1. **What is newborn vitamin A supplementation (NVAS)?** NVAS is a promising new intervention to reduce infant mortality in Southern Asia that involves supplementing infants shortly after birth with a single, large oral dose of vitamin A (50,000 IU).

2. **Are newborn infants at risk for vitamin A deficiency?** Early infancy appears to represent a period of high risk with respect to vitamin A deficiency, in part because infants (of even well-nourished mothers) are born with low liver and total body stores of vitamin A, yielding a reserve that is capable of supporting physiological needs for only a few weeks (1-5). There are reasons to believe that young infants in Southern Asia are particularly vulnerable to vitamin A deficiency. Studies have shown that breastfeeding mothers of low socioeconomic status in this region tend to have poor vitamin A status (6,7) and insufficient breast milk concentrations of vitamin A (6, 8-12) to adequately meet their infants’ needs. Low concentrations of vitamin A in breast milk and inadequate breast milk intake, coupled with poor complementary food quality or frequent infection, can reduce an infant’s ability to achieve normal vitamin A status.

3. **What is the evidence base for claiming that NVAS reduces infant mortality in Southern Asia?** NVAS has been tested in three field trials in Southern Asia (Indonesia, India, and Bangladesh), each of which has reported significant reductions of 15% or more in infant mortality in the first six months of life (13-15).

The meta-analysis based on these three trials suggests that the risk of death from all causes in the first six months of life can be reduced by approximately 21% when newborns within the region are given a 50,000 IU oral dose of vitamin A (16,17). The findings from all three trials are consistent with previous studies reporting 25-35 percent mortality reduction following vitamin A supplementation of children six months through six years of age in Southern Asia and Sub-Saharan Africa (18-20).

4. **How soon must NVAS be given to a newborn to have a mortality impact?** In all three Southern Asian trials that showed a significant mortality reduction, ≥80 percent of newborns were dosed within 48 hours of birth. Therefore, the weight of the evidence points to the need to dose infants within the first two days of life.

Data on whether a survival benefit can be expected if infants are dosed beyond this time period are sparse. Data from the India trial showed no survival impact if infants were dosed after 14 days of age (13). There is no mortality benefit compared to controls when infants were supplemented with high-potency vitamin A (100,000IU) between one and five months of age in Nepal (45), India, Ghana, and Peru (46). This also suggests that age at dosing influences the survival benefit of vitamin A in early infancy.

5. **Is there evidence that NVAS reduces infant mortality in Africa?** Data on the effect of newborn vitamin A supplementation from Africa remain sparse and contradictory (21, 22). Further evidence is needed before any scientific conclusion for the African region can be made.

6. **Can maternal postpartum vitamin A supplementation reduce infant mortality risk?** Maternal vitamin A supplementation with 200,000 IU vitamin A during the immediate postpartum period has been implemented in many countries with endemic vitamin A deficiency to raise the concentration of vitamin A in breast milk and thereby protect the breastfed infant (23). While studies have shown that this intervention can improve breast milk retinol concentrations (9, 24-26) and temporarily improve infant vitamin A status, it appears insufficient to bring infants into adequate vitamin A status through six months of age (9, 25, 26).

A recent randomized trial in Kenya reported no impact on infant vitamin A liver stores with a maternal postpartum dose of 400,000 IU vitamin A. However, a significant impact was observed when infants were directly supplemented with 100,000 IU at 14 weeks of age.
age (25). This indicates that direct dosing of infants is more likely to raise liver stores and improve infant vitamin A status than supplementing mothers postpartum to increase breast milk and consequently infant levels of vitamin A.

Moreover, to date the only positive evidence of impact on infant mortality through six months of age comes from the Asian trials that directly supplemented infants at or near birth. There is no evidence that maternal postpartum vitamin A supplementation reduces overall infant mortality through six months of age, although several trials have reported reduced infant morbidity with postpartum vitamin A supplementation (24, 27).

7. What biologic mechanisms might explain the impact of NVAS on infant mortality? Mechanisms by which newborn vitamin A intake could decrease infant mortality are not fully understood, but are likely to involve the role of vitamin A in supporting postnatal organ and tissue development that could affect maturation and function of host defenses against infection (1). For example, vitamin A is essential for early lung and airway tissue differentiation, growth, development, and immunity (28-31). Healthier lungs may provide a measure of protection against early infantile pneumonia.

In India, newborn vitamin A supplementation delayed nasopharyngeal pneumococcal colonization by two months of age (32), likely reflecting stronger defenses against a leading cause of early childhood acute respiratory infection (33) and meningitis (34). The findings are also consistent with earlier reports from India that vitamin A-deficiency poses greater risk of nasopharyngeal bacterial colonization in young children (35).

In Indonesia, clinic visits for cough and fever, suggestive of pneumonia, were reduced in vitamin A-supplemented infants (14). Evidence emerging from South India has suggested that vitamin A given shortly after birth is likely to reduce severity of illness and fatality associated with diarrhea, dysentery, and fever in the first four months of life (36).

Early neonatal vitamin A repletion might also accelerate gastrointestinal development, function, and defenses that could lag from perinatal vitamin A deficiency. Vitamin A supplementation of infants in India (37) and the Gambia (38) has improved intestinal integrity, suggesting a potential for early neonatal vitamin A to strengthen the gut mucosa, local immunity and, therefore, resistance to diarrhea.

Collectively, these findings are consistent with known roles of vitamin A in maintaining host resistance to infection by maintaining epithelial integrity (the “barrier function”) and immune competence, but are also consistent with essential roles of vitamin A in regulating lung development and function, and thus susceptibility to damage from the embryonic period through neonatal life in a number of mammalian species.

8. Is it safe to give 50,000 IU to newborn infants? Evidence from short- and long-term studies suggest that risk of acute side effects following oral delivery of 50,000 IU of vitamin A early in infancy is minimal. Slight increases in the rates of bulging fontanelle (i.e., protrusion of the membrane-covered opening between the parietal bones and the neighboring bones of an infant’s skull) have been reported among infants less than six months of age dosed with vitamin A versus placebo.

Where it has been observed, a bulging fontanelle attributed to vitamin A supplementation in early infancy has been clinically mild and self-limiting – that is, it disappears on its own typically within 48 hours and almost entirely within 72 hours without any treatment. Generally, up to 2-4 percent of newborns may be expected to develop a bulging fontanelle (39-43). Careful studies have shown that the “bulge” results from a mild expansion of cranial volume that subsides without increasing intracranial pressure (the fontanel acts like a physiologic balloon) (40).

The best conducted study of long-term effects was carried out in Indonesia, which showed no ill effects at three years in terms of cognitive, motor, and behavior testing (44). Another less well-documented study in Bangladesh has showed a similar result.

9. Is it safe to give newborns 50,000 IU of vitamin A and give the mother a high-dose of vitamin A at the same time? Evidence from two trials suggests that administering the postpartum and neonatal dose at the same time is safe. In an HIV-positive population in Harare, Zimbabwe, 839 mother/infant pairs were randomized to receive 400,000 IU (in two doses of 200,000 IU) and 50,000 IU vitamin A or a placebo/ placebo (for mother and infant), respectively, and followed for two days post-dosing for assessment and identification of problems, including bulging fontanelle (41). The incidence of reported side-effects was low and did not differ by group.

In South Asia, the only study that addresses this question is the trial in Bangladesh that provided mothers with weekly doses of vitamin A, beta-carotene, or placebo throughout pregnancy and early lactation and randomized their newborns to receive 50,000 IU vitamin A or placebo at birth (47). Rates of bulging fontanelle reported by mothers were approximately
2 percent and did not differ by maternal or infant supplement group (Klemm R, in press).

10. Is there any evidence that NVAS reduces neonatal mortality? The studies to date were designed to assess the impact of NVAS on mortality through six months of age and did not have a large enough sample size to examine the impact on neonatal mortality (first 28 days of life). Differences in survival between newborns who received vitamin A compared to those that received placebo in two community-based trials conducted in South Asia were observed starting at approximately two weeks of age (13, 15) and continuing until around three to four months of age. A preliminary pooled analysis of these two trials shows a marginally significant 14 percent reduction on neonatal mortality (RR=0.86, 95% CI: 0.73, 1.00; p=0.06) (Klemm R, unpublished).

11. Are reliable stocks of 50,000 IU vitamin A capsules available, and if so, how can they be obtained? For the initial South Asian research trials, where administration of the newborn vitamin A was performed in a controlled setting, private manufacturers were specifically contracted to produce the supplements in a similar way as the other higher doses of VACs used in public health programs.

As the research has moved from the clinical trials to the operations research, the Micronutrient Initiative is working with a private manufacturer on product development of a 50,000 IU supplement specific for newborn infants that would be suitable for settings where different delivery strategies may be considered, including one where the supplement may be administered at birth in the absence of a trained health worker. These are being tested in pilot projects in two countries in South Asia to obtain additional information on safety, shelf-life, consumer acceptability, ease of administration, packaging, and labeling in order to further develop a specification for a newborn-specific 50,000 IU vitamin A supplement that manufacturers can be commissioned to produce for such programs.

References


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