PROPOSAL TO REVISE WHO RECOMMENDATION ON PREVENTIVE VITAMIN A SUPPLEMENTATION FOR INFANTS <6 MONTHS IN HIGH MORTALITY SETTINGS:

EVIDENCE TO RECOMMEND PREVENTIVE VITAMIN A SUPPLEMENTATION OF INFANTS <6 MONTHS OF AGE IS INSUFFICIENT:
DELETION OF 50000IU CAPSULE DOSAGE FORM PROPOSED

INTRODUCTION

Vitamin A deficiency is a public health problem in more than half of all countries, especially in Africa and South-East Asia, hitting hardest young children and pregnant women in low-income countries (1).

In countries where vitamin A deficiency is a public health problem, WHO and UNICEF recommend periodic, high-dose vitamin A for 6-59 month old children, either as routine programmes or linked to sick-child visits and national poliomyelitis immunization days (1). This is based on a systematic review of published evidence from sub-Saharan Africa and South-East Asia that showed a 23% reduction in child mortality with this intervention (2).

Whether vitamin A supplementation should be extended to infants less than 6 months of age has been a subject of research for over a decade. Randomized controlled trials in 1-5 month old infants, including large WHO supported multi-centre trials, showed no benefit vitamin A supplementation (50,000 I.U. or 100,000 I.U. single dose or 25,000 I.U. given three times) on mortality, morbidity and growth during follow up period (3-5). Randomized controlled trials of neonatal vitamin A supplementation, including two large trials published in 2008, have reported inconsistent effects of the administration of a 50,000 IU vitamin A dose on infant mortality (6-10). Currently, the Model List of Essential Medicines for Children lists a 50000IU capsule, and an oral oily solution, 100000IU/ml that would be indicated for this purpose.

In order to look at the issue comprehensively, WHO commissioned a systematic review of the literature on the efficacy of vitamin A supplements administered in the first 6 months of life in reducing infant mortality and morbidity. This report has not yet been published in full but a brief summary of it is provided below.

RESULTS OF A SYSTEMATIC REVIEW OF EFFICACY OF VITAMIN A SUPPLEMENTATION OF INFANTS <6 MONTHS OF AGE IN REDUCING INFANT MORTALITY

The systematic review identified 8 randomized controlled trials (RCTs) that had examined the effect of vitamin A supplementation in the first 6 months of life on infant mortality in high mortality settings, 6 trials that reported effects on morbidity and 12 that had investigated adverse effects (11).
Among the 8 RCTs that considered mortality outcomes, 5 had initiated supplementation in the neonatal period, 2 in the 1-5 month period and one had supplemented 0-5 month old infants. Four of these trials were conducted in Asia, 3 in Africa and one was a multi-centre trial involving Asia, Africa and Latin America. Two of the trials were cluster-randomized and the remaining were individually randomized. Total dose used ranged between 50,000 I.U and 100,000 I.U. There was no evidence of publication bias.

A meta-analysis indicated no evidence of a significant effect of the intervention on mortality during the neonatal period or during infancy (pooled relative risk 0.96, 95% confidence interval 0.82 to 1.12; random effects model). There was no evidence of reduction of diarrhoea or pneumonia specific mortality in 3 studies that reported cause-specific mortality.

Stratification by study factors including age at supplementation, attrition rate, concurrent maternal vitamin A supplementation, number of vitamin A doses, period for which follow up was conducted did not show any significant differences in any of the subgroups.

Pooling the results of the 6 studies that reported on morbidity, there was no significant effect on diarrhoea (6 trials), acute respiratory infections (4 studies) or all-cause clinic visits (4 studies).

The analysis of the 12 studies that were considering the adverse effects, carried out with a random effects model, indicated that there was a significantly higher risk for developing a bulging fontanel following any dose of vitamin A (RR 1.53, 95% CI 1.03 to 2.27), a second dose of vitamin A (RR 3.60, 95% CI 1.65 to 7.87), and a third dose of vitamin A (RR 3.14, 95% CI 1.72 to 5.74) but the risk was not significantly increased after a single dose of vitamin A (RR 1.35, 95% CI 0.96 to 1.90).

RATIONALE FOR THE PROPOSAL

About a decade ago WHO recommended preventive vitamin A supplementation of infants under 6 months of age with a 50,000 I.U. dose (1). The recently conducted systematic review of evidence in this area does not support this recommendation. Current evidence does not support the statement that preventive vitamin A supplementation of infants <6 months of age in high mortality settings reduces mortality and morbidity during infancy. Conversely, there is evidence that multiple vitamin A doses and may be associated with bulging fontanelle.

PROPOSAL

WHO should revise its current recommendation and indicate that vitamin A supplementation of infants <6 months with a dose of 50,000 I.U. is not a recommended intervention to reduce child morbidity and mortality in high child mortality settings. The 50,000 I.U. vitamin A formulation may continue to be used for the treatment of clinical vitamin A deficiency in infants under 6 months of age.

The Expert Subcommittee is requested to consider adding a note in the EMLC to specify that vitamin A supplementation of infants <6 months for preventing infant mortality and morbidity in high child mortality settings is not an indication for the use of the 50,000 I.U. or 100,000 formulation of vitamin A. Alternatively, consider adding a note to specify that 50,000 I.U. dose is for use only for treatment of clinical vitamin A deficiency in infants under 6 months of age.
REFERENCES


