World Health Organization

Guideline:

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

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WHO Guideline[1]

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

Summary

Vitamin A deficiency affects about 19 million pregnant women and 190 million preschool-age children, mostly from the World Health Organization (WHO) regions of Africa and South-East Asia. Infants and children have increased vitamin A requirements to support rapid growth and to help them combat infections. Member States have requested guidance from WHO on the effects and safety of vitamin A supplementation in infants and children 6–59 months of age as a public health strategy in support of their efforts to achieve the Millennium Development Goals.

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

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

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

Scope and purpose

This guideline provides global, evidence-informed recommendations on the use of vitamin A supplements in infants and children 6–59 months of age for the reduction of morbidity and mortality.

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

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

Background

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

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

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

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

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

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

Summary of evidence

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

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

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

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

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

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

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

Recommendation

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

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