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## EAACI guideline

### Preventing the development of food allergy in infants and young children (2020 update)

Halken, Susanne; Muraro, Antonella; de Silva, Debra; Khaleva, Ekaterina; Angier, Elizabeth; Arasi, Stefania; Arshad, Hasan; Bahnson, Henry T.; Beyer, Kirsten; Boyle, Robert; du Toit, George; Ebisawa, Motohiro; Eigenmann, Philippe; Grimshaw, Kate; Hoest, Arne; Jones, Carla; Lack, Gideon; Nadeau, Kari; O'Mahony, Liam; Szajewska, Hania; Venter, Carina; Verhasselt, Valérie; Wong, Gary W.K.; Roberts, Graham; European Academy of Allergy and Clinical Immunology Food Allergy and Anaphylaxis Guidelines Group

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# EAACI guideline: Preventing the development of food allergy in infants and young children (2020 update)

Susanne Halken<sup>1</sup>  | Antonella Muraro<sup>2</sup>  | Debra de Silva<sup>3</sup>  | Ekaterina Khaleva<sup>4</sup>  | Elizabeth Angier<sup>5</sup> | Stefania Arasi<sup>6</sup>  | Hasan Arshad<sup>7,8,9</sup> | Henry T. Bahnson<sup>10</sup> | Kirsten Beyer<sup>11</sup> | Robert Boyle<sup>12,13</sup> | George du Toit<sup>14</sup> | Motohiro Ebisawa<sup>15</sup>  | Philippe Eigenmann<sup>16</sup>  | Kate Grimshaw<sup>8,17</sup> | Arne Hoest<sup>1</sup> | Carla Jones<sup>18</sup> | Gideon Lack<sup>19,20,21,22</sup> | Kari Nadeau<sup>23</sup>  | Liam O'Mahony<sup>24</sup> | Hania Szajewska<sup>25</sup>  | Carina Venter<sup>26</sup>  | Valérie Verhasselt<sup>27</sup> | Gary W. K. Wong<sup>28</sup>  | Graham Roberts<sup>4,7,9</sup> | European Academy of Allergy and Clinical Immunology Food Allergy and Anaphylaxis Guidelines Group

<sup>1</sup>Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark

<sup>2</sup>Department of Women and Child Health, Food Allergy Referral Centre Veneto Region, Padua University Hospital, Padua, Italy

<sup>3</sup>The Evidence Centre Ltd, London, UK

<sup>4</sup>Clinical and Experimental Sciences and Human Development in Health, Faculty of Medicine, University of Southampton, Southampton, UK

<sup>5</sup>Primary Care, Population Science and Medical Education, Faculty of Medicine, University of Southampton, Southampton, UK

<sup>6</sup>Allergy Unit - Area of Translational Research in Pediatric Specialities, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

<sup>7</sup>NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK

<sup>8</sup>Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK

<sup>9</sup>The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport, UK

<sup>10</sup>Benaroya Research Institute and Immune Tolerance Network, Seattle, WA, USA

<sup>11</sup>Department of Pediatric Respiratory Medicine, Immunology and Critical Care Medicine, Charite Universitätsmedizin Berlin, Berlin, Germany

<sup>12</sup>National Heart and Lung Institute, Imperial College London, London, UK

<sup>13</sup>Centre for Evidence-based Dermatology, University of Nottingham, Nottingham, UK

<sup>14</sup>Department of Paediatric Allergy, Division of Asthma, Allergy and Lung Biology, MRC & Asthma UK Centre in Allergic Mechanisms of Asthma, King's College London, Guy's and St Thomas' NHS Foundation Trust, London, UK

<sup>15</sup>Department of Allergy, Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagami National Hospital, Sagami, Japan

<sup>16</sup>Pediatric Allergy Unit, Department of Women-Children-Teenagers, University Hospitals of Geneva, Geneva, Switzerland

<sup>17</sup>Department of Dietetics, Salford Royal NHS Foundation Trust, Salford, UK

<sup>18</sup>Allergy UK, Sidcup, UK

<sup>19</sup>Paediatric Allergy Research Group, Department of Women and Children's Health, Faculty of Life Sciences and Medicine, School of Life Course Sciences, London, UK

<sup>20</sup>Peter Gorer Department of Immunobiology, School of Immunology and Microbial Sciences, King's College London, London, UK

<sup>21</sup>Children's Allergy Service, Evelina London Children's Hospital, Guy's and St Thomas' Hospital, London, UK

<sup>22</sup>Asthma UK Centre in Allergic Mechanisms of Asthma, London, UK

<sup>23</sup>Department of Paediatrics, Stanford University School of Medicine, Stanford, CA, USA

<sup>24</sup>Departments of Medicine and Microbiology, APC Microbiome Ireland, National University of Ireland, Cork, Ireland

<sup>25</sup>Department of Paediatrics, Medical University of Warsaw, Warsaw, Poland

Susanne Halken, Antonella Muraro and Graham Roberts equally contributed to this work.

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<sup>26</sup>Section of Allergy and Immunology, University of Colorado and Children's Hospital Colorado, Aurora, CO, USA

<sup>27</sup>School of Molecular Sciences, University of Western Australia, Perth, WA, Australia

<sup>28</sup>Department of Paediatrics, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China

#### Correspondence

Antonella Muraro, Department of Women and Child Health, Referral Centre for Food Allergy Diagnosis and Treatment Veneto Region, Padua University Hospital, Italy.  
Email: muraro@centroallergiealimentari.eu

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#### Abstract

**Background:** This guideline from the European Academy of Allergy and Clinical Immunology (EAACI) recommends approaches to prevent the development of immediate-onset / IgE-mediated food allergy in infants and young children. It is an update of a 2014 EAACI guideline.

**Methods:** The guideline was developed using the AGREE II framework and the GRADE approach. An international Task Force with representatives from 11 countries and different disciplinary and clinical backgrounds systematically reviewed research and considered expert opinion. Recommendations were created by weighing up benefits and harms, considering the certainty of evidence and examining values, preferences and resource implications. The guideline was peer-reviewed by external experts, and feedback was incorporated from public consultation.

**Results:** All of the recommendations about preventing food allergy relate to infants (up to 1 year) and young children (up to 5 years), regardless of risk of allergy. There was insufficient evidence about preventing food allergy in other age groups. The EAACI Task Force suggests avoiding the use of regular cow's milk formula as supplementary feed for breastfed infants in the first week of life. The EAACI Task Force suggests introducing well-cooked, but not raw egg or uncooked pasteurized, egg into the infant diet as part of complementary feeding. In populations where there is a high prevalence of peanut allergy, the EAACI Task Force suggests introducing peanuts in an age-appropriate form as part of complementary feeding. According to the studies, it appears that the most effective age to introduce egg and peanut is from four to 6 months of life. The EAACI Task Force suggests against the following for preventing food allergy: (i) avoiding dietary food allergens during pregnancy or breastfeeding; and (ii) using soy protein formula in the first 6 months of life as a means of preventing food allergy. There is no recommendation for or against the following: use of vitamin supplements, fish oil, prebiotics, probiotics or synbiotics in pregnancy, when breastfeeding or in infancy; altering the duration of exclusive breastfeeding; and hydrolysed infant formulas, regular cow's milk-based infant formula after a week of age or use of emollients.

**Conclusions:** Key changes from the 2014 guideline include suggesting (i) the introduction of peanut and well-cooked egg as part of complementary feeding (moderate certainty of evidence) and (ii) avoiding supplementation with regular cow's milk formula in the first week of life (low certainty of evidence). There remains uncertainty in how to prevent food allergy, and further well-powered, multinational research using robust diagnostic criteria is needed.

#### KEYWORDS

food allergy, guidelines, prevention

#### Key Message

EAACI suggests: 1. avoiding the use of regular cow's milk formula as supplementary feed for breastfed infants in the first week of life. 2. introducing well-cooked, but not raw egg or uncooked pasteurized egg into the infant diet as part of complementary feeding. 3. in populations where there is a high prevalence of peanut allergy, introducing peanuts in an age-appropriate form as part of complementary feeding.

## 1 | INTRODUCTION

Allergic reactions to foods such as hen's egg, cow's milk and peanut can impair an individual's health and quality of life and have substantial healthcare costs.<sup>1,2</sup> The prevalence is high, for example, in high-income countries, and up to one in ten people live with a food allergy, with the highest prevalence amongst infants and young children.<sup>1</sup>

In 2014, the European Academy of Allergy and Clinical Immunology (EAACI) released a guideline to help countries, clinicians and families prevent food allergy.<sup>3</sup> The guideline has now been updated to include the latest research.

This guideline provides evidence-based recommendations about approaches for preventing the development of IgE-mediated / immediate-onset food allergy (hereafter 'food allergy'). This is defined as a reproducible adverse reaction to food mediated by an immunologic mechanism. The guideline does not focus on preventing conditions that may be associated with food allergy such as food sensitization, eczema or non-IgE-mediated conditions. Some populations are at greater risk of developing food allergy than others, including those with atopic heredity, eczema or IgE sensitization. The guideline examines interventions for those at increased risk and those at general risk of food allergy. Table 1 provides a glossary of key terms used throughout. The guideline provides recommendations for healthcare professionals to consider when assisting families to make decisions about how to prevent food allergy. Individual circumstances should be considered at all times. The primary audience is clinical allergists, paediatricians, primary care and other healthcare professionals.

This guideline does not cover the treatment of existing food allergy. The recommendations are intended for infants that have not developed food allergy. Where there is a suspicion of food allergy, infants and children should be referred to a specialist allergy service for careful evaluation and proper management.

The guideline focuses on preventing food allergy in infants (up to 1 year old) and young children (up to 5 years) as this is where evidence was available. It sets out a recommendation about each intervention, and briefly provides the reason for the recommendation and whether or not the recommendation is strongly proposed for universal implementation. It also provides practical implications for professionals and families. The accompanying online supplement summarizes key themes in the research evidence and the factors considered when making recommendations. Details about the research evidence upon which the guideline is based have been published separately and are not repeated here.<sup>4</sup> Young children with symptoms suggestive of food allergy should be referred to a specialist centre for assessment and further management.

## 2 | METHODOLOGY

### 2.1 | Stakeholder involvement

The guideline was developed by an EAACI Task Force with representatives from 11 countries. Participants included a variety

of disciplinary and clinical backgrounds, including allergists (specialist and subspecialists), paediatricians, primary care, patient representatives, immunologists, dieticians, statisticians and researchers. Methodologists led a systematic review of evidence, and clinical academics formulated recommendations for clinical care. Product manufacturers and other stakeholders had an opportunity to comment as part of a public consultation process at the final stage.

### 2.2 | Guideline approach

The Task Force implemented the Appraisal of Guidelines for Research and Evaluation framework (AGREE II).<sup>5</sup> This included having representation from a range of stakeholders, systematically searching for and appraising relevant literature, minimizing bias and using a systematic approach to formulate and present recommendations (the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach).

EAACI intends to update this guideline in 2026 unless there are significant advances before then.

### 2.3 | Collating evidence of effectiveness

Clinical questions were generated and prioritized by the Task Force. The key clinical question was '*what is the effectiveness and safety of interventions to prevent the development of IgE-mediated / immediate-onset food allergy in infants, children and adults?*'

The Task Force worked with independent researchers to undertake a systematic review of research evidence (PROSPERO registration CRD42019127457). The methodology has been published<sup>6</sup> so far is only briefly described here. The reviewers searched 11 bibliographic databases, the reference lists of identified studies and 35 systematic reviews, and contacted experts in the field for trials published between 1946 and 31 October 2019.

Our systematic review<sup>4</sup> included 46 studies: 41 randomized controlled trials (hereafter 'trials') and, in the case of breastfeeding only, five prospective cohort studies with at least 1000 participants at general risk of food allergy or at least 200 participants at increased risk of food allergy. Studies involving infants, children and adults were eligible, but only studies about preventing food allergy during infancy and early childhood were identified.

As per the GRADE approach,<sup>7</sup> study findings were extracted and compiled using evidence profiles and summary of findings tables as published in the systematic review online materials.<sup>4</sup>

### 2.4 | Formulating and reviewing recommendations

The Task Force met regularly in person and virtually over an 18-month period. For each intervention, the Task Force considered the effect on food allergy outcomes across all studies, not solely

**TABLE 1** Key terms

Term	Definition
Certainty of evidence	The extent to which the evidence can be relied upon, rated as very low, low, moderate and high. The GRADE approach was used to decide on the certainty of evidence, including risk of bias, directness, consistency and precision of the estimates.
Complementary feeding	WHO defines complementary feeding as the process starting when breastmilk alone is no longer sufficient to meet the nutritional requirements of infants. <sup>9</sup> In recognition that not all infants may be fed breastmilk and in line with ESPGHAN <sup>75</sup> and EFSA, <sup>10</sup> this guideline defined complementary feeding as the process of introducing foods and liquids alongside with breastfeeding (or infant formula if applicable) when breastmilk (or infant formula) no longer meets the nutritional requirements of infants. WHO advises that complementary feeding should start from 6 mo of age, <sup>9</sup> but some choose to start from four to 6 mo of age, often with increasing amounts of foods in a developmentally appropriate consistency, which is also in line with a recent statement from EFSA. <sup>10</sup>
Cow's milk protein	Cow's milk protein, which may include formats such as yoghurt and cheese
Early childhood	Up to 5 y old
Food allergy	Reproducible adverse reaction to food mediated by an immunologic mechanism, involving specific IgE (IgE-mediated), cell-mediated (non-IgE-mediated) or both IgE and cell-mediated mechanisms. For the purposes of this guideline, the term 'food allergy' is used as shorthand to mean IgE-mediated/ immediate-onset food allergy.
IgE-mediated / immediate-onset food allergy	Food allergy shown or suspected to be IgE-mediated, often with onset within hours after exposure. Solely non-IgE-mediated food reaction (eg eosinophilic oesophagitis / gastroenteritis) conditions are not included.
Increased risk	Greater risk of food allergy due to having a condition associated with food allergy such as eczema or asthma or having immediate relatives with a history of any allergy, atopic dermatitis, asthma or hay fever.
Infant	Up to 1 y old
Infant formula	Formula for use as a complete or partial substitute for human milk. The protein source can be cow's milk, goat's milk, soya protein isolates, or hydrolysed whey or casein protein. The content of infant formulas is regulated and appropriate for the infant needs. In this guideline, regular infant formula refers to standard cow's milk formula where the protein is not hydrolysed. Infant formula may be based on partially hydrolysed cow's milk protein, whereas extensively hydrolysed cow's milk based infant formulas and amino acid-based formulas are designated 'exempt formulas' intended for special medical purposes, such as cow's milk allergy.
Prebiotic	Non-digestible substances that provide a beneficial physiologic effect for the host by selectively stimulating the favourable growth or activity of a limited number of indigenous bacteria.
Probiotic	Live microorganisms, which, when administered in adequate amounts, may confer a health benefit on the host.
Regardless of the risk of food allergy	Regardless of whether the target group is at increased risk of food allergy or general / undifferentiated risk
Sensitization	Detectable specific IgE antibodies, either by means of skin prick test or determination of specific IgE antibody levels in a serum sample
Significant	Statistically significant, $P < .05$
Synbiotic	A combination of prebiotic(s) and probiotic(s) that may beneficially affect the host by improving the survival and activity of beneficial microorganisms in the gut
Trial	Randomized controlled trial (RCT)

individual studies. The populations and interventions were too heterogeneous to allow meta-analysis. Only intention-to-treat analyses were considered.

In addition, the applicability and generalizability of results, consistency of study findings and risk of bias were considered for each topic area. From this information, the Task Force made a judgement about the overall certainty of evidence regarding an intervention. The Task Force also drew on patient organizations and expert opinion to consider the balance of benefits versus harms, preferences and values, and resource implications and feasibility.<sup>8</sup> These factors were drawn together to formulate evidence-based recommendations for clinical care.

In line with the GRADE approach, the Task Force used specific wording to denote whether a recommendation was 'for' or 'against' an intervention (direction) and whether a recommendation was strong or conditional (strength). Table 2 sets out the wording conventions used. This guideline uses the wording 'The EAACI Task Force suggests' to denote a conditional recommendation. A conditional recommendation is still a recommendation for or against a particular intervention, it simply means that there may not be sufficient evidence about effectiveness or harms to conclude that this is the best approach in every case or that it should be universally implemented in all policy and practice.

**TABLE 2** Wording conventions used in this guideline for recommendations

Strength and direction	Guideline wording	Implications for practice	Policy implications
Strong recommendation for an intervention	'The EAACI Task Force recommends ...'	Most people in this situation should be offered the intervention	The recommendation can be adopted as a policy in most situations
Conditional recommendation for an intervention	'The EAACI Task Force suggests ...'	Many people in this situation should be offered the intervention. However, for others, different choices will be appropriate. Clinicians could help each patient make decisions consistent with the patient's preferences	The recommendation can be adopted as a policy in many situations. The specific context may mean that it is not relevant, as refined by stakeholders
Conditional recommendation against an intervention	'The EAACI Task Force suggests against ...'	Many people in this situation should not be offered the intervention. However for others, different choices will be appropriate. Clinicians could help each patient make decisions consistent with the patient's preferences	The recommendation can be adopted as a policy in many situations. The specific context may mean that it is not relevant, as refined by stakeholders
Strong recommendation against an intervention	'The EAACI Task Force recommends against ...'	Most people in this situation should not use this intervention	The recommendation can be adopted as a policy in most situations
No recommendation	'There is no recommendation for or against using ...'	Different choices will be appropriate for different people. Clinicians could help each patient make decisions consistent with the patient's preferences	Policies may differ depending on context and should be developed with the involvement of a wide range of stakeholders

The Task Force used specific wording to describe the strength of evidence and effect size supporting the recommendations (see Table 3).

All recommendations were agreed by consensus, except for the timing of the introduction of peanuts where 72% of eligible members who chose to vote were in favour of a conditional recommendation and 28% favoured a strong recommendation.

A draft of this guideline was externally peer-reviewed by invited experts from a range of organizations, countries and professional backgrounds. The draft guideline was also publicly available on the EAACI website for a 3-week consultation period in July 2020 to allow a broader array of stakeholders to comment. The chairs read all the comments and proposed changes as a result. The entire Task Force was then given the opportunity to review comments and approved the proposed edits.

### 2.5 | Editorial independence and managing conflicts of interest

The guideline development process was funded by EAACI. The funder did not have any influence on the recommendations or decision to publish.

Task Force members declared any potential conflicts of interest at the outset, middle and end of the activity. They did not take part in decisions about recommendations where they might be perceived as having a commercial interest directly related to the guideline decision. GL and KN were not involved in voting on recommendations on the timing of introduction of complementary foods. Investigators involved in studies reviewed as part of the guideline process participated in discussing and voting on these recommendations but always represented a small minority of the task force.

Evidence about effectiveness was compiled independently by methodologists who had no conflict of interests.

## 3 | RECOMMENDATIONS

Table 4 summarizes the guideline recommendations. The following sections briefly justify the recommendations. The individual studies are not described in detail as these are included in our systematic review<sup>4</sup> and online supplement. Table S1 (online supplement) lists the effect sizes and confidence intervals associated with each intervention. The online supplement also contains further information about the factors considered for each recommendation.

The recommendations relate to preventing the development of food allergy in infants and young children because there was insufficient evidence to make recommendations relating to older children or adults. All recommendations apply to infants and young children at general risk of food allergy and those at increased risk.

WHO global feeding guidance recommends that all infants are exclusively breastfed for the first 6 months of life and continue breastfeeding the first 2 years of life.<sup>9</sup> This guideline supports this global

**TABLE 3** Wording conventions used in this guideline about evidence of effect sizes

Certainty of evidence	Size of effect			
	None / minor / not clinically meaningful (0% to 39% relative change)	Small and important (40% to 60% relative change)	Medium (61% to 80% relative change)	Large (81%+ relative change)
High	X does not reduce / increase food allergy	X reduces / increases food allergy slightly	X reduces / increases food allergy	X results in a large reduction / increase in food allergy
Moderate	X probably does not reduce / increase food allergy	X probably reduces / increases food allergy slightly	X probably reduces / increases food allergy	X probably results in a large reduction / increase in food allergy
Low	X may not reduce / increase food allergy	X may reduce / increase food allergy slightly	X may reduce / increase food allergy	X may result in a large reduction / increase in food allergy
Very low	X may have little to no effect on food allergy, but the evidence is very uncertain			

Note: Small, medium and large effect sizes were all required to be deemed clinically important in order to be considered as a substantive effect.

recommendation. It does also recognize that in developed countries, (i) sometimes there is a need for a breastmilk substitute, and in these cases, an infant formula is recommended; (ii) some families choose to start complementary feeding earlier, between four and 6 months, which is also in agreement with a recent statement from European Food Safety Authority (EFSA)<sup>10</sup>; and (iii) early complementary feeding need not have a negative impact on breastfeeding.<sup>11,12</sup>

### 3.1 | Dietary avoidance or introduction of allergens

#### 3.1.1 | Maternal dietary avoidance

The EAACI Task Force suggests against restricting the consumption of potential food allergens during pregnancy or breastfeeding in order to prevent food allergy in infants and young children (see online supplement Table S2).

##### *Reason for recommendation*

Our systematic review identified five trials about this topic in women at increased risk, two of which focused on dietary avoidance alone<sup>13,14</sup> and three combined with another intervention.<sup>15–17</sup> The review concluded that avoiding potential food allergens during pregnancy, when breastfeeding or in infancy, alone or combined with other interventions, may have little to no effect on food allergy in early childhood, but the evidence is very uncertain.

The majority of trials found no reduction in the prevalence of food allergy when women avoided dietary allergens such as egg and milk. The harm associated with avoiding foods during pregnancy and breastfeeding may be greater than any potential reduction in food allergy. Food allergens do not exist in isolation so removing food groups may also reduce the intake of vital nutrients and fibre, adversely affecting the health of women and their infants.<sup>18</sup>

##### *Strength of recommendation*

This guideline is against maternal avoidance of dietary food allergens, but this is not the strongest recommendation possible because the certainty of evidence is very low. There were only a small number of studies, they contained varying interventions, and there was very low certainty about their effect on food allergy.

##### *Practical implications*

Professionals should encourage women to not restrict consumption of specific allergenic foods. Rather, they should follow local guidelines, eating a healthy, balanced diet when pregnant and breastfeeding. This applies regardless of the infant's risk of food allergy.

#### 3.1.2 | Introducing hen's egg into the infant diet

The EAACI Task Force suggests introducing well-cooked hen's egg, but not raw egg or uncooked pasteurized egg, into the infant diet as



**TABLE 4** Recommendations for preventing the development of food allergy

Recommendation	Certainty of evidence
<b>Recommendations supporting interventions</b>	
The EAACI Task Force suggests introducing well-cooked hen's egg, but not raw egg or uncooked pasteurized egg, into the infant diet as part of complementary feeding to prevent egg allergy in infants.	Moderate
In populations where there is a high prevalence of peanut allergy, the EAACI Task Force suggests introducing peanuts into the infant diet in an age-appropriate form as part of complementary feeding in order to prevent peanut allergy in infants and young children.	Moderate
The EAACI Task Force suggests avoiding supplementing with cow's milk formula in breastfed infants in the first week of life to prevent cow's milk allergy in infants and young children	Low
<b>Recommendations against interventions</b>	
The EAACI Task Force suggests against restricting consumption of potential food allergens during pregnancy or breastfeeding in order to prevent food allergy in infants and young children.	Very low
The EAACI Task Force suggests against introducing soy protein-based formula in the first 6 mo of life to prevent cow's milk allergy in infants and young children.	Very low
The EAACI Task Force suggests against using bacillus Calmette-Guérin (BCG) vaccination to prevent food allergy in infants and young children.	Low
<b>No recommendation made</b>	
There is no recommendation for or against using breastfeeding to prevent food allergy in infants and young children, but breastfeeding has many benefits for infants and mothers and should be encouraged wherever possible.	Very low
For infants who need a breastmilk substitute, there is no recommendation for or against the use of regular cow's milk-based infant formula after the first week of life to prevent food allergy.	Low
There is no recommendation for or against using partially or extensively hydrolysed formula to prevent food allergy in infants and young children. When exclusive breastfeeding is not possible, many substitutes are available for families to choose from, including hydrolysed formulas.	Low
There is no recommendation for or against vitamin supplementation or fish oil supplementation in healthy pregnant and/or breastfeeding women and/or infants to prevent food allergy in infants and young children.	Very low
There is no recommendation for or against prebiotics, probiotics or synbiotics for pregnant and/or breastfeeding women and/or infants alone or in combination with other approaches to prevent food allergy in infants and young children.	Low
There is no recommendation for or against using emollients as skin barriers to prevent food allergy in infants and young children.	Low
There is no recommendation for or against using preventive oral immunotherapy to prevent food allergy in infants and young children.	Low

part of complementary feeding to prevent egg allergy in infants (see online supplement Table S3).

#### *Reason for recommendation*

Our systematic review included two trials about cooked egg<sup>11,12,19</sup> and three about raw or pasteurized egg in general- and increased-risk infants.<sup>11,12,20,21</sup> An additional subgroup analysis from one of the cooked egg studies has since been published.<sup>22</sup> The evidence suggests that introducing small amounts of cooked, but not raw egg or uncooked pasteurized, hen's egg into the infant diet as part of complementary feeding probably reduces the risk of egg allergy in infancy.

The benefits of introducing well-cooked egg probably outweigh potential harms.

The Task Force does not support early introduction of raw egg or uncooked pasteurized egg because the potential harms may outweigh the benefits. Studies found adverse reactions, including anaphylactic reactions.<sup>11,12,20,21</sup>

#### *Strength of recommendation*

This guideline supports the introduction of well-cooked egg into the infant diet, but this is not the strongest recommendation possible because the certainty of evidence is moderate. There were only a small number of studies about cooked egg, their results were inconsistent, and there was only moderate to low certainty about the effect on egg allergy.

Evidence about raw egg or uncooked pasteurized egg was of low certainty. The available trials had inconsistent findings.

#### *Practical implications*

Healthcare professionals in countries where egg allergy is an issue could encourage families with infants at general and increased risk to start introducing about half of a well-cooked, small egg twice a week as part of complementary feeding from four to 6 months of age. This is in agreement with the recent European Food Safety Authority statement.<sup>10</sup> This amount of egg is based on a trial that found that eating at least 2 grams of egg white protein per week prevented egg allergy.<sup>11,12</sup> One other trial successfully prevented egg allergy with



smaller amounts [PETIT study]. The trials utilized hard-boiled egg (10–15 minutes), but we would consider that equivalent amounts of egg in well-baked foods would also be appropriate.<sup>23</sup>

### 3.1.3 | Introducing peanuts into the infant diet

In populations with a high prevalence of peanut allergy, the EAACI Task Force suggests introducing peanuts in an age-appropriate form as part of complementary feeding in order to prevent peanut allergy in infants and young children (see online supplement Table S4).

#### *Reason for recommendation*

Our systematic review included three trials about this, one in general-risk and two in increased-risk infants.<sup>11,12,24</sup> The review found that in populations with a high prevalence of peanut allergy, introducing regular peanut consumption from 4 to 11 months of life in infants at increased risk probably results in a large reduction in peanut allergy in early childhood compared with completely avoiding peanut for the first 5 years.

The benefits probably outweigh potential harms. Data from the trials included in the review and additional observational studies suggest that it is safe to introduce age-appropriate forms of peanut into the diet in the first year of life. Some adverse reactions have been reported, mostly mild.<sup>25–27</sup>

#### *Strength of recommendation*

This guideline supports the introduction of peanut into the infant diet in populations with a high prevalence of peanut allergy, but this is not the strongest recommendation possible because the certainty of evidence is moderate. The studies included in our review used different outcomes, population risk levels and interventions, and there was moderate to low certainty about their effect on peanut allergy. There was some inconsistency in the results. One study introduced peanut along with five other foods. Two studies focused on infants at very high risk and compared with complete abstinence from peanut for 5 years rather than more usual exposure. All of the studies took place in the UK. Therefore, the generalizability of the findings is uncertain and this led to a conditional recommendation.

#### *Practical implications*

In counties where peanut allergy is prevalent, healthcare professionals could encourage families to introduce peanuts as part of complementary feeding. Professionals should advocate introducing peanut in an age-appropriate form alongside continued breastfeeding. It appears that the most effective age to introduce is from four to 6 months of life. The evidence of benefit relates mainly to those at very increased risk, but this could be encouraged in those at general risk as well because many cases of peanut allergy are seen in this lower risk group.<sup>28</sup>

Peanut should be introduced in an age-appropriate form to avoid any risk of choking or inhalation. For example, infants could be given one heaped teaspoons of diluted peanut butter (2g peanut protein)

each week.<sup>11,12</sup> We suggest that peanut should not be the first solid to be introduced into the infant diet. The EAACI Task Force makes no recommendation for countries with a low prevalence of peanut allergy. In these countries, peanuts should be included in the diet according to normal eating habits and local recommendations.

## 3.2 | Breastfeeding and infant formula

### 3.2.1 | Breastfeeding

There is no recommendation for or against using breastfeeding to prevent food allergy, but breastfeeding has many benefits for infants and mothers and should be encouraged wherever possible (see online supplement Table S5).

#### *Reason for recommendation*

Our systematic review included seven studies about breastfeeding.<sup>29–33</sup> The review concluded that breastfeeding has many benefits for infants and mothers, but it may not reduce the risk of food allergy or cow's milk allergy.

The evidence was of low certainty because it is based on observational studies as it is difficult ethically to undertake randomized trials of breastfeeding.

Breastfeeding meets all of the nutritional needs of infants up to 6 months of age and is recommended by WHO.<sup>34</sup> Breastfeeding may also reduce societal costs associated with ill health.<sup>35</sup> Therefore, the balance of benefits and harms is in favour of breastfeeding, even though there is insufficient evidence about benefits related to preventing food allergy.

#### *Practical implications*

While breastfeeding may not prevent food allergy, professionals should support breastfeeding given its other positive benefits.<sup>36</sup> Professionals need to also sensitively support families that do not breastfeed their infants.

### 3.2.2 | Supplementation with cow's milk formula in the first week of life

The EAACI Task Force suggests avoiding supplementing with cow's milk formula in breastfed infants in the first week of life to prevent cow's milk allergy in infants and young children (see online supplement Table S6).

#### *Reason for recommendation*

Our systematic review included one trial about this.<sup>37</sup> The review found that avoiding supplementation with regular cow's milk formula in breastfed infants during the first three days of life may result in a large decrease in the risk of cow's milk allergy in early childhood.

The World Health Organization (WHO) also warns that any supplementation may be associated with a reduction in breastfeeding<sup>34</sup>

and most healthy, mature infants do not need any supplementation to breastfeeding.

#### *Strength of recommendation*

This guideline supports avoiding supplementation with cow's milk formula in the first week of life amongst breastfed infants, but this is not the strongest recommendation possible because the evidence is of low certainty. There was only one trial available, and it contained multiple interventions, making it difficult to apply the findings to practice. However, the trend is supported by other studies not eligible for the review, which also found increased incidence of cow's milk allergy when cow's milk formula was used a temporary feed in the first week of life.<sup>29,30</sup>

#### *Practical implications*

Healthcare professionals and families could avoid supplementation with cow's milk formula in breastfed infants in the first week of life. It is important to support breastfeeding, and breastfeeding is usually sufficient with no need for supplementation in healthy, term-born infants. If needed, the family should seek advice from healthcare professionals. Other possible temporary supplementary options might include, for example, donor breastmilk, hydrolysed formula, amino acid formula or water, depending on clinical, cultural and economic factors.

### 3.2.3 | Regular consumption of cow's milk formula

For infants who need a breastmilk substitute, there is no recommendation for or against the use of regular cow's milk-based infant formula after the first week of life to prevent food allergy (see online supplement Table S7).

#### *Reason for recommendation*

Our systematic review included seven trials about this.<sup>38-44</sup> The review concluded that introducing conventional cow's milk-based formula after the first week of life did not have a consistent impact on the development of cow's milk allergy in infancy or early childhood.

There do not appear to be significant harms associated with regular consumption of cow's milk-based formula for either general-risk or increased-risk infants after 3 months of age although WHO has warned that any supplementation may be associated with a reduction in breastfeeding.<sup>34</sup>

#### *Strength of recommendation*

No recommendation could be made as the evidence is of low to very low certainty. The studies investigated different interventions, duration and comparators.

#### *Practical implications*

Breastfeeding is natural and beneficial and should be the preferred approach where possible. Where a breastmilk substitute is required, cow's milk-based formulas are preferred to standard cow's milk during the first year of life, due to nutritional value and ease of digestion.

### 3.2.4 | Hydrolysed infant formula

There is no recommendation for or against using partially or extensively hydrolysed formula to prevent cow's milk allergy in infants. When exclusive breastfeeding is not possible, many substitutes are available for families to choose from, including hydrolysed formulas (see online supplement Table S8).

#### *Reason for recommendation*

Our systematic review included nine trials about this.<sup>16,17,29,30,38-40,45,46</sup> The review found that partially or extensively hydrolysed whey or casein formula may not reduce the risk of cow's milk allergy compared with conventional cow's milk formula. There is no consistent evidence that hydrolysed formula reduces the risk of food allergy nor is there consistent evidence that hydrolysed formula causes harm. There was little to no evidence that one type of hydrolysed formula was more effective than others.

The evidence here is of low certainty. Trials used different formulas, introduced them at different times, often had small samples and often did not use robust diagnostic criteria for food allergy.

#### *Practical implications*

Breastfeeding of all infants is preferable, but when a breastmilk substitute is needed, professionals could help families consider the best possible alternative for a family's individual circumstances. The options discussed could include a hydrolysed infant formula.

### 3.2.5 | Soy protein formula

The EAACI Task Force suggests against introducing soy protein formula in the first 6 months of life to prevent cow's milk allergy in infants and young children (see online supplement Table S9).

#### *Reason for recommendation*

Our systematic review included one trial about this.<sup>40</sup> The review concluded that soy-based formula may have little to no effect on cow's milk allergy in early childhood, but the evidence is very uncertain.

There may be more potential harms than benefits from using soy protein formula for the prevention of food allergy. There are concerns about high concentrations of phytate, aluminium and phyto-oestrogens (isoflavones), which might have detrimental effects in the first 6 months of life.<sup>47</sup>

#### *Strength of recommendation*

This guideline is against the use of soy protein formula in the first 6 months of life, but this not the strongest recommendation possible because the evidence is of very low certainty. There was one pertinent trial, which did not use a robust definition of food allergy.

*Practical implications*

Soy protein formula is unlikely to protect against cow's milk allergy. It may be considered for infants who cannot have dairy-based products because of cultural, medical, religious or family reasons such as a vegan lifestyle, persistent lactose intolerance or galactosaemia.<sup>48</sup> Professionals should discuss the benefits and potential harms fully with families.

**3.3 | Supplements, prebiotics and probiotics****3.3.1 | Vitamin and fish oil supplements**

There is no recommendation for or against vitamin supplementation or fish oil supplementation in healthy pregnant and/or breastfeeding women and/or infants to prevent food allergy in infants and young children (see online supplement Table S10).

*Reason for no recommendation*

Our systematic review included eight trials about vitamin or fish oil supplements in general- or increased-risk populations.<sup>49-56</sup> The review found that vitamin supplements for pregnant and/or breastfeeding women or infants may have little to no effect on food allergy in early childhood, but the evidence is very uncertain.

The review found that fish oil supplements during pregnancy, when breastfeeding or in infancy, may not reduce food allergy in infancy or early childhood. However, when taken during pregnancy and continued during breastfeeding, fish oil may reduce food allergy slightly in young children at increased risk.

There was no consistent evidence that these supplements cause harm in healthy women and infants.

The evidence about vitamin supplements was of very low certainty, and the evidence about fish oil was of low certainty. Studies used different supplements, doses, timelines, target groups and combinations of interventions.

*Practical implications*

Women who are not getting the recommended daily allowances of vitamins, minerals and omega-3 through their diet may benefit from supplementation for health reasons, according to national guidance, but not for the purposes of preventing food allergy in infants.

**3.3.2 | Prebiotics, probiotics and synbiotics**

There is no recommendation for or against prebiotics, probiotics or synbiotics for pregnant and/or breastfeeding women and/or infants alone or in combination with other approaches to prevent food allergy in infants and young children (see online supplement Table S11).

*Reason for no recommendation*

Our systematic review included nine trials about this.<sup>57-65</sup> The review found that prebiotics, probiotics and synbiotics for mothers and infants may have little to no effect on food allergy in infancy

and early childhood, but the evidence is very uncertain. There is no evidence that they cause harm in healthy women and infants.

The evidence here was of very low certainty. The studies differed in size, duration of supplementation, type of supplementation, timing of supplementation, diagnostic criteria and duration of follow-up. The clinical effects and safety of any single probiotic or combination of probiotics, prebiotics or synbiotics cannot be extrapolated to other probiotics as they are immunologically distinct. This makes it difficult to provide a clear recommendation.

*Practical implications*

Professionals should help families consider the pros and cons of different prebiotics, probiotics or synbiotics, being clear that they may have little to no effect on the development of food allergy. Where professionals decide to use these in premature infants, caution is advised. Professionals should consider advising against their use where immunosuppression may be possible.

**3.4 | Other approaches****3.4.1 | BCG vaccination**

The EAACI Task Force suggests against using bacillus Calmette-Guérin (BCG) vaccination to prevent food allergy in infants and young children. Our systematic review included two studies about this in general-risk infants.<sup>56,66</sup> The review concluded BCG vaccination may have little to no effect on food allergy in infancy and early childhood, but the evidence is very uncertain (see online supplement Table S12). This recommendation is based on low certainty evidence, with some harms noted for immunodeficient infants.<sup>67</sup>

BCG is part of the immunization schedule in many countries where tuberculosis prevalence is high. Families should be encouraged to follow the immunization programmes for their country. Our recommendation is against using the vaccination for preventing food allergy.

**3.4.2 | Emollients**

There is no recommendation for or against using emollients as skin barriers to prevent food allergy in infants. Our systematic review included one trial about this.<sup>65</sup> It concluded that emollients may have little to no effect on food allergy in infancy and early childhood, but the evidence is very uncertain (see online supplement Table S13). A further trial, published after our systematic review, found that emollients did not reduce food allergy at 2 years in high-risk infants.<sup>68</sup> Different emollients may have different effects.<sup>69</sup>

**3.4.3 | Preventive house dust mite oral immunotherapy**

There is no recommendation for or against using oral immunotherapy to prevent food allergy in infants. Our systematic review

**TABLE 5** Considerations for implementing recommendations made in this guideline

Topic	Barriers to implementation	Facilitators to implementation	Audit criteria	Resource implications
Introducing cooked egg into the infant diet	Infants may not enjoy the texture or taste until later in infancy.	Knowledge about the preventive impact amongst parents and healthcare professionals.	Proportion of infants who are eating 2 grams or more of egg white protein by 6 mo of life.	Minimal, egg is readily available in most countries.
Introducing peanut into the infant diet	Families with known peanut allergy may want to refrain from introducing peanut in the home due to risk of allergic reactions in other family members. Parents may not wish to feed their infants quantities of monosaturated fat. It may be difficult to feed infants peanut butter or peanut snacks.	Knowledge about the preventive impact amongst parents and healthcare professionals.	Proportion of infants who are eating 2 grams or more of peanut protein a week by 6 mo of life in countries with a high prevalence of peanut allergy.	Minimal, peanuts are a low-cost source of protein.
Avoiding supplementation with cow's milk formula in the first week of life	Standard cow's milk formula has historically been used in some countries as a supplementation in the first week of life, often without reason and without parent knowledge.	Breastfeeding is usually sufficient in healthy infants who have lower nutritional needs in the first few days of life. Knowledge about the potential deleterious impact of supplementation and about alternative supplements amongst parents and healthcare professionals.	Proportion of healthy term-born infants who are not given standard cow's milk formula as a supplementation in the first week of life.	Minimal as alternatives such as water, glucose water, breastmilk, hydrolysed formula or amino acid formula are relatively inexpensive in the quantities required.
Avoiding introducing raw (pasteurized) egg into the infant diet	None, except for certain lifestyles, where this is a normal part of infant feeding.	Knowledge about potential harms amongst parents and healthcare professionals.	Proportion of healthy infants who are not given raw egg or uncooked pasteurized egg the first 6 mo.	No additional resources are needed.
Pregnant and breastfeeding women following a usual diet, not avoiding potential food allergens	None, except for those following a vegan lifestyle.	Knowledge about potential harms amongst parents and healthcare professionals.	Proportion of healthy pregnant / breastfeeding women on a normal healthy diet.	No additional resources are needed.
Avoiding the use of soy protein formula for food allergy prevention	Families with lactose intolerance or following a vegan lifestyle may find it difficult to find alternatives.	Knowledge about potential harms and alternatives amongst parents and healthcare professionals.	Proportion of healthy infants who are not given soy protein formula.	None as alternatives are similar in cost.
Avoiding BCG vaccination for food allergy prevention	BCG vaccination programmes are important for TB prevention and there are established programmes in some countries. The vaccination has benefits, but not for the prevention of food allergy.	Knowledge about potential harms amongst parents and healthcare professionals.	None.	No additional resources are needed.

included one trial of preventive house dust mite oral immunotherapy in increased-risk infants.<sup>70,71</sup> The review concluded that oral immunotherapy may have little to no effect on the development of food allergy in infancy and early childhood, but the evidence is very uncertain (see online supplement Table S14).

## 4 | DISCUSSION

### 4.1 | Implications

This guideline will help healthcare professionals consider evidence alongside a family's individual circumstances when considering how to prevent the development of food allergy. Where the guideline makes no recommendation, professionals should work with families to consider the best options based on the family's situation, risk, preferences and resources. The intention should always be to prevent food allergy whilst avoiding unnecessary harms, interventions, restrictions and cost for families and for society.

The overall message from the guideline is that mothers and infants should follow a healthy and balanced diet, consistent with what is usual for the community and family, rather than trying to prevent food allergy by avoiding certain foods or taking supplements.

The recommendations should be viewed in the broader context of nutritional status and health. This guideline supports WHO, which prioritizes breastfeeding, preferably exclusively for at least 6 months, though breastfeeding may not in itself prevent food allergy. However, introducing complementary feeds from four to 6 months in developed countries is in line with the recent EFSA statement and has been demonstrated to be safe.<sup>10–12,26</sup> Where a breastmilk substitute is used, the best alternative should be recommended, such as an infant formula adapted to the nutritional needs of infants. Some families may prefer a hydrolysed formula, though there is no clear evidence that this prevents food allergy. We suggest avoiding supplementation of cow's milk-based formula in breastfed infants during the first week of life as this may be associated with increased food allergy, but there is no evidence that avoiding regular use of cow's milk-based formula after the first week prevents food allergy.

Recent research has suggested that introducing cooked hen's egg and peanut in an age-appropriate form as part of complementary feeding may prevent the development of allergy to egg and peanut, the latter in countries with a high prevalence of peanut allergy. This is similar to recommendations in other current guidelines.<sup>72,73</sup>

There may be a number of facilitators and barriers that may affect the implementation of these recommendations, including historical and cultural habits and socioeconomic systems (Table 5). Education of professionals and families is paramount.

### 4.2 | Strengths and limitations

A strength of this guideline is that it is informed by a balance of evidence and expert opinion. A comprehensive systematic review was

undertaken evaluating the evidence according to well-established GRADE methods. We focused on randomized controlled trials to provide the highest quality available evidence. This differs from previous systematic reviews, which have synthesized the results of different studies.<sup>4</sup> The review was led by independent methodologists with no conflicts of interest.

It is a strength that the recommendations were not only based on the best available evidence, but also expert clinical and patient opinion, balancing benefits and harms and considering values and preferences. The clinical recommendations were developed by a multidisciplinary Task Force representing a range of countries, disciplines and clinical backgrounds, including primary care and patient organizations.

Where the evidence was not clear or sufficient, the Task Force discussed the area in depth, took into account diverse opinions and came to consensus agreement. This approach means that the guideline may be different from the conclusions of systematic reviews, which only take into account the published evidence.

A limitation of the guideline is that there are heterogeneity and gaps in existing knowledge, making it difficult to draw firm conclusions. Much of the research does not use robust diagnostic criteria for food allergy, and there are other methodologic weaknesses meaning that most recommendations are based on evidence from lower quality study designs. The heterogeneity in the studies, including different study populations, variations in interventions at different ages and duration, and varying definitions of food allergy and high-risk infants made it challenging to interpret the evidence. It was not appropriate to undertake meta-analysis to combine such heterogeneous studies.

Another limitation is the restricted focus on preventing food allergy, not including other symptoms that patients may experience in a broader context. Some of the interventions may have effects on other allergic conditions. Conditions such as atopic eczema and food sensitization were not considered.

### 4.3 | Research gaps

There is much left to learn about preventing food allergy. Table 6 sets out key priorities. Some of these require new high-quality studies, whereas other questions may be answered by further analysis of existing studies and combining data where appropriate.

Food allergy often develops in infancy or young childhood. For some types of food allergy, such as cow's milk and egg, the prognosis is good and the child may develop tolerance in the first years of life. For other types, such as peanut allergy, this is seldom the case. Therefore, it is essential that research into the development of food allergy is conducted at the relevant ages and when symptoms are likely to be present.

Where possible, evidence should be derived from double-blind, placebo-controlled randomized trials. Future studies should include robust diagnostic criteria for food allergy. Food allergy may present with various symptoms that are not unique to allergy.

**TABLE 6** Gaps in the evidence for prevention of food allergy

Gaps	Suggestion to address	Priority
Confirmatory evidence about introduction of peanuts in a wider range of populations, especially about the amount, formulation, timing and duration	Large community-based randomized controlled trial to assess the effectiveness of early introduction of peanut into the infant diet to prevent peanut allergy in a variety of countries and populations. Further analyses of data from existing studies	High
Confirmatory evidence that supplementation with cow's milk formula in the first week of life is deleterious	Additional effectiveness data from large randomized controlled trials	High
Further information, using robust study designs, about the impact on food allergy prevention of hydrolysed formulas currently on the market versus conventional cow's milk-based formula in the first months of life	Large randomized controlled trials using challenge-proven diagnostic criteria for food allergy	High
Confirmatory evidence about introduction of cooked egg especially about the amount, formulation, timing and duration	Large randomized controlled trials. Further analyses of data from existing studies	Moderate
Information about whether continued breastfeeding whilst complementary feeding is established affects allergy development	Large randomized controlled trial	Moderate
Information about whether the diversity of the infant and maternal diet affects allergy development	Community-based randomized controlled trial	Moderate
Information on whether emollients and skin care reduces the risk of food allergy	Large randomized controlled trials	Moderate
Whole infant diet in relationship to the development of food allergy	Large observational studies	Moderate
Information about whether the timing of introducing cow's milk protein in a variety of products impacts on development of food allergy	Community-based randomized controlled trial	Low
Information about different types of prebiotics, probiotics and synbiotics as evidence is sparse and mixed, including information about specific strains, doses, timing and duration	Large randomized controlled trials	Low
Confirmation about whether fish oil has an impact as evidence is mixed	Community-based randomized controlled trial	Low

Therefore, parental reports may not be a reliable measure of food allergy. Diagnosis should be confirmed by controlled elimination challenges.<sup>74</sup>

A high priority gap is the need for evidence about the early introduction of peanut into the infant diet in countries other than the UK to demonstrate that the recommendation about peanut introduction is generalizable to other populations. Similar evidence for tree nuts and other key food allergens is also required.

Other high priorities include the optimum timing of introduction of cow's milk protein into the infant diet and the value of hydrolysed formula.

#### 4.4 | Conclusion

This guideline supports breastfeeding and provides simple recommendations, which require minimal cost or resources. However, there is a need to invest in robust education and promotional campaigns to help parents, professionals, policymakers and commissioners understand the best ways to ensure a healthy and balanced diet

and to reduce food allergy in infants and young children. Investing in education, including at the community and primary care level, may reduce the need for later input from specialists.

The recommendations about avoiding supplementation with cow's milk-based formula in the first week of life in breastfed infants and introducing cooked egg and peanut in an age-appropriate form as part of complementary feeding are new since EAACI published guidelines in 2014. Implementing these recommendations, being mindful of family and community preferences, may help to alleviate the burden of food allergy amongst individuals and families and also reduce societal healthcare costs.

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### CONFLICT OF INTERESTS

DdS, EA, EK, GW, HA, SA and VV declared no potential interests. AM has received research grants from Aimmune; and speaker's fees from DBV, Aimmune, Mylan, ALK and Nestle. AH has received speaker's fees from Nestle, Bristol-Myers and ALK. CJ served as an employee of Allergy UK; and has received funding from Abbott, Aimmune, Allergy Therapeutics, DAOsin, DBV, Danone, Nutricia, Mead Johnson (Reckitt Benckiser), Sanofi-Genzyme and Thermo Fisher. CV has received research grants from Reckitt Benckiser and National Peanut Board; and speaker's/lecture material fees from Danone, Abbott, Nestle, Mead Johnson and Nestle Nutrition Institute. GdT has received research grants from Aimmune, DBV, NIH (LEAP study) and Action Medical Research (EAT study); and education fees from Allergy Academy. GL has received research grants from NIH (LEAP study) and Action Medical Research (EAT study); served as a consultant for DBV, Aravex, Aimmune, ALK, Novartis and Sanofi-Genzyme; and served as a shareholder of DBV and Mission Mighty Me. GR has received research grants from NIH (LEAP study) and Action Medical (EAT study); served as a consultant for Nutricia; and served as an editor-in-chief for Clinical & Experimental Allergy. HB served as a consultant for DBV; and has received research grants from NIH (LEAP study) and Action Medical (EAT study). HS served as a consultant for Danone, Nestle and Nutricia; has received speaker's fees from Danone, Hipp, Nestle and Nutricia; and served as an editor for Journal of Ped Gastroenterology and Nutrition (to June 2019). KB has received research grants from Aimmune, ALK, Danone, DBV, DST Diagnostic, Good Mills, Hipp, Hycor, InfectoPharm, Thermo Fisher and VDI; served as a consultant for Aimmune, ALK, Bausch & Lomb, Bencard, Danone, DBV, Hipp, Hycor, InfectoPharm, Mabyon, Meda Pharma, Mylan, Nestle, Novartis; and has received speaker's fees from Aimmune, Allergopharma, Bencard, Danone, InfectoPharm, Meda Pharma, Mylan, Nestle and Thermo Fisher. KG served as a consultant for Nutricia, Nestle and Reacta Biotech; and has received speaker's fees from Abbott and Mead Johnson. KN has received research grants from NIAID, FARE and EAT; served as a consultant for Novartis, Regeneron, Sanofi, Astellas, Nestle, Genetech, Aimmune Therapeutics and DBV Technologies; and served as a shareholder of Before Brands, Alladapt and ForTra. LO'M has received research grants from SFI and GSK; has received speaker's fees from Nestle and Nutricia; and served as a consultant for PrecisionBiotics. ME has received speaker's fees from DBV Technologies and Mylan. PE has received research grants from LETI, Nestle and Thermo Fisher; served as a consultant for Danone, Novartis, ALK, DBV and Abbott; and served as an editor-in-chief for PAI. RB has received consultancy fees from DBV Technologies and Prota Therapeutics, for expert witness work related to food anaphylaxis and infant formula claims; and served as a senior editor for Cochrane and joint editor-in-chief for Clinical and Experimental Allergy. SH served as a consultant for ALK and has received research grants from ALK. Task Force members

were not involved in reviewing data or making final recommendations about areas where they had a declared interest. GL and KN were not involved in recommendations about the introduction of infant formulas or complementary foods.


### AUTHOR CONTRIBUTIONS

SH: Chair of the EAACI Food Allergy Prevention Guideline Update Task Force; conceptualization of the guideline process; manuscript drafting; final decision-makers and guarantors. AM: Chair of the EAACI Food Allergy Prevention Guideline Update Task Force; conceptualization of the guideline process; final decision-makers and guarantors. GR: Process coordination; conceptualization of the guideline process; extraction of additional data; decision-makers and guarantors. DdS: conceptualization of the guideline process; extraction of additional data; manuscript drafting. SA: Analysis of specific sections. KB: Analysis of specific sections. RB: Analysis of specific sections. GdT: Analysis of specific sections. PE: Analysis of specific sections. EK: Analysis of specific sections; extraction of additional data. HS: Analysis of specific sections. CV: Analysis of specific sections. CJ: Patient group representative. All authors satisfied the international authorship criteria and critically reviewed the guideline drafts and suggested edits.

### PEER REVIEW

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### ORCID

Susanne Halcken  <https://orcid.org/0000-0003-0161-8278>  
 Antonella Muraro  <https://orcid.org/0000-0002-5026-5862>  
 Debra de Silva  <https://orcid.org/0000-0001-8413-5487>  
 Ekaterina Khaleva  <https://orcid.org/0000-0002-2220-7745>  
 Stefania Arasi  <https://orcid.org/0000-0002-8135-0568>  
 Motohiro Ebisawa  <https://orcid.org/0000-0003-4117-558X>  
 Philippe Eigenmann  <https://orcid.org/0000-0003-1738-1826>  
 Kari Nadeau  <https://orcid.org/0000-0002-2146-2955>  
 Hania Szajewska  <https://orcid.org/0000-0002-4596-2874>  
 Carina Venter  <https://orcid.org/0000-0002-7473-5355>  
 Gary W. K. Wong  <https://orcid.org/0000-0001-5939-812X>  
 Graham Roberts  <https://orcid.org/0000-0003-2252-1248>

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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