**EAACI guideline: preventing the development of food allergy in infants and young children (2020 update) – online supplement**

This supplement sets out some of the factors that the Task Force considered when formulating recommendations.

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**TABLE S1: OVERALL SUMMARY OF EFFECT SIZES**

| **Intervention** | **Timing/type** | **Absolute effect** | **Age, relative risk (RR)**  **(95% CI)** | **Certainty of evidence** | **Overall conclusion** | **Studies**  **(participant no.)** |
| --- | --- | --- | --- | --- | --- | --- |
| Dietary avoidance of food allergens | Pregnancy | 2% increase | Prevalence FA at 0-1.5 years 1.67 (0.38 to 7.22) | Very low | Little to no effect | 1 RCT (198) |
| Pregnancy and breastfeeding | 0% change | Prevalence of cow’s milk 0-1.5 years 1.01 (0.15 to 7.02) | Very low | Little to no effect | 1 RCT (164) |
| Pregnant and/or breastfeeding women and infants | 8% to 11% decrease | Prevalence of FA 0-1 year 0.31 (0.07 to 1.41)  Prevalence FA at 1 years 0.3 (0.12 to 0.77) | Very low | Little to no effect | 2 RCTs (399) |
| Avoiding standard cow’s milk-based formula | Avoiding standard cow’s milk formula | Range 22% decrease to 2% increase | Multiple outcomes | Low | May not reduce or increase | 7 RCTs (4327) |
| Avoiding supplement of cow’s milk in first week of life | 6% decrease | Prevalence cow’s milk allergy 0-2 years 0.10 (0.01 to 0.77) | Low | Avoiding supplementation may decrease | 1 RCT (312) |
| Introducing complementary foods | Cooked hen’s egg from 6 months | 29% decrease | Prevalence egg allergy at 1 year 0.22 (0.08 to 0.54) | Moderate | Probably reduces | 1 RCT (147) |
| Raw egg or uncooked pasteurised egg from 4 months | 18% decrease to 2% increase | Prevalence egg allergy at 1 year range 0.65 to 3.3 (see supplement) | Low | May not reduce | 3 RCTs (1289) |
| Peanut from median 7.8 months in increased risk | 12% to 23% decrease | Prevalence peanut allergy 5 years range 0.14 to 0.35 | Moderate | Probably large reduction | 2 RCTs (640) |
| 6 allergenic foods from 3 months | 2% decrease | Prevalence FA 1-3 years 0.8 (0.51 to 1.25) | Low | May not reduce | 1 RCT (1303) |
| Breastfeeding | Infancy | Range 3% decrease to 2% increase | Multiple outcomes | Low | May not reduce | 7 studies (15046) |
| Hydrolysed formula | Partially hydrolysed in infancy | Range 34% decrease to 11% increase | Multiple outcomes | Low | May not reduce | 5 RCTs (3572) |
| Extensively hydrolysed in infancy | Range 4% decrease to 2% increase | Multiple outcomes | Low | May not reduce | 5 RCTs (3221) |
| Hydrolysed formula plus dietary avoidance | Range 9% to 11% decrease | 0-1.5 years cow’s milk allergy 0.18 (0.01 to 3.37) | Very low | Little to no effect | 2 RCTs (470) |
| Soy-based formula | Infancy | 1% increase | Prevalence cow’s milk allergy 0-2 years 1.35 (0.48 to 3.81) | Very low | Little to no effect | 1 RCT (620) |
| Vitamins | Pregnancy | 6% increase | Prevalence FA 0-3 years 1.92 (0.57 to 6.5) | Very low | Little to no effect | 1 RCT (180) |
| Breastfeeding | 18% increase | Prevalence FA 0-2 years 3.42 (1.02 to 11.77) | Very low | Little to no effect | 1 RCT (164) |
| Infancy | 2% increase | Prevalence 0-1 year 1.33 (0.76 to 2.33) | Very low | Little to no effect | 1 RCT (975) |
| Fish oil | Pregnancy | Range 4% decrease to 1% increase | Multiple outcomes | Low | May not reduce | 2 RCTs (789) |
| Pregnancy and breastfeeding | 14% decrease | Prevalence 0-1 year 0.13 (0.02 to 0.95) | Low | May decrease slightly | 1 RCT (145) |
| Infancy | 3% decrease | Prevalence 0-1 year 0.81 (0.47 to 1.42) | Very low | Little to no effect | 1 RCT (420) |
| Breastfeeding and infants | 2% increase | Prevalence 0-1.5 years 1.24 (0.62 to 2.50) | Low | May not reduce | 1 RCT (655) |
| Prebiotics | Infancy | 12% decrease | Prevalence 0-1.5 years 0.28 (0.08 to 1.0) | Very low | Little to no effect | 1 RCT (240) |
| Probiotics | Infancy | Range 2% to 4% decrease | Multiple outcomes | Low | May not reduce | 3 RCTs (563) |
| Pregnancy, BF and/or infancy | 10% increase | Prevalence cow’s milk allergy 0-2 years 1.87 (0.74 to 4.69) | Very low | Little to no effect | 2 RCTs (256) |
| Prebiotics plus probiotics | Probiotics in pregnancy and infants plus prebiotic in infants | 1% decrease | Prevalence FA 0-2 years 0.89 (0.51 to 1.55) | Low | May not reduce | 2 RCTs (1116) |
| Other | Synbiotics | 0% change | Prevalence FA 1 year 1.03 (0.63 to 1.68) | Low | May not reduce | 1 RCT (459) |
| Emollients | 2% decrease | Prevalence FA 1 year 0.81 (0.49 to 1.33) | Low | May not reduce | 1 RCT (459) |
| Prophylactic oral immunotherapy | 6% decrease | Prevalence FA 0-1 year 0.38 (0.1 to 1.9) | Very low | Little to no effect | 1 RCT (111) |
| BCG vaccination | 0% change | Prevalence FA 0-13 months 1.48 (0.67 to 3.29) | Very low | Little to no effect | 2 RCTs (4543) |

FA: food allergy.

**AVOIDING POTENTIAL DIETARY FOOD ALLERGENS**

**Table S2: 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**

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| --- | --- | --- | --- |
| **Evidence of effectiveness** | **Balance of benefits and harms** | **Preferences and values** | **Feasibility and resources** |
| There is very low certainty evidence about pregnant and breastfeeding women avoiding dietary food allergens to reduce food allergy in their infants and young children.  There were five trials in women at increased risk, two of which focused on dietary avoidance alone and three combined with another intervention.  One trial examined avoiding cow’s milk and egg during pregnancy (cumulative food allergy incidence 0-1.5 years RR 1.67, 95% confidence interval (CI) 0.38 to 7.22, p>0.05, very low certainty) (Fälth-Magnusson 1992).  Another examined milk and egg exclusion during the third trimester of pregnancy and whilst breastfeeding (cow’s milk allergy cumulative incidence 0-1.5 years RR 1.01, CI 0.15 to 7.02, p>0.05, low certainty) (Lilja 1989).  Another trial examined dietary avoidance amongst breastfeeding women and infants for 12 months coupled with bedroom and living room treatments every three months (food allergy cumulative incidence 0-1 year RR 0.31, CI 0.07 to 1.41, p>0.05, very low certainty) (Arshad 1992).  Two trials combined food allergen avoidance with hydrolysed formulas (results described in hydrolysed formula table) (Zeiger 1992, Odelram 1996). | The potential harm associated with avoiding foods during pregnancy and breastfeeding may be greater than any potential reduction in food allergy.  Health authorities in many countries state that it is important that women have a healthy, well-rounded diet when pregnant and breastfeeding. Cutting out food groups can limit nutrients and may adversely affect the health of women and their babies. Food allergens do not exist in isolation so removing food groups may also reduce intake of vital nutrients as well as other immunomodulatory components such as fibre (Venter 2018). | No specific societal preferences or values were considered to affect this recommendation.  Healthy pregnant and breastfeeding women can continue with their usual diet, in line with cultural and family preferences. If the usual diet does not provide all the nutrients required, dietary advice may be helpful. | No issues related to feasibility or resource use affected this recommendation.  It is feasible for pregnant and breastfeeding women to continue their usual diet rather than avoiding food allergens.  Eating a healthy, varied diet may have cost implications but dietetic input can assist mothers to have a healthy diet at lower cost. Dietary restrictions may also have cost implications, as ‘free from’ foods can be more expensive than standard foods. |

**INTRODUCING POTENTIAL DIETARY FOOD ALLERGENS**

**Table S3: The EAACI Task Force suggests introducing well-cooked hen’s egg, but not only pasteurised or raw egg, into the infant diet as part of complementary feeding to prevent egg allergy in infants**

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| **Evidence of effectiveness** | **Balance of benefits and harms** | **Preferences and values** | **Feasibility and resources** |
| There is moderate certainty evidence that introducing small quantities of cooked egg (around 2g egg protein per week) into infant diets as part of complementary feeding may prevent food allergy in infants. The effect on young children is uncertain.  One trial in high risk infants used cooked egg (equivalent of boiled egg) doses of 50mg per day (equivalent to 1/160th of an egg) from six to nine months and 250mg per day thereafter until 12 months (egg allergy at 1 year RR 0.22, CI 0.08 to 0.54, p<0.05, moderate certainty). This trial used much smaller amounts of egg compared to other studies (Natsume 2017). Another trial in general risk infants found no statistically significant reduction in egg allergy from introducing cooked egg alongside other foods from three months (Perkin 2016). A subgroup analysis of high risk infants in this trial, not included in the systematic review, suggested a possible reduction in egg allergy in those consuming cooked egg from 3-4 months of age (Perkin 2019).  Early introduction of raw egg or uncooked pasteurised hen’s egg powder probably does not reduce the risk of egg allergy. One trial focused on infants at general risk (1 year prevalence RR 3.30; CI 0.35 to 31.32; p>0.05, low certainty) (Bellach 2017). Two trials were conducted in infants at increased risk (1 year prevalence RR 0.75; CI 0.48 to 1.17, p>0.05 and RR 0.65; CI 0.38 to 1.11, p>0.05, low certainty; Palmer 2013, Palmer 2017). | Weighing the balance of potential benefits against harms appears to be in favour of benefits for cooked egg.  Two randomised trials found no harm from introducing cooked egg (as boiled egg) into the infant diet at around three to six months (Natsume 2017, Perkin 2016), though the amounts introduced in one trial were small (Natsume 2017). There were no harms in general or increased risk populations so the recommendation could apply to all, even though there was no statistically significant evidence of effectiveness amongst those at general risk.  The harms of introducing raw egg or uncooked pasteurised egg ‘early’ may outweigh any potential benefits.  Meta-analysis combining the data from increased risk infants suggests a potential benefit (Matsumoto 2018), but this is insufficient evidence to recommend introducing raw egg or uncooked pasteurised egg early when harms are taken into account.  Four randomised trials (Bellach 2017, Palmer 2013, Palmer 2017, Tan 2016) found that introducing raw egg or uncooked pasteurised egg at four to six months of age was associated with higher rates of adverse events, including anaphylactic reactions.  WHO recommends that breastfeeding continues for as long as feasible (WHO 2016). WHO highlights that introducing any food allergens ‘early’ has the potential to reduce breastfeeding. This was not seen in the EAT trial (Perkin 2016), and not indicated in a recent EFSA report (ESFA 2019). | This recommendation applies to countries where egg is a usual part of the diet and where egg allergy is an issue.  The usual start of complementary feeding differs across countries and families, as does the extent to which egg is a common part of the diet. Introducing well cooked egg into the diet from four to six months of age is based on lack of harm (Perkin 2016) and potential for benefit compared to later introduction (Perkin 2019; Ierodiakonou 2016). The evidence is insufficient to be more specific but fits in with the recent European Food Safety Authority report (EFSA 2019).  Breastfeeding has many benefits for infants (Stuebe AM 2017). Professionals should advocate introducing egg alongside continued breastfeeding ([https://www.who.int/activities/promoting-baby-friendly-hospitals/ten-steps-to-successful-breastfeeding](https://eur03.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.who.int%2Factivities%2Fpromoting-baby-friendly-hospitals%2Ften-steps-to-successful-breastfeeding&data=01%7C01%7Cg.c.roberts%40soton.ac.uk%7C2ab91f37cfc84a4ba17708d81dc0ba3f%7C4a5378f929f44d3ebe89669d03ada9d8%7C0&sdata=X%2FqAI9OXBJqF9479SmsCjBPRKEPxwCz7I%2BxEBASFJSg%3D&reserved=0), last accessed 4th July 2020). | Egg is readily available in most countries so there should not be significant cost implications to introduce it if it is already part of the family diet.  There may be issues with the feasibility of introduction. One trial found that eating at least 2 grams of egg white protein per week prevented egg allergy (Perkin 2016). Due to the texture, infants may not be ready to eat hard cooked egg until after six months of age. We consider that egg can be given in equivalent amounts mixed with other ingredients as part of a well cooked/baked meal. Hard boiled eggs can be pureed and added to other foods or cooked egg powder is available as an alternative. |

**Table S4: 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**

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| --- | --- | --- | --- |
| **Evidence of effectiveness** | **Balance of benefits and harms** | **Preferences and values** | **Feasibility and resources** |
| There is moderate certainty evidence that introducing peanut in an age-appropriate form as part of complementary feeding may prevent food allergy in infants and young children at increased risk.  Two trials introduced the equivalent of three heaped teaspoons of peanut butter per week (6g) to infants with severe eczema and/or egg allergy from four to 11 months (median 7.8 months) and maintained weekly intake for five years. One trial included infants with positive skin prick test to peanut and one without (overall RR for peanut allergy incidence at 5 years 0.18, CI 0.10 to 0.35, p<0.05, moderate certainty, du Toit 2015). Introducing peanut did not statistically significantly reduce the overall risk of tree nut allergy or the overall risk of food allergy (du Toit 2018).  Another trial in general risk infants found no statistically significant reduction in food allergy by introducing peanut along with five other foods from three months (Perkin 2016). Subgroup analysis with those at increased risk found reduced food and egg allergy and a non-significant reduction in peanut allergy (Perkin 2019). | There appear to be more benefits than harms, though most of the data come from two trials (published as one paper) in a country with a high prevalence of peanut allergy. This means that the impacts of a population-wide switch to early regular peanut consumption will not be known for some time.  Two randomised controlled trials found no severe reactions when introducing peanut (du Toit 2015, Perkin 2016), although there were some non-severe reactions at introduction. Participants with a high degree of peanut sensitisation were excluded from one study so this may affect the safety profile.  There are some other potential harms. Early introduction of peanut could increase cases of choking or inhalation if advice to use age-appropriate forms is not followed. Increased environmental exposure to peanut may promote sensitisation to peanut in younger siblings and elicit reactions in siblings with peanut allergy.  One study found that early consumption of peanuts had no negative nutritional consequences and resulted in decreased intake of processed snacks (Feeney 2016). | Countries have different rates of peanut consumption and allergy. We do not have any randomised controlled trial data from low peanut allergy prevalence population. So this recommendation applies to families in populations where peanuts are part of the diet and where there is a high prevalence of peanut allergy.  Peanuts have long been a part of the infant diet in some countries such as Israel (du Toit 2008).  In families where peanut is not routinely eaten, there may be reluctance to introduce peanuts to infants, especially in families with peanut allergy.  The usual start of complementary feeding differs across countries and families. Introducing peanut into the diet from four to six months of age in populations of high prevalence is based on lack of harm (Perkin 2016) and potential for benefit for introduction before infant develop peanut allergy (Peters 2017). The evidence is insufficient to be more specific but fits in with the recent European Food Safety Authority report (EFSA 2019).  Breastfeeding has many benefits for infants (Stuebe AM 2017). Professionals should advocate introducing peanut alongside continued breastfeeding ([https://www.who.int/activities/promoting-baby-friendly-hospitals/ten-steps-to-successful-breastfeeding](https://eur03.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.who.int%2Factivities%2Fpromoting-baby-friendly-hospitals%2Ften-steps-to-successful-breastfeeding&data=01%7C01%7Cg.c.roberts%40soton.ac.uk%7C2ab91f37cfc84a4ba17708d81dc0ba3f%7C4a5378f929f44d3ebe89669d03ada9d8%7C0&sdata=X%2FqAI9OXBJqF9479SmsCjBPRKEPxwCz7I%2BxEBASFJSg%3D&reserved=0), last accessed 4th July 2020). | This recommendation applies to whole populations, regardless of whether infants are at general or increased risk of peanut allergy. Those at lower risk contribute to the population burden of peanut allergy (O’Connor 2016, Koplin 2016) so early introduction of peanut has the potential for benefit in this group as well as those at increased risk.  It is inexpensive to feed infants peanut butter or similar foods when this is already part of the usual family diet.  However, regular peanut ingestion may be difficult to achieve. In one trial, 38% of participants did not adhere to peanut consumption (Perkin 2016). This trial indicated that a weekly consumption of 2 gram peanut protein was required to prevent allergy. Factors associated with lower compliance included maternal age, ethnic minority families and severe eczema. There may be a need for targeted approaches to increase adherence and potential benefit in these populations. |

**BREASTFEEDING AND INFANT FORMULA**

**Table S5: There is no recommendation for or against using breastfeeding to prevent food allergy in infants, but breastfeeding has many benefits for infants and mothers and should be encouraged wherever possible**

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| **Evidence of effectiveness** | **Balance of benefits and harms** | **Preferences and values** | **Feasibility and resources** |
| There is very low certainty evidence about the impact of breastfeeding on food allergy.  Five large birth cohort studies examined whether breastfeeding infants at general risk reduced the risk of food allergy (cow’s milk allergy RR ranged between 0.38 and 2.08). Only two of these used robust diagnostic criteria and these two studies found contrasting results. One found that exclusive breastfeeding was associated with a lower incidence of challenge-proven cow’s milk allergy at 18 months (Høst 1988). The other did not find a statistically significant association, though it also randomised infants to other interventions if breastfeeding was not sufficient (Saarinen 2000).  The other three studies found no statistically significant association between breastfeeding and the development of food allergy/cow’s milk allergy at one year (Kim 2011, Tariq 1998) or four years (Kull 2002), but these studies did not use robust diagnostic criteria for food allergy.  These conflicting findings and the low certainty of evidence mean that it is not possible to draw conclusions about whether breastfeeding prevents food allergy in general risk infants.  There were no large prospective studies about whether breastfeeding reduces the risk of food allergy in those at increased risk. | There is no consistent evidence that breastfeeding prevents the development of food allergy, but neither is there evidence that breastfeeding causes harm related to food allergy in healthy infants and mothers.  Breastfeeding has many health benefits for infants and mothers not related to the prevention of food allergy (Chowdhury 2015, Horta 2015, Nguyen 2017, Sankar 2015). It meets all of the nutritional needs of infants up to six months.  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. | WHO recommends exclusive breastfeeding for the first six months and continued breastfeeding for two years or beyond (WHO 2016).  Breastfeeding is natural and is the preferred approach where possible. Some infants are not fully breastfed, including for medical reasons, cultural preferences, societal barriers, lack of maternity leave and lack of support (Beake 2017, Haroon 2013). | Breastfeeding is inexpensive and accessible to most families (Walters 2016). There is a continuing need for resources to educate healthcare professionals and families about the benefits of breastfeeding and to allow women sufficient maternity leave and support for ongoing breastfeeding (Wood 2016)(([https://www.who.int/activities/promoting-baby-friendly-hospitals/ten-steps-to-successful-breastfeeding](https://eur03.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.who.int%2Factivities%2Fpromoting-baby-friendly-hospitals%2Ften-steps-to-successful-breastfeeding&data=01%7C01%7Cg.c.roberts%40soton.ac.uk%7C2ab91f37cfc84a4ba17708d81dc0ba3f%7C4a5378f929f44d3ebe89669d03ada9d8%7C0&sdata=X%2FqAI9OXBJqF9479SmsCjBPRKEPxwCz7I%2BxEBASFJSg%3D&reserved=0), last accessed 4th July 2020).  Suboptimal breastfeeding may be associated with additional healthcare costs for mothers and infants (Bartick 2010, Pokhrel 2015) and wider societal and healthcare costs (Stuebe 2017). |

**Table S6: 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.**

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| **Evidence of effectiveness** | **Balance of benefits and harms** | **Preferences and values** | **Feasibility and resources** |
| There is low certainty evidence that use of cow’s milk-based formula in breastfed infants during the first week of life may increase the risk of cow’s milk allergy in infants and young children.  One randomised controlled trial found that avoiding supplementation with cow’s milk-based 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 (cumulative incidence 0-2 years RR 0.10, CI 0.01 to 0.77, p<0.05, Urashima 2019). The trial is difficult to interpret because it included a range of interventions over different periods, cow’s milk allergy was a secondary outcome and only equivocal cases had a cow’s milk challenge. | The potential harms of supplementation with cow’s milk-based formula outweigh benefits given that other options are available.  A randomised controlled trial (Urashima 2019), a quasi-randomised controlled trial (Saarinen 2000), a large prospective birth cohort (Host 1988) and a case control study (Kelly 2018) all found increased food allergy or cow’s milk allergy when cow’s milk-based formula was used as a supplementary feed in the first week of life.  WHO warns that any supplementation may be associated with a reduction in breastfeeding (WHO 2016).  It is important to support breastfeeding, and usually breastfeeding is sufficient with no need for supplementation in healthy, term born infants. If needed, the family should seek advice from healthcare professionals.  It is important that infants receive appropriate nutrition, but alternatives are available. | Historical practice amongst health professionals and lack of awareness of potential harms amongst some parents and professionals may mean that cow’s milk-based formula is preferred over other supplementation alternatives. | Not all mothers are able to breastfeed their infants in the first few days of life. Other feed options are available if supplementation is needed. Possible temporary supplementary options might include, for example, donor breastmilk, hydrolysed formula, amino acid formula or water, depending on clinical, cultural and economic factors. These are listed as they are not associated with an increase in the risk of developing food allergy.  Feasibility may be an issue as patient representatives and clinicians have reported that, in some settings, health professionals may supplement with cow’s milk-based formula without parents knowing. Parents without information or support who are having difficulty breastfeeding may also turn to formula so it is important to discuss appropriate feed options and support breastfeeding. |

**Table S7: 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.**

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| **Evidence of effectiveness** | **Balance of benefits and harms** | **Preferences and values** | **Feasibility and resources** |
| There is low certainty evidence about the most appropriate time to introduce regular consumption of cow’s milk-based formula in order to prevent cow’s milk allergy.  Seven trials examined this in general and increased risk infants. The overall conclusion was that early or delayed introduction of regular consumption of cow’s milk-based formula did not consistently affect the incidence of cow’s milk allergy.  Two trials in general risk preterm or very preterm infants found no statistically significant impact on food allergy when cow’s milk proteins (preterm formula or human milk fortifier) were introduced from birth (Lucas 1990) or hospital discharge at around seven weeks (Zachariassen 2011). In the latter study all infants received small amounts of cow’s milk-based human milk fortifier from day 10 until discharge.  In infants at increased risk, one trial found no statistically significant change in the risk of parental reported food allergy from delaying the introduction of cow’s milk-based formula in favour of using soy or hydrolysate formula at the cessation of breastfeeding (Lowe 2011).  Other studies relevant to the introduction of cow’s milk are summarised in the tables about hydrolysed formula and breastfeeding. | There appears to be no benefit for preventing cow’s milk allergy by delaying the introduction of regular use of cow’s milk formula if a formula is needed.  There do not appear to be significant benefits from introducing regular use of cow’s milk formula into the infant diet ‘early’ or avoiding such introduction until after six months. Neither do there appear to be significant harms related to development of food allergy after the first week of life, see the table about introducing regular cow’s milk formula the first week of life. In most of these studies, cow’s milk-based formulas were introduced after the termination of breastfeeding after around three months of age, and there is insufficient evidence for the period before this.  The effects of introducing other cow’s milk protein remain uncertain. A trial that introduced yoghurt from three months along with five other foods from four months found no significant harms (Perkin 2019).  Some countries suggest avoiding whole milk until nine months due to concerns over nutritional value, iron deficiency anaemia and intestinal bleeding.  WHO warns that any supplementation may be associated with a reduction in breastfeeding (WHO 2016) although this was not seen in the EAT study (Perkin 2016). | Breastfeeding is natural and WHO states this should be the preferred approach where possible (2016). Where a breastmilk substitute is used, cow’s milk-based infant formulas may be preferred to standard cow’s milk during the first year of life, due to nutritional value and ease of digestion.  There may be differences in national guidelines and preferences about when whole milk, yoghurt and other cow’s milk proteins are introduced. | Cow’s milk-based infant formulas are readily available and nutritionally adequate if families choose to use them. |

**Table S8: There is no recommendation for or against using partially or extensively hydrolysed formula to prevent food allergy in infants. When exclusive breastfeeding is not possible, many substitutes are available for families to choose from, including hydrolysed formulas**

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| **Evidence of effectiveness** | **Balance of benefits and harms** | **Preferences and values** | **Feasibility and resources** |
| There is low certainty evidence about hydrolysed formulas. The evidence focuses on infants at increased risk of food allergy. Seven trials compared hydrolysed to non-hydrolysed formula but used different formulas, introduced them at different times, often had small samples and five trials did not use robust diagnostic criteria for food allergy.  One trial found that partially hydrolysed formula from birth reduced the incidence of challenge-proven cow’s milk sensitivity at 12 months, mostly due to a reduction in the first six months (Vandenplas 1992). Another found reduced risk of challenge-proven cow’s milk allergy at 12 months when extensively hydrolysed formula was combined with maternal and infant dietary avoidance from birth (Zeiger 1992). Five trials found no statistically significant reduction in food allergy from partially (Lowe 2011, Oldaeus 1997, von Berg 2003) or extensively hydrolysed formula when used alone (Mallet 1992, Oldaeus 1997, von Berg 2003) or in combination with dietary avoidance of food allergens (Odelram 1996). In three of these (Lowe 2011, Oldaeus 1997, Odelram 1996) formula was introduced only after cessation of breastfeeding after 3-6 months.  Two trials found no statistically significant difference in food allergy prevention between partially and extensively hydrolysed formula or extensively hydrolysed whey or casein based formula (Halken 1993, Halken 2000).  None of the studies found an allergy prevention effect when using hydrolysed formula after the age of six months. | There is no consistent evidence of benefit related to food allergy from hydrolysed formula, but neither is there robust consistent evidence that using hydrolysed formula causes harm (Boyle 2016).  There are many different types of hydrolysed formula and studies about benefits and harms are not always available for each specific formula. Variations in the degree of hydrolysis, protein source and hydrolysis method contribute to differences among hydrolysates so it is difficult to generalise benefits and harms.  Hydrolysed formulas fulfil infant nutritional needs in the first four to six months (Vandenplas 2019).  WHO suggests that marketing of hydrolysed formula for allergy prevention could reduce breastfeeding (WHO 2016).  There has been speculation about increased levels of advanced glycation end-products in hydrolysed formula (Baskara 2017).  . | Breastfeeding of all infants is preferable for the health of mother and child. When breastfeeding is not possible the best alternative should be chosen for a family’s individual circumstances and preferences.  In hydrolysed formulas the allergen content is lower than in standard cow’s milk formula and some families may prefer this (Høst 1988, Mäkinen-Kiljunen 1990, Rosendal 2000).  Breast milk and cow’s milk formula have been found to be more palatable than hydrolysed formula, which may be important with older infants. | Breastfeeding is low cost. Breast milk substitutes vary in cost and between countries. Hydrolysed formulas cost more than breastfeeding and usually more than standard cow’s milk formula (Ng. 2019, Bhanegaonkar 2015).  In some countries, subsidies are available for hydrolysed formula. |

**Table S9: The EAACI Task Force suggests against introducing soy protein formula in the first six months of life to prevent food allergy in infants and young children**

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| **Evidence of effectiveness** | **Balance of benefits and harms** | **Preferences and values** | **Feasibility and resources** |
| Based on very low certainty evidence, soy protein formula does not appear to prevent the development of food allergy in infants and young children.  One randomised controlled trial in infants at increased risk found that soy protein formula, introduced only after cessation of breastfeeding, did not statistically significantly reduce the risk of food allergy compared to cow’s milk formula or hydrolysed formula (Lowe, 2011). This trial was at high risk of bias and did not use robust diagnostic criteria for food allergy.  No trials were identified about infants at general risk of food allergy. | There may be more potential harms than benefits from using soy protein formula for the prevention of food allergy in infants.  Various soy protein formulas are available for feeding full term infants, but these have no nutritional advantage over cow’s milk protein formulas and contain high concentrations of phytate, aluminum, and phytoestrogens (isoflavones), which might have detrimental effects in the first six months of life (ESPGHAN 2006). Soy protein formula also contains glucose which may affect a baby’s teeth.  WHO warns that any supplement may reduce breastfeeding (WHO 2016). | Breastfeeding of all infants is preferable, but when this is not possible the best alternative should be chosen for a family’s individual circumstances and preferences.  Families may wish to consider soy protein formula for infants who cannot have dairy-based products because of cultural, medical or religious reasons such as a vegan lifestyle, persistent lactose intolerance or due to galactosemia. In this case, the potential benefits and harms of soy should be discussed fully. | Breastfeeding is low cost. Breast milk substitutes vary in cost and between countries. Soy protein formulas are available in many countries, but are more expensive than breastfeeding and likely more expensive than cow’s milk-based formula. |

**SUPPLEMENTS**

**Table S10: 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**

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| **Evidence of effectiveness** | **Balance of benefits and harms** | **Preferences and values** | **Feasibility and resources** |
| There is very low certainty evidence about the impact of vitamin A, D and polyunsaturated fatty acids on the prevention of food allergy in infants and young children. There is not enough consistent high quality research to make a recommendation but most evidence does not suggest a benefit.  Three randomised controlled trials found no statistically significant reduction in the risk of food allergy for vitamin D taken by pregnant women at general risk (Goldring 2013), breastfeeding women at increased risk (Norizoe 2014) or infants at increased risk (Rosendahl 2019). All studies had a high risk of bias and used different doses.  One randomised controlled trial found no statistically significant reduction in food allergy from vitamin A supplements alone or in combination with BCG vaccination for general risk infants (Kiraly 2013).  Three randomised controlled trials found no statistically significant reduction in food allergy from fish oil for pregnant women at increased risk (Dunstan 2013, Palmer 2013), infants at increased risk (D’Vaz 2012) or breastfeeding mothers and infants at general risk (Manley 2011). One trial found a reduced risk of food allergy when fish oil was taken by pregnant and breastfeeding women at increased risk (Furujhelm 2011). | There is no consistent evidence that vitamin supplements or fish oil supplements prevent the development of food allergy in infants, but neither is there evidence that these supplements cause harm in healthy infants and mothers.  It is difficult to weigh the benefits and potential harms because studies use different doses and regimes. | There are differences in vitamin and fish consumption in different countries. Country specific guidance may also differ. | The European Food Safety Authority (EFSA) advises pregnant and breastfeeding women to consume 100-200 mg preformed DHA (supplement) per day, in addition to the 1-2 servings of seafood (particularly fatty fish) per week that is recommended for the general population. The studies of effectiveness for preventing food allergy used higher amounts.  Pregnant women who are not achieving the recommended daily allowances through their diet may benefit from supplementation. However, healthy women and infants with a varied diet likely do not need to consume supplements, which can be expensive. |

**Table S11: 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**

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| **Evidence of effectiveness** | **Balance of benefits and harms** | **Preferences and values** | **Feasibility and resources** |
| There is low certainty evidence about currently evaluated prebiotics, probiotics and synbiotics. The evidence available suggests that these may not prevent the development of food allergy, but there is not enough consistent high quality research to make a recommendation because the preparations and doses used varied widely.  A randomised controlled trial found that infant formula with oligosaccharides (prebiotics) was associated with a lower incidence of food allergy and cow’s milk allergy at 18 months compared to standard formula in general risk infants (Ivakhnenko 2013).  Five trials found no statistically significant reduction in the risk of food allergy from probiotics for pregnant and breastfeeding women (Kalliomaki 2003, Niers 2009), infants at general risk (Plummer 2019, Prescott 2008) or infants at increased risk (Morisset 2011). In increased risk families, two randomised controlled trials found no significant reduction in the risk of food allergy from probiotics for pregnant women and infants plus prebiotic for infants (Kukkonen 2011, Marschan 2008).  One trial found no significant reduction in food allergy in general risk infants receiving synbiotics (Bifidobacterium bifidum OLB6378 plus fructo-oligosaccharides) with or without emollient skin barriers from birth to six months (food allergy prevalence at 1 year RR 1.03, CI 0.63 to 1.68, p>0.05, Dissanayake 2019). | There is no consistent evidence that prebiotics, probiotics or synbiotics prevent the development of food allergy, but neither is there evidence that they cause harm. The available studies differed in size, duration of supplementation, type of supplementation, timing of supplementation, diagnostic criteria and duration of follow-up. This makes it difficult to generalise about benefits and harms.  Commonly available probiotics, prebiotics and synbiotcs generally have a good general safety record (Bafeta 2018), but they have not been extensively tested for the prevention of food allergy. Preparations intended for vulnerable patient populations need to be rigorously tested (Sanders 2016). | There are no societal preferences or values that affect this recommendation. | Not all probiotics are equal. The clinical effects and safety of any single probiotic or combination of probiotics should not be extrapolated to other probiotics. The same applies to prebiotics and synbiotics.  The costs associated with the use of these supplements varies widely. |

**OTHER APPROACHES**

**Table S12: The EAACI Task Force suggests against using Bacillus Calmette-Guérin (BCG) vaccination to prevent food allergy in infants and young children**

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| **Evidence of effectiveness** | **Balance of benefits and harms** | **Preferences and values** | **Feasibility and resources** |
| There is low certainty evidence about BCG vaccination for preventing food allergy. The evidence available suggests that BCG vaccination does not prevent the development of food allergy in infants.  Two randomised controlled trials found that the timing of BCG vaccination did not statistically significantly reduce the risk of food allergy in infants at general risk (food allergy prevalence at 1 year 1.17, CI 0.55 to 2.48, Kiraly 2013; cumulative prevalence 0-13 months RR 1.48, CI 0.67 to 3.29, p>0.05, Thøstesen 2017). These studies were in different populations (one in West Africa) and neither used robust diagnostic criteria for food allergy.  No trials were identified about infants at increased risk of food allergy. | There may be more potential harms than benefits from using BCG vaccination for the prevention of food allergy in infants.  There are health benefits associated with BCG vaccination in children at risk of tuberculosis. However, there is a concern that BCG vaccination could cause adverse consequences in immunodeficient infants (Marciano 2014, Norouzi 2012).  BCG is part of the immunisation schedule in many European countries where tuberculosis prevalence is high and this recommendation does not affect those programmes. Families should be encouraged to follow the immunisation programs for their country. The recommendation is only against using the vaccination for preventing food allergy. | No specific societal preferences or values were considered to affect this recommendation. | BCG is part of standard immunisation schedules in many European countries, so incurs costs for governments rather than families. The recommendation not to use this vaccination for the prevention of food allergy has no known resource implications. |

**Table S13: There is no recommendation for or against using emollients as skin barriers to prevent food allergy in infants and young children**

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| **Evidence of effectiveness** | **Balance of benefits and harms** | **Preferences and values** | **Feasibility and resources** |
| It has been hypothesised that skin barriers could have a preventive effect on food allergy by normalising skin barrier function. This in turn could reduce the chance that cutaneous contact with food results in the development of food allergy. However, there is low certainty evidence about using emollients as skin barriers to prevent food allergy in infants.  One randomised controlled trial in children at general risk found no statistically significant reduction in the risk of food allergy from combined emollient and/or synbiotic use (Dissanayake 2019). This study did not use robust diagnostic criteria for food allergy.  A further large randomised controlled trial was published after our systematic review was completed (Chalmers 2020). It found that using emollients over the first year of life in increased risk infants did not lead to a reduction in confirmed food allergy at two years of age. | There is no consistent evidence of benefit related to food allergy from skin barriers, but neither is there consistent evidence that using skin barriers causes harm related to food allergy.  It is difficult to weigh benefits and harms due to the paucity of evidence. Different types of emollients may have different benefits and risks (Sindher 2020). | No specific societal preferences or values were considered to affect this recommendation. | Emollients are widely available and inexpensive in most European countries. |

**Table S14: There is no recommendation for or against using preventive house dust mite oral immunotherapy to prevent food allergy in infants and young children**

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| **Evidence of effectiveness** | **Balance of benefits and harms** | **Preferences and values** | **Feasibility and resources** |
| There is low certainty evidence about the effect of prophylactic oral immunotherapy for the prevention of food allergy in infants.  In increased risk infants, one randomised controlled trial of prophylactic house dust mite oral immunotherapy found no statistically significant reduction in food allergy but the study was not powered for this outcome ((food allergy cumulative incidence 0-1 year 0.38, CI 0.1 to 1.9, p>0.05, Zolkipli 2015).  There were no trials of prophylactic immunotherapy in general risk populations. | There is no consistent evidence that prophylactic oral immunotherapy prevents food allergy but neither is there consistent evidence that this causes harm.  Immunotherapy is increasingly used to treat food allergy and other allergies (Pajno 2018), and there is evidence about its preventive impact on the progression of rhinitis to asthma (Halken 2017). However, the only evidence available about food allergy is from one small proof of concept study, so additional evidence is required before weighing up benefits and harms and making recommendations. | No specific societal preferences or values were considered to affect this recommendation. | Allergen immunotherapy is relatively expensive. |

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