Prevention of Food Allergy during Late Infancy and Early Childhood

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Introduction

The normal immunological response to food antigens is geared to the induction of tolerance, that is to say, unresponsiveness in the case of their further ingestion. Allergic sensitization may be considered as a failure or a breaking of immunological tolerance. It is becoming clearer and clearer that the development of oral tolerance is highly dependent on the intestinal microflora; indeed the intestinal bacteria have the ability to induce the formation of cytokines of Th1 immunity (particularly of INFγ) and also IL-10 and IL-12, which counteract the Th2-dependent allergic sensitization and favor the state of Th1/Th2 equilibrium that prevails later in life in normal children [1].

Since colonization of the digestive tract takes place in the first few months of life, it can be postulated that a ‘window of sensitization’ exists in early life [2]. In fact, infants are particularly prone to develop allergic sensitization to food antigens and this propensity usually does not extend beyond early childhood.

Epidemiological data show that the prevalence of allergic conditions continues to increase, at least in the developed world [3]. It is difficult to imagine how genetic factors, the most important risk factors for developing allergic diseases, could be responsible for such a trend. Among the environmental factors that could explain this rise in prevalence, two seem particularly worthwhile to consider because they may lead to prevention: (1) the increased exposure to (new) environmental/oral sensitizing agents that may be fought by exclusion diets, and (2) the decreased bacterial load resulting from the increased practice of cesarean delivery, the widespread use of sterile food, and the frequent prescription of oral antibiotics during infancy which may favor the Th2 allergic immunological reaction. This increased prevalence of allergic conditioning might be counteracted by the use of probiotics which would restore the normal Th1/Th2 equilibrium [4].
The present review will try to answer the following three questions: (1) is the ‘sensitization window’ still open during the weaning period, at the time of introduction of solid foods; (2) is it still possible to prevent/reduce food allergy by exclusion diets during the weaning period, and (3) is it possible to prevent/reduce food allergy by using probiotics in the first months of life?

**Introduction of Solids as a Factor of Food Allergy**

From a vast observational prospective study in New Zealand concerning 1,123 nonselected children, it was clearly apparent that, although the occurrence of atopic dermatitis at 2 years of age was mainly linked to a familial history of atopy, the second risk factor was the early introduction, before 4 months of age, of foods other than milk which increased by 50% (17.8% as opposed to 12.6%; p < 0.05) the risk observed in infants who received solids before the age of 4 months, despite breastfeeding, compared to the risk in children who received solids later [5]. Furthermore, in this group of children a significant correlation was observed between the frequency of atopic dermatitis and the number (but not the type or quantity) of solid foods (‘beikost’) introduced before the age of 4 months [5]. Ten years later, the sensitizing effect of this early introduction in the same cohort of children was confirmed: the risk of developing atopic dermatitis was 2.9 times greater in the group of children who had ingested more than 4 different solids compared to those who had taken none [6]. On the contrary the age at introduction and the number of new solid foods had no influence on the later occurrence of asthma [7].

The same effect was not observed in a smaller intervention study conducted in Sweden in 375 nonselected children. In 177 of them at 3 years of age, the avoidance of fish and citrus fruit during the first year of life did not modify the incidence of allergic signs and symptoms (skin tests, vomiting) triggered by their ingestion compared with the incidence observed in a control group of 198 children who were freely allowed to eat fish and citrus fruit during their first year of life [8]. However, in this study the age at first encounter of the allergen was not controlled and could have been rather late.

The sensitizing effect of ‘beikost’ was strikingly demonstrated in a group of 135 Swedish children from ‘at-risk’ families with a history of atopy, breastfed until the age of 6 months (or receiving an extensively hydrolyzed formula in case of failure of breastfeeding) in whom 65 of them were allowed solid foods (potatoes, carrots, meat, cereals, eggs, fish, fruits) from the age of 3 months compared to 70 infants who were exclusively breastfed until 6 months of age. At 1 year, the frequency of atopic dermatitis was half in the second group (14%) compared to the first one (35%; p < 0.01); all children receiving the same diet during their second semester [9]. Similarly food allergy, defined as a skin rash or vomiting after ingestion of a food item, was five times more frequent (37%) in the group of children receiving solid foods early (after the
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age of 3 months), compared to those receiving solid foods after the age of 6 months (7%; p < 0.001). The foods most frequently responsible for sensitization were eggs, cow’s milk, fish, strawberries, tomatoes and citrus fruit. Challenges with these foods 1 month after the initial reaction were still more frequent (but not significantly) in the early than in the late diversification group; 2–3 months later the difference disappeared [9]. The latter finding was interpreted as indicating a nonspecific and transient sensitization in the case of early introduction of solids in the infant regimen. Four years later the same group of children was again examined. Although atopic disease was more common in the early solid food group (40% of 62 children) compared to the late solid group (20% of 51), the difference was not significant; a similar prevalence of food allergy (6 and 4%, respectively) was not significantly different in the 2 groups. Interestingly, pollen allergy and asthma were equally or more prevalent at that age than eczema and food allergy. Furthermore pollen allergy was significantly more frequent in the early solid food group (37%) than in the late one (20%; p = 0.04); the same trend was noted for asthma, but did not reach significance [10]. This study suggests that solid food introduction is associated with increased risks of both precocious and later atopic manifestations.

These few studies are more than 10 years old; nevertheless no additional study focusing on this question has been made in the last years.

Prevention of Food Allergy by Exclusion Diets during the Weaning Period

Apart from the Swedish study [9, 10], no other study has tried to confirm the preventive effect of a late/restricted introduction of solid foods during the weaning period on the occurrence of allergic disease.

Conversely most of the recent studies concerned with preventing food allergy include in their design the late and ordered introduction of solids in the intervention group together with the use of breast milk, hydrolysate and exclusion diets in the mother during pregnancy or, more often, lactation. This is particularly true in the best conducted study [11] and the most frequently cited study by Zeiger et al. [12] who associated maternal cow’s milk, egg, nuts and soy exclusion during the third trimester of pregnancy and lactation, and breast milk/casein extensive hydrolysate for 6 months and delayed cow’s milk and solids for 6–36 months (nuts and eggs) in infants to maximize prevention. In the control group the introduction of solids was allowed after 4 months and was complete at 1 year of age. The cumulated prevalence of all allergic manifestations was significantly lower in the ‘prophylactic’ group (16%) than in the control group (27%; p = 0.004) at 1 but not at 2 years of age. This difference was linked to a significant reduction in the prevalence of eczema, urticaria, digestive symptoms (p < 0.03 for the combination), whereas the
prevalence of asthma and rhinitis was not modified [12]. At 3 and 4 years of age (78% of the children enrolled could be examined), the cumulated and actual prevalences of all allergic manifestations were not different between the 2 groups of children. Only the cumulative prevalence of food allergy (eczema, urticaria, diarrhea or vomiting twice after an oral challenge with eggs, cow's milk, nuts or fish) were significantly reduced in the prophylactic group (p < 0.01), whereas the actual prevalences were identical in both groups indicating that the cumulated effect at 3 and 4 years was obtained during the first 2 years of life [13].

In a study with a similar design (exclusion diet for the mother during lactation, exclusive breast milk or extensive protein hydrolysate until the introduction of solid foods after 9 months of age, free diet after 1 year) with the addition of anti-house dust mite treatment of mattresses and the children's rooms, not only eczema and food allergy but also asthma could be prevented in the ‘treatment’ compared to the control group [14].

More recently two studies have shed more light on the late introduction of solids in the preventive effect observed in the above studies. The first one aimed at comparing the allergy-prevention effect of a partially hydrolyzed formula with two extensively hydrolyzed formulas in Danish infants at high risk of developing allergic diseases [15]. The formulas were given along with breast milk until the end of the 4th month. Mothers had unrestricted diets during pregnancy and lactation. After the age of 4 months unrestricted diets and conventional cow's milk-based formula were given to the infants as needed. The outcome of the study was that the partially hydrolyzed formula was less effective than the extensively hydrolyzed formula in preventing cow's milk allergy. However, the most striking result was the globally low rate of cow's milk allergy in the 4 groups (3 formula groups and an exclusively breast-fed group) varying from 0.6 to 4.7%, even though the dietetic intervention did not include either maternal diet during lactation or dietary restriction for the exclusion of children after the age of 4 months. Food allergy controlled by a challenge was observed in only 2.5%, cow's milk allergy in 1.7% and egg allergy in 1.3% of 478 infants. This low rate of allergic manifestations was attributed to the high frequency of breastfeeding by the authors who questioned the need for dietary restrictions after the first 4 months of life [15].

In the multicenter Study on the Prevention of Allergy in Children in Europe, prevention (in 349 infants) comprised breastfeeding until 6 months of age supplemented, if necessary, by a hypoallergenic formula; gradual introduction of solid foods after 6 months; cow's milk, egg and fish being introduced after 12 months of age, and nuts after 3 years, and the use of dust-mite allergen-impermeable protection of the mattresses. In the control group (n = 347) exclusive breastfeeding was recommended for at least 3 months, and the introduction of solids was delayed until 6 months of age and cow's milk until 12 months of age. There was a significant reduction regarding
sensitization to any allergen test at 1 year of age (against Der p, Der f, egg, milk; 6.2% in the prophylactic group versus 10.7% in the control group, p < 0.03). There was only a tendency toward a reduction in definite allergy against 1 of the 4 allergens in the prophylactic (3.1%) versus the control (6%) group [16]. However, the 2 groups were not very different with regard to age at introduction of solids, and ages were rather late.

It seems, therefore, that accumulated evidence suggests that delaying the introduction of solid food might reduce the risk of clinical food allergy and eczema. However the magnitude of the effect is not well known (precise and important in one study [9, 10], and confounded with other measures in all other studies [12, 16]) and the duration of avoidance is not known at all. Although there is a consensus to avoid solid foods before 3–4 months of age, at present there are no studies enabling a decision on how long preventive measures need to be maintained. Furthermore, avoidance of oral allergens may not be appropriate: a recent study concerning peanut allergy suggests that sensitization to food allergens may also occur though the cutaneous route if the allergen comes into contact with inflamed skin and that, indeed, in this case the best prevention would be to avoid emollients containing peanut oil since in that study the risk of eczema was not associated with the ingestion of peanuts by the mother during pregnancy or lactation, or with consumption of peanuts by the infants [17].

Prevention of Atopic Disease through the Use of Probiotics

As the inverse association between infections early in life and allergic disease and the role of the commensal gastrointestinal microflora in promoting a Th1-type immunity essential in controlling Th2 allergic inflammation are being better understood, it was logical to try to prevent the occurrence of atopic disease in children by giving them probiotics in infancy [4, 18].

In a small randomized double-blind study it was possible to demonstrate that specific probiotic strains (*Bifidobacterium lactis* Bb-12 or *Lactobacillus GG*) added to an extensively hydrolyzed whey formula were able to significantly improve the skin condition (assessed by the SCORAD method) of 18 infants with atopic eczema receiving the supplemented formulas compared to 9 infants receiving the unsupplemented formula (p = 0.002) [18].

In a more important randomized placebo-controlled trial concerning 159 infants and their mothers in families with a history of atopic disease, capsules containing either a placebo or 10^{10} CFU of *Lactobacillus GG* were given 2–4 weeks before delivery to the mother and for 6 months to the infants. Children were examined at ages 3, 6, 12, 18 and 24 months. Atopic eczema was diagnosed in 35% of the children aged 2 years. The frequency of atopic eczema in the probiotic group was half that of the placebo group: 15/64 (23%) vs. 31/68 (46%), RR 0.51 (95% CI 0.32–0.84) [19]. Two years
later the effect was still observed: 14 of 53 children receiving lactobacillus had developed eczema compared to 25 of 54 receiving placebo (RR = 0.57, 95% CI 0.33–0.97), suggesting that the preventive effect of *Lactobacillus GG* on eczema extended beyond infancy [20]. Although these studies need to be confirmed, they open a new avenue in the prevention of atopic manifestations.

It is satisfactory to note that the recent progress in our understanding of mucosal immunity and the role of the bacterial burden on the development of tolerance in infancy make it possible to envisage food allergy prevention strategies other than exclusion diets whose efficiency is still being discussed with regard to the magnitude, the uncertain time frame, and the need for careful nutritional follow-up of the children.

**References**

Discussion

Dr. M. Hoekstra: Thank you Dr. Schmitz for your interesting introduction and all the data you have shown us. I would like to suggest splitting the discussion in two parts, and first talk about solids. Is your question about the introduction of solids?

Dr. Gracey: My question is about the environment. There seems to be a marked difference between the prevalence of allergic diseases in children in so-called developing countries and in industrialized countries and a lot of that has been related to environmental marker levels of biological contaminations either in the home or in the environment at large. This also applies to populations that are in transition from their traditional contaminated environments going into environments where standards of hygiene are much better, and the rates of allergic disease seem to increase when children move to a more hygienic environment. I wonder whether you would care to comment on this.

Dr. Schmitz: Indeed, you are summarizing what is known as the hygiene hypothesis which states that there is an inverse relationship between the bacterial burden during the first months of life and the later occurrence of allergy. This is a tempting hypothesis, although Dr. Fritsché a moment ago did not seem to be convinced by its scientific basis. From what I have read (I am not an allergologist) I would say that there are good studies which speak in favor of it, for example those studies which were conducted a few years ago in Germany, Austria, and Denmark, mainly regarding the occurrence of eczema, or eczema and food allergy in children living on farms compared to children living outside farms, and showing less allergy in the first group. Probably this is not enough to explain all allergic diseases because there is also pollution which plays on a completely different ground. In this regard, the very often cited German study comparing the rate of allergy in western compared to eastern Germany was interesting. Contrary to what people expected, the rate of asthma was greater in western Germany compared to eastern Germany but other allergies were greater in eastern Germany mainly because of industrial pollution. So certainly the hygiene hypothesis explains part of the rise in allergic diseases and probably this is true for eczema and food allergy. For other allergic conditions, asthma for example, it is probably more difficult to say.

Dr. M. Hoekstra: Are there any other general questions about the environment?

Dr. Michaelsen: Not about the environment but about the introduction of solids. You mentioned the study by Saarinen and Kajosaari [1] that mentioned citrus fruits and fish as hyperallergenic, and I know that many countries in Europe exclude hyperallergenic foods throughout the first year of life, which I think is not based on any evidence at all. Do you agree with that?

Dr. Schmitz: I completely agree. I was amazed by the fact that we had absolutely no data to back these habits. Excluding hyperallergenic foods during the first year of life is opening the umbrella for protection, but we don’t know whether this is really useful or not. In this regard it is interesting to see that Halken et al. [2], in the discussion of their article, suggest that there is no reason to postpone solids.
Dr. M. Hoekstra: Very recently there was a study published by Zutavern et al. [3] from Munich who were unable to show any relationship between the timing of the introduction of solids and the prevalence of allergic disease. I think the group was about 500 children, it was published in *Archives of Diseases in Childhood*.

Dr. Schmitz: Was it part of the SPACE study?

Dr. M. Hoekstra: It was part of the SPACE study.

Dr. Heymans: There was a meeting recently in which the investigators from the Academic Hospital in Groningen, The Netherlands, who have a unit for food allergy, presented their results on the sensitization of those children who are not exposed to certain food allergens for a prolonged period, the so-called exclusion diet. They could not show any difference after 1 and 2 years of sensitization taking IgE as a marker. So I think there is no proof yet and still we do it.

Dr. Schmitz: Yes, I agree.

Dr. Michaelsen: I just wanted to add that excluding fish for the first year of life is a serious exclusion from the diet. Fish contains n-3 fatty acids, high amounts of minerals, vitamin D and many other important nutrients. I think we have to try to advise these countries that there is no evidence supporting the exclusion of fish.

Dr. Keller: I would like to hypothesize on whether a difference is made between breastfed and non-breastfed children and the time point of introduction to solids. In analogy to celiac disease, it could be wise to introduce not multiple but a single solid food during the breastfeeding period, perhaps between 4 and 6 months or so, in contrast to non-breastfed children in whom it may be introduced later. This is just speculation. What is your opinion?

Dr. Schmitz: Someone in the audience made the same proposition a moment ago, and it is tempting after the work of Ivarsson et al. [4]. However this depends very much on the length of the breastfeeding period, and although this is possible for example in Scandinavia where women breastfeed until at least 4–6 months of age, in France it would be very difficult to make the same proposition because the average duration of breastfeeding there is around 6 weeks.

Dr. M. Hoekstra: I have a question about these old studies by Fergusson and Saarinen. If I recall well, these groups were not randomized, meaning that it is not possible to actually compare these groups on outcome parameters, that is very difficult. So we must be very cautious with the interpretation of these studies.

Dr. Badr-Eldin: I wonder about the studies which compared the impact of giving solid foods versus just breastfeeding; whether all these studies were controlling for the mothers diet as well?

Dr. Schmitz: It depends from paper to paper. In Kajosaari’s paper the mothers were not controlled, if I remember correctly. There are not so many, and for example in Zeiger’s paper some foods were forbidden but the remaining food was free. So it is difficult to control the food of the mother, which might also be dangerous.

Dr. El-Din Amry: Based upon your nice presentation can I conclude that if we are obliged to introduce foods in the first 6 months of life, for example because the mother is working and so on, is yogurt the best alternative because it is very rich in probiotics?

Dr. Schmitz: Yes it is a good idea. I would not fight against adding yogurt in the 5th month of life for example. I don’t know if probiotics are still important at that time because the ‘sensitization’ window has probably already closed by then.

Dr. M. Hoekstra: Before continuing on probiotics, can I ask you one more question about solids, the effect of the timing of the introduction of solids. Why has this never been done in a randomized control trial? I think it is easy to perform and is the type of study to investigate a question like this.

Dr. Schmitz: I agree but the timing of the introduction of solids is so much linked to local habits that randomization is difficult to envisage. We could decide now that we
should start something like that because in fact, you are right, it has not been done, but I think we are at the border between science and use, and it is probably difficult to randomize use.

Dr. Caroli: I would like to make a comment. You said that there is a delayed introduction of solid food at 4–6 months. In my opinion we shouldn’t say delayed because according to the WHO this is a proper introduction of food around 6 months of age, because if we keep saying that it is delayed we allow pediatricians and mothers to give food other than breast milk or formula before that age. Then my question is, you spoke about solid foods but solid food is a very wide range of foods in terms of proteins, also in terms of fats. Do you have any data on n-3 and n-6 intake in introducing solid food earlier than 6 months of age because both are involved in the development of immunity, so I think it could be an interesting area of work.

Dr. Schmitz: Yes, that is a good point and it was just raised by Dr. Michaelsen a moment ago that excluding fish may be dangerous in this regard. I am not aware of any study having been interested in such a topic. With regard to your first comment, of course I agree but I said delayed because in many countries there is still a tendency to give solids before 4 months of age.

Dr. Badr-Eldin: I just wanted to add to what my colleague just said; giving yogurt is almost a national habit in Egypt, and mothers are used to introduce it right after 40 days or 2 months of life. We keep telling them not to give it but they do. So we telling them to use the yogurt from powder milk or dry milk because this might decrease the possibility of inducing atopy. I am not sure whether this is right or not because, after all, the incidence of atopy, eczema in particular, is not that much in Egypt, but perhaps asthma is very frequent. So I am not sure if we should continue advising the mothers not to give this yogurt as early as they do.

Dr. Schmitz: Probably Dr. Michaelsen might like to comment. If you want to have the effect of probiotics, the bacteria in the yogurt need to be living, which is not the case in many industrialized yogurts, and this must be taken into consideration when feeding yogurt early, e.g. at 6 weeks of age. Furthermore you must consider that if you give yogurt you give proteins and allergens at the same time as bacteria and probiotics, and I don’t know which component of yogurt is most important with regard to your question, but Dr. Michaelsen will answer.

Dr. Michaelsen: Starting that early is certainly not recommended. There are several problems. One is that the early introduction of cow’s milk can provoke microscopic bleeding from the intestine which is especially the case before the age of 6 months. Another important problem is that starting before the age of 4 months will result in a high renal solid load. The kidneys are still immature and might not be able to excrete the high amounts of protein and minerals present in human milk. So it is better not to introduce yogurt before the age of 6 months.

Dr. Heymans: May I remark on that because I think the introduction of beikosts is also based on the nutritional content of the beikosts given, iron, manganese, all kind of vitamins. I don’t think that a yogurt, unless it is made of a follow-on formula, is wise to start because you don’t provide the right micronutrients that actually have to come from beikosts, so that is something that should be taken into account [5].

Dr. Salminen: I completely agree with the previous speakers, and one major thing with yogurt is also that the strains in yogurt are based on technological properties, not on physiological properties, so most of the yogurts I would not call probiotic. Probiotic needs to be defined and some health-promoting activity should be shown in scientific studies before something can be called probiotic.

Dr. Sinaasappel: Can you explain the second last slide you showed us? You made the conclusion that lactobacillus GG was helpful for preventive measurements for allergic diseases, but as far as I could see from that slide, it was just the opposite.
Dr. Schmitz: Which slide?

Dr. Sinaasappel: The second last one.

Dr. M. Hoekstra: The one about the primary prevention and the follow-up study at the age of 4 years with respect to the incidence of rhinitis.

Dr. Sinaasappel: As far as I can see in the last row there is an increase in eczema, that has to be turned around, the rest is all right.

Dr. Schmitz: Yes, you are right.

Dr. M. Hoekstra: The problem is that the rest is all right, so there is a tendency for rhinitis and asthma to increase in the group who received lactobacillus.

Dr. Schmitz: You are completely right; there is no comment in the paper on this fact, there is only a comment on eczema which weakens the study.

Dr. M. Hoekstra: Any more comments on this study?

Dr. Paerregaard: Another thing that was puzzling about that study was that among the children who actually developed atopic eczema the severity was comparable in the placebo group and in the intervention group evaluated by SCORAD. That was a bit puzzling because it would be expected that the children who actually developed eczema would have less severity if treated by probiotics.

Dr. Schmitz: I agree with you, that was pointed out already.

Dr. M. Hoekstra: I do have some methodological problems with this study which was characterized by a large number of dropouts at the 1st year evaluation and at the 4th year. The second problem I have with this study is that there was no difference in sensitization between the 2 groups, so it is hard to say that the use of probiotics in this study resulted in a decrease in atopic eczema because with respect to sensitization nothing was seen. The last problem I have is that almost all the studies performed on probiotics were performed by one group, and I think it is a very good scientific principle that research should be repeated by other groups.

Dr. Schmitz: Sure, but we are waiting for the other groups.

Dr. Gracey: In the Indian subcontinent, apart from what happens in Egypt, fermented milks, usually in the form of curds, are given traditionally and very widely to young children. I am not aware of any scientifically documented studies that show that these are beneficial or not, and I am unaware of microbiological investigations that would support the use in this way. I know that there are people from the subcontinent in this room, and I wonder if anyone from Bangladesh or India or anywhere else for that matter would care to comment on what is clearly a very important subject for many millions of children in that part of the world.

Dr. Verloove: Perhaps we should broaden the question to more people in this room because these habits concerning early nutritional habits are so widely different all around the world. Moreover I was a bit amazed about the easy way you suggested doing a randomized control trial, on nutrition, in infants, looking at well baby clinics and what you hear there, that is impossible. I mean people just give their children to eat what they eat themselves or whatever. So my question to the audience would be are there studies in other countries with other cultures regarding nutrition in the early months of life, and haven't they been compared yet. I mean there must be other ways, observational studies that you can get out of these difficulties.

Dr. Schmitz: One of the first Nestlé Nutrition Workshops I attended, at least 20 years ago, was on weaning habits, and at that time the whole workshop showed that there were great differences from country to country inside Europe, as you just said, and it was impossible to find a scientific basis for these uses and whether they were detrimental or not; I am not sure that we know much more now than 20 years ago.

Dr. M. Hoekstra: In my opinion it is very difficult to compare different populations only on their varying behaviors with regard to the introduction of foods. It is the same with the yogurt question in Egypt, if you compare populations you also compare differences in environment, differences in genetic makeup. So if you really want to know
the effect of yogurt in Egypt, you have to randomize it, and that is the same difficulty when you compare populations.

Dr. Heymans: Things are difficult, but sometimes although they are difficult they are not impossible. We performed a study on the early introduction of cow’s milk in newborn infants in the Netherlands, a randomized, double-blind, placebo-controlled prospective trial. We were able to include more than 1,500 children, and we were even able to follow them for 6 years. We could not show that early exposure to cow’s milk in a normal population has any effect on sensitization or allergy later in life [6]. If the population and study design are chosen carefully and I think especially in Europe that it is possible to perform studies like this. The only thing is the right motivation and some money are needed for it, and sometimes the industry will to help to overcome these barriers.

Dr. Schmitz: Certainly you are right but then the question is whether it is worthwhile to enroll 1,500 children, well babies, to answer a question such as whether it is good or not to introduce citrus or orange at 6 or 3 months. It is such hard work to answer such a seemingly not so important question that eventually it is not done.

References
