Today, the interactions between probiotics and immunity are increasingly well understood. Thanks to a strong research program dedicated to immunity, encompassing innovative in vitro, in vivo and clinical studies, scientists at Lallemand Health Solutions are now able to draw a better picture of the pathways involved and the clear benefits of selected probiotic strains.

On this basis, we have been able to design a portfolio of probiotic strains to address various issues of immune health for different target groups: children, adults or seniors.

Defenses and tolerance: two sides of the same coin

The immune system’s main function is to protect our body from diseases through the recognition and clearance of pathogens (viruses, bacteria), or infected or cancerous cells etc.

The corollary is the recognition of self and environmental antigens (food, air borne substances...) as non-harmful: this is immune-tolerance.

In a perfect world, the immune system performs these two roles perfectly: this is homeostasis, or healthy state. But when the immune response is overwhelmed, infections and diseases can occur. On the other side, poor immune tolerance can be translated into allergic reaction or auto-immune disease (cf. Th1-Th2 balance boxed text).

The immune system matures and evolves through life [1] (Figure 1): specific defences or tolerance issues can arise at each stage of life.

- In infants and children, as the system is immature, infections are common and atopic disorders are a consequence of hypersensitivity (eczema, asthma).
- In adulthood, the immune response is mature, with a great pool of memory cells. However, stress factors can alter the balance and the body becomes more vulnerable to acute or chronic infections.
- As the body ages, so does the immune system. It loses its plasticity and infections are more common. In addition, chronic inflammation is a common denominator of many old-age health issues.

Probiotics and immunity: a close relationship

The relationship between the immune system and the gut microbiota is scientifically backed-up. It appears that the digestive microflora plays a key role in the development and maintenance of immune defences. The microflora is particularly involved in the regulation of the Th1-Th2 balance (see boxed text) and the modulation of cytokines production.

In the same way as the immune system, the digestive microbiota evolves through life and its balance is impacted by stress factors.

In this context, the use of probiotics, able to balance and interact with the host microbiota, has appeared as a potential strategy to positively influence the immune response. Over the past 15-20 years research has shown the effects of probiotics at different levels:

- First, they influence the barrier effect; probiotics help protect the gut surface from potential pathogens and prevent their translocation from the gut lumen by increasing mucin production and improving tight-junction between epithelial cells, or by competing with pathogen binding.
Certain probiotics have the ability to modulate the non-specific innate immune response.

Specific probiotics are even able to activate the specific adaptive immune response, for a third level of protection.

Today, the interaction between probiotics and immunity are better understood and backed by clinical data. Thanks to a thorough research program dedicated to immunity, scientists at Lallemand Health Solutions are now able to draw a better picture of the pathways involved in the interactions of their specific strains with the immune response.

Immune pathways are diverse and complex and after several years of development, researchers at Lallemand Health Solutions have fine-tuned a specific DNA microarray to evaluate the interactions of probiotic bacteria with the host immune pathways (picture). This micro-array gathers 1354 human genes related to innate immunity and barrier defences.

Primary data have been published, showing the immune-modulating effects of the strains *Bifidobacterium bifidum* Rosell-71, *Bifidobacterium infantis* Rossell-33 and *Lactobacillus helveticus* Rosell-52: when combined together, the three bacteria had a major impact on attenuating expression of genes connected to a Th1 antiviral innate immune response [2].

Further studies looked at the consequences of these strains interactions with human epithelial cells challenged with a pro-inflammatory stimulus [3]. This time, a whole genome microarray was used, allowing to look at the whole genome level. This evaluation confirmed that the three strains exert potent immunomodulating effect, and their synergetic potential:

- Each strain showed strain specific attenuation of global gene modulation in this inflammatory model.

- The multi-strain combination had a greater impact at attenuating global gene modulation compared to single strains, illustrating synergetic effect.

The same conclusions had been shown in initial in vivo studies which corroborate the in vitro data:

In a Th1 immune response model (enterotoxigenic Escherichia coli challenge in rats), it was showed that a two-week preventive treatment with the combination of three strains exerted a significant effect on the animals' health and immune status [4]. This was concomitant with a modulating effect on the Th1 response: levels of pro-inflammatory cytokines were decreased, while anti-inflammatory cytokine IL-4 increased.

In a Th2 model (rats challenged with extracellular pathogen Nippostrongylus brasiliensis), pro-inflammatory factors were also significantly reduced by the probiotics (Figure 2).

These pre-clinical programs are backed by clinical studies in children [5] and stressed adults [6] that confirm 1) The positive interaction of specific probiotics with the immune system 2) The synergetic activity of the three probiotic strains in vivo. These clinical studies are further detailed in the sections below dedicated to children and adults.

Thanks to these pre-clinical and clinical data, we have been able to develop a broad portfolio of probiotic strains and combinations to address various populations’ needs: children, adults, seniors.

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**The Th1-Th2 balance**

The helpers T lymphocytes (CD4⁺) are major cytokines producers. They have been divided between Th1 and Th2 subsets according to the type of cytokines they produce:

- **Th1 cells** produce mainly pro-inflammatory cytokines (interferon-γ, IL-2, IL-3, TNF-β), involved in the destruction of intracellular parasites (cellular immunity).

- **Th2 cells** produce anti-inflammatory cytokine IL-10, and interleukins 4, 5, and 13; IL-4 being associated with the promotion of IgE (humoral immunity).

In homeostasis there is an equilibrium between the Th1 and Th2 immune response: the Th1-Th2 balance.

An excess of Th1 response would lead to chronic inflammatory state and is involved in autoimmune diseases. Whereas an excessive Th2 response has been linked to allergic reactions (excessive IgE production).
Addressing children immunity

Children’s immune system is maturing and children are at higher risk of infections or atopic disorders (Th2 reaction). Young children are prone to colds and may have 8 to 12 of them every year. Atopic dermatitis usually starts within the first six months of life and its prevalence is 14% among children under four.

Probiotics that can help stimulate the immune defences and modulate the Th1-Th2 balance could help on both sides.

Benefits in reducing infection risk have been demonstrated in a clinical study with a combination of three strains: *Bifidobacterium bifidum* Rosell-71, *Bifidobacterium infantis* Rosell-33 and *Lactobacillus helveticus* Rosell-52. This combination proved beneficial effect in a children randomized study on the prevention of common winter infections [5].

The multi-center study was conducted in France and involved 135 healthy, school-age children (3 to 7 years old) who had suffered from at least three episodes of ear-nose-throat (ENT), bronchopulmonary or gastric disorders during the course of the previous winter. Children were supplemented daily with either the probiotic preparation or a matched placebo for three months:

- The relative risk of developing any infection was significantly reduced by 25% as compared to placebo (P<0.05) (Figure 3).
- The number of children who missed at least one day of school due to adverse health event was significantly reduced by 40% (P<0.05).

In the particular case of gastrointestinal infections, which are very frequent in children, the benefits of probiotics are well established. Probiotic yeast *Saccharomyces cerevisiae boulardii* is largely documented for this indication.

Studies have also confirmed that the association of well described *Lactobacillus* strains (*Lactobacillus rhamnosus* Rosell-11 and *Lactobacillus helveticus* Rosell-52) is effective for various gastrointestinal diseases such as antibiotic-associated diarrhoea and acute gastroenteritis in children [7]. Studies have also shown that *Bifidobacterium lactis* LA94 can help shorten the duration of gastroenteritis, in particular in cases of rotavirus diarrhea [8, 9].

**Atopic dermatitis** (AD) is frequent in children. The positive effect of probiotics on the Th1-Th2 balance indicates a good potential in alleviating AD symptoms.

Chernyshov investigated the effects of *Lactobacillus* Rosell-11 and *Lactobacillus* Rosell-52 combination (Lacidofil®) on the clinical symptoms of AD (represented by SCORAD – SCORing Atopic Dermatitis – clinical tool) and the quality of life for patients and their families. In one report, 36 children up to age 4 with AD were given emollient with LACIDOFIL® [10]. After one month treatment, SCORAD improved from 40.82±4.00 to 24.67±3.32 (P<0.001). Additionally, quality of life ratings were significantly greater following treatment (P<0.05).

In a separate study, 58 children with AD up to age 4 were randomised to receive either emollient and Lacidofil® or emollient alone (control group). Children treated with Lacidofil® experienced a greater reduction in clinical symptoms than children treated with emollient alone (Fig. 4). Additionally, Lacidofil® increased IgG4 to cow milk proteins, signifying improved immune tolerance [11].

**Figure 2**: Reduction of pro-inflammatory cytokine TNF-α (*: significant difference vs. control (not infected); +: Significant difference vs. *N. brasiliensis* (infected, not treated)) (Cazzola et al., 2010a).

**Figure 3**: Effects of probiotic administration in children at risk of common winter infections; p=0.044 (Cazzola et al., 2010b).

**Figure 4**: Lacidofil® reduced the percentage of AD patients with marked reduction in SCORAD (P=0.02) (Chernyshov, 2009).

Based on these evidences, a selection of probiotic strains is proposed for children specific probiotic formula:
In healthy adults, common infections such as cold and flu can be frequent and contagious, particularly during winter or at the seasonal transitions. Adults get an average of two to four colds per year, mostly between September and May. In addition, chronic stress and high intensity exercise increase the risk of common infections due to an immunosuppressive effect. Thus, populations exposed to high degrees of physical and environmental stress, such as sportsmen and daily-life stressed people, may suffer from an increased incidence of upper respiratory tract illness.

A recently published clinical study investigates the benefits of individual probiotic strains on the occurrence of common infections (cold and flu) in stressed subjects (academically stressed students, a model of acute stress) (Fig. 5). It was concluded from this unique study that: “Daily intake of Bifidobacterium bifidum R0071 provides benefits related to cold and flu outcomes during acute psychological stress” [6].

Moreover, this study, which involved 585 subjects, used powerful statistical predictive models. These allowed highlighting interesting effects of other parameters on the probability of reporting a day of cold/flu in stressed participants:

- **Level of stress**: the higher the level of stress the more sensitive to develop cold/flu symptoms.
- **Gender**: women reported more cold days, more severe cold symptoms and higher levels of stress during the 6-week intervention.

The probiotic effect was all the more important in these susceptible groups.

Another clinical study shows interesting benefits of another probiotic strain (*Lactobacillus helveticus* LAFTI® L10) to support the immune response in stressed adults [12].

A double-blind, randomized, parallel group, placebo-controlled clinical study was conducted during the winter period in order to estimate the effects of *L. helveticus* LAFTI® L10 on winter infections such as common cold and flu. Three hundred students, who normally suffer from at least two colds a year, were included in the ten-week study. The study showed a significant reduction of the number of systemic symptoms by 12.2% in the probiotic group, moreover the symptoms were less severe with the probiotic. As a result, the probiotic significantly reduced the need for medication: the total number of days with medication intake (mainly analgesics) was reduced by 23% (Fig. 6).

**Figure 6: Effect of a ten-week treatment on the need for medication linked to cold and flu (mostly pain killers) (Eccles et al., 2008).**

The same strain was also beneficial in training athletes, another sub-population at higher risk of lower immune defenses [13]: a pre-post intervention study was conducted with *L. helveticus* LAFTI® L10 in two groups of well-trained recreational athletes: 18 ‘healthy’ athletes and 9 fatigued athletes, suffering of fatigue, recurrent sore throats, and impaired performance. The study showed that:

- Fatigued athlete have an impaired immune response: before the probiotic treatment, the two groups showed a significant difference in interferon-γ (IFN-γ) levels, a cytokine involved in protection against virus infections. Fatigued athletes showed less secretion of IFN-γ from blood CD4+ T cells than healthy controls, which could explain the reactivation of Epstein Barr virus disease in these athletes, responsible for recurrent sore throat.
Probiotics for Immunity

L. helveticus LAFTI® L10 treatment restored the impaired immune response: after one month of L. helveticus LAFTI L10 administration, CD4+ T cells secretion of IFN-γ in fatigued athletes was restored to the levels found in healthy athletes. For the healthy group, IFN-γ level in saliva also increased. The results of this study are correlated with previous in vivo studies whereby L. helveticus LAFTI L10 induced the production of IFN-γ in challenged animals.

Based on the documentation of our probiotic strains and the issues of adult immunity, a selection of probiotic strains is available to formulate specific solutions:

<table>
<thead>
<tr>
<th>Strains</th>
<th>Global Immune Support</th>
<th>Common winter Infections</th>
<th>Suppressed immune function in athletes &amp; stressed people</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bifidobacterium bifidum Rosell-71</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Bifidobacterium infantis Rosell-33</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Lactobacillus helveticus Rosell-52</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Lactobacillus helveticus LAFTI L10</td>
<td>+++</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Bifidobacterium longum Rosell-175</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Lactobacillus rhamnosus Rosell-343</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Lactobacillus paracasei LAFTI L26</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Lactobacillus brevis HA-112</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Lactobacillus fermentum HA-179</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Saccharomyces boulardii</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

Immunity in Seniors

Probiotics and the elderly go a long way! Nobel Prize winner Elie Metchnikoff, the father of probiotics, discovered the benefits of lactic ferments while searching for the fountain of youth... In his book The Prolongation of Life: Optimistic Studies, published in 1910, he linked the body degeneration to the presence of “putrefactive bacteria” in the intestine. By observing the exceptional longevity and good health of Eastern European populations who consumed fermented dairy products on a daily basis, he then attributed health benefits to lactic-acid producing bacteria: probiotics were born!

Today, empirical observations have given way to clinical studies and in vitro research, corroborating Metchnikoff’s theory that certain probiotics can help aging populations.

The elderly are more susceptible to infectious diseases such as influenza, which can deteriorate into more serious conditions such as pneumonia. This is partly due to immunosenescence: there is a strong body of evidence showing that aging is accompanied by severe alterations in the immune system. Among these changes are alterations in T-cell subpopulation size, cytokine secretion pattern, cell replicative capacity and antibody production. This can result in a poorer response to vaccines and an impaired control of latent viruses. Another consequence is the profound modification within the cytokine network leading to the development of a low-grade inflammatory status, known as “inflammaging”. This chronic inflammatory status has been linked to a continuous antigenic load and stress. It appears to be the price paid to immunological memory.

![Figure 7: Proposed relationship between immunity and digestive microflora in elderly populations.](image)

The digestive microflora is also affected by ageing. In particular, its diversity is reduced. Levels of *Bifidobacteria* decline and species breakdown is altered [14]. On the other hand, the proportion of *Clostridia, Lactobacilli, Streptococci* and *Enterobacteria* increase (Figure 7).

It has been advocated that modulating the gut microbiota by increasing *Bifidobacteria* level is a good strategy in the elderly. Several studies have shown a positive impact of certain *Bifidobacterium* supplementation on gut microflora balance (increased fecal *Bifidobacteria*).

Clinical trials in stressed adults and children also indicate that specific strains are able to induce immune-protection in at-risk populations [5, 6]. The fact that *L. helveticus LAFTI® L10* is able to help restore a depressed immune response in athletes also indicates a good potential in seniors with a lowered immune response. Such probiotic strains have a potential to alleviate the effect of immunosenescence. Moreover, the combination of *Lactobacillus* Rosell-52 and *Bifidobacterium* Rosell-175 has shown potential in clinical trial to reduce the physiological [15] and psychological [16] symptoms of stress, with positive effects at brain level. Such results indicate promising benefits in inflamming, linked to chronic stress.

Figure 8 summarizes the potential benefits of probiotics in the elderly.

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Figure 8: Potential benefits of probiotics to support an ageing immune response.

Based on the properties of our probiotic strains and the issues of seniors’ immunity, specific strains have been selected to address this specific population group:

<table>
<thead>
<tr>
<th>Strains</th>
<th>Global Immune Support</th>
<th>Influenza &amp; Respiratory tract infections</th>
<th>Inflammating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactobacillus helveticus R0011</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Bifidobacterium bifidum R0071</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bifidobacterium infantis R0033</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Lactobacillus helveticus LAF1 R010</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bifidobacterium longum R0035</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lactobacillus rhamnosus R0011</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Bifidobacterium lactis LAFTB94</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Bifidobacterium infantis HA-116</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lactobacillus rhamnosus HA-111</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lactobacillus brevis HA-112</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lactobacillus paracasei HA-196</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Conclusion

The evidence of probiotics benefits on immunity are growing strong, with proven benefits in boosting immune defences and balancing the Th1-Th2 balance. Lallemand Health Solutions continues to document the mechanistic and clinical effects of its specific strains, in particular from the Bifidobacteria and Lactobacilli species. Based on current data we have designed a portfolio of potential strains to be used alone or in combination for synergistic effect, to formulate specific probiotic solutions for targeted applications in children, adults or seniors.

In addition, the company has the long-standing probiotic formulation expertise necessary to help health supplements companies develop the right solution to differentiate itself on the immune health market. These strains can be formulated into specific solutions, associated to certain vitamins or minerals for example, in formats adapted to each target population: capsules, convenient orodispersible sticks, sachets to dissolve in drinks or food etc.

REFERENCES


4- Cazzola M, Tompkins T.A. and Materia M. G. Immunomodulatory impact of a symbiotic in TH1 and TH2 models of infection Ther Adv Respir Dis 2010a - vol. 4 no. 4 259-270

5- Cazzola M, Pham-Thi N, Kerihuel JC, Durand H, Bohbot S. Efficacy of a symbiotic supplementation in the prevention of common winter diseases in children: a randomized, double-blind, placebo-controlled pilot study. Ther Adv Respir Dis. October 2010b vol. 4 no. 5 271-278


8- Erdoğan, Özlem; Tanyeri, Bilge; Torun, Emel; Gönülülü, Erdem; Arslan, Hüseyin; Erbenek, Ufuk; Öktem, Faruk. The Comparison of the Efficacy of Two Different Probiotics in Rotavirus Gastroenteritis in Children. Journal of Tropical Medicine, Volume 2012, Article ID 787240, p 1-5.


12- Eccles et al. A study on winter infections in students. Common Cold Centre and Healthcare Clinical Trials, Cardiff School of Biosciences, Cardiff University. – Internal report – 2008


About Lallemand
Lallemand Inc. is a privately owned Canadian company specialising in the development, production and marketing of yeast and bacteria, as well as other ingredients linked to these microorganisms or their markets.

Lallemand Health Solutions
Lallemand Health Solutions (LHS) consolidates the internationally recognized probiotic manufacturers Institut Rosell and Harmonium International.
Backed by a rich history and 80 years of expertise in probiotic research and development, Lallemand Health Solutions offers a full line of ready-to-market probiotic formula and helps its partners designing their own custom & complex formulations using Harmonium, LAFTI® or Rosell Probiotic strains together with our proprietary protective technologies. Because, from the lab to the shelf, LHS controls the overall manufacturing process of its products, the company can ensure customers are receiving the highest quality standard of probiotic formulation. Cooperation spells success: we provide our partners with the full support they need to develop, register, and market their products in their own market, making of Lallemand Health Solutions a complete probiotic solutions provider.
Lallemand Health Solutions is covering more than 30 countries across five continents ready to service your probiotic needs.
For more information, please visit www.lallemand-health-solutions.com, or contact healthsolutions@lallemand.com.

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