No material published in Beneficial Microbes may be reproduced without first obtaining written permission from the publisher.

The author may send or transmit individual copies of this PDF of the article, to colleagues upon their specific request provided no fee is charged, and further provided that there is no systematic distribution of the manuscript, e.g. posting on a listserv, website or automated delivery. However posting the article on a secure network, not accessible to the public, is permitted.

For other purposes, e.g. publication on his/her own website, the author must use an author-created version of his/her article, provided acknowledgement is given to the original source of publication and a link is inserted to the published article on the Beneficial Microbes website by referring to the DOI of the article.

For additional information please visit www.BeneficialMicrobes.org.
1. Introduction

The rapid expansion of the probiotic market has resulted in a growing number of products ostensibly targeting the wellbeing of pregnant women and their newborns. The term ‘ostensibly’ is used as few of these products have actually been tested in humans, based upon a sparsity of evidence published in peer-reviewed journals. Despite this discrepancy, under the International Scientific Association for Probiotics and Prebiotics (ISAPP), we convened a meeting in Washington, DC, USA, of researchers interested in these areas, to determine whether published data provided sufficient reason to consider probiotic supplementation during pregnancy and early life.

The rationale comes from the fact that maternal, foetal and infant morbidity and mortality is often associated with infectious organisms (Lawn et al., 2010; Van Dillen et al., 2010) against which some probiotic strains can act (Deng et al., 2015; Reid et al., 1987). In addition, successful human reproduction has evolved under a close association with beneficial microbes (Aagaard et al., 2014; Barbonetti et al., 2011; Eckert et al., 2003), therefore supplementing the beneficial ones could benefit the host (Figure 1).

The approach we took was to discuss three topics:

- What do we know about nutrition, maternal stress, microbiome and foetal development?
- What would be the basis for microbiota intervention at which stages of gestation?
How would we potentially enhance the gut and/or vaginal microbiota to pass certain microbes to baby at birth, administer probiotics to breast-feeding mother (or enhance infant feeds?) to influence post-natal development?

The following is a summary of the discussions and subsequent review of the literature.

2. Pre-conception and early development

The presence of vaginal lactobacilli appears to be important for fertilisation and sperm motility (Barbonetti et al., 2011). In that study, they showed that soluble factors produced by Lactobacillus brevis, Lactobacillus salivarius, and Lactobacillus plantarum, prevented membrane lipid-peroxidation of Escherichia coli-exposed spermatozoa, thus preserving their motility. The use of strains not commonly found in the reproductive tract suggested that this protective effect might be produced across a spectrum of lactobacilli. A study of 96 semen samples that measured semen quality (volume, sperm concentration, motility, Kruger’s strict morphology, antisperm antibody (immunoglobulin A – IgA), Atypical, and leukocytes) showed that lactobacilli were associated with healthy quality (Weng et al., 2014). It has been known for some time that lactobacilli are dominant in the vagina and male urethra of healthy individuals (Bowie et al., 1977; Bruce et al., 1973), so it is not surprising to find them in semen. However, their role in actual conception is intriguing.

Nutrients are obviously essential for health, but surprisingly, apart from overall calories, protein, calcium, iron, zinc and folic acid, there is no good understanding of the range of nutrients necessary for the development of different organs, vascular system, skeleton of the foetus, and none on the role of microbes and their metabolites from the mother or at the foetal-maternal interface. Nutrition is important during pregnancy to promote the healthy growth and development of the foetus, and nutrition counselling is clearly beneficial, and along with exercise can reduce the risk of gestational diabetes (Cordero et al., 2015). From the first to third trimester, the maternal gut microbiota become more diverse and the immune system becomes more inflammatory, the latter in a process required for birthing. The supplementation of folic acid to prevent some birth defects preconception; iron to prevent anaemia; calcium and vitamin D for bone development; and perhaps other vitamins and minerals, are all general recommendations made throughout pregnancy. Avoidance of excessive exposure to environmental pollutants such as mercury, and of intake of antibiotics and certain other pharmaceutical agents is also recommended, even if not necessarily practiced (Hassoun-Barhamji et al., 2015; Schoeman et al., 2010).

3. Stress as a confounder

A variety of stresses were discussed that can impact pregnancy. Physical injury from trauma, including military combat, and the subsequent post-traumatic stress disorder, can be detrimental to a sustained healthy pregnancy (Shaw et al., 2014). Partner abuse increases the likelihood of a neonate having an adverse outcome (Alhusen et al., 2014). It is disturbing that partner abuse, especially emotional, is rife in many countries, compounding the disparity of the males being older and more likely addicted to drugs and alcohol partnering with young females with a lower educational level (Bagcchi, 2015; Ibrahim et al., 2015). Personal and social violence are most pervasive and destructive systematic violation of human rights.

Figure 1. Factors involved in risk of failed pregnancy, and targets for probiotic supplementation from conception to early development.
A study of two large longitudinal cohorts showed that children of women who experienced severe childhood abuse were more likely to be overweight and smoke in adolescence and early adulthood compared with children of women who reported no abuse (Roberts et al., 2014). In addition, violence against the mother increases the risk of autism spectrum disorder in her offspring (Roberts et al., 2015). This emphasises that adverse health outcomes can occur decades after the traumatic event. It would be foolhardy to suggest that probiotic intake can overcome the severe stress effects of such trauma, but a lowering of anxiety and perhaps aggressive behaviour through gut-vagal nerve mechanisms is worthy of testing (Bailey, 2014), particularly given studies showing probiotics can reduce exam stress (Marcos et al., 2004) and psychological distress measured particularly by the Hopkins Symptom Checklist HSCL-90 scale (global severity index, P<0.05; somatisation, P<0.05; depression, P<0.05; and anger-hostility, P<0.05), the Hospital Anxiety and Depression Scale (HADS global score, P<0.05; and HADS-anxiety, P<0.06), and by the CCL (problem solving, P<0.05) and the urinary free cortisol level (P<0.05) (Messoudi et al., 2011).

4. Chronic malnutrition

Nutrition is a fundamental asset of human capital. Malnutrition disempowers individuals by aggravating infection and illness, lowering educational attainment and diminishing livelihood skills and family savings. Globally 165 million children are stunted and 80% of those live in 14 countries including Bangladesh (Black et al., 2013; UNICEF, 2013). Under-nutrition underlies about 3.1 million deaths of children aged less than 5 years annually (Bhutta et al., 2013; UNICEF, 2013). In Bangladesh, the prevalence of malnutrition is very high and many women and children suffer from one or more forms of wasting, stunting, underweight, vitamin A deficiency, iodine deficiency disorders and anaemia. Though the country has made good progress in the last decade; 41% of children aged under five years still suffer from moderate to severe stunting, an indicator for chronic malnutrition. There is clearly a role for probiotic food in alleviating malnutrition. A yoghurt not supplemented with probiotic, but that provides 30% required daily intake of iron, zinc, iodine and vitamin A has been introduced in Bangladesh with resultant improvements in height gain after one year (Sazawal et al., 2013). A study from India showed the potential to alleviate stunting by improving gut-barrier function, nutrient uptake and lowering diarrhoeal rates (Saran et al., 2002) (Table 1). The widely available, nutrient-rich Moringa oleifera provides another means to supplement probiotic fermented milk in developing countries (Van Tienen et al., 2011), including for pregnant women (Bisanz et al., 2015).

5. Foetal brain development

The foetal brain develops early in gestation and matures post-birth. Its composition is mostly fat cells. Malnutrition is well known to diminish cognitive function. Long-chain polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) improve neural development in humans resulting in improved cognition and linguistic skills (EPA) and visual and memory processing (DHA) (Bisanz et al., 2015). The foetal brain develops early in gestation and matures post-birth. Its composition is mostly fat cells. Malnutrition is well known to diminish cognitive function. Long-chain polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) improve neural development in humans resulting in improved cognition and linguistic skills (EPA) and visual and memory processing (DHA) (Bisanz et al., 2015).

<table>
<thead>
<tr>
<th>Strains</th>
<th>Timing of administration</th>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactobacillus brevi cd2, Lactobacillus salivarius fv2, and Lactobacillus plantarum fv9</td>
<td>pre-conception</td>
<td>reduce risk of sperm lipid peroxidation and aid sperm motility and viability</td>
</tr>
<tr>
<td>Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14</td>
<td>pre-conception and during 1st to 3rd trimester</td>
<td>reduce recurrence of bacterial vaginosis and heavy metal uptake</td>
</tr>
<tr>
<td>L. rhamnosus GG and Bifidobacterium lactis Bb-12</td>
<td>first trimester</td>
<td>reduce risk of gestational diabetes</td>
</tr>
<tr>
<td>L. rhamnosus LPR and Bifidobacterium longum BL999 or Lactobacillus paracasei ST11 and B. longum BL999</td>
<td>for the last two months of pregnancy and first two months of breastfeeding</td>
<td>reduce the risk of atopic eczema</td>
</tr>
<tr>
<td>Lactobacillus fermentum CECT5716 or L. salivarius CECT5713 or Bifidobacterium infantis</td>
<td>for three weeks before delivery</td>
<td>to reduce risk of mastitis and improve infant health through it being in breast milk</td>
</tr>
<tr>
<td>B. lactis Bb-12 and L. rhamnosus GG</td>
<td>from week 20 of pregnancy to term then to newborn for first 6 months</td>
<td>reduce the risk of allergic disease</td>
</tr>
<tr>
<td>Bifidobacterium breve, Bifidobacterium bifidum, B. longum, B. infantis, and L. rhamnosus HA-111</td>
<td>first day of life of premature baby until discharge</td>
<td>to prevent NEC</td>
</tr>
<tr>
<td>L. reuteri ATCC 55730 50 ml curd containing Lactobacillus acidophilus</td>
<td>2-5 years of age</td>
<td>for oral health to reduce plaque and caries</td>
</tr>
<tr>
<td></td>
<td>2-5 years of age</td>
<td>reduce stunting</td>
</tr>
</tbody>
</table>
and sensorimotor integration (Janssen and Kiliaan, 2014). A study has shown that supplementation of the maternal diet with cod liver oil containing 1,183 mg/10 ml DHA, 803 mg/10 ml EPA and a total of 2,494 mg/10 ml summation operator n-3 polyunsaturated fatty acids correlated with improved mental processing scores of the children at four years of age (Helland et al., 2003). It is feasible that maternal ingestion of probiotic strains producing compounds such as alpha linoleic acid (Yang et al., 2014), could also improve foetal brain development and subsequent childhood cognition. The ability of *Bifidobacterium breve* to produce alpha linolenic acid (Rosberg-Cody et al., 2004), raises the concept of administering it as a probiotic in the 3rd trimester for foetal neural development. As this species is generally regarded as safe, it could be tested, although how success would be measured is difficult to define. Another potential mechanism is the production by the probiotics of neurochemicals that can influence cognition (Lyte and Cryan, 2014).

Progress in the development of modern imaging techniques to assess brain size and function and track auditory and organ development in the foetus (Girardi, 2015; Lagercrantz, 2014) has made it possible to study the brain before and after maternal probiotic intervention. However, this invariably require a period of stillness that is not easy to acquire and is expensive due to time on the imaging system. We look forward to seeing functional data that correlates improvements in the foetal and infant brain following probiotic use.

### 6. The basis for probiotic use before and during pregnancy

As stated, there is a basis for examining probiotic use during pregnancy. The following section will list probiotic strains that could be considered to improve reproductive outcomes. No claim is made that these strains are conclusively proven to safely and effectively confer these benefits, but there is merit to further studies.

#### Oral health

Oral diseases remain a factor in poor pregnancy outcomes, with studies suggesting that periodontal bacteria can directly infect the uteroplacenta and the foetus, and systemic inflammation can activate preterm labour at the maternal-foetal interface (Cetin et al., 2012). Recent work has demonstrated that probiotic bacteria can decrease oral pathogen levels and also influence salivary and gingival levels of caries related factors, including *Streptococcus mutans* (Saha et al., 2014). There appears to be a good rationale for using probiotics during the prenatal period for supplementation of dental hygiene. However, these studies have focused on infants, and thus there is insufficient level of evidence to provide specific recommendations for treating pregnant women.

On the other hand, various studies support the use of probiotics for infants. Early administration of *Lactobacillus reuteri* ATCC 55730 from birth and during the first year of life is associated with reduced caries prevalence and gingivitis score in the primary dentition at 9 years of age (Stensson et al., 2014). This conclusion was based upon clinical and radiographic examination of the primary dentition and carious lesions, plaque and gingivitis, and determination of *mutans streptococci*, lactobacilli and salivary secretory IgA. In another study, the failure to reduce *S. mutans* colonisation using *Bifidobacterium lactis*, xylitol or sorbitol twice daily for an average of 14 months via novel slow-release pacifier or a spoon (daily dose of 10^10 cfu and polyol 200-600 mg) emphasises that not all probiotic strains work (Taipale et al., 2012).

In a randomised, controlled, double-blind trial healthy young volunteers used lozenges containing a combination of *Lactobacillus rhamnosus* GG and *B. lactis* Bb-12 or lozenges without added probiotics (control group, n=31) for 4 weeks (Toiviainen et al., 2015). At baseline and at the end of the test period, the plaque index (PI) and gingival index (GI) were determined, and stimulated saliva was collected. The probiotic lozenge decreased both PI and GI (P<0.05) while no changes were observed in the control group. However, no probiotic-induced changes were found in the microbial compositions of saliva in either group. The probiotic lozenge improved the periodontal status without affecting the oral microbiota. Short-term probiotic consumption decreased the amount of plaque which was associated with a clinical impact: a decrease in gingival inflammation.

#### Reproductive health

Bacterial vaginosis (BV) diminishes the ability to conceive and increases the risk of preterm delivery (Li et al., 2012), perhaps mediated by specific strains of *Leptotrichia/Sneathia*, BVAB1 and *Mobiluncus* (Nelson et al., 2014). The case has been made for replenishing and maintaining lactobacilli before and during pregnancy. Intervention studies have been undertaken to prove efficacy of *L. rhamnosus* GR-1 and *L. reuteri* RC-14 taken orally, but the control group rate for preterm labour was too low to make definitive conclusions despite some evidence of an effect (A.D. Bocking et al., unpublished data; Krauss-Silva et al., 2011). Nevertheless, the safe use of the *L. rhamnosus* GR-1 and *L. reuteri* RC-14 combination orally per day in young women using oral contraceptive pills (Atallah et al., 2005) could also improve reproductive health.

A study has shown that supplementation of the maternal diet with omega-3 polyunsaturated fatty acids correlated with improved mental processing scores of the children at four years of age (Helland et al., 2003). It is feasible that maternal ingestion of probiotic strains producing compounds such as alpha linoleic acid (Yang et al., 2014), could also improve foetal brain development and subsequent childhood cognition. The ability of *Bifidobacterium breve* to produce alpha linolenic acid (Rosberg-Cody et al., 2004), raises the concept of administering it as a probiotic in the 3rd trimester for foetal neural development. As this species is generally regarded as safe, it could be tested, although how success would be measured is difficult to define. Another potential mechanism is the production by the probiotics of neurochemicals that can influence cognition (Lyte and Cryan, 2014).
et al., 2014) could be extremely important as excessive levels of heavy metals exist in women (Schoeman et al., 2010), and these can have detrimental effects on foetal neurodevelopment. The latter probiotic action has clinical significance particularly in the developing world.

The use of probiotics to prevent preterm labour by reducing the risk of BV has a good clinical rational and is supported by a series of in vitro and animal studies (Yang et al., 2015). However, in Brazilian and Canadian clinical trials using these strains, treatment has been short in duration therapy (A.D. Bocking, unpublished data; Krauss-Silva et al., 2011). Given that BV recurrence can occur at any time, it makes better sense to administer the GR-1/RC-14 probiotics orally each day from the second trimester to term. With no apparent safety concerns, such treatment may also reduce urinary tract infection rates (Beerepoot et al., 2012) and improve gut function.

Given the increased incidence of obesity and diabetes, we explored the potential to apply probiotics over and above nutrition counselling and exercise (Van Poppel et al., 2014). The recently discovered association between gut microbiota composition and host metabolism and obesity (reviewed in Cani et al., 2014) has created research interest in gut microbiology during pregnancy. Significant changes in gut microbiota composition associated with weight, weight gain and cholesterol levels have been reported to occur during pregnancy (Koren et al., 2012; Santacruz et al., 2010). Moreover, the pregnancy-induced changes in gut microbiota composition have been shown to lead to obesity in experimental animals (Koren et al., 2012). Based on these observations, it has been hypothesised that modulating the maternal microbial environment by certain probiotics during pregnancy might reduce the risk of excessive weight gain and gestational diabetes (GDM). In line with this notion, supplementation with the probiotics L. rhamnosus GG and B. lactis Bb-12 together with dietary counselling starting from the first trimester of pregnancy reduced the risk of GDM from 36 to 13% and resulted in lower blood glucose and insulin concentrations and improved glucose tolerance in a randomised, controlled trial of 256 pregnant women from Finland while dietary counselling alone had no impact on GDM risk (Lahtinen et al., 2009). These promising results warrant confirmation in larger clinical trials.

The potential to influence newborn health via the mother’s milk, has been raised by the finding that probiotic Lactobacillus fermentum CECT5716 or L. salivarius CECT5713 reach the mammary ducts after three weeks oral administration in women with mastitis (Arroyo et al., 2010). Thus, presumably if a woman took these strains in the third trimester, they could be passed on to the newborn through breast feeding, as well as helping to prevent mastitis. To recommend this for newborn health, studies would be required, and strains such as Bifidobacterium longum subsp. infantis of potential more importance to the newborn (Underwood et al., 2013, 2015; Zivkovic et al., 2011) should be tested. Such approaches may be of interest in women intending to have an elective caesarean (C) section, a procedure that is highly common practice in developed countries.

7. Elective Caesarean section issues

The rising rates of C section (both elective and emergency after labour) in developed countries; approaching 31% in the USA (Neu and Rushing, 2011) is a significant issue with important implications for the ‘adequacy and diversity’ of the initial infant microbiome (Mueller et al., 2015). The process of vaginal birth enables the mother’s reproductive tract microbiome to serve as the ‘starter culture’ for the infant microbiome (Domínguez-Bello et al., 2010). With no maternal vaginal/intestinal microbiome transfer to the infant occurring with C section, the infant microbiome is less diverse (Azad et al., 2013). Adverse effects for infants reported to be associated with C section include higher risk of allergy and infection in the short term (Neu and Rushing, 2011), autoimmune and coeliac disease in the medium term (Decker et al., 2010) and obesity and metabolic syndrome in the longer term (Mueller et al., 2005).

Strategies to overcome this apparent disadvantage in caesarean born infants could include administration of a ‘designer’ evidence-based probiotic via the mother prebirth, or to the infant after birth; or using personalised transfer of the mother’s own vaginal microbiome to the baby’s mouth and/or wiped over skin surfaces at birth. These are in addition to the passage of microbes that occur from breast milk/skin surfaces. The administration of a probiotic supplement raises questions as the timing, composition (species, different strains for different targeted conditions), dose and safety. This will be discussed in a later section.

The transfer of mother’s vaginal organisms using a gauze swab that is administered to the baby requires consideration of risk/benefit. At risk is the potential that maternal pathogens including Group B streptococci may be transferred, despite the mother receiving antibiotics. When repeat C section is planned, screening for pathogens (including sexually transmitted viruses and bacteria), should be undertaken in advance and subject to the health regulatory processes including ethics and study in a controlled fashion where follow-up is mandated. One trial is underway by M.G. Domínguez-Bello (personal communication) with no outcomes as yet available. In their method after screening: (1) a gauze is placed in mother’s vagina for 1 h and extracted before C section; (2) the newborn is exposed to the vaginal gauze (mouth first, then face, then rest of body). In addition to the concerns over pathogens, it is also unclear to what extent the mother’s
faecal microbiota, which contacts the newborn via vaginal birthing, affects infant microbiome development, as no exposure to faeces occurs with C section.

8. Probiotics in early life

Breastfeeding is associated with reduced risk of a wide range of infectious, inflammatory, immune-mediated and metabolic disorders (reviewed in Rautava and Walker, 2009). These beneficial effects are in part mediated by direct passive immune-protection provided by factors including immunoglobulins, defensins, Toll-like receptors and oligosaccharides in breast milk. In addition, human milk contains a variety of active immunomodulatory molecules such as hormones, cytokines and growth factors. The nutrient and microbial contents of human milk are clearly critical for the health of the recipient, not just for the intestine (reviewed in Collado et al., 2015). Our understanding of the role and significance of microbes and immune factors in human milk for child health is currently rudimentary. Recovering L. reuteri in the milk after oral intake and presumably internal transfer from the gut has been reported (Abrahamsson et al., 2009). We would like to see this or another probiotic strain added to pasteurised donor milk, to assess whether nutrition, immunological and microbiological benefits are accrued, since rates of breastfeeding have been declining in the developed world.

In addition to potentially delivering probiotics via the mother’s milk, the newborn may receive probiotics via direct administration. The consumption of B. lactis Bb12 and L. rhamnosus GG from week 20 of gestation to the first 6 months of the baby’s life as a supplement to human milk, has the potential to reduce the risk of allergic disease, and uptake of environmental toxins. The latter has been discussed for L. rhamnosus GR-1, but the GG strain also binds to heavy metals (Bisanz et al., 2014) and to potent aflatoxins that can induce illness (Gratz et al., 2007).

The basis for early administration of probiotics to reduce the risk of childhood atopic disease is based upon aberrant early gut colonisation patterns preceding the development of atopic manifestations (Abrahamsson et al., 2012; Kalliomäki et al., 2001). Further corroboration for the role of early microbial contact in the development of atopic disorders has been obtained from experimental animal models (Stefka et al., 2014). Several randomised clinical trials in which probiotic intervention has been used in an attempt to prevent atopic disease in the infant have been published and the results have been promising but also conflicting. The discrepancies in the efficacy of probiotic intervention may be due to differences in the probiotic strains, matrix and dosage used, the target population or the timing and route of probiotic intervention (Isolauri et al., 2012). A recent systematic review and meta-analysis of clinical trials suggests that the probiotic intervention should be commenced antenatally through the pregnant mother and continued after birth in order to be effective (Panduru et al., 2015). Consistently with this interpretation, maternal supplementation with the probiotic combinations of L. rhamnosus LPR and B. longum BL999 or Lactobacillus paracasei ST11 and B. longum BL999 for the last two months of pregnancy and the first two months of breastfeeding significantly reduced the risk of atopic eczema at the age of two years in high-risk infants in a double-blind, placebo controlled clinical trial (Rautava et al., 2012). For high-risk birth cohorts, supplementation with L. rhamnosus HN001 (6×10^9 cfu/day) from 35 weeks gestation until 6 months of breastfeeding plus infant supplementation from birth until 2 years halved the cumulative prevalence of eczema at 2 and 4 years (Wickens et al., 2013).

Another study followed a similar process of administering a probiotic (B. bifidum W23, B. lactis W52 and Lactococcus lactis W58) to pregnant women (6 weeks before delivery) and to the newborn (for one year), with the result of an altered microbiota at two year follow-up in atopic children (Rutten et al., 2015).

There is a magnitude of evidence to indicate that probiotics can prevent necrotising enterocolitis (NEC) in premature babies (Lau and Chamberlain, 2015), yet few intensive care units employ this approach. This is all the more baffling in countries like Canada, where there is supposed to be universal health care. A number of formulations have been used successfully, but none compared with each other, so it is not easy to recommend one specific product over another. The advantage to the one used in some Canadian sites, containing B. breve, B. bifidum, B. longum, B. infantis, and L. rhamnosus HA-111 is the latter two species have been shown to be important in infant health (Janvier et al., 2014). In clinical trials in preterm infants who were predominately caesarean-born, NEC incidence was reduced by administration of B. infantis BR 02 96579, B. lactis Bb12 and S. thermophilus Th-4 15957 DMSZ in a total dose of 10^8 with reduced sepsis by half in the subgroup ≥28 weeks (Jacobs et al., 2013).

There are some similarities between NEC and neonatal sepsis, in terms of symptomatic presentation and timing, but for the most part probiotics have not yet been proven to prevent sepsis. This is perhaps surprising, if the rationale for preventing infection is to increase the proportion of beneficial bacteria in the host, which appears to work effectively to prevent NEC. Potentially, Bifidobacterium strains lack factors, such as hydrogen peroxide and other antimicrobial substances present in lactobacilli that are needed to inhibit pathogen colonisation. But a study of 585 newborns <33 weeks or birthweight <1,500 g randomised to receive standard milk feed supplemented with L. rhamnosus GG once a day until discharge, starting with the first feed or placebo, showed no effect on sepsis (Dani et al., 2002),
that can help before, during and after therapy, leads to us recommending them for consideration (Table 1).

9. Conclusions and recommendations

For the most critical part of human life – conception to early development – surprisingly little research has been done to understand the key nutrients and microbes that support optimal health. The rationale for probiotic administration has some substance – human evolution with fermented foods, microbes associated with many health benefits – but the mechanisms by which strains actually confer health still remain elemental. The optimal time to administer probiotics to improve cognitive function, reduce atopic and infectious disease, and prevent premature birth, requires more study, along with dose and duration. In this review, a case is made to include probiotic supplementation as part of a healthy pregnancy and with breastfeeding for early infant health (Table 1). The field would be helped if every company selling products ostensibly for maternal and infant health, funded independent studies that examine these factors. In addition, the vast investments in the first 1,500 days projects around the world from governments and NGO’s risk failing if significant investment in the microbial contribution to resolution is not included in parallel. In this way, it is reasonable to expect that the extent to which microbial intervention can improve the health and well-being of mother and infant, can be determined, and evidence-based advocacy passed on to people around the world. The fact that there are some probiotic products thereby countering that argument. The recent finding that a strain of L. plantarum included in a food matrix could reduce the incidence of early onset neonatal sepsis in newborns in India (Panagrahi, unpublished data), suggests that strain selection is critical.

Interestingly, a study of 94 preterm infants found a significantly lower incidence of rhinovirus respiratory tract infections with prebiotics galacto-oligosaccharide and polydextrose mixture, or probiotic L. rhamnosus GG from days 3 to 60 of life, compared to placebo (Luoto et al., 2014). This again illustrates distant site effects following oral administration.

In developing countries, vaginal birthing and exclusive breastfeeding continue at high rates, but issues remain with maternal and infant morbidity and mortality. Ironically, despite studies showing that certain probiotic products can benefit women and infants in developing countries, the products are either not made available or are too expensive for the majority of the population. Apart from being almost unethical, it means that potentially life-saving interventions are not reaching people who already face challenges of poor access to effective health care, lack of finances, and poor nutrition. The creation of community kitchens where probiotic yogurt is affordably produced and made available, has the potential to help millions of people (Reid, 2010; Sybesma et al., 2015).

Acknowledgements

We appreciate support from ISAPP and for the contributions made to the discussions at the workshop by Andrea Roberts, Kaouther Ben Amor, Jodi Bettler, Howard Cash, Rhodri Cusack, Gabriele Gros, Flavia Indrio, Mark Lyte, Bo Mollstam, Pirjo Nuutila, Pinaki Panagrahi, Bruno Pot, Margriet Schoterman, Catherine Stanton, and Dan Tancredi.

References


Lactobacillus rhamnosus

Lactobacillus paracasei

Beneficial Microbes 7(3)


Reid, G., Bruce, A.W., Fraser, N., Heinemann, C., Owen, J. and Henning, B., 2001. Oral probiotics can resolve urogenital infections. FEMS Immunology and Medical Microbiology 30: 49-52.


Yang, S., Li, W., Challis, J.R., Reid, G., Kim, S.O. and Bocking, A.D., 2014. Probiotic Lactobacillus rhamnosus GR-1 supernatant prevents lipopolysaccharide-induced preterm birth and reduces inflammation in pregnant CD-1 mice. American Journal of Obstetrics and Gynaecology 211: 44.e1-44.e12.
