World Health Organization

Guideline:

Vitamin A supplementation in infants and children 6–59 months of age

WHO Library Cataloguing-in-Publication Data

Guideline: vitamin A supplementation in infants and children 6–59 months of age.

1.Vitamin A – administration and dosage. 2.Vitamin A deficiency – prevention and control. 3.Child, Preschool. 4.Infant nutrition. 5.Guidelines. I.World Health Organization.

ISBN 978 92 4 150176 7 (NLM classification: WD 110)

Design and layout: Alberto March

Suggested citation

WHO. *Guideline: Vitamin A supplementation in infants and children 6–59 months of age*. Geneva, World Health Organization, 2011.

Contents

Acknowledgements

This guideline was coordinated by Dr Lisa Rogers under the supervision of Dr Juan Pablo Peña-Rosas, with technical input from Dr Rajiv Bahl, Dr Luz Maria de Regil, Ms Tracey Goodman and Dr Jose Martines. Thanks are due to Dr Regina Kulier and the staff at the Guidelines Review Committee Secretariat for their support throughout the process. Thanks are also due to Dr Davina Ghersi for her technical advice and assistance in the preparation of the technical consultations for this guideline and Mr Issa T. Matta and Mrs Chantal Streijffert Garon from the World Health Organization (WHO) Office of the Legal Counsel for their support in the management of conflicts of interest procedures. Ms Grace Rob and Mrs Paule Pillard from the Micronutrients Unit, Department of Nutrition for Health and Development, provided logistic support.

WHO gratefully acknowledges the technical input of the members of the WHO/United Nations Children's Fund (UNICEF) Steering Committee, the Vitamin A Supplementation Guideline Group and the External Experts and Stakeholders Panel. WHO is also grateful to the Cochrane Editorial Unit for its support in coordinating the update of the systematic reviews used to inform this guideline and the evidence summary of findings.

Financial support

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

WHO Guideline[1]

Vitamin A supplementation in infants and children 6–59 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 and children 6–59 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.

In settings where vitamin A deficiency is a public health problem, vitamin A supplementation is recommended in infants and children 6–59 months of age as a public health intervention to reduce child morbidity and mortality (strong recommendation). The quality of the available evidence for all-cause mortality was high, whereas for all other critical outcomes it was moderate to very low. The quality of the available evidence for outcomes in human immunodeficiency virus (HIV)-positive children was moderate for all-cause mortality.

[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 6–59 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 Annex 1 and other documents listed in the references.

Background

Vitamin A deficiency is a major public health problem affecting an estimated 190 million preschool-age children, mostly from the World Health Organization (WHO) regions of Africa and South-East Asia (*1*). Infants and children have increased vitamin A requirements to promote rapid growth and to help combat infections. Inadequate intakes of vitamin A at this age could lead to vitamin A deficiency, which, when severe, may cause visual impairment (night blindness) or increase the risk of illness and mortality from childhood infections such as measles and those causing diarrhoea (*2*).

The combination of childhood underweight, micronutrient deficiencies (iron, vitamin A and zinc) and suboptimal breastfeeding is responsible for 7% of deaths and 10% of the total disease burden (*3*). Vitamin A deficiency alone is responsible for almost 6% of child deaths under the age of 5 years in Africa and 8% in South-East Asia (*3*). Vitamin A supplementation in children 6–59 months of age living in developing countries is associated with a reduced risk of all-cause mortality and a reduced incidence of diarrhoea (*4*). The mechanisms by which vitamin A reduces mortality are not fully understood, and it is not clear whether its action is mediated through the correction of underlying deficiencies or through adjuvant therapeutic effects. Vitamin A supplementation may improve gut integrity and therefore decrease the severity of some diarrhoeal episodes (*5*). The role of vitamin A in innate and adaptive immunity may also include reducing susceptibility to and/or severity of other infections (*6, 7*).

Many countries have integrated strategies to deliver vitamin A supplements to infants and children in their national health policies (*8, 9*). The delivery of vitamin A has been integrated into routine health services, for example through the establishment of biannual "special days", when vitamin A supplementation is combined with other child survival interventions such as deworming or nutrition education. Vitamin A supplements are also commonly distributed as part of the Expanded Programme on Immunization (especially at 9 months, alongside measles vaccination). In 2009, about 77% of preschool children in more than 103 priority countries received two doses of vitamin A supplements (*10*).

Provision of high doses of vitamin A every 6 months until the age of 5 years was based on the principle that a single, large dose of vitamin A is well absorbed and stored in the liver, and then mobilized, as needed, over an extended period of time (*11*). A dose of 100 000 International Units (IU) in infants 6–11 months of age and 200 000 IU in children 12–59 months of age is considered to provide adequate protection for 4–6 months, with the exact interval depending on the vitamin A content of the diet and the rate of utilization by the body (*8, 12*).

In most children 6–59 months of age, a dose of 100 000–200 000 IU of vitamin A is well tolerated, although side-effects such as headache, nausea or vomiting, and diarrhoea have been reported in 3–7% of these children (*13*). However, these symptoms are transient, with the large majority starting and disappearing within 24 hours of dosing. There are no known deaths attributed solely to vitamin A toxicity due to overconsumption of vitamin A (*13*).

On a per-child basis, vitamin A supplementation is considered a low-cost intervention. Most of the vitamin A used during supplementation campaigns is supplied in gelatin capsules which cost approximately US$ 0.02 each (*14*), with an estimated cost of US$ 1–2 for delivery per child per year (*15*). The total cost of supplementation per death averted is estimated at US$ 200–250 (*16, 17*).

Summary of evidence

Two existing Cochrane systematic reviews assessing the effects and safety of vitamin A supplementation in children 6–59 months of age were updated for this guideline (*4, 18*). One review evaluated the effectiveness of vitamin A supplements in the prevention of morbidity and mortality in children 6–59 months of age (*4*). It showed that giving vitamin A supplements to children reduces the rates of mortality and some diseases. A meta-analysis of 17 trials (11 in Asia, 5 in Africa and 1 in Latin America) for all-cause mortality indicated that vitamin A reduces the overall risk of death by 24% (risk ratio (RR) 0.76; 95% confidence interval (CI) 0.69–0.83). When an unpublished cluster-randomized trial involving one million children in north India (the DEVTA trial) was considered, vitamin A supplementation reduced the effect size of all-cause mortality from 24% to 12% (RR 0.88; 95% CI 0.84–0.94). Due to limited availability of information on the DEVTA trial the quality of this trial could not be assessed.

Seven trials indicated that vitamin A supplementation significantly reduces diarrhoea-related mortality (RR 0.72; 95% CI 0.57–0.91), although mortality specifically due to measles (five trials: RR 0.80; 95% CI 0.51–1.24) or respiratory disease (seven trials: RR 0.78; 95% CI 0.54–1.14) was not reduced. The occurrence of new episodes of diarrhoea decreased (13 trials: RR 0.85; 95% CI 0.82–0.87). There was no significant effect on the incidence of respiratory disease (nine trials: RR 1.14; 95% CI 0.95–1.37), or hospitalizations due to diarrhoea or pneumonia.

There was a significantly increased risk of vomiting within the first 48 hours of supplementation with 100 000–200 000 IU of vitamin A (three trials: RR 2.75; 95% CI 1.81–4.19). Only one study reported data on bulging fontanelles as most studies

included children over 1 year of age and thus would not have assessed this side-effect. There was no significant effect of vitamin A supplementation when the data were stratified by national child mortality rates (data from countries with low versus high child mortality rates) (*4*). It was not possible to perform subgroup analyses for dose and frequency of supplementation as the analyses were underpowered and any effects would have been attributed to chance.

The second review assessed whether micronutrient supplements, including vitamin A, are safe and effective in reducing morbidity and mortality in adults and children with human immunodeficiency virus (HIV) infection (*18*). It included five trials on vitamin A supplementation in children with a total of 1120 participants; only three trials (262 participants, all in Africa) contributed data on all-cause mortality. The data suggest that vitamin A reduces the overall risk of death (RR 0.55; 95% CI 0.37–0.82).

The overall quality of the evidence for all-cause mortality was high, whereas it was moderate to very low for the remaining critical outcomes (Annex 1). The quality of the available evidence for outcomes in HIV-positive children was moderate for all-cause mortality.

The effect of vitamin A supplementation on antibody response to measles vaccination has recently been evaluated in an additional review (*19*). A meta-analysis of seven trials indicated that vitamin A supplementation at 6 or 9 months of age did not affect the measles vaccine response (seroconversion rates). No study has prospectively assessed the impact of co-administration of vitamin A and measles vaccine on child mortality.

Recommendation

High-dose vitamin A supplementation is recommended in infants and children 6–59 months of age in settings where vitamin A deficiency is a public health problem[1] (*strong recommendation*[2]).

A suggested vitamin A supplementation scheme for infants and children 6–59 months of age is presented in Table 1.

[1] Determination of vitamin A deficiency as a public health problem involves estimating the prevalence of deficiency in a population by using specific biochemical and clinical indicators of vitamin A status. Classification of countries based on the most recent estimates is available in reference (*1*).

[2] 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 want the recommended course of action and only a small proportion would not. Implications for clinicians 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.

Table 1

Suggested vitamin A supplementation scheme for infants children 6–59 months of age

Target group	Infants 6–11 months of age (including HIV+)	Children 12–59 months of age (including HIV+)
Dose	100 000 IU (30 mg RE) vitamin A	200 000 IU (60 mg RE) vitamin A
Frequency	Once	Every 4–6 months
Route of administration	Oral liquid, oil-based preparation of retinyl palmitate or retinyl acetate[a]	
Settings	Populations where the prevalence of night blindness is 1% or higher in children 24–59 months of age or where the prevalence of vitamin A deficiency (serum retinol 0.70 µmol/l or lower) is 20% or higher in infants and children 6–59 months of age	

IU, international units; RE, retinol equivalent.

[a] An oil-based vitamin A solution can be delivered using soft gelatin capsules, as a single-dose dispenser or a graduated spoon (*20*). Consensus among manufacturers to use consistent colour coding for the different doses in soft gelatin capsules, namely red for the 200 000 IU capsules and blue for the 100 000 IU capsules, has led to much-improved training and operational efficiencies in the field.

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 6–59 months of age (*8*).
- The above recommendation can also be applied in populations where infants and children may be infected with HIV.
- The magnitude of the effect may differ across settings and populations, possibly due to the extent of vitamin A deficiency or the availability of other nutrients (e.g. dietary intake of vitamin A will differ across locations and the effects of supplementation may be smaller in places with greater access to vitamin A-rich foods or with regular consumption of vitamin A-fortified foods).
- This intervention should be used along with other strategies to improve vitamin A intakes, such as dietary diversification (*21*) and food fortification (*22*).

- Adverse effects within 48 hours of receiving supplements containing 100 000–200 000 IU vitamin A are usually mild and transient, with no long-term consequences. Adverse effects may include bulging of open fontanelles in younger infants, and nausea and/or vomiting and headache in older children with closed fontanelles.

- Vitamin A supplements should be delivered to children 6–59 months of age twice yearly, during health system contacts. This should be marked on the child health card, or integrated into other public health programmes aimed at improving child survival, such as polio or measles national immunization days, or biannual child health days delivering a package of interventions such as deworming, distribution of insecticide-treated mosquito nets and immunizations.

- A quality assurance process should be established to guarantee that supplements are manufactured, packaged and stored in a controlled and uncontaminated environment (*23*).

- When determining the vitamin A status of a population, guidelines on indicators for assessing vitamin A deficiency should be referred to (*24, 25*).

- 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 and children 6–59 months of age should be referred to in these cases (*8, 26*).

Dissemination, adaptation and implementation

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.

Adaptation and implementation

As this is a global guideline, it should be adapted to the context of each Member State. Prior to implementation, a vitamin A supplementation programme should include well-defined objectives that take into account available resources, existing

policies, appropriate delivery and communication channels, and potential stakeholders and suppliers. Ideally, interventions should be implemented as part of an integrated strategy that includes control of nutritional deficiencies; the programme should begin as a pilot and scaled up as the evidence grows and resources allow.

To ensure that WHO global guidelines and other evidence-informed recommendations for micronutrient interventions are better implemented in low- and middle-income countries, the Department of Nutrition for Health and Development works with the WHO Evidence-Informed Policy Network (EVIPNet) programme. EVIPNet promotes partnerships at country level between policy-makers, researchers and civil society to facilitate policy development and implementation through use of the best available evidence.

Monitoring and evaluation of guideline implementation

A plan for monitoring and evaluation with appropriate indicators is encouraged at all stages. The impact of this guideline can be evaluated within countries (i.e. monitoring and evaluation of the programmes implemented at scale) and across countries (i.e. the adoption and adaptation of the guideline globally). The WHO Department of Nutrition for Health and Development, Micronutrients Unit, jointly with the Centers for Disease Control and Prevention (CDC) International Micronutrient Malnutrition Prevention and Control (IMMPaCt) programme, and with input from international partners, has developed a generic logic model for micronutrient interventions in public health to depict these plausible relationships between inputs and expected MDGs by applying the micronutrient programmes evaluation theory (*27*). Member States can adjust the model and use it in combination with appropriate indicators for designing, implementing, monitoring and evaluating the successful scaling-up of nutrition actions.

For evaluation at the global level, the WHO Department of Nutrition for Health and Development is developing a centralized platform for sharing information on nutrition actions in public health practice implemented around the world. By sharing programme details, specific country adaptations and lessons learnt, this platform will provide examples of how the guidelines are being translated into nutrition actions. To be successful, this platform will need to be a collaborative effort, where the work of the entire international community can be shared, so countries worldwide can benefit as they attempt to implement nutrition actions.

Implications for future research

Discussion with the guideline group members and the External Experts and Stakeholders Panel highlighted the limited evidence in some areas, meriting further research on vitamin A supplementation in infants and children 6–59 months of age, in particular, in the following areas:

- effect of different doses of vitamin A on the critical outcomes of morbidity and mortality, and stratification of the data by sex, length of follow-up, vaccination status and subsequent vitamin A supplementation;
- the role of vitamin A supplementation in countries with high measles immunization rates and its effect on measles-related mortality;
- comparative analysis of the different delivery mechanisms of vitamin A (capsules versus droppers for delivery of supplemental vitamin A, food fortificants);
- identification of field-friendly clinical and biochemical indicators of vitamin A status and vitamin A stores;
- co-interventions that may interact with vitamin A, for example other nutrients (such as vitamin D) and vaccines (such as diphtheria, tetanus, polio).

Guideline development process

This guideline was developed in accordance with the WHO evidence-informed guideline development procedures, as outlined in the *WHO handbook for guideline development* (*28*).

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 2). 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 3). 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 4). 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 5). 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 question and modified them as needed. They scored the relative importance of each outcome from 1 to 9 (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 and children 6–59 months of age, along with the outcomes that were identified as critical for decision-making, are listed in PICO format in Annex 5.

The Cochrane Collaboration was commissioned to search, review and generate systematic reviews, evidence profiles and the "Summary of findings" table[1] (Annex 1). Two existing Cochrane reviews on vitamin A supplementation in children were updated, and the up-to-date Review Manager Software (RevMan) files, obtained from the Cochrane Editorial Unit, were customized to reflect the critical outcomes previously identified (outcomes not relevant to this guideline were excluded). The RevMan files were exported to the GRADE profiler software to prepare the evidence summaries according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for assessing the overall quality of the evidence

[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.

(*29*) (Annex 1). 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 reviews 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 6). 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 guideline 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 guideline and submitted it for clearance by WHO before publication.

Management of conflicts of interest

According to the rules in the WHO *Basic documents* (*30*), 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)* (*31*). 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 provitamin 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 recommendation 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 the formal *WHO handbook for guideline development* (*28*) procedures. WHO welcomes suggestions regarding additional questions for evaluation in the guideline when it is due for review.

References

1. *Global prevalence of vitamin A deficiency in populations at risk 1995–2005. WHO Global Database on Vitamin A Deficiency*. Geneva, World Health Organization, 2009 (http://whqlibdoc.who.int/publications/2009/9789241598019_eng.pdf, accessed 21 May 2011).

2. Sommer A, West KP Jr. *Vitamin A deficiency: health, survival, and vision*. New York, Oxford University Press, 1996.

3. *Global health risks: mortality and burden of disease attributable to selected major risks*. Geneva, World Health Organization, 2009 (http://www.who.int/healthinfo/global_burden_disease/GlobalHealthRisks_report_full.pdf, accessed 20 May 2011).

4. Imdad A et al. Vitamin A supplementation for preventing morbidity and mortality in children from 6 months to 5 years of age. *Cochrane Database of Systematic Reviews,* 2010, (12):CD008524 (http://onlinelibrary.wiley.com/o/cochrane/clsysrev/articles/CD008524/pdf_fs.html, accessed 20 May 2011).

5. Villamor E, Fawzi WW. Effects of Vitamin A supplementation on immune responses and correlation with clinical outcomes. *Clinical Microbiology Reviews*, 2005, 3: 446–464.

6. Stephensen CB. Vitamin A, infection, and immune function. *Annual Review of Nutrition*, 2001, 21:167–192.

7. Ross AC. Vitamin A supplementation and retinoic acid treatment in the regulation of antibody responses in vivo. *Vitamins and Hormones*, 2007, 75:197–222.

8. WHO, UNICEF, IVACG Task Force. *Vitamin A supplements: a guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia*, 2nd ed. Geneva, World Health Organization, 1997 (http://whqlibdoc.who.int/publications/1997/9241545062.pdf, accessed 20 May 2011).

9. WHO, UNICEF. *Integration of vitamin A supplementation with immunization: policy and programme implications*. Geneva, World Health Organization, 1998 (http://whqlibdoc.who.int/hq/1998/WHO_EPI_GEN_98.07.pdf, accessed 20 May 2011).

10. *The state of the world's children 2011*. New York, United Nations Children's Fund, 2011.

11. West KP Jr, Sommer A. *Delivery of oral doses of vitamin A to prevent vitamin A deficiency and nutritional blindness. A state-of-the-art review*. Nutrition Policy Discussion Paper No 2. Rome, United Nations Administrative Committee on Coordination, Subcommittee on Nutrition, 1987.

12. Swaminathan MC, Susheela TP, Thimmayamma VS. Field prophylactic trial with a single annual oral massive dose of vitamin A. *American Journal of Clinical Nutrition*, 1970, 23:119–122.

13. Bauernfeind JC. *The safe use of vitamin A*. Washington, DC, International Vitamin A Consultative Group, 1980.

14. Micronutrient Initiative. *Vitamin A: the scope of the problem*. Ottawa, Micronutrient Initiative, 2011 (www.micronutrient.org/English/View.asp?x=577&id=440, accessed 31 January 2011).

15. West KP Jr, Klemm RDW, Sommer A. Vitamin A saves lives. Sound science, sound policy [commentary]. *World Nutrition*, 2010, 1:211–229.

16. Ching P et al. Childhood mortality impact and costs of integrating vitamin A supplementation into immunization campaigns. *American Journal of Public Health*, 2000, 90:1526–1529.

17. MOST, USAID. *Cost analysis of the national vitamin A supplementation programs in Ghana, Nepal, and Zambia: a synthesis of three studies*. Arlington, VA, USAID, 2004 (http://www.mostproject.org/IVACG/GhanaNepalZambiaSythesis.pdf, accessed 20 May 2011).

18. Irlam JH et al. Micronutrient supplementation in children and adults with HIV infection. *Cochrane Database of Systematic Reviews,* 2010, (12):CD003650 (http://onlinelibrary.wiley.com/o/cochrane/clsysrev/articles/CD003650/pdf_fs.html, accessed 20 May 2011).

19. Savy M et al. Landscape analysis of interactions between nutrition and vaccine responses in children. *Journal of Nutrition*, 2009, 139:2154S–2218S.

20. *WHO model list of essential medicines – 16th list (updated)*. Geneva, World Health Organization, 2010 (http://www.who.int/medicines/publications/essentialmedicines/Updated_sixteenth_adult_list_en.pdf, accessed 20 May 2011).

21. WHO, FAO. *Vitamin and mineral requirements in human nutrition,* 2nd ed. Geneva, World Health Organization, 2004 (http://whqlibdoc.who.int/publications/2004/9241546123.pdf, accessed 20 May 2011).

22. Allen L et al., eds. *Guidelines on food fortification with micronutrients.* Geneva, World Health Organization, 2006 (http://www.who.int/nutrition/publications/micronutrients/9241594012/en/index.html, accessed 20 May 2011).

23. *Quality assurance of pharmaceuticals: meeting a major public health challenge*. *the WHO Expert Committee on Specifications for Pharmaceutical Preparations.* Geneva, World Health Organization, 2007 (http://www.who.int/medicines/publications/brochure_pharma.pdf, accessed 20 May 2011).

24. *Indicators for assessing vitamin A deficiency and their application in monitoring and evaluating intervention programmes*. Geneva, World Health Organization, 1996 (WHO/NUT/96.10; http://www.who.int/nutrition/publications/micronutrients/vitamin_a_deficieny/WHONUT96.10.pdf, accessed 20 May 2011).

25. *Serum retinol concentrations for determining the prevalence of vitamin A deficiency in populations.* Vitamin and Mineral Nutrition Information System. Geneva, World Health Organization, 2011 (WHO/NMH/NHD/MNM/11.3; (http://www.who.int/vmnis/indicators/retinol.pdf, accessed 18 April 2011).

26. *Treating measles in children*. Geneva, World Health Organization, 2004 (WHO/EPI/TRAM/97.02 (updated 2004); http://www.who.int/immunization_delivery/interventions/TreatingMeaslesENG300.pdf, accessed 04 May 2011).

27. WHO/CDC. Logic model for micronutrient interventions in public health. Vitamin and Mineral Nutrition Information System. Geneva, World Health Organization, 2011 (WHO/NMH/NHD/MNM/11.5; http://www.who.int/vmnis/toolkit/WHO-CDC_Logic_Model.pdf, accessed 20 May 2011).

28. *WHO handbook for guideline development*. Guidelines Review Committee. Draft March 2010. Geneva, World Health Organization, 2010.

29. Atkins D et al. Grading quality of evidence and strength of recommendations. *British Medical Journal*, 2004, 328:1490.

30. *Basic documents*, 47th ed. Geneva, World Health Organization, 2009 (http://apps.who.int/gb/bd/, accessed 19 May 2011).

31. *Guidelines for declaration of interests (WHO experts)*. Geneva, World Health Organization, 2010.

Annex 1 GRADE "Summary of findings" table

Vitamin A supplementation in infants and young children 6–59 months of age

Patient or population: Infants and young children 6–59 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
All-cause mortality Follow-up: 12–96 weeks	**RR 0.76** (0.69–0.83)	194 798 (17 studies)	⊕⊕⊕⊕ **high**	Inclusion of the DEVTA trial reduced the effect size. RR 0.76 (95% CI 0.69–0.83) to RR 0.88 (95% CI 0.84–0.94)
All-cause mortality (HIV+ children) Hospital files or verbal autopsy forms Follow-up: 6–24 months	**RR 0.55** (0.37–0.82)	262 (3 studies)	⊕⊕⊕⊖ **moderate**[1]	
Diarrhoea-related mortality Follow-up: 48–104 weeks	**RR 0.72** (0.57–0.91)	90 951 (7 studies)	⊕⊕⊕⊖ **moderate**[2]	Total number of participants reflects number randomized to studies. The analysis combined cumulative risk and risk per/1000 years follow-up
Measles-related mortality Follow-up: 52–104 weeks	**RR 0.80** (0.51–1.24)	88 261 (5 studies)	⊕⊕⊕⊖ **moderate**[3]	Total number of participants reflects number randomized to studies. The analysis combined cumulative risk and risk per/1000 years follow-up
Lower respiratory tract infection-related mortality Follow-up: 48–104 weeks	**RR 0.78** (0.54–1.14)	90 951 (7 studies)	⊕⊕⊖⊖ **low**[2,3]	Total number of participants reflects number randomized to studies. The analysis combined cumulative risk and risk per/1000 years follow-up

CI, confidence interval; RR, risk ratio; HIV, human immunodeficiency virus.

* 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] Imprecision due to few deaths and small HIV+ groups in the three studies included in the meta-analysis.

[2] The risk of bias assessments determined that Daulaire (1992) and Herrera (1992) were at risk of selection bias. Detection bias put the results of Daulaire (1992) at a high risk of bias. Attrition bias was considered to put the results of Chowdhury (2002) at a high risk of bias. Baseline imbalance was noted for Agarwal (1995).

[3] The wide confidence intervals around the pooled effect estimate included both a reduction and an increase in the risk of mortality with vitamin A.

For details of studies included in the review, see reference (*4*).

(Continued overleaf)

(*Continued from previous page*)

Vitamin A supplementation in infants and young children 6–59 months of age

Patient or population: Infants and young children 6–59 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
Diarrhoea-related hospital admission (HIV+ children) Maternal recall Follow-up: 6–18 months	**RR 0.25** (0.05–1.15)	194 (1 study)	⊕⊕⊕⊖ **moderate**[1]	Only one study reported on this outcome
Diarrhoea incidence Ratio of rates of episodes per child Follow-up: 24–60 weeks	**RR 0.85** (95% CI 0.82– 0.87)	69 972 (13 studies)	⊕⊕⊖⊖ **low**[2,3]	
Acute respiratory infection-related hospital admission (HIV+ children) Maternal recall Follow-up: 6–18 months	**RR 0.6** (0.15–2.44)	194 (1 study)	⊕⊕⊕⊖ **moderate**[1]	Only one study reported on this outcome
Lower respiratory tract infection-related morbidity – incidence Mean episodes/child per year Follow–up: mean 52 weeks	**RR 1.14** (95% CI 0.95–1.37)	19 566 (9 studies)	⊕⊖⊖⊖ **very low**[4-6]	
Vomiting Follow-up: 0.14–52 weeks	**RR 2.75** (1.81–4.19)	2994 (3 studies)	⊕⊕⊖⊖ **low**[7,8]	

CI, confidence interval; RR, risk ratio; HIV, human immunodeficiency virus.

* 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] Imprecision due to wide variation in confidence intervals, which translates into wide variation in absolute effect.

[2] The risk of bias assessment determined that four studies contributing just over 25% weight of the estimated effect were at risk of selection or attrition bias.

[3] The I^2 was 95%, and the results of Cheng (1993), Chowdhury (2002) and Herrera (2002) demonstrated clear evidence of benefit and were discordant with the results of the other studies.

[4] The risk of bias assessment determined that Cheng (1993), Chowdhury (2002) and Kartasasmita (1995) were at high risk of attrition bias.

[5] Diagnostic procedures were not consistent across the studies.

[6] The confidence intervals around the pooled effect included small benefit and a meaningful increase in the risk of respiratory tract infections.

[7] The follow-up was spread between 1 day and 52 weeks.

[8] There was some evidence of underreporting of adverse events in some of the studies, and the low number of trials giving data in relation to the large number of studies included overall, means that this selective reporting of adverse events cannot be excluded.

For details of studies included in the review, see reference (*4*).

Annex 2

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 3 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 4 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 5

Effects and safety of vitamin A supplementation in infants and children 6–59 months of age

a. Should vitamin A supplements be given to infants and children 6–59 months of age?
b. If so, at what dose and frequency?

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

Population:
- Infants and children 6–59 months of age living in countries where vitamin A deficiency may be of public health concern
- Subpopulations:
  - By child (under 5) mortality rates: countries with low versus high rates
  - By interaction with immunization: children receiving vitamin A around the time of measles vaccination versus other times
  - By child HIV status: HIV-positive versus HIV-negative versus mixed/unknown
  - By exposure to additional vitamin A: children who also received vitamin A supplementation during the first 28 days of life and/or at 1–5 months of age versus those who had not received vitamin A before

Intervention:
- Any oral vitamin A supplement
- Subgroup analyses:
  - By dose: standard dose (100 000 IU for children 6–11 months of age and 200 000 IU for children 12–59 months of age) versus other doses
  - By frequency: every 4–6 months versus other
  - By timing: receipt of first dose at 6 months of age versus at 9-month measles contact versus other

Control: Placebo or no treatment

Outcomes: *Critical*
- Mortality within the follow-up period:
  - Any cause
  - Acute respiratory infections
  - Diarrhoea
  - Measles
- Hospitalization/clinic visits (number and duration) within the follow-up period:
  - Any cause
  - Acute respiratory infections
  - Diarrhoea
  - Adverse effects within 72 hours after receiving supplement
  - 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 most critical outcomes • Low quality of evidence for the side-effect of vomiting
Values and preferences:	• This intervention has been in place for many years now and is acceptable to most but not all • Other options (i.e. fortification) may be preferred in order to reach a larger proportion of the target population
Trade-off between benefits and harm:	• There is benefit of reducing mortality with few side-effects • However, one cannot rule out that in certain settings there may not be a benefit • There is concern that those who need this intervention the most may not be reached
Costs and feasibility:	• Capsules are available at a minimal cost • There is a moderate cost of delivering the intervention • In the least developed countries, coverage of vitamin A supplementation is the highest, so there is evidence that these children can be reached • Child health days are one mechanism by which countries may deliver a set of interventions to large proportion of the population (along with deworming, bed nets) • Programmes delivering vitamin A alone (without other interventions) may be more costly • There is a need to have a fixed place and time for distribution of this and other health interventions • Longer-term solutions may be needed

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

ISBN 978 92 4 150176 7