Newborn Vitamin A Supplementation

Frequently Asked Questions

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 (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

1. West KP, Jr. Public health impact of preventing vitamin A deficiency in the first six months of life. In: Delange FM, West KP,Jr, editors. Micronutrient Deficiencies in the First Months of Life. Vevey, Switzerland: Karger; 2003. p. 103-28.

2. Shah RS, Rajalakshmi R, Bhatt RV, Hazra MN, Patel BC, Swamy NB, et al. Liver stores of vitamin A in human fetuses in relation to gestational age, fetal size and maternal nutritional status. Br J Nutr. 1987;58:181-9.

3. Montreewasuwat N, Olson JA. Serum and liver concentrations of vitamin A in Thai fetuses as a function of gestational age. Am J Clin Nutr. 1979;32:601-6.

4. Gebre-Medhin M, Vahlquist A. Vitamin A nutrition in the human foetus. A comparison of Sweden and Ethiopia. Acta Paediatr Scand. 1984;73:333-40.

5. Ganguly C, Mukherjee KL. Relationship between maternal serum vitamin A and vitamin A status of the corresponding fetuses. J Trop Pediatr. 1988;34:313-5.

6. ice AL, Stoltzfus RJ, de Francisco A, Kjolhede CL. Low breast milk vitamin A concentration reflects an increased risk of low liver vitamin A stores in women. Adv Exp Med Biol. 2000;478:375-6.

7. Yamini S, West KP,Jr, Wu L, Dreyfuss ML, Yang DX, Khatry SK. Circulating levels of retinol, tocopherol and carotenoid in nepali pregnant and postpartum women following long-term beta-carotene and vitamin A supplementation. Eur J Clin Nutr. 2001;55:252-9.

8. Vinutha B, Mehta MN, Shanbag P. Vitamin a status of pregnant women and effect of post partum vitamin A supplementation. Indian Pediatr. 2000;37:1188-93.

9. Rice AL, Stoltzfus RJ, de Francisco A, Chakraborty J, Kjolhede CL, Wahed MA. Maternal vitamin A or beta-carotene supplementation in lactating Bangladeshi women benefits mothers and infants but does not prevent subclinical deficiency. J Nutr. 1999;129:356-65.

10. Radhika MS, Bhaskaram P, Balakrishna N, Ramalakshmi BA, Devi S, Kumar BS. Effects of vitamin A deficiency during pregnancy on maternal and child health. BJOG. 2002;109:689-93.

11. Stoltzfus RJ, Humphrey JH. Vitamin A and the nursing mother-infant dyad: Evidence for intervention. Adv Exp Med Biol. 2002;503:39-47.

12. Haskell MJ, Brown KH. Maternal vitamin A nutriture and the vitamin A content of human milk. J Mammary Gland Biol Neoplasia. 1999;4:243-57.

13. Rahmathullah L, Tielsch JM, Thulasiraj RD, Katz J, Coles C, Devi S, et al. Impact of supplementing newborn infants with vitamin A on early infant mortality: Community based randomised trial in southern India. BMJ. 2003;327:254.

14. Humphrey JH, Agoestina T, Wu L, Usman A, Nurachim M, Subardja D, et al. Impact of neonatal vitamin A supplementation on infant morbidity and mortality. J Pediatr. 1996;128:489-96.

15. Klemm RD, Labrique A, Christian P, Rashid R, Shamim AA, Katz J, Sommer A, West KP Jr. Newborn Vitamin A Supplementation Reduced Infant Mortality in Rural Bangladesh, Pediatrics (in press)

16. West KP,Jr. Newborn vitamin A dosing: Policy implications for Asia and Africa. Micronutrient Forum Abstracts, Istanbul, Turkey, 16-18 April 2007.

17. Bhutta ZA, Ahmed T, Black RE, Cousens S, Dewey K, Giugliani E, et al. What works? Interventions for maternal and child undernutrition and survival. Lancet. 2008;371:417-40.

18. Sommer A, West KP,Jr. Vitamin A deficiency: Health, survival and vision. New York: Oxford University Press; 1996.

19. Fawzi WW, Chalmers TC, Herrera MG, Mosteller F. Vitamin A supplementation and child mortality. A meta-analysis. JAMA. 1993;269:898-903.

20. Beaton BH, Martorell R, Aronson K, Edmonston B, McCabe G, Ross AH, B. Effectiveness of vitamin A supplementation in the control of young child morbidity and mortality in developing countries. ACC/SCN; 1993.

21. Malaba LC, Iliff PJ, Nathoo KJ, Marinda E, Moulton LH, Zijenah LS, et al. Effect of postpartum maternal or neonatal vitamin A supplementation on infant mortality among infants born to HIV-negative mothers in zimbabwe. Am J Clin Nutr. 2005;81:454-60.

22. Benn CS. Effect of 50,000 IU vitamin A given to newborns and infants in guinea-bissau, west-africa. Policy implications for Asia and Africa. Micronutrient Forum Abstracts, Istanbul, Turkey, 16-18 April 2007. 2007.

23. WHO/UNICEF/IVACG Task Force. Vitamin A supplements-A guide to their use in the treatment and prevention of vitamin A deficiency and xeropthalmia. World Health Organization, Geneva; 1998.

24. Roy SK, Islam A, Molla A, Akramuzzaman SM, Jahan F, Fuchs G. Impact of a single megadose of vitamin A at delivery on breastmilk of mothers and morbidity of their infants. Eur J Clin Nutr. 1997;51:302-7.

25. Ayah RA, Mwaniki DL, Magnussen P, Tedstone AE, Marshall T, Alusala D, et al. The effects of maternal and infant vitamin A supplementation on vitamin A status: A randomised trial in Kenya. Br J Nutr. 2007;98:422-30.

26. Bahl R, Bhandari N, Wahed MA, Kumar GT, Bhan MK, WHO/CHD Immunization-Linked Vitamin A Group. Vitamin A supplementation of women postpartum and of their infants at immunization alters breast milk retinol and infant vitamin A status. J Nutr. 2002;132:3243-8.

27. Basu S, Sengupta B, Paladhi PK. Single megadose vitamin A supplementation of Indian mothers and morbidity in breastfed young infants. Postgrad Med J. 2003;79:397-402.

28. Zile MH. Function of vitamin A in vertebrate embryonic development. J Nutr. 2001;131:705-8.

29. Chytil F. The lungs and vitamin A. Am J Physiol. 1992;262:L517-27.

30. Zachman RD. Role of vitamin A in lung development. J Nutr. 1995;125:1634S-8S.

31. Antipatis C, Ashworth CJ, Grant G, Lea RG, Hay SM, Rees WD. Effects of maternal vitamin A status on fetal heart and lung: Changes in expression of key developmental genes. Am J Physiol. 1998;275:L1184-91.

32. Coles CL, Rahmathullah L, Kanungo R, Thulasiraj RD, Katz J, Santhosham M, et al. Vitamin A supplementation at birth delays pneumococcal colonization in south Indian infants. J Nutr. 2001;131:255-61.

33. Garenne M, Ronsmans C, Campbell H. The magnitude of mortality from acute respiratory infections in children under 5 years in developing countries. World Health Stat Q. 1992;45:180-91.

34. Obaro SK, Monteil MA, Henderson DC. The pneumococcal problem. BMJ. 1996;312:1521-5.

35. Chandra RK. Increased bacterial binding to respiratory epithelial cells in vitamin A deficiency. BMJ. 1988;297:834-5.

36. Tielsch JM, Rahmathullah L, Thulasiraj RD, Katz J, Coles C, Sheeladevi S, et al. Newborn vitamin A dosing reduces the case fatality but not incidence of common childhood morbidities in south India. J Nutr. 2007;137:2470-4.

37. McCullough FS, Northrop-Clewes CA, Thurnham DI. The effect of vitamin A on epithelial integrity. Proc Nutr Soc. 1999;58:289-93.

38. Thurnham DI, Northrop-Clewes CA, McCullough FS, Das BS, Lunn PG. Innate immunity, gut integrity, and vitamin A in Gambian and Indian infants. J Infect Dis. 2000;182 Suppl 1:S23-8.

39. Baqui AH, de Francisco A, Arifeen SE, Siddique AK, Sack RB. Bulging fontanelle after supplementation with 25,000 IU of vitamin A in infancy using immunization contacts. Acta Paediatr. 1995;84:863-6.

40. Agoestina T, Humphrey JH, Taylor GA, Usman A, Subardja D, Hidayat S, et al. Safety of one 52-mumol (50,000 IU) oral dose of vitamin A administered to neonates. Bull World Health Organ. 1994;72:859-68.

41. Iliff P, Humphrey JH, Mahomva AI. Tolerance of large doses of vitamin A given to mothers and their babies shortly after delivery. Nutr Res. 1999;19:1437-46.

42. Humphrey JH, Ichord RN. Safety of vitamin A supplementation of postpartum women and young children. Food Nutr Bull. 2001;22:311-9.

43. de Francisco A, Chakraborty J, Chowdhury HR, Yunus M, Baqui AH, Siddique AK, et al. Acute toxicity of vitamin A given with vaccines in infancy. Lancet. 1993;342:526-7.

44. Humphrey JH, Agoestina T, Juliana A, Septiana S, Widjaja H, Cerreto MC, et al. Neonatal vitamin A supplementation: Effect on development and growth at 3 y of age. Am J Clin Nutr. 1998;68:109-17.

45. West KP,Jr, Katz J, Shrestha SR, LeClerq SC, Khatry SK, Pradhan EK, et al. Mortality of infants < 6 mo of age supplemented with vitamin A: A randomized, double-masked trial in Nepal. Am J Clin Nutr. 1995;62:143-8.

46. Randomised trial to assess benefits and safety of vitamin A supplementation linked to immunisation in early infancy. WHO/CHD immunisation-linked vitamin A supplementation study group. Lancet. 1998;352:1257-63.

47. West KP,Jr, Christian P, Klemm RD, Labrique A, Rashid M, Shamim AA, et al. The JiVitA bangladesh project: Research to improve nutrition and health among mothers and infants in rural South Asia. Sight and Life Newsletter. 2006;1:10-4.

Visit www.a2zproject.org for other publications on newborn vitamin A supplementation.

This publication is made possible by the generous support of the American people through the United States Agency for International Development (USAID) under the terms of Cooperative Agreement No. GHS-A-00-05-00012-00. The contents are the responsibility of the Academy for Educational Development and do not necessarily reflect the views of USAID or the United States Government. **July, 2008**