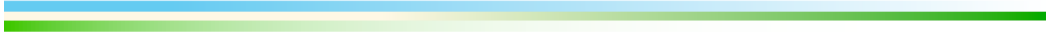




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Vitamin A supplementation in pregnant women



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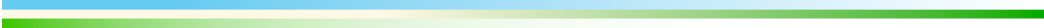
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Summary

Maternal mortality rates remain high, with approximately 1000 women dying from complications related to pregnancy or childbirth worldwide every day. Vitamin A deficiency affects about 19 million pregnant women, mostly from the 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. Member States have requested guidance from the World Health Organization (WHO) on the effects and safety of vitamin A supplementation in 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 recommendations, and to vote on the strength of the recommendations, 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 pregnancy as part of routine antenatal care is not recommended for the prevention of maternal and infant morbidity and mortality (strong recommendation). In areas where vitamin A deficiency is a severe public health problem, vitamin A supplementation in pregnancy is recommended for the prevention of night blindness (strong recommendation). The quality of the available evidence for maternal mortality was found to be high, whereas for all other critical outcomes it was moderate.

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 pregnant women for the prevention of morbidity, mortality and night blindness 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, improvement of maternal health (MDG 5). 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 recommendations and a summary of the supporting evidence. Further details of the evidence base are provided in Annexes 1 and 2 and other documents listed in the references.

Background

Worldwide, approximately 1000 women die every day from complications related to pregnancy or childbirth (1). Almost all of these deaths occur in developing countries and most could be averted by preventing complications such as severe bleeding (haemorrhage), infections, high blood pressure, obstructed labour, unsafe abortion and diseases such as malaria, anaemia and human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) during pregnancy (2). Although between 1997 and 2007 there was a decrease in the number of infant deaths from 60 to 40 per 1000 live births, infant mortality rates remain high in World Health Organization (WHO) regions such as Africa, Eastern Mediterranean and South-East Asia (3). Neonatal deaths account for 36% of deaths among children under 5 years of age worldwide (4). These deaths are mainly due to prematurity and low birth weight (31%), neonatal infections (26%), birth asphyxia (lack of oxygen at birth) and birth trauma (23%). A non-negligible proportion of neonates die because of congenital anomalies (6.8%), other non-infectious perinatal causes (5.7%), tetanus (5%) and diarrhoeal diseases (2.6%).

Vitamin A deficiency also remains a public health problem among women, affecting an estimated 19 million pregnant women (5), with the highest burden found in the 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 and maturation, 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 (6, 7). Thus, there is an increased need for vitamin A during pregnancy, although the additional amount required is small and the increased requirement is limited to the third trimester. The recommended nutrient intake (RNI) of vitamin A for women during pregnancy is 800 µg retinol equivalents (RE)/day (8), which may be difficult to achieve through the diet alone in vitamin A-deficient areas. Dietary sources of provitamin A include vegetables such as carrot, pumpkin, papaya and red palm oil; animal foods rich in preformed vitamin A include dairy products (whole milk, yogurt, cheese), liver, fish oils and human milk (7, 8).

Although pregnant women are susceptible to vitamin A deficiency throughout gestation, deficiency is most common in the third trimester due to accelerated fetal development and the physiological increase in blood volume during this period (9, 10). In a pregnant woman with moderate vitamin A deficiency, the fetus can still obtain sufficient vitamin A to develop appropriately, but at the expense of the maternal vitamin A stores (11). Vitamin A deficiency may also occur during periods when infectious disease rates are high and/or during seasons when food sources rich in vitamin A are scarce (12). The prevalence of night blindness (a consequence of vitamin A deficiency) is also more common in the third trimester of pregnancy, and populations with a prevalence $\geq 5\%$ are considered to have a significant public health problem with regard to vitamin A deficiency (5, 13). It is currently estimated that 9.8 million pregnant women are affected by night blindness worldwide (5).

There is some indication that low doses of vitamin A supplements given on a daily or weekly basis, starting in the second or third trimester, can reduce the severity of decline in maternal serum retinol levels during late pregnancy and the symptoms of night blindness (14). One study has suggested that 12 weeks of supplementation is needed to prevent decline in serum retinol levels (15).

Vitamin A is available in multiple vitamin formulations for prenatal care in some countries. When provided alone, the compounds most commonly used are retinyl palmitate and retinyl acetate in tablet form or oil-based solutions. Alternative forms of delivery include fish liver oils, β -carotene, and a combination of β -carotene and vitamin A. Recommended doses of vitamin A supplements are generally well tolerated by pregnant women; however, vitamin A may become toxic for the mother and her fetus when levels of intake exceed 10 000 IU daily or 25 000 IU weekly (16). β -carotene, a precursor of vitamin A, may be preferred over vitamin A supplements in pregnant women because excess of β -carotene is not known to cause birth defects (17).

The symptoms of acute vitamin A toxicity include dizziness, nausea, vomiting, headaches, blurred vision, vertigo, reduced muscle coordination, skin exfoliation, weight loss and fatigue (18). Toxicity generally results from excessive ingestion of vitamin A supplements but regular intake of large amounts of liver, although usually not a problem in vitamin A-deficient areas, may also result in toxicity due to its high content of vitamin A (19).

Summary of evidence

Two Cochrane systematic reviews assessing the effects and safety of vitamin A supplementation in pregnant women were updated for this guideline (20, 21). The first review evaluated the effectiveness of vitamin A (or one of its derivatives) supplementation in pregnancy, alone or in combination with other vitamins and minerals, in relation to maternal and newborn outcomes (20). It showed that giving vitamin A supplements to women during pregnancy had no effect on the risk of maternal mortality (three trials: risk ratio (RR) 0.78; 95% confidence interval (CI) 0.55–1.10), perinatal mortality (one trial: RR 1.01; 95% CI 0.95–1.07), neonatal mortality (three trials: RR 0.97; 95% CI 0.90–1.05) or stillbirth (one trial: RR 1.06; 95% CI 0.98–

1.14). In one trial, vitamin A supplementation reduced the risk of maternal night blindness (RR 0.70; 95% CI 0.60–0.82). All trials that investigated maternal and perinatal mortality used weekly supplementation with vitamin A. WHO performed an additional meta-analysis after excluding one study conducted only in HIV-positive pregnant women. The only critical outcome affected by the removal of this study was neonatal mortality, although the effect of vitamin A supplementation remained non-significant (two trials: RR 1.00; 95% CI 0.88–1.14) (Annex 1).

The second review evaluated the effectiveness and safety of vitamin supplementation with regard to the risk of spontaneous miscarriage, maternal adverse outcomes and fetal and infant adverse outcomes (21). The review found no difference in total fetal loss (including miscarriages or combined miscarriages and stillbirths) in women given vitamin A compared with placebo (one trial: RR 1.04; 95% CI 0.92–1.17), β -carotene compared with placebo (one trial: RR 1.03; 95% CI 0.91–1.16), vitamin A with or without multivitamins compared with multivitamins (excluding vitamin A) or placebo (one trial: RR 0.80; 95% CI 0.53–1.21), or vitamin A plus iron and folic acid compared with iron and folic acid (three trials: RR 1.01; 95% CI 0.61–1.66). Similarly, there was no difference in the rates of stillbirth and neonatal deaths between women given any type of vitamin A, alone or in combination with β -carotene, multivitamins or iron and folic acid, compared with controls.

The overall quality of the available evidence for maternal mortality was high, whereas for all other critical outcomes it was moderate (Annex 2).

Recommendations

- Vitamin A supplementation is not recommended during pregnancy as part of routine antenatal care for the prevention of maternal and infant morbidity and mortality (*strong recommendation*¹).
- In areas where there is a severe public health problem related to vitamin A deficiency², vitamin A supplementation during pregnancy is recommended for the prevention of night blindness (*strong recommendation*¹). A suggested vitamin A supplementation scheme is presented in Table 1.

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.

² 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 (5).

Table 1

Suggested vitamin A supplementation scheme in pregnant women for the prevention of night blindness in areas with a severe public health problem related to vitamin A

Target group	Pregnant women
Dose	Up to 10 000 IU vitamin A (daily dose) OR Up to 25 000 IU vitamin A (weekly dose)
Frequency	Daily or weekly
Route of administration	Oral liquid, oil-based preparation of retinyl palmitate or retinyl acetate
Duration	A minimum of 12 weeks during pregnancy until delivery
Settings	Populations where the prevalence of night blindness is 5% or higher in pregnant women or 5% or higher in children 24–59 months of age

IU, international units

Remarks

- This guideline replaces previous recommendations for vitamin A supplementation in mothers for the prevention of vitamin A deficiency (22) and for improving the vitamin A status of mothers and their infants (23).
- Other interventions such as dietary diversification (8) and food fortification (24) can be used along with vitamin A supplementation to improve vitamin A intakes.
- Pregnant 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 healthy eating during pregnancy (25).
- A single dose of a vitamin A supplement greater than 25 000 IU is not advisable, particularly between day 15 and day 60 following conception (day 0); beyond 60 days after conception, the safety of a single dose of vitamin A greater than 25 000 IU is uncertain. The risk for non-teratogenic developmental toxicity is likely to diminish as pregnancy advances (23).

- There is no demonstrated benefit from taking vitamin A supplements in populations where the habitual vitamin A intakes exceed at least three times the RNI (about 8000 IU or 2400 µg RE), and the potential risk of adverse events increases with higher intakes (above 10 000 IU) if supplements are routinely taken (23).
- A quality assurance process should be established to guarantee that supplements are manufactured, packaged and stored in a controlled and uncontaminated environment (26).
- When determining the vitamin A status of a population, guidelines on indicators for assessing vitamin A deficiency should be referred to (27, 28).
- 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 (22).

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, this intervention 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 the 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 programme evaluation theory (29). 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 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

- Additional research on vitamin A supplementation in pregnant women may be useful for further informing policy decisions; however, this should be considered in context with other interventions that show more potential to reduce mortality.
- If further studies are conducted, they should investigate the optimal dosing of vitamin A supplements and the duration and frequency of supplementation during pregnancy required to reduce night blindness.
- Evidence on vitamin A (preformed and provitamin A carotenoids) supplementation (with other recommended vitamins and minerals such as iron and folic acid) in the last trimester of pregnancy for improving levels of retinol in breast milk and its consequent delivery to the breastfed child should be reviewed and summarized.

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](#) (30).

Advisory groups

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

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

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

Scope of the guideline, evidence appraisal and decision-making

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

The first guideline group meeting was held on 19–20 October 2009 in Geneva, Switzerland, to finalize the scope of the questions and rank the critical outcomes and populations of interest. The guideline group members discussed the relevance of each 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 pregnant women, along with the outcomes that were identified as critical for decision-making, are listed in PICO format in Annex 6.

The [Cochrane Collaboration](#) was commissioned to search, review and generate systematic reviews, evidence profiles and the “Summary of findings” table¹ (Annex 2). Two existing Cochrane reviews on vitamin A supplementation in pregnant women were updated, and the up-to-date Review Manager Software (RevMan) files, obtained from the Cochrane Editorial Unit, were customized in order 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 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 (31) (Annex 2). GRADE considers: the study design; the limitations of the studies in terms of their conduct and analysis; the consistency of the results across the available studies; the directness (or applicability and external validity) of the evidence with respect to the populations, interventions and settings where the proposed intervention may be used; and the precision of the summary estimate of the effect.

Both the systematic 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 and discuss the draft recommendations and to determine their strength, taking into consideration: (i) desirable and undesirable effects of this intervention; (ii) the quality of the available evidence; (iii) values and preferences related to the intervention in different settings; and (iv) the cost of options available to health-care workers in different settings (Annex 7). Consensus was defined as agreement by simple majority of the guideline group members. WHO staff present at the meeting as well as other external technical experts involved in the collection and grading of the evidence were not allowed to vote. There were no strong disagreements among the 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](#) (32), 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)* (33). 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.

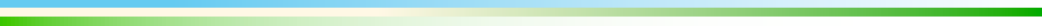
Plans for updating the guideline

The recommendations in this guideline will be reviewed in 2015. If new information is available at that time, a guideline review group will be convened to evaluate the new evidence and revise the recommendations. 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](#) procedures (30). WHO welcomes suggestions regarding additional questions for evaluation in this guideline when it is due for review.

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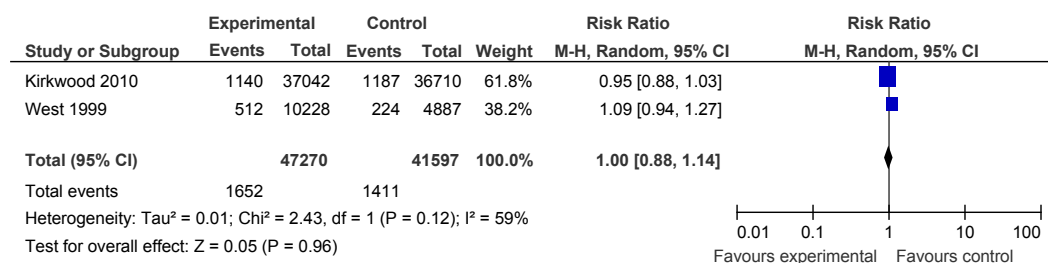
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Annex 1 Additional analyses

Figure A.1

Forest plot for neonatal mortality in studies evaluating vitamin A supplementation in pregnancy



CI, confidence interval; M-H, Mantel-Haenszel

For details of studies included in the review, see reference (20).

Annex 2 GRADE “Summary of findings” table

Vitamin A supplementation in pregnant women

Patient or population: Pregnant women

Settings: Countries in which vitamin A deficiency may be a public health concern

Intervention: Vitamin A supplementation alone

Outcomes	Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)*	Comments
Maternal mortality (while pregnant or within 42 days of pregnancy)	RR 0.78 (0.55–1.10)	101 574 (3 studies)	⊕⊕⊕⊕ high ¹	
Maternal night blindness (incidence during pregnancy)	RR 0.70 (0.60–0.82)	10 608 (1 study)	⊕⊕⊕⊖ moderate ²	Only one study reported on this outcome
Maternal ocular lesions	Not estimable	0 (0 studies)		None of the studies reported on this outcome
Total fetal loss (including miscarriages or combined miscarriages and stillbirths) Follow-up: 24 weeks	RR 1.04 (0.92–1.17)	11 723 (1 study)	⊕⊕⊕⊖ moderate ²	Only one study reported on this outcome
Neonatal mortality Follow-up: 28 days	RR 1.00 (0.88–1.14)	88 867 (2 studies)	⊕⊕⊕⊖ moderate ²	
Perinatal mortality (number of stillbirths and deaths in the first week of life)	RR 1.01 (0.95–1.07)	76 176 (1 study)	⊕⊕⊕⊖ moderate ^{2,3}	Only one study reported on this outcome
Infant morbidity	Not estimable	0 (0 studies)		None of the studies reported on this outcome
Sepsis	Not estimable	0 (0 studies)		None of the studies reported on this outcome
Birth defects	Not estimable	0 (0 studies)		None of the studies reported on this outcome
Stillbirths	RR 1.06 (0.98–1.14)	78 835 (1 study)	⊕⊕⊕⊖ moderate ^{2,3}	Only one study reported on this outcome

CI, confidence interval; RR, risk ratio.

*GRADE Working Group grades of evidence:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We have moderate confidence in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.

¹ The authors considered that the pooled effect estimate was not biased by the design of the studies or their analysis of data. Following correspondence received from the trialists for Kirkwood (2010) (see reference (20), the loss to follow-up for this study was 8%: the data from this study are not at risk of attrition bias.

² With only one study included, inconsistency is unknown rather than unobserved.

³ The authors considered that the result was not biased by study design or data analysis. Following correspondence received from the trialists for Kirkwood (2010) (see reference (20), the loss to follow-up for this study was 8%: the data from this study are not at risk of attrition bias.

For details of studies included in the review, see reference (20).

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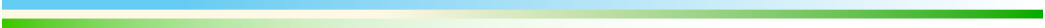
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Annex 6 Questions in Population, Intervention, Control, Outcomes (PICO) format

Effects and safety of vitamin A supplementation in women during pregnancy

- a. Should vitamin A supplements be given to pregnant women?
- b. If so, at what dose, frequency and duration for the intervention?

- Population:**
- Pregnant women living in countries where vitamin A deficiency may be of public health concern
 - Subpopulations:
 - By infant mortality rates: countries with low versus high rates
 - By maternal mortality rates: countries with low versus high rates
 - By prevalence of HIV in the general population: countries with a low versus high prevalence
- For infant outcomes only*
- By infant exposure to additional vitamin A: infants who received a vitamin A supplement within the first 28 days of life and/or at 1–5 months of age versus those who received no additional vitamin A
 - By breastfeeding initiation: early initiation (within 1 hour of birth versus other)
 - By breastfeeding practices: exclusively breastfed at 3 versus 6 months versus others as defined using [WHO Indicators for assessing infant and young child feeding practices](#)
- Intervention:**
- Any oral vitamin A supplement alone
 - Oral vitamin A supplement given in combination with other micronutrients
 - Subgroup analyses:
 - By dose and regimen: daily (10 000 IU) or other
 - By regimen: daily versus weekly
 - By duration of intervention
 - By trimester of pregnancy in which supplementation was started
- Control:**
- Placebo or no treatment
 - Micronutrient supplements (ie. iron-folic acid) without vitamin A (to assess the additive effect of vitamin A)
 - Supplements containing β -carotene
- Outcomes:**
- Critical*
- Maternal*
- Mortality
 - Clinical signs of vitamin A deficiency at any time after supplement has been given
 - Night blindness
 - Ocular lesions
 - Adverse effects during pregnancy: miscarriage
- Infant*
- All-cause mortality–perinatal/neonatal/all
 - Morbidity
 - Sepsis
 - Birth defects (any)
 - Stillbirths
- Setting:**
- All countries



Annex 7 Summary of considerations for determining the strength of the recommendation

Quality of evidence:	• Moderate to high quality of evidence of no effect for the critical outcomes, except for night blindness, for which one study showed a beneficial effect in populations with a high prevalence of night blindness
Values and preferences:	• Without clear evidence of benefit, practitioners and pregnant women may not readily accept this intervention
Trade-off between benefits and harm:	• Potential benefit of preventing night blindness in populations with a high prevalence of night blindness (one study conducted in a population with a 10% prevalence of night blindness). In the same study, a reduction of maternal mortality was also observed • No evidence of harm
Costs and feasibility:	• Minimal cost • Feasible but feasibility may diminish in the light of other interventions now available for pregnant women (e.g. iron-folic acid supplementation)

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