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Developing a Novel, Sustainable, and Acceptable Complementary Feeding Product using Caterpillar Cereal for Infants and Young Children in the Democratic Republic of Congo

By

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Table of Contents

Index of Tables

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ABSTRACT

Background: Adequate nutrition in early life is important for brain development and growth in infants and young children. Young children in developing countries like the Democratic Republic of Congo (DRC) are vulnerable to poor nutrition after 6 months of age when breast milk is supplemented with complementary foods that provide inadequate protein and micronutrients. The World Health Organization recommends complementary feeding with animal-source foods in order to avoid micronutrient deficient states. Animal-source foods are not readily available in many Central African countries. However, caterpillars are a common staple in adult diets and may be suitable for complementary feeding for infants and young children.

Objectives: Create a macro- and micronutrient-rich cereal made from locally available and abundant caterpillars to be used for complementary feeding in rural DRC. Test the biochemical properties and acceptability of this cereal.

Design/Methods: We developed a cereal made from dried caterpillars, ground corn, palm oil, sugar and salt, and measured its macro- and micronutrient content using standard laboratory techniques: Kjeldahl method for analysis of protein content, Soxhlet method for determination of lipid content and spectrophotometry for determination of iron, lead and mercury. We cultured the cereal to determine if it was free from microbiologic contamination. Maternal and infant acceptability was evaluated among 20 mothers and their 8-month-old infants. Mothers were instructed in the preparation of the cereal and asked to evaluate the cereal in five domains using a five-point Likert scale (1=dislike very much to 5=like very much). During the following week, they fed their infants a 30-gram portion daily. Infant acceptability was based on daily consumption during the last 4 days of feeding and the occurrence of any adverse signs or symptoms.

Results: We produced a caterpillar cereal that had suitable macro- and micronutrient content for complementary feeding. The cereal was free from Enterobacteria, *Staphylococcus aureus, Salmonella, Shigella,* yeast and fungus contamination. Mothers' median ratings for cereal characteristics were: overall impression=4, taste=5, smell=4, texture=4, color=5, and consistency=4. All infants consumed more than 75% of the daily portions, with 5 infants consuming 100%. No serious adverse feeding events were reported.

Conclusions: Caterpillar cereal has appropriate macro- and micronutrient content for complementary feeding, and is acceptable to mothers and infants in the DRC. Therefore, this cereal may be a satisfactory substitute for animal-source foods.

PART I: Research Paper

BACKGROUND

In children under five years of age, malnutrition is responsible for 2.1 million deaths annually and 91 million disability adjusted life years (DALYs).[1] Stunting, defined as height-for-age Z score 2 standard deviations or more below appropriate World Health Organization standards, is a consequence of chronic poor nutrition and has been associated with multiple negative health outcomes, including increased mortality, poor cognitive and school performance, delayed motor development, impaired physical performance, reduced income in adulthood and lower birth weight in offspring.[2,3] If stunting from malnutrition is not reversed by the age of 2 years, the adverse effects are likely to be permanent.[4] The prevalence of stunting varies around the globe, but the developing world is disproportionately affected. In the Democratic Republic of Congo (DRC), the stunting prevalence in children under five years of age is estimated to be greater than 40%.[1]

Children from 3 months to 36 months are particularly vulnerability to insults affecting linear growth.[5] This vulnerable period includes the period after exclusive breast-feeding, when complementary foods are introduced into the diet. Malnutrition from inadequate complementary feeding is a serious problem in many developing countries where complementary foods consist of starch-based cereals or gruel that may provide sufficient energy but inadequate protein and micronutrients.[6] Micronutrient deficiencies are associated with stunting of growth and other serious health consequences including anemia and a greater susceptibility to infection.[7]

Authoritative guidelines on ideal complementary feeding recommend the daily consumption of animal-source foods in order to achieve adequate intakes of deficient nutrients, specifically iron and zinc, which are not achievable with plant-based diets alone.[6,8,9] Animal-source foods are not readily available in many developing countries, including the DRC. Insects have played a critical role in the diet of many people in Central Africa, with 70% of the population of Kinshasa, the capital of the DRC, consuming insects.[10,11] Dried caterpillars have a protein and micronutrient content similar to beef.[11,12] A cereal made from dried caterpillars may be an alternative to meat as a source of protein and micronutrients. The overall goal of this project is to create a novel cereal made from caterpillars and other locally available ingredients that is an acceptable complementary food for infants in the DRC. This cereal will be micronutrient-rich to combat the effects of deficiency states, including stunting.

Problems with behavioral and social compliance to feeding interventions limit the efficacy of food supplementation.[13-15] Feeding programs have had limited success if little attention was paid to socio-cultural influences on infant feeding, including maternal attitude.[16] Both maternal and infant and acceptability of food sources are important indicators of compliance with a feeding intervention and lack of compliance results in errant conclusions about the potential benefits of previous dietary interventions.[17] In this paper, we report the results of the biochemical and microbiologic analyses of a cereal made from caterpillars and the investigation of maternal and acceptability of the cereal.

METHODS

Cereal Development

We developed a cereal made from dried caterpillars, ground corn, sugar, salt and palm oil. We chose these ingredients based on the nutritional requirements of young children, the dietary habits of the population and the availability of these products in the local markets of the DRC. We chose corn because it constitutes a basic food source for many populations in the DRC, and its use in infant food is common throughout the country. We chose palm oil as a source of lipids, and the addition of palm oil produced a cereal of a more desirable color. Palm oil also contributes β-carotene, a precursor of vitamin A. We added small amounts of sugar and salt for palatability. Cereal production conformed to international standards on the formulation of foods intended for infants and children up to two years of age outlined in the Codex Alimentarius.[18, 19]

To make the cereal, we processed each of the cereal components separately and then mixed them together to create the final product.

1) Caterpillar flour: The caterpillars were initially washed and soaked in water for 30 minutes then dried in the sun. Dried caterpillars were crushed in a grinding mill and filtered to a flour of fine granularity and uniform consistency.

2) Corn flour: Kernels were initially filtered in a sleeve with broad mesh to remove foreign material from the corn. Twice, the kernels were soaked in water at room temperature and rinsed. The kernels were dried in the sun, crushed in a grinding mill and filtered to a flour of fine granularity and uniform consistency.

3) Palm oil: Oil required no processing before mixing.

4) Sugar and salt: Each ingredient was crushed separately to obtain a fine powder.

We mixed caterpillar flour, corn flour, salt and sugar in a basin. The proportion of caterpillar flour to corn flour is 1:1. We added palm oil to the mixture and dried the final mixture in an oven at 60° C for 24 hours. We removed the cereal from the oven, weighed it and placed in plastic sachets, which were hermetically sealed. We assured hygienic production of cereal by cleansing all equipment prior to the cereal production, assuring personal hygiene of all personnel including hand washing, and the required use of masks and hair coverings during cereal production.

Chemical and Microbiologic Testing

We performed chemical analyses on a sample of each batch of cereal. All analyses were conducted at the Research Institute in Sciences and Health in Kinshasa. To measure water content, we dried the cereal at a temperature between 100-105°C followed by cooling in a desiccating chamber. Weights were performed periodically until a standardized weight was achieved. We used the Kjeldahl method for analysis of protein content,[20] by digesting the cereal in sulfuric acid at a high temperature using SO_4K_2 and SO_4Cu as catalysts. We added concentrated alkali (NaOH) to the digest to convert ammonium to free ammonia that was distilled, collected and titrated in the presence of an acidic solution. The percentage of nitrogen was calculated from milliequivalents of ammonia per grams of the sample by multiplying by a standard conversion factor then converted to crude protein content by using a second standardized conversion factor. We used the Soxhlet method to determine lipid content in which lipids were extracted from the cereal using an organic solvent by backward flow under refrigeration. We placed the product in a drying oven to evaporate the organic solvent and then weighed it.

We performed microbiologic analyses on a sample of each batch of cereal to assess for the presence of microbes. We tested for the total organism count, and for the presence of Enterobacteria, *Staphylococcus aureus*, *Salmonella*, *Shigella*, yeast and fungus. A sample was plated on each of the following specific medium cultures: MacConkey, cellulose with blood, Hektoen and Mannitol Salt culture and the media were incubated at 37°C for 24 hours. We suspended any recovered colonies in mediums for identification, including: citrate of Simmons, Kliger, and Mannitol. After incubation, we isolated fungus on Sabouraud cellulose agar. All organisms were identified based on colony morphology.

Maternal and Infant Acceptability

We recruited 5 mother-infant dyads from health centers in each of four communities (Karawa Urbain, Karawa Cite, Bokpasi, Bogon) in the rural Equateur province of the DRC. We enrolled healthy male and female infants between the ages of 8 and 10 months and their mothers. We excluded infants with inter-current illness that may have interfered with oral intake, infants of multiple gestation, infants with congenital anomalies, and infants likely to receive free or subsidized complementary foods.

We provided each mother with a sachet containing a 30-gram portion of dry caterpillar cereal. We instructed mothers to cook the cereal in 100 mL of boiling water to a puree consistency. To assess maternal acceptability, we asked mothers to rate five features of the prepared cereal: smell, taste, texture, color and consistency. Their responses were ranked on a five point Likert scale, from “dislike very much” to “like very much.” We defined maternal acceptability as a median score for each feature of the cereal of 3 or greater and the upper limit of the lowest quartile of equal to or greater than 2. We also defined maternal acceptability as a 90% consent rate to participate in the one-week infant feeding trial.

To assess infant acceptability, we supplied each participating mother with a one-week supply of caterpillar cereal (7 sachets containing 30 grams of dry cereal each), and instructed each woman to feed her infant the cereal daily. Study personnel visited the home three times during the week to reinforce preparation instructions, observe feedings and monitor for signs or symptoms of feeding intolerance. On the eighth day of the trial, study personnel collected all unconsumed cereal from the preceding three days and surveyed mothers about their infant's health and feeding status during the trial. We based cereal consumption on the amount the infant consumed during the last 4 days of the trial. We defined infant acceptability as 100% of infants consuming greater than or equal to 75% of the cereal allotment during the last four days of the trial and all infants being free from adverse symptoms attributable to cereal consumption.

The Institutional Review Boards at the University of North Carolina at Chapel Hill and Kinshasa School of Public Health approved this study. The trial was registered through clinicaltrials.gov (NCT01258647).

RESULTS

The macro- and micronutrient content of the cereal are listed in Table 1. A 30-gram portion of the cereal contains 6.9 grams of protein, 6.3 grams of fat, 12.0 grams of carbohydrate and yielded 132 kilocalories. A 30-gram portion contained micronutrients, including 3.8 mg of iron and 3.8 mg of zinc. The cereal was free of microbiologic contaminants from *Salmonella*, *Shigella*, Enterobacteria, *Staphylococcus aureus*, yeast, and fungus (Table 2).

Twenty maternal-infant dyads were enrolled in the study to determine cereal acceptability. One dyad voluntarily withdrew after enrollment. On a five-point Likert scale (5=like very much), mothers' median scores for cereal characteristics were: overall impression 4 (range 4-5), taste 5 (3-5), smell 4 (3-5), texture 4 (3-5), color 5 (2-5), and consistency 4 (4-5) (Table 2).

All participating infants consumed more than 75% of the daily cereal portions during the last four days of the trial. Five infants (26%) consumed 100% of the cereal. One infant experienced vomiting during the first day of the study and continued the trial without further symptoms. No other adverse feeding events were reported.

DISCUSSION

We prepared a cereal from locally available constituents that appears to have sufficient macro- and micronutrients for complementary feeding. Lutter and Dewey have proposed an ideal composition for fortified complementary foods.[21] They propose quantities of macronutrients in complementary foods for 6-11 month old infants including 176 kilocalories, 3-4.5 grams of protein, and 4.8 grams of fat. A 30-gram portion of this caterpillar cereal provides sufficient macronutrients to meet these standards.

Lutter and Dewey propose an iron intake of 11 mg of non-heme iron, assuming an iron bioavailability of approximately 10%.[21] Less dietary iron is necessary from animal-source foods that have heme-associated iron and is approximately 30%

bioavailable.[22] Heme proteins in non-insect animals are usually found in muscle in the form of myoglobin and hemoglobin, but heme is also found in cytochrome and catalases.[23] The primary source of heme iron in caterpillars is in cytochromes, and we presume that its bioavailability is similar to the heme iron of myoglobin and hemoglobin.[23, 24] In addition, insects have iron bound to non-heme molecules, ferritin and holoferritin. Iron associated with these proteins is typically in the ferrous state, which increases its bioavailability, and iron bound to these proteins appears to be more bioavailable than iron in the form of reduced salts. Therefore, it is likely that the bioavailability of iron in caterpillars is similar to beef, and that the content of iron in our cereal will be sufficient to meet the requirements of infants.

Zinc is critical for cellular growth, and its deficiency is associated with stunting. Our cereal contains 3.8 mg of zinc in a daily portion, which approaches the recommended range of zinc intake in complementary feeding products for infants of 4-5 mg.[25] Although there are no specific quantitative data for the appropriate daily requirements of B vitamins for infants, caterpillars contain riboflavin, niacin, pantothenic acid, pyridoxine, biotin, folic acid and cobalamins.[12]

Human sensory testing of complementary feeding products predicts the acceptability of the introduction of the products' use within target populations.[26] Sensory evaluation of the food product including smell, taste, and color, as well as consumption of food products have been described as indicators of positive acceptability.[27] We chose to evaluate both maternal acceptability and infant consumption of cereal to provide an appropriate socio-cultural framework for the introduction of this complementary food into infants' diets. Previous studies on acceptability have focused on comparing two food products to each other.[17, 28] Because this cereal is a novel product made from locally available ingredients, a study comparing caterpillar cereal to a fortified cereal product which was not locally available was deemed unreasonable. Based on our strategy of evaluation, caterpillar cereal was found to be acceptable to mothers and infants.

Caterpillar cereal appears to be a promising strategy for use as complementary feeding; however, we recognize some limitations to this intervention. Although caterpillar cereal is designed to be easily integrated into existing food practices by using it as an additive to the usual dietary habits of children, the volume of cereal that we used may be a challenge for children at 6-8 months of age to consume. Furthermore, although the iron content of caterpillars is heme-associated, it is not clear if the absorption of this micronutrient will be sufficient to prevent iron deficiency.

Using locally available food products, we developed a caterpillar-based cereal that has the appropriate macro- and micronutrient content for infant complementary feeding. This cereal is acceptable to both mothers and infants in a rural area of the DRC. Because the ingredients are locally available and the production of this cereal is simple, this cereal is likely to be a sustainable alternative for complementary feeding. However, this cereal will need to be tested in an efficacy trial to determine if it will have positive effects on micronutrient deficiencies and linear growth.

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Table 1: Content of a 30-gram Portion of Caterpillar Cereal

Macronutrients		Micronutrients	
Energy, Kcal	≈ 132	Iron, mg	3.8
Protein, g	6.9	Zinc, mg	3.8
Fat, g	6.3	Magnesium, mg	9.4
Carbohydrate, g	12.0	Copper, mg	3.7

Table 2: Microbiologic Assays

Enrichment Media	Quantifying Media	Result
Peptone water	Blood Agar (total organism count)	Negative
	MacConkey Agar (Enterobacteria)	Negative
	Mannitol Salt Agar (*Staphylococcus aureus*)	Negative
	Sabouraud Agar (yeast and fungus)	Negative
Selenite	Blood Agar (total organism count)	Negative
	Hectoen (*Salmonella*)	Negative
	Salmonella Shigella Agar	Negative
Thioglucolate	Blood Agar (total organism count)	Negative
	Mac Conkey Agar (*Enterobacteria*)	Negative
	Mannitol Salt Agar (*Staphylococcus aureus*)	Negative
	Sabouraud Agar (yeast and fungus)	Negative

Table 3: Maternal Acceptability

Cereal Characteristics	*Maternal Opinion, n*				
	1 Dislike very much	2	3 Neutral	4	5 Like very much
1. Overall impression	0	0	0	11	8
2. Taste	0	0	1	6	12
3. Smell	0	0	1	9	9
4. Texture	0	0	1	12	6
5. Color	0	1	0	7	11
6. Consistency	0	0	0	10	9

PART II: Systematic Review of the Literature

Effective Strategies to Prevent Stunting of Linear Growth: A Systematic Review

BACKGROUND

A child's growth is usually classified as stunted if his or her height is 2 standard deviations or more below age-appropriate World Health Organization (WHO) Standards. Stunting might be a consequence of chronic poor nutrition and has been associated with multiple negative health outcomes, including poor cognitive and school performance, delayed motor development, impaired physical performance, reduced income in adulthood and lower birth weight in offspring.[1] Stunting may begin during fetal life and early childhood when nutritional requirements are very high to support rapid growth and development.[2] Children in infancy (3-6 months) to early childhood (24-36 months) show particular vulnerability to insults affecting linear growth.[3] This time period coincides with the time when complementary foods are introduced into the diet, after the typical period of exclusive breast-feeding.

The causes and etiology of stunting are not as well understood as is the timing in which it occurs. The causes are likely to be multi-factorial and include: 1) nutrient deficiencies: energy, macronutrients, micronutrients and toxic factors; 2) infection, including mucosal injury of the gastrointestinal tract and systemic effects of illness; and 3) mother-infant interaction, including maternal nutritional stores at birth and behavioral interactions.[3] Several studies have highlighted the importance of micronutrient deficiencies in growth failure.[4]

The burden of suffering from stunting rests largely in the developing world, most notably in Sub-Saharan Africa and Southeast Asia.[6] For example, the prevalence of stunting in children under the age of 5 years in the Democratic Republic of Congo

(DRC) is estimated to be greater than 40%.[6] The problem of stunting is particularly severe in Africa because few locally available foods are rich in nutrients, available throughout the year, and accessible to impoverished families. Animal-source foods have better bioavailability of important micronutrients, like iron, than plant based foods, but are in limited supply in developing countries.

General nutrition interventions could prevent 10-15% of stunting in developing nations and prevent one in eight deaths in children under 36 months of age,[7] but the best nutrition strategy to prevent stunting in the developing world is largely unknown. A variety of strategies, including single or multiple micronutrient (MMN) supplementation, food-based interventions, and fortification have been used to prevent stunting and other outcomes of infant malnutrition.[7] The components of a “one-size-fits all” food based intervention have not been determined and rigorous study about the effects on growth are lacking.[8]

A systematic review was published in 2008 by Dewey and Adu-Afarwuah examining the efficacy and effectiveness of complementary feeding interventions in developing countries.[9] The purpose of this systematic review will be to update the previous review, focusing on randomized control trials (RCTs) or pseudo-RCTs of dietary interventions that supplement the diet of young children in the developing world to reduce stunting of linear growth.

METHODS

I searched PubMed on 12/2/2011 using keywords including complementary feeding, weaning food, growth, stunting, micronutrient, and developing country

(Appendix). I limited the search to include only human studies in children 0-18 years. I focused my search to the time period 2006-2011, because the previously reported systematic review included the time period 1996-2006. I examined the titles and abstracts of all of the retrieved citations for relevance to complementary feeding, micronutrient intake, stunting of growth and developing countries. Only randomized control trials or quasi-randomized control trials using a dietary intervention were included in the review. In order to be included, linear growth had to be analyzed in the study as either a primary or secondary outcome and height-for-age had to be included among the outcome measures. I excluded trials that did not begin the intervention before three years of age and those that were not available in English.

I examined the evidence for potential sources of bias according to the method outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[10] I classified bias as selection bias (sequence generation, allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selective outcome reporting). An overall ranking of bias risk was assigned as low, moderate or high.

I used the approach outlined in Dewey and Adu-Afarwuah to determine the effect size on linear growth, with the following equation:

$$\text{Effect Size (ES)} = \frac{\text{Mean for intervention group} - \text{Mean for comparison group}}{\text{Pooled Standard Deviation (SD)} = \text{Average of the SDs for Intervention and comparison groups}}$$

The null hypothesis corresponds to an effect size of zero, and a nonzero value indicates the degree of departure from the null hypothesis. Effect size is grossly categorized as small (around 0.2) in which the combined area of the two populations overlaps more than 85.3%, medium (around 0.5) and large (around 0.8) indicating a population so separated that almost half of the areas do not overlap.[11] Intervention groups were compared to control groups, if available. If no control group was available, the intervention was compared to the group that had an intervention that would presumably have the least effect on linear growth.

Results

My initial PubMed Search yielded 462 articles (Figure). After reviewing the titles, 109 abstracts were reviewed for applicability. Fifteen abstracts were selected and the papers were reviewed. Eight studies were included in the analysis[12-19]. These studies represented a pooled patient number of 4916. The interventions lasted between 3 and 12 months and were conducted in 10 countries. Children from age 6 months to 5 years were included. One trial grouped all children under five years of age in their intervention. Five trials studied MMN fortified foods or additives and three focused on single micronutrient supplementation. One study included an education intervention in addition to a food supplementation. Comparison groups varied in each trial: some compared to placebo while others compared to groups fed an alternative complementary feeding product.

All of the studies were randomized controlled trials or quasi-randomized controlled trials. Three of the studies were considered high level of evidence with low risk of bias. Three studies were classified as moderate in quality given some risk of bias and two of the studies had a high risk of bias (Table 1).

The results of the feeding interventions were somewhat inconsistent, 5 showed a positive effect on linear growth and 3 demonstrated a negative effect on linear growth (Table 2). The combined mean effect size for all trials was 0.01 (-0.35 – 0.36) for the outcome of linear growth. The effect size was small in a majority of the studies. None of the studies showed a statistically significant difference between intervention and control groups in regards to growth. However, in a subgroup analysis performed by Dijkhuizen, Winichagoon, Wieringa et. al, children who were initially classified as anemic at baseline and received zinc supplementation in their study, had a statistically significantly higher height-for-age Z-scores than those receiving placebo (p=0.005).[19] Only minimal side effects were reported in all of the feeding trials.

Discussion

The results of this systematic review did not show a statistically significant effect of dietary supplementation with single or multiple micronutrients on linear growth. This finding is consistent with the previous systematic review that showed small and mixed results for interventions that provided food supplementation during complementary feeding.[9] Although single site trials have shown efficacy with feeding interventions on child mortality, they have had limited effect on linear growth.

A possible explanation for the negative findings in this review could be that many of the trials did not follow patients for a sufficient length of time to assess differences in linear growth. Two of the trials that consisted of interventions greater than 6 months had positive effects on growth, although small in effect size and not reaching statistical significance. Another possible explanation is the trials included interventions that began after a “critical” period of intervention. Most trials began around 6 months of age, after the time period of exclusive breast-feeding, as recommended by the WHO, however, many studies report that exclusive breastfeeding is not practiced in a large number of maternal-infant dyads.[20, 21] As a result, mechanisms leading to serious diseases like iron deficiency anemia might already have begun and be irreversible.[22]

Prevention of stunting of linear growth is a complex problem with multiple etiologies. Therefore, strategies that are aimed at alleviating one etiology, such as provision of micronutrients might fail to prevent stunting because of the influence of other factors. Additional studies evaluating the complex etiology of stunting, including maternal-infant interactions, the integrity of the gut mucosa and its ability to absorb key nutrients, and the role of inter-current infections need to be performed.

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Appendix: PubMed Search Strategy

(("trace elements"[MeSH Terms] OR ("trace"[All Fields] AND "elements"[All Fields]) OR "trace elements"[All Fields] OR "micronutrient"[All Fields] OR "trace elements"[Pharmacological Action] OR "micronutrients"[MeSH Terms] OR "micronutrients"[All Fields] OR "micronutrients"[Pharmacological Action]) OR fortified[All Fields] OR complementary[All Fields] OR ("weaning"[MeSH Terms] OR "weaning"[All Fields]) OR ("dietary supplements"[MeSH Terms] OR ("dietary"[All Fields] AND "supplements"[All Fields]) OR "dietary supplements"[All Fields])) AND (("growth and development"[Subheading] OR ("growth"[All Fields] AND "development"[All Fields]) OR "growth and development"[All Fields] OR "growth"[All Fields] OR "growth"[MeSH Terms]) OR ("growth disorders"[MeSH Terms] OR ("growth"[All Fields] AND "disorders"[All Fields]) OR "growth disorders"[All Fields]) OR stunting[All Fields] OR ("body height"[MeSH Terms] OR ("body"[All Fields] AND "height"[All Fields]) OR "body height"[All Fields]) OR ("growth and development"[Subheading] OR ("growth"[All Fields] AND "development"[All Fields]) OR "growth and development"[All Fields] OR "development"[All Fields]) OR ("nutritional status"[MeSH Terms] OR ("nutritional"[All Fields] AND "status"[All Fields]) OR "nutritional status"[All Fields]) OR ("child nutrition disorders"[MeSH Terms] OR ("child"[All Fields] AND "nutrition"[All Fields] AND "disorders"[All Fields]) OR "child nutrition disorders"[All Fields]) OR ("infant nutrition disorders"[MeSH Terms] OR ("infant"[All Fields] AND "nutrition"[All Fields] AND "disorders"[All Fields]) OR "infant nutrition disorders"[All Fields])) AND (("developing countries"[MeSH Terms] OR ("developing"[All Fields] AND "countries"[All Fields]) OR "developing countries"[All Fields]) OR ("world health"[MeSH Terms] OR ("world"[All Fields] AND "health"[All Fields]) OR "world health"[All Fields]) OR ("poverty"[MeSH Terms] OR "poverty"[All Fields])) AND ("humans"[MeSH Terms] AND (Clinical Trial[ptyp] OR Randomized Controlled Trial[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] OR Comparative Study[ptyp] OR Controlled Clinical Trial[ptyp] OR Evaluation Studies[ptyp] OR Journal Article[ptyp] OR Multicenter Study[ptyp]) AND ("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms]) AND ("2006/01/01"[PDAT] : "2011/11/30"[PDAT]))

Table 1: Assessment of Bias

Article	Random Sequence Generation	Allocation Concealment	Blinding of participants/ personnel	Blinding of outcome assessment	Incomplete Outcome Data	Selective Reporting	Overall Risk of Bias
Giovanni, 2006	+	+	+	+	+	+	Low
Lopez de Romana, 2006	?	-	-	?	-	-	High
Owino, 2007	+	+	+	?	+	+	Moderate
Lutter, 2008	-	-	-	-	+	+	High
Phuka, 2008	+	+	-	+	+	+	Low
Silva, 2008	?	?	?	?	+	+	Moderate
Dijkhuizen, 2008	+	+	+	+	+	+	Low
Ekbote, 2011	?	?	?	?	+	+	Moderate