Health Sciences, University of Manitoba

William Diehl-Jones, RN, PhD
Thesis co-supervisor
Scientist, Manitoba Institute for Child Health

Dr. Maureen Heaman, RN, PhD
Thesis co-supervisor
Professor, College of Nursing
University of Manitoba

Dr. Aaron Chiu, MD, FRCPC, FAAP
Committee Member
Associate Professor, Section of Neonatology
University of Manitoba
Dr. James Friel, PhD
Committee Member
Professor, Department of Nutritional Sciences
University of Manitoba

Appendix M

Email Reminder to Neonatologists

From: Yenly Catherine Londono Calle [XXX XXX XXX XXX XXX XXXX]
Subject: A Survey of Neonatologists about Factors Associated with Use of Probiotics for Premature Infants

UNIVERSITY OF MANITOBA

A Survey of Neonatologists about Factors Affecting the Use of Probiotics for Premature Infants

Dr. XXX XXX

Your input is appreciated!

You have been contacted because you are a neonatologist who is listed in the 2011 Directory of Newborn Intensive Care Units and Neonatologists of the USA and Canada, which was published by the American Academy of Pediatrics.

Almost a week ago, I invited you to participate in this brief online survey because **you play a key role** in the decision making process regarding feeding practices in the Canadian NICUs.
This study is part of my data collection for my PhD dissertation about **Factors that Affect Routine Use of Probiotics for Premature Infants**. Probiotics are currently an area of great clinical interest in neonatal intensive care and are seldom used in Neonatal Intensive Care Units (NICUs) in Canada and The United States.

If you have already completed the survey, thank you!

If you have not participated in the survey, you still have the opportunity to do so. Please complete the survey today if possible. **The survey will take approximately 8-10 minutes.**
If you complete the survey your name will be entered in a drawing for a chance to receive an iPad mini. Please visit the following website to complete the survey:
http://FluidSurvey™s.com/s/neos_survey/?lang=en&code=

If you are a nurse who has worked within the last 6 months in NICUs across Canada and/or The United States, and your unit does not routinely implement probiotics in preterm infant feeds OR if your unit is in the process of implementing the use of probiotics, we would very much like to hear from you.

Although there are no direct benefits to you participating in this survey, your input will help to provide information about factors that may be influencing probiotic use in the NICUs. This study does not pose any risk to the participants.

It would be greatly appreciated if you participate in my internet survey on probiotics. **If you decide to participate, you will be asked questions that pertain to knowledge about probiotics and factors influencing the non-use of probiotics, as well as some demographic questions.**

We appreciate your time and consideration in completing this survey. Should you wish to take part in the survey, please go to the survey now: **[Invite Link:en]**
Your participation is anonymous and voluntary. This research had been approved by the Education/Nursing Research Ethics Board at the University of Manitoba. If you have any concerns or questions, you may contact the Human Ethics Coordinator at XXX XXX XXXX or by email at XXX XXX XXX XXX XXX XXXX.

The survey is accessible through FluidSurvey™™. Any identifying information will be removed by a research technician at the Manitoba Center for Nursing and Health Research Center (MCNHR), and data will remain anonymous.
The data will be downloaded by the MCNHR, transferred to the principal investigator and stored in a secure password-protected computer in room 268 Helen Glass Center for Nursing at the University of Manitoba. The data collected will be destroyed from the computer hard drive after 5 years.

A brief summary of the findings will be available after June 2015 at the following website: http://umanitoba.ca/faculties/nursing/academic_staff/diehl_jones.html
You are under no obligation to participate in the survey or to respond to any questions you do not wish to answer. Your submission of a completed survey will be taken as evidence of your consent to participate. Once the survey is submitted, the data can no longer be removed because the data is submitted anonymously.

If you have any question about the survey, please contact:
- Yenly Londono: XXX XXX XXXX; email: XXX XXX XXX
- Dr. William Diehl-Jones: XXX XXX XXXX; e-mail: XXX XXX XXX

We thank you in advance for your participation.

Best wishes,

Yenly Catherine Londoño MNSc, RN, PhD(c)
Principal Investigator
Applied Health Sciences, University of Manitoba

William Diehl-Jones PhD, RN
Thesis co-supervisor
Scientist, Manitoba Institute for Child Health

Dr. Maureen Heaman, RN, PhD
Thesis co-supervisor
Professor, College of Nursing
University of Manitoba

Dr. Aaron Chiu, MD, FRCPC, FAAP
Committee Member
Associate Professor, Section of Neonatology
University of Manitoba

Dr. James Friel, PhD,
Committee Member
Professor, Department of Nutritional Sciences
University of Manitoba

Appendix N

First Email to CANN members

First Follow up Email: re: **A Survey of Nurses in NICUs about Factors Affecting the Use of Probiotics for Premature Infants**

Dear CANN member,

This email is being sent to you by the Canadian Association of Neonatal Nurses on behalf of Ms. Yenly Londoño. She was a neonatal nurse but currently a graduate student whose PhD dissertation focuses on premature infant's nutrition. *Her study targets Neonatal Nurses, Nurse Managers, Nurse Educators (NE), Clinical Nurse Specialists (CNS), and Nurse Practitioners (NP) who work in NICUs across Canada and The United States.*

A Survey of Nurses in NICUs about Factors Affecting the Use of Probiotics for Premature Infants

Your input is appreciated!

Dear Nursing colleague,

Almost a week ago, I contacted you to participate in a brief online survey that is part of my data collection for my PhD dissertation about **Factors that Affect Routine Use of Probiotics for Premature Infants**. Probiotics are currently an area of great clinical interest in neonatal intensive care and are seldom used in Neonatal Intensive Care Units (NICUs) in Canada and The United States.

If you have already completed the survey, thank you!

If you have not participated in the survey, you still have the opportunity to do so. Please complete the survey today if possible. **The survey will take approximately 8-10 minutes.**

If you complete the survey your name will be entered in a drawing for a chance to receive an iPad mini. Please visit the following website to complete the survey: www.probionurses.com

If you are a nurse who has worked within the last 6 months in NICUs across Canada and/or The United States, and your unit does not routinely implement probiotics in preterm infant feeds OR if your unit is in the process of implementing the use of probiotics, we would very much like to hear from you.

Although there are no direct benefits to you participating in this survey, your input will help to provide information about factors that may be influencing probiotic use in the NICUs. This study does not pose any risk to the participants.

It would be greatly appreciated if you participate in my internet survey on probiotics. **If you decide to participate, you will be asked questions that pertain to knowledge about probiotics and factors influencing the non-use of probiotics, as well as some demographic questions.**

We appreciate your time and consideration in completing this survey. Should you wish to take part in the survey, please go to the survey now: www.probionurses.com

Your participation is anonymous and voluntary. This research had been approved by the Education/Nursing Research Ethics Board at the University of Manitoba. If you have any concerns or questions, you may contact the Human Ethics Coordinator at XXX XXX XXXX or by email at XXX XXX XXX XXX XXX XXXX.

The survey is accessible through FluidSurvey™™. Any identifying information will be removed by a research technician at the Manitoba Center for Nursing and Health Research Center (MCNHR), and data will remain anonymous.

The data will be downloaded by the MCNHR, transferred to the principal investigator and stored in a secure password-protected computer in room 268 Helen Glass Center for Nursing at the University of Manitoba. The data collected will be destroyed from the computer hard drive after 5 years.

A bief summary of the findings will be available after June 2015 at the following website: http://umanitoba.ca/faculties/nursing/academic_staff/diehl_jones.html

You are under no obligation to participate in the survey or to respond to any questions you do not wish to answer. Your submission of a completed survey will be taken as evidence of your consent to participate. Once the survey is submitted, the data can no longer be removed because the data is submitted anonymously.

If you have any question about the survey, please contact:

- Yenly Londono: XXX XXX XXXX; email : XXX XXX XXX XXX XXX XXXX
- Dr. William Diehl-Jones: XXX XXX XXXX; e-mail: XXX XXX XXX XXX XXX XXXX

We thank you in advance for your participation.

Best wishes,

Yenly Catherine Londoño, RN, MNSc, PhD(c)
Principal Investigator
Applied Health Sciences, University of Manitoba

William Diehl-Jones, RN, PhD

Thesis co-supervisor
Scientist, Manitoba Institute for Child Health

Dr. Maureen Heaman, RN, PhD
Thesis co-supervisor
Professor, College of Nursing
University of Manitoba

Dr. Aaron Chiu, MD, FRCPC, FAAP
Committee Member
Associate Professor, Section of Neonatology
University of Manitoba
Dr. James Friel, PhD
Committee Member
Professor, Department of Nutritional Sciences
University of Manitoba

Appendix O

Final Email Reminer to Neonatologists

From: Yenly Catherine Londono Calle [XXX XXX XXX XXX XXX XXXX]
Subject: A Survey of Neonatologists about Factors Associated with Use of Probiotics for Premature Infants

UNIVERSITY OF MANITOBA

A Survey of Neonatologists about Factors Affecting the Use of Probiotics for Premature Infants

Dr. XXX XXX

You have been contacted because you are a neonatologist and were listed in the 2011 Directory of Newborn Intensive Care Units (NICUs) and Neonatologists of the USA and Canada, which was published by the American Academy of Pediatrics.

Almost a week ago, I invited you to participate in this brief online survey because **you play a key role** in the decision making process regarding feeding practices in the Canadian NICUs. **The survey will take approximately 8-10 minutes**.

This study is part of my data collection for **my PhD dissertation about Factors that Affect Routine Use of Probiotics for Premature Infants**. Probiotics are currently an area of great clinical interest in neonatal intensive care and are seldom used in Neonatal Intensive Care Units (NICUs) in Canada and The United States.

If you have already completed the survey, thank you! If you have not participated in the survey, we would like to again request your assistance through completion of the survey. We plan to end this study next week, so we wanted to email everyone to make sure you had a chance to participate.

If you complete the survey your name will be entered in a drawing for a chance to receive an iPad mini: **http://FluidSurvey™s.com/s/neos_survey/?lang=en&code=**
If you are a neonatologist who has been practicing in the last 6 months in Neonatal Intensive Care Units (NICUs) across Canada and/or The United States, and your unit does not routinely implement probiotics in preterm infants feeds OR it is in the process of implementation, we would very much like to hear from you.

Although there are no direct benefits to you in participating in this survey, your input will help to provide

information about factors that may be influencing on probiotic use in the NICUs. This study does not pose any risk to the participants.

It would be greatly appreciated if you participate in my internet survey on probiotics. If you decide to participate, you will be asked some demographic questions, as well as questions that pertain to knowledge about probiotics and other aspects of this practice.

We appreciate your time and consideration in completing this survey. Should you wish to take part in the survey, please go to the survey now: **http://FluidSurvey™s.com/s/neos_survey/?lang=en&code=**
Your participation is anonymous and voluntary. This research had been approved by the Education/Nursing Research Ethics Board at the University of Manitoba. If you have any concerns or questions, you may contact the Human Ethics Coordinator at XXX XXX XXX or by email at XXX XXX XXX XXX XXX XXXX.

The survey is accessible through FluidSurvey™TM. Any identifying information will be removed by a research technician at the Manitoba Center for Nursing and Health Research Center (MCNHR), and data will remain anonymous.
The data will be downloaded by the MCNHR, transferred to the principal investigator and stored in a secure password-protected computer in room 268 Helen Glass Center for Nursing at the University of Manitoba. The data will be destroyed from the computer hard drive after 5 years.
A brief summary of the findings will be avaialbe after June 2015 at the following website:
http://umanitoba.ca/faculties/nursing/academic_staff/diehl_jones.html

You are under no obligation to participate in the survey or to respond to any questions you do not wish to answer. Your submission of a completed survey will be taken as evidence of your consent to participate. Once the survey is submitted, the data can no longer be removed because the data is submitted anonymously.

If you have any question about the survey, please contact:
- Yenly Londono: XXX XXX XXXX; email : XXX XXX XXX XXX XXX XXXX
- Dr. William Diehl-Jones: XXX XXX XXXX; e-mail: XXX XXX XXX XXX XXX XXXXXXX XXX XXX XXX XXX XXXX

We thank you in advance for your participation.

Best wishes,

Yenly Catherine Londoño MNSc, RN, PhD(c)
Principal Investigator
Applied Health Sciences, University of Manitoba

William Diehl-Jones PhD, RN
Thesis co-supervisor
Scientist, Manitoba Institute for Child Health

Dr. Maureen Heaman, RN, PhD
Thesis co-supervisor
Professor, College of Nursing
University of Manitoba

Dr. Aaron Chiu, MD, FRCPC, FAAP
Committee Member
Associate Professor, Section of Neonatology
University of Manitoba

Dr. James Friel, PhD,
Committee Member
Professor, Department of Nutritional Sciences
University of Manitoba

Appendix P

Final Reminder Email to CANN Members

Second Follow up Email: re: **A Survey of Nurses in NICUs about Factors Affecting the Use of Probiotics for Premature Infants**

Instructions: Please email the attached reminder message to all the CANN members on February 2, 2015.

Email subject Line: **A Survey of Nurses in NICUs about Factors Affecting the Use of Probiotics for Premature Infants**

Dear CANN member,

This email is being sent to you by the Canadian Association of Neonatal Nurses on behalf of Ms. Yenly Londoño. She was a neonatal nurse but currently a graduate student whose PhD dissertation focuses on premature infant's nutrition. *Her study targets Neonatal Nurses, Nurse Managers, Nurse Educators (NE), Clinical Nurse Specialists (CNS), and Nurse Practitioners (NP) who work in NICUs across Canada and The United States.*

A Survey of Nurses in NICUs about Factors Affecting the Use of Probiotics for Premature Infants

In the past, I contacted you to participate in a brief online survey that is part of my data collection for my PhD Dissertation about **Factors that Affect Routine Use of Probiotics for Premature Infants**.

Nurses working in NICUs have an important role in feeding practices in Neonatal Intensive Care Units (NICUs). Probiotics supplements for premature infants are an area of great clinical interest in neonatal intensive care.

If you have not participated in the survey, we would like to again request your assistance through completion of the survey. We plan to end this study next week, so we wanted to email everyone to make sure you had a chance to participate.

The survey will take approximately 8-10 minutes. **If you complete the survey your name will be entered in a drawing for a chance to receive an iPad mini**: www.probionurses.com

If you are a nurse who has been practicing in the last 6 months in Neonatal Intensive Care Units (NICUs) across Canada and/or The United States, and your unit does not routinely implement probiotics in preterm infants feeds OR it is in the process of implementation, we would very much like to hear from you.

Although there are no direct benefits to you in participating in this survey, your input will help to provide information about factors that may be influencing on probiotic use in the NICUs. This study does not pose any risk to the participants.

It would be greatly appreciated if you participate in my internet survey on probiotics. If you decide to participate, you will be asked some demographic questions, as well as questions that pertain to knowledge about probiotics and other aspects of this practice.

We appreciate your time and consideration in completing this survey. Should you wish to take part in the survey, please go to the survey now: www.probionurses.com

Your participation is anonymous and voluntary. This research had been approved by the Education/Nursing Research Ethics Board at the University of Manitoba. If you have any concerns or questions, you may contact the Human Ethics Coordinator at XXX XXX XXX or by email at XXX XXX XXX XXX XXX XXXX.

The survey is accessible through FluidSurvey™™. Any identifying information will be removed by a research technician at the Manitoba Center for Nursing and Health Research Center (MCNHR), and data will remain anonymous.

The data will be downloaded by the MCNHR, transferred to the principal investigator and stored in a secure password-protected computer in room 268 Helen Glass Center for Nursing at the University of Manitoba. The data will be destroyed from the computer hard drive after 5 years.

A bief summary of the findings will be avaialbe after June 2015 at the following website: http://umanitoba.ca/faculties/nursing/academic_staff/diehl_jones.html

You are under no obligation to participate in the survey or to respond to any questions you do not wish to answer. Your submission of a completed survey will be taken as evidence of your consent to participate. Once the survey is submitted, the data can no longer be removed because the data is submitted anonymously.

If you have any question about the survey, please contact:

- Yenly Londono: XXX XXX XXXX; email : XXX XXX XXX XXX XXX XXXX
- Dr. William Diehl-Jones: XXX XXX XXXX; e-mail: XXX XXX XXX XXX XXX XXXX

We thank you in advance for your participation.

Best wishes,

Yenly Catherine Londoño, RN, MNSc, PhD(c)
Principal Investigator
Applied Health Sciences, University of Manitoba

William Diehl-Jones, RN, PhD
Thesis co-supervisor

Scientist, Manitoba Institute for Child Health

Dr. Maureen Heaman, RN, PhD
Thesis co-supervisor
Professor, College of Nursing
University of Manitoba

Dr. Aaron Chiu, MD, FRCPC, FAAP
Committee Member
Associate Professor, Section of Neonatology
University of Manitoba
Dr. James Friel, PhD
Committee Member
Professor, Department of Nutritional Sciences
University of Manitoba

Appendix Q

Email invitation to Neonatal Nurses

A Survey of Nurses in NICUs about Factors Affecting the Use of Probiotics for Premature Infants

Dear XXX XXX

Your input is appreciated!

I am graduate student in the PhD program in Applied Health Sciences at the University of Manitoba, Canada with work experience in neonatal care and I am contacting you because at the { * insert conference name } you provided me with your contact information and expressed an interest in participating in my future study about neonatal nutrition. I would like to provide you with more information about my study and give you an invitation to participate.

Currently, I am collecting data for my dissertation about **Factors that Affect Use of Probiotics for Premature Infants.** ***I am inviting Neonatal Nurses, Nurse Managers, Nurse Educators (NE), Clinical Nurse Specialists (CNS), and Nurse Practitioners (NP who work in Neonatal Intensive Care Units (NICUs) in Canada and/or The United States to participate in this survey.***

Probiotics are currently an area of great clinical interest and are seldom used in NICUs in Canada and The United States.

The survey will take approximately 8-10 minutes to complete. If you decide to participate, you will be asked questions that pertain to knowledge about probiotics and factors influencing the non-use of probiotics, as well as some demographic questions. In addition, **if you complete the survey your name will be entered in a drawing for a chance to receive an iPad mini.**

Please visit the following website to complete the survey: **www.probionurses.com**
Although there are no direct benefits to you participating in this survey, **your input will greatly help to provide information about factors that may be influencing probiotic use in NICUs**.
This study does not pose any risk to the participants.
Your participation is anonymous and voluntary. This research has been approved by the Education/Nursing Research Ethics Board at the University of Manitoba. If you have any concerns or questions, you may contact the Human Ethics Coordinator at XXX XXX XXXXor by email at XXX XXX XXX XXX XXX XXXX.

The survey is accessible through FluidSurvey™™. Any identifying information will be removed by a research technician at the Manitoba Center for Nursing and Health Research Center (MCNHR) and data will remain anonymous.

The data will be downloaded by the MCNHR, transferred to the principal investigator and stored in a secure password-protected computer in room 268 Helen Glass Center for Nursing at the University of Manitoba. The data will be destroyed from the computer hard drive after 5 years. The survey findings will be published in a peer reviewed journal, presented at academic meetings and used for educational purposes. A brief summary of the findings will be availabe after June 2015 at the following website:
http://umanitoba.ca/faculties/nursing/academic_staff/diehl_jones.html

For any further questions or comments, do not hesitate to contact me at XXX XXX XXX XXX XXX XXXX or by phone at XXX XXX XXXX. My doctoral co-supervisor is Dr. William Diehl-Jones, RN, who is a scientist at the Manitoba Institute for Child Health. He can be reached at XXX XXX XXX XXX XXX XXXX or at XXX XXX XXXX.
You are under no obligation to participate in the survey or to respond to any questions you do not wish to answer. Your submission of a completed survey will be taken as evidence of your consent to participate. Once the survey is submitted, the data can no longer be removed because the data are submitted anonymously.

If you begin to answer the survey questions and change your mind about taking part, you can log off by simply closing the browser. If you opt to withdraw from the survey, your data will not be used in the study. Only data from completed surveys will be analyzed.
We appreciate your time and consideration in completing this survey. Should you wish to take part in the survey, please go to the survey website now:
www.probionurses.com
We thank you in advance for your participation!

Best wishes,

Yenly Catherine Londoño MNSc, RN, PhD(c)
Principal Investigator
Applied Health Sciences, University of Manitoba

William Diehl-Jones PhD, RN
Thesis co-supervisor
Scientist, Manitoba Institute for Child Health

Dr. Maureen Heaman, RN, PhD
Thesis co-supervisor
Professor, College of Nursing
University of Manitoba

Dr. Aaron Chiu, MD, FRCPC, FAAP
Committee Member
Associate Professor, Section of Neonatology
University of Manitoba

Dr. James Friel, PhD,
Committee Member
Professor, Department of Nutritional Sciences
University of Manitoba

Conference name:

* 5th National Advanced Practice Neonatal nurses conference in Honolulu, Hawaii, April 23-26, 2014
5th Canadian Neonatal Nurses Association National conference Montreal, Feb. 10-12, 2013
9thNational Advanced Practice Neonatal Nurses Conference in New Orleans, April 18-21, 2012

Appendix R

Email Reminder to Neonatal Nurses

A Survey of Nurses in NICUs about Factors Affecting the Use of Probiotics for Premature Infants

Dear [Name]
Your input is appreciated!

Almost a week ago, I contacted you to participate in a brief online survey that is part of my data collection for my PhD dissertation about **Factors that Affect Routine Use of Probiotics for Premature Infants**. Probiotics are currently an area of great clinical interest in neonatal intensive care and are seldom used in Neonatal Intensive Care Units (NICUs) in Canada and The United States.
If you have already completed the survey, thank you!

If you have not participated in the survey, you still have the opportunity to do so. Please complete the survey today if possible. **The survey will take approximately 8-10 minutes.**

If you complete the survey your name will be entered in a drawing for a chance to receive an iPad mini. Please visit the following website to complete the survey:
www.probionurses.com

If you are a nurse who has worked within the last 6 months in NICUs across Canada and/or The United States, and your unit does not routinely implement probiotics in preterm infant feeds OR if your unit is in the process of implementing the use of probiotics, we would very much like to hear from you.
Although there are no direct benefits to you participating in this survey, your input will help to provide information about factors that may be influencing probiotic use in the NICUs. This study does not pose any risk to the participants.
It would be greatly appreciated if you participate in my internet survey on probiotics. **If you decide to participate, you will be asked questions that pertain to knowledge about probiotics and factors influencing the non-use of probiotics, as well as some demographic questions.**
We appreciate your time and consideration in completing this survey. Should you wish to take part in the survey, please go to the survey now: **www.probionurses.com**

Your participation is anonymous and voluntary. This research had been approved by the Education/Nursing Research Ethics Board at the University of Manitoba. If you have any concerns or questions, you may contact the Human Ethics Coordinator at XXX XXX XXXX or by email at XXX XXX XXX XXX XXX XXXX.

The survey is accessible through FluidSurvey™™. Any identifying information will be removed by a research technician at the Manitoba Center for Nursing and Health Research Center (MCNHR), and data will remain anonymous.
The data will be downloaded by the MCNHR, transferred to the principal investigator and stored in a secure password-protected computer in room 268 Helen Glass Center for Nursing at the University of Manitoba. The data collected will be destroyed from the computer hard drive after 5 years.

A bief summary of the findings will be available after June 2015 at the following website: http://umanitoba.ca/faculties/nursing/academic_staff/diehl_jones.html
You are under no obligation to participate in the survey or to respond to any questions you do not wish to answer. Your submission of a completed survey will be taken as evidence of your consent to participate. Once the survey is submitted, the data can no longer be removed because the data is submitted anonymously.
If you have any question about the survey, please contact:

- Yenly Londono: XXX XXX XXXX; email : XXX XXX XXX XXX XXX XXXX
- Dr. William Diehl-Jones: XXX XXX XXXX; e-mail: XXX XXX XXX XXX XXX XXXX

We thank you in advance for your participation!

Yenly Catherine Londono, MNSc, RN, PhD(c)
Principal Investigator
Applied Health Sciences, University of Manitoba

William Diehl-Jones PhD, RN
Thesis co-supervisor
Scientist, Manitoba Institute for Child Health

Dr. Maureen Heaman, RN, PhD
Thesis co-supervisor
Professor, College of Nursing
University of Manitoba

Dr. Aaron Chiu, MD, FRCPC, FAAP
Committee Member
Associate Professor, Section of Neonatology
University of Manitoba

Dr. James Friel, PhD
Committee Member
Professor, Department of Nutritional Sciences
University of Manitoba

Appendix S

Final Reminder to Neonatal Nurses

A Survey of Nurses in NICUs about Factors Affecting the Use of Probiotics for Premature Infants

Dear [Name]
Your input is appreciated!

 In the past, I contacted you to participate in a brief online survey that is part of my data collection for my PhD dissertation about **Factors that Affect Routine Use of Probiotics for Premature Infants**. Probiotics are currently an area of great clinical interest in neonatal intensive care and are seldom used in Neonatal Intensive Care Units (NICUs) in Canada and The United States.
If you have already completed the survey, thank you!

If you have not participated in the survey, you still have the opportunity to do so. Please complete the survey today if possible. **The survey will take approximately 8-10 minutes.**

If you complete the survey your name will be entered in a drawing for a chance to receive an iPad mini. Please visit the following website to complete the survey:
www.probionurses.com

If you are a nurse who has worked within the last 6 months in NICUs across Canada and/or The United States, and your unit does not routinely implement probiotics in preterm infant feeds OR if your unit is in the process of implementing the use of probiotics, we would very much like to hear from you.
Although there are no direct benefits to you participating in this survey, your input will help to provide information about factors that may be influencing probiotic use in the NICUs. This study does not pose any risk to the participants.
It would be greatly appreciated if you participate in my internet survey on probiotics.

If you decide to participate, you will be asked questions that pertain to knowledge about probiotics and factors influencing the non-use of probiotics, as well as some demographic questions.
We appreciate your time and consideration in completing this survey. Should you wish to take part in the survey, please go to the survey now: **www.probionurses.com**

Your participation is anonymous and voluntary. This research had been approved by the Education/Nursing Research Ethics Board at the University of Manitoba. If you have any

concerns or questions, you may contact the Human Ethics Coordinator at XXX XXX XXXX or by email at XXX XXX XXX XXX XXX XXXX.
The survey is accessible through FluidSurvey™™. Any identifying information will be removed by a research technician at the Manitoba Center for Nursing and Health Research Center (MCNHR), and data will remain anonymous.
The data will be downloaded by the MCNHR, transferred to the principal investigator and stored in a secure password-protected computer in room 268 Helen Glass Center for Nursing at the University of Manitoba. The data collected will be destroyed from the computer hard drive after 5 years.

A bief summary of the findings will be available after June 2015 at the following website: http://umanitoba.ca/faculties/nursing/academic_staff/diehl_jones.html
You are under no obligation to participate in the survey or to respond to any questions you do not wish to answer. Your submission of a completed survey will be taken as evidence of your consent to participate. Once the survey is submitted, the data can no longer be removed because the data is submitted anonymously.
If you have any question about the survey, please contact:

- Yenly Londono: XXX XXX XXXX; email : XXX XXX XXX XXX XXX XXXX
- Dr. William Diehl-Jones: XXX XXX XXXX; e-mail: XXX XXX XXX XXX XXX XXXX

We thank you in advance for your participation!

Yenly Catherine Londono, MNSc, RN, PhD(c)
Principal Investigator
Applied Health Sciences, University of Manitoba

William Diehl-Jones PhD, RN
Thesis co-supervisor
Scientist, Manitoba Institute for Child Health

Dr. Maureen Heaman, RN, PhD
Thesis co-supervisor
Professor, College of Nursing
University of Manitoba

Dr. Aaron Chiu, MD, FRCPC, FAAP
Committee Member
Associate Professor, Section of Neonatology
University of Manitoba

Dr. James Friel, PhD
Committee Member
Professor, Department of Nutritional Sciences
University of Manitoba

Appendix T

Ethics Approval

Human Ethics
208-194 Dafoe Road
Winnipeg, MB
Canada R3T 2N2
[redacted]

UNIVERSITY OF MANITOBA | Research Ethics and Compliance
Office of the Vice-President (Research and International)

APPROVAL CERTIFICATE

July 11, 2014

TO: **Yenly Londono** (Advisors Diehl-Jones/Heaman)
Principal Investigator

FROM: **Lorna Guse, Chair**
Education/Nursing Research [redacted]

Re: **Protocol #E2014:061**
"A Survey of Current Practices and Factors Associated with Health Care Professionals' Use of Probiotics"

Please be advised that your above-referenced protocol has received human ethics approval by the **Education/Nursing Research Ethics Board**, which is organized and operates according to the Tri-Council Policy Statement (2). **This approval is valid for one year only**.

Any significant changes of the protocol and/or informed consent form should be reported to the Human Ethics Secretariat in advance of implementation of such changes.

Please note:

- **If you have funds pending human ethics approval, please mail/e-mail/fax (261-0325) a copy of this Approval (identifying the related UM Project Number) to the Research Grants Officer in ORS in order to initiate fund setup. (How to find your UM Project Number: http://umanitoba.ca/research/ors/mrt-faq.html#pr0)**

- **if you have received multi-year funding for this research, responsibility lies with you to apply for and obtain Renewal Approval at the expiry of the initial one-year approval; otherwise the account will be locked.**

The Research Quality Management Office may request to review research documentation from this project to demonstrate compliance with this approved protocol and the University of Manitoba *Ethics of Research Involving Humans*.