Preventing immediate-onset food allergy in infants, children and adults
Systematic review protocol

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Title page

1. **Full title of manuscript, concise and informative, not exceeding 100 characters**

Preventing immediate-onset food allergy in infants, children and adults: systematic review protocol

2. **Authors’ full names**

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4. Statement of author contributions

All authors jointly developed the content for this article. CS and DdS developed an initial draft for refinement by GR, SH and AM. All other authors contributed further refinements and quality assured the material in writing and verbally. GR acted as the final decision maker and guarantor. All authors have made substantial contributions to conception and design of this paper, been involved in drafting the manuscript or revising it critically for important intellectual content, given final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

5. Running title, not exceeding 40 characters and spaces

Preventing food allergy: review protocol

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7. Word count; number of tables and figures

Abstract: 272 words
Main text: 3000 words
Tables: 0
Figures: 1

Note: the original article submitted was under the word limit but in order to briefly address each of the comments of the reviewers we have had to increase the number of words and the number of references (34).

8. Material in the electronic repository, if applicable

A file has been submitted for consideration as an online supplement. This contains example search strategy, example data extraction form and example data display tables.

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Preventing immediate-onset food allergy in infants, children and adults: systematic review protocol

i. Statement with potential conflict of interests related to the manuscript content

The authors declared no conflict of interest in preparing a protocol for a systematic review.

Some of the authors have professional affiliations related to the content of the review to be conducted as set out below. During the conduct of the review itself, these authors will not be involved in decisions about study selection, data extraction or analysis of studies in fields where they have a declared interest.

The following authors declared no potential interests: CS, DdS, EA, HA, SA, VV.
The following authors declared interests as follows:

AM: Research: Aimmune; Speaker: DVB, Aimmune, Mylan, ALK, Nestle;

AH: Speaker: Nestle, Bristol-Myers, ALK;

CV: Research: ThermoFisher. Speaker: Danone, Abbott, Nestle, Mead Johnson;

CJ: Employee of Allergy UK. Allergy UK has received funding from Abbott, Aimmune, Allergy Therapeutics, DBV, Danone, Nutricia, Mead Johnson, Sanofi-Genzyme;

GdT: Research: Aimmune, DBV, NIH (LEAP study), Action Medical (EAT study). Education: Allergy Academy;


GR: Research: NIH (LEAP study), Action Medical (EAT study). Consultant: Nutricia. Editor: Journal of Ped Gastroenterology and Nutrition;


KB: Research: Aimmune, ALK, Berliner Sparkasson Stiftung, Danone, DBV, DST Diagnostic, Good Mills, Hipp, Hycor, Infectopharm, ThermoFisher, VDI, EU, German Research Foundation, BMBF. Consultant: Alimmune, ALK, Allergopharma, Bausch & Lomb, Bencard, Danone, Hycor, Di-Text, Hammer und Rall Media, Infectopharm, Mabylon, Meda Pharma, Mylan, Nestle, Unilever;

KG: Consultant: Nutricia, Abbott, Mead Johnson, Reacta Biotech;

RB: Consultant: Diary Goat Cooperative, Cochrane Children and Families.
ii. Financial support

The European Academy of Allergy and Clinical Immunology (EAACI) will fund the systematic review to support the development of European guidelines. The funder had no role in the development of the protocol. The funder will not have any role in the conduct of the review or its publication.

iii. Abstract and keywords

Background

More than 17 million people across Europe have allergies to food and the burden of food allergies is increasing. In 2014 the European Academy of Allergy and Clinical Immunology (EAACI) published guidelines for preventing food allergy. Important research has been published since then and it is essential to ensure the guidelines reflect the latest evidence. A systematic review will be undertaken to help prepare new guidelines due to be published in 2020.

Methods

Eleven bibliographic databases will be searched from inception to 31 October 2019 for randomised controlled trials about any intervention designed to prevent the development of new cases of immediate-type / IgE-mediated food allergy in infants, children and adults. There are few randomised controlled trials about the impact of breastfeeding on food allergy so prospective cohort studies about breastfeeding with at least 1,000 participants at general risk or 200 at high risk of food allergy will also be eligible. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach will be used to assess the certainty of the evidence and tabulate summary data. The risk of bias in individual trials will be assessed using the Cochrane risk of bias tool. All data extraction and quality appraisal...
will be undertaken independently by two reviewers in partnership with a taskforce of EAACI members.

Conclusions
Preventing food allergy has the potential to improve personal wellbeing and reduce societal healthcare costs. It is important that forthcoming European guidelines take the latest research into account. Past reviews have tended to focus on single interventions or combined food allergy with other outcomes, making it difficult to draw robust conclusions about potential impacts for policy and practice.

Keywords: Food allergy, IgE-mediated, Prevention, Infants, Children, Adults
Introduction

Rationale

About 17 million people in Europe have an allergy to foods such as cow’s milk, hen’s egg or peanut. The prevalence of food allergy is increasing. In Western countries, challenge-diagnosed food allergy has been reported to be as high as 10%, with the highest prevalence amongst infants and young children. There is also evidence of increasing prevalence in developing countries.

Food allergy can affect people’s wellbeing and result in costly medical visits and treatments. Food is an integral part of daily living so food allergy can have a substantial impact on the quality of life of those affected and their families. It also has a financial burden. A study in Europe found that the annual household cost of food allergy was €3,961 per affected child, including direct and indirect costs. This is broadly equivalent to estimated direct and indirect costs of $4,184 per affected child per year in the US.

In 2014, the European Academy of Allergy and Clinical Immunology (EAACI) released guidelines to help countries, clinicians and families consider the practical things that could be done to prevent food allergy and areas where more evidence was needed. Since that time, additional research has been published, including studies focused on preventing food allergy by introducing allergenic foods early into infants’ diets. It is important that European countries benefit from new guidelines, based on the latest evidence.

A number of recent systematic reviews are available and provide useful insights. However these reviews tend to combine food allergy with other outcomes or to focus on one specific intervention, such as infant formula or prebiotics. It is difficult to compare interventions because the inclusion criteria and measurement approaches vary across reviews. Some reviews, including a previous review by EAACI, have drawn conclusions based on studies of widely differing quality.

Objective
This paper sets out the protocol for a systematic review to support updating the EAACI food allergy guidelines, which are due for release in 2020. The protocol is constructed in line with the PRISMA-P checklist.\textsuperscript{19,20} It has been developed by a taskforce made up of EAACI members, which includes allergy, gastroenterology, primary care, dietetics and immunology clinicians, researchers, patient representatives and information specialists (all authors).

The aim of the systematic review is to assess the effectiveness and safety of any approach (interventions) for preventing the development of immediate-type or IgE-mediated food allergy (outcome) in infants, children and adults (population) compared to any other intervention or placebo (comparator).

Figure 1 provides a population, intervention, comparison and outcomes (PICO) statement.

The review protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO): registration number CRD42019127457. Any updates to the protocol will be made via PROSPERO.
Methods

Eligibility criteria

Studies will be eligible for inclusion in the review if they meet the following criteria:

- Population: infants (defined as up to 1 year old), children (13 months to 17 years) and/or adults (18+ years) with or without an increased risk for developing allergic disease and with or without any sensitisation or atopic manifestations. For the purposes of the review ‘increased risk’ will be defined as having a risk factor such as eczema or asthma or having immediate relatives with a history of food allergy, asthma, hay fever or other allergies.\(^{22}\)
- Intervention: any intervention to prevent the development of new cases of immediate-onset or IgE-mediated food allergy. This includes dietary initiatives and skin barrier initiatives.
- Comparator: any comparator, including placebo, no intervention or any other intervention or combination of interventions.
- Outcomes: studies that include the measurement of new cases of food allergy as a pre-defined outcome.
- Timeframe: published from database inception to 31 October 2019.

There will be no language or geographical restrictions.

Randomised controlled trials will be eligible for inclusion in the review. Where repeated reports of the same study are identified, the most up-to-date publication with food allergy as an outcome will be included unless there is a good clinical reason to use data from an earlier publication.

In addition, for research related to breastfeeding, prospective cohort studies with at least 1,000 participants at undifferentiated risk or at least 200 participants at increased risk of food allergy will be eligible for inclusion. This is because previous reviews\(^ {16,18}\) have shown that there is a lack of randomised controlled trials in this area and ethical issues preclude randomisation of infants to be breastfed or not. These sample size numbers have been selected as cut-off points as a proxy for studies large enough to provide credible trends.
given the expected proportions in populations who may develop food allergy. Food allergy affects around 2% of the general population, so to be sufficiently powered to detect even moderate effect sizes or association, studies need to be reasonably large. The sample size requirements will only be applied to prospective cohort studies of breastfeeding.

Studies will be excluded if they:

- focus exclusively on non-IgE-mediated food allergy
- focus on reactions to food that have been referred to as ‘food intolerance’ or non-immune food hypersensitivity
- include ‘sensitivity’, ‘hypersensitivity’ or similar as an outcome rather than ‘food allergy’ or specific food allergies
- aim to prevent potential manifestations of food allergy such as eczema but do not include an explicit diagnosis of food allergy. It is recognised that food allergy may have many different manifestations but these may also have other causes
- are systematic or non-systematic reviews, discussion papers, non-research letters and editorials, case studies, observational studies apart from those listed above regarding breastfeeding, animal studies, abstracts, studies not available in full form or unpublished material

These inclusion and exclusion criteria will be used at abstract and full text stages.
Information sources

Eleven bibliographic databases will be searched by an information specialist for studies published from database inception to 31 October 2019:

- Cochrane Library (ISSN 1465-1858) comprising Cochrane Database of Systematic Reviews (CDSR), Database of Reviews of Effectiveness (DARE), CENTRAL (Trials), Methods Studies, Health Technology Assessments (HTA) and Economic Evaluations Database (EED)
- CINAHL (Ebscohost, Cumulative Index to Nursing and Allied Health Literature)
- Embase (OVID)
- ISI Web of Science (Thomson Web of Knowledge)
- MEDLINE (OVID)
- WHOLIS (World Health Organization Library Information System)
- PAHO (Pan American Health Organization database)
- Science Citation Index and Social Sciences Citation Index
- TRIP Database (www.tripdatabase.com)
- WHO ICTRP (World Health Organization International Clinical Trials Registry Platform; www.who.int/ictrp)
- US National Institutes of Health Ongoing Trials Register (Clinicaltrials.gov, NIH web)

Unpublished research is not eligible for inclusion, but the trial registries in the list above will be searched to identify studies that may since have been published.

A search strategy has been devised on OVID MEDLINE and adapted for other databases (see online supplement for the search terms). The search strategy was developed with input from methodologists and information specialists (DdS, CS) working in partnership with clinicians and patient representatives (all other authors). To retrieve randomised controlled trials, the Cochrane strategy for identifying trials in MEDLINE will be used: sensitivity- and precision-maximising version.23

Additional references will be located by searching the reference lists of systematic reviews and identified studies and through discussion with experts in the field who are part of a taskforce developed for this purpose.
Selection process
Two reviewers (DdS, CS) will independently screen the titles and abstracts of potentially relevant studies to shortlist them for full text review. The reviewers have received training and have undertaken other systematic reviews.

Full text copies of all studies identified as potentially relevant by either reviewer will be obtained and their eligibility for inclusion assessed independently by the two reviewers using a checklist containing the inclusion criteria. Studies that do not fulfil all of the inclusion criteria will be excluded. Any discrepancies will be resolved by consensus and, if necessary, arbitration by a third reviewer (GR). Inter-rater agreement will be calculated using percentage agreement levels. Data will be available to calculate Kappa if required.
Once a shortlist of studies for inclusion is generated, a summary of each study will be reviewed by the entire EAACI guidelines taskforce to ensure clinicians and patient representatives agree with methodologists about eligibility and so that the experts can suggest any additional studies for consideration that have not been identified by the bibliographic searches. Each taskforce member will then be assigned to a topic group and will review the full text of all studies about that topic. These taskforce groups will recommend studies eligible for meta-analysis based on whether appropriately similar populations, interventions and outcome measures have been used in the studies to allow clinically meaningful compilation.

Data collection and management
Search results will be stored using Endnote X9 reference management software.

Data will be extracted from the selected studies including citation details, funder, country of study, study type, population type, sample number, food allergy risk status, intervention, comparator, outcome measures, and study outcome data (in the format of estimates, confidence intervals and p-values where available). The primary outcome of interest is new cases of immediate type / IgE-mediated food allergy. Data about adverse events will also be extracted where available. The rationale is that the effectiveness for prevention needs to be weighed against any safety issues or other adverse consequences. Given the variety of interventions that have been tested, studies are unlikely to have measured the same outcomes or used the same measurement approaches, so the review will extract the data in the form provided by individual studies.

Data will be independently extracted in duplicate into a customised data extraction form by two reviewers (CS, DdS) who have received training. The checklists used for screening and for data extraction will be piloted with a sample of studies, comparing results across two reviewers. A sample form is included in the online supplement. Any data extraction discrepancies will be resolved by discussion with arbitration by a third reviewer if consensus cannot be reached (GR). Agreed data will be stored in an Excel spreadsheet.

In addition, data extraction will be checked by the EAACI guidelines taskforce, divided into small groups. Taskforce members will only be part of topic review groups if they have no potential interests declared about a topic area. The purpose of clinicians and patients...
checking data extraction is to increase accuracy, ensure that clinically relevant outcomes have been extracted and ensure that the clinical and patient experts are aware of the study findings for interpretation.

Risk of bias in individual studies
The risk of bias will be examined at outcome level (using the GRADE approach described below) and at the level of individual studies. Randomised controlled trials will be assessed using the Cochrane Effective Practice and Organisation of Care (EPOC) risk of bias tool. Prospective cohort studies about breastfeeding will be assessed using the domains from the Strengthening the Reporting of Observational Studies in Epidemiology tool (STROBE). These tools were used when creating previous EAACI guidelines and have been chosen to aid consistency of EAACI reviews over time. The EAACI Taskforce was aware of alternative tools such as ROB-2 and ROBINS-I but felt that it was important to be consistent with 2014 guidelines in the bias assessment. The domains in EPOC are similar to the newer ROB-2 tool. A member of a Cochrane Collaborative group will review the quality assessments to ensure alignment with latest good practice (RB).

Two reviewers will independently assess the risk of bias for each study. This will then be checked with the EAACI taskforce topic review groups to make sure that clinical and patient representative views are included. Any discrepancies will be resolved by consensus and, if necessary, arbitration by the senior reviewer (GR). The risk of bias information will be used when analysing whether there is certainty of evidence overall for particular interventions.

Data synthesis
The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist will be used to guide the reporting of the systematic review.

The overall certainty of evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. GRADE is a framework for developing and presenting summaries of evidence to support clinical practice recommendations. A bespoke summary of findings table and evidence profile will be constructed for the primary outcome of new cases of food allergy. The online supplement provides the planned templates.
In addition, GRADE provides a framework for examining meta-biases such as the risk of publication bias. A funnel plot will be used to explore potential publication bias if six or more studies are available about any intervention, and tested by Egger’s regression test and Begg’s rank correlation test. The EAACI Taskforce will review the body of evidence about each intervention to develop a consensus about potential meta-bias.

If there were both observational studies and randomised controlled trials available about breastfeeding, then each study would be quality assessed and summarised in the same way as for other topics, with narrative analysis of themes from all of the evidence weighed against risk of bias.

Due to the heterogeneous nature of interventions and populations, the reviewers expect to undertake a narrative synthesis of all topics, summarising the results descriptively and drawing attention to any differences in outcome based on age or risk profile. The reviewers will examine whether interventions have been found to be more or less effective for groups at general or increased risk of food allergy because past research has found different effects or magnitude of effects (including safety outcomes) dependent on familial risk of allergy.

For some topics, such as hydrolysed infant formula or the early introduction of egg or peanut into infant diets, meta-analyses have already been conducted. The reviewers will draw on these in the review narrative rather than replicating existing work.

If the following criteria are met, additional random-effects meta-analysis will be undertaken: three or more studies about a topic are available; studies provide sufficiently detailed quantitative data to allow compilation; the data available are measured in a similar manner; the populations have a similar demographic and risk profile, and no other relevant meta-analysis has been published. Random-effects modelling has been selected to avoid overweighting studies with the largest sample sizes.

A statistician will be part of the review team (see Acknowledgements) and if appropriate will conduct the meta-analysis with the Comprehensive Meta-Analysis (version 3) software developed by Biostat. Odds ratios with 95% confidence intervals will be reported as a measure of overall effect size. The Comprehensive Meta-analysis program weights studies
by inverse variance rather than by sample size. This is a method of aggregating random
variables where each variable is weighted in inverse proportion to its variance in order to
minimise the variance of the weighted average. The inverse variance is roughly proportional
to sample size, but is a more nuanced measure. The pooled mean effect size will be
calculated using the random effects model. The $Q_{\text{within}}$-statistic will be used to assess the
heterogeneity of studies and quantified with the $I^2$ statistic. Probability value less than 0.1 will
be used to suggest statistically significant heterogeneity. Heterogeneity will be considered
low, moderate and high when the values are below 25%, between 25% and 75%, and above
75%, respectively. Subgroup analysis by age and food allergy risk profile will be undertaken
if supported by the data.

The review will be published and an online supplement will contain summary information
about each included study as well as tables summarising the outcomes associated with each
intervention.

Discussion
Preventing food allergy is important given its high societal and healthcare costs. However,
available evidence needs to be carefully evaluated to reach conclusions about which
preventative strategies should be routinely implemented.

The food allergy prevention guidelines released by EAACI in 2014\textsuperscript{6} have helped countries
adapt and strengthen their policies for the prevention of food allergy. Since the publication of
the European guidelines, several other societies and national bodies have released their
own guidelines or consensus statements.\textsuperscript{29-32} However, further important research has
emerged in this area so the European guidelines are being updated to take account of this.

This systematic review will not merely update a previous systematic review by EAACI,\textsuperscript{18}
because a number of lessons have been learnt and built into this protocol. Firstly, consistent
with other international guidelines, a GRADE approach will be used so that the focus is on a
defined and comparable outcome and so meta-biases can be accounted for. This will allow
clear links between the certainty of evidence and guideline recommendations.

Secondly, the review will include only primary studies rather than systematic reviews so that
data about the outcome of interest can be appropriately extracted and so that the quality and
outcomes of studies can be compared. Other systematic reviews are available and will be drawn on as a source of citations and for meta-analyses where appropriate, but previous reviews do not cover the entire range of interventions of interest or focus exclusively on food allergy.

Thirdly, the review will focus only on randomised controlled trials rather than, including a wide range of study designs as previously. This will ensure that it is easier and more appropriate to combine data and make robust recommendations than when study designs are heterogeneous and when quality varies substantially.

Fourthly, patient representatives and clinicians will be involved at all stages, from developing the protocol through to extracting data, assessing quality and synthesising the results. An international taskforce has been set up to support this. Drawing on lessons from other reviews, taskforce members will only be involved in analysing and discussing research about topics where they have no declared interests.

Finally, a statistician will be part of the taskforce to ensure appropriate expertise to combine data quantitatively if the data warrants this.

Implementing guidelines can be challenging and there has been considerable debate about how prevention interventions should be put into practice. One of the key issues supporting the implementation of guidelines may be their credibility, both from a scientific and reputational perspective. Strengthening the rigour and consistency of the methodology used to compile evidence in this review will support up to date and well considered recommendations to guide national policy and individual practice. The review will supplement the clinical expertise and experience that is key in considering what will be most appropriate for infants, children and adults in different parts of Europe.

v. Acknowledgments
The authors acknowledge the financial support of EAACI and the intellectual support of the EAACI Food Allergy and Anaphylaxis Guidelines Group. Tee Bahnson, Benaroya Research Institute, US will be the statistician for the group.

vi. References
1. European Academy of Allergy and Clinical Immunology. 17 million Europeans allergic to food; allergies in children doubled in the last 10 years. Zurich, Switzerland: EAACI; 2011.


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vii. Tables
None included

viii. Figure legends
Figure 1: Populations, interventions, comparators and outcomes of interest
- Infants (up to 1 year)
- Children (13 months to 17 years)
- Adults (18+)
- At general risk or high risk of allergy

**Intervention**
- Any intervention to prevent immediate or IgE-mediated food allergy

**Comparator**
- Any comparator including placebo, no intervention or alternative intervention

**Outcomes**
- New cases of immediate or IgE-mediated food allergy as predefined outcome
- Rate of adverse events