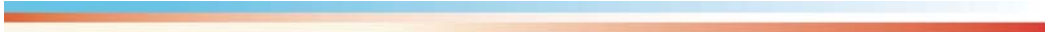




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Guideline:

Neonatal vitamin A supplementation



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Summary

Infants and young children have increased vitamin A requirements to support rapid growth and to help combat infections. Member States have requested guidance from the World Health Organization (WHO) on the effects and safety of vitamin A supplementation in the neonatal period (first 28 days of life) as a public health strategy.

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; 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.

Neonatal vitamin A supplementation is not recommended as a public health intervention to reduce infant morbidity and mortality (strong recommendation). The quality of the available evidence for mortality-related outcomes was found to be moderate. Mothers should continue to be encouraged to exclusively breastfeed infants for the first 6 months to achieve optimal growth, development and health.

Four randomized, double-blind, placebo-controlled trials are currently being conducted in Pakistan, India, Ghana and Tanzania to assess the feasibility of delivering neonatal vitamin A supplements through health workers and to evaluate the efficacy of neonatal vitamin A supplementation in improving child survival. In addition, there are ongoing studies on the impact of neonatal vitamin A supplementation on immune function and organ maturation, and an animal study on the metabolism of vitamin A at birth is also in progress. The results of these studies will provide further knowledge to help inform updates to this guideline in the future.

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 the neonatal period (first 28 days of life) for the reduction of morbidity and mortality during infancy.

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 19 million pregnant women and 190 million preschool-age children, mostly from the World Health Organization (WHO) regions of Africa and South-East Asia (1). Infants and young children have increased vitamin A requirements to support rapid growth and to help combat infections. Generally, infants are born with low vitamin A stores (2) and are dependent on external sources, most importantly breast milk, for optimization of their vitamin A levels and body stores. In low- and middle-income countries, infants are likely to receive inadequate amounts of vitamin A from breast milk due to poor maternal nutritional status. However, inadequate vitamin A levels at this age may lead to vitamin A deficiency which, when severe, can cause visual impairment (night blindness), anaemia, weakened resistance to infections, and can also increase the risk of illness and death from common childhood infections such as measles and those causing diarrhoea (3).

In countries where vitamin A deficiency is a public health problem, programmes providing high-dose vitamin A supplements to children 6–59 months of age are being implemented as a child survival strategy. These programmes are reaching 71% of this population in developing countries (4).

There has been considerable interest in vitamin A supplementation in the neonatal period, which was initially proposed as a means to increase the body's vitamin A stores at this age (5), and more recently as a strategy to improve infant survival. However, while three trials, conducted in Indonesia, India and Bangladesh, have shown a reduction in mortality during infancy (5–7), four other trials, conducted in Nepal, Zimbabwe and Guinea-Bissau, did not find any overall reduction in infant mortality (8–11). When the results from the two trials conducted in Guinea-Bissau were pooled, a differential effect was seen by sex, with boys showing reduced mortality and girls showing increased mortality, although a pooled meta-analysis of the other studies did not show this difference (12).

Vitamin A may decrease the risk and/or severity of infections by strengthening the epithelial barrier and by boosting the neonatal immune responses in those at risk of

vitamin A deficiency through actions particularly on the development and functions of the various cells of the immune system (13). Vitamin A may also be involved in the development of an appropriate balance of key regulatory immune cells and specific mucosal antibodies in the gut (13); this is essential in the first days of life as the neonatal immune system has to balance its defensive role against pathogenic invasion with tolerance to the developing commensal gut flora. Because of the role of vitamin A in the maturation of organs, including the lung, through the orderly growth and maintenance of epithelial tissues and development of the immune system, neonatal vitamin A supplementation could potentially have an impact on an infant's resistance to infection and diarrhoea, which is the cause of approximately 30% of neonatal deaths (14, 15). Vitamin A supplementation in older infants and children has been shown to have a heterogeneous effect on respiratory infections (16), suggesting that the potential for unanticipated effects mediated via the immune system should also be considered in younger infants.

Administration of vitamin A in recommended doses is not associated with serious or long-term side-effects. However, a single high dose of vitamin A can cause transient acute side-effects in infants, such as bulging fontanelles, vomiting, diarrhoea, loss of appetite and irritability. The most common of these is bulging of the fontanelles, but this is benign and not associated with acute or long-term neurodevelopmental effects (17, 18).

Summary of evidence

Three systematic reviews (12, 19, 20) have evaluated the effects and safety of neonatal vitamin A supplementation, of which one evaluated the role of vitamin A supplementation in only term neonates (born between 37 and 42 weeks' gestation) in developing countries, with respect to prevention of mortality and morbidity (19). However, the studies in this review enrolled infants identified in the study settings with no restrictions regarding gestational age of either less than or more than 37 weeks at birth. Thus the use of term only data was not possible in all instances. There was no effect of vitamin A supplements on infant mortality at 12 months of age (four trials: risk ratio (RR) 1.02; 95% confidence interval (CI) 0.87–1.20). Limited data showed no significant effect of vitamin A supplements on the outcomes of mortality related to respiratory infection (one trial: RR 0.66; 95% CI 0.11–3.95) and diarrhoea (one trial: RR 0.40; 95% CI 0.08–2.03). Data on adverse events in all infants during the first 48–72 hours after supplementation were available for pooling in only two studies. There was a significant increase in the risk of bulging fontanelles (RR 1.38; 95% CI 1.04–1.82) but not vomiting (RR 0.88; 95% CI 0.74–1.05) or diarrhoea (RR 0.92; 95% CI 0.77–1.09).

One systematic review evaluated the role of vitamin A supplementation in infants less than 6 months of age, with a subgroup analysis for age at initiation of supplementation (neonatal period, that is, from birth to less than 1 month of age), in low- and middle-income countries with respect to prevention of mortality and morbidity, and other effects, until 1 year of age (20). Analysis of data from seven trials showed no significant reduction in the relative risk of mortality during infancy, from the period of initiation of supplementation to the last follow-up until 1 year of age, in neonates supplemented with vitamin A as compared with controls (RR 0.94; 95% CI

0.79–1.12). The remaining analyses were combined for all infants 0–6 months of age. There was no evidence of a reduced risk of morbidity or mortality related specifically to diarrhoea or acute respiratory infection with vitamin A supplementation. There was a non-significant increase in the occurrence of bulging fontanelles within 1 week following administration of the first dose of vitamin A (doses ranged from 25 000 IU to 100 000 IU), but there was no evidence of an increased risk of vomiting, irritability or diarrhoea.

The meta-analysis assessing the survival effect of vitamin A given to neonates within a few days of birth in six trials found no significant effect of vitamin A supplements on all-cause mortality and no differential effect of the intervention on boys versus girls (12).

The overall quality of the available evidence for the mortality-related outcomes was moderate and the quality of evidence for adverse outcomes ranged from moderate to high for various adverse outcomes (Annex 1).

Recommendation

At the present time, neonatal vitamin A supplementation (that is, supplementation within the first 28 days after birth) is not recommended as a public health intervention to reduce infant morbidity and mortality (*strong recommendation*¹).

Remarks

- Neonatal vitamin A supplementation may reduce mortality in the first 6 months of life in some settings, with some minor, transient side-effects, although these findings are inconsistent.
- In developing the recommendation, high value was placed on avoidance of harm, given the uncertainty of the evidence and the conflicting results of research studies, as well as costs and feasibility concerns.
- Mothers should be encouraged to exclusively breastfeed their infants during the first 6 months of age to achieve optimal growth, development and health (21).
- Recommendations for the treatment of xerophthalmia are not covered in this guideline. Existing guidelines for the treatment of xerophthalmia in infants less than 6 months of age should be referred to in these cases (22).

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.

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 the 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

- Four randomized, double-blind, placebo-controlled trials are currently being conducted in Pakistan, India, Ghana and Tanzania to assess the feasibility of delivering neonatal vitamin A supplements through health workers and to evaluate the efficacy of neonatal vitamin A supplementation in improving child survival. All these studies are using a cluster randomized design. Recruitment and follow-up for the Pakistan study has been completed and data analysis is in progress. The studies from India, Ghana and Tanzania are being supported by WHO and are expected to be completed by 2013. In addition, studies to understand the impact of neonatal vitamin A supplementation on immune function and organ maturation, as well as an animal study on the metabolism of vitamin A at birth, are in progress and will provide further knowledge to help inform future updates to this guideline.
- Further research is needed on the effects of neonatal vitamin A supplementation on infant morbidity and mortality in the first half of infancy in different settings. These should also include anthropometric measures, maternal micronutrient status (vitamin A), breastfeeding patterns and breast milk vitamin A concentrations.
- Efforts should be made to stratify the effect of supplementation by age at which vitamin A is administered after birth, prematurity and intrauterine growth retardation.
- Focus should be placed on populations with endemic maternal vitamin A deficiency and high infant mortality.
- Possible interactions with vaccination status and sex also need to be tested.
- Studies should be conducted to elucidate the biological mechanisms that may underlie the effects of vitamin A supplements on organ maturation and immune function in human infants (23).
- The rationale of neonatal vitamin A supplementation relies on its potential use as an infant survival strategy because of the feasibility of delivery

immediately after birth. However, operational research on how to reach most babies in developing countries within 2 days of birth is required in general, and not exclusively in the context of neonatal vitamin A supplementation.

- A pooled analysis of all existing trials may be conducted to explore the effects of neonatal vitamin A supplementation stratified by the following characteristics, subject to availability of information: time of supplementation (first 24 hours, 48 hours, 72 hours or within the first week of life); season in which supplementation was carried out; sex; vaccines received during follow-up; birth weight, and if possible, gestational age; maternal vitamin A status; time of initiation of breastfeeding; maternal human immunodeficiency virus (HIV) status; maternal vitamin A supplementation; and subsequent infant vitamin A supplementation.
- Additional research is also needed on the development of better indicators of vitamin A status in neonates.

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](#) (24).

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 (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 neonatal vitamin A supplementation, 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). Two existing reviews on vitamin A supplementation in neonates 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 (25) (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

¹ As part of the Cochrane pre-publication editorial process, reviews are commented on by external peers (an editor, and two referees who are 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.

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* (26), 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)* (27). 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.

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- 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 ^{13}C 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 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](#) (24) procedures. WHO welcomes suggestions regarding additional questions for evaluation in the guideline when it is due for review.

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Annex 1 GRADE “Summary of findings” table

| Neonatal vitamin A supplementation | | | | |
|--|-------------------------------|----------------------------------|--|------------------------------|
| Patient or population: Neonates | | | | |
| Settings: Low- and middle-income countries | | | | |
| Intervention: Vitamin A supplementation | | | | |
| Outcomes | Relative effect (95% CI) | Number of participants (studies) | Quality of the evidence (GRADE)* | Comments |
| Mortality within the first year of life (outcome measured at last available time point) Follow-up: 6–12 months | RR 0.94 (0.79–1.12) | 38 865 (7 studies) | ⊕⊕⊕⊕ moderate ¹ | |
| Respiratory-related mortality at 12 months Follow-up: 12 months | RR 0.66 (0.11–3.95) | 1839 (1 study) | ⊕⊕⊕⊕ moderate ² | Only one study reported |
| Diarrhoea-related mortality at 12 months Follow-up: 12 months | RR 0.40 (0.08–2.03) | 1839 (1 study) | ⊕⊕⊕⊕ moderate ^{3,4} | Only one study reported |
| Measles-related infant mortality at 12 months | Not estimable | 0 (0 studies) | | None of the studies reported |
| Morbidity within the first year of life | Not estimable | 0 (0 studies) | | None of the studies reported |
| Respiratory-related morbidity at 12 months | Not estimable | 0 (0 studies) | | None of the studies reported |
| Diarrhoea-related morbidity at 12 months | Not estimable | 0 (0 studies) | | None of the studies reported |
| Adverse events: bulging fontanelle Follow-up: 3 days | RR 1.38 (1.04–1.82) | 3158 (2 studies) | ⊕⊕⊕⊕ high | |
| Adverse events: vomiting Follow-up: 3 days | RR 0.88 (0.74–1.05) | 3159 (2 studies) | ⊕⊕⊕⊕ moderate ^{5,6} | |
| Adverse events: diarrhoea Follow-up: 3 days | RR 0.92 (0.77–1.09) | 3159 (2 studies) | ⊕⊕⊕⊕ moderate ^{7,8} | |

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

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 There was variation between the results of the studies.

² The confidence intervals around the point estimate were wide, including both a significant benefit of the intervention and an increase in the risk of acute respi

³ Due to lack of more than one study, the inconsistency is unknown.

⁴ The confidence intervals around the point estimate were wide, including both a significant benefit of the intervention and an increase in the risk of diarrhoea-r

⁵ Only two of the included studies reported this outcome. The authors note that data reported on this outcome specified different time points and could not be

⁶ In view of the high event rates for this outcome, the width of the confidence intervals led to substantial variation in the absolute effect from a protective effect to risk of vomiting.

⁷ There was a high level of statistical heterogeneity (I^2 80%).

⁸ Only two of the included studies reported this outcome. The authors note that data reported on this outcome specified different time points and could not be

For details of studies included in the reviews, see references (12,19 and 20).

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Annex 5

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

Effects and safety of neonatal vitamin A supplementation

- a. Should vitamin A supplements be given to neonates?
- b. If so, at what dose and time after birth?

- Population:**
- Neonates 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 exposure to vitamin A: neonates whose mothers received vitamin A supplementation in pregnancy or in the postpartum period versus no maternal supplementation/unknown
 - By breastfeeding initiation: early initiation (within 1 hour of birth versus other)
 - By breastfeeding practices: exclusively breastfed at 3 months versus 6 months versus others as defined using [WHO Indicators for assessing infant and young child feeding practices](#)
 - By birth weight (very low birth weight (<1500 g) versus low birth weight (<2500 g) versus normal weight (≥2500 g))
 - By gestational age at birth (<34 weeks versus <37 weeks versus ≥37 weeks)
- Intervention:**
- Any oral vitamin A supplement given to newborn (50 000 IU versus other doses) in the neonatal period (0–28 days)
 - Subgroup analysis:
 - By timing of intervention: dose intended to be given within first 48 hours of birth versus later in the neonatal period (2–28 days)
- Control:**
- Placebo or no treatment
- Outcomes:** *Critical*
- Mortality within 0–12 months of life:
 - Any cause
 - Acute respiratory infections
 - Diarrhoea
 - Measles
 - Hospitalization/clinic visits (number and duration) during 0–12 months of life:
 - Any cause
 - Acute respiratory infections
 - Diarrhoea
 - Adverse effects within 72 hours after receiving supplement:
 - Bulging fontanelles
 - Vomiting
 - Other
- Setting:** All countries



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

- Quality of evidence:**
- Moderate to high quality of evidence for all critical outcomes, including adverse effects
- Values and preferences:**
- Most mortality occurs in the first month of life and interventions to reduce this mortality are valuable
 - Some mothers may not be willing to give a supplement to their newborns
 - Concern that this intervention may send conflicting messages to mothers who are exclusively breastfeeding
- Trade-off between benefits and harm:**
- There is uncertainty if the benefits outweigh the harms
 - Some evidence of potential benefit
 - Analysis from studies by one research team suggest potential harm in girls, although four other studies by other groups (one with unpublished data) did not suggest this
- Costs and feasibility:**
- This is a complicated intervention and may not be easily implemented. Operational research still needed
 - Implementing this intervention may take away from other existing programmes (e.g. early initiation of breastfeeding, colostrum)

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