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Probiotics and immune modulation: reducing risk for cold and flu

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Abstract

The common cold and flu are very common human diseases affecting all age groups. There are no cures for the common cold which is caused by over 200 viruses, although vaccines against influenza viruses are available. The potential beneficial effects of probiotics for the common cold have been widely studied. Meta-analyses show that probiotics have general benefits, with some strains performing better than others. This review focuses on the effects of probiotics on the common cold and flu. We discuss the aetiology of and immune responses to cold viruses and the possible mechanisms of action of probiotics. In addition, we review specific clinical studies investigating probiotic efficacy in respiratory infections in children and adults. We also discuss whether probiotic consumption for reducing risk of colds and flu could result in cost savings for society.

Introduction

The health effects of probiotic consumption for various diseases are being increasingly investigated. Benefits include amelioration of acute and antibiotic-associated diarrhoea, a reduction in the risk of respiratory infections and atopic dermatitis, improvement in childhood milk allergy, and relief of irritable bowel syndrome. The exact mechanisms by which probiotics elicit these benefits are unknown, but many likely involve interactions with the immune system and are disease and probably probiotic strain specific [1]. As probiotics are considered dietary supplements and not pharmaceuticals, their use and associated health benefits are not systematically documented.

This review focuses on probiotics and on the most common infectious disease in mankind: the common cold. We discuss the aetiology of cold viruses, the immune responses they provoke and the possible antiviral mechanisms of probiotics from the viewpoint of immune modulation. In addition, we review clinical studies investigating the use of specific probiotics in respiratory infections. Finally, we discuss the economic aspects in terms of probiotic consumption for the prevention of colds and flu and possible cost savings for society.

Aetiology of colds and flu

Acute upper respiratory tract infection, also known as the common cold or flu, is the most common disease in humans. It consists of a heterogeneous group of mostly mild upper respiratory tract illnesses, with symptoms including na-

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sal congestion, runny nose, sore throat, cough, headache, and, especially in children, fever. The prevalence of the common cold is particularly high in children who on average have six to ten episodes annually compared to two to three episodes in the adult population. In addition, the duration of symptoms is longer in children compared to adults [2]. The high incidence and recurrence rate place a heavy burden on national healthcare services as the common cold is a leading reason for general practitioner visits and for antibiotic prescriptions in children. In addition, the common cold and flu have a significant impact on quality of life and are associated with indirect costs due to absenteeism from work and from school/day care [3, 4].

In a majority of cases the common cold is caused by over 200 types of known cold viruses. The most prevalent viruses are picornaviruses (rhinoviruses and enteroviruses) which have more than 150 serotypes. Together with coronaviruses, these pathogens account for most common cold episodes [5, 6]. Cold viruses spread via nasal secretions that can be transmitted through the air or by hand-to-hand and surface-to-hand contact. The highest viral concentrations in nasal secretions occur during the first 3 days of infection.

As the common cold is caused usually by a virus, current treatment is limited to pharmacological agents directed at specific symptoms. These treatments (antihistamines, nasal decongestants and analgesics) have limited effectiveness, generally relieving the target symptom by only 15–25% at the peak of activity, and are associated with bothersome side effects. There are no effective preventative medicines for virus-associated colds and flu apart from seasonal influenza vaccines. However, some dietary supplements have shown benefits when taken prophylactically for the common cold. Vitamin C has shown consistent benefits for shortening cold episodes in meta-analyses, but the evidence is less reliable for vitamin D, zinc, yeast β-glucans, *Echinacea purpurea* and ginseng [7–10]. Recent meta-analyses show that probiotics could offer clear benefits against upper respiratory illnesses [11].

Immune responses against cold and flu viruses

The common cold starts with the entry of a cold virus into respiratory epithelial cells. The virus replicates inside these cells causing an anti-viral innate immune response [12]. After a few hours, the infected cells secrete cytokines and interferons which alert yet uninfected cells to the presence of the virus and cause them to upregulate their virus defence mechanisms. At the same time cytokines attract and activate innate immune cells, such as neutrophils and monocytes, that contain the early infection and induce further signalling of the innate immune response. Also attracted are natural killer (NK) cells that are able to kill virus-infected cells. A few days after infection, the presence of viral antigens and the activation of innate immunity leads to the induction of mucosal IgA and T helper 1 (Th1) dominated immune responses. The Th1 immune response specifically targets intracellular pathogens and is characterized by the presence of the cytokines interferon gamma (IFN-γ) and interleukin-12 (IL-12). At the same time, the viral loads in the respiratory epithelium start to decline. The Th1 immune response finally eradicates the virus and generates memory T cells that can respond to secondary infections more rapidly. In addition, protective IgG antibody levels against secondary infection are established about 1 week after the primary infection.

The Th1 immune responses and inflammation are controlled by the secretion of the anti-inflammatory cytokine IL-10 and by the action of regulatory T cells (Treg). Activation of the immune cells is important for defence against respiratory viruses, but on the other hand, the host inflammatory response is the major cause of symptoms [13]. For example, symptom severity during rhinovirus infection has been shown to correlate with host inflammatory response. Interestingly, subclinical common cold infections may pass unnoticed, and in fact approximately 10–20% of rhinovirus carriers are asymptomatic [14]. This indicates that the inflammatory response that causes the symptoms may not be necessary to eradicate the virus.

Potential mechanisms of probiotics against cold viruses

Probiotics are likely to have an impact throughout the gut mucosa by balancing the local microbiota, by inhibiting the growth of pathogenic microorganisms [15], and by stimulating local and systemic immune responses [16]. As already mentioned, many probiotic health benefits are strain specific, and not species or genus specific [1] Therefore, no single probiotic strain will provide all the desired benefits, not even strains of the same species, and not all strains of the same species will be effective against particular conditions [17]. The specific interaction of probiotics between the cells and other microbes in the gut is thought to be the result of metabolites produced by probiotics and the structure of the cells. Probiotics are recognized by an array of receptors in and on the immune cells that activate a network of genes and proteins creating a signature response to the specific microbe.

The most important site of immunomodulatory probiotic action is the small intestine, which is less densely populated by the commensal microbiota and has a thinner mucus layer. These conditions allow relatively high temporal probiotic concentrations to be achieved in the small intestine where there is close contact between the epithelium and immune cells. Probiotics have been shown to adhere to the mucosa and intestinal epithelium, thus competitively excluding pathogen attachment, which improves probiotic survival in the intestinal tract (Fig. 1). Probiotics secrete immunomodulatory compounds that directly influence the function of the underlying epithelium. The interaction of some probiotics with the epithelium has been shown to strengthen the epithelial layer, decreasing the passage of harmful microbial metabolites through the epithelium, thus reducing the inflammatory stimulus. Probiotics also induce the production of antimicrobial substances and the secretion of sIgA into the lumen, contributing to the control of microbiota and anti-pathogenic activity.

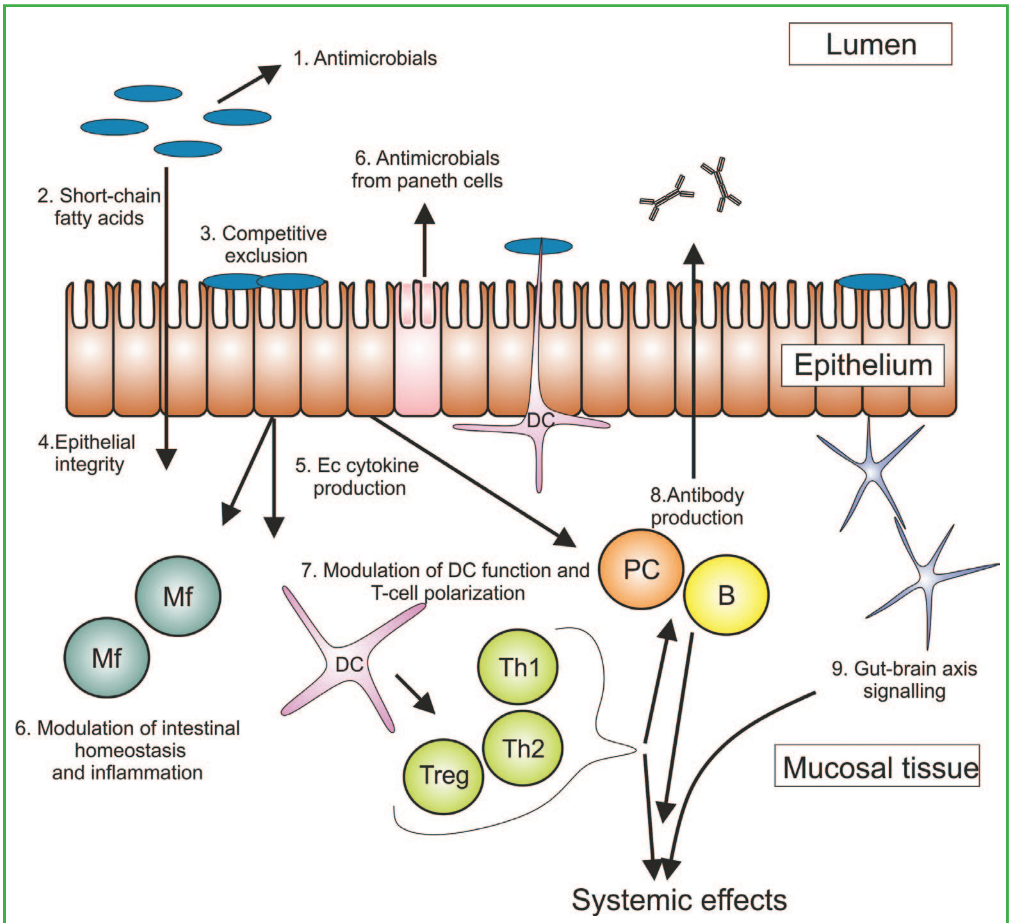

Figure 1 - Schematic presentation of the mechanisms of probiotic action. Probiotics produce antimicrobial molecules (1) that inhibit the growth of other bacteria. In the gut lumen, short-chain fatty acids (2) decrease pH levels, thus inhibiting pathogen growth, and also act as an energy source for the epithelium. (3) Probiotics bind to the epithelium, restricting access by other bacteria. (4) Interaction with the epithelium increases tight junction integrity between the cells and (5) modulates cytokine expression thus affecting immune cell function involving macrophages, dendritic cells, T cells and B cells. (6) Furthermore, probiotics improve homeostasis in the intestine by stimulating the production of antimicrobial agents from the epithelium. (7) Dendritic cells sense the cytokine environment and scan the lumen for microbes which collectively determines what type of signals will be delivered to naive T cells that will develop into different lineages with specific functions. Some T and B cells may travel to other sites in the body (systemic effects). (8) One of the T cell functions is to help facilitate antibody production. Signals from the epithelium also have an impact on antibody production.
(9) Probiotics have an impact on the gut–brain axis that may influence hormonal regulation of the entire immune system. *B* B cell, *DC* dendritic cell, *Ec* epithelial cell, *Mf* macrophage, *N* neutrophil, *NK* natural killer cell, *Th* T-helper cell, *Treg* regulatory T cell

Epithelial cells simultaneously send signals to immune cells in the mucosal tissue (lamina propria) which change and modulate the function of the intestinal tissue and the immune cells.

The mechanism of modulation of respiratory immunity by intestinal immune stimulation has not been clearly established. However, it is known that about three quarters of all immune system cells are located in the intestine that acts as a main priming site for the entire immune system. The importance of the microbiota is exemplified by germ-free mice that have under-developed immune systems and are more prone to pathogens. Thus, signals derived from microbiota are essential for the homeostasis of the intestinal and extra-intestinal immune system. These signals drive the development of the immune system from birth and maintain homeostasis throughout the life of an organism [18]. As probiotics may change the composition of gut microbiota, its metabolism and interaction with immune system cells, changes induced by probiotics alter the function of the immune system cells in the intestine and these effects may be transferred to respiratory tract immune responses as well. The exact mechanisms of how the effect is transmitted are still somewhat speculative, but are likely to include trafficking of the immune system cells between tissue compartments, microbial metabolites release into the circulation and hormonal regulation of the immune system by the gut–brain axis [19–21] (Fig. 1).

Specific probiotics against colds and flu

Accumulating evidence suggests that probiotics may have favourable effects against the common cold [22]. The latest meta-analyses show that probiotics reduce the incidence of common cold episodes [11, 23], the risk or duration of common cold episodes [11, 24], and antibiotics use and cold-related school absence [11] when taken prophylactically. Also, probiotic use can reduce symptom severity and duration [25]. However, it should be taken into account that research on the efficacy of probiotics against the common cold has been conducted in populations of different ages and genetic backgrounds, using many different strains, combinations and doses. Therefore, pooling all these data creates a bias as the effect of probiotics is generally dependent on the dose, population and strain. Thus, a species- and population-based approach is necessary when examining the efficacy of probiotics against the common cold.

The most investigated and most common commercially available probiotic species are *Lactobacillus* ssp. and *Bifidobacterium* ssp. Several studies have investigated the effectiveness of these probiotic species against colds and flu from childhood to old age. In this review, we concentrate on community-based studies conducted in children (>1 to 18 years of age) and adults (>18 to <60 years of age), as these age groups suffer from the common cold most often and thus account for the majority of economic losses related to this disease. In addition, this review focuses on studies conducted with the most accessible and most extensively studied strains, namely *L. rhamnosus* GG, *L. acidophilus* NCFM, *L. casei* DN-114 001, *B. animalis* ssp. *lactis* Bi-07, *B. animalis* ssp. *lactis* Bl-04 and *B. animalis* ssp. *lactis* Bb-12.

Children

Community studies investigating the efficacy of probiotics against the common cold in healthy children in day care are listed in Table 1. Five clinical trials have been conducted with *L. rhamnosus* GG alone or in combination with other probiotic bacteria. Four of these studies included healthy children attending day care [26–29] and one included otitis-prone children [30]. These studies indicate that *L. rhamnosus* GG alone has a beneficial effect on the incidence of the common cold [26, 28, 29] and also may reduce symptom duration [29], absence from day care and number of antibiotic treatments [26, 29]. Studies where *L. rhamnosus* GG was consumed in combination with other probiotic strains did not seem to not provide significant benefit in reducing common cold outcomes in either healthy or otitis-prone children [27, 30].

Two clinical trials have been conducted with *L. acidophilus* NCFM alone or together with *B. lactis* Bi-07 [31, 32]. The first included underweight (but otherwise healthy) children [31] and the other

Study design	Probiotic	Subjects	Cold and flu outcomes: probiotic vs placebo			Absence from day care	Antibiotic treatments
			Incidence	Duration	Severity		
R, DB, PC, 7 mo [26]	L.GG	594 day care children (1–6 yrs)	17% Relative reduction in severe infections, *p*=0.05; age adjusted *p*=0.13	Days with respiratory symptoms: 21 vs 23, *p*=0.28	Symptom score: 34 vs 40, *p*=0.1	–0.9 d (4.9 vs 5.8 d), *p*=0.03; adjusted *p*=0.09	44% vs 54%, *p*=0.03; age adjusted *p*=0.08
R, DB, PC, 3 mo [29]	L.GG	281 day care children (1–7 yrs)	Number of children with RTIs: 43.2% vs 67.6%, *p*<0.0010 Upper RTIs 41.7% vs 66.9%, *p*<0.001 Lower RTIs: 2.9% vs 3.5%, *p*=0.759 Number of RTIs >3 d: 28.1% vs 49.3%, *p*<0.01	Median –4 d (0 vs 4 d), *p*<0.001	Not tested	–2 d (3.1 vs 5.1 d), *p*<0.001	None required antibiotic treatment
R, DB, PC, 6.5 mo [28]	L.GG	523 day care children (2–6 yrs)	Respiratory symptoms: 4.71 vs 5.67 days/month (IRR 0.83; 95% CI 0.78 to 0.88); *p*<0.001 Episodes/month: 0.59 vs 0.55 (IRR 1.06; 95% CI 0.96 to 1.16); *p*=0.24	No effect: median 8 vs 8 d	Not tested	Not tested	35% vs 34%, *p*=0.8
R, DB, PC, 6 mo [30]	L.GG, Lc705, *B. breve* 99, *Propionibacterium freudenreichii* PJS	309 otitis-prone children (10 mo–6 yrs)	AOM: 72% vs 65%, *p*=ns Recurrent RTIs: >4: OR 0.56. 95% CI 0.31 to 0.99, *p*=0.046 >6: OR 0.59, 95% CI 0.34 to 1.03, *p*=ns	AOM 5.6 (IQR 3.5–9.4) vs 6.0 (IQR 4.0–10.5) d, *p*=ns	Not tested	Not tested	No differences between groups
R, DB, PC, 7 mo [27]	L.GG, La-5, Bb-12	240 day care children (1–3 yrs)	Number of days with RTI: 25.4 vs 25.1, *p*=0.63	Symptom period: 5.4 vs 4.7 d, *p*=0.88	Not tested	7.5 vs 8.5 d, *p*=0.16 (includes GI infections)	Not tested
R, DB, PC, 4 mo [31]	NCFM+Bi-07+FOS with and without nutritional supplement	626 underweight children (1–6 yrs)	No effect in total population In subgroup (3–5 year olds) mean n of sick days: 14.2 vs 20.1, *p*=0.047	Not tested	Not tested	Not tested	No effect
R, DB, PC, 6 mo [32]	NCFM NCFM+ Bi-07	326 children (3–5 yrs)	NCFM: RR: fever –43% (*p*=0.015), cough –41% (*p*=0.028) NCFM+Bi-07: RR: fever –66% (*p*=0.01), cough –56% (*p*=0.005), rhinorrhea –48% (*p*=0.04)	NCFM: 2.0 d NCFM+Bi-07: 3.1 d	Not tested	NCFM: 1.6 d, *p*=0.01 NCFM+Bi-07: 1.4 d, *p*=0.01	NCFM: 16.4% vs 54.8%, *p*=0.0002 NCFM+Bi-07: 9% vs 54.8%, *p*<0.0001
Open label, R, DB, 5 mo [33]	DN-114 001	251 children (3–12 yrs)	No effect on URTIs; lower incidence of LRTIs: 32% vs 49%	No effect on URTIs; shorter duration of LRTIs	Not tested	No differences between groups	Not tested
Open label, R, DB, 1.5 mo [34]	DN-114 001	381 children (3–8 yrs)	3–8 yrs: no effect on URTIs; some beneficial impact on quality of life	Not tested	Not tested	–0.37 d	Not tested
R, DB, PC, 3 mo [35]	DN-114 001	638 day care children (3–6 yrs)	Upper RTIs per 100 person-days: –18% (IRR: 0.82, 95% CI 0.68 to 0.99), *p*=0.036	Not tested	Not tested	No effect	n=58 vs n=69, *p*=0.002

AOM acute otitis media, Bb-12 *Bifidobacterium animalis* ssp. lactis Bb-12, Bi-07 *Bifidobacterium animalis* ssp. *lactis* Bi-07, *CI* confidence interval, *d* day, *DB* double blind, DN-114 001 *Lactobacillus casei* DN-114 001, *FOS* fructo-oligosaccharide, *IQR* interquartile range, *IRR* incidence rate ratio, La-5 *Lactobacillus acidophilus* La-5, Lc705 *Lactobacillus rhamnosus* Lc705, L.GG *Lactobacillus rhamnosus* GG, *LRTI* lower respiratory tract infection, *GI* gastrointestinal, *mo* month, NCFM *Lactobacillus acidophilus* NFCM, *ns* not significant, *OR* odds ratio, *PC* placebo controlled, *R* randomized, *RR* risk ratio, *RTI* respiratory tract infection, *URTI* upper respiratory tract infection, *yrs* years

Table 1 - Clinical trials assessing probiotic efficacy for the common cold and flu in children

healthy children [32]. In a subgroup of 3–5-year-old underweight children, *L. acidophilus* NCFM together with *B. lactis* Bi-07 seemed to reduce the mean number of days of respiratory tract infection (RTI) and gastro-intestinal illness combined, but this effect was not seen in the total population nor were reductions seen in other outcomes [31]. In contrast, in healthy children attending day care, *L. acidophilus* NCFM both alone and in combination with *B. lactis* Bi-07 significantly reduced common cold symptom incidence and duration, absence from day care, and number of antibiotic treatments [32].

The effectiveness of *L. casei* DN-114 001 against the common cold in children has been investigated in three studies [33–35]. These indicate that *L. casei* DN-114 001 may reduce the incidence of upper RTI [35] and lower RTI incidence and duration [33]. In addition, *L. casei* DN-114 001 seems to provide some benefit in reducing absences from day care [34] and number of antibiotic treatments [35].

Adults

The details of four community-based studies in healthy adults consuming probiotics are given in Table 2. College students consuming *L. rhamnosus* GG together with *B. lactis* Bb-12 had a shorter duration of the common cold and a lower symptom score compared to those taking a placebo [36]. In addition, subjects consuming probiotics had fewer absences from school but not from work. However, no effect was seen on common cold incidence. On the other hand, in another study, *B. lactis* Bb-12 consumption alone in adults did not seem to provide significant benefit against common cold incidence and severity, or absence from work [37]. However, interestingly, illness duration shortened by 2–3 days, but this effect was also seen with yoghurt without *B. lactis* Bb-12. The same study also explored the effects of Bb-12 on NK and T cell function during common cold episodes, but found no differences in T cell IFN-γ, TNF-α and IL-12 secretion between plain yoghurt, yoghurt with *B. lactis* Bb-12, or a *B. lactis* Bb-12 capsule.

The effects of *L. casei* DN-114 001 on the common cold were investigated in one community-based study in healthy shift workers [38]. No correlation was seen between *L. casei* DN-114 001 consumption and a reduction in common cold incidence, duration and severity, absence from work, or antibiotic/other medication consumption. When immune markers were investigated, leukocyte and neutrophil counts increased in the *L. casei* DN-114 001 group in subjects with rhinopharyngitis. Similarly, absolute NK cell count increased in subjects with the common cold, rhinopharyngitis, a sore throat or a lower RTI.

The effect of *B. lactis* Bl-04 and the combination of *L. acidophilus* NCFM and *B. lactis* Bi-07 on the incidence of common cold symptoms was investigated in healthy active adults [39]. A significant reduction in the risk of contracting the common cold was seen in subjects consuming *B. lactis* Bl-04, but not in those consuming *L. acidophilus* NCFM together with *B. lactis* Bi-07. However, in both groups, time to experience a common cold episode was increased. The duration of common cold episodes was shorter in both probiotic groups, but the differences were not statistically significant. No differences were seen in common cold severity or in the number of antibiotic treatments. When immune markers from a subset of 125 subjects were analyzed [40], no significant effects between probiotic and placebo groups were observed on cytokines, white cell differentials, PBMC neutrophil or monocyte phagocytic activity, or NK cell function from before to after supplementation. However, when compared with control, some immunomodulatory effect was seen with *B. lactis* Bl-04 and *L. acidophilus* NCFM/*B. lactis* Bi-07 in terms of higher macrophage inflammatory protein 1 and lower plasma matrix metallo-proteinase 1, respectively.

Interestingly, one study also explored the possible mechanisms of action of probiotics against cold viruses in an experimental rhinovirus challenge model [41]. In this pilot trial, 59 healthy subjects received 100 ml of fruit juice supplemented with 109 cfu of live or heat-inactivated *L. rhamnosus* GG or control juice daily for 6 weeks. After 3 weeks, rhinovirus was inoculated intra-nasally into subjects and infection symptoms were followed

Study design	Probiotic	Subjects	Cold and flu outcomes: probiotic vs placebo			Absence from day care	Antibiotic treatments
			Incidence	Duration	Severity		
R, DB, PC, 5 mo [39]	Bl-04 NCFM+Bi-07	464 Healthy active adults	Bl-04: 27% risk reduction of having an episode (*p*=0.022), 0.7 mo increase in time-to-illness NCFM+Bi-07: 19% risk reduction of having an episode (*p*=0.15), 0.9 mo increase in time-to-illness	Bl-04: 6.3 vs 7.4 d, *p*=0.25 NCFM+Bi-07: 7.0 vs 7.4 d, *p*=0.82	Participants with severe illness: Bl-04: 19% vs 20%, *p*=ns NCFM+Bi-07: 16% vs 20% d, *p*=ns	Not tested	No differences between groups in use of antibiotics or cold and flu medications
R, DB, PC, 3 mo [36]	L.GG+Bb-12	231 Healthy young adults	URTI cases: 84 vs 83, *p*=ns	Duration –2 d, *p*=0.001	Symptom score 34%, *p*<0.001	Missed school days –0.2 d, *p*=0.002 Missed work days no difference, *p*=0.429	Not tested
R, CO, 4 treatments for 4 wks [37]	Bb-12	30 Healthy adults	No difference between groups	–2 or 3 days (with yoghurt alone, Bb-12 yoghurt or Bb-12 capsule), *p*=0.0509	No differences between groups, *p*=0.0632	No differences between groups, *p*=0.4220	Not tested
R, DB, PC, 3 mo [38]	DN-114 001+yogurt cultures	1000 Healthy shift workers	No difference between groups in URTI incidence	Mean 6.5 vs 6.9 d, *p*=0.182 (includes GI infections)	Subjects with severe symptoms: 8% vs 8.2%, *p*=ns (includes GI infections)	No differences between groups in sick leave occurrence or duration	No differences between groups in any medication for RTI and GI infections

Bb-12 *Bifidobacterium animalis* ssp. *lactis* Bb-12, Bl-04 *Bifidobacterium animalis* ssp. *lactis* Bl-04, Bi-07 *Bifidobacterium animalis* ssp. *lactis* Bi-07, *CI* confidence interval, *CO* cross-over, *d* day, *DB* double blind, DN-114 001 *Lactobacillus casei* DN-114 001, *GI* gastrointestinal, L.GG *Lactobacillus rhamnosus* GG, NCFM *Lactobacillus acidophilus* NFCM, *ns* not significant, *PC* placebo controlled, *R* randomized, *RTI* respiratory tract infection, *URTI* upper respiratory tract infection, *wk* week

Table 2 - Clinical trials assessing probiotic efficacy for the common cold and flu in adults

for 5 days. No differences were found between the groups in any of the outcome measures (rhinovirus infection rate, and the occurrence or severity of cold symptoms), possibly due to the pilot scale design and small sample size.

To conclude, specific probiotics may be beneficial in reducing the symptoms of the common cold in healthy children and in adults, although some strains seem to be more effective than others. However, more research with larger cohorts is required which also addresses the antiviral and immunological mechanisms of probiotics.

Probiotics provide public health and economic benefits to society

Attempts to reduce the risk, severity or duration of a disease normally produce side effects and incur costs, which, however, can be outweighed by the benefits. In the pharmaceutical arena, we also accept a certain risk in the form of side effects. But how do these factors compare when we are considering the common cold and probiotics? In general, the economic cost of individual common colds is relatively small, but because the disease is so widespread and recurs, the overall burden can be substantial, depending on the compensation provided nationally and on how the prevailing culture deals with the common cold.

Probiotics are relatively inexpensive, but require prolonged consumption in order to have an effect on the common cold, at least in winter, thus adding to the expense. This cost would have to be carried by the individual as national healthcare systems do not provide compensation. Probiotics do not prevent the common cold but rather reduce the risk, so efficacy also needs to be taken into account.

In a recent publication, Lenoir-Wijnkoop and colleagues [42] attempted to calculate the economic impact of probiotic use on the common cold in the French population. A model French population was constructed on a scale of 1/1,000, taking into account age distribution (small children are more likely to get ill), smoking status (smokers are more likely to contract the common cold) and community setting (being at school, in day care or in an open office exposes individuals to more infection then when working individually). Two meta-analyses were used to estimate probiotic success rate, one by Hao and co-workers [23] and another by King and co-workers [24]. The incidence of common cold infections was retrieved from a database, while costs for medication, visits to general practitioners, loss of income and compensation by the healthcare system were calculated from publicly available data for France. The costs for probiotics were also estimated.

Using data from King and co-workers, Lenoir-Wijnkoop and colleagues indicated that the French population would have 2.383 million fewer days sick with common RTIs and 581,000 fewer days of sick leave, resulting in savings of €84.4 million, €14.6 million and €16.2 million for society, the national healthcare system and families, respectively. Data from Hao and co-workers suggested 6.639 million fewer sick days and 1,453,000 fewer days of sick leave, resulting in savings of €253.6 million, €37.7 million and €131.1 million, respectively. The largest savings could actually be generated by targeting young children as they have the highest incidence of the common cold and associated costs.

However, a few limitations must be mentioned. Not all common cold infections are reported to general practitioners and so the incidence and consequently the benefits may be underestimated. The data were collected during the cold and flu season of 2011–2012, which was actually rather mild, and thus on average a larger effect could be possible. Some members of the French population already consume probiotics and thus already benefit from them, so the effect size may be overestimated. The additional costs of probiotics could be reduced if, for example, a plain yogurt was replaced by a probiotic one, or increased if dietary supplements were purchased or probiotic yogurts did not replace a plain yogurt. Finally, the study does not take into account the 'herd effect': when everybody is more resistant to the common cold, it spreads less and the risk of exposure is consequently reduced.

Despite these uncertainties, there is a strong indication that probiotics provide both health and economic benefits against the common cold. They are certainly better than vitamin C [43], similar to hand washing [44], less effective than face masks [45] and, interestingly, as good as or better than neuraminidase inhibitors [46].

Summary and conclusions

Over 200 viruses can cause the common cold and flu in humans, resulting in considerable costs and economic loss to society. Despite much research, effective and safe treatments are not yet available.

The immune response against cold viruses in the respiratory epithelium involves complex interactions between epithelial cells, cytokines and immune cells, leading ultimately to virus eradication after several days of infection.

The intestine plays a major role in the immune system and in the immune response against pathogens. The effects of probiotics against the common cold and flu are likely mediated via the small intestine and include trafficking of immune system cells between tissue compartments, microbial metabolite release into the circulation, and hormonal regulation of the immune system by the gut–brain axis.

Recent studies and meta-analyses indicate that probiotic use reduces the risk of contracting the common cold by lowering the incidence of the disease and shortening the duration of episodes and/or symptoms. Effects are, however, strain and dose specific, and antiviral mechanisms attributed to the probiotic function should receive more attention in the future.

From an economic perspective, consumption of probiotics during the cold season seems to provide substantial cost savings for society in terms of reduced visits to general practitioners and fewer absences from work and day care/school.

Human and Animal Rights

This article does not contain any studies with human or animal subjects performed by the any of the authors.

Conflict of Interest

Liisa Lehtoranta, Markus Lehtinen and Arthur Ouwehand are employed by DuPont Nutrition and Health, Kantvik, Finland, DuPont manufactures and markets probiotics.

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