



Understanding the role of probiotics and prebiotics in preventing allergic disease: evidence and methodological issues

Research in the area of prevention of allergic disorders through modification of the intestinal microbiota by provision of probiotics and/or prebiotics is relatively new. This paper briefly summarizes evidence regarding the role of probiotics and/or prebiotics in reducing the risk of allergy. There are studies that show a protective effect, no effect or even a predisposing effect of using probiotics and/or prebiotics in preventing allergic disease. A variety of methodological issues are likely to contribute to current uncertainty. These include differences in the study population (high-risk vs unselected population), optimal strain selection (all probiotics are not equal), differences in definitions of outcomes, timing and duration of the interventions, and a lack of repeat studies.

KEYWORDS: allergy • atopy • child • infant • meta-analysis • microbiota • nutrition • prebiotics • prevention • probiotics • randomized control trial • synbiotics

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The rising number of children and adults with allergic disorders, such as asthma, allergic rhinitis, atopic dermatitis and food allergy, worldwide is a major public health concern [1]. The origins of this increase are still not well understood. However, it is now clear that, among other factors, impaired oral tolerance, which is a specific suppression of cellular and/or humoral immune responses to an antigen, contributes to the development of allergic diseases. For the development of oral tolerance, contact with microbes is crucial [2]. It has been hypothesized that, among other causes, aberrant gut microbiota, due to factors such as the mode of delivery (vaginal vs cesarean), use of antibiotics in the early neonatal period and mode of feeding (breast vs formula feedings), contributes to the development of allergic diseases. If so, prevention of allergic disorders through modification of intestinal microbiota via the provision of probiotics and/or prebiotics is of interest.

Probiotics are live microorganisms administered in adequate amounts that confer a beneficial health effect on the host [3]. In principle, this definition applies to probiotics in food, and it excludes references to the term 'biotherapeutic agents' and beneficial microorganisms not used in food. In practice, however, the definition is used regardless of the delivery mode, and probiotics can be found in food, dietary/nutritional supplements, drugs and medical foods. Prebiotics are "nondigestible food components that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited

number of bacteria in the colon and thereby improving host health" [4]. In infants, oligosaccharides, such as galactooligosaccharides and fructooligosaccharides, are commonly used as prebiotics as they increase the fecal counts of bifidobacteria. Finally, the term 'synbiotic' is used "when a product contains both probiotics and prebiotics" [5].

A number of concepts have been considered as the rationale for using probiotics/prebiotics in the prevention of allergic disorders. Among them are improved hygiene and the reduced exposure of the immune system to the microbial stimulus early in childhood, which may contribute to the rising number of allergic disorders worldwide [6]. Second, there exists a difference in the neonatal gut microbiota that may occur before or match the timing of the early development of atopy. Atopic subjects have more Clostridia and tend to have fewer bifidobacteria than nonatopic subjects [7]. Finally, evidence suggests a critical role for a stable commensal gut microbiota in the maturation of the early immune system.

This article briefly summarizes evidence regarding the role of probiotics and/or prebiotics in reducing the risk of allergy, and discusses some methodological issues to help clarify why the data are conflicting.

Evidence on probiotics

A number of meta-analyses on the effect of probiotics for preventing eczema have been published [8–12]. The methodological approaches used and a summary of the results is presented in TABLE 1.

Table 1. Comparison of the meta-analyses on the effects of probiotics on the prevention of allergic diseases.

Author (year)	Question	Methodology	Literature search	Type of study	Unpublished trials
Osborn and Sinn (2007)	Well defined: to determine the effect of probiotics given to infants for the prevention of allergic diseases or food hypersensitivity	Well covered	CENTRAL (issue 1, 2007), MEDLINE and CINAHL (February 2007); EMBASE, PREMEDLINE; reference lists; abstracts from some conferences	RCTs and quasi-RCTs	Not clear
Lee <i>et al.</i> (2008)	Well covered: to summarize clinical trial findings on probiotics for pediatric atopic dermatitis	Well covered	PubMed and Cochrane databases (up to July 2007); reference lists; authors were contacted if the study did not provide sufficient data	RCTs	Not included
Betsi <i>et al.</i> (2008)	Well covered: to synthesize the evidence of the effectiveness of probiotics for the treatment or prevention of atopic dermatitis in children	Well covered	PubMed, EMBASE and the Cochrane Library (1997–2007)	RCTs	Not clear
Doege <i>et al.</i> (2012)	Well covered: to assess the impact of probiotics intake during pregnancy on the development of eczema in children	Well covered	PubMed and Ovid, including EMBASE (up to June 2009); reference lists	RCTs	Not clear
Pelucchi <i>et al.</i> (2012)	Well covered: to investigate whether probiotic use during pregnancy and early life decreases the incidence of atopic dermatitis and IgE-associated atopic dermatitis	Well covered	MEDLINE, EMBASE, Cochrane Library (up to October 2011); reference lists	RCTs	Not included

LGG: *Lactobacillus GG*; RCT: *Randomized controlled trial*.

Only a Cochrane review (search date: 2007) concluded that there is insufficient evidence to recommend the addition of probiotics to infant foods for the prevention of allergic diseases, including food hypersensitivity [8]. The authors of the other meta-analyses, in general, stated that probiotics are effective, particularly if the probiotics are administered both pre- and post-natally. Caution should be exercised so one does not over-interpret the results of meta-analyses when all probiotics have been evaluated together [13]. Only one of the meta-analyses by Doege *et al.* differs from those previously published [11]. While it presents pooled data, it also separately presents data from studies that used mixtures of probiotics and studies that used *lactobacilli*. Of note,

only the *lactobacilli* were proven to be effective. Still, different *lactobacilli* were pooled together, calling for caution when interpreting the pooled effect. As the effects of different probiotic micro-organisms are not equivalent, the most relevant data are those related to specific probiotic strains. A summary of them, recently discussed in detail elsewhere [14,15], is presented in TABLE 2.

Evidence on prebiotics

Previously, a Cochrane review [16] (search date: February 2007) found only two randomized controlled trials (RCTs) that provided data on allergic disease outcomes for 432 infants [17,18]. A recently published update (search date: August 2012) identified additional data for two

Table 1. Comparison of the meta-analyses on the effects of probiotics on the prevention of allergic diseases (cont.).

Language	Study quality	Heterogeneity	RCTs/ participants	Conclusion	Comment	Ref.
No language restriction	Yes (using standardized criteria)	Heterogeneity discussed or assessed	Six RCTs reported allergic disease and/or food hypersensitivity (in 1549 out of 2080 enrolled infants)	Insufficient evidence to recommend the addition of probiotics to infant feeds for the prevention of allergic disease or food reactions	Concerns regarding the quality of studies and inconsistency of findings between trials. Further studies are needed to confirm the results	[8]
English only	Yes (using a standardized protocol)	Heterogeneity considered	Six RCTs (n = 1581)	Current evidence is more convincing for probiotics' efficacy in the prevention rather than the treatment of pediatric atopic dermatitis	Criticism for combining the results from five studies on probiotics with results from one study on synbiotics. Moreover, data from the same study population at different time intervals were combined	[9]
English only	Not formally assessed	Narrative synthesis	Three RCTs (n = 1429)	Probiotics, especially LGG, seem to be effective for the prevention of atopic dermatitis	Conclusions based on only three RCTs; the review's methodological limitations call for caution	[10]
Not clear	Yes (according to the Centre for Reviews and Dissemination guidance)	Heterogeneity considered	Seven RCTs (n = 2843)	Probiotics, especially <i>Lactobacilli</i> , reduce the risk of atopic eczema	Presents pooled data and separate data from studies that used mixtures of probiotics and studies that used <i>Lactobacilli</i> . Still, different <i>Lactobacilli</i> were pooled together, calling for caution when interpreting the pooled effect	[11]
English only	Not formally assessed (except for double-blinding)	Heterogeneity considered	18 publications based on 14 RCTs	Moderate role of probiotics in the prevention of atopic dermatitis and IgE-associated atopic dermatitis in infants	Different probiotics were pooled together. Caution is needed when interpreting the results	[12]

LGG: *Lactobacillus GG*; RCT: Randomized controlled trial.

previously included RCTs, as well as two new RCTs [19,20]. Thus, this update included four RCTs enrolling 1428 infants [21]. The authors of this Cochrane review concluded that there is some evidence that prebiotic supplementation may reduce the risk of eczema. However, it is unclear whether the use of prebiotics should be restricted to infants at high risk of allergy or whether prebiotics may have an effect in low-risk populations. It is also unclear whether prebiotic supplementation may have an effect on other allergic diseases including asthma. As with probiotics, the effects of different prebiotics are not equivalent. Thus, the most relevant data are those related to specific prebiotics. Data on specific prebiotics are presented in TABLE 3.

Evidence on synbiotics

No systematic review focusing specifically on synbiotics was found. In one recent, double-blind RCT conducted in Finland, 1223 pregnant women carrying high-risk infants were randomly assigned to receive *Lactobacillus rhamnosus*, *Bifidobacterium breve*, and *Propionibacterium freudenreichii*, or placebo, for 2–4 weeks before delivery. Their infants received the same preparation plus galactooligosaccharides (i.e., a synbiotic) or placebo for 6 months after delivery. At 2 years in the group of infants fed synbiotics, a significantly higher proportion of infants had a reduction in eczema (relative risk [RR]: 0.81; 95% CI: 0.66–0.99) and in atopic eczema (RR: 0.70; 95% CI: 0.51–0.96). However, there

Table 2. Effects of specific probiotics on the prevention of allergic diseases.

Probiotic	Author (year)	Population	Intervention (dose CFU)	Before delivery	After delivery	Follow-up (years)	Atopic dermatitis (effect size)	Ref.
High-risk population								
LGG	Kalliomäki <i>et al.</i> (2001)	132/159	1 × 10 ¹⁰	2–4 weeks	6 months (to BF mothers or directly to infants)	2	RR: 0.51 (0.32–0.84)	[29]
	Kalliomäki <i>et al.</i> (2003)					4	RR: 0.57 (0.33–0.97)	[30]
	Kalliomäki <i>et al.</i> (2007)					7	RR: 0.64 (0.45–0.92)	[31]
	Rautava <i>et al.</i> (2002)	57/62	2 × 10 ¹⁰	2–4 weeks	3 months BF mothers only	1	NS	[33]
	Kopp <i>et al.</i> (2008)	94/105	5 × 10 ⁹ , twice daily	4–6 weeks before delivery	6 months		RR: 0.96 (0.38–2.33)	[25]
	Boyle <i>et al.</i> (2011)	210/250	1.8 × 10 ⁸	1 month	–	1	NS	[34]
	Ou <i>et al.</i> (2012)	128/191	1 × 10 ¹⁰	From second trimester	6 months to BF mother or non-BF infant	3	NS	[39]
LGG + Bb12	Rautava <i>et al.</i> (2006)	72/81	LGG 1 × 10 ¹⁰ Bb12 1 × 10 ¹⁰	–	From start of infant formula to 12 months	1	NS	[40]
<i>L. rhamnosus</i> LP, <i>B. longum</i> BL999	Rautava <i>et al.</i> (2012)	205/241	1 × 10 ⁹ each	2 months	2 months to BF mother	2	OR: 0.17 (0.08–0.35)	[41]
<i>L. paracasei</i> ST11, <i>B. longum</i> BL999							OR: 0.16 (0.08–0.35)	
<i>L. acidophilus</i> LAVRI A1	Taylor <i>et al.</i> (2007)	178/226	3 × 10 ⁹	–	6 months	1	NS	[24]
	Prescott <i>et al.</i> (2008)	153/226				2.5	NS	[42]
	Jensen <i>et al.</i> (2012)	123/226				5	NS	[43]
<i>L. reuteri</i> ATCC 55730	Abrahamsson <i>et al.</i> (2007)	188/232	1 × 10 ⁸	1 month	12 months	2	NS (but IgE-eczema)	[44]
<i>L. rhamnosus</i> HN001	Wickens <i>et al.</i> (2008)	446/512 (2 years)	6 × 10 ⁹	1 month	6 months if BF + to an infant	2	HR: 0.51 (0.3–0.85)	[26]
	Wickens <i>et al.</i> (2012)	425/512 (4 years)			2 years	4	HR: 0.57 (0.39–0.83)	[27]
<i>B. animalis</i> HN019	Wickens <i>et al.</i> (2008)		9 × 10 ⁹			2	NS	[26]
	Wickens <i>et al.</i> (2012)					4	NS	[27]
<i>B. longum</i> BL999, <i>L. rhamnosus</i> LPR	Soh <i>et al.</i> (2009)	245/253	2.8 × 10 ⁸	–	6 months	1	NS	[45]
<i>B. bifidum</i> W23, <i>B. lactis</i> W52, <i>L. lactis</i> W58	Niers <i>et al.</i> (2009)	98/156	1 × 10 ⁹ of each strain	1 month	12 months	2	Reduced at 3 months; later NS	[46]
BF: Breastfeeding or breastfed; HR: Hazard ratio; LGG: Lactobacillus GG; NS: Not significant; OR: Odds ratio; RR: Relative risk.								

Table 2. Effects of specific probiotics on the prevention of allergic diseases (cont.).

Probiotic	Author	Population	Intervention (dose CFU)	Before delivery	After delivery	Follow-up (years)	Atopic dermatitis (effect size)	Ref.
High-risk population (cont.)								
<i>B bifidum</i> BGN4, <i>B lactis</i> AD011, <i>L acidophilus</i>	Kim <i>et al.</i> (2010)	68/112	1.6 × 10 ⁹ of each strain	1–2 months	3 months to BF mother, than to an infant up to age 4–6 months	1	Reduced p < 0.029	[47]
Unselected population								
LGG + Bb12	Huurre <i>et al.</i> (2008)	140/171	LGG 1 × 10 ¹⁰ Bb12 1 × 10 ¹⁰	From first trimester	End of BF (two mothers only)	1	NS	[48]
LGG + Bb12 + <i>Lacidophilus</i> La5	Dotterud <i>et al.</i> (2010)	278/415	LGG 5 × 10 ¹⁰ Bb 12 5 × 10 ⁹ <i>L. acidophilus</i> La5 5 × 10 ¹⁰	1 month	3 months to BF mothers	2	OR: 0.51 (0.3–0.87)	[49]
<i>Lactobacillus</i> F19	West <i>et al.</i> (2009)	171/179	1 × 10 ⁸	–	4–13 months in cereals	1	Reduced p < 0.05	[35]

BF: Breastfeeding or breastfed; HR: Hazard ratio; LGG: Lactobacillus GG; NS: Not significant; OR: Odds ratio; RR: Relative risk.

was no significant difference between groups in the cumulative incidence of all allergic diseases (RR: 0.90; 95% CI: 0.75–1.08) [22]. Probiotic treatment showed no effect on the incidence of all allergic diseases by the age of 2 years, but significantly prevented eczema and especially atopic eczema [22]. The results suggest an inverse association between atopic diseases and colonization of the gut by probiotics.

No allergy preventive effect that extended to the age of 5 years was achieved with perinatal supplementation of probiotic bacteria to high-risk mothers and children. It conferred protection only to cesarean-delivered children [23].

Methodological issues

Overall, with regard to the use of probiotics and/or prebiotics for allergy prevention, there are studies that demonstrate a protective effect or no effect. Some, at least for the secondary outcomes, show even a predisposing effect [24,25]. In addition to genes and environmental factors, a variety of methodological issues are likely to contribute to these inconsistent results that are briefly discussed below.

■ Population

Similar to other allergy prevention studies, almost all of the trials were carried out in populations at high risk of allergy, typically defined as the presence of at least one parent or sibling

affected by an allergic disease. Thus, the results, whether positive or negative, may be applicable only to such a population. Only a few studies that examined the effect of probiotics on allergy were carried out in unselected birth cohorts with regard to allergy risk (TABLES 2 & 3).

■ Intervention

All probiotics are not equal. The efficacy and safety of each probiotic microorganism has to be studied separately, as they have different effects. This has been clearly documented in a double-blind RCT (n = 474) by Wickens *et al.* [26,27]. The supplementation of both the pregnant mothers and infants with *L. rhamnosus* HN001, but not with *Bifidobacterium animalis* lactis HN019, reduced the cumulative prevalence of eczema at 2 years by 50% [26]. The protective effect of *L. rhamnosus* HN001 against eczema, when given for the first 2 years of life only, extended to 4 years of age (90% follow-up) [27]. Thus, the clinical effects of any single probiotic or combination of probiotics should not be extrapolated to other probiotics. Likewise, not all prebiotics or synbiotics are equal. The efficacy (and safety) should be established for each product.

■ Outcomes

Ideally, the diagnosis of allergic diseases should be based on widely agreed-upon criteria. However, in most of the included studies,

Table 3. Effects of specific prebiotics on the prevention of allergic diseases.

Prebiotic	Author	Population	Intervention (dose CFU)	Before delivery	After delivery	Follow-up	Atopic dermatitis (effect size)	Ref.
High-risk population								
GOS/FOS (90/10%)	Moro <i>et al.</i> (2006)	206/259	Extensively hydrolyzed formula + GOS/FOS (0.8 g/dl)	–	6 months	6 months	RR: 0.42 (0.2–0.8)	[17]
	Arslanoglu <i>et al.</i> (2008)	134/152				2 years	RR: 0.49 (0.24–1.00)	[50]
Unselected population								
Polydextrose, GOS	Ziegler <i>et al.</i> (2007)	n = 116	Standard infant formula with polydextrose and GOS	–	4 months	4 months	RR: 1.62 (0.62–4.26)	[18]
Polydextrose, GOS, lactulose		n = 106	Standard infant formula with polydextrose and GOS and lactulose				RR: 0.6 (0.12–3.16)	
GOS/FOS, acidic OS	Grüber <i>et al.</i> (2010)	n = 830	Standard infant formula + GOS/FOS (9:1; 6.8 g/l) and acidic OS (1.2 g/l)	–	1 year	1 year	RR: 0.58 (0.35–0.97)	[19]
GOS/FOS, acidic OS	Niele <i>et al.</i> (2013)	n = 94 Preterm or low birth weight infants (<32 weeks or birth weight <1500 g, or both)	Breast milk or preterm formula + GOS/FOS (in increasing doses to a maximum of 1.5 g/kg/d)	–	From day 3 to day 30	1 year	RR: 1.05 (0.41–2.65)	[20]
OS: Oligosaccharides; FOS: Fructooligosaccharides; GOS: Galactooligosaccharides; RR: Relative risk.								

OS: Oligosaccharides; FOS: Fructooligosaccharides; GOS: Galactooligosaccharides; RR: Relative risk.

heterogeneous definitions made direct comparisons between the studies difficult. The single most studied outcome was atopic dermatitis. Only in some trials was the severity of atopic dermatitis assessed. This is despite the fact that it has been recommended that scoring of eczema severity should be reported, as it allows differentiating mild cases from more severe disease [28].

In a number of studies, in addition to clinically relevant outcomes, skin prick tests or specific IgE blood levels have been assessed. A positive test result is indicative of allergic sensitization, but does not necessarily represent a clinically relevant allergy. Studies by Kalliomäki *et al.* documented that in offspring at risk for atopic disease, *Lactobacillus* GG (LGG) given pre- and post-natally reduced the risk of atopic eczema by half at up to 7 years of age [29–31]; however, there was no reduction in atopic sensitization. The latter finding suggests that it might be worthwhile to study nonatopic individuals.

■ Timing & duration of administration

Different prevention regimens, particularly with regard to the administration of probiotics, have been studied, including:

- Prenatal (during pregnancy) and postnatal (to lactating mothers or directly to infants; most of the studies). While the results are inconsistent, overall they suggest that combined pre- and post-natal administration may be crucial for the preventive effect of probiotics;
- Prenatal administration to pregnant women only (up until delivery). It has been shown that maternal supplementation with probiotics may influence the composition of the infant's gut microbiota [32] and increase anti-inflammatory and immunoregulatory factors in breast milk and cord blood [33]. However, in one RCT conducted in 250 pregnant women carrying infants at high risk of allergic disease, the authors found that administration prenatally

of LGG only from 36 weeks of gestation until delivery did not reduce the risk of eczema in children at 1 year of age (RR: 0.88; 95% CI: 0.63–1.22) or IgE-associated eczema (RR: 0.94; 95% CI: 0.53–1.68) [34];

- Postnatal administration only (to breastfeeding mother or nonbreastfed infant). While the majority of the studies focused on prenatal and/or early postnatal administration, the results of a trial carried out in Sweden suggest that administration initiated at weaning may be sufficient [31]. This RCT conducted in 171 unselected infants found that compared with placebo, administration of *Lactobacillus* F19 in complementary food from 4 to 13 months of age reduced the cumulative incidence of eczema from 22 to 11% ($p < 0.05$). The authors proposed that the mechanism could be mediated by a higher Th1/Th2 ratio in infants receiving *Lactobacillus* F19 [35].

■ Optimal dose

The optimal dose and treatment duration of pre-/pro-biotic administration have not been clearly established. The lack of benefit in some of the studies may be due to an insufficient dose and/or duration of the intervention.

■ Importance of repeat studies

Only a very limited number of pre-/pro-biotics have been assessed in more than one study. One such an example is LGG. The results from studies by Kalliomäki *et al.* [29] and by Kopp *et al.* [25] that assessed the effect of LGG use for the primary prevention of atopic dermatitis, which were carried out based on almost identical protocols, demonstrate the importance of such repeat studies.

Kalliomäki *et al.* randomized 159 pregnant women who had atopic disease, who had ≥ 1 first-degree relative (e.g., mother, father or older sibling) with atopy, or who had a partner with atopy [29]. Mothers were allocated to receive LGG (10^{10} CFU) or placebo for 2–4 weeks before delivery. After delivery, either breastfed infants or the remaining infants received the allocated intervention for 6 months. Compared with the placebo group, in the LGG group there was significant reduction in infant eczema at the ages of 2 years (RR: 0.51; 95% CI: 0.32–0.84), 4 years (RR: 0.57; 95% CI: 0.33–0.97) [30], and 7 years (RR: 0.64; 95% CI: 0.45–0.92) [31]. There was no significant difference between groups in the prevalence of asthma in childhood (RR: 3;

95% CI: 0.3–28) or in the prevalence of allergic rhinitis (RR: 2; 95% CI: 0.75–5.6).

In a double-blind RCT involving 105 mother–infant pairs, Kopp *et al.* randomized 105 pregnant women from families with ≥ 1 member with atopic dermatitis to receive LGG or placebo both pre- and post-natally. The infants also received LGG or placebo after birth. Kopp *et al.* found a similar risk of atopic dermatitis in children aged 2 years in the LGG and the placebo groups (RR: 0.96; 95% CI: 0.38–2.33) [25]. Notably, children with ≥ 5 episodes of wheezing bronchitis were more common in the LGG group than in the placebo group.

Thus, whereas Kalliomäki *et al.* reported that LGG use exerts a preventive effect on the development of atopic eczema [29], Kopp *et al.* observed no effect of LGG use on the prevention of atopic dermatitis [25].

Taken together, these studies underscore the importance of repeat studies. There are various factors that discourage simple repetition (duplication) of trials that could clarify the effect of a given probiotic. These factors include a lack of scientific novelty and/or a lack of interest by potential sponsors in cases involving the administration of a commercially available pre-/pro-biotic product that has been proven effective in a single study. Still, as a rule, repeat studies are needed, as a single study is, rightly, never sufficient to change clinical practice.

In summary, the methodological problems in the available studies (and the lack of a universally accepted mechanism regarding how pre-/pro-biotics work) contribute to the current uncertainty.

Safety

Earlier, the Committee of Nutrition of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition commented on pre-/pro-biotic-supplemented infant formulas. Administration of these formulas often begins in early infancy, sometimes at birth when the gut microbiota is not fully established. Factors that influence microbiota may permanently affect the development of the ecosystem, and the daily administration of such products is often prolonged (several weeks or months). Thus, the mode of delivery is similar to that used in allergy prevention interventions. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition concluded that for healthy infants, available scientific data suggest that the administration of the pre-/pro-biotic-supplemented infant formulae studied so far does not raise

safety concerns with regard to growth and short-term adverse effects [36]. However, the safety and clinical effects of one probiotic microorganism (or prebiotic) should not be extrapolated to other probiotic microorganism(s). Of concern, there have been instances of bacteremia with use of select probiotic bacteria in high-risk populations. Endocarditis, pneumonia and meningitis have very rarely been reported in association with *Lactobacilli* [37]. There needs to be continued surveillance for adverse reactions, such as infections, especially among high-risk groups.

Recommendations from scientific societies

In 2010, the American Academy of Pediatrics concluded that the results of some studies support the prophylactic use of probiotics during pregnancy and lactation and during the first 6 months of life in infants who are at risk of atopic disorders [38]. Further confirmatory evidence is necessary before a recommendation for routine use can be made. There may be some long-term benefit of prebiotics in reducing atopy in otherwise healthy children. However, again, confirmatory studies are needed before any recommendations can be made [38].

In 2012, based on a qualitative and narrative review, the World Allergy Organization concluded that probiotics do not have an established role in the prevention of allergy. The World Allergy Organization also noted that no single probiotic supplement or class of supplements has

been demonstrated to efficiently influence the course of any allergic manifestation or long-term disease or to be sufficient to do so [15].

The recommendations from these two organizations are hard to argue against. In particular, there is a need to determine which microorganisms or prebiotic products are suitable for use and in what type of population.

Conclusion & future perspective

Further well-conducted clinical trials using validated outcome measures are recommended to further identify populations at high risk of allergy that would benefit most from probiotic and/or prebiotics therapy, confirm the efficacy of the interventions proven to be effective in a single trial, evaluate the efficacy of other probiotic strains and prebiotics, and determine the most effective dosing schedule.

Humans have ten-times more microbial cells than human cells, with the highest concentration of microorganisms located within the digestive tract. Approximately 1000 different species have been identified with current microbiological techniques. These microbiota mediate many key functions, including metabolic, trophic and protective (barrier) functions. Many of the microbes maintain health, while others are potential pathogens and can cause illness. Although the concept is not new, surprisingly little is known about the exact role and mechanisms by which these microorganisms contribute to human health or disease, as well as in the context of allergic

Executive summary

Background

- It has been hypothesized that, among other causes, aberrant gut microbiota, due to factors such as mode of delivery (vaginal vs caesarean), use of antibiotics in the early neonatal period and mode of feeding (breast vs formula feedings), contributes to the development of allergic diseases.
- Prevention of allergic disorders through modification of gut microbiota via the provision of probiotics and/or prebiotics is currently being evaluated.

Evidence

- There are studies that show a protective effect, no effect, or even a predisposing effect of using probiotics and/or prebiotics for preventing the allergic condition.

Methodological issues

- A variety of methodological problems are likely to contribute to current uncertainty.
- The issues include differences in the study populations (high-risk vs unselected population); optimal strain selection (all probiotics are not equal); differences in definitions of outcomes (ideally, the diagnosis should be based on widely agree-upon criteria); timing and duration of the intervention (pre- and/or post-natal supplementation); and a lack of repeat studies.

Conclusion

- Further well-conducted clinical studies using validated outcome measures are recommended to:
 - Further identify populations at high risk of allergy that would benefit most from probiotic and/or prebiotic therapy;
 - Confirm the efficacy of the interventions proven to be effective in a single trial;
 - Evaluate the efficacy of other probiotic strains and prebiotics;
 - Determine the most effective dosing schedule.

diseases. However, over the last decade or so, there has been a remarkable renewal of interest in this topic, at least partially due to recent developments in molecular technology. Much more is expected to be learned in the near future.

Overall, research in the area of prevention of allergic disorders through modification of intestinal microbiota is relatively new. Currently, there is insufficient evidence to recommend the administration of pre- and/or pro-biotics for the prevention of allergic disease. Long-term RCTs are necessary to establish whether manipulation of the gut microbiota can safely decrease the risk of allergic disease. If yes, it needs to be determined which interventions are suitable and in what type of population. In addition to mechanistic studies, further well-conducted, clinical studies using validated outcome measures are

recommended to further identify populations at high risk of allergy that would benefit most from probiotic and/or prebiotic therapy; evaluate the efficacy of other probiotic strains and prebiotics; and determine the most effective dosing schedule.

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