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Chapter 42

Probiotics and Prebiotics for Prevention of Viral Respiratory Tract Infections

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1 INTRODUCTION

Upper respiratory tract infection (URTI) that presents clinically as the common cold is the most common illness in humans. It is responsible for a large absenteeism from school and work and lowers efficiency and productivity. According to US data, 12% of adults and 33% of children with URTI visit a physician, which includes an estimated 25 million individuals annually in the United States. Approximately 30% of them will receive a prescription for antibiotics. The direct medical costs related to the common cold (e.g., physician visits, secondary infections, and medications) were an estimated $17 billion in 1997. Indirect costs owing to missed work because of illness or caring for an ill child were estimated at $25 billion per year. Apart from this economic loss, billions of dollars are spent on unproven remedies (Allan and Arroll, 2014; Gern, 2010; Rerksuppaphol and Rerksuppaphol, 2012).

There are over 200 different types of viruses that cause URTI. Human rhinoviruses (HRV) are the largest group, comprising over 150 serotypes, which account for 24-52% of clinical cases. Influenza viruses, respiratory syncytial virus (RSV), and adenoviruses are also major causative agents of both upper and lower RTIs. Other viruses (e.g., parainfluenza viruses and coronaviruses) can also cause respiratory diseases, ranging from mild URTI to pneumonia. No pathogen is identified in 31-57% of URTIs, likely because of poor collection technique, low pathogen count due to sampling late in the illness, or previously unidentified agents. Recently, several new viruses associated with respiratory diseases, such as human bocavirus, human metapneumovirus, and the new coronaviruses, have been identified as well (Allan and Arroll, 2014; Lehtoranta et al., 2014b).

HRV has consistently been identified as the most common cause of the common cold. HRVs are traditionally associated with URTI, otitis media, and sinusitis. In recent years, the increasing implementation of PCR assays for respiratory virus detection in clinical laboratories has facilitated the recognition of HRV as a lower respiratory tract pathogen, particularly in patients with asthma, infants, elderly patients, and immunocompromised hosts (Goodall et al., 2014; Jacobs et al., 2013). It has been estimated that 5.2 million children under 5 years of age die every year due to preventable infectious diseases like pneumonia and diarrhea (Black et al., 2008; Bryce et al., 2005).

Strategies that are most likely to prevent respiratory infections include hand hygiene, breast milk, using a mask, administration of different immunostimulants, probiotics, prebiotics, and synbiotics. Strategies that are likely to be beneficial include regular exercise, balanced diet, adequate sleep and low psychological stress, prevention of air pollution and environmental tobacco smoke, vitamin D, vitamin A, garlic, zinc, and ginseng. The efficacy of some strategies is unknown, such as vitamin C, echinacea, and antiviral drugs (Ahanchian et al., 2012).

The importance of the gastrointestinal tract microbiota in the generation of mucosal immune responses and mucosal tolerance has been largely documented and its interaction with the respiratory pathology is a new area for research. Some studies revealed that probiotics have a preventive effect against colds. Based on a Cochrane Review of 14 randomized controlled trials, probiotics were better than placebo in reducing the number of episodes of acute URTIs and reducing antibiotic use, while there were no differences in the mean duration of an episode and no increase in adverse events (Hao et al., 2015). Fortification with probiotics, functional foods, may provide one feasible intervention to reduce the burden of common childhood morbidities such as viral respiratory infections through the modulation of intestinal microbiota and enhancing

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mucosal immunity and even can increase quality of life (Heydarian et al., 2010; Jafari et al., 2013). On the other hand, administration of antibiotics in patients with URTI has a negative effect on the immune system and resulted in incompetent virus-specific CD4+ and CD8+T cell responses (Ichinohe et al., 2011). Viral respiratory tract infections are more important in specific age groups (e.g., preterm infants or the elderly) and also individuals with underlying disease such as asthma.

1.1 Viral Infections and Asthma

In vitro infection of airway epithelial cells from asthmatic and healthy adults with HRV have demonstrated that asthmatic cells produce less IFN-β and IFN-λ making them potentially more susceptible to infection. URTI is the main cause of asthma exacerbations in children and adults and a major risk factor for admission in hospital every autumn. Asthmatic patients are concerned about acute asthma exacerbations following a common cold, asking how to minimize the risk during the winter viral season. Acute exacerbations are associated with decreased lung growth and, as such, add to both the cost and morbidity associated with asthma. Viral respiratory infections are the most common cause of asthma exacerbations in children (80-85%) and are a major risk factor for admission to a hospital. HRVs are the most common viral agents. Current drugs for the prevention and treatment of virus-induced exacerbation of asthma are poorly effective, and novel alternative therapies are needed. There are a growing number of clinical trials using probiotics, prebiotics, and synbiotics for the prevention of respiratory infections in asthmatic individuals. Proposed mechanisms include probiotics compete against pathogens; increase the barrier function in respiratory epithelium; immunostimulatory effects by enhancing cellular immunity with increased activity of natural killer cells and macrophages in airways (Hales et al., 2012; Holt and Sly, 2011).

Recent research interest has focused more on the role that respiratory viral infections play in the inception of asthma. Epidemiological studies have shown an increased risk of asthma with lower respiratory tract infection (LRTI) caused by HRV even more than RSV. It is proposed that a synergistic interaction exists between viral infection and allergic sensitization, suggesting a "two hit" model for induction of persistent asthma. This information provides a series of novel strategies for the primary prevention of asthma by the prevention of either allergic sensitization or LRTI by probiotics or immunostimulants (Ahanchian et al., 2012).

1.2 Viral Infection in Infants

Infectious disease is the most important cause of morbidity in infants. Worthy of note is that 11% of all infants are born premature that means 12.9 million infants per year worldwide. Preterm infants carry a heightened risk of infectious ailments, both bacterial and viral. RTIs are a major cause of mortality and morbidity worldwide, particularly during the early years of life, with rhinovirus being the main pathogen. Although strict hygiene measures have been shown to reduce viral transmission, no definitive preventive measures have thus far been discovered for the effective control of this entity. Gut microbiota modulation with specific prebiotics, probiotics, or both could offer a cost-effective tool in the fight against RTIs, hopefully also in the developing world (Luoto et al., 2014; Rautava et al., 2009).

2 MECHANISMS OF ACTION

Certain probiotic lactic acid bacteria strains, termed immunobiotics, can exert their beneficial effect on the host through their immunomodulatory activity. Immunobiotics have been used for the development of functional foods with the ability to stimulate mucosal immunity to provide protection in other mucosal sites distant from the gut. Studies have shown that oral administration of immunobiotics is able to increase resistance against respiratory viral infections.

The induction of antiviral cytokines such as interferons (IFNs), as well as proinflammatory cytokines and chemokines, upon antigen recognition in epithelial cells or underlying effector cells such as macrophages, dendritic cells, and neutrophils play a key role in virus infections by initiating cell-mediated viral elimination and adaptive immune responses.

The proposed mechanisms include the production of type I IFNs, the activity of NK cells, the generation of Th1 responses as well as the production of specific antibodies, and the regulation of inflammatory lung injury (Farid et al., 2011; Zelaya et al., 2014).

Probiotics mediate their antiviral effects against respiratory viruses, possibly by eliciting systemic immune responses via the gut or enhancing cellular immunity in the airways with increased activity of natural killer cells and macrophages. In the gut epithelial cells and/or antigen-presenting cells, probiotics are recognized by toll-like receptors and modulate cytokine expression patterns through epithelial cells and through underlying professional antigen-presenting cells, such as macrophages and dendritic cells.

As probiotics functions are strain dependent, different probiotic bacteria have been associated with variable stimuli to the human innate and adaptive immune system and comediate metabolic and immune homeostasis, with different levels of success. In an experimental model of lung inflammation based on the administration of the artificial viral pathogen-associated molecular pattern, in order to mimic the proinflammatory and physiopathological consequences of RNA viral infections in the lung, after oral administration of *Lactobacillus rhamnosus* CRL 1505 and CRL 1506, the authors found that CRL 1506 had no effect, whereas CRL 1505 increased bronchoalveolar lavage concentrations of interleukin (IL)-6, IFN-γ, and IL-10, and the number of pulmonary $CD3^+CD4^+IFN\text{-}\gamma^+$ T cells. The preventive effects on the respiratory airway immunity induced by CRL 1505 suggested that, if the target of probiotic administration is to prevent recurrent URTIs, an appropriate strain of *L. rhamnosus* should be selected (Esposito et al., 2014). Zelaya et al. (2014) demonstrated that the preventive treatment with the probiotic bacteria beneficially modulates the fine tune balance between clearing respiratory viruses (RSV and influenza virus) and controlling immune-coagulative responses in the lung, allowing normal lung function to be maintained in the face of a viral attack. Their data also pinpoint a crucial role for IL-10 in the immune protection induced by *L. rhamnosus* CRL 1505 during respiratory viral infections.

Moreover, studies demonstrated that *L. rhamnosus* CRL 1505 is able to increase the number of $CD3^+CD4^+IFN\text{-}\gamma^+$ T cells in the gut, induce a mobilization of these cells into the respiratory mucosa, and improve local production of IFN-γ and the activity of lung antigen presenting cells (Villena et al., 2012).

RSV susceptible infants exhibit characteristics of Th2 responses and, in general, a Th2 immune response is favored during RSV infection, especially in younger hosts. Researchers showed that treatment of infant mice with *L. rhamnosus* CRL 1505 significantly improved the production of IFN-γ in response to RSV infection and increased the capacity of mice to clear the virus. Others demonstrated that *L. rhamnosus* CRL 1505 significantly reduces lung viral loads and tissue injuries after the challenge with RSV through its capacity to beneficially modulate proinflammatory IL-10 and Th1/Th2 balances in the respiratory tract (Chiba et al., 2013). Orally administered *L. rhamnosus* CRL 1505 induces a mobilization of $CD3^+CD4^+IFN\text{-}\gamma^+$ T cells from the gut into the respiratory mucosa and improve local production of IFN-γ (Villena et al., 2012).

There is also evidence that intranasally administrated probiotics protect against respiratory virus infection by stimulating innate immune responses directly in the respiratory epithelium (Park et al., 2013). Sublingual *L. rhamnosus* protected against influenza virus infection by enhancing mucosal secretory IgA production, T and NK cell activity, and lung IL-12 levels (Lee et al., 2013) (18).

Strains of lactobacilli and bifidobacteria provide protection against respiratory virus infections also by inducing the synthesis of virus-specific immunoglobulins in the respiratory secretions and in serum (Kobayashi et al., 2011). It was reported that the oral administration of the *Bifidobacterium breve* YIT 4064 protected mice against influenza virus challenge through an enhancement of the humoral immune response (Yasui et al., 1999).

Prebiotics are defined as nondigestible, but fermentable, foods that beneficially affect the host by selectively stimulating the growth and activity of one species or a limited number of species of bacteria in the colon. Synbiotics, defined as a combination of a probiotic and a prebiotic, aim to increase the survival and activity of proven probiotics in vivo, as well as stimulating indigenous bifidobacteria and lactobacilli (Quigley, 2010). The exact mechanism involved in systemic immune modulation by prebiotics is currently unknown. They may influence host innate and T-cell responses during a respiratory viral infection by modulation of the Th1/Th2 responses in the lungs. The innate immune system of the gut may be improved by prebiotics. Several studies report an increase in intestinal mucosal surface IgA but not serum concentration of IgA, IgG, and IgM. Studies showed that changes in the microbiota induced by dietary oligosaccharides increased viral clearance and systemic Th1 responses (Schijf et al., 2012).

Figure 42.1 shows a summary of possible antiviral effect mechanisms of probiotics in respiratory virus infections:

1. Binding directly to the virus and inhibiting virus attachment to the host cell receptor.
2. Adhesion of probiotics on the epithelial surface may block viral receptor sites in a nonspecific manner, or by competing for specific carbohydrate receptors.
3. Probiotics may induce mucosal regeneration: intestinal mucins may bind to viruses and inhibit their adherence to epithelial cells.
4. Probiotics also show direct antimicrobial activity against viruses by producing antimicrobial substances.
5. Induction of low-grade nitric oxide (NO) production may have antiviral activities.
6. Modulation of immune responses through epithelial cells, macrophages, and dendritic cells (DCs).
7. After activation, $CD8^+$ T lymphocytes differentiate into cytotoxic T lymphocytes, which destroy virus-infected cells.
8. $CD4^+$ T lymphocytes differentiate into Th1 and Th2 cells.
9. T-helper cells type 1 (Th1) activates phagocytes, promoting virus killing.

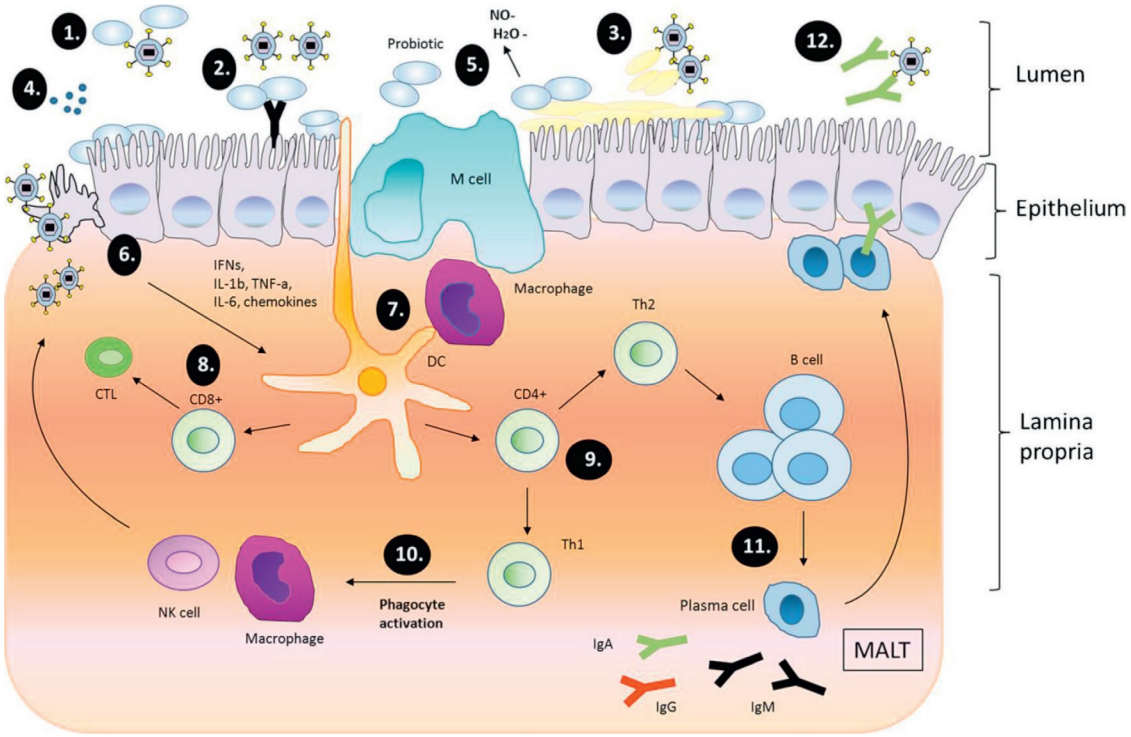

FIGURE 42.1 Schematic presentation of possible antiviral effect mechanisms of probiotics in respiratory virus infections.
Adapted from Lehtoranta, with permission.

10. Th2 cells induce proliferation of B-cells, which travel to the secondary lymphatic organs in mucosa-associated lymphoid tissue (MALT) and differentiate into immunoglobulin (Ig)-producing plasma cells, which may migrate back to the infection site.
11. Secretory antibodies neutralize the virus (Lehtoranta et al., 2014b).

3 CLINICAL TRIALS

3.1 Children

Young children have an average of 6-8 episodes of common cold per year and 10-15% have at least 12 infections per year. Children in day care centers have 50% more colds due to more exposure to the virus. Asthma and allergic rhinitis may also increase the risk of viral infections. There are several trials using probiotics in different age groups of children with or without specific underlying disorders.

3.1.1 Preterm Infants

Premature infants lack initial maturation signals as a result of their immature immune system and disturbed development of their gut microbiota. The probable causes include delayed introduction of enteral feeding, lack of fresh breast milk, frequent antibiotic use, and the environment of the neonatal intensive care unit. Consequently, these infants have more susceptibility to infections.

Identifying safe and cost-effective strategies for the prevention of RTIs are essential. A randomized trial by Lo Skiavo et al. indicated that preterm infants who were treated orally with a liquid probiotic based on *E. faecium* L3 in a dose of 0.5 ml (5×10^3 CFU) 3 times a day for 14 days had a significant decrease of the frequency of infectious complications: 20.7% against 53.9% in the control group patients (Lo Skiavo et al., 2014).

In a recent randomized, double-blind, placebo-controlled trial, 94 preterm infants (gestational age >32 and <36 weeks) were allocated to receive oral prebiotics (galacto-oligosaccharide and polydextrose mixture, 1:1), a probiotic (*L. rhamnosus* GG, ATCC 53103), or placebo between days 3 and 60 of life. A significantly lower incidence of RTIs was detected in infants receiving prebiotics (rate ratio, 0.24; 95% CI, 0.12-0.49; $P<0.001$) or probiotics (RR, 0.50; 95% CI, 0.28-0.90;

P 5.022) compared with those receiving placebo. Also, the incidence of rhinovirus-induced episodes, which comprised 80% of all RTI episodes, was found to be significantly lower in the prebiotic (RR, 0.31; 95% CI, 0.14-0.66; *P* 5.003) and probiotic (RR, 0.49; 95% CI, 0.24-1.00; *P* 5.051) groups compared with the placebo group (Luoto et al., 2014).

3.1.2 Term Infants

Infants are considered prone to infections as their immune system is not fully developed. Infections are considered one of the leading causes of death in this age group. Available, safe, and cost-effective ways to prevent infection can reduce infant morbidity and mortality. In a randomized trial, infants requiring formula before the age of 2 months were recruited, and a formula supplemented with the probiotics *L. rhamnosus* GG and *Bifidobacterium lactis* Bb-12 or placebo was administered daily until the age of 12 months. Antibiotics were prescribed for 10 out of 32 (31%) infants receiving probiotics and 24 out of 40 (60%) infants receiving placebo. During the first year of life, 9 out of 32 (28%) infants receiving probiotics and 22 out of 40 (55%) infants receiving placebo encountered recurrent respiratory infections (RR 0.51 (95 % CI 0.27, 0.95); *P*¼0.022) (Rautava et al., 2009).

In another RCT, 109 newborn infants were assigned randomly to receive *Bifidobacterium animalis* ssp. *lactis* BB-12 or placebo until the 8th month of life. At the age of 8 months, BB-12 was recovered in the feces of 62% of the infants receiving the BB-1. The infants receiving BB-12 were reported to have experienced fewer respiratory infections (65% vs. 94%; risk ratio 0.69; 95% CI 0.53, 0.89; *P*¼0.014) than the control infants (Taipale et al., 2011). A combination of *L. rhamnosus* GG and *B. animalis* ssp. *lactis* Bb12 in healthy newborns reduced the occurrence of recurrent RTIs, but not the incidence of acute otitis media (Rautava et al., 2009).

3.1.3 Healthy Children in Day Care and Schools

Children who attend day care centers are at 2-3 times greater risk for developing a respiratory tract infection than children who stay at home. This has a significant financial burden for both the family and society. Providing a reliable strategy for the prevention of day care infections is required (Hojsak et al., 2010a). Hojsak et al. conducted a RCT in 281 children who attend day care centers to receive *Lactobacillus* GG at a dose of 10^9 colony-forming units in 100 ml of a fermented milk product or placebo. Compared to the placebo group, children in the LGG group had a significantly reduced risk of URTIs, a reduced risk of RTIs lasting longer than 3 days, and a significantly lower number of days with respiratory symptoms (Hojsak et al., 2010b).

In a similar study of long-term consumption of probiotic milk containing *Lactobacillus* GG, there was also a relative reduction of 17% in the number of children suffering from respiratory infections with complications and a 19% relative reduction in antibiotic treatments for respiratory infection in the *Lactobacillus* group than placebo (Hatakka et al., 2001).

In another study, no differences were reported between the *L. rhamnosus* GG and the control groups in the respiratory symptom episodes (Kumpu et al., 2013).

A meta-analysis of RCTs investigating the role of *L. rhamnosus* GG in the prevention of respiratory infections in children showed that *L. rhamnosus* GG has the potential to reduce the risk of URTIs, incidence of acute otitis media, and antibiotic use. There were no significant differences between the *L. rhamnosus* GG and the control groups in the incidence of lower RTIs (Liu et al., 2013).

Other researchers used strains other than *L. rhamnosus* GG. The preschoolers receiving the *L. casei rhamnosus* treatment had 0.30 times lower odds of doctor-diagnosed viral infection than the control group (Lin et al., 2009). In healthy infants, treatment with *L. reuteri* SD 112 or *B. animalis* ssp. *lactis* Bb12 was not effective in reducing the incidence or duration of RTIs. *L. reuteri* SD 112 resulted in fewer days of absence from day care due to illness, lower number of days with fever, and fewer clinical visits (Niittynen et al., 2012; Weizman et al., 2005).

Some trials investigated the effectiveness of combinations of probiotics or combinations of probiotics and prebiotics (synbiotics) on URTIs. A combination of *L. rhamnosus* GG, *L. rhamnosus* LC 705, *B. breve* Bb99, and *P. freudenreichii* ssp. *shermanii* JS children reduced the occurrence of recurrent RTIs (Hatakka et al., 2007). A combination of *L. acidophilus* and *B. bifidum* in healthy children reduced the duration of acute RTI symptoms and school absence (Liu et al., 2013).

However, a combination of 12 bacteria including *Lactobacillus*, *Bifidobacterium*, *Streptococcus*, and *Enterococcus* was not able to reduce the number of RTIs (Lin et al., 2009). A mixture of four probiotic species (*L. rhamnosus* GG and LC 705, *B. breve* Bb99, and *Propionibacterium freudenreichii* ssp. *shermanii*) prescribed to pregnant mothers carrying infants at high risk for allergy for 4 weeks before delivery and infants received a synbiotic containing the same probiotics with 0.8 g of galacto-oligosaccharides, daily for 6 months after birth. During the 6-month intervention, antibiotics were prescribed less often in the synbiotic group than in the placebo group (23% vs. 28%). Throughout the 2 years of follow-up period,

respiratory infections occurred less frequently in the synbiotic group than placebo (mean: 3.7 vs. 4.2 infections) (Kukkonen et al., 2008).

Some studies showed that using a probiotic mixture might be more effective, although efficacy of the probiotic mixtures may be reduced by inhibitory effects between different probiotic strains (Kianifar et al., 2014).

Viral respiratory infections are the most common cause of recurrent wheezing episodes and asthma exacerbations in children. Probiotics may be beneficial in these children by lowering the viral infections in addition to their antiinflammatory effects. In a pilot study, the authors concluded that laser acupuncture and probiotics (a suspension of *E. faecalis*) has a beneficial clinical effect on bronchial hyperreactivity in school-age children with intermittent or mild persistent asthma and might be helpful in the prevention of acute respiratory exacerbations (Stockert et al., 2007).

In a double-blind, placebo-controlled, multicenter trial, 90 infants with atopic dermatitis, age <7 months, were randomized to receive an extensively hydrolyzed formula with *B. breve* M-16V and a galacto-/fructo-oligosaccharide mixture or the same formula without synbiotics during 12 weeks. After 1 year, the prevalence of "frequent wheezing" and "wheezing and/or noisy breathing apart from colds" was significantly lower in the synbiotic than in the placebo group (13.9% vs. 34.2%). Significantly less children in the synbiotic than in the placebo group (5.6% vs. 25.6%) had started to use asthma medication (van der Aa et al., 2011).

OM-85 BV (Broncho-Vaxom) is an immunostimulant extracted from eight bacterial pathogens of the upper respiratory tract. Several randomized clinical trials have shown that OM-85 BV can reduce the number of URTIs by 25-50% compared with placebo in adults and children with a history of recurrence. Razi et al. (2010) showed that after using 1 capsule of OM-85 per day for 10 days each month for 3 consecutive months caused a 37.9% reduction in wheezing attack in the group given OM-85 BV compared with the group given placebo. A recent study on 62 children with asthma and recurrent respiratory infection showed that OM-85 reduces the occurrence of acute respiratory infection and improves serum levels of human beta-defensins 1(hBD-1), IgA, and IgG (Liao and Zhang, 2014).

3.2 Adults and the Elderly

Despite great advances in medicine, viral infections such as the common cold continue to cause a considerable economic burden, due to loss in productivity and high medical costs. In a randomized trial, 479 healthy adults (aged 18-67) were supplemented daily with vitamins and minerals with or without the probiotic bacteria (*Lactobacillus gasseri, Bifidobacterium longum, B. bifidum*) for at least 3 months during two winter/spring periods. The total symptom score, the duration of common cold episodes, and days with fever during an episode were lower in the probiotic-treated group than in the control group (de Vrese et al., 2005). In another study, consumption of *Lactobacillus plantarum* and *Lactobacillus paracasei* reduced the incidence of acquiring one or more common cold episode from 67% in the control group to 55% in the probiotic group. Also, the number of days with common cold symptoms was significantly reduced from 8.6 days in the control group to 6.2 days in the probiotic group, during the 12-week period (Berggren et al., 2011). In healthy adults, *L. fermentum* reduced the number of RTIs and increased antigen-specific IgA formation after influenza virus vaccination (Olivares et al., 2007). A combination of *L. rhamnosus* GG and *B. animalis* reduced both the duration and severity of upper respiratory infections (Smith et al., 2013).

In Finnish conscripts who received a daily chewable probiotic tablet containing *L. rhamnosus* GG and *B. animalis* ssp. *lactis* or a control tablet, probiotics did not reduce nasopharyngeal viral occurrence. However, probiotics decreased the presence of picornaviruses after 3 months, which may imply that probiotics play a role against viruses causing the common cold (Lehtoranta et al., 2014a). In male elite distance runners, *L. fermentum* reduced the duration of RTI symptoms, but not the incidence of RTIs or the severity of symptoms (Cox et al., 2010). A recent systematic review performed by King et al. revealed significantly fewer numbers of days of illness per person, shorter illness episodes by almost a day, and fewer numbers of days absent from work in participants who received a probiotic intervention than in those who had taken a placebo (King et al., 2014).

Some studies could not show any benefit of probiotics in prevention of incidence, duration, or severity of symptoms in adult individuals (de Vrese et al., 2005; Gleeson et al., 2012; Tiollier et al., 2007; Winkler et al., 2005).

The proportion and absolute number of individuals above the age of 65 years are increasing in most countries, particularly in industrialized nations. The human immune function undergoes adverse changes with aging including involution of the thymus, decline of naive T-cell numbers, reduction in T-cell repertoire diversity, and accumulation of specific memory T cells, which potentially leads to an increased risk of infections. Achieving optimal success in preventing and controlling infections among the elderly requires new strategies to oppose the age-associated alterations of the immune system.

A meta-analysis of the results of these two independent studies concluded that consumption of yogurt fermented with *L. bulgaricus* OLL1073R-1 augmented natural killer cell activity and reduced the risk of catching the common cold (about 2.6 times lower) in elderly individuals (Makino et al., 2010). A multicentric, double-blind study, involving 1072 volunteers

(median age = 76.0 years) randomized for consumption of either dairy products containing the probiotic strain *Lactobacillus casei* or without probiotics for 3 months. Reduction in both episode and cumulative durations was also significant for all URTIs and for rhinopharyngitis (Guillemard et al., 2010).

In Japan, a multicenter study was conducted on 154 elderly persons who used day care at four facilities in Tokyo. They used fermented milk containing *L. casei* strain Shirota (LcS) and placebo drinks as control drinks and concluded that fermented milk containing LcS probably reduces the duration of acute URTIs (Fujita et al., 2013).

However, other studies using *L. casei Shirota* or a combination of *L. rhamnosus* GG, *L. rhamnosus, B. breve,* and *P. freudenreichii* had no effect on the number RTIs or the duration of RTI symptoms (Van Puyenbroeck et al., 2012).

4 SUMMARY

Acute RTIs are the most common reason for people to seek medical help in developed countries and account for up to 75% of all antibiotic use in high-income countries. In low-income and middle-income countries, severe diarrhea and pneumonia are the leading causes of infections leading to death in children younger than 5 years of age. Strategies that are most likely to prevent respiratory infections include hand hygiene, breast milk, the administration of different immunostimulants, probiotics, prebiotics, and synbiotics (Ahanchian et al., 2012).

Microbiota is shaped by genetic and environmental factors including mode of delivery; breast feeding and diet; farm or urban living; vitamin D status; and antibiotic consumption.

This knowledge stimulated interest in the use of probiotics and prebiotics as the intentional introduction and encouragement of specific microbes to shape immune system development. Probiotics and synbiotics have been used successfully for different medical problems, and a growing number of clinical trials have shown the effectiveness of their usage for the prevention and management of respiratory infections. Clinical trials in human subjects show promising data demonstrating that specific probiotic strains are able to shorten the duration or reduce the incidence of respiratory infections. However, only a few clinical studies have investigated the effects of probiotics on specific viruses.

It should be noted that the effects of probiotics are highly strain-specific and the adequate amount of bacteria transferred into the gut may be crucial. It may be too soon to judge the role that probiotics may play in the prevention of the common cold because there are many strains of probiotics with established immunomodulatory effects yet to be tried with the particular goal of seeking their effects on respiratory infections. A better understanding of the effects of different probiotic strains and their combination, selection of the most beneficial strains, the dose and timing of supplementation for various age groups, and a deeper insight into their mechanisms of action are needed for the validation of specific strains carrying a potential to modify the frequency and severity of RTIs (Homayouni Rad et al., 2013). Functional foods such as probiotic milk or yogurt containing well-defined probiotic strains may reduce the risk of catching the common cold and represent a simple, safe, effective, and available method for preventing respiratory infections especially in developing countries. Further research to establish the role of probiotics and prebiotics in the treatment and prevention of RTIs is required and should also clarify if any susceptible subgroups of respiratory diseases exist, and how these subgroups benefit from supplementation with certain probiotic strains.

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