



World Health
Organization

Guideline:

**Vitamin A
supplementation in
pregnancy for reducing
the risk of mother-to-child
transmission of HIV**

WHO Library Cataloguing-in-Publication Data

Guideline: vitamin A supplementation in pregnancy for reducing the risk of mother-to-child transmission of HIV.

1.Vitamin A – administration and dosage. 2.Vitamin A deficiency – complications. 3.Pregnancy. 4.Disease transmission, Vertical – prevention and control. 5.HIV infections – prevention and control. 6.Prenatal nutrition. 7.Guidelines. I.World Health Organization.

ISBN 978 92 4 150180 4

(NLM classification: WD 110)

© World Health Organization 2011

All rights reserved. Publications of the World Health Organization are available on [the WHO web site \(www.who.int\)](http://www.who.int) or can be purchased from WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland (tel.: +41 22 791 3264; fax: +41 22 791 4857; e-mail: bookorders@who.int).

Requests for permission to reproduce or translate WHO publications – whether for sale or for noncommercial distribution – should be addressed to WHO Press through the WHO web site (http://www.who.int/about/licensing/copyright_form/en/index.html).

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

Design and layout: Alberto March

Suggested citation

WHO. *Guideline: Vitamin A supplementation in pregnancy for reducing the risk of mother-to-child transmission of HIV*. Geneva, World Health Organization, 2011.

Contents	Acknowledgements	iv
	Financial support	iv
	Summary	1
	Scope and purpose	2
	Background	2
	Summary of evidence	3
	Recommendation	4
	Remarks	4
	Dissemination	4
	Implications for future research	4
	Guideline development process	5
	<i>Advisory groups</i>	
	<i>Scope of the guideline, evidence appraisal and decision-making</i>	
	Management of conflicts of interest	7
	Plans for updating the guideline	8
	References	9
Annex 1	GRADE “Summary of findings” table	11
Annex 2	Members of the WHO/UNICEF Steering Committee for guidelines on vitamin A supplementation	12
Annex 3	Members of the Vitamin A Supplementation Guideline Group, WHO Secretariat and external resource experts	13
Annex 4	Members of the External Experts and Stakeholders Panel	16
Annex 5	Questions in Population, Intervention, Control, Outcomes (PICO) format	19
Annex 6	Summary of considerations for determining the strength of the recommendation	20



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 Gheri 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.

Summary

Over 1000 new cases of mother-to-child transmission of the human immunodeficiency virus (HIV) occur worldwide every day, making this the main route of transmission of HIV infection in children. Vitamin A deficiency affects about 19 million pregnant women, mostly from the WHO regions of Africa and South-East Asia. Both HIV infection and pregnancy are considered to be risk factors for vitamin A deficiency. During pregnancy, vitamin A is essential for maternal health and for the healthy development of the fetus. Member States have requested guidance from the World Health Organization (WHO) on the effects and safety of vitamin A supplements for HIV-positive pregnant women as a public health strategy.

WHO has developed the present evidence-informed recommendations 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 HIV-positive pregnant women is not recommended as a public health intervention for the prevention of mother-to-child transmission of HIV (strong recommendation). The quality of the available evidence was found to be moderate for mother-to-child transmission of HIV and child death, and very low for maternal death. All pregnant women, including those living with HIV/acquired immune deficiency syndrome (AIDS), should be encouraged to receive adequate nutrition through consumption of a healthy balanced diet.

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 for reducing the risk of mother-to-child transmission of the human immunodeficiency virus (HIV) in populations where vitamin A deficiency may be a public health concern.

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), improvement in maternal health (MDG 5) and combating HIV/acquired immune deficiency syndrome (AIDS), malaria and other diseases (MDG 6). 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

In 2009, an estimated 370 000 children contracted HIV in the perinatal or breastfeeding period (1). Over 1000 new cases of mother-to-child transmission of HIV occur daily worldwide, making this the main route of transmission of HIV infection in children (1, 2). The transmission of the virus from the mother to the child can occur during pregnancy, delivery or while breastfeeding (3–5). The severity of maternal HIV infection, the vaginal mode of delivery and presence of advanced HIV disease can increase the risk of transmission. Nutritional status can also be a contributing factor and vitamin A deficiency has been associated with an increase in the risk of transmission of the virus from mother to child (2, 4).

Vitamin A deficiency remains a public health problem among women, affecting an estimated 19 million pregnant women (6), with the highest burden found in the World Health Organization (WHO) regions of Africa and South-East Asia. During pregnancy, vitamin A is essential for the health of the mother as well as for the health and development of the fetus. This is because vitamin A is important for cell division, fetal organ and skeletal growth, maintenance of the immune system to strengthen defences against infection, and development of vision in the fetus as well as maintenance of maternal eye health and night vision (7, 8). During pregnancy, serum retinol levels decline, particularly in the third trimester; this may be due to the physiological increment in blood volume or due to an acute phase response, and it can be exacerbated by an inadequate vitamin A intake (9, 10). Night blindness, an early sign of vitamin A deficiency, is associated with infectious diseases (4, 10). Both HIV infection and pregnancy are considered to be risk factors for vitamin A deficiency (11).

Current strategies to reduce mother-to-child transmission of HIV include antiretroviral therapy (ART), elective caesarean section delivery and use of the most appropriate infant feeding options (12–15). However, in some low- and middle-

income countries with high rates of infections, these strategies might not be practical because of the costs associated with the need to determine the HIV status of the mother and the need for skilled personnel for delivery (2, 5, 12, 16); hence effective, affordable and simple strategies are needed for the prevention of mother-to-child transmission of HIV. Because a pregnant HIV-infected woman and her child are susceptible to nutritional deficiencies, including vitamin A (4), and because vitamin A plays an important role in immune function (17–19), vitamin A supplementation in pregnancy has been suggested as a potential low-cost intervention to reduce the risk of mother-to-child transmission of HIV. The acute phase response to infection can reduce serum retinol concentrations (20) used to determine vitamin A status. Observational studies have shown a link between low serum retinol and disease severity or the risk of mother-to-child transmission of HIV. Thus, the levels of serum retinol may not be a reliable predictor of the efficacy of a vitamin A intervention because low serum retinol in such situations may be more an index of disease severity rather than nutritional status.

In countries where vitamin A deficiency is a public health problem, WHO recommends periodic administration of high-dose vitamin A supplements to children 6–59 months of age to reduce mortality (21). Although vitamin A supplements are not recommended as part of routine antenatal care for the prevention of maternal and infant morbidity and mortality, they are recommended in pregnant women for the prevention of night blindness in areas where there is a severe public health problem of vitamin A deficiency (22). The evidence for benefits of vitamin A supplementation in HIV-positive women for the prevention of mother-to-child transmission of HIV in observational studies has been conflicting thus far (2).

Summary of evidence

An updated Cochrane systematic review was used to assess the effects and safety of vitamin A supplements in reducing the risk of mother-to-child transmission of HIV (2). This review also evaluated the effect of vitamin A supplementation in HIV-positive women on infant and maternal mortality and morbidity. A meta-analysis indicated that vitamin A supplementation in HIV-positive pregnant women has no significant effect on mother-to-child transmission of HIV compared with controls in children followed up at 3–24 months of age (three trials: risk ratio (RR) 1.05; 95% confidence interval (CI) 0.78–1.41). However, there was significant heterogeneity in the results of the trials, with one trial showing a significant increase in mother-to-child transmission of HIV (23). There was no evidence that vitamin A supplementation in HIV-positive pregnant women had an effect on maternal death (one trial: RR 0.49; 95% CI 0.04–5.37) or child death by 24 months of age (two trials: RR 1.03; 95% CI 0.88–1.20). None of the trials provided any information on the potential adverse effects of vitamin A supplementation in pregnancy.

The overall quality of the available evidence for the outcomes of mother-to-child transmission of HIV and child death was graded as moderate, whereas the quality of evidence for the outcome of maternal death was very low (Annex 1).

Recommendation

Vitamin A supplementation in HIV-positive pregnant women is not recommended as a public health intervention for reducing the risk of mother-to-child transmission of HIV (*strong recommendation*¹).

Remarks

- Women should be encouraged to receive adequate nutrition, which is best achieved through consumption of a healthy balanced diet, and to refer to guidelines on nutrient requirements for people living with HIV/AIDS (24) and guidelines on HIV and infant feeding (15).
- Recommendations for the treatment of xerophthalmia are not covered in this guideline. Existing guidelines for the treatment of xerophthalmia in women of reproductive age should be referred to in these cases (25).

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

- The guideline group members agreed that additional research in this area is of low priority.
- If new research is to be conducted, an appropriately powered, randomized controlled trial to assess the additive effect of vitamin A supplementation in pregnant women being treated with ART on the risk of mother-to-child transmission of HIV may be helpful.

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.

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](#) (26).

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 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 (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 pregnancy for reducing the risk of mother-to-child transmission of HIV, 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” table¹ (Annex 1). One existing Cochrane review on vitamin A supplementation in pregnancy for reducing the risk of mother-to-child transmission of HIV was updated, and the up-to-date Review Manager Software (RevMan) file, obtained from the Cochrane Editorial Unit, was customized in order 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 the evidence summaries according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for assessing the overall quality of the available evidence (27) (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 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 and discuss the draft recommendation and determine its strength, taking into consideration: (i) desirable and undesirable effects of this intervention; (ii) 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.

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](#) (28), 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)* (29). 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

A vitamin A trial conducted between September 1997 and December 2000 in Bloemfontein, Free State, South Africa, has been identified (30, 31) but it has not yet been published.

The recommendation in this guideline will be reviewed in 2014. 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](#) (26) procedures. WHO welcomes suggestions regarding additional questions for evaluation in this guideline when it is due for review.

References

1. UNAIDS, WHO. *Global report: UNAIDS report on the global AIDS epidemic*. Geneva, Joint United Nations Programme on HIV/AIDS (UNAIDS), 2010 (http://www.unaids.org/globalreport/documents/20101123_GlobalReport_full_en.pdf, accessed 25 March 2011).
2. Wiysonge CS et al. Vitamin A supplementation for reducing the risk of mother-to-child transmission of HIV infection. *Cochrane Database of Systematic Reviews*, 2011, (1):CD003648 (<http://www2.cochrane.org/reviews/en/ab003648.html>, accessed 25 March 2011).
3. Horvath T et al. Interventions for preventing late postnatal mother-to-child transmission of HIV. *Cochrane Database of Systematic Reviews*, 2009, (1):CD006734 (<http://www2.cochrane.org/reviews/en/ab006734.html>, accessed 25 March 2011).
4. Coutsooudis A. The relationship between vitamin A deficiency and HIV infection: review of scientific studies. *Food and Nutrition Bulletin*, 2001, 22:235–247.
5. *Consultation on Nutrition and HIV/AIDS in Africa: Evidence, lessons and recommendations for action Durban, South Africa, 10–13 April 2005*. Geneva, World Health Organization, 2005 (http://www.who.int/nutrition/topics/consultation_nutrition_and_hiv/aids/en/index.html, accessed 25 March 2011).
6. *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 25 March 2011).
7. Downie D et al. Moderate maternal vitamin A deficiency alters myogenic regulatory protein expression and perinatal organ growth in the rat. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 2005, 288:73–79.
8. Food and Nutrition Board, Institute of Medicine. Vitamin A. In: *Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc*. Washington, DC, National Academy Press, 2001:82–146.
9. *Indicators for assessing vitamin A deficiency and their application in monitoring and evaluation intervention programmes*. Geneva, World Health Organization, 1996 (http://www.who.int/nutrition/publications/micronutrients/vitamin_a_deficiency/WHONUT96.10.pdf, accessed 25 March 2011).
10. Dibley MJ, Jeacocke DA. Vitamin A in pregnancy: impact on maternal and neonatal health. *Food and Nutrition Bulletin*, 2001, 22:267–284.
11. Semba RD et al. Maternal vitamin A deficiency and mother-to-child transmission of HIV-1. *Lancet*, 1994, 343:1593–1597.
12. Volmink J et al. Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection. *Cochrane Database of Systematic Reviews*, 2007, (1):CD003510 (<http://www2.cochrane.org/reviews/en/ab003510.html>, accessed 25 May 2011).
13. Newell ML. Vertical transmission of HIV-1 infection. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 2000, 94:1–2.
14. Read JS, Newell M-L. Efficacy and safety of cesarean delivery for prevention of mother-to-child transmission of HIV-1. *Cochrane Database of Systematic Reviews*, 2005, (4): CD005479 (<http://www2.cochrane.org/reviews/en/ab005479.html>, accessed 29 May 2011).

15. WHO et al. *Guidelines on HIV and infant feeding. 2010. Principles and recommendations for infant feeding in the context of HIV and a summary of evidence.* Geneva, World Health Organization, 2010 (http://whqlibdoc.who.int/publications/2010/9789241599535_eng.pdf, accessed 25 March 2011).
16. McIntyre J. Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection: RHL commentary (last revised: 22 August 2007). *The WHO Reproductive Health Library.* Geneva, World Health Organization (http://apps.who.int/rhl/hiv_aids/jmicom/en/index.html, accessed 25 March 2011).
17. Ross AC, Stephensen CB. Vitamin A retinoids in antiviral responses. *FASEB Journal*, 1996, 10:979–985.
18. Semba RD. The role of vitamin A and related carotenoids in immune function. *Nutrition Reviews*, 1998, 56:S38–S48.
19. Fawzi WW. Nutritional factors and vertical transmission of HIV-1. Epidemiology and potential mechanisms. *Annals of the New York Academy of Sciences*, 2000, 918:99–114.
20. Thurnham DI et al. Effects of subclinical infection on plasma retinol concentrations and assessment of prevalence of vitamin A deficiency: meta-analysis. *Lancet*, 2003, 362:2052–2058.
21. *Guideline: vitamin A supplementation in infants and children 6–59 months of age.* Geneva, World Health Organization, 2011 (http://whqlibdoc.who.int/publications/2011/9789241501767_eng.pdf, accessed 25 July 2011).
22. *Guideline: vitamin A supplementation in pregnant women.* Geneva, World Health Organization, 2011 (http://whqlibdoc.who.int/publications/2011/9789241501781_eng.pdf, accessed 20 March 2012)
23. Fawzi WW et al. Randomized trial of vitamin supplements in relation to vertical transmission of HIV-1 in Tanzania. *Journal of Acquired Immune Deficiency Syndromes*, 2000, 23:246–254.
24. *Nutrient requirements for people living with HIV/AIDS: report of a technical consultation.* Geneva, World Health Organization, 2003 (<http://whqlibdoc.who.int/publications/2003/9241591196.pdf>, accessed 25 March 2011).
25. 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 25 March 2011).
26. *WHO Handbook for guideline development.* Guidelines Review Committee. Draft March 2010. Geneva, World Health Organization, 2010.
27. Atkins D et al. Grading quality of evidence and strength of recommendations. *British Medical Journal*, 2004, 328:1490.
28. *Basic documents*, 47th ed. Geneva, World Health Organization, 2009 (<http://apps.who.int/gb/bd/>, accessed 19 May 2011).
29. *Guidelines for declaration of interests (WHO experts).* Geneva, World Health Organization, 2010.
30. Chikobvu P et al. Lessons learned in establishing a randomised controlled trial to investigate the effect of vitamin A on vertical transmission of HIV. *Southern African Journal of Epidemiology and Infection*, 2000, 15:19–22.
31. Joubert G et al. Consent for participation in the Bloemfontein vitamin A trial: how informed and voluntary? *American Journal of Public Health*, 2003, 93:582–584.

Annex 1 GRADE “Summary of findings” table

Vitamin A supplementation in pregnancy for reducing the risk of mother-to-child transmission of HIV				
Patient or population: HIV-positive pregnant women				
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
Maternal mortality	RR 0.49 (0.04–5.37)	728 (1 study)	⊕⊖⊖⊖ very low ¹⁻³	Only one study reported on this outcome
Viral load/CD4 count (adverse effects) during pregnancy	Not estimable	0 (0 studies)		None of the studies reported on this outcome
HIV infection in child Follow-up: 3–24 months	RR 1.05 (0.78–1.41)	2022 (3 studies)	⊕⊕⊕⊖ moderate ⁴	
Child mortality Follow-up: 24 months	RR 1.03 (0.88–1.20)	1635 (2 studies)	⊕⊕⊕⊖ moderate ⁵	None of the studies reported on this outcome

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 Allocation, generation and concealment were not described. The study had an unclear risk of bias.

² In view of the single study that contributed data to this outcome, the degree of inconsistency is unknown rather than unobserved.

³ The imprecision around the relative effect is compatible with a very large increase in risk and a significant reduction in risk of maternal death.

⁴ High level of statistical heterogeneity; study results are discordant.

⁵ Wide confidence intervals around the pooled effect estimate.

For details of studies included in the review, see reference (2).

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

Dr Rintaro Mori

University of Tokyo
Tokyo, Japan
Paediatrics

Professor Michael Clarke

University of Oxford
Oxford, England
Methods

Dr A. Catherine Ross

Pennsylvania State University
University Park, United States of America
Vitamin A, immunology

Dr Anna Coutsooudis

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

Dr Isabella Sagoe-Moses

Ghana Health Service – Ministry of Health
Accra, Ghana
Programme Manager

Dr M. Monir Hossain

Bangladesh Institute of Child Health and
Dhaka Shishu (Children) Hospital
Sher-e-Bangla Nagar
Dhaka, Bangladesh
Neonatology

Dr Claudia Saunders

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

Dr Jean Humphrey

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

Dr Prak Sophonneary

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

Dr Yustina Anie Indriastuti

Indonesian Medical Doctor Nutrition
Society
Jakarta, Indonesia
Programme Manager

Dr Charles Stephensen

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

Dr Marzia Lazzarini

Institute for Maternal and Child Health
Trieste, Italy
Methods, paediatrics

Dr Sherry Tanumihardjo

University of Wisconsin
Madison, United States of America
Vitamin A metabolism

Dr Pavitra Mohan

UNICEF India Country Office
New Delhi, India
Paediatrics

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 Aguentaou

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 HIV-positive women during pregnancy

- a. Should vitamin A supplements be given to HIV-positive women during pregnancy to reduce mother-to-child transmission of HIV?
- b. If so, at what dose, and frequency and duration for the intervention?

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

- Population:**
- HIV-positive pregnant women living in countries where vitamin A deficiency may be of public health concern
 - Subpopulations:
 - By antiretroviral therapy (ART): receiving versus not receiving
- Intervention:**
- Any oral vitamin A supplement alone
 - Oral vitamin A supplement given in combination with other micronutrients
 - Subgroup analysis:
 - Dose and regimen: daily (10 000 IU) or weekly (25 000 IU) versus other doses
- Control:**
- Placebo or no treatment
 - Micronutrient supplements without vitamin A (to assess the additive effect of vitamin A)
- Outcomes:**
- Critical*
- Maternal
- Mortality
 - Adverse effects during pregnancy
 - Viral load/CD4 count
- Infant
- HIV status of infant
 - All-cause mortality within 0–6, 0–12 and 0–24 months of life
- Setting:** All countries



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

- Quality of evidence:**
- Moderate for two critical outcomes from three good randomized controlled trials
 - Very low quality of evidence for maternal mortality from only one study with wide confidence intervals
- Values and preferences:**
- No overall benefit on reducing transmission of HIV
 - Antiretroviral therapy (ART) is now available (was not available at the time that the trials were conducted)
- Trade-off between benefits and harm:**
- No apparent benefit of vitamin A supplementation
 - There is potential for harm (one study) but this is unclear at the present time
- Costs and feasibility:**
- Minimal cost
 - Feasible but feasibility may diminish in the light of other more beneficial interventions now available for pregnant women (e.g. ART, iron-folic acid supplementation)

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 150180 4



9 789241 501804