

Probiotics and prebiotics: clinical effects in allergic disease

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Purpose of review

This paper summarizes recent publications on probiotics and prebiotics in allergic disease. It focuses on clinical studies of prevention or treatment of allergic disease.

Recent findings

Studies suggest a role for certain probiotics (alone or with prebiotics) in the prevention of atopic eczema. Treatment during the prenatal period appears to be important for beneficial effects. The use of probiotics for the treatment of established allergic disease is less promising, despite some positive results. A Cochrane systematic review concluded that, when the results for the different probiotic strains used in clinical trials are pooled, probiotics are not effective for the treatment of eczema. There are fewer studies of prebiotics for the treatment or prevention of allergic disease, but data suggest that prebiotic-supplemented formulas may be effective for preventing eczema in infants at high risk of developing allergic disease when breast-feeding is not possible.

Summary

Allergic diseases continue to increase in prevalence worldwide, and primary prevention of allergic disease has proved an elusive goal. Probiotic bacteria represent the most promising intervention for primary prevention that has been studied to date, and definitive intervention studies should now be a research priority.

Keywords

allergic disease, immune function, intestinal microbiota, prebiotics, probiotics

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Introduction

There has been a rapid rise in the prevalence of allergic and autoimmune disorders in recent decades [1]. Reduced exposure to microbial stimuli associated with a modern lifestyle is suggested to have contributed to this rise [1]. The intestinal microbiota represents the greatest microbial exposure throughout life and the acquisition of the early intestinal microbiota is the newborn infant's first major microbial challenge. Intestinal microbiota development has been shown to play an important role in immune regulation and the induction and/or maintenance of tolerance to environmental antigens and self-antigens. Infants with eczema have altered intestinal microbiota compared with nonallergic children, with reduced numbers of the genus *Bifidobacterium* and increased levels of clostridia (*Clostridium difficile*), staphylococci (*Staphylococcus aureus*) and *Escherichia coli* [2–5]. These differences were observed prior to onset of disease [2,4,6], and presence of *E. coli* or *C. difficile* at age 1 month was associated with increased risk for developing eczema, recurrent wheeze and allergic sensitization [2]. Manipulation of the intestinal microbiota during infancy may, therefore, provide an approach to the prevention or treatment of allergic conditions.

Probiotics and prebiotics can modulate early development of intestinal microbiota [7–9] and have been proposed for the prevention or treatment of allergic disorders. In this paper, the clinical effects of probiotics, prebiotics and synbiotics in the prevention and treatment of allergic disease are reviewed. Probiotics are defined as 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host' [10]. Prebiotics are selectively fermented ingredients that allow changes in the composition and/or activity of gastrointestinal microbiota that confer benefits upon host well being [11]. The term synbiotic refers to combinations of probiotics and prebiotics. Postbiotics are probiotic fermentation products such as short-chain fatty acids, and will not be discussed in this review.

Treatment of allergic disease

Studies of probiotics, prebiotics or synbiotics in treatment of allergic disease are discussed.

Probiotics and prebiotics for the treatment of eczema

Most studies assessing probiotic effects in the treatment of allergic disease have focused on eczema with or without associated food allergy in infants and children. The

majority of studies involving eczema have evaluated *Lactobacillus* species either alone or in combination with other probiotic bacteria, and some have examined *Bifidobacterium* species. Early studies in small numbers of infants and children reported improvement in eczema [scoring atopic dermatitis (SCORAD) or symptoms] following treatment with *Lactobacillus rhamnosus* GG (LGG), *Bifidobacterium lactis* Bb-12, or *B. breve* M-16V [12–14]. In two of these studies, probiotic treatment resulted in more rapid improvement in eczema as compared with placebo at early time points – SCORAD improved significantly in the probiotic treatment groups but not the placebo groups at early time points; however, by 2–6 months, SCORAD was equivalent in treatment and placebo groups [13,14]. A larger study of *L. fermentum* VR1-003PCC in children with eczema [15] also demonstrated improvements in eczema severity and extent with probiotic-treated infants but not placebo-treated infants; however, SCORAD, parental perception of eczema, impact of eczema on the family and topical corticosteroid use were not significantly different between active and placebo groups [15].

In contrast to these initial studies, more recent and/or larger trials have failed to confirm beneficial effects of probiotics for the treatment of eczema [16–21]. A small crossover study assessing the efficacy of a probiotic yoghurt containing *L. paracasei* Lpc-37, *B. lactis* 420 and *L. acidophilus* 74-2 in 15 adults with atopic dermatitis reported a trend towards reduced SCORAD with probiotic treatment (15.5 reduction); however, this effect did not reach statistical significance ($P=0.081$) [22]. Interestingly, in two studies showing no overall effect, subgroup analyses revealed improvements in SCORAD following treatment with LGG (Viljanen) or the combination of *L. rhamnosus* HN001 and *B. lactis* HN019 (Sistek) for a subgroup of children with immunoglobulin E (IgE)-associated ('atopic') eczema [19,20]. Probiotic treatment was associated with low-grade inflammation, as evidenced by moderate increases in C-reactive protein and interleukin (IL)-6, which the authors suggested may suppress inflammation by inhibiting production of other inflammatory factors (tumour necrosis factor alpha, chemokines, interferon gamma) and inducing IL-10 and immunoglobulin A (IgA) production [23].

Our recent systematic review and a meta-analysis by others evaluating the use of probiotics for the treatment of eczema [24,25^{••}] concluded that probiotics do not appear to be effective for the treatment of eczema and there is insufficient evidence to support their use for this condition. Our Cochrane systematic review [25^{••}] included 12 studies [12–21,26,27] (summarized in Table 1) but not the recent study by Roessler *et al.* [22]. We found no significant reduction in eczema symptoms with probiotic treatment compared with placebo [mean differ-

ence 0.90 points on a 20-point visual analogue scale, 95% confidence interval (CI) –1.04 to 2.84], and no significant difference in investigator-rated eczema severity between probiotic and placebo treatments (588 participants) (Fig. 1) [25^{••}]. Subgroup analysis by eczema severity or presence of atopy did not identify a population with different treatment outcomes [25^{••}]. Significant heterogeneity was noted between studies, which may be explained by the use of different probiotic strains. Therefore, lack of effect based on pooled data from different probiotics does not exclude the possibility that a certain strain or a strain combination could still be effective. A recent meta-analysis by Michail *et al.* [28^{••}] reported a significant difference favouring probiotics in reducing the SCORAD Severity Index score (mean change from baseline –3.01, 95% CI –5.36 to –0.66, $P=0.01$), and children with moderately severe disease were more likely to benefit; however, this magnitude of effect is of limited clinical significance. Topical application of probiotic for the treatment of atopic dermatitis was recently evaluated in a single study that reported significantly reduced SCORAD score and pruritus following treatment with topical *Vitreoscilla filiformis* lysate cream compared with placebo and decreased loss of sleep compared with the start of the treatment [29]. Future studies evaluating topical approaches would be of interest.

Placebo-controlled studies of prebiotics and synbiotics for treatment of eczema are scarce. A small study assessing the efficacy of kestose, a fructooligosaccharide (FOS), reported significantly lower median SCORAD score in the active vs. placebo groups after 6 weeks (25.3 vs. 36.4, $P=0.04$) and 12 weeks (19.5 vs. 37.5, $P<0.001$) of treatment [30]. Treatment with a synbiotic preparation of *Bifidobacterium breve* M-16V and a mixture of galactooligosaccharide (GOS) and FOS did not improve the SCORAD score compared with placebo, although synbiotic treatment did result in significantly greater improvement in SCORAD in a subgroup of infants with IgE-associated eczema [31].

Probiotics for the treatment of food allergy

Although there are mechanistic data to suggest that probiotics may have a role in the treatment of food allergy by promoting gut barrier integrity [32], suppressing intestinal inflammatory responses [14,33], and inducing IgA production and tolerogenic immune responses, there is currently no evidence that such an approach is effective for induction of tolerance in the clinical setting. A randomized double-blind placebo-controlled (DBPC) study [34^{*}] of 119 infants with cow's-milk allergy (confirmed by food challenge) found no effect of probiotic supplementation (*L. casei* CRL431 and *B. lactis* Bb-12 for 12 months) on acquisition of tolerance to cow's milk. In a small mechanistic study [35] over 3 years of children with sensitization to egg, peanut or cow's milk and clinical

Table 1 Randomized controlled trials of probiotic with or without prebiotic supplementation for the treatment of eczema

Study	Methods	Participants	Interventions	Outcomes
Brouwer <i>et al.</i> [16]	3-month parallel group RCT	50 formula-fed infants with eczema and suspected CMA	Test: eHF with <i>L. rhamnosus</i> or LGG at 5×10^9 cfu/100 ml, Control: eHF without probiotic	SCORAD
Folster-Holst <i>et al.</i> [17]	8-week parallel group RCT	53 children with eczema	Test: 1×10^{10} cfu/day LGG, Control: microcrystalline cellulose	Global assessment, QoL score, SCORAD, medication use
Gruber <i>et al.</i> [18]	12-week parallel group RCT	106 infants with eczema; SCORAD 15–40	Test: 1×10^{10} cfu/day LGG, Control: placebo capsule	SCORAD, medication use
Hattori <i>et al.</i> [12]	3-month parallel group RCT	17 children with eczema, suspected CMA, low fecal <i>Bifidobacterium</i> level	Test: eHF with prebiotic and <i>B. breve</i> M16-V at $5-15 \times 10^9$ cfu/day, Control: eHF with prebiotic and no probiotic	Eczema severity scoring scale
Isolauri <i>et al.</i> [13]	6-month parallel group RCT	27 breast-fed infants with eczema	Test: eHF with Bb-12 at 1×10^9 cfu/g or LGG at 3×10^8 cfu/g, Control: eHF without probiotic	SCORAD
Kirjavainen <i>et al.</i> [27]	Parallel group RCT (variable treatment duration as the study was terminated prematurely due to adverse events)	27 infants with eczema and suspected CMA	Test: eHF with LGG at 3×10^{10} cfu/kg/day, Control: eHF without probiotic	SCORAD
Majamaa and Isolauri [14]	1-month parallel group RCT	31 children with eczema and suspected CMA	Test: eHF with LGG at 5×10^8 cfu/g; Control: eHF without probiotic	SCORAD
Passeron <i>et al.</i> [26]	3-month parallel group RCT	48 children with eczema; SCORAD >14	Test: prebiotic powder with <i>L. rhamnosus</i> Lcr35 at 3.6×10^9 cfu/day; Control: prebiotic powder alone	Global assessment, SCORAD
Rosenfeldt <i>et al.</i> [21]	6-week cross-over RCT	58 children with eczema	Test: <i>L. rhamnosus</i> 19070–2 and <i>L. reuteri</i> DSM12246 at 2×10^{10} cfu/day; Control: skim milk powder + dextrose	Global assessment, SCORAD, medication use
Sistek <i>et al.</i> [19]	12-week parallel group RCT	60 children with eczema, atopy, SCORAD >10	Test: <i>L. rhamnosus</i> and <i>B. lactis</i> at 2×10^{10} cfu/day; Control: microcrystalline cellulose	SCORAD
Viljanen <i>et al.</i> [20]	4-week parallel group RCT	252 infants with eczema and suspected CMA	Test: cow's milk elimination, eHF and LGG at 10^{10} cfu/day or probiotic mix, Control: cow's milk elimination and eHF	SCORAD
Weston <i>et al.</i> [15]	8-week parallel group RCT	56 children with eczema; modified SCORAD ≥ 25	Test: <i>L. fermentum</i> VR1–003PCC 2×10^9 cfu/day; Control: maltodextrin placebo	Global assessment, QoL score, SCORAD, medication use

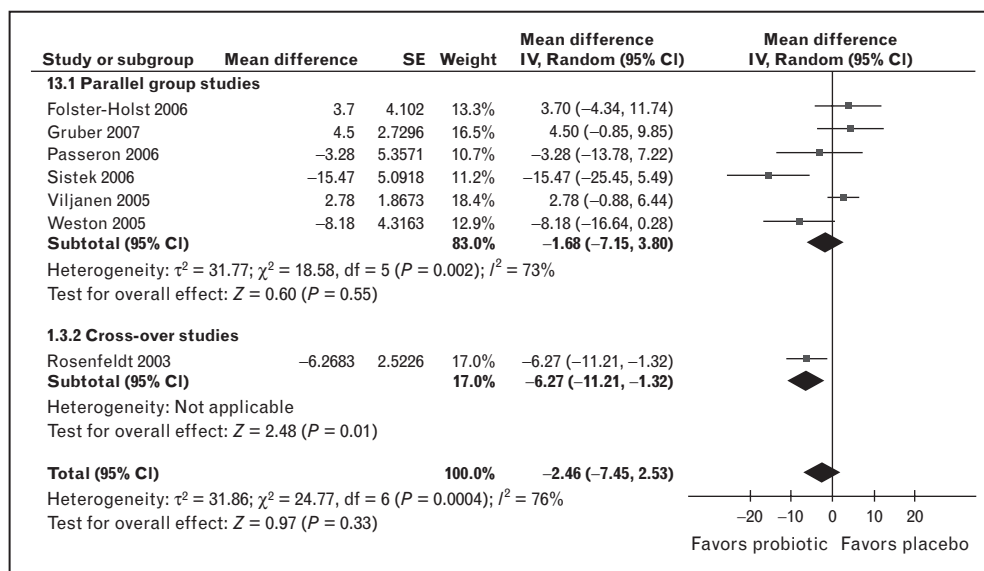
cfu, colony forming units; CMA, cow's milk allergy; eHF, extensively hydrolysed formula; LGG, *Lactobacillus rhamnosus* GG; QoL, quality of life; RCT, randomized controlled trial; SCORAD, scoring atopic dermatitis. Reproduced with permission from [25**].

symptoms, oral administration of a probiotic mix (predominantly *Lactobacillus* and *Bifidobacterium* species for 3 months) failed to influence sensitization (skin prick test size or allergen-specific IgE levels) or ex-vivo immune responses. Of note, in contrast to other studies that have suggested individual probiotic bacteria can be expected to have similar in-vivo and in-vitro effects, the probiotic mix in this study induced opposite effects *in vitro* as compared with *in vivo* [35]. In the study by Viljanen *et al.* [20] discussed in the preceding section, a subgroup of 120 infants with eczema had concomitant cow's milk allergy confirmed by DBPC food challenge, and subgroup analysis of data for this group revealed no difference in eczema severity at the end of probiotic treatment (mean difference 1.15 points on SCORAD scale, 95% CI –3.20 to 5.50). Therefore, current evidence indicates that probiotic treatment does not modify the natural course of

food allergy or reduce eczema severity in infants with concurrent eczema and cow's milk allergy. To our knowledge, prebiotics have not been evaluated for the treatment of food allergy in randomized controlled trials (RCTs).

Probiotics for the treatment of allergic rhinitis, asthma and vernal keratoconjunctivitis

DBPC studies of probiotic treatment for allergic rhinitis and asthma provide conflicting results, and studies of prebiotics in this area are limited. Many studies have included mixed-patient populations with allergic rhinitis or asthma rather than either condition alone. DBPC studies in adolescents with allergic rhinitis reported improvements in quality of life scores and rescue antihistamine use following 3–4 weeks treatment with *L. paracasei* [33] or *Bacillus clausii* [36–38]. In contrast,

Figure 1 Meta-analysis of published and unpublished data from randomized controlled trials of probiotics for the treatment of eczema

Seven of 12 published trials could be included in this meta-analysis, which shows the effect of probiotic treatment on eczema severity (SCORAD score, scale 0–102) at the end of treatment [25**]. SCORAD, scoring atopic dermatitis.

DBPC studies in children evaluating *Tetragenococcus halophilus* Th221 or a combination of *L. acidophilus* NCFM and *B. lactis* BI-04 found no significant differences between treatment and placebo groups, although high-dose *T. halophilus* Th221 was associated with improvement in symptoms from baseline which was not seen in the placebo group [39], and *L. acidophilus* NCFM/*B. lactis* BI-04 reduced eosinophil infiltration into the nasal mucosa [40]. Studies in adults with Japanese cedar pollen seasonal allergic rhinitis have failed to demonstrate clear beneficial effects (*B. longum* BB536, *L. casei* strain Shirota (LcS), *L. acidophilus* L-92, or a fermented milk containing LGG and *L. gasseri* TMC1551) [41–43], although some reported improved nasal blockage [44], nasal symptom-medication scores [44,45], eye symptoms [41] or eye symptom-medication scores [43]. Studies in mixed-patient populations – children aged 2–5 years with asthma and/or allergic rhinitis treated with *L. casei* [46], or adults and children with asthma/allergic rhinitis/oral allergy syndrome treated with LGG – reported no beneficial effects [47]. A study [48] of adults with asthma failed to demonstrate beneficial effects following treatment with a strain of *L. acidophilus*. A small open pilot study [49] reported improved clinical symptoms in patients with vernal keratoconjunctivitis following treatment with eye drops containing inactivated *L. acidophilus*; however, randomized controlled studies are required to confirm these effects. In summary, studies of probiotics for the treatment of allergic rhinitis and asthma are conflicting. There is currently insufficient evidence to suggest a role for probiotics in the treatment of allergic

rhinitis or allergic conjunctivitis. There is no evidence to support a role for probiotic treatment in asthma.

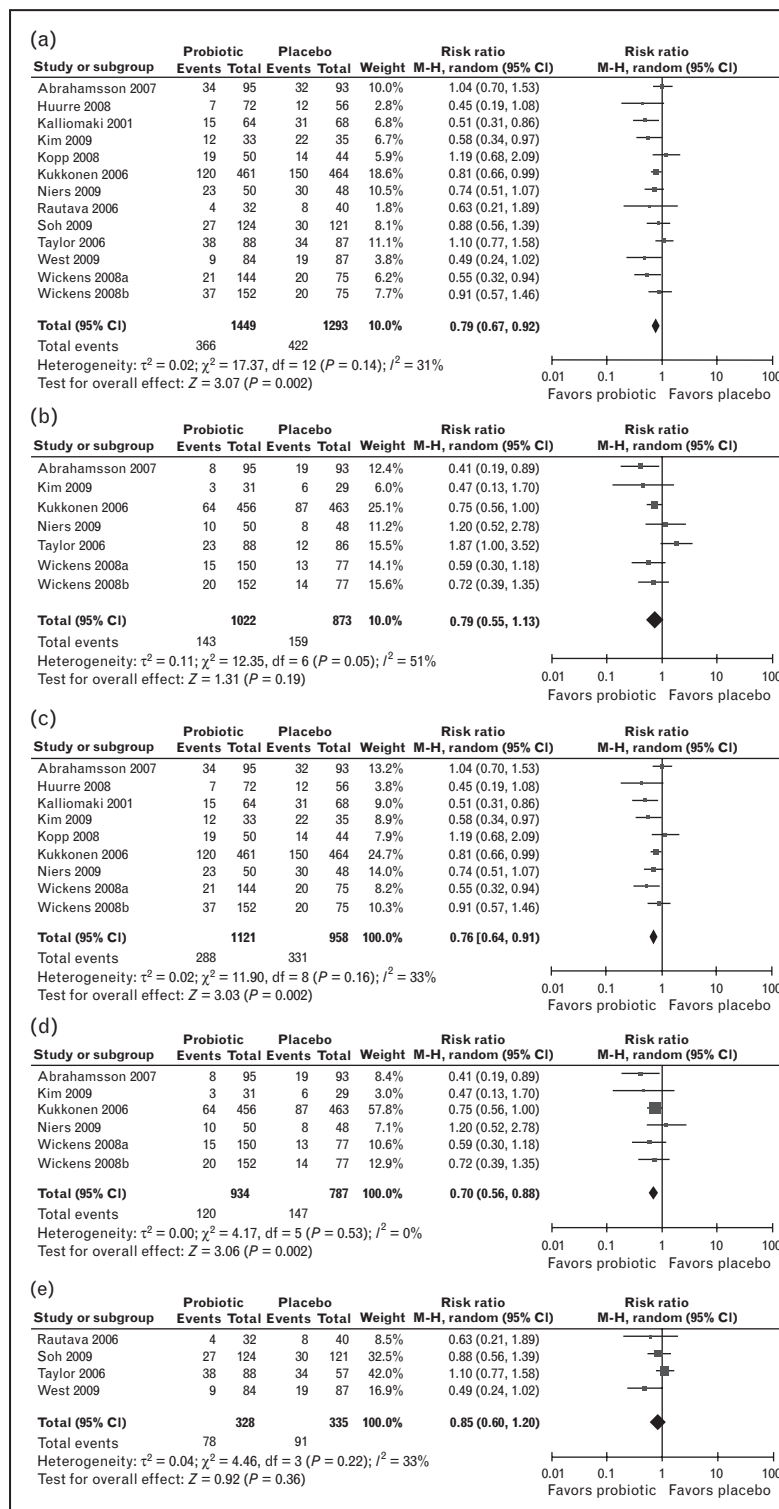
Prevention of allergic disease

Studies evaluating probiotics, prebiotics or synbiotics for the prevention of allergic disease are discussed.

Probiotics and synbiotics

At the time of this review, 13 RCTs [50–52,53*,54–56,57**,58–61,62*] evaluating various probiotic bacteria used alone or in combination with other probiotics (and also prebiotics in one study) have been reported. Meta-analysis of these studies (excluding one study [58] that was reported in abstract form) revealed a significant protective effect of probiotic treatments for eczema but not IgE-associated eczema (Fig. 2a and b). Nine studies (evaluating 10 interventions) involved a combined prenatal (last 2–6 weeks of pregnancy) and postnatal (6–24 months) treatment – nine probiotic interventions [52,53*,57**,58–61,63] and one synbiotic [54]. All but two of these studies recruited infants at increased risk of allergic disease (first-degree relative with allergic disease) – the studies by Huurre *et al.* [59] and Dotterud *et al.* [58] recruited an unselected population of mothers. Seven of the 10 prenatal/postnatal treatments resulted in significantly less eczema in the first 2 years of life – a reduced cumulative incidence of eczema [58,60,63], IgE-associated eczema [52], or both [54,57**] at age 2 years was reported with six treatments; and one treatment resulted in a reduced cumulative incidence of

Figure 2 Meta-analyses of randomized controlled trials of probiotics for the prevention of eczema



(a) Meta-analysis of published data from randomized controlled trials of probiotics with or without prebiotics for the prevention of eczema. One study reported in abstract form [58] could not be included in the meta-analysis. (b) Meta-analysis of published data from randomized controlled trials of probiotics with or without prebiotics for the prevention of IgE-associated eczema. (c) Meta-analysis of published data from randomized controlled trials of probiotics with or without prebiotics for the prevention of eczema, wherein treatment was commenced prenatally. (d) Meta-analysis of published data from randomized controlled trials of probiotics with or without prebiotics for the prevention of IgE-associated eczema, wherein treatment was commenced prenatally. (e) Meta-analysis of published data from randomized controlled trials of postnatal probiotics for the prevention of eczema, without a prenatal component to treatment. IgE, immunoglobulin E.

parent-reported eczema and doctor-diagnosed eczema at age 3 months but not at 1 or 2 years of age, with no effect on IgE-associated eczema [61]. Three of the 10 prenatal/postnatal treatments had no beneficial effects on eczema or IgE-associated eczema at age 1 or 2 years [53[•],57^{••},59]. We performed a meta-analysis of studies that evaluated combined prenatal and postnatal treatment and found a significant protective effect with probiotic/prebiotic treatment for both eczema (Fig. 2c) and IgE-associated eczema (Fig. 2d). The majority of treatments failed to modify infant sensitization. However, treatment with *L. reuteri* [52] or a combination of *B. lactis* BB12 and LGG [59] were both associated with significantly reduced sensitization in infants of allergic or sensitized mothers and *L. reuteri* was additionally associated with a trend to reduced sensitization for all infants in the treatment group [52].

Three of the four studies [51,55,56] that evaluated postnatal (without prenatal) treatment with various probiotic bacteria reported no beneficial effects on the development of eczema, IgE-associated eczema or sensitization at 12 months. Meta-analysis of these four revealed no effect of treatment on the development of eczema (Fig. 2e). Moreover, postnatal treatment with *L. acidophilus* LAVRI-A1 was instead associated with an increased risk of both IgE-associated eczema [relative risk (RR) 1.87] and atopic sensitization (RR 1.63) at 1 year [56], and increased sensitization was still evident at 2.5 years of age (although eczema was no longer significantly different between groups) [64]. One study reported a reduced cumulative incidence of eczema at 13 months following treatment with *L. paracasei* F19 during weaning (from 4 to 13 months of age) [62[•]]. Two of these postnatal studies [51,56] recruited high-risk infants with a family history of allergic disease, whereas the other two studies [55,62[•]] included formula-fed infants irrespective of allergic disease family history.

Other allergic disease outcomes (recurrent wheeze, asthma, allergic rhinitis, food allergy) were assessed in five studies. Kukkonen *et al.* [54] found no difference in the cumulative incidence of all allergic diseases or IgE-associated allergic diseases, and Dotterud *et al.* [58] found no difference in asthma or allergic rhinitis at age 2 years. However, Kopp *et al.* [53[•]] reported an almost three-fold increased risk of recurrent wheezing bronchitis at age 2 years with LGG, and trends to increased wheezing or asthma were noted in two other studies [50,56]. Additional data on asthma and allergic rhinitis outcomes will become available as further follow-up analyses are performed on the above studies.

Several interesting observations emerge when the findings from prevention studies are considered together. Firstly, the majority of combined prenatal/postnatal treat-

ments were effective in reducing eczema and/or IgE-associated eczema in the first 1–2 years of life, whereas the majority of treatments involving only a postnatal component of therapy failed to reduce the risk for eczema and/or IgE-associated eczema. This suggests that a prenatal component of treatment is important for beneficial effects. Secondly, administration of a probiotic mix (LGG, *L. acidophilus* LA-5, *B. lactis* Bb-12) solely to women from 36 weeks of pregnancy to 3 months postpartum without direct infant supplementation was sufficient to reduce the cumulative incidence and prevalence of eczema at 2 years [58], indicating that direct infant probiotic supplementation in early life may not be an absolute requirement for protective effects. Consistently with this, in the studies by Kalliomaki and coworkers [63,65], the greatest protective effects of LGG treatment were observed in breast-fed infants for whom probiotic was administered to their mothers during pregnancy and breast-feeding, without direct administration to the infant until after 3 months of age. The beneficial effects in these breast-fed infants may have been related to increased breast-milk transforming growth factor (TGF) β -2 levels in breast-feeding mothers treated with LGG [65]. Thirdly, in the study by Wickens *et al.* [57^{••}], which evaluated two different probiotic treatments compared with placebo, *L. rhamnosus* HN001 resulted in beneficial effects on eczema but *B. animalis* subsp. *lactis* HN019 did not, despite the fact that both strains were associated with immunomodulatory effects in cord blood and breast milk [66[•]]. This emphasizes the specificity of clinical effects of probiotic bacteria and our current limited understanding of the immune mechanisms mediating protective effects. Fourthly, Kopp *et al.* evaluated prenatal and postnatal LGG treatment using the same dose and a similar protocol to the original Kalliomaki *et al.* study, but, contrary to the Kalliomaki *et al.* study, they found no effects on eczema [50,53[•],63,67]. The reasons for the discrepancy between the Kalliomaki *et al.* [50,63,67] and Kopp *et al.* [53[•]] studies are not understood; however, genetic or dietary differences in the study populations may have contributed to these discrepant outcomes. It has been reported that gene polymorphisms in innate receptors may modify immune responses following signalling through these receptors. For example, CD14/-1721 polymorphisms can modulate the protective effects of farm-milk ingestion on development of eczema [68] – in children from two cohort studies of farm exposure and allergic disease, the protective effects of farm-milk ingestion were strongest amongst children with CD14/-1721 AA genotype, intermediate in those with AG genotype, and absent for the GG genotype [68]. It is likely that the ability of microbial exposures (including probiotics and prebiotics) to modulate immune responses and protect against the development of allergic disease is influenced by genetic factors in the individual.

In summary, current studies suggest a potential role for probiotics or synbiotics in the prevention of eczema and/or IgE-associated eczema. Prenatal treatment appears necessary for protective effects, highlighting the importance of prenatal influences on the development of infant immune responses. It is not known whether ongoing postnatal therapy is also important, and results of our study evaluating prenatal (without postnatal) treatment for the prevention of eczema (www.nottingham.ac.uk/ongoingskintrials; trial no. 36) will provide insights in this regard. Careful selection of appropriate probiotic bacteria for future studies will be important, which may be aided by in-vitro, preclinical and pilot studies. A Cochrane systematic review of some of these prevention studies concluded that, although a reduction in eczema was observed, further studies are required to determine whether the findings for eczema are reproducible [69]. However, it should be noted that there is a data-entry error in analysis 1.5 of the Cochrane systematic review for the study of Rautava *et al.* [65], which resulted in an overestimation of the effectiveness of probiotics for eczema prevention, and additional studies have since been completed, so that the conclusions should be interpreted with these considerations in mind. Our own meta-analyses, which include additional studies published since the Cochrane meta-analysis (Fig. 2a–e), suggest that probiotics may be an effective intervention for preventing eczema or IgE-associated eczema, particularly if treatment is administered both prenatally and postnatally. There is currently no evidence that probiotics are of benefit for prevention of other allergic conditions. An important limitation of meta-analyses of studies evaluating probiotics for the prevention of allergic diseases is that data have been pooled from studies conducted with a variety of different probiotic combinations. Indeed, strain selection has been clearly demonstrated to be a critically important factor in the ability of probiotic strains to prevent eczema [57••].

Prebiotics

There have been two studies of prebiotics for the prevention of eczema. The first study, by Moro and co-workers [70•,71], evaluated GOS/FOS (0.8 g/100 ml) vs. maltodextrin placebo supplemented into extensively hydrolysed formula during the first 6 months of life for the prevention of eczema in high-risk infants with parental history of allergy. At 6 months, there was a significantly reduced risk of eczema (RR 0.42) with the GOS/FOS treatment [71]; at 2 years, this protective effect was still evident (RR 0.49), and recurrent wheeze (RR 0.37) and allergic urticaria (RR 0.15) were also significantly reduced [70•]. A study by Ziegler *et al.* [72] in healthy term infants not selected on the basis of family history of allergy compared two prebiotic supplements (polydextrose/GOS 50:50, 4 g/l; polydextrose/GOS/lactulose 50:33:17, 8 g/l) with control formula and reported

an increased rate of eczema with polydextrose/GOS but not with polydextrose/GOS/lactulose as compared with placebo; however, the validity of this finding is uncertain as it is unclear when the eczema outcome was assessed and no information is provided regarding the criteria for determining the presence of eczema. Although the effects of prebiotics for the prevention of eczema in high-risk infants seem promising in one study, further studies are required to confirm this finding [69]. It should be noted that the positive study evaluated prebiotic use in a very specific population – infants with a family history of allergic disease, who had formula feeding introduced within the first 2 weeks of life, were fed an extensively hydrolysed whey formula, and completely ceased breastfeeding before 6 weeks of age. Prebiotic oligosaccharides are present at high concentration in human breast milk. Therefore, if prebiotics do have a role in eczema prevention, their role is likely to be as an additive to infant formula in those infants in whom exclusive breast-feeding cannot be maintained during the first weeks of life. This contrasts with the possible role of probiotics, which may be effective in both formula and breast-fed infants for the primary prevention of allergic disease. Further prebiotic eczema prevention trials are underway internationally, which will clarify the effects of prebiotic supplementation in different populations.

Conclusion

Studies suggest a potential role for selected probiotics in the prevention of eczema, especially IgE-associated eczema [69]. Our meta-analysis presented in this review (Fig. 2a–e), which includes additional studies published since the Cochrane meta-analysis by Osborne *et al.* [69] in 2007, further suggests that a prenatal component of treatment is important for beneficial effects. It may be important to continue treatment during the postnatal period for maximal effect, and indirect administration to mothers while breastfeeding may be especially beneficial. In contrast, administration of probiotics solely in the postnatal period has not proved beneficial (Fig. 2e). In order to translate the promising findings regarding probiotic intervention for eczema prevention into a meaningful public health intervention, further work is needed to clarify the optimal dose and combinations of bacterial strains, whether there is added benefit in combining probiotic with prebiotic, the optimal timing for intervention, and the patient populations who would most benefit from such therapies. There have been fewer studies of prebiotics for the prevention of allergic disease [69]. The role of prebiotics may be limited to use in infants who cannot be exclusively breast-fed for the first weeks of life.

Studies examining the use of probiotics for the treatment of allergic disease have been less promising. A recent Cochrane systematic review [25••] concluded that

probiotics were not effective for the treatment of eczema. As with prevention, the potential efficacy of treatment of eczema with probiotics and prebiotics is likely to be specific to strains and combinations. Studies of probiotics for the treatment of asthma and allergic rhinitis provide conflicting results and further studies are required.

Acknowledgement

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 682–683).

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