Oral and nasal probiotic administration for the prevention and alleviation of allergic diseases, asthma and chronic obstructive pulmonary disease

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Abstract

Interaction between a healthy microbiome and the immune system leads to body homeostasis, as dysbiosis in microbiome content and loss of diversity may result in disease development. Due to the ability of probiotics to help and modify microbiome constitution, probiotics are now widely used for the prevention and treatment of different gastrointestinal, inflammatory, and, more recently, respiratory diseases. In this regard, chronic respiratory diseases including chronic obstructive pulmonary disease (COPD), asthma and allergic rhinitis are among the most common and complicated respiratory diseases with no specific treatment until now. Accordingly, many studies have evaluated the therapeutic efficacy of probiotic administration (mostly via the oral route and much lesser nasal route) on chronic respiratory diseases. We tried to summarise and evaluate these studies to give a perspective of probiotic therapy via both the oral and nasal routes for respiratory infections (in general) and chronic respiratory diseases (specifically). We finally concluded that probiotics might be useful for allergic diseases. For asthmatic patients, probiotics can modulate serum cytokines and IgE and decrease eosinophilia, but with no significant reduction in clinical symptoms. For COPD, only limited studies were found with uncertain clinical efficacy. For intranasal administration, although some studies propose more efficiency than the oral route, more clinical evaluations are warranted.

Key words: Oral probiotics: Nasal probiotics: Chronic obstructive pulmonary disease: Asthma: Allergic diseases

Introduction

The incidence of chronic pulmonary obstructive disease (COPD), asthma and allergic rhinitis has increased throughout the world. COPD, for example, is now the fourth cause of mortality, and 358 million individuals had asthma in 2015, especially during acute phases of exacerbation (i.e. AECOPD)[1]. Although the Human Microbiome Project (HPM) did not include the lower respiratory tract, it was conducted in 2008 to discover the complete human microbiome content as well as its delicate relationship with the body system in health and disease. Soon after, metagenomics studies evaluating the content and diversity of the human lower respiratory tract microbiome demonstrated that the immune system balances and adjusts the respiratory microbiome as a yin-yang model (symbiosis) so that any disruption of this inter-balance could result in a disease state. Besides, more studies after that demonstrated the impact of microbiome diversity, i.e. dysbiosis during chronic respiratory diseases. In this regard, probiotics as a set of living micro-organisms are used to amend this dysbiosis

and re-establish a good microbiome content (symbiosis). Accordingly, probiotics primarily used for gastrointestinal and inflammatory diseases such as antibiotic-associated diarrhoea and inflammatory bowel disease (IBD) are now used for acute and chronic respiratory diseases[2,3]. The underlying concept here is the effect of the intestinal immune system on other body sites such as the lower respiratory system (gut–lung axis). In this regard, probiotics administration (mostly orally) has been now largely evaluated, as promising for the prevention and treatment of acute respiratory infections such as pneumococcal pneumonia and influenza viruses, and, to a lesser extent, for chronic respiratory diseases including COPD, asthma, and allergic rhinitis with the various outcomes. Furthermore, the application of the nasal administration route, as another administration route, for some chronic pulmonary diseases is a new and interesting issue with controversial clinical trial results. Altogether, despite many studies having been carried out, not many studies have reviewed the impact of probiotics therapy for chronic

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respiratory diseases. The present review aimed to evaluate the clinical and para-clinical applications of orally and nasally administered probiotics for major chronic respiratory diseases, including chronic obstructive pulmonary disease (COPD), asthma and allergic rhinitis. In the present review, the microbiome changes in asthma, allergy and COPD are first characterised, and after evaluating the interaction of the microbiome with the mucosal immune system, therapeutic applications of oral and nasal probiotics for chronic lung diseases are described.

Microbiome changes in asthma and allergy

Asthma is an airway chronic inflammatory disease characterised by coughing, sneezing, wheezing, dyspnoea, and reversible airflow obstruction that is caused by eosinophil and mast cell-secreted inflammatory cytokines[4]. Respiratory allergic diseases such as atopy and allergic rhinitis also have a similar mechanism of pathogenicity in the lung with asthma. Despite currently available therapeutic strategies including avoiding allergens and improving the signs and symptoms through inhaled corticosteroids, β_2 agonists, and anti-leukotrienes, asthma still has no specific treatment as well as high healthcare costs during exacerbations[5]. According to the hygiene hypothesis, increased levels of hygiene and antibiotic overuse can interrupt the homeostasis of the body microbiome, promote immune system responses, and increase the risk of allergies and chronic respiratory diseases, mainly due to altering the composition of the microbiome[6,7]. A study showed that the consumption of unpasteurised and untreated cows' milk is associated with less asthma and allergy development in infants[8]. The prevalence of asthma would decrease later in childhood for infants with poor hygiene conditions as they are subjected to various populations of micro-organisms[9]. Besides, children with older brothers or sisters or those who have close contact with pets have lower rates of asthma and atopic diseases[2]. Higher exposure of non-pathogenic micro-organisms to the human body in early childhood may lead to higher stimulation and training of the immune system, and, subsequently, reduces inflammatory and allergic reactions in the body. Likewise, studies have demonstrated different lung microbiome compositions of asthmatic patients compared with healthy subjects. For example, studies showed that the colonisation rate of *Chlamydia pneumoniae* in sputum samples of non-atopic asthmatic patients was higher than that of the healthy population[10,11]. In addition, the colonisation rate of *Streptococcus pneumoniae* and *Haemophilus influenzae* in upper airways has a positive correlation with persistent wheezing, eosinophilia and higher IgE secretion[6,11-13]. Besides, the type and load of colonising bacteria, the exposure period and the genetic background are important. For example, increased loads of airway pathogenic bacteria correlate positively with hypersensitivity[12]. Therefore, any dysbiosis (replacing a healthy microbiome with bad ones) in airway/gut normal microflora may lead to the colonisation of pathological bacteria that, in turn, can cause inflammatory cascades and disease progression in the lungs[14].

Interestingly, not only is dysbiosis in the airway microbiome correlated in most cases with asthma and allergic rhinitis, but also dysbiosis in the gut microbiome may have a similar condition.

Several studies have demonstrated a significant relationship between gut microbiome composition and the exacerbation or development of allergic diseases[10-12,14,15]. Following Caesarean section delivery, diet and drug consumption during pregnancy, dysbiosis in the gut microbiome can lead to local and systemic allergic diseases in childhood[16,17]. Cesarean section delivery increases allergy to milk and eggs by two-fold[18], and also augments the risk of asthma in the first 6 years of life in children, possibly due to the increased colonisation of *Clostridium difficile* in the intestine of infants. Another study in infants with food allergies showed a decreased diversity of the gut microbiome with a significant shift toward Enterobacteriaceae rather than *Bacteroides*[19]. The colonising microbiome of a vaginally delivered infant's skin, mouth and bowel is often similar to that of the mother and correlates with a lower incidence of allergic diseases in childhood[18]. How changes in intestinal microbiome content can result in developing or exacerbating conditions in another body organ is not entirely understood. Generally, any disruption in the composition of the gut microbiome (through antibiotics, diet and lifestyle) may result in disrupting the mucosal immune tolerance mechanism, increased inflammatory responses, and disease development[20]. The biodiversity hypothesis states that the gut microbiome interacts with intestinal immune cytokines affecting lung immune system cells, and diminishes pulmonary inflammation. Hence, more diverse gut microbiota may lead to a lower risk of asthma later in life. As an example, there is a significant relationship between the presence of *Acinetobacter* spp. on the skin or in the intestinal tract and the lower prevalence of asthma as well as raising IL-10 as an immune tolerance regulator[12,15]. The role of the respiratory microbiome in developing respiratory diseases is summarised in Fig. 1.

Microbiome changes in chronic obstructive pulmonary disease

COPD is a chronic lung disease causing emphysema and airway obstruction with breath shortness, cough and sputum production. The most common cause of the disease is cigarette smoking and air pollutants, to which prolonged exposure can trigger lung inflammatory responses and lead to narrowing small airways and lung tissue destruction[21]. It is now evident that respiratory infections are a significant cause of COPD exacerbations[22,23], as many studies have shown that the load of the microbiome in COPD patients' lungs correlates significantly with the severity and progression of the disease. Although the overall structure of the microbiome remains primarily intact in COPD patients, its diversity begins to decrease, and, most often, dysbiosis may present[24,25]. In a study by Huang *et al.*[14] comparing the stable COPD patients with chronic bronchitis patients, no changes were found in the microbial composition of airways. Also, there was no difference in the structure and diversity of the microbiome of sputum before and after an exacerbation, but certain limited types of potentially pathogenic bacteria became dominant, including an increase in Proteobacteria, and a decrease in Actinobacteria, Clostridia and *Bacteroides*[14]. Also, Garcia-Nuñez *et al.*[26] showed that the microbiome diversity of lungs is decreased following COPD progression. Notably, little
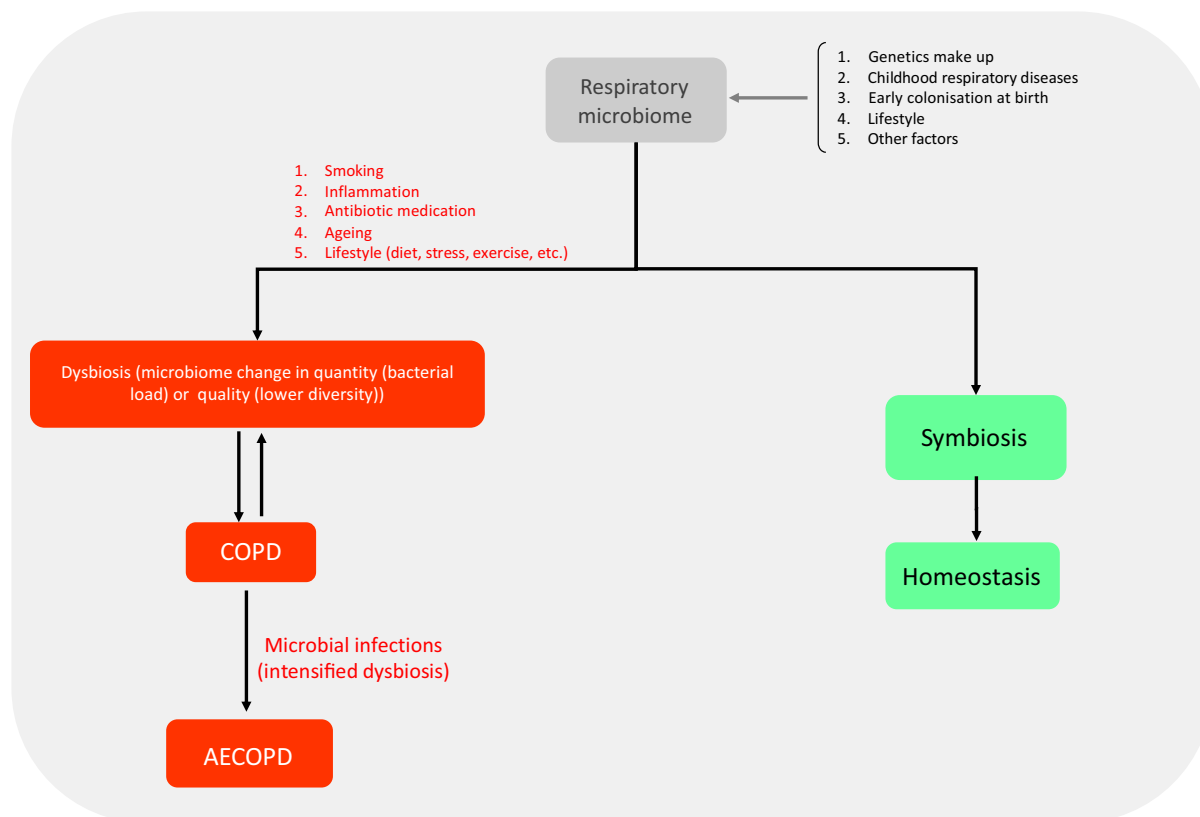
Fig. 1. Role of the respiratory microbiome in developing respiratory diseases. The structure of the respiratory microbiome is based on several factors and has a central role in promoting exacerbations. Several risk factors such as smoking are involved resulting in symbiosis or dysbiosis of the microbiome. At last, homeostasis or inflammation/infection are the outcomes of the immune system–respiratory microbiome interaction. AECOPD may be the possible outcome of this interaction. COPD, chronic pulmonary obstructive disease; AECOPD, acute exacerbation of chronic pulmonary obstructive disease.

changes could be seen in the lung microbiome both in pre- and early stages of COPD exacerbations[14,27]. In the study of Galiana *et al.*[28], the microbiome diversity of COPD patients' lungs was decreased more in the severe stage than in the mild/moderate stage, and *H. influenzae* was more prevalent in the severe stage, while Actinomycete spp. were dominant in mild/moderate stage. The relationship between lung potentially pathogenic bacteria colonisers and the severity of inflammation may be a key to understanding the pathogenesis of COPD exacerbations. The proliferation of potentially pathogenic bacteria is associated with increased airway inflammation that, in turn, provides a basis for the destruction of lung parenchyma and disease progression[14,22]. The 'vicious cycle' hypothesis argues that following cigarette smoke or other factors that mediate the disruption of the lung microbiome, an inflammation process starts in the lungs resulting in an imbalance of the protease–antiprotease system. This, in turn, leads to airway obstruction, parenchymal damage, and consequently increased colonisation of pathogenic bacteria in the lungs. Pathological evaluations of COPD airways have also shown an increase in lymphatic follicles, confirming the relationship between microbiome dysbiosis and COPD exacerbation[14].

Interaction of microbiome with the mucosal immune system

Both the upper and lower parts of the airways possess their specific immune systems. The upper airway is covered with columnar epithelial and goblet cells to deal with airway pathogenic microbes, and, through the mucociliary movements, removes germs[29]. Also, the mucous lining of these surfaces acts as a physical barrier to prevent the penetration of microbes and contains antimicrobial agents and glycoproteins such as IgA, mucins and phagocyte cells. The upper airway is distinct from the lower airway due to the presence of a wide variety of healthy microflora (mostly symbiotic Firmicutes and Actinobacteria) involved in maintaining the homeostasis of the lower airway region[30]. In the lower airways, the density of protective materials is higher so that at least twelve functionally active mucins have been identified to date[29,31].

The microbiome content helps to improve the regional immune system and functions as the first line of defence against foreign pathogens[32-34]. The lower airway microbiome originates mostly from the upper part (especially the oropharynx) that transiently migrates to the lower regions and then is consistently phagocytosed by the regional immune system (transient but not resident 'TBNR')[24]. The lymphatic tissues of the immune system diffused throughout the mucosal surfaces (including gut-associated lymphoid tissue, bronchial-associated lymphoid tissue and nasal-associated lymphoid tissue) start to develop from birth, mainly under the impact of microbial antigens[24,35]. In the intestinal mucosa, after taking up and processing foreign antigens by dendritic cells, the immune response is developed

as either an immune response or tolerance[36,37]. Production of IL-12 and interferon-γ stimulates the T helper 1 (Th1) response (cell-mediated immunity). However, IL-4, IL-5, IL-6 and IL-13 stimulate Th2 responses (humoral immunity); and releasing IL-10 and transforming growth factor-β (TGF-β) can induce dendritic cells to trigger T-regulatory cells[38]. The evolution of the immune system starting before birth is mostly mediated through Th2 immune responses, and, after birth, changes toward Th1 responses[39]. From infancy to maturity, the production of Th1 cytokines increases and prevents infancy asthma and allergy induced by the Th2 inflammatory responses. There is a reverse relationship between the serum level of IgE and the interferon-γ concentration[40]. The gastrointestinal microbiome is assumed to balance Th1/Th2 responses in the lungs. The lung microbiome promotes naive T cells to differentiate toward Th1 cells and cell-mediated immunity by recognising and attaching to pattern recognition receptors and stimulating dendritic cells to produce a large number of anti-inflammatory cytokines such as TGF-β as well as to decrease serum levels of pro-inflammatory cytokines such as TNF-α and IL-1β[41]. The gut microbiome keeps the lung healthy in two ways: (1) it modulates the lung inflammatory responses through shifting Th2 toward Th1 responses; and (2) it promotes T-regulatory responses[42]. Several studies have shown that *Lactobacillus* species induce the expression of IL-12 and TNF-α.

On the other hand, *Bifidobacterium* species diminish IL-12 and interferon-α levels and increase IL-10 levels[43]. Besides, the increased rates of *Lactobacillus rhamnosus* and *L. reuteri* in the intestine of IBD patients were associated with increased peripheral T-regulatory cells[44]. Also, the increased growth of *L. casei* could down-regulate TNF-α and decrease IL-6, possibly due to the ability to reduce activated T cells in the lamina propria[45]. This phenomenon, 'gut–lung crosstalk', states that the healthy gastrointestinal microbiome plays critical roles in establishing the mucosal immune system homeostasis, resulting in suppressing respiratory inflammatory diseases. Thus, any dysbiosis in the ecological niche may lead to chronic inflammatory diseases[12]. For example, a study suggested that following dysbiosis in the intestinal microbiome (decrease of *Lactobacillus* and *Bifidobacterium* species and increase of *Enterococcus* and *Bacteroides*), the inflammatory cytokines IL-1β, TNF-β and IL-8 were increased in the mucus of IBD patients. Furthermore, lamina propria T cells produced high levels of IL-6 that are associated with microbial dysbiosis[46-48]. Although the lung microbiome–mucosal immunity interactions have not been studied as much as the intestinal microbiome, as many studies imply, these findings draw attention to the possibility of administrating probiotic supplements containing a healthy microbiome for the treatment of acute and chronic respiratory diseases[6-9,18,20].

Therapeutic applications of oral probiotics in chronic lung diseases

According to the WHO, probiotics are live micro-organisms which, when administered in adequate amounts confer a health benefit on the host[49]. Probiotics were used for the first time in 1970 on farm animals to improve the animals' feeding and survival[50]. For humans, probiotic administration was first used to

transfer a normal microbiome from healthy individuals to irritable bowel syndrome patients (faecal bacterio-therapy)[51]. Soon, it was demonstrated that by restoring the healthy microbiome in patients and bringing it back to the normal condition, the symptoms of inflammation might be ameliorated[35]. Afterward, probiotic administration was extensively used in various infections including gastrointestinal and respiratory infections (firstly) as well as some chronic respiratory diseases. In this regard, many studies used probiotics for the treatment of gastrointestinal infections, including acute diarrhoea, antibiotic-associated diarrhoea, traveller's diarrhoea and IBD[51-57]. For example, a study showed that the successful treatment rate of antibiotic-associated diarrhoea patients treated with *Lactobacillus* GG was 70 % higher than of the controls[54]. Also, several studies have shown that administrating *Lactobacillus* GG, *Escherichia coli* Nissle, and a probiotic mixture can be as effective as the standard therapy in IBD patients[53,58]. In recent years, clinical trials with probiotics for the treatment of respiratory diseases have also increased dramatically[59-77]. Most of these studies have used oral supplements of *Lactobacillus* and *Bifidobacterium* spp. and have mostly reported the reduced severity of inflammatory symptoms in both chronic and acute respiratory diseases[58,59,78-81]. For example, a study by Hojsak *et al*.[78] showed that infants who received *Lactobacillus* probiotics were less affected by acute respiratory infections than the control group. Another study also showed that the administration of *L. gasseri* and *Bifidobacterium* probiotics could significantly reduce the duration and severity of the common cold (by as much as 2 d)[79]. A meta-analysis by Barraud *et al*.[80] evaluating the impact of probiotic administration for critically ill intensive care unit (ICU) patients showed that therapy with probiotics could reduce the duration of ICU admission by up to 2·2 d and decreased the rate of ventilator-associated pneumonia by up to 10 %. In contrast, in some studies, probiotics had no significant impact on reducing mortality rates in ICU patients[82]. For example, in a study by Gleeson *et al*.[81] evaluating the effects of a probiotic supplement during 4 months in men and women engaged in endurance-based physical activities on the incidence of upper respiratory tract infections and immune markers, they found that the number of infection episodes was significantly higher in the control group, and saliva IgA was higher in the group administrated probiotics. For more information, clinical trials that administrated probiotics for chronic respiratory diseases are summarised in Table 1. In a meta-analysis including twelve studies on therapy with probiotics in allergic rhinitis patients, administrating oral probiotics could improve at least one clinical sign, decrease the rate of exacerbations, and reduce the administration of allergic rhinitis-relieving medication in nine studies[59]. Probiotics, as anti-inflammatory agents, can suppress the increase of IgE levels in seasonal allergies and decrease allergic symptoms[83]. Furthermore, *Lactobacillus* GG probiotic consumption for at least 3 months during pregnancy and breast-feeding could reduce the rate of allergic eczema in infants due to the increase of TGF-β in breast milk[60]. Miraglia *et al*.[84] applied a bifidobacteria mixture (*B. longum* BB536, *B. infantis* M-63, *B. breve* M-16V) in children with seasonal allergic rhinitis with intermittent asthma through a

Table 1. Clinical trials that administrated probiotics for respiratory infections

Disease	Title	Intervention	Location	ClinicalTrials.gov identifier
VAP				
	Lactobacillus GG in the Prophylaxis of Ventilator Associated Pneumonia	Dietary supplement: *Lactobacillus* GG, placebo	USA	NCT00613795
	Probiotic Prophylaxis for Microbiome Modulation and VAP or Infections Prevention in Multitrauma Patients	Dietary supplement: LactoLevure® Other: placebo	Greece	NCT03074552
	Probiotics to Prevent Severe Pneumonia and Endotracheal Colonization Trial (PROSPECT)	Drug: *Lactobacillus rhamnosus* GG (probiotic), placebo (microcrystalline cellulose)	Canada	NCT02462590
	Inhibition Effects of Probiotics on Pathogens Associated With VAP	Other: *Lactobacillus* bacteria	Turkey	NCT02928042
	Lactobacillus GG in the Prophylaxis of Ventilator Associated Pneumonia	Dietary supplement: *Lactobacillus* GG, placebo	USA	NCT00613795
Influenza				
	Probiotic and Influenza Vaccination to Reducing Influenza-like Illness Incident in Elderly	Biological: Flubio Dietary supplement: Lacidofil Other: placebo vaccine, placebo probiotic	Indonesia	NCT03695432
	PRIMAGE (Probiotics, Immunity and Ageing)	Dietary supplement: prebiotic and probiotic mix	UK	NCT01066377
	Use of Probiotics to Prevent Influenza	Dietary supplement: probiotics Other: probiotic placebo	Canada	NCT01720329
	Evaluation of the Safety and Effectiveness of a Probiotic Bacterium to Boost the Immune Response to Influenza Vaccines	Biological: Fluvax Drug: PCC® (*L. fermentum* VRI 003)	Australia	NCT00294788
	Bifidobacterium Lactis HN019 Supplementation for Prevention of Influenza Infection in Healthy Adults	Dietary supplement: *Bifidobacterium* lactis HN019 Dietary supplement: placebo	USA	NCT01258842
	Effect of Drinking Fermented Milk on Immune Response	Dietary supplement: drinking fermented milk Dietary supplement: placebo Biological: seasonal influenza vaccine (H1N1, H3N2, PhuB)	Not mentioned	NCT02909842
	Safety of Synbiotics as an Adjuvant to Influenza Vaccine in Elderly	Biological: synbiotic AKSB	USA	NCT01304771
	Safety of *Lactobacillus Rhamnosus* GG Versus Placebo in Elderly Subjects Receiving Live Attenuated Influenza Vaccine (LAIV)	Biological: *L. rhamnosus* GG ATCC 53103 (LGG) Biological: placebo Biological: live attenuated influenza vaccine	USA	NCT01545349
Respiratory tract infections				
	Probiotics in Respiratory Tract Infections in Children	Dietary supplement: *L. acidophilus* DDS-1 B *lactis* UABLA-12 Dietary supplement: placebo	Ukraine	NCT01510938
	Measuring the Influence of Kefir on Children's Stools on Antibiotics (MILK)	Other: *kefir*, placebo	USA	NCT00481507
	Effect of Probiotics on Health-related Quality of Life in College Students With Upper Respiratory Infections	Dietary supplement: probiotics, placebo	USA	NCT01657643
	A Nutritional Trial on Effect of Probiotic Yoghurt Containing *Lactobacillus Rhamnosus* Yoba 2012 on Respiratory Tract Infection and Other Health Outcomes Among Children Aged 3–6 Years in Southwest Uganda	Dietary supplement: *L. rhamnosus* yoba 2012	Uganda	NCT03990220
	Lactobacillus Rhamnosus GG in the Middle Ear and Adenoid Tonsil	Dietary supplement: *L. rhamnosus* GG	Not mentioned	NCT02110732
	Rhinovirus Study with *Lactobacillus Rhamnosus* GG	Other: fruit juice with *L. rhamnosus* GG, version 1 Other: fruit juice with *L. rhamnosus* GG, version 2 Other: standard fruit juice	USA	NCT01229917
	Yogurt Study in children 2–4 Years Old Attending Daycare (SIPPY II)	Other: probiotic strain Bb-12, no Bb-12	USA	NCT00760851
	Probiotics and Infections in Children Attending Day Care Centers	Dietary supplement: probiotic Other: placebo	Finland	NCT01014676
	The Effect of a Probiotic on Upper Respiratory Tract Infections (PIP-U)	Dietary supplement: probiotic strain, placebo	UK	NCT03636191
	The Efficacy of a Probiotic Product on Acute Upper Respiratory Tract Infections (Common Cold) in Healthy Children	Dietary supplement: Probi Defendum®, placebo	Italy	NCT02640352
	Probiotics, Respiratory and Intestinal Microbiome and Respiratory Tract Infections in Children	Combination product: *Bacillus clausii* Other: sterile water	Mexico	NCT03683927

Table 1. (*Continued*)

Disease	Title	Intervention	Location	ClinicalTrials.gov identifier
	Fermented Milk on the Appearance of Common Winter Infectious Diseases	Dietary supplement: fermented milk, placebo	Italy	NCT02367612
	Effect of the Consumption of Fermented Milk on Common Infections in Adults Submitted to Multi-Stressor Situation	Other: 1. Fermented dairy product containing the probiotic *L. casei* DN-114 001 (Actimel®) Other: 2. Non-fermented dairy product (control)	France	NCT01315418
	Study of the Effect Of Probiotics on Respiratory Morbidity After Influenza Vaccination of Elderly in Nursing Homes	Drug: *L. casei* Shirota	Belgium	NCT00849277
	Bifidobacterium Animalis Subsp. *Lactis* for Lowering the Risk of Common Infections in Hospitalized Children (PROBIC II)	Dietary supplement: *B. animalis* subsp. *lactis*	Croatia	NCT01702766
	Oral Supplement for Pregnant and Lactating Mothers	Dietary supplement: milk supplement 1 and 2	Philippines	NCT01073033
	Recurrent Wheezing in Infants: Risk Factors and Prevention with Probiotics	Drug: beclomethasone, probiotics, placebo	Brazil	NCT02113072
	Impact of Probiotic Use on Immune Cell Function in Children	Dietary supplement: probiotic	USA	NCT02687503
	Probiotic Supplementation and Endurance Performance in Cyclists and Masters Runners	Dietary supplement: probiotics Other: placebo	Israel	NCT02756221
	Effect of Probiotics in Reducing Infections and Allergies in Young Children Starting Daycare (ProbiComp)	Dietary supplement: probiotic (2×10^9 CFU/d), placebo	Denmark	NCT02180581
	Effect of Probiotics in Reducing Infections and Allergies in Young Children During the Complementary Feeding Period (ProbiComp)	Dietary supplement: probiotic (10^9 CFU/d) Probiotic (10^8 CFU/d) Other: placebo	Denmark	NCT02032056
	The Effect of a Probiotic on Protection against Upper Respiratory Tract Infections in Children	Dietary supplement: probiotic, placebo	Sweden	NCT01935986
	The Effect of Probiotics on Infections in Toddlers	Dietary supplement: probiotics	Denmark	NCT00823056
Tuberculosis	Safety and Immunogenicity of Nyaditum Resae® Probiotic to Protect from Tuberculosis	Dietary supplement: Nyaditum resae® 10e4, Nyaditum resae® 10e5 Other: distilled water	Spain	NCT02076139
	Study to Evaluate the Tolerability and Immunogenicity of Nyaditum Resae® Probiotic Administered to the Pediatric Population in Contact with Tuberculosis With or Without Latent Tuberculosis Infection	*Dietary supplement: Nyaditum resae® 10e5 of heat-killed Mycobacterium manresensis* Other: placebo	Spain	NCT02581579
Common cold	Effect of Probiotic on Rhinovirus Induced Colds (MK EPRIC)	Biological: *B. animalis* subsp. lactis Bl-04 Other: sucrose	Not mentioned	NCT02679807
	Effect of Probiotic on the Innate and Adaptive Host Response to Rhinovirus (EPIARR)	Dietary supplement: *B. lactis* Bl-04, placebo Biological: rhinovirus	USA	NCT01669603
	Probiotics in Prevention of Common Cold	Dietary supplement: probiotic, placebo	Germany	NCT02013934
Rhinosinusitis	Sinonasal Microbiome Transplant as a Therapy for Chronic Rhinosinusitis Without Nasal Polyps (CRSsNP)	Procedure: microbiome transplant	Sweden	NCT03122795
	Use of Probiotics as an Adjunctive Treatment for Chronic Rhinosinusitis	Drug: probiotic containing *L. rhamnosus* R0011 strain Other: placebo	Not mentioned	NCT00396162
Sinusitis	Safety of Intranasal Irrigation Probiotics in Healthy Volunteers	Other: probiotics	Canada	NCT02933918
Pneumonia	Probiotic Enteral Administration in Mechanically Ventilated Patients	Dietary supplement: Ergyphilus	France	NCT00122408
Respiratory tract infections/asthma	Probiotics and Infections in Conscripts in Military Service	Dietary supplement: probiotic Other: placebo	Finland	NCT01651195

VAP, ventilator-associated pneumonia; CFU, colony-forming units.

double-blind randomised trial. They concluded that the bifido-bacteria mixture was able to significantly improve allergic rhinitis symptoms and quality of life. Di Pierro et al.[85] applied a mixture of *Bifidobacterium animalis* subsp. *lactis* BB12 and *Enterococcus faecium* L3 administered 3 months before or during the development of atopy and concluded that when administered in the 3 months before the development of atopy (as a prophylactic), the probiotics reduced atopy symptoms. However, reduced efficacy was not observed when the mixture was given as the treatment. Another study by Watts et al.[86] evaluated in allergic rhinitis the efficacy of a probiotic supplement (probiotik®pur; Ecologic® AllergyCare) administered orally for 8 weeks for the improvement in quality-of-life scores, and change in symptoms, and as a result, a clinically meaningful response was observed in 63 % of participants. In addition, in the study by Choi et al.[87], the oral administration of *L. plantarum* CJLP133 and CJLP243 alleviated birch pollen-induced allergic rhinitis and concluded that the oral administration of probiotics could reduce symptoms of allergic rhinitis in mice by recovering Th1/Th2 balance through increasing the Th1-type immune response. On the other hand, although many studies have demonstrated the beneficial effects of probiotics to reduce inflammatory markers in eczema and allergy patients[6-9,63,64], some studies have reported that probiotic administration neither prevented eosinophilia nor improved disease symptoms in seasonal allergic rhinitis patients[61,62] or in children with allergic diseases[65,66]. It seems that probiotics do not have any effect on immune system mechanisms leading to allergic sensitisation; instead, their major impact is to ameliorate the disease severity by suppressing the inflammatory cells involved in allergy and eczema. Several studies have reported similar results for probiotic administration for the prevention and treatment of allergic diseases and eczema in children. In a review by Cuello-Garcia et al.[67], a decline was reported in the incidence of eczema in children who received probiotics prenatally, albeit there was no such reported effect for other allergic diseases. Ye et al.[88] systemically reviewed and meta-analysed the therapeutic effect of probiotics on allergic rhinitis for a total of sixteen clinical trials (randomised controlled trials) involving 1374 patients and concluded that compared with the placebo group, probiotics could effectively reduce the symptoms of allergic rhinitis patients, and different probiotics indicated no differences in improving disease symptoms. Also, a study in 2016 showed similar results confirming the positive effects of probiotic administration on eczema and seasonal allergy[68]. Despite all, some reports have yet found no significant effects of probiotics for improving wheezing, rhino-conjunctivitis, and asthma prevention[64,66]. For asthma, since it has a chronic disease nature and is influenced by multiple genetic and environmental factors, these studies have reported different results comparing with allergic diseases. Several clinical trials examining the impact of probiotics on asthma indicated that, in contrast to allergic rhinitis, administration of probiotics by the oral route did not affect asthma[69,70]. The subjects of these studies were children and adults with mild to moderate asthma. Bacterial species used as probiotics included *L. casei*, *E. faecalis*, *L. rhamnosus* and *L. acidophilus*. Also, in studies that examined the risk of food allergy, the administration of probiotic

supplements had no significant effect on reducing food allergies or asthma[70]. Surprisingly, the study of Kalliomäki et al.[71] monitoring clinical outcomes for 5 years reported that the administration of *Lactobacillus* GG-containing probiotics even increased the risk of allergy and asthma compared with the placebo group. There are also other studies confirming no clinical efficacy of probiotic administration for asthma patients[61,72]. In the meta-analysis by Das et al.[69] probiotics had neither an impact on the prevention of asthma in at-risk infants nor for the treatment of moderate/severe asthmatic patients. However, only one study could find a positive relationship between the administration of probiotics and longer periods of no symptoms[69]. On the other hand, some studies comparing cytokine levels and inflammatory responses following the use of probiotics have indicated positive effects. Other studies reported that although probiotic administration had no significant impacts on clinical manifestations of asthma, it could decrease serum levels of IgE[73-75]. For example, the study by Chen et al.[76] showed that the daily consumption of *L. gasseri* for 2 months in 6- to 12-year-old asthmatic children had positive effects on both clinical symptoms and cytokine levels. The severity of symptoms as well as the patients' peak expiratory flow rate were improved. Another study confirmed the increased blood levels of TNF-α, interferon-δ and IL-12 in asthmatic patients[76]. It is noteworthy that there is contradictory evidence about the time of probiotic consumption and clinical findings. Probiotic consumption was more effective in reducing the risk of asthma and atopic disease while administered either prenatally or postnatally. In addition, the effect of probiotic consumption for reducing serum IgE was absolutely more evident in a long period of follow-up[71,77,89,90]. These results are in agreement with the hygiene hypothesis stating that the lack of exposure to micro-organisms in early childhood can imbalance the Th1/Th2 response and lead to IgE-mediated immune responses. Elevated levels of plasma C-reactive protein (CRP) are related to the risk of eczema and allergy to cows' milk in children. Probiotic administration can also lead to a decrease in the plasma level of CRP and can lower cows' milk related eczema and allergy before 2 years old. Also, the plasma concentration of IL-10 (as an anti-inflammatory cytokine that is inversely associated with CRP level) increases after probiotic administration. Probiotics can also induce the secretion of local inflammatory markers that correlate with a lower incidence of IgE-mediated allergic diseases[75,91]. In addition, some studies have reported that extending the period of probiotic consumption can improve therapeutic outcomes. Furthermore, the prenatal administration of probiotics is another factor that increases its effectiveness. Several investigations indicated that prenatal probiotic administration lasting until the neonatal period could reduce the severity of asthma compared with children who received probiotics only after birth[60,77,92,93], mainly due to shifting towards Th1 responses[35]. Although probiotics have more therapeutic effects in allergic diseases than asthma, serum inflammatory factors including IgE, IL-1 and TGF-β are increased in both diseases. Due to the disease's pathological nature, asthma is more chronic than other lung inflammatory diseases and has multiple pathological causes such as airway fibrosis and polymorphonuclear infiltration[4]. Accordingly, despite improving

inflammatory factors and cytokines, probiotics could not significantly improve asthma signs and symptoms. In this regard, a meta-analysis confirmed that serum IgE levels as well as atopic sensitisation are significantly decreased in patients administrated probiotics through a time-dependent manner, but had no effect on asthma[59]. Although many studies investigated therapeutic applications of probiotics in allergy and asthma patients, due to the chronic nature of COPD and the role of environmental factors in developing COPD, few studies have been done to date evaluating the clinical application of probiotics for COPD patients. In a study administrating orally *L. rhamnosus* and *B. breve* (as probiotics), and short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides (as prebiotics) on mice with emphysema (destruction of the lung parenchyma mostly seen in COPD patients), the reduced infiltration of alveolar macrophages into lungs and a subsequent reduced damage were observed[94]. Given the close relationship between emphysema and COPD in terms of clinical and epidemiological properties, it seems that probiotics could reduce the inflammation and severity of COPD. In addition, there is a potential application of probiotics for COPD management via natural killer (NK) cells. It is known that the function of NK cells is disrupted during COPD progression. Since the daily administration of *Lactobacillus* as probiotics can increase the activity of NK cells[35], probiotics administration in COPD patients can reduce inflammatory responses and symptom severity. Clinical trials that administrated probiotics for chronic respiratory diseases are summarised in Table 2.

Overall, studies to evaluate the clinical efficacy of probiotics for the treatment of COPD are limited. Although most of these studies demonstrate a considerable change in the blood level of inflammatory cytokines, indicating some para-clinical efficacies, there are limited benefits of the therapeutic efficacy of probiotics to improve COPD. Since several environmental and personalised factors are involved in the pathophysiology of COPD, the clinical success of probiotic therapy in these patients needs more analytical case–control and cohort assessments. Taken together, the clinical efficacy of probiotic administration for the prevention and amelioration of chronic respiratory diseases can be classified as follows: (1) in allergic rhinitis and eczema: probiotics are effective for the improvement of clinical symptoms, exacerbation periods and inflammatory markers; (2) in asthma: probiotics could only reduce blood inflammatory cytokines, with only a few reports for improving the clinical symptoms; and (3) in COPD: the studies are so limited with no definite conclusion, warranting more investigation.

Nasal administration of probiotics for chronic respiratory diseases

The route of probiotic administration is one of the most important factors affecting its efficacy. Until now, most studies evaluating the effect of probiotics have paid attention to the oral administration route, while the nasal administration route has less been considered. More recently, however, other routes, including the nasal administration route, have been examined in several studies for the administration of probiotics in respiratory

diseases with significant results[95]. The nasal route makes it possible for the formulated probiotic to arrive directly and affect the lungs. The intranasal administration of probiotics was used first in 2001 for the treatment of influenza disease, due to the possibility to directly access the target organ[95]. Some studies have shown that the use of this method in patients with influenza H1N1 reflects significant clinical and para-clinical advantages over the oral route[90,95-98]. Since then, several studies have been conducted for the intranasal administration of probiotics mostly against the influenza virus, pneumoviruses (PVM) and syncytial virus infections through animal models and the results have shown an increased level of pro-inflammatory cytokines and a significant reduction of disease severity[99-106]. Some studies on nasal probiotic administration for respiratory infections are summarised in Table 3. For example, in a study by Youn et al.[104], it was shown that probiotic nasal administration not only decreases viral titration in chicken pulmonary tissues but also diminishes the disease transmission between chickens, suggesting that nasal probiotic therapy is a good approach to increase the efficacy of chicken vaccination against animal transmissible viral diseases. Besides, the studies of Yang et al.[102] and Yeo et al.[105] separately introduced the nasal administration route as an effective method to increase immunity against the influenza virus to diminish mortality rates and sequels. These studies claimed that the intranasal route is more efficient than the oral route due to increasing T cell-mediated immunity in the nasal group[102,105]. Overall, intranasal studies on H1N1 infections confirmed the effective role of probiotics for the treatment of influenza through stimulating the Th1 response and changing IL-10 and IL-12 cytokines to result in the involvement of T-regulatory cells and balance the immune system. Besides viral infections, nasal probiotics have also been used for bacterial respiratory infections including pneumococcal pneumonia[107,108], otitis media[109] and chronic sinusitis[110], and promoting immune systems for defence during infections[96,111]. Probiotic administration was also effective in allergic reaction responses, as evaluated in some studies. Co-administration of the nasal probiotic *L. plantarum* with some allergens such as Derp1 and BetV1 was studied and the results showed that immune cells were induced to produce interferon-γ, IL-12 and IL-10 for higher activating Th1 cells, and to decrease significantly eosinophilia in bronchoalveolar lavage (BAL) samples[112]. Also, serum factors that play an important role in allergy formation are more reduced through the nasal administration route. In addition, due to the increase in IgA levels in mucosal surfaces, probiotics can play a preventive role for allergies. These results show that nasal probiotics can be used to reduce the severity of allergic reactions[112-114]. Finally, some studies that compared the efficacy of oral and nasal probiotics have mostly claimed that the nasal route can be clinically more effective than the oral route for respiratory diseases. For example, the study of Pellaton et al.[90] compared the impact of oral and nasal probiotics administration on airway inflammation, showing that although the infiltration of inflammatory cells was decreased in bronchoalveolar lavage (BAL) fluid for both routes, it was statistically significant only in the nasal group with the following changes: a reduction in the number of infiltrating neutrophils, lymphocytes, and eosinophils, a reduction in the level of IL-5 and IgE; a reduction in resealing exotoxins from inflammatory cells; and an increase in the number

Table 2. Clinical trials that administrated probiotics for chronic respiratory diseases

Disease	Title	Intervention	Location	ClinicalTrials.gov identifier
Allergic rhinitis				
	The Efficacy and Safety of Probiotics eN-Lac® Capsules of Children with Perennial Allergic Rhinitis	Probiotics: *Lactobacillus paracasei* GMNL-32 (eN-Lac®) Other: placebo	Taiwan	NCT01116778
	Effect of Probiotic *Lactobacillus Paracasei* Lp-33 for the Management of Rhinitis in Individuals Sensitized to Allergens (BionAtlanta)	Dietary supplement: placebo Dietary supplement: *L. paracasei* LP-33	France	NCT01096615
	Probiotic Administration and Perennial Allergic Rhinitis	Dietary supplement: *L. paracasei* probiotic strain Dietary supplement: placebo	Switzerland	NCT01779895
	Influence of Probiotics on Prevention of Atopy, Atopic Disease and Immunological Responses	Dietary supplement: probiotics Other: placebo	Singapore	NCT00318695
	House Dust Mite Allergen Reduction in Bedding: Purotex Impregnated Covers of Bekaert Textiles (Purotex Covers)	Other: use of Purotex-treated bedding covers Other: placebo	Belgium	NCT01997606
	The Anti-allergic Effects of Specific Probiotics	Behavioural: probiotic or placebo yogurt consumed daily Device: Mini Rhinoconjunctivitis Quality of Life Questionnaire Procedure: blood sample, nasal lavage	Canada	NCT00480129
	Effect of a Probiotic on Seasonal Allergic Rhinitis Symptoms	Dietary supplement: probiotic, maltodextrin	Germany	NCT01653652
	Use of Probiotic Bacteria in the Prevention of Allergic Disease in Children 1999–2008	Drug: mixture of probiotic bacteria and prebiotic oligosaccharide	Finland	NCT00298337
	Immune-modulatory Effect of Probiotic Strain on Grass Pollen Allergic Individuals	Dietary supplement: maltodextrin, probiotic	Switzerland	NCT01660698
	Effect of a Probiotic on Grass Pollen Allergic Rhinitis Subjects	Dietary supplement: *L. paracasei* fermented milk	Switzerland	NCT01150253
	Probiotics for Birch Pollen Allergy	Biological: *L. acidophilus* and *Bifidobacterium lactis* Biological: placebo	Finland	NCT00746226
Asthma				
	Safety of VSL#3 in Adult Asthmatics	Biological: VSL#3, VSL#3 or placebo	USA	NCT00852124
	The Effect of Probiotics on Asthma Risk in Animal Laboratory Workers (prob&asthma)	Drug: probiotic formula Other: placebo oral capsule	Brazil	NCT03021161
	Probiotics and Allergic Diseases (Probiotics)	Biological: LP GMNL-133 capsule, LF GM-090 capsule, LP GMNL-133 + LF GM-090 capsule, placebo	Taiwan	NCT01635738
	Oral Probiotic Administration to Modulate the Airway Microbiome in Obese Asthmatic Subjects	Dietary supplement: Seeking Health ProBiota Bifido	USA	NCT03157518
	Probiotics and Capsaicin Evoked Coughs (PCEC)	Dietary supplement: BioGaia-DSM17938 Other: placebo comparator: placebo control	Canada	NCT03603522
	Prevention of Asthma and Allergy by Probiotic *Lactobacillus* GG (FRALAC)	Drug: *L. rhamnosus* strain GG ATCC 53103 (LGG, 10^{10} CFU)	Germany	NCT00490425
	Use of a Probiotic Supplement to Prevent Asthma in Infants	Dietary supplement: probiotic, placebo	USA	NCT00113659
Allergy				
	Primary Prevention of Allergic Disease in Early Child by *Lactobacillus Reuteri*	Dietary supplement: *L. reuteri* Dietary supplement: placebo	Philippines	NCT01285830
	Effects of the Direct Interaction Between *Streptococcus Salivarius* 24SMBc and *Streptococcus oralis* 89a and the Respiratory Epithelium in Children	Combination product: *Streptococcus salivarius* 24SMBc + *Strept. oralis* 89a Combination product: fluticasone + mometasone Other: placebo	–	NCT03449836
	Pre-, Peri- and Postnatal Programming and Origins of Disease: Early Targeting the Epidemics of Allergy and Overweight (NAMI)	Behavioural: dietary counselling and placebo, dietary counselling and probiotics, dietary supplement: placebo capsules	Finland	NCT00167700
	Double Blind Controlled Trial of an Extensively Hydrolysed Formula With a Probiotic *vs.* an Extensively Hydrolysed Formula Without a Probiotic	Other: extensively hydrolysed formula with a probiotic, extensively hydrolysed formula without a probiotic	Netherlands	NCT01181297
	Oral Probiotics to Allergic Pregnant Mother and Their Offspring to Prevent Allergic Disease	Diagnostic test: physician diagnoses a history of asthma or eczema or allergic rhinitis or healthy pregnant women	Taiwan	NCT03873792

Table 2. (*Continued*)

Disease	Title	Intervention	Location	ClinicalTrials.gov identifier
Asthma Allergic rhinitis	Influence of Probiotic VSL#3 Administration on Metabolic and Immunological Profile of the Milk of Breastfeeding Mothers	Dietary supplement: VSL#3 probiotic preparation Other: placebo VSL#3	Italy	NCT01367470
	Influence of Probiotics on Atopy With Focus on Respiratory Allergic Diseases- Follow-up to 7 Years	–	Singapore	NCT00826189
	Primary Prevention of Atopic Disease by Perinatal Administration of Probiotics	Dietary supplement: probiotic bacteria, placebo	Netherlands	NCT00200954
	Influence of Probiotics on Atopy, Immunological Responses and Gut Microflora - Follow-up to 5 Years	Dietary supplement: probiotic Other: placebo	Singapore	NCT00365469
	Prevention Allergic Disease of Infant With Probiotics During Pregnancy and Neonatal Period	Dietary supplement: *L. rhamnosus* GG	Taiwan	NCT00325273
	Seasonal Allergic Rhinitis Study (SAR)	Dietary supplement: *L. casei* Shirota (LcS) Dietary supplement: placebo	UK	NCT01123252
	Impact in Off-spring of Mothers after Perinatal Daily Intake of a Probiotic	Dietary supplement: probiotic Biological: placebo	Norway	NCT00159523
Allergy/asthma	Beneficial Effects of *Lactobacillus Reuteri* DSM 17938 Supplementation on Asthmatic Children	Dietary supplement: antileukotrienes + *Lactobacillus reuteri*, antileukotrienes + placebo	Italy	NCT01241084
	Probiotics in the Prevention of Allergies, Obesity and Caries (ELEFANT)	Dietary supplement: *Lactobacillus* F19, placebo	Sweden	NCT00894816
COPD	Prevention of Acute Exacerbation in Subjects With COPD by Bacterial Decolonization in the Lower Respiratory Tract (PAEAN)	Dietary supplement: oral probiotics Drug: aerosol-inhaled amikacin Biological: combined vaccination	China	NCT03449459
Respiratory tract infections/asthma	Probiotics and Infections in Conscripts in Military Service	Dietary supplement: probiotic Other: placebo	Finland	NCT01651195

CFU, colony-forming units; COPD, chronic obstructive pulmonary disease.

Table 3. Studies of nasal probiotic administration for respiratory infections

Administration route	Disease	Aim/target group	Probiotics (administration)	Immunological effects	Clinical effects	Reference
Nasal (v. oral)	H1N1	Immune evaluation/mice	Lactobacillus paracasei and L. plantarum (12 episodes in 4 d)	↓ Eotaxin and IL-5 ↓ Eosinophilic inflammation ↑ Neutrophilia, macrophage infiltration	–	(90)
Nasal	H1N1	Immune evaluation and survival efficacy/mice	L. casei Shirota (3 d, three times per d)	↑ Cell immunity in the airway; no significant differences in IL-12, TNFα, IL-4	↑ Survival rate ↓ Influenza viral titre	(95)
Nasal (v. oral)	H1N1	Immune evaluation and survival efficacy/mice	L. rhamnosus, live and dead (21 d before exposure)	↑ IL-12, IgA ↓ IL-6, TNFα	↑ Survival rate	(96)
Nasal	H1N1	Immune evaluation and survival efficacy/mice	L. pentosus (once daily for 3 d)	↑ Splenic NK activity, modulating the Th1/Th2 induced (IL-12) and (IFNγ)	↑ Anti-allergic effects ↑ Survival rate	(97)
Nasal	H1N1	Immune evaluation and survival efficacy/mice	L. rhamnosus GG (3 d, once per d)	↑ IL-1β, TNFα, MCP, IL-12	↓ Disease symptoms ↑ Survival rate	(98)
Nasal	Pneumovirus infection	Immune evaluation and preventive efficacy/mice	L. plantarum and L. reuteri (on day 7 and 14 before PVM challenge)	↓ IFN inducible protein (CXCL10/IP-10) ↓ TNF and exotoxin-2	↑ Survival rate against lethal sequelae	(99)
Nasal	RSV	Immune evaluation and preventive efficacy/mice	Lactobacillus Lr05-Lr06 (2 consecutive days)	↑ IFNα, IFNβ and IL-10	Viable Lr-05 and Lr-06 strains increase infant mouse resistance to RSV infection; only heat-killed Lr-05 increased resistance	(101)
Nasal (v. oral)	H9N2	Immune evaluation and preventive efficacy/chickens	L. plantarum (on days 1, 2 and 3)	↑ T cell responses and mucosal sIgA and IgG levels	Stronger immune responses; effective protection against challenge; reduced body weight loss	(102)
Nasal	Influenza virus	Immune evaluation and therapeutic efficacy/mice	L. fermentum (six times in 21 d)	↑ Th1 cytokines ↓ IL-2, IFNγ, IL-4, IL-5, IL-10 (or unchanged)	Efficiently improves resistance against lethal influenza infection	(105)
Nasal	Pneumonia virus of mice	Immune evaluation and therapeutic efficacy/mice	L. plantarum and L. reuteri (on days 7 and 14)	↓ Suppression of proinflammatory cytokines ↓ Neutrophil recruitment to the lung	↑ Survival rate	(106)
Nasal (v. oral)	Pneumococcal infection	Immune evaluation and preventive efficacy/mice	L. rhamnosus (5 d after BCD)	↑ Respiratory innate immune response	↓ Pneumococcal colonisation of lung and bacteraemia	(107)
Nasal	Pneumococcal pneumonia	Immune evaluation and preventive efficacy/mice	L. rhamnosus CRL1505 (2 consecutive days)	↑ TNFα, IFNγ and IL-10	↓ Permeability of the BAL–capillary barrier, and general cytotoxicity ↓ Lung tissue damage	(108)
Nasal	Otitis media	Therapeutic efficacy/children	Streptococcus sanguinis and L. rhamnosus (one dose 10 d before surgery)	↓ IL-1, IL-6 and IL-8 ↓ IL-10 (not significant)	Significant clinical recovery considering the lower fluid level and more air in the middle ear	(109)
Nasal	Pneumococcal infection	Immune evaluation and preventive efficacy/mice	L. rhamnosus CRL-1505 (2 d)	↑ Spleen and lung B cells ↑ Anti-pneumococcal antibodies	Less susceptibility to Strept. pneumoniae	(116)
Nasal	Otitis media	Therapeutic efficacy/children	Strept. salivarius and Strept. oralis (one dose)	–	↓ Risk of otitis media ↓ Severity grade	(117)

NK, natural killer; Th1, T helper 1; Th2, T helper 2; IFN, interferon; MCP, macrophage chemotactic protein; PVM, pneumoviruses; RSV, respiratory syncytial virus; sIgA, secretory IgA; BCD, balanced conventional diet; BAL, bronchoalveolar lavage.

Probiotics and allergic and respiratory diseases

Table 4. Studies of nasal probiotic administration for chronic respiratory diseases

Administration route	Disease	Aim/target group	Probiotics (administration)	Immunological effects	Clinical effects	Reference
Nasal	Allergy (induced by rParj1)	Immune evaluation/ mice	VSL-3 mixture (on days 1–4 and 6–9 before exposure)	Induced maturation and cytokine production by dendritic cells ↑ IL-10 and IFNα ↓ Serum-specific IgG1 ↓ Lung IL-13 and IL-4	–	[111]
Nasal	Allergy (induced by Derp 1)	Immune evaluation and preventive efficacy/mice	*Lactobacillus plantarum* (on days 1, 2, 3, 4 and 7, 8, 9 and 10)	↑ IFNγ and IL-12 and IL-10 ↓ Allergen-specific IgE ↓ BAL eosinophilia	Prevent the development of the allergic response	[112]
Nasal	Birch pollen allergy	Immune evaluation/ mice	Bet v 1-producing *L. plantarum* and *Lactococcus lactis*	↓ IgE ↓ IL-5 ↑ sIgA	–	[113]
Nasal (*v.* oral)	Allergy	Immune evaluation/ mice	*L. casei*	↑ IL-17 ↑ Serum BLG-specific IgG2a and IgG1 responses No BLG-specific IgE	–	[114]
Nasal (*v.* oral)	Allergic rhinitis	Therapeutic efficacy/ adults	Combined live *Clostridium* and *Bifidobacterium* capsules (Changlekang) (6 weeks)	↑ IL-10 and TGF-β1	Improve ocular symptoms and the quality of life in allergic rhinitis patients. Not significant improvement in symptoms score and quality of life score	[118]
Nasal	Allergic asthma	Preventive efficacy/ mice	*L. rhamnosus* GG and *L. rhamnosus* GR-1 (eight times on days 1–4 and 8–11)	↓ BAL eosinophil counts ↓ Lung IL-13 and IL-5 ↓ Serum Bet v1-specific	↓ Airway hyperreactivity	[119]

IFN, interferon; BAL, bronchoalveolar lavage; sIgA, secretory IgA; BLG, bovine β-lactoglobulin; TGF-β1, transforming growth factor-β1.

of nasal cavity T-regulatory cells and FOXP3 (forkhead box P3) cells expressing CD25 and CD5. All these changes can lead to a reduction in the severity of inflammation in the lungs. The increased efficacy of intranasal probiotics in comparison with the oral route can be due to the stronger stimulation of airway immune cells in the nasal cavity and upper respiratory tract. In addition, the direct entrance of these bacteria into the airways could lead to replacement of the pathogenic microbiome (dysbiosis) with the healthy one (symbiosis), which in turn decreases the rate of acute exacerbations. In addition, previous studies have demonstrated that only 20 % of inhaled drugs for asthma are absorbed through the lung tissue and the remaining is absorbed and metabolised systemically resulting in systemic complications[115]. Accordingly, it seems that nasal administration can cause systematic effects by stimulating mucosal lymphoid tissues in the gastrointestinal tract. Also, symbiotic bacteria living in the gastrointestinal tract can prevent the entrance of unknown pathogens to deeper parts by maintaining the integrity of the epithelial wall[110]. Such a mechanism could probably apply to inhaled probiotics. Some important studies on nasal probiotic administration for chronic respiratory diseases are summarised in Table 4. In general, the results of intranasal probiotic studies for respiratory infections and also some allergic diseases may suggest that nasal probiotic administration can efficiently help to modulate immune responses and decrease the severity of immune reactions for chronic respiratory diseases including asthma, COPD and allergy, even

sometimes more applicable than the oral route. However, how probiotics affect the airway immune system of the lungs and respiratory system, and what is the exact mechanisms of the interaction is still poorly understood and warrants further studies.

Conclusion

Different studies have various conclusions about the impact of the administration of probiotics in chronic respiratory diseases. Although they have shown the effectiveness of probiotics mostly for the prevention (and in some cases for the treatment) of digestive diseases, there are controversial results for probiotic administration in some chronic respiratory diseases. For allergic diseases, it is found to be effective; for asthmatic patients, it can modulate the serum cytokines and IgE and decrease eosinophilia, but with no significant reduction in clinical symptoms; and for COPD, only limited studies were found with uncertain clinical efficacy. It seems that this efficacy depends on various factors including the type of disease, duration of administration, environmental and personal factors and, most importantly, the route of administration. For intranasal administration, some studies propose more efficacy than the oral route. The direct entrance and contact of a probiotic micro-organism to respiratory epithelial cells might be a reason why the nasal administration is more effective. It is noteworthy that nasal probiotic

administration most often was used for acute respiratory diseases/infections (although allergic rhinitis is a chronic inflammatory condition), but it could provide a promising approach for other chronic inflammatory conditions. In general, due to limited studies performed now, it is difficult to determine the impact of nasal administration of probiotics definitively, and it warrants more investigation.

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Nutrition Research Reviews

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