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NUTRITION

Stimulating the Body's Defences (Part II)

LactoB HN001™ immune benefits during early life

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Introduction

The human gut microbiome is a complex and biologically active ecosystem of trillions of microbes[1] participating in the overall well-being of an individual. Approximately 70% of the body's immune cells resides in the gastrointestinal system, and the gut microbial population existing as a balanced ecosystem is essential for promoting a healthy immune system and providing protection against pathogens and gastrointestinal (GI) disorders[2].

An optimal immune system relies on adequate nutrition and the presence of a healthy microbiota (or microflora). At birth, the gastrointestinal (GI) tract of a newborn is often considered sterile or germ free and primarily gets inoculated with maternal microflora during the birthing process through vaginal or skin contact. Indeed, mode of birth (vaginal or caesarean birth) can have a significant impact on the initial state of the developing microbiome[3]. Once established over the first few years of life, the composition of the microbiota remains relatively stable. However, multiple factors can still influence the microflora of an infant, including genetics, health status, diet (e.g. the type of feeding, use of dietary supplements), the environment, and use of antibiotics and other drugs (Figure 1)[4]. Microbial diversity plays a crucial role in the maintenance and maturation of an infants' immune system. Certain bacteria contribute by preventing the growth of harmful bacteria and protecting against infection[1] and that is why these microbes are commonly referred to as friendly or good bacteria. In return, the GI tract provides nutrition and protection for the microbial community residing in the gut[5].

Microbial diversity is now considered a critical biomarker of a healthy gut and any disruption in gut homeostasis, such as reduced microbial diversity or (microbial imbalance), is associated with poor health outcomes[4]. Changes in the microbial density has been shown to increase pathogen susceptibility, and so increase bacterial infections. Also, several studies have reported that gut microbial dysbiosis may be involved in the development of type 1 diabetes and obesity[1], possibly due to their involvement in glucose and insulin metabolism[7]. Therefore, early establishment of a healthy and balanced gut microbiota is an important step in attaining and maintaining a healthy immune system. For more details on the development and enhancement of a healthy immune system refer to the NZMP SureStart™ White Papers titled "Stimulating the Body's Defences" and "The Probiotic Effect".

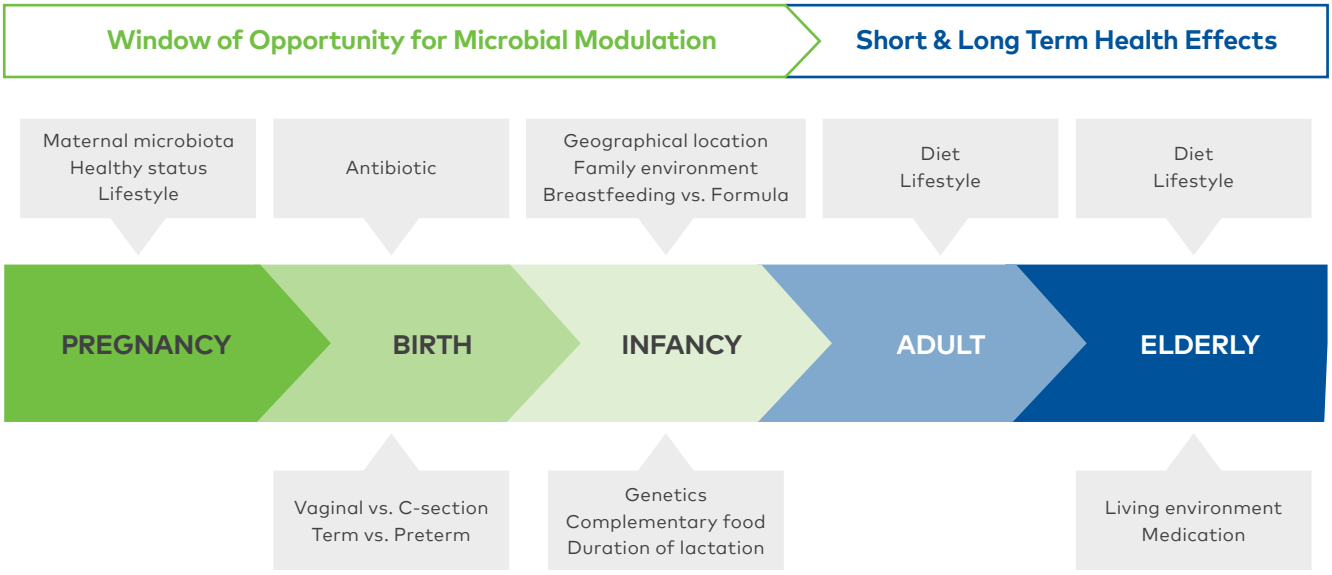

Figure 1: Factors determining microbiota composition in mother and infant[6] (taken from Rodríguez et al 2015).

BENEFITS OF A HEALTHY GUT MICROBIOTA

During the early period of life, the gut microbiota plays a key role in the maturation of the immune system and its regulation. For instance, it can help reduce the risk of infectious diseases (such as Necrotizing Enterocolitis (NEC), diarrhoea, colds and flus), and can help to provide protection against immune disorders such as allergy[1,8,9]. The gut microbiota builds a complex barrier against pathogenic bacteria and can promote the integrity of the gut barrier by reducing inflammation, ultimately shaping the architecture of a healthy immune system[10].

The microbial community of the gut is a crucial component of the human metabolic activities. Gut microbes play an important role in extracting energy from food and help regulate the absorption and metabolism of dietary nutrients[11]. They can also facilitate the digestion of residual food components particularly fibres and complex carbohydrates, and thereby produce important nutrients that are available to the host, including the release of short-chain fatty acids (SCFAs), branched-chain amino acids (BCAAs), vitamins and other bioactives[3,12]. Furthermore, the metabolites from the gut microflora can lower the pH in the GI tract promoting the absorption of minerals that are critical to the body's everyday functions[13]. Therefore, improving the diversity and composition of the gut microbiome is vital for the overall wellbeing of an individual. This wide-spread recognition of health promoting gut bacteria has encouraged the modulation of the microbiota towards more favourable/friendly microbiota by using diet, probiotics and prebiotics.

PROBIOTICS: FOOD FOR A HEALTHY GUT

The concept of using diet and nutrition to create or maintain a healthy GI tract microbiota for healthy digestion is not new. The diet plays an important role in promoting the growth and composition of the gut microbiota; dietary prebiotics and probiotics are commonly recommended to support gut health and enhance immunity[11,14].

According to the World Health Organisation (WHO), probiotics are defined as live micro-organisms that, when administered in adequate amounts, confer a health benefit on the host (FAO/WHO 2001). Most probiotics belong to bacterial species found naturally in the gastrointestinal microflora, and are often referred to as "friendly bacteria" or "good bacteria"[15]. Numerous pre-clinical and clinical studies have demonstrated the positive effect of certain probiotics strains on immunity and have reported the efficacy for protecting against illness and prevention of infections. The health benefits of probiotics are strain specific, such that the functional benefits identified for each probiotic strain cannot be generalized to all other strains.

The scientific naming of probiotics follows a conventional naming system of: Genus, species, sub-species (if required), and strain (Figure 2). Of the probiotics strains on the market *Bifidobacterium* (genus) *animalis* (species) sbsp. *lactis* (sub-species) HN019™ (strain) and *Lactocaseibacillus* (genus) *rhamnosus* (species) HN001™ (strain) are among the two most popular probiotics studied. The research on these strains has included a variety of health benefit outcomes including protecting against diarrhoea[16], reduced length of hospitalisation in children with acute gastroenteritis[16] and prevention of eczema[9,17].

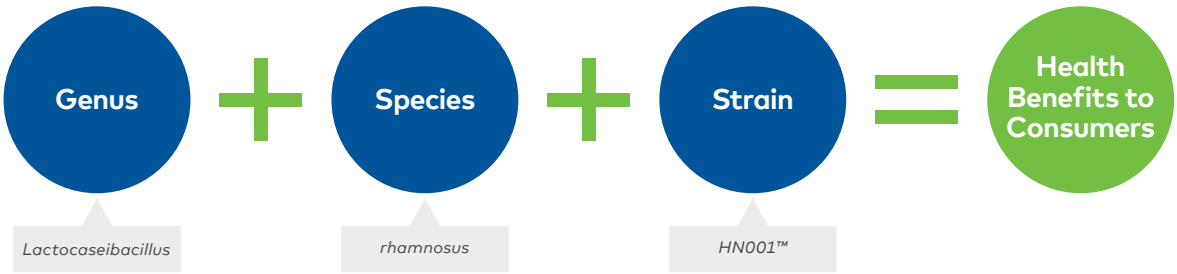

Figure 2: How to choose your Probiotics: Probiotic benefits are strain specific and not all probiotics are the same

SURESTART™ LACTOB HN001™

Lactocaseibacillus subspecies *rhamnosus* HN001™ strain , commercially known as SureStart™ LactoB HN001™ , is a gram-positive bacterium, a naturally occurring organism with no known pathogenic activities[18]. It is broadly classified as a member of Lactic Acid Bacteria (LAB), a group of microbes involved in the production of lactic acid as the major metabolic end product of carbohydrate metabolism. The LAB strains have the potential to survive gastric passage and can rapidly colonize (at least transiently) the mammalian intestinal mucosa imparting several health benefits.

SureStart™ LactoB HN001™ was originally isolated from a cheddar cheese and has been the focus of research due to its long history of safe use in foods and its health promoting role[17,19]. Over the past 20 years, a systematic and rigorous research programme has been undertaken in conjunction with independent research groups to ensure a comprehensive evaluation of its safety and efficacy. This research programme included preclinical research and clinical studies in a range of populations and across key stages of life with evidence demonstrating that SureStart™ LactoB HN001™ has various immune and gut health benefits[20–23]. Research has also shown that HN001™ may also help to protect against the development of allergy in at-risk infants and holds the potential to reduce the risk of gestational diabetes in pregnant mothers[9,24].

BENEFITS OF *L. RHAMNOSUS* HN001™ FOR IMMUNITY DEVELOPMENT AND PROTECTION AGAINST ALLERGY AND ECZEMA

In the last few decades, the prevalence of immune-mediated health conditions such as allergy and other autoimmune diseases are on the rise, with Atopic Dermatitis (AD) or eczema being the most prevalent manifestation of allergy in infancy[25]. The aetiology of allergy is multifactorial, affecting up to 2.5% of the general population and up to 10% of infants in some countries[26,27]. While the main cause of AD/eczema is not known, studies suggest that there is a significant difference between the gut microbial composition of infants with or without AD, indicating the key involvement of infant gut microbiota[28].

Emerging evidence on the importance of early life microbial exposure and its colonization in gut microflora in reducing the risk of allergy or AD or eczema[9], has led to the sudden popularity of probiotic usage[29,30]. Probiotic interventions are thought to improve gut health by stabilizing the intestinal barrier and stimulating the production of interleukin (IL) IL-10 and Immunoglobulin A (IgA) [18,31]. Several animal and human studies have highlighted the benefits of probiotic interventions in improving gut health[18,32]. Most of these studies have used *Lactocaseibacilli* or *Bifidobacteria* species that may promote the production of cytokines, including IL-10,IL-12, transforming growth factors (TGF)-ß, and interferon (INF)-γ and help regulate the immune system to reduce allergic inflammation[29,31]. A clinical study by Sistek et al[33] reported that in children with AD aged 1 to 11 years, those who had food sensitisation benefited from the consumption of two different probiotics SureStart™ LactoB HN001™ and SureStart™ BifidoB HN019™, with a reduction in the extent and severity of AD. Following this a clinical study by Wickens et al [32], investigated the functionality of SureStart™ LactoB HN001™ and SureStart™ BifidoB HN019™ used separately for the prevention of allergy and eczema during the first 2 years of life. The study showed that consumption of SureStart™ LactoB HN001™ during the last trimester by the mother and then in the child until 2 years of age significantly reduced the prevalence of any eczema by almost half. The study also showed that SureStart™ LactoB HN001™ was a safe and well-tolerated probiotic for infants between the age of 0 to 24 months. Furthermore, intake of SureStart™ LactoB HN001™ boosted the frequency of *L. rhamnosus* species in the infants' feces, indicating the ability of the probiotic strain to transit the GI tract and to improve the gut bacterial community.

The major strength of the study was that the individual impact of two probiotic strains were investigated and it was found that only SureStart™ LactoB HN001™ had a protective effect against the pathogenesis of eczema in this at-risk group. This indicates that not all probiotic strains exhibit the same effects and that only specific probiotic strains are effective in preventing the development of allergic disease. Further follow-up of the children in the studies at 4, 6 and 11 years of age showed the long term protective benefits of SureStart™ LactoB HN001™[34–36]. These studies showed that the benefits of consuming SureStart™ LactoB HN001™ during the first 2 years of life persisted long after consumption was ceased, with significantly lower prevalence of eczema observed up until the age of 11 years[34]. This study was a significant piece of work in demonstrating the specific role of *L. rhamnosus* HN001™ in preventing allergy, eczema and influencing the immune system that continued for at least 9-10 years after the intervention was stopped, suggesting the beneficial impact of early life dietary intervention in providing long term protection against allergic disease phenotypes.

BENEFITS OF *L. RHAMNOSUS* HN001™ FOR GESTATIONAL DIABETES

Gestational Diabetes Mellitus (GDM) is a pregnancy-induced metabolic condition characterized by abnormal glucose tolerance during the first or second trimester of pregnancy. It is the most common health concern among pregnant women affecting up to 15% of pregnant women globally[37]. Women with GDM are at increased risk of being affected by other pregnancy complications such as pre-eclampsia, premature membrane rupture, and caesarean section, while in the long term, it increases the risk of developing Type 2 Diabetes (T2D) post-delivery[38,39]. Furthermore, offspring of GDM-affected mothers are at higher risk of developing metabolic complications and are more predisposed to obesity and T2D in later life than babies born from healthy mothers[40,41], leading to a cycle of disease across generations.

Lifestyle interventions, including diet and physical exercise, are the most simple and cost-effective way of treating or preventing GDM[42]. However, another emerging potential interventions is the use of probiotics, possibly due to its positive impact on glucose metabolism and reducing insulin resistance, specifically from consuming products containing *Lactocaseibacillus* or *Bifidobacterium*[43,44]. A large study of 265 Finnish women showed that a probiotic supplement (*L. rhamnosus* and *B. lactis*) during the perinatal period reduced the prevalence of GDM[44]. A study by Karamali et al.[43] demonstrated that supplementation with probiotics (*L. acidophilus*, *L. casei* and *B. bifidum*), is an effective strategy for improving the glycaemic control, triglycerides and VLDL cholesterol concentrations in women diagnosed with GDM. A more recent study by Wickens et al (2018)[34] showed that supplementing pregnant mothers with SureStart™ LactoB HN001™ could reduce the prevalence of GDM by 68% particularly among older women (aged ≥ 35 years) and in those with a history of GDM. It is believed that SureStart™ LactoB HN001™ alters the composition of the gut microbiota, thereby improving insulin sensitivity and inflammation in the host, reducing the susceptibility towards GDM. To our knowledge this is the first study that reports the positive role of probiotics in preventing GDM with unbiased selection criteria and still found results favouring reduced prevalence of GDM. Furthermore, this study showed that consuming SureStart™ LactoB HN001™, a well characterised, patented probiotic strain, had no adverse effects on participating mothers, birth outcome or on their babies, indicating it is a safe intervention to take from early pregnancy.

BENEFITS OF *L. RHAMNOSUS* HN001™ FOR MENTAL WELLNESS

Depression is a serious medical condition characterised by the feeling of sadness or depressed mood and in some cases loss of interest in activities you once enjoyed. There are several biological and environmental factors that play important roles in the aetiology of depression. For females, the period during pregnancy and after birth (postpartum) can have an additional impact on the risk of developing depressive symptoms[45,46].

Postnatal depression (PND) affects nearly 10-15% of women, impairing their ability to care for and bond with their child(ren). Over the last 2 decades, a growing number of reports have demonstrated a well-established relationship between depressed mothers and adverse child outcomes[47–49]. Despite the increasing prevalence of prenatal and postnatal depression, mothers are reluctant to take antidepressant medication and are more interested in pursuing alternative or non-pharmacologic depression treatments. This highlights the need for a safe and effective way of preventing depression and anxiety[50].

There has been a growing interest in the role of the microbiome on brain health and stress related mental illness disorders, via a bidirectional pathway between the peripheral and Central Nervous System (CNS) called the gut-brain-axis[51]. Gut microbial dysbiosis or reduction in microbial colonization is known to trigger chronic low-grade intestinal inflammation, resulting in several detrimental health outcomes including depression and anxiety[52]. Because diet plays an instrumental role in modifying the gut ecosystem, altering the diet (including consuming prebiotics and probiotics) is recommended as the most natural way of influencing mental health and brain functioning[53].

It is becoming increasingly clear that consumption of traditional diets and functional foods can be used to modulate the microbiome-and Gut-brain axis, to improve mental health and reduce the likelihood of depression[54]. In 2005, probiotics were first suggested as adjuvant therapy for depression and later on the term 'psychobiotic' was coined by Prof. Ted Dinan (Clinical psychiatrist) to describe bacteria which specifically improve mental health and mood[55,56]. Several animal studies have demonstrated improved stress-related behaviours (such as anxiety- or depression-like symptoms) when administered probiotic supplements. It appears that a number of mechanisms may be involved that may assist the (CNS), such as signalling via the Hypothalamic Pituitary Adrenal axis (HPA axis), the vagus nerve, or and the enteric neurons[57].

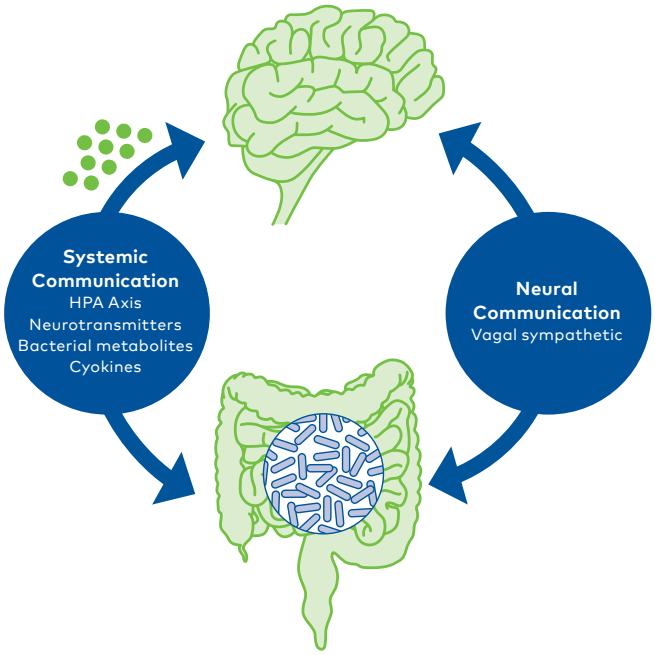

Figure 3: Bidirectional communication between microbiome and the brain - the "Gut-brain axis"[58] (Taken from Mayer 2014)

Although many human studies have shown the positive role of probiotics in supporting gut health and immunity, only certain probiotic species have shown beneficial effects related to mental health[58]. A recent study by Slykerman et al[59] demonstrated the positive impact of probiotics supplementation with SureStart™ LactoB HN001™ in postpartum healthy women, when compared to a placebo group. They showed that mothers who consumed SureStart™ LactoB HN001™ had fewer symptoms of depression and postnatal anxiety. This is the first time that symptoms of mental health in women post-partum were evaluated as a part of a nutrition clinical study. This study provides scientific evidence that probiotic supplementation with SureStart™ LactoB HN001™ may help to lower the risk of postnatal depression and anxiety when consumed from early pregnancy up to 6 months following childbirth.

Summary

While there are a large number of potential probiotics available in the market offering a range of health benefits, it is clear that each strain has its own set of benefits, which requires clinical research to prove its ability to positively influence health. The link between probiotics and maternal and infant health will continue to be explored as a natural way of enhancing immunity and improving overall health including mental well-being of both mother and her baby.

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