

## TECHNICAL BRIEF

# Postpartum Vitamin A Supplementation: Evaluating the Evidence for Action

Amy L. Rice, PhD

## BACKGROUND

Scientific and policy-making groups have issued somewhat conflicting statements about the benefits of postpartum vitamin A supplementation programs over the past few years (de Benoist et al, 2001; IVACG, 2002; Ross, 2002; Sommer, 2005). This has led some public health professionals to question the value of providing vitamin A supplements to women immediately after delivery as a strategy for improving maternal and child health.

## PURPOSE OF BRIEF

This brief reviews the scientific rationale for postpartum supplementation and examines the available evidence on whether or not this intervention can improve the nutritional status, breast milk quality, and functional health outcomes in mothers and children. The results suggest that program planners may need to balance the evidence that vitamin A supplementation improves the health status in women and children against programmatic costs. Thus far, there is evidence that postpartum vitamin A supplementation does not completely correct deficiency in severely deficient women and children, little evidence that it improves functional health outcomes, and recent evidence for potential risks and benefits unique to HIV-positive populations.

## METHODOLOGY

Published studies evaluating the impact of postpartum vitamin A supplementation were reviewed. These included trials in which women were given vitamin A supplements (200,000 IU–400,000 IU orally) within eight weeks of delivery. Several of these trials also included vitamin A supplementation for the infants. Additional background documents about vitamin A deficiency, breastfeeding, and the evolution of vitamin A supplementation guidelines were reviewed and selected publications about these issues are cited.

## GLOBAL PREVALENCE OF VITAMIN A DEFICIENCY

Vitamin A deficiency remains a widespread public health problem among women and children. Over 20 percent of all preschool age children (~130 million) and nearly six percent of all pregnant women (~7 million) suffer from vitamin A deficiency and its adverse health consequences (West, 2002; Rice et al, 2004). The majority of vitamin A deficient women and children currently live in South Asia or Sub-Saharan Africa, in the same countries where vitamin A supplementation programs for children over six months of age have helped reduce high child mortality rates. But while more than 60 countries now have supplementation programs for preschool age children, fewer have launched large-scale program initiatives to address the problem among younger infants or in women of reproductive age.

## ADVERSE EFFECTS OF VITAMIN A DEFICIENCY

### HIV-negative Populations

Vitamin A deficiency (often defined using low serum retinol concentrations as an indicator of deficiency) is known to increase the risk of blindness and death among children in HIV-negative populations (Sommer and West, 1996) and to adversely affect maternal health. Night-blindness, a well-known sign of vitamin A deficiency, has been associated with higher rates of morbidity among pregnant Nepali women (Christian et al, 1998) as well as higher rates of mortality during the early postpartum period (Christian et al, 2000).

### HIV-positive Populations

The interpretation of low serum retinol concentrations in HIV-positive individuals is complicated by the body's response to infections and trauma. During the acute phase of an infection,

retinol-binding protein, which is part of the chemical complex that ferries retinol through the bloodstream on its way from the liver to other tissues, is called into action elsewhere and temporarily disappears from the circulation. As a result, serum retinol concentrations decrease. More severe infections cause more dramatic declines, but serum retinol concentrations generally rebound after the acute event has passed. However, in HIV-positive individuals with chronically activated immune systems, low serum retinol concentrations may indicate a more active viral infection, true vitamin A deficiency, or a combination of both. Reliable methods for correctly identifying the underlying condition(s) have yet to be developed.

Along similar lines, the interpretation of population level studies that assess vitamin A status based on serum retinol concentrations is more complicated in the context of HIV. For example, although observational studies of pregnant women showed that low serum retinol concentrations were associated with higher rates of maternal-to-child transmission of HIV, the results of the subsequent supplementation trials which provided varying amounts of vitamin A and/or beta-carotene to women before, during, and/or after pregnancy have been disappointing. Trials conducted in Malawi, South Africa, and Zimbabwe found no protective effect, while another in Tanzania observed an increased risk of transmission (Wiysonge et al, 2005). Did vitamin A fail to reduce HIV transmission rates because: the women were not vitamin A deficient; they did not respond to supplementation; the risk of maternal-to-child transmission is not increased by inadequate maternal vitamin A status; or by some combination of these and/or other factors? The reason remains unclear.

On the other hand, the trial in Zimbabwe also found that low maternal serum retinol concentrations were associated with a ten-fold greater risk of sexual acquisition of HIV among HIV-negative women, and preliminary data suggest that supplementation of vitamin A deficient, HIV-negative women may lower their own risk of acquiring HIV (Humphrey et al, 2006). These examples illustrate that more work is needed to identify the unique health risks associated with vitamin A deficiency in the context of HIV.

## SCIENTIFIC RATIONALE FOR POSTPARTUM SUPPLEMENTATION AMONG HIV-NEGATIVE WOMEN

Several proven strategies exist for improving the vitamin A status of HIV-negative women and their breastfeeding infants. Figure 1 provides a conceptual framework that shows how maternal vitamin A supplementation, infant vitamin A

supplementation, and dietary vitamin A intake may affect women's and children's vitamin A status and potentially lead to better functional health outcomes, including improved growth and immune function, reduced morbidity, and improved survival rates.

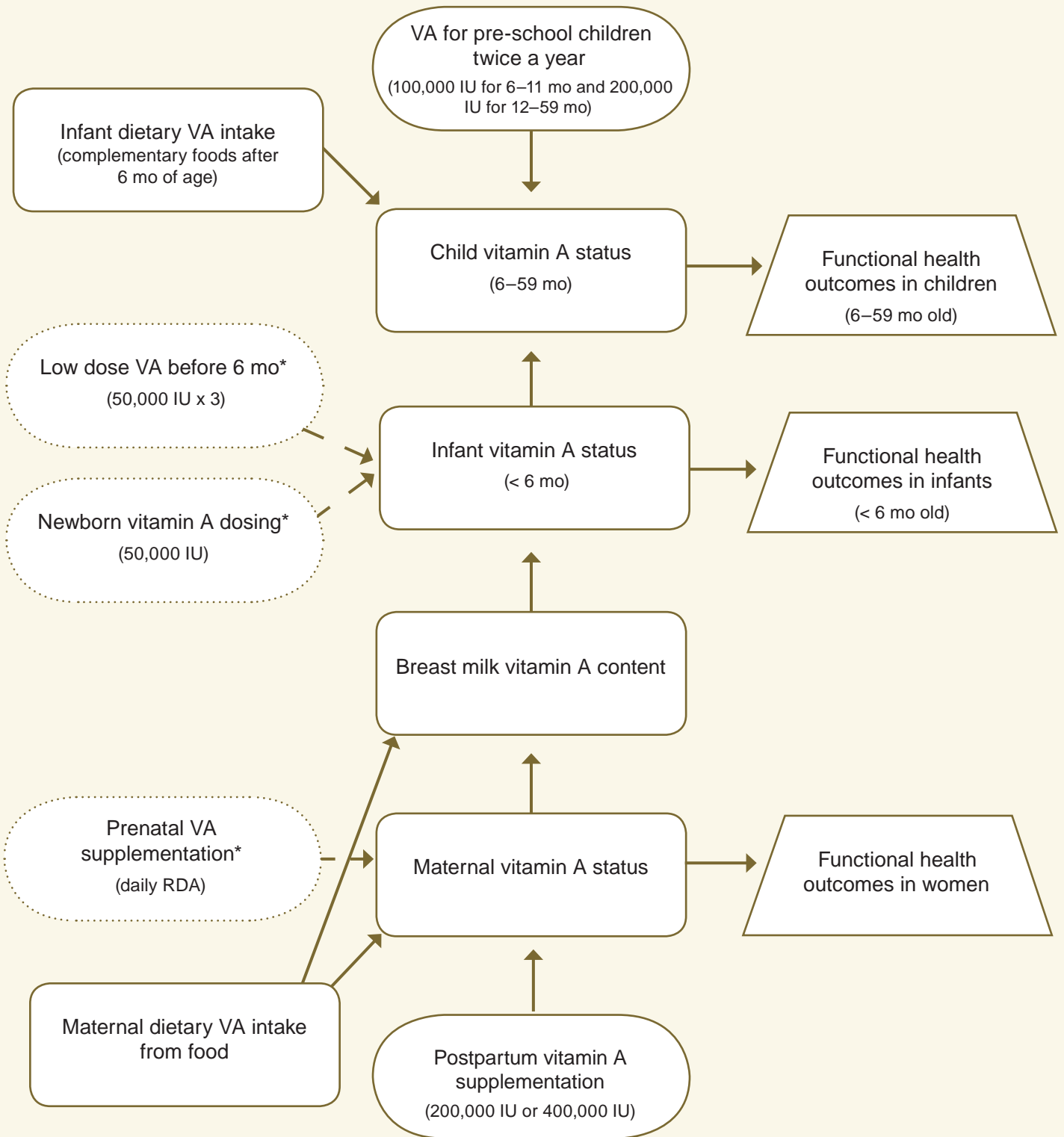
Studies among populations presumed to be HIV negative clearly show that maternal dietary intake is an important determinant of vitamin A status and breast milk vitamin A concentrations (Haskell and Brown, 1999; Newman, 1993). Intervention trials have demonstrated that it is possible to improve maternal vitamin A status and/or breast milk vitamin A concentrations by providing low-dose vitamin A or beta-carotene supplements to women before, during, and after pregnancy (Baylin et al, 2005; Tanumihardjo et al, 1996; Yamini et al, 2001), through food fortification programs (Arroyave et al, 1974; Muhilal et al, 1988) and in the form of food-based interventions (de Pee et al, 1998; de Pee et al, 1995; de Pee et al, 1998; Villard and Bates, 1987). However, the effectiveness of these approaches varies and appears to be influenced by women's underlying vitamin A status. Women who are more severely deficient tend to be more responsive to intervention.

Postpartum vitamin A supplementation (i.e. giving women a large dose of vitamin A that is 200,000 IU or more within the first six weeks after delivery) is another strategy for improving maternal and infant vitamin A status and health outcomes. Postpartum supplementation is designed to improve women's vitamin A status and to increase the vitamin A content of breast milk (Stolzfus and Humphrey, 2002). This is meant to protect the mother's vitamin A reserves, while addressing one of the fundamental reasons that children become vitamin A deficient—low dietary vitamin A intake from breast milk (Miller et al, 2002).

Breast milk represents the single most important source of vitamin A for very young infants. All infants are naturally born with low body stores of vitamin A and depend upon vitamin A-rich colostrum and breast milk to meet their physiological need for vitamin A and other nutrients needed for proper growth and development. For well-nourished women and infants, nearly 60 times as much vitamin A will be transferred from mother to infant during breastfeeding as compared to pregnancy (Stolzfus, 1994).

Unfortunately, mothers with compromised nutritional status produce breast milk with levels of vitamin A that are too low to meet their infants' immediate physiological needs and for infants to build liver stores of vitamin A for the future. Without adequate stores, infants are at greater risk of developing vitamin A deficiency and dying during their first few years of life.

**Figure 1.** Pathway to improved vitamin A status and functional health outcomes in mothers, infants, and children



\* Under consideration in current revision of WHO Guidelines

## EVIDENCE REGARDING POSTPARTUM VITAMIN A SUPPLEMENTATION

Table 1 (see pages 6–9) summarizes the results of 17 different publications from trials designed to evaluate the impact of postpartum vitamin A supplementation. The studies are presented by the dose of vitamin A the women received (200,000 IU, 300,000 IU, or 400,000 IU) and then by the date of publication, with earlier studies listed first. The only study that compared two different doses of vitamin A (200,000 IU vs. 400,000 IU), rather than vitamin A versus a non-dosed group, is listed at the end of the table.

The trials from Bangladesh, Ghana, India, Indonesia, Peru, and Thailand were conducted among women whose HIV status was unknown, but is presumed to be HIV negative. Only the recent study in Zimbabwe was designed to address questions related to vitamin A and HIV and tested the HIV status of women and children throughout the follow-up period of the trial.

The majority of these studies were designed to examine the relationship between maternal and/or infant vitamin A supplementation and biochemical outcomes (serum retinol or liver stores of vitamin A in women and/or children, or breast milk retinol). A handful of trials included other measures of health or nutritional status, including infant growth and immune function, and infant or maternal morbidity. The only trial conducted in an HIV-endemic population also assessed the incidence of maternal-to-child transmission of HIV, the acquisition of HIV among women, as well as maternal and child morbidity and mortality rates.

Nearly all of the trials conducted among the presumably HIV-negative populations in Bangladesh, Ghana, India, Indonesia, Peru, and Thailand found short-term beneficial effects on biochemical outcomes (i.e. serum retinol, breast milk retinol, or liver stores of vitamin A), but only one documented adequate vitamin A status at the end of the study period among all of the women who received vitamin A (Tchum et al, 2006). None of the studies that assessed infant vitamin A status found that vitamin A deficiency was completely eliminated by dosing their mothers. In most cases vitamin A supplementation had either no overall effect on the functional health outcomes measured (infant morbidity or infant growth) or a slightly positive effect (infant morbidity). In Zimbabwe, where the vitamin A status of women was generally adequate at delivery, postpartum supplementation of HIV-negative women had no overall effect on infant mortality rates, on women's risk of acquiring HIV, or on mortality rates among women. However, low maternal serum retinol concentrations were associated with a ten-fold greater risk of sexual acquisition of HIV, and preliminary data from a small subset of women suggest that supplementing HIV-negative women with low serum retinol concentrations may lower this risk. Additional work is currently

underway to investigate this last issue (J Humphrey, personal communication).

Among HIV-positive women in Zimbabwe, postpartum vitamin A supplementation had no overall effect on maternal-to-child transmission of HIV, on child mortality rates between birth and 24 months of age, or on maternal morbidity or mortality rates. However, the effect of vitamin A supplementation differed for certain subgroups. Infants infected with HIV during delivery had prolonged survival if they themselves received vitamin A at birth (irrespective of whether their mothers received vitamin A), while infants who were HIV negative at six weeks of age (but potentially infected after this point in time) experienced higher mortality at 24 months of age if either they and/or their mothers had received vitamin A. Among women, postpartum supplementation had no overall effect on the rate of hospitalization or sick clinic visits, but supplementation was associated with reduced clinic visits for malaria, cracked and bleeding nipples, pelvic inflammatory disease, and vaginal infections.

In summary, the available evidence suggests that postpartum supplementation results in modest, short-term improvements in maternal and child vitamin A status (measured as higher serum retinol concentrations, higher liver vitamin A stores, or higher breast milk vitamin A concentrations) and only minor improvements, if any, in functional health outcomes for mothers and their children. These potential benefits are summarized in Table 2 (see page 9).

## CONFUSION AROUND THE VALUE OF POSTPARTUM SUPPLEMENTATION AND WHAT TO DO

Two different factors deserve consideration.

- There is no universally recognized benchmark for measuring “success”
- The most recent recommendations were not widely disseminated

### No Universally Recognized Definition of Success

There is no universally recognized indicator for measuring the “success” of this intervention, at least in terms of biological efficacy. Opinions seem to differ about what this intervention should accomplish when it is being implemented properly and new mothers are receiving vitamin A supplements in a timely fashion after delivery. For some, improving biochemical indicators of vitamin A status without changing functional health outcomes among women and children is of questionable value, while others feel that improving maternal vitamin A status, increasing breast milk vitamin A concentrations, or



increasing vitamin A stores among infants is sufficient justification for launching a postpartum vitamin A supplementation program.

Thus, some of the confusion about the value of postpartum dosing programs may simply be a lack of clarity about how “success” should be defined. Improving vitamin A status, breast milk vitamin A concentrations, and functional health outcomes may all be goals of maternal and child health programs. Policy makers and program managers need to be sure they are clear about what they want to accomplish and what postpartum supplementation programs may be able to deliver.

### Most Recent Recommendations Were Not Widely Disseminated

The last set of vitamin A supplementation guidelines jointly published by the World Health Organization (WHO), UNICEF, and the International Vitamin A Consultative Group (IVACG) appeared in 1997 and recommended a single 200,000 IU dose of vitamin A for postpartum women soon after delivery (WHO/UNICEF/IVACG Task Force, 1997). Since that time, many of the countries that initiated supplementation programs for postpartum women based their policies on these guidelines.

In the meantime, updated guidelines have been formulated and agreed on by experts convened during an informal technical consultation organized by the WHO in 2000 and an expert panel meeting convened by IVACG in 2001. The updated guidelines recommend a 400,000 IU dose of vitamin A for postpartum women (given in the form of 2 doses of 200,000 IU at least 24 hours apart—see Table 3 on page 10) based on the findings of previous studies that documented limited benefits of dosing women with 200,000 IU or 300,000 IU after delivery. These recommendations were presented to the public health nutrition community at the XX IVACG meeting in Vietnam in 2001 and have been published in policy statements (IVACG, 2002) and in the scientific literature (de Benoist et al, 2001; Ross, 2002).

However, many health professionals may not be aware of these newer recommendations because they have not appeared in the same format or been as widely disseminated to an international audience as the joint guidelines previously published by WHO, UNICEF, and IVACG. WHO is currently in the process of revising these guidelines.

The scientific rationale for postpartum supplementation remains unchanged—that is, finding a safe and effective way to improve the vitamin A status of women and children. The best available evidence suggests that this intervention provides short-term, but measurable, benefits for many women and their infants. Although the evidence for improvements in functional health outcomes is not strong for postpartum supplements

alone, given the low cost of the intervention and the available platforms for its delivery, a strong argument can be made for its inclusion as one component in a comprehensive micronutrient program in vitamin A deficient populations (see Figure 1 on page 3).

## CONCLUSIONS AND RECOMMENDATIONS

Country-level decision-makers always need to balance the costs, benefits, and potential risks (if any exist) of an intervention against the available resources and their program goals. These decision-makers rely heavily on policy recommendations from WHO for assistance in guiding these decisions. The new WHO policy recommendations about vitamin A supplementation will need to be clear about what postpartum supplementation can accomplish. Country-level decision makers and program planners should consider their own context and determine whether implementing a postpartum vitamin A supplementation program can help them reach their particular goals in a cost-effective manner.

At the time this brief was finalized, December 2006, WHO had initiated a comprehensive review of its recommendations for vitamin A supplementation. Therefore, it would be sensible for country decision-makers to await the updated recommendations before making changes in their own policies and programs.

**Table 1.** Impact of postpartum vitamin A supplementation on vitamin A status and functional health outcomes in women, infants, and children

Vitamin A dose, study site, author and year	Total number of study participants and treatment groups <sup>1</sup>	Follow-up period	Primary outcomes	Comparisons between supplementation (vitamin A or beta-carotene) and control (placebo or nothing) groups <sup>2</sup>
<b>200,000 IU</b>				
Bangladesh, Roy et al, 1997	50 mother-infant pairs <ul style="list-style-type: none"> <li>• 200,000 IU vitamin A <i>or</i></li> <li>• Nothing given to women (within 24 hr after delivery)</li> </ul>	9 mo	<ul style="list-style-type: none"> <li>• Biochemical indicators (women)</li> <li>• Morbidity (infants and women)</li> </ul>	<ul style="list-style-type: none"> <li>• Maternal serum retinol and breast milk retinol higher through 3 and 6 mo postpartum, respectively</li> <li>• Lower incidence of infant morbidity and pedal edema in women</li> </ul>
India, Bhaskaram and Balakrishna, 1998	100 mother-infant pairs <ul style="list-style-type: none"> <li>• 200,000 IU vitamin A <i>or</i></li> <li>• Placebo given to women (within 24 hr after delivery)</li> <li>• Plus oral polio vaccine given to all infants between 24 and 72 hours of birth</li> </ul>	3 mo	<ul style="list-style-type: none"> <li>• Biochemical indicators</li> <li>• Immune response to polio immunization (infants)</li> </ul>	<ul style="list-style-type: none"> <li>• Breast milk retinol higher through 45 days postpartum</li> <li>• No effect on infant serum retinol</li> <li>• No effect on infant immune response to polio vaccine</li> </ul>
Bangladesh, Rice et al, 1999	222 mother-infant pairs <ul style="list-style-type: none"> <li>• 200,000 IU VA given to women at 1-3 wk postpartum, then daily placebos until 9 mo postpartum <i>or</i></li> <li>• Placebos from 1-3 wk to 9 mo postpartum <i>or</i></li> <li>• Beta-carotene (7.8 mg) from 1-3 wk to 9 mo postpartum</li> </ul>	9 mo	<ul style="list-style-type: none"> <li>• Biochemical indicators</li> <li>• No functional health outcomes</li> </ul>	<ul style="list-style-type: none"> <li>• Maternal liver stores of VA and breast milk retinol improved among women receiving VA (at 3 mo) and women receiving beta-carotene (Semba et al, 1995)</li> <li>• Infant liver stores of VA improved among the VA treatment group (Christian et al, 2001)</li> </ul>
Ghana, India, Peru, Anonymous, 1998 and Bahl et al, 2002	9424 mother-infant pairs <ul style="list-style-type: none"> <li>• 200,000 IU vitamin A to women (18-42 days after delivery) and 25,000 IU to infants with the first three doses of DPT/oral poliomyelitis vaccine (at 6, 10, and 14 wk), then 25,000 IU VA to infants at 9 mo <i>or</i></li> <li>• Placebo to women (18-42 days after delivery) and placebo to infants at the three vaccination time points, then 100,000 IU VA to infants at 9 mo</li> </ul>	12 mo	<ul style="list-style-type: none"> <li>• Biochemical indicators</li> <li>• Side effects within 48 hrs of administration of vitamin A</li> <li>• Infant anthropometry</li> <li>• Infant morbidity</li> <li>• Infant mortality (6, 9 and 12 mo)</li> </ul>	<ul style="list-style-type: none"> <li>• Breast milk retinol increased at 2 mo</li> <li>• Infant serum retinol concentrations and liver stores of VA increased at 6 mo of age</li> <li>• Slight increase in the rate of bulging fontanelle (but all groups &lt;1%)</li> <li>• No effect on growth</li> <li>• No effect on infant morbidity</li> <li>• No effect on infant mortality</li> </ul>
India, Vinutha et al, 2000	109 mother-infant pairs <ul style="list-style-type: none"> <li>• 200,000 IU vitamin A <i>or</i></li> <li>• Nothing given to women (within 48 hr of delivery)</li> </ul>	3 mo	<ul style="list-style-type: none"> <li>• Biochemical indicators</li> <li>• Infant anthropometry</li> </ul>	<ul style="list-style-type: none"> <li>• Breast milk retinol and infant serum retinol increased at 3 mo</li> <li>• No effect on growth</li> </ul>

1 The studies were individually randomized trials with approximately equal number of participants per treatment group.

2 Comments refer to comparisons between women (or their infants) who received vitamin A vs. women (or their infants) who received a placebo (or no intervention), unless otherwise noted.

Vitamin A dose, study site, author and year	Total number of study participants and treatment groups <sup>1</sup>	Follow-up period	Primary outcomes	Comparisons between supplementation (vitamin A or beta-carotene) and control (placebo or nothing) groups <sup>2</sup>
India, Basu et al, 2003	300 mother-infant pairs <ul style="list-style-type: none"> <li>• 200,000 IU vitamin A <i>or</i></li> <li>• Nothing given to women (within 48 hr of delivery)</li> </ul>	6 mo	<ul style="list-style-type: none"> <li>• Biochemical indicators</li> <li>• Infant morbidity</li> </ul>	<ul style="list-style-type: none"> <li>• Breast milk retinol increased through 4 mo</li> <li>• Infant serum retinol increased through 5 mo</li> <li>• Decreased incidence and duration of episodes of diarrhea and acute respiratory infections</li> <li>• Decreased incidence of febrile illnesses and measles</li> </ul>
<b>300,000 IU</b>				
Thailand, Thangankul et al, 1974	191 mother-infant pairs <ul style="list-style-type: none"> <li>• 300,000 IU VA given to women within 3 days of delivery and nothing to infants <i>or</i></li> <li>• Nothing given to women and 50,000 IU VA given to infants within 3 days of delivery <i>or</i></li> <li>• Nothing given to women and nothing given to infants</li> </ul>	10.5 mo	<ul style="list-style-type: none"> <li>• Biochemical indicators</li> <li>• Infant morbidity</li> </ul>	<ul style="list-style-type: none"> <li>• Maternal serum retinol increased through 9 mo (in group where women got VA)</li> <li>• Infant serum retinol increased through 7.5 mo (in groups where mother or infant got VA)</li> <li>• Breast milk retinol increased through 6 mo (in group where women got VA)</li> <li>• Incidence of illness highest in placebo-placebo group</li> </ul>
Indonesia, Stoltzfus et al, 1993	153 mother-infant pairs <ul style="list-style-type: none"> <li>• 300,000 IU vitamin A <i>or</i></li> <li>• Placebo given to women (1-3 wk of delivery)</li> </ul>	8 mo	<ul style="list-style-type: none"> <li>• Biochemical indicators</li> </ul>	<ul style="list-style-type: none"> <li>• Maternal serum retinol increased through 6 mo</li> <li>• Breast milk retinol increased through 8 mo</li> <li>• Prevalence of low serum retinol and low liver stores decreased among infants at 6 mo</li> </ul>
India, Venkataro et al, 1996	909 mother-infant pairs <ul style="list-style-type: none"> <li>• 300,000 IU VA given to women at 7-14 days postpartum and 200,000 IU to infants at 6 mo <i>or</i></li> <li>• 300,000 IU to women and placebo to infants <i>or</i></li> <li>• Placebo to women and placebo to infants</li> </ul>	12 mo	<ul style="list-style-type: none"> <li>• Infant morbidity</li> </ul>	<ul style="list-style-type: none"> <li>• No impact on the incidence or duration of diarrhea or acute respiratory infections in children</li> </ul>
<b>400,000 IU</b>				
Indonesia, Muhilal and Permaesih, 1985	160 mother-infant pairs <ul style="list-style-type: none"> <li>• 400,000 IU vitamin A <i>or</i></li> <li>• Placebo given to women (1-5 mo postpartum)</li> </ul>	6 mo (infants 6-12 mo old)	<ul style="list-style-type: none"> <li>• Biochemical indicators</li> </ul>	<ul style="list-style-type: none"> <li>• Breast milk retinol increased at 3 mo post supplementation</li> <li>• Infant serum retinol increased at 6 mo post supplementation</li> </ul>
Zimbabwe, Illiff et al, 1999	896 mother-infant pairs <ul style="list-style-type: none"> <li>• 400,000 IU VA to women and 50,000 IU to infants <i>or</i></li> <li>• Placebo to women and infants shortly after delivery (~24 hr)</li> </ul>	~ 30 hr after dosing	<ul style="list-style-type: none"> <li>• Side effects of dosing women and infants with vitamin A</li> </ul>	<ul style="list-style-type: none"> <li>• Vitamin A was well tolerated by newly delivered mothers and their babies</li> </ul>

Vitamin A dose, study site, author and year	Total number of study participants and treatment groups <sup>1</sup>	Follow-up period	Primary outcomes	Comparisons between supplementation (vitamin A or beta-carotene) and control (placebo or nothing) groups <sup>2</sup>
Zimbabwe, Malaba et al, 2005	9208 HIV-negative mother-infant pairs <ul style="list-style-type: none"> <li>• 400,000 IU vitamin A to women and 50,000 IU vitamin A to infant <i>or</i></li> <li>• 400,000 IU vitamin A to women and placebo to infant <i>or</i></li> <li>• Placebo to women and 50,000 IU to infant <i>or</i></li> <li>• Placebo to women and placebo to infant within 96 hr of delivery</li> </ul>	12 mo	<ul style="list-style-type: none"> <li>• Infant mortality</li> <li>• Biochemical indicators (subset of 375 women)</li> </ul>	<ul style="list-style-type: none"> <li>• No effect of maternal or infant vitamin A supplementation on infant mortality</li> <li>• Maternal serum retinol increased at 6 wk among the groups of women who received vitamin A</li> </ul>
Zimbabwe, Humphrey et al, 2006	4495 mother-infant pairs (HIV-positive women) <ul style="list-style-type: none"> <li>• 400,000 IU vitamin A to women and 50,000 IU vitamin A to infant <i>or</i></li> <li>• 400,000 IU vitamin A to women and placebo to infant <i>or</i></li> <li>• Placebo to women and 50,000 IU to infant <i>or</i></li> <li>• Placebo to women and placebo to infant within 96 hr of delivery</li> </ul>	24 mo	<ul style="list-style-type: none"> <li>• Mother-to-child transmission (MTCT) of HIV</li> <li>• HIV-free survival (among infants)</li> <li>• Mortality in HIV-exposed infants</li> </ul>	<ul style="list-style-type: none"> <li>• No effect of maternal or infant VA supplementation on breastfeeding associated MTCT</li> </ul> <p><b>Child mortality at 24 mo</b></p> <p><i>Among all infants combined</i></p> <ul style="list-style-type: none"> <li>• No overall effect of maternal or infant VA supplementation on child mortality</li> </ul> <p><i>Among infants infected with HIV during pregnancy</i></p> <ul style="list-style-type: none"> <li>• No effect of maternal or infant VA supplementation</li> </ul> <p><i>Among infants infected with HIV during delivery</i></p> <ul style="list-style-type: none"> <li>• No effect of maternal VA supplementation</li> <li>• Reduced mortality among infants directly supplemented with VA</li> </ul> <p><i>Among infants exposed to HIV who were not HIV-positive at birth or 6 wk of age</i></p> <ul style="list-style-type: none"> <li>• Increased mortality associated with maternal or infant VA supplementation</li> </ul>
Zimbabwe, Humphrey et al, 2006	9562 mothers (HIV-negative women) <ul style="list-style-type: none"> <li>• 400,000 IU vitamin A to women <i>or</i></li> <li>• Placebo to women within 96 hr of delivery</li> </ul>	24 mo	<ul style="list-style-type: none"> <li>• HIV seroconversion among women at 12 and 24 months</li> <li>• Serum retinol concentrations (subset of 398 women)</li> </ul>	<ul style="list-style-type: none"> <li>• No overall effect of maternal VA supplementation on incidence of HIV at 12 or 24 months</li> <li>• Women with low serum retinol concentrations (&lt;0.7 µmol/L) were ~10 times more likely to seroconvert than women with higher serum retinol concentrations</li> </ul>



Vitamin A dose, study site, author and year	Total number of study participants and treatment groups <sup>1</sup>	Follow-up period	Primary outcomes	Comparisons between supplementation (vitamin A or beta-carotene) and control (placebo or nothing) groups <sup>2</sup>
Zimbabwe, Zvandasara et al, 2006	14,110 mothers (HIV-negative and HIV-positive women) <ul style="list-style-type: none"> <li>• 400,000 IU vitamin A to women <i>or</i></li> <li>• Placebo to women within 96 hr of delivery</li> </ul>	24 months	<ul style="list-style-type: none"> <li>• Maternal mortality</li> <li>• Health care utilization</li> <li>• Serum retinol concentrations (subset of 398 women)</li> </ul>	<ul style="list-style-type: none"> <li>• No effect of maternal VA supplementation on maternal mortality among either HIV-negative or HIV-positive women</li> <li>• Among HIV-positive women, VA supplementation had no effect on rates of hospitalization or overall sick clinic visits, but did reduce clinic visits for malaria, vaginal infections, pelvic inflammatory disease, and cracked and bleeding nipples</li> <li>• VA supplementation improved serum retinol concentrations among HIV-negative, but not HIV-positive women</li> </ul>
<b>400,000 IU vs. 200,000 IU</b>				
Ghana, Tchum et al, 2006	167 mothers <ul style="list-style-type: none"> <li>• 400,000 IU vitamin A (in 2 divided doses of 200,000 IU administered 24 hr apart) <i>or</i></li> <li>• 200,000 IU vitamin A within 6 wk of delivery</li> </ul>	5 months	<ul style="list-style-type: none"> <li>• Serum retinol concentrations in women</li> <li>• Liver stores of vitamin A (modified-relative-dose-response test) in women</li> </ul>	<ul style="list-style-type: none"> <li>• Women's liver stores of vitamin A improved after supplementation in both treatment groups; both groups had adequate liver stores 5 months after dosing</li> <li>• No improvement in serum retinol concentrations in either group of women</li> </ul>

**Table 2.** Potential benefits of a postpartum vitamin A supplementation program among vitamin A-deficient populations of women

Potential benefit for women and/or children *	Yes	Maybe	Probably not
Improve maternal liver stores of vitamin A	+++		
Improve maternal serum retinol concentrations	++		
Improve breast milk vitamin A concentrations	+++		
Improve infant liver stores of vitamin A	++		
Improve infant serum retinol concentrations	+	+	
Reduce infant morbidity	+	+	
Reduce infant mortality			+
Reduce maternal morbidity	+	+	
Reduce maternal mortality			+
Reduce maternal-to-child transmission of HIV			+
Reduce acquisition of HIV in vitamin A-deficient women		?	

\* Benefits measured prior to 6 months postpartum before the infants themselves become eligible to participate in a national vitamin A supplementation program for children

**Table 3.** Schedule for high-dose vitamin A supplementation of postpartum women in vitamin A-deficient populations

Amount of vitamin A	Dosing schedule	Time frame
400,000 IU	2 doses of 200,000 IU each, given at least 24 hours apart to facilitate absorption	As soon as possible after delivery, but not more than 6 weeks after childbirth

Adapted from Sommer and Davison, 2002

## AUTHOR

Amy L. Rice, PhD, Bloomberg School of Public Health, Johns Hopkins University

January 2007

## Literature Cited

- Anonymous (1998) 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* 352: 1257–1263.
- Arroyave, G., Beghin, I., Flores, M., Soto de Guido, C. S. & Ticas, J. M. (1974) Effects of the intake of sugar fortified with retinol, by the pregnant women and infant whose diet is usually low in vitamin A. Study of the mother and child. *Arch Latinoam Nutr* 24: 485–512.
- Bahl, R., Bhandari, N., Wahed, M. A., Kumar, G. T. & Bhan, M. K. (2002) Vitamin A supplementation of women postpartum and of their infants at immunization alters breast milk retinol and infant vitamin A status. *J Nutr* 132: 3243–3248.
- Basu, S., Sengupta, B. & Roy Paladhi, P. K. (2003) Single megadose vitamin A supplementation of Indian mothers and morbidity in breastfed young infants. *Postgrad Med J* 79: 397–402.
- Baylin, A., Villamor, E., Rifai, N., Msamanga, G. & Fawzi, W. W. (2005) Effect of vitamin supplementation to HIV-infected pregnant women on the micronutrient status of their infants. *Eur J Clin Nutr* 59: 960–968.
- Bhaskaram, P. & Balakrishna, N. (1998) Effect of administration of 200,000 IU of vitamin A to women within 24 hrs after delivery on response to PPV administered to the newborn. *Indian Pediatr* 35: 217–222.
- Christian, P., West, K. P., Jr., Khattry, S. K., Katz, J., Shrestha, S. R., Pradhan, E. K., LeClerq, S. C. & Pokhrel, R. P. (1998) Night blindness of pregnancy in rural Nepal—nutritional and health risks. *Int J Epidemiol* 27: 231–237.
- Christian, P., West, K. P., Jr., Khattry, S. K., Kimbrough-Pradhan, E., LeClerq, S. C., Katz, J., Shrestha, S. R., Dali, S. M. & Sommer, A. (2000) Night blindness during pregnancy and subsequent mortality among women in Nepal: effects of vitamin A and beta-carotene supplementation. *Am. J. Epidemiol.* 152: 542–547.
- Christian, P., West, K. P., Jr., Khattry, S. K., LeClerq, S. C., Kimbrough-Pradhan, E., Katz, J. & Shrestha, S. R. (2001) Maternal night blindness increases risk of mortality in the first 6 months of life among infants in Nepal. *J Nutr* 131: 1510–1512.
- de Benoist, B., Martines, J. & Goodman, T. (2001) Vitamin A supplementation and the control of vitamin A deficiency: summary of recommendations and clarifications. *Food Nutr Bull* 22: 335–337.
- de Pee, S., Bloem, M. W., Gorstein, J., Sari, M., Satoto, Yip, R., Shrimpton, R. & Muhilal (1998) Reappraisal of the role of vegetables in the vitamin A status of mothers in Central Java, Indonesia. *Am J Clin Nutr* 68: 1068–1074.
- de Pee, S., Bloem, M. W., Satoto, Yip, R., Sukaton, A., Tjiong, R., Shrimpton, R., Muhilal & Kodyat, B. (1998) Impact of a social marketing campaign promoting dark-green leafy vegetables and eggs in central Java, Indonesia. *Int J Vitam Nutr Res* 68: 389–398.
- de Pee, S., West, C. E., Muhilal, Karyadi, D. & Hautvast, J. G. (1995) Lack of improvement in vitamin A status with increased consumption of dark-green leafy vegetables. *Lancet* 346: 75–81.
- Haskell, M. J. & Brown, K. H. (1999) Maternal vitamin A nutriture and the vitamin A content of human milk. *J Mammary Gland Biol Neoplasia* 4: 243–257.

- Humphrey, J. H., Hargrove, J. W., Malaba, L. C., Iliff, P. J., Moulton, L. H., Mutasa, K., Zvandasara, P., Nathoo, K. J., Mzengeza, F. et al. (2006) HIV incidence among post-partum women in Zimbabwe: risk factors and the effect of vitamin A supplementation. *AIDS* 20: 1437–1446.
- Humphrey, J. H., Iliff, P. J., Marinda, E. T., Mutasa, K., Moulton, L. H., Chidawanyika, H., Ward, B. J., Nathoo, K. J., Malaba, L. C. et al. (2006) Effects of a single large dose of vitamin A, given during the postpartum period to HIV-positive women and their infants, on child HIV infection, HIV-free survival, and mortality. *J Infect Dis* 193: 860–871.
- Iliff, P. J., Humphrey, J. H., Mahomva, A. I., Zvandasara, P., Bonduelle, M., Malaba, L. C. & Nathoo, K. J. (1999) Tolerance of large doses of vitamin A given to mothers and their babies shortly after delivery. *Nutr Res* 19: 1437–1446.
- IVACG. *The Annecy accords to assess and control vitamin A deficiency: summary of recommendations and clarifications*. 2002. Washington, DC, ILSI.
- Malaba, L. C., Iliff, P. J., Nathoo, K. J., Marinda, E., Moulton, L. H., Zijenah, L. S., Zvandasara, P., Ward, B. J. & Humphrey, J. H. (2005) 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* 81: 454–460.
- Miller, M., Humphrey, J., Johnson, E., Marinda, E., Brookmeyer, R. & Katz, J. (2002) Why do children become vitamin A deficient? *J Nutr* 132: 2867S–2880S.
- Muhilal, Murdiana, A., Azis, I., Saidin, S., Jahari, A. B. & Karyadi, D. (1988) Vitamin A-fortified monosodium glutamate and vitamin A status: a controlled field trial. *Am J Clin Nutr* 48: 1265–1270.
- Muhilal & Permaesih D (1985) Dampak perberian vitamin A dosis tinggi pada ibu menyusui terhadap status vitamin A anak. *Penelit Gizi Makanan* 8: 5–19.
- Newman, V. *Vitamin A and breast-feeding: a comparison of data from developed and developing countries*. 1993. San Diego, California, Wellstart International.
- Rice, A. L., Stoltzfus, R. J., de, F. A., Chakraborty, J., Kjolhede, C. L. & Wahed, M. A. (1999) Maternal vitamin A or beta-carotene supplementation in lactating Bangladeshi women benefits mothers and infants but does not prevent subclinical deficiency. *J Nutr* 129: 356–365.
- Rice, A. L., West, K. P., Jr. & Black, R. E. (2004) Vitamin A deficiency. In: *Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors: Volume 1* World Health Organization, Geneva, Switzerland.
- Ross, D. A. (2002) Recommendations for vitamin A supplementation. *J Nutr* 132: 2902S–2906S.
- Roy, S. K., Islam, A., Molla, A., Akramuzzaman, S. M., Jahan, F. & Fuchs, G. (1997) Impact of a single megadose of vitamin A at delivery on breastmilk of mothers and morbidity of their infants. *Eur J Clin Nutr* 51: 302–307.
- Semba, R. D., Susatio, B., Muhilal & Natadisastra, G. (1995) The decline of admissions for xerophthalmia at Cicendo Eye Hospital, Indonesia, 1981–1992. *Int Ophthalmol* 19: 39–42.
- Sommer, A. *Innocenti Micronutrient Research Report No. 1*. 2005. International Vitamin A Consultative Group. 5–10–2006.
- Sommer, A. & Davidson, F. R. (2002) Assessment and control of vitamin A deficiency: the Annecy Accords. *J Nutr* 132: 2845S–2850S.
- Sommer, A. & West, K. P. J. (1996) *Vitamin A deficiency: health, survival and vision*. Oxford University Press, New York, NY.
- Stoltzfus, R. J. (1994) Vitamin A deficiency in the mother-infant dyad. *SCN News* 25–27.
- Stoltzfus, R. J. & Humphrey, J. H. (2002) Vitamin A and the nursing mother-infant dyad: evidence for intervention. *Adv Exp Med Biol* 503: 39–47.
- Stoltzfus, R. J., Hakimi, M., Miller, K. W., Rasmussen, K. M., Dawiesah, S., Habicht, J. P. & Dibley, M. J. (1993) High dose vitamin A supplementation of breast-feeding Indonesian mothers: effects on the vitamin A status of mother and infant. *J Nutr* 123: 666–675.
- Tanumihardjo, S. A., Muherdiyantiningsih, Permaesih, D., Komala, Muhilal, Karyadi, D. & Olson, J. A. (1996) Daily supplements of vitamin A (8.4 mumol, 8000 IU) improve the vitamin A status of lactating Indonesian women. *Am J Clin Nutr* 63: 32–35.

- Tchum, S. K., Tanumihardjo, S. A., Newton, S., de, B. B., Owusu-Agyei, S., Arthur, F. K. & Tetteh, A. (2006) Evaluation of vitamin A supplementation regimens in Ghanaian postpartum mothers with the use of the modified-relative-dose-response test. *Am J Clin Nutr* 84: 1344–1349.
- Thanangkul, O. 1974. Jakarta, Indonesia (25–29 Nov 1974), WHO/IVACG. *Comparison of the effects of a single high dose of vitamin A given to mother and infant upon plasma levels of vitamin A in the infant.*
- Venkatarao, T., Ramakrishnan, R., Nair, N. G., Radhakrishnan, S., Sundaramoorthy, L., Koya, P. K. & Kumar, S. K. (1996) Effect of vitamin A supplementation to mother and infant on morbidity in infancy. *Indian Pediatr* 33: 279–286.
- Villard, L. & Bates, C. J. (1987) Effect of vitamin A supplementation on plasma and breast milk vitamin A levels in poorly nourished Gambian women. *Hum Nutr Clin Nutr* 41: 47–58.
- Vinutha, B., Mehta, M. N. & Shanbag, P. (2000) Vitamin A status of pregnant women and effect of post partum vitamin A supplementation. *Indian Pediatr* 37: 1188–1193.
- West, K. P., Jr. (2002) Extent of vitamin A deficiency among preschool children and women of reproductive age. *J Nutr* 132: 2857S–2866S.
- WHO/UNICEF/IVACG Task Force. *Vitamin A supplements: a guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia.* 1997. Geneva, WHO.
- Wysong, C. S., Shey, M. S., Sterne, J. A. & Brocklehurst, P. (2005) Vitamin A supplementation for reducing the risk of mother-to-child transmission of HIV infection. *Cochrane Database Syst Rev* CD003648.
- Yamini, S., West, K. P., Jr., Wu, L., Dreyfuss, M. L., Yang, D. X. & Khattry, S. K. (2001) 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* 55: 252–259.
- Zvandasara, P., Hargrove, J. W., Ntozini, R., Chidawanyika, H., Mutasa, K., Iliff, P. J., Moulton, L. H., Mzengeza, F., Malaba, L. C. et al. (2006) Mortality and morbidity among postpartum HIV-positive and HIV-negative women in Zimbabwe: risk factors, causes, and impact of single-dose postpartum vitamin A supplementation. *J Acquir Immune Defic Syndr* 43: 107–116.



**USAID**  
FROM THE AMERICAN PEOPLE



This publication was 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 the Johns Hopkins University and do not necessarily reflect the views of the USAID or the United States Government.