

EDITORIAL

Clinical & Experimental Allergy

Probiotics for the prevention of allergic disease

This editorial discusses the findings of the paper in this issue by Wickens et al. [21], pp. 1071–1079.

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Allergic diseases continue to increase in prevalence, and their epidemiology suggests that primary prevention should be possible. Yet, despite almost four decades of research since the first observation of environmental associations of atopy, we do not have a single intervention with proven efficacy for primary prevention [1, 2]. Perhaps, the most promising unproven intervention is probiotic bacteria. These were first suggested to prevent eczema by Kalliomaki et al. in 2001, who tested *Lactobacillus rhamnosus* GG (LGG) given both pre and postnatally to high risk infants, and showed a striking reduction in eczema by age 2 years [3]. The weight of evidence from at least 13 subsequent randomized controlled trials and associated meta-analyses suggests that probiotics are indeed effective for preventing eczema during the first 2 years [4]. In Kalliomaki's study, this effect persisted to age 7, but in a much larger trial, which used a mixture of four probiotics including LGG, the reduction in eczema at 2 years appeared to be lost at age 5, except in a subgroup born by Caesarean section [5, 6].

In this issue of *Clinical and Experimental Allergy*, Wickens et al. report outcomes at age 4 in their interesting probiotic prevention trial. The trial is notable for increased intensity of probiotic treatment, and comparison of two different probiotics – treatment occurred for 2 years, and was administered to both mother (1 month prenatally and during lactation) and infant. Treatment was effective at age 4 for the *Lactobacillus rhamnosus* strain, but not for the *Bifidobacterium lactis* strain, with

similar effect sizes at 4 years to 2 years. Excitingly, they also found reduced prevalence of rhinoconjunctivitis symptoms, suggesting the possibility that by preventing eczema, this intervention might impact on other features of the 'allergic march'. Although participants had been unblinded to their treatment allocation before this 4-year outcome assessment, the objective and subjective outcomes from this trial suggest that *L. rhamnosus* can reduce risk of allergic disease beyond the first 2 years of life.

So, why aren't we recommending probiotic treatment for all pregnant women and their infants, in those countries with high allergic disease prevalence?

The main issue is the inconsistency between individual study outcomes. For example, a German study with very similar design and intervention to Kalliomaki et al. showed no evidence that LGG can prevent eczema [7]. Although several studies of 'postnatal only' probiotics have been unsuccessful, one such trial was successful and a trial of 'prenatal only' probiotics was unsuccessful [8, 9]. Probiotic supplementation of lactating mothers without infant supplementation, an attractive intervention due to its simplicity, has shown positive outcomes in two studies [10, 11]. In interpreting the probiotic intervention studies, some allowance must be made for variations in dose, formulation and species of probiotic used. Wickens et al. have clearly shown that the protective effects of probiotics in this setting are species-specific [21]. Probiotic effects may also depend on host microbiota and/or genotype – the results of one recent study of a bacterial lysate for preventing eczema in infants suggested potentially important gene-environment interactions [12].

In view of the inconsistency between study findings, it is necessary to understand what we are trying to achieve at a physiological or cellular level before further developing this intervention. The most common paradigm inferred by investigators is that probiotics colonize and modify the intestinal microbiota of the

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infant and thereby influence immune programming in the intestine. This was supported by the earlier observation of lower lactobacilli and bifidobacteria in the faeces of children who later develop allergy [13]. However, these associations between early intestinal microbiota and allergy are not consistent between studies, and there is little evidence that short term probiotic treatment leads to long term modification of the intestinal microbiota in humans [14, 15]. Immunological effects *in vivo* do occur, however, – a probiotic mix which includes LGG was found to increase serum C-reactive protein, IL-10, IgE and IgA levels in infants, in a similar way to intestinal helminth infections [16]. So, perhaps the induction of chronic low-grade inflammation in the infant may be a relevant mechanism. Alternatively, probiotics may have a direct immune effect on pregnant or lactating mothers, changing the immune signals that they send to their infant via the placenta or breast milk. Probiotic supplementation certainly has detectable effects on breast milk composition, but these effects have not been consistently linked with clinical outcomes in the infant [9, 17]. The use of systematic methodologies to better understand breast milk composition, and maternal and infant microbiota may help progress

our understanding of probiotic mechanisms of action [18, 19].

We may not need to understand the precise mechanism of action to turn this into a public health intervention, but we do need some of the positive trials to be replicated, so that we can confirm which probiotics we should use and when to use them.

One important barrier to progressing this area of research is regulatory uncertainty – probiotics are usually regulated as food supplements, and although this reduces some of the regulatory requirements for their manufacturers compared to a medicine, it ultimately places limits on the precision and strength of the health claims that can be made [20]. So, even if a specific probiotic strain used at a specific dose in a specific formulation can be shown to prevent eczema, it may not be possible to state that clearly on the label.

The study of Wickens *et al.* should give us hope that an effective measure for preventing allergic disease may be around the corner, but findings such as these should also persuade the probiotic industry and regulators to move to ensure that effective probiotics come to market in the form in which they were tested, with an appropriate health claim on the label.

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