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Supplementary vitamin E, selenium, cysteine and riboflavin for preventing kwashiorkor in preschool children in developing countries (Review)

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[Intervention Review]

Supplementary vitamin E, selenium, cysteine and riboflavin for preventing kwashiorkor in preschool children in developing countries

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ABSTRACT

Background

Protein Energy Malnutrition is an important cause of child morbidity and mortality in middle- and low-income countries. It has been suggested that excessive free radical activity may be responsible for the clinical manifestation of kwashiorkor. Antioxidants may be able to curb excessive free radical activity and prevent the development of kwashiorkor in susceptible children.

Objectives

To evaluate the benefits of supplementation of vitamin E, selenium, cysteine and riboflavin (alone or in combination) in preventing kwashiorkor.

Search methods

We conducted searches of CENTRAL 2009 (*The Cochrane Library* 2009 Issue 2), MEDLINE 1966 to 2009, EMBASE 1980 to 2009, CINAHL 1982 to 2009, LILACS 1982 to 2009, Meta register of Controlled trials, Open Sigle, African Index Medicus.

Selection criteria

Randomised controlled trials (RCTs) and quasi-RCTs evaluating vitamin E, selenium, cysteine and riboflavin alone or in combination in healthy pre-school children in middle- and low-income countries.

Data collection and analysis

Two authors extracted and independently analysed data.

Main results

One cluster-RCT including 2372 children met our inclusion criteria. Children were randomised, based on household, either to a supplement containing all four micronutrients or to placebo. No statistically significant difference in the incidence of kwashiorkor between the intervention and control groups could be demonstrated at 20 weeks (RR 1.70; 95% CI 0.98 to 2.42). Nor could any statistically significant difference in all-cause mortality be demonstrated (RR 0.75; 95% CI 0.17 to 3.36).

Authors' conclusions

Based on the one available trial, we could draw no firm conclusion for the effectiveness of supplementary antioxidant micronutrients for the prevention of kwashiorkor in pre-school children.

PLAIN LANGUAGE SUMMARY

Supplementary vitamin E, selenium, cysteine and riboflavin for preventing kwashiorkor in preschool children in developing countries

Undernutrition is one of the leading underlying causes of childhood morbidity and mortality in developing countries. Providing antioxidants that would help curb excess free radicals in the body may help prevent the development of kwashiorkor. We identified one cluster-RCT that attempted to investigate this. Based on the published evidence reviewed, we could draw no firm conclusions of the benefits of supplementary antioxidants for the prevention of kwashiorkor in pre-school children. There is a need for further research in this area to be certain if antioxidant supplementation can help prevent kwashiorkor in young children.

BACKGROUND

Description of the condition

The term kwashiorkor is derived from the Ghanaian word meaning 'the disease the older child develops when the new child is born' (Williams 1935). This is because once the next sibling is born the older child, having lost his or her earlier source of nourishment in the form of breast milk, has to subsist on a maize gruel alone that is quite deficient in proteins (Laditan 1999; Williams 1935). It occurs most frequently in infants and children in developing countries.

Kwashiorkor is part of a spectrum of diseases collectively referred to as Protein Energy Malnutrition (PEM). Together with marasmus, these diseases form two ends of the disease spectrum of PEM. These disorders are believed to be a consequence of a coincident lack of dietary proteins and/or calories in varying proportions (Laditan 1999). Marasmus is characterised by severe muscle wasting. In marasmus, body weight may be reduced to less than 60% of the normal weight for that age and it carries a better prognosis than kwashiorkor. It is also possible for both conditions to overlap, when it is referred to as marasmic kwashiorkor.

Epidemiology

From the earliest clinical descriptions of kwashiorkor (Williams 1935), an association had been established with poverty and social neglect and the disease is mostly seen in developing countries (Muller 2005). Globally, it indirectly accounted for 53% of deaths among children under five between 2000 and 2003, when associated with other common childhood diseases like acute respiratory infections, diarrhoea, malaria, measles, HIV/AIDS and other causes of perinatal deaths (Muller 2005).

Although some low- and middle-income countries in Asia are beginning to report a decline in the number of cases of kwashiorkor diagnosed, the deteriorating socio-economic conditions in others, especially in certain parts of sub-Saharan Africa, continue to account for an increase in total disease burden (Sachdev 2000).

Aetiopathogenesis

The commonly acknowledged aetiology for severe PEM is extreme deficiency of macro-nutrients, i.e. protein and calories (Coward 1979; Waterlow 1984; Laditan 1999). However, the determinant of the clinical presentation along the entire disease spectrum has been the subject of some controversy and several hypotheses have been put forward to explain the pathogenesis of kwash-

iorkor. These include: protein deficiency (Williams 1935), methionine deficiency (Roediger 1995), pellagra (Gillman 1951), dietary dysadaptation (Gopalan 1968), cyanogenic glycoside toxicity (Kamalu 1993), aflatoxin poisoning (Hendrickse 1984), ADH-like effect of free ferritin (Srikantia 1958), inappropriate endocrine responses (Rao 1974), and free radical damage following excessive oxidative stress (Golden 1987). With regard to the theory of dietary dysadaptation, it is generally believed that kwashiorkor results from a failure of the body's compensatory mechanisms for severe undernutrition, while marasmus represents a compensated form. The theory of excessive oxidative stress has been proposed following observations that children with kwashiorkor seemed to have higher concentrations of biomarkers of oxidative stress when compared to marasmic children or children who did not have PEM. It was also found that these children had lower concentration of antioxidants in their blood. These abnormalities were seen to revert to normal when they were successfully treated (Golden 1987).

The hypothesis proposed by Golden and Ramdath that kwashiorkor results from an imbalance between production and safe disposal of free radicals is the basis for this systematic review. This hypothesis posits that various insults (referred to as noxae in the original paper) imposed on the patient produce free radicals, mainly lipid peroxides and toxic carbonyls. In normal children, the body is able to handle these radicals and they are dissipated without causing injury. However, it is believed that in kwashiorkor these radicals are excessive and so overwhelm the body's intrinsic dissipation system. This is as a result of the relative/absolute deficiency of certain components of the dissipation system in the form of antioxidants (Golden 1987; Golden 1998).

Issues that seem to support this hypothesis include the fact that infection, for example by the measles virus, was found to precipitate kwashiorkor and the fact that toxins, found to be present in food due to poor handling and storage, also appeared to be elevated in kwashiorkor patients. In addition, high iron levels were found in some of these children. Iron is thought to have a role because it is able to catalyse reactions that produce free radicals because of the ease with which it changes valency under redox conditions and pH. Plasma ferritin has also been demonstrated to be elevated in these children (Ogon 2006; Sive 1993; Srikantia 1958).

Glutathione, a central component of the protective repertoire by virtue of its function in helping protect sulfhydryl groups in the reduced state, is also known to be affected. It has been demonstrated to be reduced in the red blood cells of children with kwashiorkor. Low levels of glutathione have been accounted for by the fact that most of the body's store has to be channeled to detoxification reactions involving peroxides and carbonyls. Also the enzymes that function in the reduction of glutathione and reducing equivalent provision, notably glutathione reductase, Glucose-6 Phosphate Dehydrogenase and 6- phosphogluconic acid dehydrogenase, are induced in kwashiorkor (Golden 1987; Golden 1998; Jackson 1986; Sive 1993).

Clinical features

Clinically, kwashiorkor produces growth failure, which manifests itself in deranged anthropometric (body measurement) indices like weight for age, height for age, and decreased mid upper arm circumference (MUAC). Other features include generalised oedema, greatly increased predisposition to infection due to the relative immunodeficiency state, anaemia, regression in milestones, skin and hair changes; the skin lesions commonly associated with kwashiorkor include flaky paint dermatoses and fluffiness of the hair. There is also abdominal swelling, which is accounted for by hepatomegaly secondary to fatty infiltration and loss/flabbiness of the abdominal wall musculature (Laditan 1999; Ogon 2006).

Diagnosis

The Wellcome Working Party classification of protein energy malnutrition specifies the presence of a deranged weight for age value between 80% and 60% of expected in the presence of oedema for diagnosis of kwashiorkor (Laditan 1999; Wellcome Working Party 1970).

Standard *t*reatment

The treatment of kwashiorkor involves nutritional rehabilitation along guidelines issued by the World Health Organization. This involves initial hospitalisation and the sequential and systematic provision of a therapeutic diet with the adequate content of protein and calories, treatment/correction of electrolyte derangements, hypothermia, hypoglycaemia, dehydration, provision of micronutrients, treatment of infection, psychosocial stimulation and consolidation of tissue building nutrition to prevent relapse (World Health Organization 1999).

Description of the intervention

Vitamin E, selenium, cysteine and riboflavin

This systematic review is interested in appraising the effectiveness and efficacy of some antioxidants and micronutrient supplements that may be able to help correct the deficiency that predisposes susceptible children to kwashiorkor. By susceptible children, we mean children whose current socio-economic circumstances place them at risk of becoming malnourished.

We are specifically interested in vitamin E, selenium, cysteine and riboflavin either singly or delivered in combination prophylactically to children aged between six months and five years to prevent kwashiorkor.

Vitamin E - also known as alpha tocopherol - is a naturally occurring vitamin whose absorption is facilitated by optimal fat absorption in the diet. Vitamin E functions as the first line of defence against polyunsaturated fatty acid peroxidation. It does this by breaking free radical chain reactions (Murray 2000). The Recommended Daily Allowance (RDA) of vitamin E for children within the age group of interest in this review is between 4 mg/d and 7 mg/d (Murray 2000; IOM 2000a), with a tolerable upper limit of 1000 IU for adults. At present there is a paucity of data regarding the precise tolerable upper limit for children within the age group of interest (IOM 2000a).

Selenium is an integral component of glutathione peroxidase, and provides defence against hydroperoxides, another source of oxidative stress. It acts synergistically with vitamin E in its action against lipid peroxidation, which is responsible for some of the destructive effects of free radicals on cell membranes. Selenium is required in microgram quantities and is toxic in overdose. Deficiency occurs in plants and animals raised in areas where soils and drinking water have little or no selenium. Healthy populations are known to consume selenium in the range of 30 mcg/day to 500 mcg/day. The optimal range for children within the age group of interest in this review is between 15 mcg/day and 30 mcg/day (IOM 2000a). The supplement level may be in the range of 100 mcg/day to 200 mcg/day.

Cysteine is a sulphur-containing nonessential amino acid which is able to bond in a special way to proteins and maintain its structure in the body. Cysteine is a component of the antioxidant glutathione and can also function in the production of taurine, another amino acid. The body can synthesise cysteine from methionine and other building blocks. Cysteine is rarely used as a dietary supplement. N-acetyl cysteine (NAC), which contains cysteine, is more commonly used as a supplement. Cysteine, the amino acid from which NAC is derived, is found in most high-protein foods (Murray 2000).

Riboflavin or vitamin B2 is a micronutrient that acts as an integral component of two coenzymes: flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN). A coenzyme is a molecule required for the activity of another enzyme. These flavin coenzymes are critical for the metabolism of carbohydrates, fats, and proteins into energy. Because riboflavin is an important component of these flavin coenzymes, it is thought that riboflavin supplementation can increase the efficiency of energy metabolism in cells (Murray 2000). FAD and FMN are involved in the activity of the electron transport chain, an essential component of energy metabolism. Severe deficiencies in riboflavin can lower levels of coenzymes, leading to inefficient energy metabolism and consequent energy depletion. Riboflavin is a water-soluble vitamin that is found naturally in the food we eat. Sources of riboflavin include organ meats (liver, kidney, and heart) and certain plants such as almonds, mushrooms, whole grain, soybeans, and green leafy vegetables (Murray 2000). The Recommended Daily Allowance (RDA) for the age group of interest in this review is between 0.3 mg/day and 0.6 mg/day (IOM 2000b).
Most of the existing RDA recommendations currently in existence in the published literature are derived from adult values after taking into account the results of basic experimental and observational studies and making adequate statistical adjustments (IOM 1998).

Each of the above micronutrients has some antioxidant effects; however, it is believed that their antioxidant effects would be greatly enhanced if they were delivered in combination. This is because of the nature of the biochemical reactions they catalyse, which are all interlinked at different metabolic junctions.

How the intervention might work

It is thought that the micronutrients described above may correct the postulated relative deficiency of antioxidants in children who are susceptible to kwashiorkor and thereby protect them from developing kwashiorkor. This hypothesis was first proposed by Golden and Ramdath (Golden 1982; Golden 1987). Some other evidence that seems to support this theory includes the observation of some degree of clinical improvement following administration of NAC to malnourished children (Manary 2000).

Why it is important to do this review

Malnutrition remains a major problem, particularly for children living in developing countries. Globally, it indirectly accounted for 53% of deaths in children under five years old between 2000 and 2003, when associated with other common childhood diseases like acute respiratory infections, diarrhoea, malaria, measles, HIV/AIDS and other causes of perinatal deaths (Muller 2005).

There is lack of consensus on the interventions (if any) that can effectively prevent PEM among these children.

Several interventions like micronutrient supplementation, promotion of breast feeding, food fortification and dietary diversification have been utilised based on an understanding of the pathogenesis and pathophysiology of malnutrition, particularly protein energy malnutrition.
As regards antioxidants and micronutrients, there has been some speculation that they have a role to play in the pathogenesis of kwashiorkor. However, the evidence in support of this hypothesis, that the clinical manifestation of kwashiorkor in the spectrum of PEM is due to excessive free radical activity and decreased antioxidant ability of the body, is derived mainly from basic experimental and observational studies. If indeed this theory is correct, there is a

need for RCTs, and to enable this to form a strong basis for public heath practice, there is need for a systematic review of available evidence as regards the efficacy or otherwise of this intervention (Becker 1994; Sive 1993) when exploited for purposes of primary prevention.

OBJECTIVES

To evaluate the effects of supplementation of vitamin E, selenium, cysteine and riboflavin (alone or in combination) for prevention of kwashiorkor in pre-school children in low- and middle-income countries.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs (individual or cluster-randomised).
Quasi-RCTs (where allocation of treatment has been made, for example, by alternate allocation, date of birth, alphabetical order, etc).

Types of participants

Healthy children (aged between six months and five years) in community settings in low- and middle-income countries.
Studies involving children with kwashiorkor and marasmus or any other chronic illnesses were not eligible.

Types of interventions

Community-based administration for a minimum of four weeks of a formulation that consists of at least one or more of vitamin E, selenium, cysteine or riboflavin at doses over and above the RDA. We included studies if one or more of these micronutrients were administered, alone or in conjunction with others, but if the difference between the two groups is only the micronutrients of interest.
By community-based we mean that the intervention is administered at home or any other centre designated for its administration in the community.
Acceptable control conditions include placebo only.
Trials in which at least one of the intervention micronutrients (vitamin E, selenium, cysteine and riboflavin) are provided alongside other interventions, for example, health education, were eligible as long as these co-interventions were included in all groups.

Types of outcome measures

Primary outcomes

Incidence of kwashiorkor, defined as weight for age less than 80% of expected with the presence of oedema.

Secondary outcomes

1. Number of children who die from kwashiorkor.
2. Number of children who die from any cause.
3. Kwashiorkor related morbidity e.g. incidence of:
    - flaky paint dermatoses;
    - abdominal swelling with hepatomegaly and ascites;
    - psychomotor retardation.
4. Cognitive development:
    - intellectual quotient (because chronic malnutrition adversely affects cognitive development).
5. Hospitalisation: incidence and duration (for kwashiorkor).
6. Adverse events.
7. Economic data if available.

Timing of outcome assessment

Depending on availability of data, we planned to report our outcomes as short term (one month); medium term (six months); and long term (one year).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials, (CENTRAL) (*The Cochrane Library* 2009, Issue 2); MEDLINE 1955 to May 2009; EMBASE 1980 to 2009 week 20; CINAHL 1982 to May 2009; LILACS 1982 to May 2009; MetaRegister of Controlled Trials, (for ongoing trials), searched May 2009; Dissertation Abstracts searched May 2009; OpenSigle, (for grey literature), searched May 2009; and the African Index Medicus searched May 2009. The search strategies used to search these databases can be found in the following appendices:
CENTRAL Appendix 1, MEDLINE Appendix 2, EMBASE Appendix 3, CINAHL Appendix 4, LILACS Appendix 5, MetaRegister of Controlled Trials, (ongoing trials), and Dissertation Abstracts Appendix 6, OpenSigle (grey literature) Appendix 7, African Index Medicus Appendix 8.
We did not use an RCT filter in order to obtain as many related studies as possible. We also searched the reference lists of studies that met our inclusion criteria. We applied no language or date restrictions.

Searching other resources

We searched conference proceedings (conferences of paediatric and nutrition organisations held within the last decade), and contacted researchers, organisations, and pharmaceutical companies in the area by email.

We scanned references of retrieved articles and relevant reviews for potentially eligible studies. We contacted authors of included trials by email or post asking for help in clarifying relevant and missing data and to identify reports of unpublished or ongoing trials. We planned to make up to two different contact attempts per identified author (e-mail and post). We also anticipated that a great deal of relevant literature may be unpublished, or published only as in-house reports, and attempted to make contact by email or letter with relevant NGOs and experts in the field to locate reports of unpublished or ongoing studies. We contacted the following organisations: World Health Organization, World Bank, United Nations Children's Fund, World Food Programme, International Food Policy Research Institute (IFPRI), Famine Early Warning System (FEWS), The Centre for the Study of African Economies, the Institute for Agriculture and Trade Policy, InterAction.org, Oxfam, Médecins sans Frontières, DFID, UK and USAID. We were interested in information generated within the last five years as regards the websites.

We searched Clinical Trials.Gov and the WHO Clinical Trials platform to enable us to obtain information regarding ongoing trials, and also to obtain information regarding completed but unpublished trials.

We also identified experts in the field and enquired about ongoing or completed trials. We identified from the author line of retrieved papers, conference proceedings, and websites of leading universities and research centres.

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

Data collection and analysis

Selection of studies

Two authors (Odigwe and Anyanechi) independently assessed titles and abstracts of articles identified in the search to determine whether they met the inclusion criteria or not. We also checked the reference lists of all retrieved publications to search for relevant studies. We carefully assessed abstracts of retrieved studies and retrieved those with potential in full and checked them against our eligibility criteria.

A data extraction form was developed for this purpose. The two authors who applied the inclusion criteria were not blinded to the names of the authors, institutions or journal of publication. We planned that in situations where there were differences of opinion regarding suitability for inclusion, that we would have resolved this by discussion. We would have resolved any doubt during this process by consultation with a third reviewer (Ejemot Nwadiaro or Geir Smedslund) or through discussion with the editorial base. If necessary, we would have sought further information from trialists.

Data extraction and management

Two authors (Odigwe and Smedslund) independently extracted data and recorded the following data on data extraction forms: identification details of the study; method of random allocation to intervention/control groups; details about participants including baseline nutrition status; description and length of the intervention; the primary and secondary outcome measures and any information pertaining to adverse events. We also extracted data on risk of bias issues, namely method of allocation sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and issues regarding the funding of the study and source of ethical approval. We also extracted data on the results and effects of treatment. We had planned to resolve any disagreement between the reviewers by discussion and by consultation with a third reviewer (Ejemot Nwadiaro or Anyanechi), with input from the editorial base.

One author (Odigwe) entered data into Review Manager (RevMan 2008) and a second author (Smedslund) checked data.

Assessment of risk of bias in included studies

Two review authors independently assessed methodological quality according to the specifications of the latest edition of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). Review authors independently assessed the risk of bias within each included study in relation to the following five domains with ratings of 'yes' (low risk of bias); 'no' (high risk of bias); and 'unclear' (uncertain risk of bias).

Sequence generation

For allocation sequence generation, low risk of bias refers to the fact that allocation sequence was generated by a method that would completely ensure that only chance would determine to which group a patient would belong. An example of a low risk of bias method for generating allocation sequence would be the use of a table of random numbers or the use of a computer random number generator.

Description: the method used to generate the allocation sequence was described in detail so as to assess whether it should have produced comparable groups; review authors' judged: was the allocation sequence adequately generated?

We rated as follows: 'yes' (low risk of bias); 'no' (high risk of bias); and 'unclear' (uncertain risk of bias).

Allocation concealment

For allocation concealment, low risk of bias refers to the fact that the trialists made a concerted effort to ensure that at the time at which the decision was made to include trial participants in the trial and allocate them to either intervention or control groups, the trialist allocating them to these groups is completely unaware of the treatment the participant would receive in that group. An example of this would be the use of sealed opaque envelopes to conceal allocation.

Description: was the method used to conceal the allocation sequence described in sufficient detail to assess whether intervention schedules could have been foreseen in advance of, or during, recruitment? Based upon this, review authors judged whether allocation was adequately concealed?

We rated as follows: 'yes' (low risk of bias); 'no' (high risk of bias); and 'unclear' (uncertain risk of bias).

Blinding

For blinding, low risk of bias refers to the fact that a concerted effort is made to ensure that the outcome assessor and the trial participant are unaware of the treatment which they have received. For the sort of trials that would be included in this review, this could be achieved by the use of a matching placebo and the administration of the study medication by other trial staff not involved with the outcome assessment.

Description: were any measures used to blind participants, personnel and outcome assessors described so as to assess knowledge of any group as to which intervention a given participant might have received? Based upon this, review authors judged whether knowledge of the allocated intervention was adequately prevented during the study?

We rated as follows: 'yes' (low risk of bias); 'no' (high risk of bias); and 'unclear' (uncertain risk of bias).

Incomplete outcome data

Description: in instances where studies did not report complete outcome data, we attempted to obtain missing data by contacting the study authors. We extracted and reported on data on attrition and exclusions as well as the numbers involved (compared with total randomised), reasons for attrition/exclusion where reported or obtained from investigators, and any re-inclusions in analyses performed by review authors. Based upon this, review authors judged whether the researchers dealt with incomplete data. (See also 'Dealing with missing data', below.)

We rated as follows: 'yes' (low risk of bias); 'no' (high risk of bias); and 'unclear' (uncertain risk of bias).

Selective outcome reporting

Description: we attempted to assess the possibility of selective outcome reporting by investigators; based upon this, review authors judged whether reports of the study were free from suggestion of selective outcome reporting.

We rated as follows: 'yes' (low risk of bias); 'no' (high risk of bias); and 'unclear' (uncertain risk of bias)

We explored other sources of bias, particularly the sources of funding of the included studies and other study peculiarities.

Measures of treatment effect

Continuous data

We analysed continuous data where means and standard deviations were available and there was no clear evidence of skew in the distribution. If mean difference was provided, we planned to extract and utilise this for the analysis irrespective of provision of mean and standard deviation. We were interested in the change of data from the baseline.

Binary data

We analysed binary outcomes by calculating the relative risk with 95% confidence intervals.

Unit of analysis issues

Cluster-RCTs

Statistical methods for cluster-RCTs used in the review are those that are described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008).

We planned to meta-analyse all the studies together, or at least combine all the cluster-RCTs, if possible. We anticipated that we may be able to do this if the outcomes of interest in the cluster-RCTs were not correctly adjusted for clustering.

We planned to re-analyse, if possible, studies judged not to have been analysed by adjusting for clustering. We planned to extract data that would enable a re-analysis. We planned to collect data on the number of clusters (or groups) randomised to each intervention group; or the average (mean) size of each cluster, and also the outcome data ignoring the cluster design for the total number of individuals. We also planned to collect data regarding the estimate of the intracluster (or intraclass) correlation coefficient (ICC). In the event of this not being reported, we planned to obtain this from a reliable external source. We planned to contact the trialists to provide missing information that would enable us do this. However the included trial was reported in such a way that we did not need to do this.

We also sought the help of statisticians from the Developmental and Psychosocial Learning Problems Review Group to ensure that appropriate methods were utilised.

Dealing with missing data

When necessary, we planned to contact the study author(s) to supply any unreported data (for example, group means and standard deviations (SDs), details of dropouts, and details of interventions received by the control group). If a study reported outcomes only for participants completing the trial or only for participants who followed the protocol, we planned to contact the authors and ask them to provide additional information to facilitate an intention-to-treat analyses.

Assessment of heterogeneity

We assessed important clinical heterogeneity by comparing the distribution of important clinical heterogeneity factors (study participants, study setting, type of intervention and co-intervention) and methodological heterogeneity factors (randomisation, allocation concealment, blinding of outcome assessment, losses to follow up).

We assessed statistical heterogeneity by examining I^2 (Higgins 2002), a quantity which describes approximately the proportion of total variation in effect estimates that is due to true variation in effects between studies. In addition, we planned to employ a Chi^2 test of homogeneity to determine the strength of evidence against the hypothesis that all studies have the same underlying effect size.

Assessment of reporting biases

We planned to draw funnel plots (estimated treatment effects against their standard error). Asymmetry could be due to publication bias, but could also be due to a relationship between trial size and effect size (Egger 1997).

Selective outcome reporting

We addressed the issue of selective outcome reporting by internal evidence within published studies as we could not check the protocols of included studies.

Data synthesis

Where the interventions were the same or similar enough, we planned to synthesise results in a meta-analysis where there was no important clinical heterogeneity.

We planned that studies that investigated the impact of single micronutrient intervention agents would be combined only with other studies of the same micronutrient.

We planned to combine trials that contained two or more micronutrients with trials that contain at least two of the same micronutrients.

If continuous outcomes were measured identically across studies, we planned to calculate an overall mean difference and 95% confidence interval (CI). If the same continuous outcome was measured differently across studies, we planned to calculate an overall standardised mean difference (SMD) and 95% CI.

We planned to include studies with skewed data into the review but not to meta-analyse them with the data from other studies. We planned to present these data separately.

If some primary studies report an outcome as a dichotomous measure and others use a continuous measure of the same construct, we planned to conduct separate meta-analyses (one for relative risks and another for MD/SMDs); thereafter we would introduce a cut-off (with specific rationale) to enable conversion from continuous to dichotomous and conduct another analysis; thirdly, we would convert effect magnitudes from continuous to dichotomous and re-analyse. We planned to discuss any major differences in results, and attempt to explain the reason for the differences (Higgins 2003).

We planned to investigate heterogeneity using I^2 and would use a random-effects model for meta-analysis, even when I^2 was less than 25%. If I^2 was greater than 25% we still planned to conduct a random-effects meta-analysis. If, however, I^2 was greater than 50%, we planned to explore the reasons and decide whether it was appropriate to undertake a meta-analysis.

We would have considered interventions similar if the same micronutrients were administered (chemically the same and possessing similar biologic activity profile) and if the administered dose was within the supplement range, or above the recommended daily requirement for the children within the age group of interest.

Subgroup analysis and investigation of heterogeneity

Depending on the data reported in the included studies, we planned to conduct the following subgroup analyses:

1. the differential impact of studies including children younger than 24 months and those older than 24 months;
2. the differential impact of baseline nutrition status, the incidence of kwashiorkor developing in underweight versus normal weight for age children prior to randomisation;
3. the differential impact of different micronutrient combinations versus placebo;
4. the differential impact of single micronutrient administration versus combined administration.

Sensitivity analysis

We planned to perform sensitivity analyses to explore the influence of adequate allocation concealment and studies where a significant number of the participants were lost to follow up.

RESULTS

Description of studies

Results of the search

We conducted the search for relevant studies for inclusion in the review (see Appendices 1-8 for full details of the search terms and databases searched) on 21 May 2009. The search yielded a total of 164 records after duplicate records were removed using ProCite Reference Manager Software.

Two authors (CO and CA) checked the title and abstract of all records, and identified a total of 11 studies for more detailed consideration. Of these, we deemed only one trial eligible for inclusion (Ciliberto 2005). Two authors (CO and GS) independently extracted data and another author (CA) subsequently compared/verified from the trial report.

Included studies

Ciliberto 2005 was a double blind placebo controlled cluster-randomised trial that evaluated the efficacy of an antioxidant cocktail of all the four micronutrient supplements of interest. The trial was conducted in Malawi. The total trial duration was five months. The study participants were 2372 children from 2156 households aged between 12 and 48 months.

Healthy children were randomised by household to either receive the intervention or placebo. The intervention consisted of daily administration of a citrus flavoured powder containing riboflavin, vitamin E (alpha tocopherol), selenium and NAC. The placebo consisted of a similar-tasting powder with no active ingredient. The children in both groups were to drink the powder daily for 20 weeks, which was the entire trial duration. Follow up was conducted at two-weekly intervals. The researchers assessed the participants for the development of oedema, the primary outcome measure of the trial. This trial reported data for only three outcomes of interest in the review - incidence of kwashiorkor, incidence of hospitalisation and all-cause mortality.

Incidence of kwashiorkor was 3.29% in the intervention group and 1.93% in the control group. Three deaths due to all causes were reported in the intervention group and four in the control group. One of our secondary outcomes was the incidence of hospitalisation; two children were hospitalised, but no information was given as to which group they belonged. The trial did not report any data with regard to cause-specific mortality, incidence of other kwashiorkor-related morbidity like flaky paint dermatosis, abdominal swelling and ascites, psychomotor retardation, and cognitive indices. No economic data were reported. No adverse events (moderate or severe) were reported. See the 'Characteristics of included studies' table.

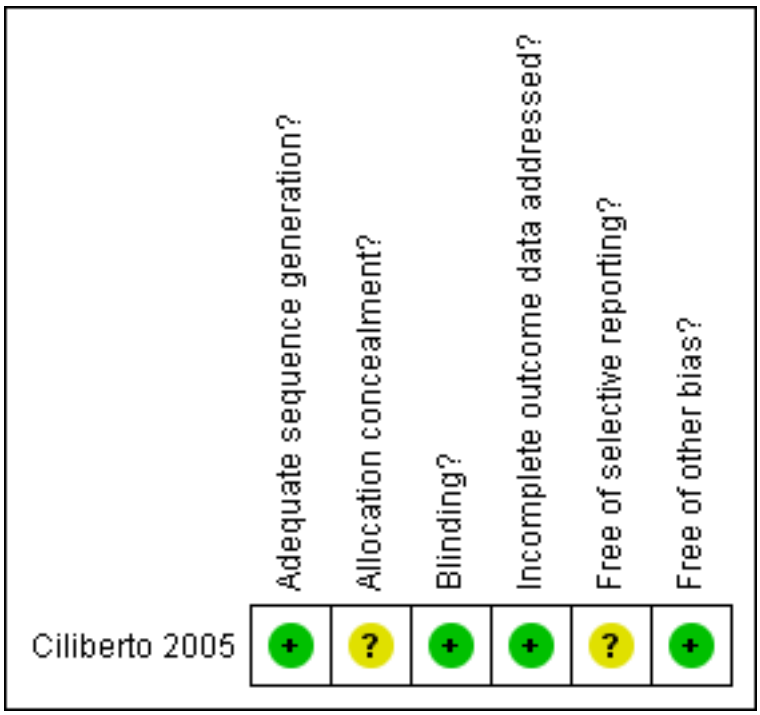
Excluded studies

We excluded the studies in question mainly because they did not address the review question with regard to prevention of kwashiorkor or were not randomised trials. Of the 11 studies that we closely scrutinised, we ultimately excluded 10 for one or both of these reasons. Because these studies did not address the review question we have not provided any further information on them. We identified no ongoing studies that would meet the inclusion criteria for this review.

Risk of bias in included studies

Figure 1

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

1. Sequence generation

Allocation sequence for the included trial was reported as generated by a computerised random number generator. Siblings received data cards with the same letter of allocation, as the unit of randomisation was the household and not the individual child. This method of generating an allocation sequence is likely to produce similar groups at baseline and we consider it adequate. Therefore we have listed the risk of bias as low.

2. Allocation concealment

The trial report clearly stated that all investigators and the caretakers of the participants were blind as to which letters (of allocation) were placebo and which contained antioxidants. However, they do not explicitly state the method used to conceal the allocation. We are therefore unable to judge the appropriateness or otherwise and have rated this as an unclear risk of bias.

Blinding

None of the children, investigators or child caretakers knew to which group a child belonged (either placebo or active powder). We have rated this as having a low risk of bias.

Incomplete outcome data

This study reported 40 children as lost to follow up. This translates to an attrition rate of 1.7%. We have rated this as a low risk of bias.

Selective reporting

We were not able to compare the study report with the protocol, but have no reason to believe the trial report is biased by selective outcome reporting after an appraisal of the study report. However, because we are not able to exhaustively investigate this, we would rate this as an unclear risk of bias

Other potential sources of bias

Funding for the study was obtained from the United States Department of Agriculture/Agricultural Research Service and the Allen Foundation, and the investigators did not report any conflicts of

interest. Furthermore, the sponsors had no role in the design, conduct or reporting of the study.
We also examined the trial report for particular issues that could bias a cluster-randomised trial, namely recruitment bias, baseline imbalance, loss of a whole cluster, and statistical analysis allowing for the cluster design (although they do not explicitly report an intracluster correlation coefficient). We have not identified any other issues that could potentially bias the study.

Effects of interventions

Primary outcome

Effect of a combination of vitamin E, selenium cysteine and riboflavin on incidence of kwashiorkor
Data reported in the one included trial (Ciliberto 2005) showed no statistically significant difference in the incidence of kwashiorkor between the intervention and control groups at 20 weeks (RR 1.70; 95% CI 0.98 to 2.42 using a statistical technique that adjusted for the clustering effect). There was a tendency to a higher incidence in the intervention group (39 children out of 1184 randomised developed kwashiorkor) than in the control group (23 children out of 1188), although this difference was not statistically significant. The confidence interval reported in the table and meta-analysis figure has not taken into consideration the fact that the reported data were from a cluster randomised trial. Our review is based on the confidence interval we have reported above, which has taken this fact into consideration.
We have found no studies which investigated the effect of individual micronutrient supplements.

Secondary outcomes

Kwashiorkor specific mortality
The study reported no data with regard to cause specific mortality.
All cause mortality
The study reported data on the effect of the intervention on all-cause mortality, which although different for the two groups (three children in intervention group versus four children in control group) as not clinically or statistically significant in either case.
Incidence and duration of hospitalisation due to kwashiorkor
A report regarding the incidence of hospitalisation among the trial participants was made (two children were hospitalised), although this was not broken down into the groups to which they had been randomised.
Other kwashiorkor related morbidity
The study reported no data on the effects of the intervention on the other outcomes we were interested in, namely kwashiorkor related morbidity (incidence of flaky paint dermatosis, incidence of abdominal swelling and ascites, incidence of psychomotor retardation).
Adverse events
There were no reported moderate or severe adverse events in either groups.
Economic data
There were no reports of economic data.

DISCUSSION

Summary of main results

This review has found that at present the administration of antioxidant supplements for the primary prevention of kwashiorkor at best has no effect on the incidence of kwashiorkor and all cause mortality.

Overall completeness and applicability of evidence

We are unable to draw any conclusions at this time regarding the applicability or otherwise of this intervention because of the general paucity of evidence from RCT that have attempted to answer this question with which the methods and findings of this trial could be compared.
The question as to the role of excessive free radical activity in the pathogenesis of kwashiorkor is one that has generated a great deal of debate over the last 20 years. More important to stakeholders in middle and low income countries is the question about the potential applicability of this knowledge in the design of an effective prevention strategy that could be applied on a massive scale in middle- and low-income countries, particularly the countries of sub-Saharan Africa.
This review sought to verify the existence of RCT evidence with respect to this issue and to ascertain the direction and strength of this evidence.

Quality of the evidence

Despite an extensive search for both published and unpublished evidence, we only identified and have reported evidence from one large cluster RCT (Ciliberto 2005) with a low risk of bias which attempted to answer this question. This trial randomised 2372 children from 2156 households to receive either a supplement powder containing Vitamin E, selenium, cysteine and riboflavin at a dose well above their recommended dietary requirement or a matched placebo and had the development of kwashiorkor as its main outcome. This trial did not find any statistically significant difference between the incidence of kwashiorkor between the two groups at 20 weeks of follow up. It also did not demonstrate any beneficial effect on all-cause mortality.

Potential biases in the review process

Our review sought any form of randomised trial evidence.We did not find and have not excluded any trials that may have appeared to attempt to answer our review question. We embarked on an extensive search and actually sought the help of individual researchers, funding institutions and research organisations active in the field of malnutrition.

Agreements and disagreements with other studies or reviews

In the light of our findings, the question also remains to be answered if similar supplements could have any clinically beneficial role in the treatment of kwashiorkor. This would still be a relevant question both from the fact that the observational studies that paved the way for the hypothesis of excessive oxidative stress were actually in ill children and also from the point of view that a proof of effectiveness would allow better use of resources towards case management rather than prevention. In the light of this review, one may think that it may also be worthwhile to re-examine the issue that the low levels of antioxidants observed in the earlier studies may be a consequence rather than a cause of kwashiorkor. To the best of our knowledge, no other systematic review has attempted to answer our research question and so we are unable to comment on the aspects of our review that may have agreed or disagreed with their findings.

AUTHORS' CONCLUSIONS

Implications for practice

There is as yet insufficient evidence to support the use of micronutrient supplementation, particularly antioxidant micronutrients, as a tool for prevention of kwashiorkor in susceptible children.

Implications for research

There is a need for other large, well conducted and reported studies that would attempt to assess the effects of antioxidant micronutrients in the primary prevention of kwashiorkor with a view to establishing the existence of a benefit or otherwise of this intervention. The trials should also include some cost effectiveness analysis. Although the included study followed up its participants long enough to demonstrate any clinically meaningful effect, future trials could still consider a longer duration of follow up, as this would in any case either throw up an existing effect which is as yet undetectable or further buttress the fact that indeed no meaningful effect exists.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ciliberto 2005

Methods	Cluster RCT conducted in 8 villages in an area of rural Malawi with a high incidence of kwashiorkor. Unit of randomisation was the household. Trial was conducted for 5 months between November 2003 and March 2004, and follow up was for 20 weeks Computer generated randomisation. Investigators and caregivers were blinded to allocation. 20 week follow up.
Participants	2372 healthy children aged between 12 and 48 months from 2156 Households. Mean ages were 28.2 and 28.5 months in intervention and control groups respectively. Indices of baseline nutrition status were mean and standard deviation of the weight for age in z-scores of the participants (-1.4 and 1.0 respectively in both groups); and the mean and standard deviation of the circumference of middle upper arm in centimetres (14.8 and 1.3 respectively in both groups) Exclusion criteria were the presence of severe chronic illness and oedema at the time of enrolment
Interventions	INTERVENTION GROUP: The intervention consisted of daily administration of a citrus flavoured powder containing 1.8 mg of riboflavin, 23 mg of vitamin E (alpha tocopherol), 55 mcg of selenium and 300 mg of N acetyl cysteine. Intervention was administered at home by the caregiver CONTROL GROUP: The placebo consisted of a similar tasting powder with no active ingredient. The children in both groups were to drink the powder daily for 20 weeks which was the entire trial duration Follow up was conducted at two-weekly intervals in the community by a study team comprising two investigators and two study nurses
Outcomes	Participants were assessed for the development of oedema by compressing the skin over both of the child's fourth metatarsal bones with a firm finger for 10 seconds; and looking for evidence of pitting. Development of oedema was the primary outcome measure of the trial. Secondary outcomes were: • number of deaths due to any cause; • rate of change in weight; • gain in circumference of the mid upper arm and length of the arm; • number of days of fever, cough and diarrhoea.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Allocation sequence for the included trial was generated by a computerised ran-

		dom number generator blocked in groups of 200. These numbers were noted on the cards with which children were randomised. Siblings received data cards with the same letter of allocation as the unit was the household and not the individual child
Allocation concealment?	Unclear risk	It was clearly stated that all investigators and the caretakers of the participants were blind as to which letters (of allocation) were placebo and which contained antioxidants. The authors do not explicitly state the method used to conceal the allocation
Blinding? All outcomes	Low risk	All the investigators (who assessed the outcomes) and child caretakers were blinded as to the content of the allocation (either placebo or active powder) each child had received
Incomplete outcome data addressed? All outcomes	Low risk	40 children were reported to have been lost to follow up. The main reasons for this, where it was known, were family moving from trial location, child not liking the taste of the intervention and carer unable to bring the child for follow up. The reasons were similar in both groups and the number of losses were similar in both groups, both in terms of the clusters and individual children. The authors reported performing an intention-to-treat analysis of the data. They reported outcomes for all the randomised participants in the groups to which they were randomised and measured outcome data in all participants up to the end of the study for most of the participants and up to the last follow up for those who died or were lost to follow up
Free of selective reporting?	Unclear risk	We were not able to compare the study report with the protocol but have no reason to believe the trial report is biased by selective outcome reporting after an appraisal of the study report. However, because we are not able to exhaustively investigate this, we would rate this as an unclear risk of bias
Free of other bias?	Low risk	We identified no particular issues that could bias a cluster RCT namely recruitment bias, baseline imbalance, loss of a

Ciliberto 2005 (*Continued*)

		whole cluster and statistical analysis allowing for the cluster design

DATA AND ANALYSES

Comparison 1. Supplements versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of kwashiorkor	1	2372	Risk Ratio (M-H, Random, 95% CI)	1.70 [1.02, 2.83]
2 Number of deaths due to any cause	1	2372	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.17, 3.36]

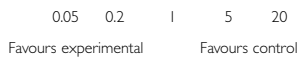
Analysis 1.1. Comparison 1 Supplements versus placebo, Outcome 1 Incidence of kwashiorkor.

Review: Supplementary vitamin E, selenium, cysteine and riboflavin for preventing kwashiorkor in preschool children in developing countries

Comparison: 1 Supplements versus placebo

Outcome: 1 Incidence of kwashiorkor

Study or subgroup	Supplement n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ciliberto 2005	39/1184	23/1188		100.0 %	1.70 [1.02, 2.83]
Total (95% CI)	**1184**	**1188**		**100.0 %**	**1.70 [1.02, 2.83]**
Total events: 39 (Supplement), 23 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.05 (P = 0.041)					
Test for subgroup differences: Not applicable					

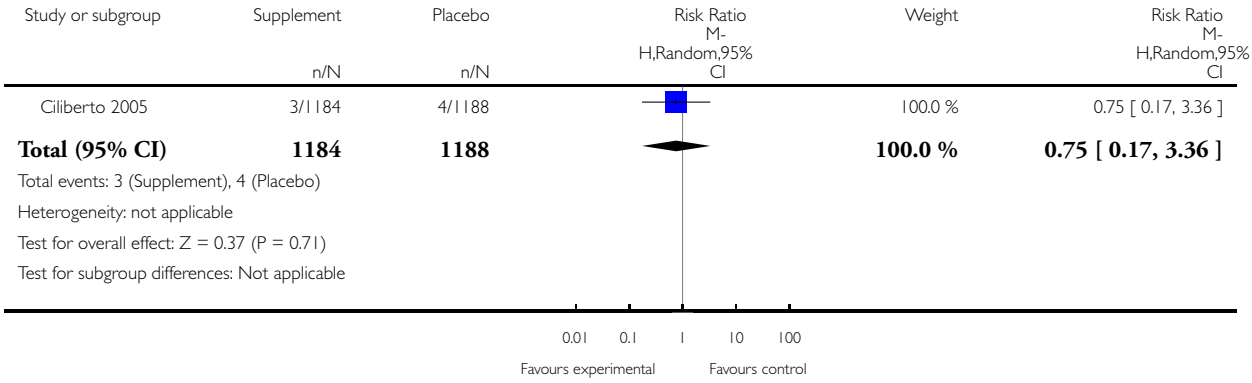


Analysis 1.2. Comparison 1 Supplements versus placebo, Outcome 2 Number of deaths due to any cause.

Review: Supplementary vitamin E, selenium, cysteine and riboflavin for preventing kwashiorkor in preschool children in developing countries

Comparison: 1 Supplements versus placebo

Outcome: 2 Number of deaths due to any cause



APPENDICES

Appendix 1. CENTRAL search strategy

CENTRAL searched via the Cochrane Library 2009 (Issue 2)

#1 MeSH descriptor Kwashiorkor, this term only
#2 kwashiorkor
#3 MeSH descriptor Protein-Energy Malnutrition, this term only
#4 (protein-energy malnutrition) or (protein calor* malnutrition)
#5 MeSH descriptor Infant explode all trees
#6 (child* or boy* or girl* or baby or babies or infant* or toddler* or preschool* or pre-school*)
#7 MeSH descriptor Vitamin E, this term only
#8 MeSH descriptor Selenium, this term only
#9 MeSH descriptor Cysteine, this term only
#10 MeSH descriptor Riboflavin, this term only
#11 vitamin e
#12 selenium
#13 cysteine
#14 cysteinate
#15 half-cystine
#16 half cystine
#17 riboflavin
#18 vitamin b 2
#19 vitamin b2
#20 vitamin g

#21 n-acetylcysteine
#22 (#1 OR #2 OR #3 OR #4)
#23 (#5 OR #6)
#24 (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21)
#25 (#22 AND #24 AND #24)

Appendix 2. MEDLINE search strategy

MEDLINE searched via OVID 1955 to May 2009

1 child, preschool/ or infant/
2 (child$ or boy$ or girl$ or baby or babies or infant$ or toddler$ or preschool$ or pre-school$).tw.
3 1 or 2
4 Vitamin E/
5 Selenium/
6 Cysteine/
7 Riboflavin/
8 vitamin e.tw.
9 selenium.tw.
10 cysteine.tw.
11 cysteinate.tw.
12 half-cystine.tw.
13 half cystine.tw.
14 riboflavin.tw.
15 vitamin b 2.tw.
16 vitamin b2.tw.
17 vitamin g.tw.
18 n-acetylcysteine.tw.
19 6 or 11 or 7 or 9 or 17 or 12 or 15 or 14 or 8 or 4 or 18 or 16 or 13 or 10 or 5
20 Kwashiorkor/
21 kwashiorkor$.tw.
22 Protein-Energy Malnutrition/
23 (protein-energy malnutrition or protein calor$ malnutrition).tw.
24 22 or 21 or 23 or 20
25 3 and 24 and 19

Appendix 3. EMBASE search strategy

EMBASE searched via OVID 1980 to 2009 week 20

1 child, preschool/ or infant/
2 (child$ or boy$ or girl$ or baby or babies or infant$ or toddler$ or preschool$ or pre-school$).tw.
3 1 or 2
4 Vitamin E/
5 Selenium/
6 Cysteine/
7 Riboflavin/
8 vitamin e.tw.
9 selenium.tw.
10 cysteine.tw.
11 cysteinate.tw.
12 half-cystine.tw.
13 half cystine.tw.
14 riboflavin.tw.

15 vitamin b 2.tw.
16 vitamin b2.tw.
17 vitamin g.tw.
18 n-acetylcysteine.tw.
19 6 or 11 or 7 or 9 or 17 or 12 or 15 or 14 or 8 or 4 or 18 or 16 or 13 or 10 or 5
20 Kwashiorkor/
21 kwashiorkor$.tw.
22 Protein Calorie Malnutrition/
23 (protein-energy malnutrition or protein calor$ malnutrition).tw.
24 22 or 21 or 23 or 20
25 3 and 24 and 19

Appendix 4. CINAHL search strategy

CINAHL searched via EBSCO 1982 to May 2009

S26 S5 and S9 and S25

S25 S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24

S24 n-acetylcysteine

S23 vitamin g

S22 vitamin b2

S21 vitamin b 2

S20 riboflavin

S19 half cystine

S18 half-cystine

S17 cysteinate

S16 cysteine

S15 selenium

S14 vitamin e

S13 (MH "Riboflavin")

S12 (MH "Cysteine")

S11 (MH "Selenium")

S10 (MH "Vitamin E")

S9 S7 or S8

S8 (child* or boy* or girl* or baby or babies or infant* or toddler* or preschool* or pre-school*)

S7 (MH "Infant")

S6 (MH "Child, Preschool")

S5 (S1 or S2 or S3 or S4)

S4 (protein-energy malnutrition) or (protein calor* malnutrition)

S3 (MH "Protein-Energy Malnutrition")

S2 kwashiorkor

S1 (MH "Kwashiorkor")

Appendix 5. LILACS search strategy

LILACS (searched via BIRME 1982 to May 2009)
(kwashiorkor or protein energy malnutrition or protein calorie malnutrition) [Key Word] and (child$ or boy$ or girl$ or baby or babies or infant$ or toddler$ or preschool$ or pre-school$) [Key Word] and (vitamin e or selenium or cysteine or cysteinate or half-cystine or hald cystine or riboflavin or vitamin b2 or vitamin g) [Key Word]

Appendix 6. Meta Register of Controlled Trials & Dissertation Abstracts search strategy

MetaRegister of Controlled Trials and Dissertation Abstracts (both searched May 2009)
SEARCH TERMS USED:
kwashiorkor or protein energy malnutrion or protein calorie malnutrition
NB. Dissertation Abstracts was searched via Dissertation Express

Appendix 7. Open Sigle search strategy

OpenSIGLE (searched May 2009)
SEARCH TERSM USED:
((kwashiokor or "protein energy malnutrition" or "protein calorie malnutrition") AND ("vitamin e" or selenium or cysteine or cysteinate or "half cystine" or riboflavin or "vitamin b2" or "vitamin g"))

Appendix 8. African Index Medicus search strategy

African Index Medicus (searched May 2009)
(kwashiorkor or protein energy malnutrition or protein calorie malnutrition) [Key Word] and (child$ or boy$ or girl$ or baby or babies or infant$ or toddler$ or preschool$ or pre-school$) [Key Word] and (vitamin e or selenium or cysteine or cysteinate or half-cystine or hald cystine or riboflavin or vitamin b2 or vitamin g) [Key Word]

CONTRIBUTIONS OF AUTHORS

Chibuzo Odigwe conceived the review question and wrote the protocol with assistance from Drs Chiedozie Anyanechi, Geir Smedslund, Regina Ejemot-Nwadiaro and Professor Michael Krawinkel.

Professor Geraldine Macdonald and Dr Jane Dennis provided assistance from the Cochrane Developmental Psychosocial and Learning Problems Group editorial base.

Drs Phil Wiffen and Sally Hopewell from the UK Cochrane Centre provided methodological support.

Jo Abbott (TSC, CDPLPG) and Anne Eisinga (Information Specialist, UK Cochrane Centre) ran the searches, and Chibuzo Odigwe and Chiedozie Anyanechi vetted the results in pairs.

Chibuzo Odigwe assessed studies for eligibility, extracted data and entered into RevMan 5.0 in pairs Geir Smedslund, Chiedozie Anyanechi and Regina Ejemot Nwadiaro checked data entry. Chibuzo Odigwe and Geir Smedslund wrote the final review with contribution from all the authors.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Insitute of Tropical Disease Research and Prevention, University of Calabar Teaching Hospital, Nigeria.

IT and Logistics Support

- College of Medical Sciences, University of Calabar, Nigeria.

Logistics support

- Federal Medical Centre, Umuahia, Nigeria.

Logistics Support

- Norweigian Knowledge Centre for the Health Services, Oslo, Norway.
- Justus Liebig University, Giessen, Germany.

External sources

- UK Cochrane Centre, Oxford, UK.

Mentorship, Training, IT, and Logistics

- Aubrey Sheiham Public Health and Primary Care Scholarship, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Antioxidants [*administration & dosage]; Cysteine [*administration & dosage]; Kwashiorkor [*prevention & control]; Micronutrients [administration & dosage]; Riboflavin [*administration & dosage]; Selenium [*administration & dosage]; Vitamin E [*administration & dosage]

MeSH check words

Child, Preschool; Humans; Infant