Primary Prevention of Food Allergy: Translating Evidence from Clinical Trials to Population-Based Recommendations

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

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List of Design Committee Members: Paul J. Turner, FRACP, PhD, Dianne E. Campbell, FRACP, PhD, Robert J. Boyle, MB ChB, PhD, and Michael E. Levin, MD (authors); Michael Schatz, MD, MS (editor)

Learning objectives:

1. To describe the issues in using study data to inform population-based interventions to prevent food allergy.

2. To understand the need to distinguish between Efficacy trials (which might reflect ideal circumstances) and Effectiveness trials (which assess effect in the "real world").

3. To identify the current knowledge and evidence gaps in strategies that have been considered to potentially prevent food allergy at a population level.

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Abbreviations used
GRADE- Grading of Recommendations Assessment, Development and Evaluation
HIV- Human immunodeficiency virus
LEAP- Learning Early About Peanut
NNT- Number needed to treat
RCT- Randomized controlled trial
WAO- World Allergy Organization

Given the prevalence and impact of childhood food allergy, there is increasing interest in interventions targeting disease prevention. Although interventions such as early introduction of dietary peanut have demonstrated efficacy in a small number of well-conducted randomized clinical trials, evidence for broader effectiveness and successful implementation at a population level is still lacking, although epidemiological data suggest that such strategies are likely to be successful, at least for peanut. In this commentary, we explore the issues of translating evidence of efficacy studies (performed under optimal conditions) to make policy recommendations at a population level, and highlight potential benefits, harms, and unintended consequences of making population-based recommendations on the basis of randomized controlled trials. We discuss the complexity and barriers to effective primary and secondary prevention intervention implementation in resource-poor settings. **(J Allergy Clin Immunol Pract 2018;6:367-75)**

Key words: *Allergy; Prevention; Peanut; Translation; Implementation*

The mainstay of food allergy management has been allergen avoidance and the provision of rescue medication in the event of accidental reactions. The lack of alternative robust treatment options, together with an increasing prevalence in many countries,[1] has created a major public health concern. This has stimulated research into the processes underlying the development of food allergy, with the aim of identifying effective prevention strategies. Such strategies may be population based or targeted to an individual, and can be divided into primary prevention (which aim to prevent disease before its onset) and secondary prevention (where early signs are targeted to mitigate or halt disease).[2]

Clinical trials are generally undertaken with significant resources, optimal conditions, and homogeneous participants with limited geographical and environmental variation. Such studies are efficacy trials—assessing the outcome of an intervention under ideal conditions. This is in contrast to effectiveness trials, which are performed under real-life, pragmatic conditions. It is insufficient to demonstrate that an intervention is successful within the confines of a randomized controlled trial (RCT) to ensure that it will be an effective intervention across the population at large.[3] Population-based interventions need to be assessed not only for level of evidence, applicability, and feasibility before recommendations are made, but they also need to be evaluated once implemented, such that their actual impact, and any unintended consequences (or harm), can be determined.

In this commentary, we discuss the main challenges and risks of using data from efficacy trials to develop public health interventions appropriate to the general population, and explore barriers to the successful implementation of measures to reduce the community burden of food allergy.

ASSESSING THE QUALITY OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS

The first requirement for any disease prevention program is ensuring the sensible and accurate translation of evidence arising from clinical trials into public health recommendations and policy. This is a complex process that is best approached in a systematic way. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group has developed a commonly used tool to evaluate the certainty of findings arising from a systematic review of the evidence,[4,5] and a separate tool to assist with making recommendations for treatment, diagnosis, or prevention.[6] These are summarized in Figure 1. In brief, the available evidence for each outcome of interest is first assessed for quality, from very low to high, according to the confidence in the evidence. This may be downgraded because of variety of reasons as outlined in Table I. Once the quality of the evidence has been assessed and considered sufficiently robust to merit consideration for translation, the applicability to the wider population must then be evaluated (Table II). A strong recommendation would be appropriate when most patients (or their families) would want the intervention, where the majority of clinicians agree that the intervention should be offered, and where the recommendations are acceptable as a public health measure to policy makers.[8]

The GRADE framework has been used by the Allergic Rhinitis and its Impact on Asthma group and working groups within the World Allergy Organization (WAO),[9] and by WAO to make recommendations regarding the use of probiotics for allergic disease prevention.[10] However, with respect to food allergy prevention, although there have been several recommendations arising from national specialist organizations, it is not clear that any of these have yet undertaken this robust approach to formulating recommendations to be implemented at a population level.

INTERVENTION STRATEGIES FOR PREVENTION OF FOOD ALLERGY

Table III summarizes existing synthesized evidence for food allergy prevention interventions of current high interest using the GRADE approach. Although it is beyond the scope of this review to discuss each intervention in detail, there are only a few interventions that currently have sufficient evidence to warrant consideration as a population-based implementation. These include early introduction of peanut and egg to the infant diet,[17] maternal probiotic supplementation during pregnancy and lactation,[10] and maternal fish oil supplementation during pregnancy.[11,12,14] The remainder of the synthesized evidence to date shows low or no evidence when assessed using the GRADE approach,[13,15,16,18,19] including allergen avoidance during pregnancy and lactation.[11-13] We do not discuss probiotics or fish oil further in this commentary, because the evidence for their effectiveness is of either indirect or low quality (Table III) and neither are widely recommended for food allergy prevention in most current guidelines.