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Vitamin A supplementation in infants 1–5 months of age

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Contents

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Financial support

WHO thanks the Government of Luxembourg for providing financial support for this work.

WHO Guideline[1]

Vitamin A supplementation in infants 1–5 months of age

Summary

Vitamin A deficiency affects about 19 million pregnant women and 190 million preschool-age children, mostly from the World Health Organization (WHO) regions of Africa and South-East Asia. Infants and children have increased vitamin A requirements to support rapid growth and to help them combat infections. Member States have requested guidance from WHO on the effects and safety of vitamin A supplementation in infants 1–5 months of age as a public health strategy in support of their efforts to achieve the Millennium Development Goals.

WHO has developed the present evidence-informed recommendation using the procedures outlined in the *WHO handbook for guideline development*. The steps in this process included: (i) identification of priority questions and outcomes; (ii) retrieval of the evidence; (iii) assessment and synthesis of the evidence; (iv) formulation of recommendations, including future research priorities; and (v) planning for dissemination, implementation, impact evaluation and updating of the guideline. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was followed to prepare evidence profiles related to preselected topics, based on up-to-date systematic reviews. An international, multidisciplinary group of experts participated in two WHO technical consultations, held in Geneva, Switzerland, on 19–20 October 2009 and 16–18 March 2011, to review and discuss the evidence and draft recommendation, and to vote on the strength of the recommendation, taking into consideration: (i) desirable and undesirable effects of this intervention; (ii) the quality of the available evidence; (iii) values and preferences related to the intervention in different settings; and (iv) the cost of options available to health-care workers in different settings. All guideline group members completed a Declaration of Interests Form before each meeting. An External Experts and Stakeholders Panel was involved throughout the process.

Vitamin A supplementation in infants 1–5 months of age is not recommended as a public health intervention for the reduction of infant morbidity and mortality (strong recommendation). The quality of the available evidence was found to be moderate for infant mortality and the side-effect of bulging fontanelles, whereas for other critical outcomes it was low. Mothers should continue to be encouraged to exclusively breastfeed infants for the first 6 months to achieve optimal growth, development and health.

[1] This publication is a WHO guideline. A WHO guideline is any document, whatever its title, containing WHO recommendations about health interventions, whether they be clinical, public health or policy interventions. A recommendation provides information about what policy-makers, health-care providers or patients should do. It implies a choice between different interventions that have an impact on health and that have ramifications for the use of resources. All publications containing WHO recommendations are approved by the WHO Guidelines Review Committee.

Scope and purpose

This guideline provides global, evidence-informed recommendations on the use of vitamin A supplements in infants and children 1–5 months of age for the reduction of morbidity and mortality.

The guideline will help Member States and their partners in their efforts to make informed decisions on the appropriate nutrition actions to achieve the Millennium Development Goals, in particular, reduction in child mortality (MDG 4). The guideline is intended for a wide audience including policy-makers, their expert advisers, and technical and programme staff in organizations involved in the design, implementation and scaling-up of nutrition actions for public health.

This document presents the key recommendation and a summary of the supporting evidence. Further details of the evidence base are provided in Annexes 1 and 2 and other documents listed in the references.

Background

Vitamin A deficiency is a major public health problem affecting an estimated 19 million pregnant women and 190 million preschool-age children, mostly from the World Health Organization (WHO) regions of Africa and South-East Asia (*1*). Infants and young children have increased vitamin A requirements to support rapid growth and to help combat infections. The vitamin A status of young infants is influenced by their liver stores of vitamin A at birth, consumption of vitamin A from breast milk and other foods, and losses due to infection, including those caused by parasites (*2*). Generally, infants are born with low liver stores of vitamin A, even when the mother has an adequate store of vitamin A (*3*). In low- and middle-income countries, infants are likely to receive inadequate amounts of vitamin A, partly due to the low vitamin A concentrations in breast milk, which is related to poor maternal nutritional status. Inadequate intakes of vitamin A at this age may lead to vitamin A deficiency which, when severe, can cause visual impairment (night blindness), anaemia, weakened resistance to infections, and can also increase the risk of illness and death from childhood infections such as measles and those causing diarrhoea (*4*).

In countries where vitamin A deficiency is a public health problem, programmes providing high-dose vitamin A supplements to children 6–59 months of age are being implemented as part of their child survival strategy, reaching 71% of this population in developing countries (*5*). In order to address the major proportion of childhood deaths under the age of 5 years, infants less than 6 months of age should be targeted in infant survival strategies. In the past, universal distribution of vitamin A supplements (50 000 IU) was recommended for non-breastfed infants less than 6 months of age and breastfed infants less than 6 months of age whose mothers did not receive postpartum vitamin A supplementation (*6*). Thus far, individual studies of single or multiple vitamin A supplementation regimens in infants 1–5 months of age have reported little effect on serum retinol concentrations and no effect on mortality, whether or not the vitamin is given alongside immunization (*7–9*).

For infants less than 6 months of age, there is substantial evidence that a dose of up to 50 000 IU of vitamin A is safe (*10*). Acute side-effects are transient and include bulging fontanelles (the most frequently reported), vomiting, diarrhoea, loss of appetite and irritability. Some studies suggest that higher rates of acute side-effects are seen when vitamin A is given concurrently with the diphtheria/tetanus/pertussis (DTP) vaccine, especially with the third dose of DTP (*8, 10*). Bulging of fontanelles after administration of a vitamin A supplement is a reflection of transient increase in cerebrospinal fluid volume; however, this has no significant effect on intracranial pressure in the vast majority and spontaneously resolves within 72 hours of dosing.

Summary of evidence

One systematic review (*11*) has evaluated the effects and safety of vitamin A supplementation in infants 6 months of age or less in low- and middle-income countries with regard to prevention of morbidity and mortality. It included a subgroup analysis by age at initiation of supplementation (post-neonatal period of 1–6 months of age). The review showed no significant effect of vitamin A supplementation in infants 6 months of age or less on the risk of mortality in the first year of life, but it showed an increase in the risk of developing bulging fontanelles. Analysis of data from three trials in which vitamin A supplementation was initiated between 1 and 6 months of age showed no effect on all-cause mortality as compared with controls (risk ratio (RR) 1.05; 95% confidence interval (CI) 0.84–1.32). The remaining analyses were conducted in all infants 0–6 months of age. There appears to be no significant effect of vitamin A supplementation on mortality or morbidity due to diarrhoea or acute respiratory infections in the first year of life. There is no effect of vitamin A supplementation on all-cause mortality, when given as a cumulative dose of either 50 000 IU or less or more than 50 000 IU, regardless of the status of maternal postpartum vitamin A supplementation. The 10 trials (six of which provided supplements in the post-neonatal period) that provided data on bulging fontanelles following any (first, second or third) dose of vitamin A showed an increased risk of this side-effect (RR 1.55; 95% CI 1.05–2.28). Few trials reported data on other adverse effects, such as vomiting, irritability, diarrhoea and fever, none of which were significant.

WHO performed additional meta-analyses that included only those studies in which infants 1–5 months of age were given supplements (Annex 1). There was no significant effect of vitamin A supplementation on mortality in the first year of life related to diarrhoea (two trials: RR 1.05; 95% CI 0.76–1.46) or respiratory infections (two trials: RR 1.20; 95% CI 0.85–1.68). Additionally, there was no significant effect of vitamin A supplementation on morbidity in the first year of life related to diarrhoea (two trials: RR 0.99; 95% CI 0.94–1.04) or respiratory infections (one trial: RR 1.06; 95% CI 0.96–1.16). There was a significant increase in the occurrence of bulging fontanelles after any dose (first, second or third) of vitamin A (six trials: RR 2.53; 95%

CI 1.27–5.03), and one trial reported a significant decrease in vomiting (RR 0.31; 95% CI 0.17–0.58). There was no effect on fever, irritability or diarrhoea as side-effects of the intervention.

The overall quality of the available evidence with regard to mortality during infancy and the side-effect of bulging fontanelles was moderate and for the other outcomes it was low (Annex 2).

The effects of vitamin A supplementation on seroconversion rates to the three poliovirus types (types 1, 2 and 3) was also recently reviewed (*12*). A meta-analysis of three trials indicated no difference in response to the polio vaccine (specific antibody titres or seroconversion rates) when vitamin A supplements or placebo were given between 1 and 5 months of age concurrently with the oral polio vaccine (OPV). Limited data indicate that vitamin A supplementation does not affect the tetanus or pertussis vaccine response, but may increase the antibody response to diphtheria vaccination. This review also addressed the effect of co-administering vitamin A with vaccines on mortality and other adverse events. A meta-analysis of five trials revealed no significant effect of receiving vitamin A supplements with the DTP vaccine on subsequent mortality (five trials: odds ratio 1.05; 95% CI 0.82–1.36) (*13*).

Recommendation

Vitamin A supplementation in infants 1–5 months of age is not recommended as a public health intervention for the reduction of morbidity and mortality (*strong recommendation*[1]).

Remarks

- This guideline replaces previous recommendations on vitamin A supplementation for the prevention of vitamin A deficiency, xerophthalmia and nutritional blindness in infants and children less than 6 months of age (*6*).
- The effects of vitamin A supplements on infants 1–5 months of age do not vary by maternal exposure to vitamin A, whether the supplement is given as a single dose or in multiple doses, or by timing of the intervention (when given alongside DTP/polio vaccine or independent of them).

[1] A strong recommendation is one for which the guideline development group is confident that the desirable effects of adherence outweigh the undesirable effects. The recommendation can be either in favour of or against an intervention. Implications of a strong recommendation for patients are that most people in their situation would desire the recommended course of action and only a small proportion would not. For clinicians the implications are that most patients should receive the recommended course of action and that adherence to this recommendation is a reasonable measure of good-quality care. With regard to policy-makers, a strong recommendation means that it can be adapted as a policy in most situations.

- Assessment of vitamin A status in the first 6 months of life is complicated by the generally lower serum retinol concentrations of infants at this age. Once guidelines for the interpretation of available indicators of vitamin A status have been developed for infants less than 6 months of age, the effect of vitamin A supplementation on the prevention of vitamin A deficiency and/or the improvement of vitamin A status in infants from low- and middle-income countries where vitamin A deficiency is endemic should be evaluated.

- Mothers should be encouraged to exclusively breastfeed their infants for the first 6 months of age to achieve optimal growth, development and health (*14*).

- Recommendations for the treatment of xerophthalmia and the use of vitamin A supplements during episodes of measles are not covered in this guideline. Existing guidelines on the treatment of xerophthalmia and measles in infants less than 6 months of age should be referred to in these cases (*6, 12*).

Dissemination

The current guideline will be disseminated through electronic media such as slide presentations, CD-ROMs and the World Wide Web, either through the WHO Micronutrients and United Nations Standing Committee on Nutrition (SCN) mailing lists or the WHO nutrition web site. Currently, the WHO Department of Nutrition for Health and Development is developing the WHO electronic Library of Evidence for Nutrition Actions (eLENA). This library aims to compile and display WHO guidelines related to nutrition, along with complementary documents such as systematic reviews and other evidence informing the guidelines, biological and behavioural rationales, and additional resources produced by Member States and global partners.

Implications for future research

- There is limited information on infants born to mothers living in populations with a high prevalence of clinical vitamin A deficiency (e.g. night blindness). If additional studies are conducted, they should be done so under careful surveillance, be appropriately powered to assess morbidity and mortality outcomes, and should include an assessment of the interactions between vitamin A (deficiency, status and/or supplementation) and immune function.

- Assessment of retinol status in the first 6 months of life is complicated by the generally lower serum concentrations of infants at this age. The serum retinol cut-off to define deficiency may need to be lowered from 0.70 µmol/l or lower and the modified relative dose response (MRDR) ratio cut-off may need to be raised from 0.06 or higher. Further research is needed to determine the appropriate cut-offs for the indicators in this age group.

Guideline development process

This guideline was developed in accordance with the World Health Organization evidence-informed guideline development procedures, as outlined in the *WHO handbook for guideline development* (*15*).

Advisory groups

A WHO/United Nations Children's Fund (UNICEF) Steering Committee for Guidelines on Vitamin A Supplementation was established in 2009 with representatives from the WHO departments of Child and Adolescent Health and Development; Immunizations, Vaccines and Biologicals; Making Pregnancy Safer; Nutrition for Health and Development; Reproductive Health and Research; and the Nutrition Section of UNICEF (Annex 3). The Steering Committee guided the development of this guideline and provided overall supervision of the guideline development process. Two additional groups were formed: an advisory guideline group and an External Experts and Stakeholders Panel.

The Vitamin A Supplementation Guideline Group included experts from various WHO expert advisory panels and those identified through open calls for specialists, taking into consideration a balanced gender mix, multiple disciplinary areas of expertise and representation from all WHO regions (Annex 4). Efforts were made to include content experts, methodologists, representatives of potential stakeholders (such as managers and other health professionals involved in the health-care process) and consumers. Representatives of commercial organizations may not be members of a WHO guideline group. The role of the guideline group was to advise WHO on the choice of important outcomes for decision-making and the interpretation of the evidence.

The External Experts and Stakeholders Panel was consulted on the scope of the document, the questions addressed, and the choice of important outcomes for decision-making, as well as with regard to review of the completed draft guideline (Annex 5). This was done through the WHO Micronutrients and SCN mailing lists, which together include over 5500 subscribers, and through the WHO nutrition web site.

Scope of the guideline, evidence appraisal and decision-making

An initial set of questions (and the components of the questions) to be addressed in the guideline was the critical starting point for formulating the recommendation; the questions were drafted by technical staff at the Micronutrients Unit, Department of Nutrition for Health and Development, in collaboration with the Nutrition Section of UNICEF, based on policy and programme guidance needs of Member States and their partners. The population, intervention, control, outcomes (PICO) format was used (Annex 6). The questions were discussed and reviewed by the Steering Committee and feedback was received from 45 stakeholders.

The first guideline group meeting was held on 19–20 October 2009 in Geneva, Switzerland, to finalize the scope of the questions and rank the critical outcomes and populations of interest. The guideline group members discussed the relevance of

each of the questions and modified them as needed. They scored the relative importance of each outcome from 1 to 9 (where 7–9 indicated that the outcome was critical for a decision, 4–6 indicated that it was important and 1–3 indicated that it was not important). The final key question on vitamin A supplementation in infants 1–5 months of age, along with the outcomes that were identified as critical for decision-making, are listed in PICO format in Annex 6.

The Cochrane Collaboration was commissioned to search, review and generate systematic reviews, evidence profiles and the "Summary of findings" table[1] (Annex 2). One review on vitamin A supplementation in infants 6 months of age or less was prepared, and the up-to-date Review Manager Software (RevMan) file, obtained from the Cochrane Editorial Unit, was customized to reflect the critical outcomes previously identified (outcomes not relevant to this guideline were excluded). The RevMan file was exported to the GRADE profiler software in order to prepare evidence summaries according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for assessing the overall quality of the available evidence (*16*) (Annex 2). GRADE considers: the study design; the limitations of the studies in terms of their conduct and analysis; the consistency of the results across the available studies; the directness (or applicability and external validity) of the evidence with respect to the populations, interventions and settings where the proposed intervention may be used; and the precision of the summary estimate of the effect.

Both the systematic review and the GRADE evidence profiles for each of the critical outcomes were used for drafting the guideline. A second guideline group meeting was held on 16–18 March 2011, in Geneva, Switzerland, to review the evidence, discuss the draft recommendation, and to determine its strength, taking into consideration: (i) desirable and undesirable effects of this intervention; (ii) the quality of the available evidence; (iii) values and preferences related to the intervention in different settings; and (iv) the cost of options available to health-care workers in different settings (Annex 7). Consensus was defined as agreement by simple majority of the guideline group members. WHO staff present at the meeting as well as other external technical experts involved in the collection and grading of the evidence were not allowed to vote. There were no strong disagreements among the group members.

The External Experts and Stakeholders Panel was again consulted on the draft guideline. Feedback was received from 12 stakeholders. WHO staff then finalized the recommendation and submitted it for clearance by WHO before publication.

[1] As part of the Cochrane pre-publication editorial process, reviews are commented on by external peers (an editor and two referees external to the editorial team) and the group's statistical adviser (http://www.cochrane.org/cochrane-reviews). The *Cochrane handbook for systematic reviews of interventions* describes in detail the process of preparing and maintaining Cochrane systematic reviews on the effects of health-care interventions.

Management of conflicts of interest

According to the rules in the WHO *Basic documents* (*17*), all experts participating in WHO meetings must declare any interest relevant to the meeting prior to their participation. The conflicts of interest statements for all guideline group members were reviewed by the responsible technical officer and the relevant departments before finalization of the group composition and invitation to attend a guideline group meeting. All guideline group members and participants of the guideline development meetings submitted a Declaration of Interests Form along with their curriculum vitae before each meeting. In addition, they verbally declared potential conflicts of interest at the beginning of each meeting. The procedures for management of conflicts of interests strictly followed the WHO *Guidelines for declaration of interests (WHO experts)* (*18*). The potential conflicts of interest declared by members of the guideline group are summarized below.

- Professor Michael Clarke declared being Director of the UK Cochrane Centre and a member of The Cochrane Collaboration. Professor Clarke was not personally involved in the preparation or management of the systematic reviews on vitamin A supplementation used for this guideline, although some of his colleagues were involved.
- Dr Jean Humphrey declared that her research unit received research grants from 1996 to 2009 for the Zimbabwe Vitamin A for Mothers and Babies Project (ZVITAMBO) from various organizations, including the Nestlé Foundation, BASF and the Pediatric AIDS Foundation, which receives its core funds from various organizations including Johnson & Johnson and the Abbott Fund. Sub-studies were also supported by Support for Analysis and Research in Africa (SARA) and Linkages Projects, both managed by the Academy for Educational Development (AED). To our knowledge, other than BASF, none of these companies nor their commercial sponsors directly or indirectly produce vitamin A supplements.
- Dr Charles Stephensen declared receiving research funds from WHO for the conduct of a human study on the efficacy of newborn vitamin A supplementation in improving immune function and from the United States National Institutes of Health for the conduct of studies on vitamin A and immune function in mice.
- Dr Sherry Tanumihardjo declared receiving remuneration as a technical consultant for the International Atomic Energy Agency (IAEA) and an honorarium from HarvestPlus. She also received research support from: HarvestPlus for a vitamin A efficacy study in Zambian children fed orange maize and for a banana study in gerbils to determine the vitamin A value of pro-vitamin A carotenoids; the United States National Institutes of Health for developing a 13C retinol isotope dilution test; the United States Department of Agriculture (USDA) for the use of α-retinol as a chylomicron tag in rats and

pigs; and WHO for mechanistic studies to understand neonatal vitamin A supplementation using the sow-piglet dyad model. In addition, she received reimbursement for travel expenses from IAEA, HarvestPlus and WHO to attend meetings. To our knowledge, neither HarvestPlus nor its commercial sponsors directly or indirectly produce vitamin A supplements.

External resource persons were invited to the meetings as observers and to provide technical input, but they did not participate in the decision-making processes.

Plans for updating the guideline

The recommendations in this guideline will be reviewed in 2016. If new information is available at that time, a guideline review group will be convened to evaluate the new evidence and revise the recommendation. The Department of Nutrition for Health and Development at the WHO headquarters in Geneva, along with its internal partners, will be responsible for coordinating the guideline update following formal *WHO handbook for guideline development* (*15*) procedures. WHO welcomes suggestions regarding additional questions for evaluation in the guideline when it is due for review.

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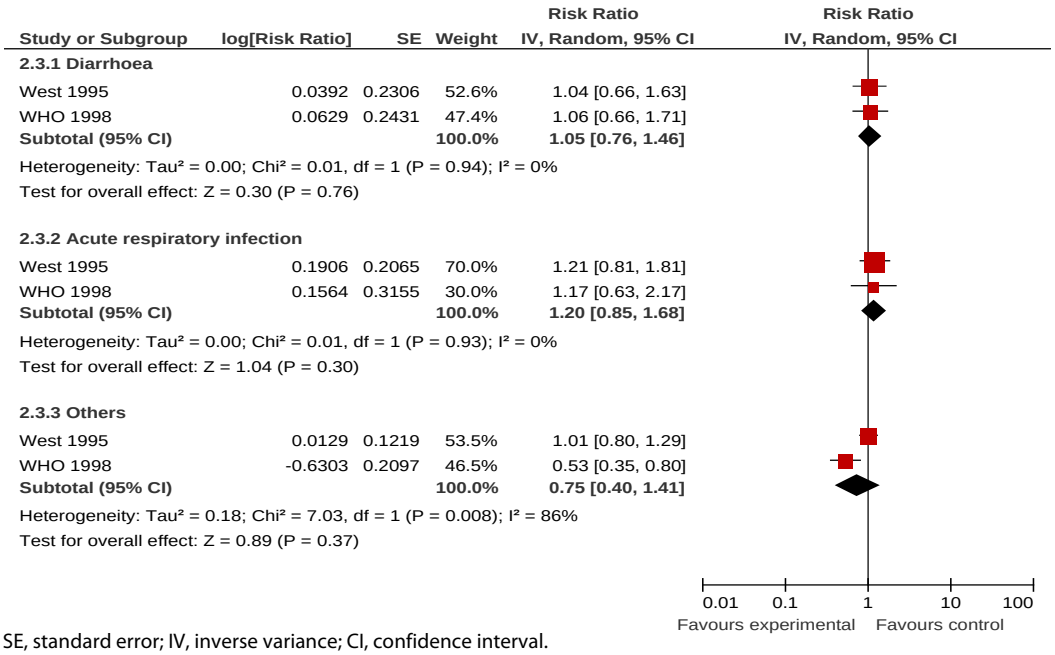
Annex 1 Additional analyses

Figure A.1

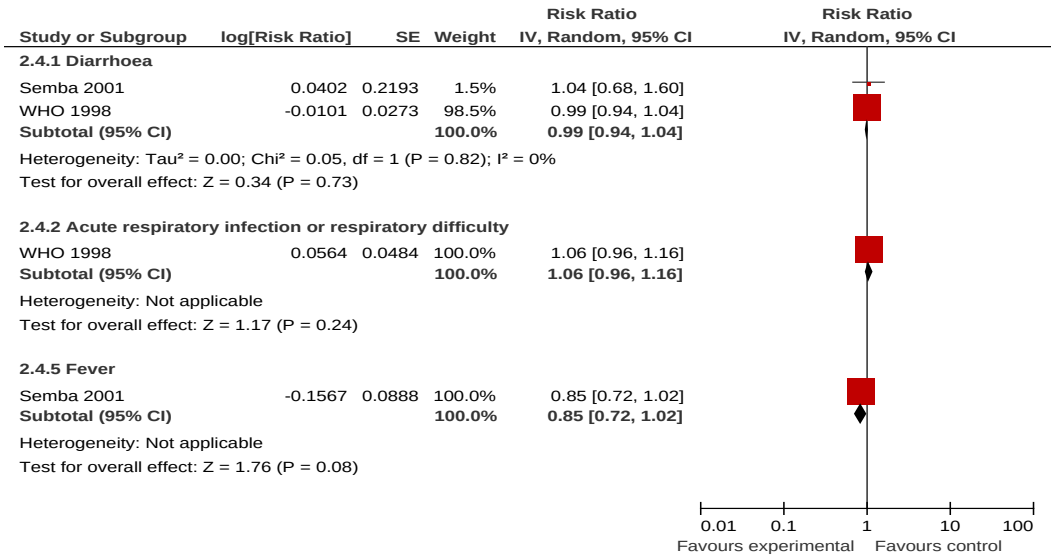
Forest plot of cause-specific mortality in the first year of life among infants given vitamin A supplements at 1–5 months of age



SE, standard error; IV, inverse variance; CI, confidence interval.
For details of studies included in the review, see reference (*11*).

Figure A.2

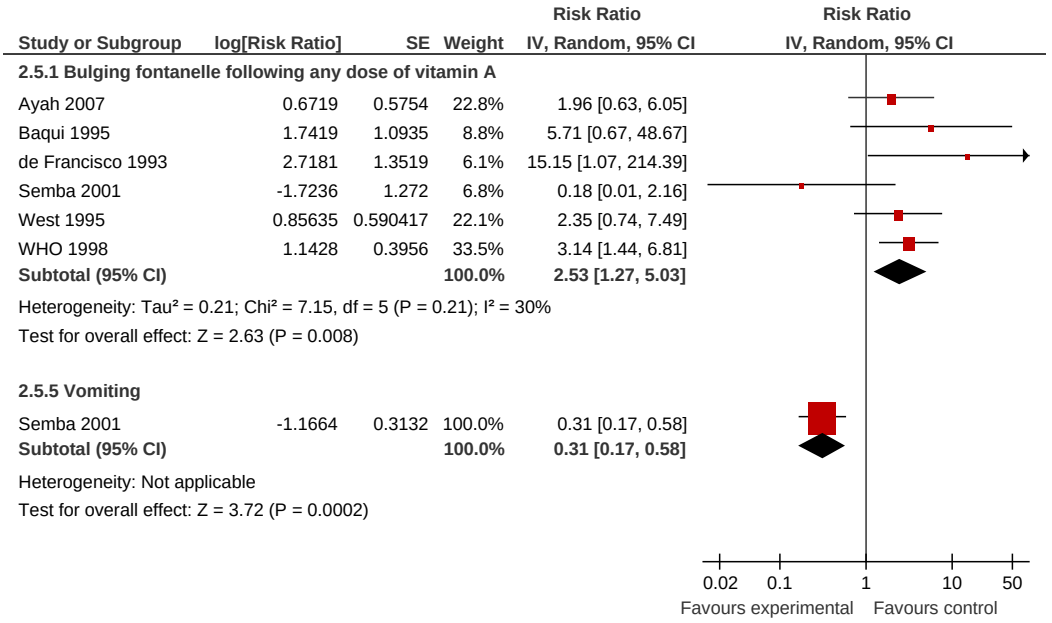
Forest plot of cause-specific mortality in the first year of life among infants given vitamin A supplements at 1–5 months of age



SE, standard error; IV, inverse variance; CI, confidence interval.
For details of studies included in the review, see reference (*11*).

Figure A.3

Forest plot of adverse effects of vitamin A supplements given to infants 1–5 months of age, in the first year of life



SE, standard error; IV, inverse variance; CI, confidence interval.
For details of studies included in the review, see reference (*11*).

Annex 2 GRADE "Summary of findings" table

Vitamin A supplementation in infants 1–5 months of age

Patient or population: Infants 1–5 months of age
Settings: Low- and middle-income countries
Intervention: Vitamin A supplementation

Outcomes	Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)*	Comments
Mortality in the first year of life (supplementation between 1 and 5 months) Follow-up: 6–9 months	**RR 1.05** (0.84–1.32)	20 537 (3 studies)	⨁⨁⨁⊖ **moderate**[1,2]	
Respiratory-related infant mortality in the first year of life (supplementation between 1 and 5 months) Follow-up: 6–9 months	**RR 1.20** (0.85–1.68)	21 342 (2 studies)	⨁⨁⨁⊖ **moderate**[3,4]	
Diarrhoea-related infant mortality in the first year of life (supplementation between 1 and 5 months) Follow-up: 6–9 months	**RR 1.05** (0.76–1.46)	21 342 (2 studies)	⨁⨁⊖⊖ **low**[4,5]	
Measles-related infant mortality in the first year of life (supplementation between 1 and 5 months)	Not estimable	0 (0 studies)		None of the studies reported on this outcome

CI, confidence interval; RR, risk ratio.
* GRADE Working Group grades of evidence:
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We have moderate confidence in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.
[1] The confidence intervals include both a reduction in the risk of all-cause mortality of 16% and an appreciable increase in the risk of mortality of 32%.
[2] Two studies were at an unclear risk of selection bias due to insufficient reporting (Newton 2005, West 1995: allocation generation and concealment). However, this was not considered to pose a serious bias for this outcome (unlikely risk of high bias – lack of clarity primarily due to inadequate reporting with intervention and control arms being reasonably balanced for confounders likely to influence mortality estimates). All trials had a low risk of bias for blinding. One small trial (Newton 2005) was at high risk of bias for incomplete outcome data reporting. Selective outcome reporting was not considered to pose a risk of bias for this outcome. The weighting of the trial (Newton 2005) with the highest risk of bias on one or more key domains was 1.6%. Thus overall, the data were not considered to have serious limitations of design.
[3] The 95% confidence intervals around the pooled effect estimate include both (i) no effect and (ii) appreciable benefit or appreciable harm.
[4] One study was at an unclear risk of selection bias due to insufficient reporting (West 1995: allocation generation and concealment). However, this was not considered to pose a serious bias for this outcome (unlikely risk of high bias – lack of clarity primarily due to aspects of reporting, with intervention and control arms being reasonably balanced for confounders likely to influence mortality estimates). Both trials had a low risk of bias for blinding. Selective outcome reporting was not considered to pose a risk of bias for this outcome. Thus overall, the data were not considered to have serious limitations of design.
[5] The 95% confidence intervals around the pooled effect estimate include both appreciable benefit and appreciable harm.

(Continued overleaf)

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Vitamin A supplementation in infants 1–5 months of age

Patient or population: Infants 1–5 months of age
Settings: Low- and middle-income countries
Intervention: Vitamin A supplementation

Outcomes	Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)*	Comments
Respiratory-related infant morbidity in the first year of life (supplementation between 1 and 5 months) Follow-up: 4–12 months	**RR 1.06** (0.96–1.16)	9424 (1 study)	⨁⨁⊖⊖ **low**[1]	Only one study reported on this outcome
Diarrhoea-related infant morbidity in the first year of life (supplementation between 1 and 5 months) Follow-up: 2–12 months	**RR 0.99** (0.94–1.04)	9891 (2 studies)	⨁⨁⊖⊖ **low**[2,3]	
Adverse effects of vitamin A supplementation: bulging fontanelles following any dose of vitamin A	**RR 2.53** (1.27–5.03)	22 731 (6 studies)	⨁⨁⨁⊖ **moderate**[4,5]	
Adverse effects of vitamin A supplementation: vomiting	**RR 0.31** (0.17–0.58)	467 (1 study)	⨁⨁⊖⊖ **low**[6]	Only one study reported on this outcome

CI, confidence interval; RR, risk ratio.
* GRADE Working Group grades of evidence:
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We have moderate confidence in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.
[1] Only one of the studies contributing data was included. Selective reporting bias cannot be excluded.
[2] One study (WHO 1998) described an adequate sequence generation and had adequate allocation concealment. For the other study there was a high risk of selection bias. Blinding was adequately reported in both studies. One study (Semba 2001) was at high risk of attrition bias and at risk of selective reporting. Only the first study (WHO 1998) was considered to be free of other sources of bias.
[3] Only two of the studies contributing data were included. Selective reporting bias cannot be excluded.
[4] Three studies (de Francisco 1993, Semba 2001, West 1995) had unclear sequence generation and unclear or inappropriate allocation concealment. For the remaining studies there was a low risk of selection bias. Blinding was adequately reported in all studies. Three studies (Baqui 1995, de Francisco 1993, Semba 2001) were at high risk of attrition bias, and only one study (WHO 1998) was free of selective reporting bias. Only one study (WHO 1998) was judged to be free of other biases.
[5] Two studies (de Francisco 1993, WHO 1998) found a statistically significant increase in the risk of bulging fontanelles after vitamin A supplementation when compared with placebo.
[6] The study had unclear sequence generation, unclear allocation concealment, and was at high risk of attrition bias and at risk of selective reporting.

For details of studies included in the review, see reference (*11*)

Annex 3 Members of the WHO/UNICEF Steering Committee for guidelines on vitamin A supplementation

WHO

Dr Rajiv Bahl
Medical Officer
Newborn and Child Health and Development Unit
Department of Child and Adolescent Health and Development

Ms Tracey Goodman
Technical Officer
Expanded Programme on Immunization Plus Unit
Department of Immunization, Vaccines and Biologicals

Dr Matthews Mathai
Medical Officer
Norms and Country Support Cooperation Unit
Department of Making Pregnancy Safer

Dr Mario Merialdi
Coordinator
Improving Maternal and Perinatal Health Unit
Department of Reproductive Health and Research

Dr Juan Pablo Peña-Rosas
Coordinator
Micronutrients Unit
Department of Nutrition for Health and Development

Dr Lisa Rogers
Technical Officer
Micronutrients Unit
Department of Nutrition for Health and Development

UNICEF

Mr Arnold Timmer
Senior Adviser
Micronutrients Unit
UNICEF Nutrition Section

Annex 4 Members of the Vitamin A Supplementation Guideline Group, WHO Secretariat and external resource experts

A. Members of the Vitamin A Supplementation Guideline Group

(Note: the areas of expertise of each guideline group member are given in italics)

Professor Hany Abdel-Aleem
Assiut University Hospital
Assiut, Egypt
Obstetrics and gynaecology

Professor Michael Clarke
University of Oxford
Oxford, England
Methods

Dr Anna Coutsoudis
University of KwaZulu-Natal
Durban, South Africa
Vitamin A, infectious disease

Dr M. Monir Hossain
Bangladesh Institute of Child Health and
Dhaka Shishu (Children) Hospital
Sher-e-Bangla Nagar
Dhaka, Bangladesh
Neonatology

Dr Jean Humphrey
Zimbabwe Vitamin A for Mothers and Babies Project (ZVITAMBO)
Harare, Zimbabwe
Vitamin A, human immunodeficiency virus (HIV)

Dr Yustina Anie Indriastuti
Indonesian Medical Doctor Nutrition Society
Jakarta, Indonesia
Programme Manager

Dr Marzia Lazzerini
Institute for Maternal and Child Health
Trieste, Italy
Methods, paediatrics

Dr Pavitra Mohan
UNICEF India Country Office
New Delhi, India
Paediatrics

Dr Rintaro Mori
University of Tokyo
Tokyo, Japan
Paediatrics

Dr A. Catherine Ross
Pennsylvania State University
University Park, United States of America
Vitamin A, immunology

Dr Isabella Sagoe-Moses
Ghana Health Service – Ministry of Health
Accra, Ghana
Programme Manager

Dr Claudia Saunders
Instituto de Nutrição Josué de Castro
Universidade Federal do Rio de Janeiro
Rio de Janeiro, Brazil
Vitamin A research programmes

Dr Prak Sophonneary
National Maternal and Child Health Center
Ministry of Health
Phnom Penh, Cambodia
Programme Manager

Dr Charles Stephensen
USDA Western Human Nutrition Research Center
Davis, United States of America
Vitamin A, immunology

Dr Sherry Tanumihardjo
University of Wisconsin
Madison, United States of America
Vitamin A metabolism

Dr Khalid Yunis
American University of Beirut
Beirut, Lebanon
Neonatology, perinatology

B. WHO

Mr Joseph Ashong
Intern (rapporteur)
Micronutrients Unit
Department of Nutrition for Health and Development

Dr Francesco Branca
Director
Department of Nutrition for Health and Development

Ms Emily Cercone
Intern (rapporteur)
Micronutrients Unit
Department of Nutrition for Health and Development

Dr Luz Maria de Regil
Epidemiologist
Micronutrients Unit
Department of Nutrition for Health and Development

Dr Chris Duncombe
Medical Officer
Anti-retroviral Treatment and HIV Care Unit
Department of HIV/AIDS

Dr Davina Ghersi
Team Leader
International Clinical Trials Registry Platform
Department of Research Policy and Cooperation

Dr Ahmet Metin Gulmezoglu
Medical Officer
Technical Cooperation with Countries for Sexual and Reproductive Health
Department of Reproductive Health and Research

Dr Regina Kulier
Scientist
Guideline Review Committee Secretariat
Department of Research Policy and Cooperation

Dr José Martines
Coordinator
Newborn and Child Health and Development Unit
Department of Child and Adolescent Health and Development

Ms Sueko Matsumura
Intern (rapporteur)
Micronutrients Unit
Department of Nutrition for Health and Development

Dr Sant-Rayn Pasricha
Intern (rapporteur)
Micronutrients Unit
Department of Nutrition for Health and Development

C. WHO regional offices

Dr Abel Dushimimana
Medical Officer
WHO Regional Office for Africa
Brazzaville, Congo

Dr Chessa Lutter
Regional Adviser
Unit on Child and Adolescent Health
WHO Regional Office for the Americas/ Pan American Health Organization
Washington, United States of America

Dr Kunal Bagchi
Regional Adviser
Nutrition and Food Safety
WHO Regional Office for South-East Asia
New Delhi, India

Dr Joao Breda
Scientist
WHO Regional Office for Europe
Copenhagen, Denmark

Dr Ayoub Al-Jawaldeh
Regional Adviser
Nutrition
WHO Regional Office for the Eastern Mediterranean
Cairo, Egypt

Dr Tommaso Cavalli-Sforza
Regional Adviser
Nutrition
WHO Regional Office for the Western Pacific
Manila, Philippines

D. External resource experts

Dr Denise Coitinho Delmuè
United Nations System Standing Committee on Nutrition (SCN)
Geneva, Switzerland

Dr Rafael Flores-Ayala
Centers for Disease Control and Prevention (CDC)
Atlanta, United States of America

Ms Alison Greig
Micronutrient Initiative
Ottawa, Canada

Mr Toby Lasserson
Cochrane Editorial Unit
London, England

Dr Lynnette Neufeld
Micronutrient Initiative
Ottawa, Canada

Dr Mathilde Savy
Institut de Recherche pour le Développement (IRD)
Montpellier, France

Dr David Tovey
Cochrane Editorial Unit
London, England

Annex 5 Members of the External Experts and Stakeholders Panel

A. Members commenting on priority questions on vitamin A supplementation (October 2009)

Engineer Alaa I. Abu Rub
Ministry of Health
Palestinian National Authority
Ramallah, West Bank and Gaza Strip

Dr Clayton Ajello
Vitamin Angels
Santa Barbara, United States of America

Dr Mohamed Ag Ayoya
UNICEF, India Country Office
New Delhi, India

Professor Hassan Aguenaou
Ibn Tofail University
Kénitra, Morocco

Mrs Deena Alasfoor
Ministry of Health
Muscat, Oman

Ms Maria Theresa Alvarez
Academy for Educational Development
(AED) – A2Z Project
Manila, Philippines

Mr Ravi Raj Atrey
SOS Children's Villages of India
New Delhi, India

Mr Shawn Baker
Helen Keller International
Dakar-Yoff, Senegal

Dr Christine Stabell Benn
Bandim Health Project
Statens Serum Institut
Copenhagen, Denmark

Dr Djibril Cissé
Helen Keller International
Dakar-Yoff, Senegal

Professor Pradeep Deshmukh
Dr Sushila Nayar School of Public Health
Mahatma Gandhi Institute of Medical Sciences
Sewagram, India

Dr Amol Dongre
Mahatma Gandhi Institute of Medical Sciences
Sewagram, India

Dr Masako Fujita
Michigan State University
East Lansing, United States of America

Dr Bishan Garg
Dr Sushila Nayar School of Public Health
Mahatma Gandhi Institute of Medical Sciences
Sewagram, India

Dr Ajay Gaur
GR Medical College
Gwalior, India

Ms Alison Greig
Micronutrient Initiative
Ottawa, Canada

Dr Laurence M. Grummer-Strawn
Centers for Disease Control and Prevention (CDC)
Atlanta, United States of America

Dr Maria Claret C.M. Hadler
Federal University of Goiás
Goiânia, Brazil

Dr Samia Halileh
Institute of Community and Public Health
Birzeit University
Birzeit, West Bank and Gaza Strip

Ms Nancy J. Haselow
Helen Keller International
Phnom Penh, Cambodia

Dr Jocelyn A. Juguan
Food and Nutrition Research Institute
Department of Science and Technology
Manila, Philippines

Dr Umesh Kapil
All India Institute of Medical Sciences
New Delhi, India

Dr Chen Ke
Maternal and Children's Health Care Hospital
Chengdu, China

Dr Klaus Kraemer
Sight and Life
Basel, Switzerland

Mr Hou Kroen
Helen Keller International
Phnom Penh, Cambodia

Dr Anand Lakshman
Micronutrient Initiative
New Delhi, India

Ms Ada Lauren
Vitamin Angels
Santa Barbara, United States of America

Dr Tingyu Li
Children's Hospital of Chongqing Medical University
Chongqing, China

Dr Georg Lietz
Newcastle University
Newcastle upon Tyne, England

Dr Kurt Long
University of Queensland
Brisbane, Australia

Dr Zeba Mahmud
Micronutrient Initiative
Dhaka, Bangladesh

Dr Najat Mokhtar
Ibn Tofail University
Kénitra, Morocco

Dr Siti Muslimatun
Southeast Asian Ministers of Education Organization
Tropical Medicine and Public Health Network (SEAMEO TROPMED)
Jakarta, Indonesia

Mr Banda Ndiaye
Micronutrient Initiative
Dakar, Senegal

Dr Lakshmi Rahmathullah
Family Health and Development Research Service Foundation
Madurai, India

Professor H.P.S. Sachdev
Maulana Azad Medical College
New Delhi, India

Dr Tina Sanghvi
Academy for Educational Development
Washington, United States of America

Ms Dimple Save
JICA-MP Reproductive Health Project
Bhopal, India

Dr Al Sommer
Johns Hopkins Bloomberg School of Public Health
Baltimore, United States of America

Dr Lize van Stuijvenberg
Medical Research Council
Cape Town, South Africa

Dr Hans Verhoef
London School of Hygiene and Tropical Medicine
London, England

Dr Sheila Vir
Public Health Nutrition and Development Centre
New Delhi, India

Dr Tobias Vogt
St Thomas Home and German Doctors Committee
Frankfurt, Germany

Dr Jian Zhang Yang
Columbia University
New York, United States of America

Dr David L. Yeung
H.J. Heinz Company Foundation
Toronto, Canada

Dr Xiaoying Zheng
Institute of Population Research, Peking University
Beijing, China

B. Members commenting on the draft guideline on vitamin A supplementation (March 2011)

Dr Christine Stabell Benn
Bandim Health Project
Statens Serum Institut
Copenhagen, Denmark

Professor Hans K. Biesalski
Department of Biological Chemistry and Nutrition
Hohenheim University
Stuttgart, Germany

Ms Nita Dalmiya
UNICEF Nutrition Section
New York, United States of America

Ms Alison Greig
Micronutrient Initiative
Ottawa, Canada

Dr Roland Kupka
UNICEF Regional Office for West and Central Africa
Dakar-Yoff, Senegal

Ms Ada Lauren
Vitamin Angels Alliance
Santa Barbara, United States of America

Dr Teresa Murguía Peniche
National Center for Child and Adolescent Health
Mexico City, Mexico

Ms Anna Roesler
Menzies School of Health Research
Casuarina, Australia

Dr Amal Saeed
University of Khartoum
Khartoum, Sudan

Dr Martha Elizabeth van Stuijvenberg
South African Medical Research Council
Cape Town, South Africa

Dr Sheila Vir Chander
Public Health Nutrition and Development Centre
New Delhi, India

Dr Frank Wieringa
Institut de Recherche pour le Développement
Marseilles, France

Annex 6

Questions in Population, Intervention, Control, Outcomes (PICO) format

Effects and safety of vitamin A supplementation in infants 1–5 months of age

a. Should vitamin A supplements be given to infants 1–5 months of age?
b. If so, at what dose, frequency and duration?

Population:

- Infants 1–5 months of age living in countries where vitamin A deficiency may be of public health concern
- Subpopulations:
  - By infant mortality rates: countries with low versus high rates
  - By infant exposure to additional vitamin A: infants who received a vitamin A supplement within the first 28 days of life versus no supplements
  - By maternal exposure to vitamin A: infants whose mothers received vitamin A supplementation during pregnancy or in the postpartum period versus no maternal supplementation/unknown

Intervention:

- Any oral vitamin A supplement
- Subgroup analyses:
  - By dose: 25 000 IU versus 50 000 IU versus other doses
  - By regimen: single versus multiple doses
  - By timing: along with DTP or oral polio vaccines or independent of them

Control: Placebo or no treatment

Outcomes: *Critical*

- Mortality within 0–6 and 0–12 months of life:
  - Any cause
  - Acute respiratory infections
  - Diarrhoea
  - Measles
- Hospitalization/clinic visits (number and duration) during 0–6 and 0–12 months of life:
  - Any cause
  - Acute respiratory infections
  - Diarrhoea
- Adverse effects within 72 hours after receiving supplement
  - Bulging fontanelles
  - Vomiting
  - Others

Setting: All countries

Annex 6 Summary of considerations for determining the strength of the recommendation

Quality of evidence:	• Moderate quality of evidence for the outcome of mortality and for the side-effect of bulging fontanelles • Remaining critical outcomes have low quality of evidence
Values and preferences:	• Not discussed as there are no apparent benefits
Trade-off between benefits and harm:	• No evidence of benefit • Evidence of some transient side-effects
Costs and feasibility:	• Feasible as can possibly be given alongside other health interventions, but interactions would need to be evaluated

For more information, please contact:

Department of Nutrition for Health and Development

World Health Organization

Avenue Appia 20, CH-1211 Geneva 27, Switzerland

Fax: +41 22 791 4156

E-mail: nutrition@who.int

www.who.int/nutrition

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