# Title page

Title:

Frequency of guideline-defined cow's milk allergy symptoms in infants: secondary analysis of EAT trial data

## Short title:

Cow’s milk allergy symptoms in infants

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## Summary conflict of interest statement

All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: Professor Lack reports grants from UK Food Standards Agency, grants from Medical Research Council, other from MRC & Asthma UK Centre, other from UK Dept of Health through NIHR, other from National Peanut Board, during the conduct of the study; personal fees and other from DBV Technologies, other from Mighty Mission Me , personal fees from Novartis , personal fees from Sanofi-Genyzme, personal fees from Regeneron, personal fees from ALK-Abello, personal fees and other from Lurie Children's Hospital, outside the submitted work; Dr Vincent reports a grant from International Society of Atopic Dermatitis (ISAD), a three month research fellowship award granted to Rosie Vincent (10000 euro bursary from Pfizer) and support from NIHR School for Primary Care Research, during the conduct of the study; Dr Radulovic reports grants from Food Standard Agency and MRC, during the conduct of the study; Dr Marrs reports other from Sponsorship of a Post-Graduate Allergy Teaching Institute which included manufacturers of hypoallergenic formula milk amongst others until their sponsorship was terminated in Summer 2019, outside the submitted work. Dr Flohr, Dr Perkin, Dr Logan, Dr MacNeill, Dr Craven and Dr Ridd have nothing to disclose.

## Statement of contribution

MJR conceived the research question and MP established its feasibility using the EAT dataset; together with RV, MJR and MP developed the project aims and objectives. RV led on data analysis with support from SJM. MJR, MP and SJMc directly supervised RV. MJR, MP, TM, FC, GL, KL and JC reviewed/agreed the mapping of iMAP to EAT questions and thresholds adopted. RV wrote the first and coordinated subsequent drafts of the manuscript, with input from all co-authors.

## Data Availability statement

The EAT data set (ITN900AD) is available through TrialShare, a public Web site managed by the Immune Tolerance Network ([www.itntrialshare.org](http://www.itntrialshare.org)).

## Ethical statement

The EAT study was approved by St Thomas’ Hospital Research Ethics Committee, Research Ethics Committee reference no. 08/H0802. Informed consent was obtained from all parents of the infants enrolled in the study.

**Word count: 3380/3500**

# ABSTRACT

Background: Non-IgE mediated Cow’s Milk Allergy (CMA) has a prevalence of less than 1% in children. Guidelines developed to help non-specialists diagnose CMA may lead to misattribution of normal symptoms and contribute to over-diagnosis of CMA. We sought to establish the frequency of symptoms during infancy associated with non-IgE mediated CMA, using the international Milk Allergy in Primary Care (iMAP) guideline as representative of CMA guidelines more generally.

Method: Secondary analysis of the EAT randomised controlled trial (ISRCTN 14254740) (1303 exclusively breastfed 3-month-old healthy infants). Key outcomes were ≥2 iMAP symptoms associated with“mild-moderate” and “severe” non-IgE mediated CMA.

Results: Whilst breastfeeding and parental atopy rates were higher than the general population, participants were otherwise similar to the population of England and Wales*.* Two or more non-IgE CMA symptoms were reported by 25% (mild-moderate) and 1.4% (severe) families each month, peaking at 38% (mild-moderate) and 4.2% (severe) at three months when participants were not directly consuming cow's milk. At six months there was no evidence of difference in the proportion of children with ≥2 mild-moderate symptoms between those consuming (34.6%) and not consuming cow’s milk (34.1%; p=0.83) nor in the proportion of children with ≥2 severe symptoms between those with (3.2%) or without eczema at baseline (2.0%; p=0.11).

*Conclusions*: Guideline-defined symptoms of non-IgE mediated CMA are very common in infants. Guidelines may promote milk allergy overdiagnosis by labelling normal infant symptoms as possible milk allergy.

**Words: 235**

**Key messages**

* We evaluated the prevalence of guideline-defined milk allergy symptoms in 1303 infants.
* 38% had multiple 'mild-moderate symptoms' at 3 months and 74% between 3 and 12 months
* Guidelines promote milk allergy overdiagnosis by labelling normal infant symptoms as possible milk allergy

# BACKGROUND

Cow’s milk allergy (CMA) affects 0.5% (95% CI 0.41-0.70) of children.1 Parental perception of CMA in preschool aged children is higher (1% - 17.5%).2 Cow’s milk protein is commonly consumed by infants through standard infant formula or in milk-containing foods. Small levels of lactoglobulin are found in breastmilk, however the quantities are below the threshold likely to trigger a reaction in more than 99% of infants with IgE mediated cow’s milk allergy.3

CMA is a reproducible immune-mediated allergic response to one or more of the proteins in cow's milk. In Immunoglobulin E (IgE)-mediated CMA there are immediate (within 2 hours) and consistently reproducible symptoms which may affect multiple organ systems.2 4 5 Diagnosis can be aided by allergy tests, but they are imperfect,6 and oral food challenge (OFC) is still subject to bias, time consuming and expensive.3 Atopic eczema/dermatitis (hereafter “eczema”) is a strong risk factor for IgE-mediated food allergy,7 especially if early onset and severe.8 Non-IgE-mediated CMA has typically delayed (between 2 and 72 hours) symptoms,4 5 and diagnosis is more challenging.5 Diagnosis is usually based on the observation of clinical improvement with cow’s milk protein avoidance, followed by relapse of symptoms with re-challenge with cow’s milk.9 Associated symptoms and signs are varied and include combinations of skin, gastrointestinal and symptoms.10 Some of these symptoms are already known to be very common in infants, adding to diagnostic difficulty: around 20% of children have eczema,11 12 colic affects 10% to 40% of infants,13 and regurgitation affecting around 50% of children in the first three months of life.14

A recent review found that all nine guidelines published between 2012 and 2019 suggest CMA as a cause of common infant symptoms,3 and guidelines are similar with overlapping symptoms (table S4). Using the UK Milk Allergy in Primary care (MAP) published in 2013 (updated as an “international” (iMAP) version in 2017 and 2019)**5 15** as a representative guideline, we sought to describe how common guideline-linked CMA symptoms are in infants, including in those with/without eczema and consuming/not consuming formula milk.

# METHODS

## Participants

We undertook a secondary analysis of infant data from the Enquiring About Tolerance (EAT) Study,16 a population based randomised control trial investigating whether the early introduction of allergenic foods into an infant’s diet reduced the risk of development of an allergy to that food.17 This study was not part of the original EAT study statistical analysis plan or protocol.

In brief, 1303 exclusively breastfed three-month-old infants in England and Wales were enrolled and randomised between 13 and 17 weeks of age into a standard introduction group (SIG) or an early introduction group (EIG). Infants in the EIG group had six allergenic foods, including cow’s milk, introduced alongside breastfeeding. In the SIG, the infants were encouraged to be exclusively breastfed until around six months. 95% of the diagnoses of IgE-mediated food allergy were achieved through a double blinded, placebo-controlled food challenge (DBPCFC). It was not possible, for logistical reasons, to undertake home challenges to confirm or refute the presence of non-IgE mediated cow’s milk allergy.

Questionnaires, in which parents reported on their infant’s general health and their consumption of the allergenic foods, were completed monthly until 12-months of age. The 3 and 12-month questionnaires coincided with a clinic visit. Symptoms which are described as ‘possible milk symptoms’ were previously determined by expert review of responses to the question ‘Since we saw your baby for the 3-month assessment/ since the last questionnaire has your infant had any adverse reaction to a food, such as eczema, breathing problems or gastrointestinal problems?’.

## Ethics and confidentiality

The EAT study was approved by St Thomas’ Hospital Research Ethics Committee, Research Ethics Committee reference no. 08/H0802. Informed consent was obtained from all parents of the infants enrolled in the study.

## Analysis

The iMAP guideline is aimed at primary care and first contact clinicians after taking an allergy focussed clinical history and physical examination, and lists symptoms and signs which may be associated with mild-moderate and severe non-IgE and IgE-mediated CMA (Table 1).5 The guidance recommends an “increased suspicion of CMA in infants with multiple, persistent, severe or treatment-resistant symptoms”, and addresses the risk of overdiagnosis when mild, transient or isolated symptoms are over-interpreted or if milk exclusion diets are not followed up by diagnostic milk reintroduction. There is limited published data on how common and persistent the symptoms identified in iMAP are in healthy infants, and there is no published validation of the 2019 iMAP guidelines.5

A consensus approach was used to map EAT questionnaire data to the iMAP listed symptoms. Three clinicians (RV, MP, and MR – a core medical trainee, consultant paediatric allergist and GP) independently assessed the guidance and discussed and agreed the most appropriate EAT questions and threshold for each symptom (considering persistence and severity). These decisions were then independently ratified by a panel comprising paediatric allergists (TM, GL, SR), a dermatologist (CF), a research fellow (KL) and a data manager (JC). In some instances, not all questions corresponded directly to symptoms listed in the guidance, and there was no corresponding data for, ’painful flatus’, ‘mucous in stool’, ‘non-specific rashes’ and ‘erythema’. For the details of the matching of EAT question items to iMAP symptoms and the agreed thresholds for persistence/severity, see Supplementary Appendix A.

Baseline characteristics of participating children were summarised by group using frequencies and proportions. Symptom data was analysed by month and across time periods (3-6, 6-9, 9-12 and 3-12 months). Denominators used are the responses from each monthly questionnaire/clinic visit attendance. All analyses were done by RV and SJM with Stata MP (version 16). While the symptoms listed in the iMAP guidance are not presented as a score, the instruction to worry more about multiple/persistent symptoms infers a count of symptoms above a certain threshold, as it might be applied in clinical practice. Monthly symptom data were presented as the number and proportion reporting that symptom above a set threshold.

A sub-group analysis was performed comparing infants with and without visible eczema at three months. Pruritis and moderate persistent eczema both are listed as iMAP mild-moderate symptoms, pruritus being strongly associated with the presence of eczema, and therefore both symptoms were excluded from both groups for this analysis. Symptom counts (mild-moderate and severe) were also compared in SIG infants consuming or not consuming cow’s milk infant formula at six months, and chi square test was performed.

Data from both arms of the study (SIG and EIG) were used, except for months 4-6 where, to avoid a confounding effect of the intervention itself during the key early introduction period through to six months of age, all analyses were restricted to data from participants in the SIG. For example, the question regarding any feeding difficulty in the preceding two weeks was asked immediately after questions determining adherence to the early introduction protocol in the EIG. Thus, differences between the two groups in the key early introduction period were conflated with difficulty achieving the level of food consumption requested of EIG infants (Table S2). The SIG had lower levels of ‘some’ and ‘great’ feeding difficulty compared to the EIG, which was most notable at four months: 7.4% (5/68) vs. 31.4% (169/538) for ‘some’; and 1.5% (1/68) vs. 7.8% (42/538) for ‘great’ feeding difficulty. Additionally, EIG families were asked to observe their infant carefully during the key early introduction period through to six months of age for the emergence of symptoms associated with food allergy. Hence, as anticipated, symptom reporting frequency was significantly greater in the EIG than in the SIG at four, five and six months (Table S2). SIG families were also encouraged to aim for exclusive breastfeeding for around six months and hence only a minority introduced solids before this time, usually because they believed that their infant was ready to start solids at this point.

# RESULTS

The baseline characteristics of all infants and caregivers showed balance between the two study groups (Table 2).17 While EAT study participants were broadly comparable to the general UK population, breastfeeding rates were higher: 100% at 3 months, 96.3% (1102/1144) at six months and 50.8% (584/1151) at 12 months in the EAT study population; compared with 42.4% at 6-8 weeks in the UK population (figures from quarter 1 2017/18).18 There was also a higher prevalence of parental atopy compared to the general population: allergy (including food allergy and atopy) was 66.0% (858/1301) in mothers, and 53.1% (691/1301) in fathers, compared with 40.8% and 30.4% respectively in a large community based study in England.19 The prevalence of self-reported food allergy in the EAT mothers was 19.4% (252/1303) and 10.6% (138/1303) in fathers, figures consistent with the estimated one-fifth of the general population who believe that they have adverse reactions to food.20 21

Between three and 12 months, the mean monthly reporting of milk-related symptoms by EAT families was 2.2% (table 3). By three years of age, 0.6% (7/1166) of the EAT participants were diagnosed with an IgE-mediated cow’s milk allergy: SIG 0.7% (4/597), EIG 0.5% (3/569). The decision to prescribe a non-cow’s milk formula milk for parent reported milk related symptoms was undertaken by participants’ GP or local paediatrician and independent of the EAT study team. The proportion of infants with milk related symptoms in months 4-12 is shown (table 3). 33 participants (20 SIG, 13 EIG) were either given extensively hydrolysed formula milk, (11 SIG, 7 EIG) or amino acid-based formula milk (9 SIG, 5 EIG), or both (1 SIG) for a median duration of three months. An average of 30% of infants consuming non-cow’s milk formula milk were still being given dairy-based solids at the same time between 5-12 months.

Use of another cow’s milk substitutes was infrequent. 14 families who reported milk related symptoms in at least one monthly questionnaire gave their infant soya formula (7 SIG, 7 EIG) for a median of 3.5 months. Most infants consuming soy formula concurrently consumed dairy solids.

## Mild-moderate iMAP symptoms

The number of infants at each month reported to have each iMAP symptom above our predefined mild/moderate threshold, for all ten months, are presented in table 4. Mean monthly reporting of individual symptoms ranged from 0.2% (blood in stools) to 45.8% (vomiting -‘reflux’ - GORD). The latter peaked at three months of age with 78.1% of EAT infants fulfilling this criterion. The temporal pattern between three and twelve months of age for individual items followed expected patterns. Colic, vomiting, and abdominal discomfort were reported most frequently at three months of age, diminishing with age. In contrast, food refusal and aversion showed the reverse trend, increasing over the first year of life. The reporting of diarrhoea also increased during infancy, whereas constipation reporting increased with solid food introduction at 6 and 7 months of age, before diminishing through to 12 months. Skin symptoms (pruritis and moderate persistent atopic dermatitis) were more stable over time.

The proportion of infants with two or more of the mild-moderate iMAP symptoms in each month was highest at three months of age (37.6%), when no infant was directly consuming cow’s milk, and reduced over time, the lowest point being 14.4% at 11 months (Figure 1). Two-thirds of infants had two or more symptoms between 3 and 12 months of age. When stratifying the follow-up period into 3 periods (3-6, 7-9 and 10-12 months) the prevalence of two or more symptoms was highest when children were between 3-6 months (table 5).

*Severe iMAP symptoms*

The number of infants reported to have each iMAP symptom above our predefined severe threshold (table S1) in each monthly questionnaire is presented in table 6. Compared with mild-moderate symptoms, the proportions of participants fulfilling the severe threshold for individual symptoms were much lower, with abdominal pain having the highest point prevalence of 13.6% at three months. Most items had a monthly reported prevalence of between 1 and 2%. Only one infant fulfilled the faltering growth definition at 12 months.

Monthly reporting of two or more items was highest at three months (4.2%), reducing to 1.4% from 3-12 months, and diminished to 0.3% at 12 months (Figure 2).

*Cow’s milk formula consumption and symptom reporting*

There was no difference in the proportion of SIG infants reported to have two or more mild-moderate iMAP symptoms between SIG infants consuming and not consuming regular formula milk at six months: 34.6% (54/156) in consumers, 34.1% (152/446) in non-consumers (p=0.83). The proportion of infants with two or more severe symptoms at six months did not differ between consumers and non-consumers of formula milk: 3.2% (5/156) versus 2.0% (9/446) respectively (p=0.11).

## Children with visible eczema at three months

Comparing infants with and without visible eczema at enrolment, there was no observed difference in the proportion reporting two or more mild-moderate symptoms (Figure 3; Panel A): mean monthly reporting of two or more mild-moderate symptoms 16.2% versus 16.9% respectively. Similarly, there was no difference in reporting of two or more severe symptoms: 1.1% versus 1.3% (figure 3; Panel B).

# DISCUSSION

A quarter of infants had two or more of the “mild-moderate” non-IgE mediated CMA symptoms every month. The proportion of affected children was highest at three months of age (37.6%), when none were being directly fed cow’s milk. The “severe” criteria were more discriminating, but 4.2% of infants still fulfilled two or more “severe” criteria at three months of age. There was no difference in reporting of symptoms between those infants in the SIG who had introduced formula at 6 months of age with those who had not. Symptom frequency was similar in children with and without eczema at baseline.

Our analysis was based on the iMAP guideline but our results are likely to apply to other CMA guidelines, given that they list similar symptoms and signs. All guidelines emphasise that diagnosis of non-IgE mediated CMA demands not only the presence of symptoms, but their improvement with cow’s milk protein exclusion, followed by relapse on reintroduction. However, in practice re-challenge is infrequently undertaken. An audit of patients prescribed hydrolysed formula in 43 South East London General Practices, found that only 21% had undergone a home challenge to confirm the diagnosis of a non-IgE mediated CMA.22 A contributing factor for this low percentage may include the strong placebo effect of prescription cow’s milk substitute formula milk for some infants’ symptoms. When 11 infants with symptoms clinically suggestive of GOR were prescribed Neocate, ten out of 11 infant’s parents reported a significant decrease in the reflux score (p=0.001), despite no change in multiple different objective measures of reflux status.23 Hence, having perceived a benefit, many parents are likely to be unwilling to cease giving their infant the prescription formula and/or to undertake a reintroduction challenge.

In the review of recent CMA guidelines, three of nine CMA guidelines were directly supported by formula manufacturers or marketing consultants, and 81% of all guideline authors reported a conflict of interest with formula manufacturers.3 Perceptions of conflict of interest are as important as actual conflicts of interest.24 Systematic reviews with financial conflicts of interest have favourable conclusions more often than those without financial conflicts of interest25. Work is underway to examine whether financial or non-financial conflicts of interest influence authors’ recommendations in clinical guidelines, opinion pieces and review articles.26

Symptoms are highly subjective, and perception of significance may differ dramatically between doctor and family. In response to criticism of the 2017 iMAP guidance as promoting overdiagnosis,27 the authors highlight that less than 2% of UK infants have CMA, that isolated symptoms should not be overinterpreted and that the diagnosis should be considered where symptoms are multiple, significant and persistent. iMAP does not purport to be a score in the way we have counted and reported symptoms. However, “multiple symptoms” is not defined, hence our use of two or more in our analyses. Persistence is also unspecified and arguably most parents attending their General Practitioner because of such symptoms will do so because they already perceive them to be significant and persistent. The iMAP guidance is most likely to be used in primary care to determine a point prevalence of symptoms, in the same way as we have determined the monthly point prevalence with the EAT data.

Data were collected as part of a trial with a large cohort of healthy infants, on a monthly prospective basis from three to twelve months. The research team (representing general practice, dermatology, allergy, and paediatrics) agreed through consensus the best options for each symptom and thresholds for severity before analysis; and ambiguity in the wording of the guidance means similar (or broader) interpretation is likely in clinical practice. EAT study questionnaire response rates were high and dropout rate was low (8.6% 112/1303).16 Completion rates increased at 12-months, which was combined with a 12-month clinic visit, when an increase in the proportion of children with two or more symptoms was noted. This suggests that those who had not completed the preceding monthly questionnaire may have had higher rather than lower symptom reporting rates.

The EAT cohort differed from the general population in that exclusive breastfeeding was universal at baseline and remained high, and parental atopy was more frequently reported. However, we have shown that the EAT cohort was otherwise broadly comparable to the population of England and Wales16. Whilst we investigated the effect of cow’s milk formula introduction in the SIG at six months of age, we cannot state whether there might be a differential effect of cow’s milk formula exposure before three months of age, although this seems very unlikely. It was not possible to exactly match the EAT questionnaire data with all iMAP symptoms, which may have led to under-estimation in the number of symptoms. The listed symptoms are subjective, both as to their presence and in their perceived severity, and the adjectives used in the guidance are also open to interpretation. Although we used our specified thresholds and focussed on infants with two or more symptoms, there may be infants with just one symptom perceived to be sufficiently problematic or severe to warrant trial of a cow’s milk protein free diet.

The prevalence of non-IgE-mediated CMA is thought to be no more than 1% in European countries.1 Guidelines that result in large numbers of infants being suspected of having a condition have the potential to lead to overdiagnosis. Although no monthly symptom data were available for the first two months of life, the temporal pattern found in this study suggests that the prevalence may have been even higher before three months of age, especially for symptoms such as vomiting and colic. Hence, the greatest concern is that normal symptoms of infancy become labelled as a potential medical problem. With 77% of infants fulfilling the ‘vomiting, reflux, GORD’ symptom at 3 months of age, the duty in an otherwise healthy child is to consider other non-allergy diagnoses and to help parents appreciate the normality of common infant symptoms. Recent guidelines for management of gastro-oesophageal reflux, where cow’s milk protein-free diet is recommended early,28 are concerning given the high frequency of ‘reflux’ symptoms in our cohort. The “seed of suspicion” of a potential non-IgE-mediated cow’s milk allergy is likely to result in increasing prescriptions of unwarranted specialised formula milks, with concomitant expense and the seeking of unvalidated allergy tests. In addition, the inference that the transmission of cow’s milk protein via breast milk might be inducing symptoms carries the real danger of undermining a mother’s confidence in breastfeeding and her willingness to continue with it.

A prospective cohort study could be used to investigate the prevalence of non-IgE mediated CMA, undertaking double blind oral food challenges to confirm or refute the diagnosis, and to investigate how many infants have medical treatments trialled for their symptoms prior to CMP exclusion trials, how many of those who undergo an exclusion trial go on to have reintroduction under the recommended conditions, and how many remain using eHF or with maternal exclusion of CMP.

The over-perception of food allergy in the general public is long standing and precedes the emergence of milk allergy guidelines for both adults29 and children.30 However, guidelines that potentially exacerbate the problem of over-diagnosis are not helpful. There is an assumption that the existence of a guideline is more beneficial than no guideline. However, well-meaning guidelines need to be supported by robust data to avoid harms from over-diagnosis that exceed the damage of missed and delayed cow’s milk allergy diagnoses that they are seeking to prevent.

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# TABLES

**TABLE 1 : A summary of 2019 iMAP guidance on possible non-IgE mediated cow’s milk allergy symptoms**

|  |  |  |
| --- | --- | --- |
|  | **Severity** | |
|  | **Mild-Moderate** | **Severe** |
| Criteria | Symptoms are mostly 2-72 hours after ingestions of CMP, usually in formula fed infants and at the onset of formula feeding. Rarely in exclusively breastfed infants. There are ‘usually several’ of the following symptoms present, with are categorised broadly into the systems of gastrointestinal or skin. The guideline reports that symptoms persisting despite first line measures are more likely to be allergy related e.g. to atopic dermatitis or reflux. | Mostly 2-72 hours after ingestion of CMP. Usually formula fed, at onset of mixed feeding, rarely in exclusively breastfed infants. One but usually more of these severe, persisting and treatment resistant symptoms”, again in the categories of gastrointestinal and skin. |
| Gastrointestinal | *- persistent irritability - ‘Colic’*  *- Vomiting - ‘Reflux’ – GORD*  *- Food refusal or aversion*  *- Diarrhoea-like stools- abnormally loose +/- more frequent*  *- Constipation – especially soft stools, with excess straining*  *- Abdominal discomfort, painful flatus*  *- Blood and/ or mucous in stool in an otherwise well infant* | *Diarrhoea, vomiting, abdominal pain, food refusal or food aversion, significant blood and/ or mucus in stools, irregular or uncomfortable stools +/- faltering growth* |
| Skin | *- Pruritis (itching), Erythema (flushing)*  *- Non-specific rashes*  *- moderate persistent atopic dermatitis* | *Severe atopic dermatitis +/- faltering growth.* |

**TABLE 2: Demographics of participants (infants and care givers) collected at baseline (3 months)**

|  |  |  |
| --- | --- | --- |
|  | Standard Intervention Group (SIG) | Early Intervention Group (EIG) |
| Ethnicity of child |  |  |
| White | 547/651 (84.0%) | 557/652 (85.4%) |
| Mixed | 71/651 (10.9%) | 48/652 (7.4%) |
| Asian or Asian British | 11/651 (1.7%) | 17/652 (2.6%) |
| Black or Black British | 19/651 (2.9%) | 22/652 (3.4%) |
| Chinese or other ethnic group | 3/651 (0.5%) | 8/652 (1.2%) |
| Mother |  |  |
| Age (years) |  |  |
| ≤ 20 | 2/651 (0.3%) | 2/652 (0.3%) |
| 21-25 | 21/.651 (3.2%) | 25/652 (3.8%) |
| 26-30 | 155/651 (23.8%) | 150/652 (23.0%) |
| 31-35 | 281/651 (43.2%) | 249/652 (38.2%) |
| 36-40 | 148/651 (22.7%) | 184/652 (28.2%) |
| 41 + | 44/651 (6.8% | 42/652 (6.4%) |
| Maternal smoking during pregnancy | 25/650 (3.9%) | 21/651 (3.2%) |
| Home |  |  |
| Location |  |  |
| Urban | 503/650 (77.4%) | 503/651 (77.3%) |
| Rural - non-farm | 132/650 (20.3%) | 127/651 (19.5%) |
| Rural - farm | 15/650 (2.3%) | 21/651 (3.2%) |
| Pets in the home | 290/650 (44.6%) | 264/651 (40.6%) |
| Family history |  |  |
| *Asthma* |  |  |
| Mother | 174/650 (26.8%) | 168/651 (25.8%) |
| Father | 153/650 (23.5%) | 142/651 (21.8%) |
| Sibling | 86/650 (13.2%) | 72/651 (11.1%) |
| *Eczema* |  |  |
| Mother | 428/650 (34.2%) | 227/651 (34.9%) |
| Father | 137/650 (21.1%) | 123/651 (18.9%) |
| Sibling | 190/650 (29.2% | 206/651 (31.6%) |
| *Hay fever* |  |  |
| Mother | 345/650 (46.9%) | 285/651 (43.8%) |
| Father | 267/650 (41.1%) | 262/651 (40.3%) |
| Sibling | 85/650 (13.1%) | 65/651 (10.0%) |
| *Food Allergy* |  |  |
| Mother | 110/650 (16.9%) | 142/651 (21.8%) |
| Father | 65/650 (10.0%) | 73/651 (11.2%) |
| Sibling | 113/650 (17.4%) | 116/651 (17.8%) |

**TABLE 3: EAT parent reported milk-related symptoms**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Month | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | Mean monthly percentage (412) |
| Study group | SIG | | | SIG+EIG | | | | | |  |
| %  n/N | 0.2%  1/621 | 0.7%  4/612 | 3.8%  23/609 | 4.1%  44/1085 | 2.6%  27/1050 | 2.2%  23/1053 | 2.2%  22/1010 | 1.8%  18/1013 | 2.8%  32/1151 | 2.2% |

Data collected from 4-12 months

**TABLE 4: Mild-Moderate iMAP item frequency at each timepoint**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Proportion (number) of children above mild-moderate threshold for symptom | | | | | | | | | | Mean monthly proportion across 3 to 12 months |
| Months | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **3-12** |
| Intervention group | **SIG+EIG** | **SIG** | | | **SIG+EIG** | | | | | |  |
| iMAP symptom |  |  |  |  |  |  |  |  |  |  |  |
| Persistent irritability - 'Colic' | 27.8%  (341/1225) | 15.5%  (96/621) | 9.3%  (57/612) | 4.6%  (29/597) | 4.4%  (47/1070) | 4.3%  (45/1050) | 3.1%  (32/1032) | 2.6%  (26/1000) | 1.9%  (19/1007) | 2.0%  (23/1151) | 7.6% |
| Vomiting - 'Reflux' – GORD | 78.1%  (957/1225) | 77.0%  (478/621) | 71.4%  (437/612) | 59.3%  (354/597) | 50.0%  (535/1070) | 39.1%  (410/1050) | 29.9%  (309/1032) | 23.1%  (231/1000) | 18.4%  (185/1007) | 12.0%  (138/1151) | 45.8% |
| Food refusal or aversion\* | - | 0.8%  (5/621) | - | 18.4%  (111/603) | - | - | 19.4%  (202/1041) | - | - | 23.8%  (273/1147) | 15.6% |
| Diarrhoea- like stools - abnormally loose +/- more frequent | 8.7%  (106/1224) | 8.7%  (54/621) | 8.2%  (50/612) | 6.5%  (39/597) | 9.4%  (100/1070) | 11.5%  (121/1050) | 12.7%  (131/1031) | 16.1%  (161/1000) | 16.0%  (161/1007) | 19.5%  (224/1147) | 11.7% |
| Constipation- especially soft stools, with excess straining | 9.6%  (118/1224) | 4.8%  (30/621) | 7.2%  (44/612) | 12.4%  (74/597) | 12.7%  (136/1070) | 7.9%  (83/1050) | 7.0%  (72/1031) | 5.1%  (51/1000) | 4.9%  (49/1007) | 4.1%  (47/1147) | 7.6% |
| Abdominal discomfort, painful flatus | 27.8%  (341/1225) | 15.5%  (96/621) | 9.3%  (57/612) | 4.6%  (29/597) | 4.4%  (47/1070) | 4.3%  (45/1050) | 3.1%  (32/1032) | 2.6%  (26/1000) | 1.8%  (19/1007) | 2.0%  (23/1151) | 7.6% |
| Blood and/or mucus in otherwise well infant | - | - | 0.2%  (1/612) | 0.2%  (1/597) | 0.1%  (1/1070) | - | - | - | - | - | 0.2% |
| Pruritis (itching), Erythema (flushing) | 10.8%  (132/1225) | 12.7%  (79/621) | 14.9%  (91/612) | 16.6%  (100/601) | 15.7%  (168/1071) | 15.7%  (165/1050) | 16.8%  (174/1034) | 16.1%  (161/1000) | 14.7%  (148/1007) | 15.6%  (180/1151) | 15.0% |
| Moderate persistent atopic dermatitis | 4.6%  (56/1225) | 6.8%  (42/621) | 7.7%  (47/612) | 8.2%  (49/601) | 7.2%  (77/1071) | 6.4%  (65/1050) | 7.0%  (66/1033) | 6.3%  (63/1000) | 5.8%  (58/1007) | 6.9%  (79/1151) | 6.7% |
| One or more symptom | 86.4%  1058/1225 | 84.1%  522/621 | 79.6%  487/612 | 75.3%  454/603 | 65.7%  1007/1071 | 58.4%  613/1050 | 59.1%  615/1041 | 46.9%  469/1000 | 42.7%  430/1007 | 53.5%  616/1151 | 65.2% |
| Two or more symptoms | 37.6%  460/1225 | 30.8%  191/621 | 27.6%  169/612 | 34.2%  206/603 | 24.3%  260/1071 | 20.9%  219/1050 | 24.3%  253/1041 | 17.6%  176/1000 | 14.4%  145/1007 | 21.6%  249/1151 | 25.3% |

\* only collected at 4, 6, 9 & 12 months

**Table 5: The number of infants meeting the thresholds for two or more different symptoms in the mild-moderate non-IgE mediated CMA iMAP guideline in specific periods of infancy**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Age Group | | | | |
| Two or more mild-moderate “non-IgE CMA symptoms” | 3-6 months (SIG) | **7-9 months** (SIG & EIG) | **10-12 months** (SIG & EIG) | **3-12 months** (SIG & EIG) | **3-12 months** (SIG) |
| %  (n) | 60.3%  (389/645) | 39.2%  (452/1153) | 32.2%  (382/1186) | 73.5%  953/1296) | 72.0%  467/649 |

**TABLE 6: Severe iMAP item frequency at each timepoint**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Monthly timepoint | | | | | | | | | | |
| Severe items | SIG+EIG | SIG | | | SIG+EIG | | | | | | Mean monthly proportion across 3 to 12 months |
|  | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 3-12 |
| Vomiting | 9.9%  (121/1225) | 6.4%  (40/621) | 6.2%  (38/612) | 4.4%  (26/597) | 3.9%  (42/1070) | 3.3%  (35/1050) | 2.1%  (22/1032) | 1.2%  (12/1000) | 1.7%  (17/1007) | 0.7%  (8/1151) | 4.0% |
| Food refusal or food aversion\* | - | 0.2%  (1/621) | - | 3.0%  (18/603) | - | - | 3.3%  (34/1041) | - | - | 4.0%  (46/1147) | 1.1% |
| Diarrhoea | 1.7%  (22/1224) | 1.1%  (7/621) | 1.5%  (9/612) | 0.7%  (4/597) | 0.6%  (6/1070) | 1.3%  (14/1050) | 1.7%  (17/1031) | 1.4%  (14/1000) | 1.0%  (10/1007) | 2.2%  (25/1147) | 1.3% |
| Irregular or uncomfortable stools | 1.0%  (12/1224) | 0.2%  (1/621) | 0.7%  (4/612) | 1.3%  (8/597) | 1.8%  (19/1070) | 1.1%  (12/1050) | 0.8%  (8/1031) | 0.8%  (8/1000) | 0.3%  (3/1007) | 0.3%  (3/1147) | 0.8% |
| Abdominal pain | 13.6%  (160/1225) | 4.4%  (27/621) | 2.6%  (16/612) | 2.2%  (13/597) | 1.7%  (18/1070) | 1.4%  (15/1050) | 0.8%  (8/1032) | 0.6%  (6/1000) | 1.0%  (10/1007) | 0.4%  (5/1151) | 2.9% |
| Significant blood and/or mucus in stools | - | - | 0.2%  (1/612) | 0.2%  (1/597) | 0.1%  (1/1070) | - | - | - | - | - | 0.2% |
| Severe atopic dermatitis | 0.8%  (10/1225) | 1.6%  (10/621) | 1.3%  (8/612) | 2.2%  (13/601) | 1.5%  (15/1071) | 1.1%  (11/1050) | 1.2%  (11/1033) | 0.7%  (6/1000) | 0.5%  (5/1007) | 1.0%  (10/1151) | 1.2% |
| "+/- faltering growth | - | - | - | - | - | - | - | - | - | - | 0.1%  (1/1151) |
| 1 or more symptoms | 21.0%  270/1286 | 12.1%  78/644 | 10.8%  69/638 | 10.9%  69/631 | 7.4%  89/1203 | 6.4%  76/1194 | 7.9%  94/1194 | 3.9%  46/1187 | 3.9%  46/1185 | 7.9%  93/1182 | 9.2% |
| 2 or more symptoms | 4.2%  54/1286 | 1.6%  10/644 | 1.4%  9/638 | 2.2%  5/631 | 1.2%  14/1203 | 1.3%  15/1194 | 0.8%  10/1194 | 0.3%  3/1187 | 0.3%  3/1185 | 0.3%  4/1182 | 1.4% |

\* only collected at 4, 6, 9 & 12 months

**FIGURES**

**FIGURE 1: The proportion of infants with mild-moderate non-IgE iMAP symptoms**

\*Months 4-6 SIG only, other months both groups.

**FIGURE 2: The proportion of infants with severe non-IgE mediated CMA iMAP symptoms**

\*Months 4-6 SIG only, other months both groups.

**FIGURE 3:** **Proportion of infants with and without eczema with two or more of the (A) mild-moderate and (B) severe non-IgE CMA iMAP symptoms**