# Combining Vitamin A Distribution with EPI Contacts

## A Report of an International Vitamin A Consultative Group (IVACG) Task Force

### Executive Summary

The simultaneous administration of supplemental moderate-to-large doses of vitamin A in populations who are deficient has not resulted in an adverse effect on vaccines administered at the routinely recommended ages in Expanded Programme on Immunization (EPI) programs in the studies conducted to date. For some antigens, administration of vitamin A has resulted in improved antibody responses in vitamin A-deficient animals and (in limited studies) children. There have been no adverse effects on the immune response to polio vaccines or Diphtheria, Tetanus, and Pertussis (DTP) antigens. No adverse effects are anticipated on the response to other antigens based upon animal data and human evidence accumulated to date, but additional studies are indicated for *Haemophilus influenzae* conjugate, hepatitis B, Bacillus Calmette-Guerin (BCG) and yellow fever vaccines before definitive conclusions can be stated.

Recommended doses of vitamin A at EPI visits are 100,000 international units (IU) for infants 6 – 11 months of age, and 200,000 IU for older children. A dose of vitamin A should be given to infants and children 6 months to 5 years of age during one of two annual rounds of national immunization days (NIDs) in vitamin A-deficient areas. For practical purposes, no minimum interval needs to be specified for vitamin A administration with EPI routine visits and NIDs.

## OPTIMAL DOSE RECOMMENDATIONS

1. 100,000 IU of vitamin A is the appropriate dose for multiple administration with EPI visits from 6 months through 11 months of age, and 200,000 IU at 12 months of age and older.
2. The recommendation, made at the meeting hosted by WHO and UNICEF in January 1998, to administer one dose of vitamin A to infants and children 6 months to 5 years of age during one of the two rounds in National Immunization Days (NIDs) seems, from available data, appropriate.[1] No minimum interval needs to be specified for vitamin A administration with EPI visits and NIDs, because large doses clear rapidly.
3. Existing data suggest it is safe to include doses of 25,000 IU at multiple EPI visits, including NIDs, during the first 6 months of life. The goal would be to maximize benefits among infants 6 to 11 months of age. WHO should consider giving vitamin A supplements during the first 5 months of age in immunization programs currently providing supplements after 6 months of age.

## I. Objectives

At the request of the World Health Organization/Expanded Programme on Immunization (WHO/EPI), the International Vitamin A Consultative Group (IVACG) assembled a task force to (*a*) review available data on the optimal dose for vitamin A administration with EPI visits; (*b*) review the effect of vitamin A on the immune response to EPI antigens from published and unpublished studies; (*c*) identify additional studies that need to be conducted; and (*d*) prioritize these needed studies.

## II. EPI Perspective

WHO/EPI is committed to a program of vitamin A supplementation, but needed IVACG recommendations regarding the safety of the effects of vitamin A on the immune response when administered with EPI antigens.[1] In particular, WHO/EPI sought advice for programs and/or research required that would enable EPI to (1) recommend administration of vitamin A with DTP, hepatitis B and Hib vaccines during the first year of life; (2) recommend use of vitamin A in conjunction with yellow fever immunization where high prevalence of deficiency exists; and (3) provide guidance on the safety and potential value of simultaneous use of BCG and vitamin A supplementation at birth.

## III. Optimal Dose of Vitamin A

Data regarding the safety and effectiveness of vitamin A supplementation in doses of 25,000, 50,000, and 100,000 international units (IU) administered to children under 12 months of age were reviewed. Vitamin A administered after 6 months of life is routinely associated with reduced mortality among supplemented children in deficient populations.[2, 3] Data among younger infants is equivocal. Hence the primary reason for administering vitamin A in the first 6 months of life is to build body stores and minimize the depletion of vitamin A reserves that could adversely impact on infant survival in the second six months of life. In Indonesia, a single dose of 50,000 IU at birth was associated with a significant reduction in infant mortality.[4] However, studies elsewhere have observed no measurable benefit on infant mortality when doses of 25,000, 50,000, or 100,000 IU[5 – 7] of vitamin A were administered in the first few months of life. No significant long-term adverse effects have been noted with doses of 25,000 IU to 50,000 IU. Most trials have reported excess risk of bulging fontanelles in approximately 1% to 5% of infants with open fontanelles, which disappeared in 24 to 72 hours.[3, 7 – 10] No increase in intracranial pressure was associated with bulging fontanelles as measured by Doppler ultrasound.[8] In Indonesia, a bulging fontanelle was not associated with any long-term neurodevelopmental abnormalities at 3 years of age assessed by Bayleys II developmental tests.[11] In Nepal, long term follow-up of infants who had received 100,000 IU of vitamin A at 1 to 3 months of age revealed a non-statistically significant tendency toward higher mortality in supplemented infants.[6]

## IV. WHO Three-Country Study

The data from the three-country (Ghana, India, and Peru) supplementation study coordinated by WHO was reviewed.[12] Baseline serum retinol levels were surprisingly low, especially since Peru is known to have no clinically evident public health problem with vitamin A deficiency. Levels among vitamin A-supplemented infants were significantly higher than placebo recipients at 6 months of age (3 months after the last dose); as to be expected, no difference in retinol levels were noted at 9 months of age (6 months after the last dose). This is consistent with serum retinol kinetics observed in other trials in infants less than 6 months of age. No effects on morbidity or mortality were observed, though the overall mortality after 6 weeks of age was lower than would normally be anticipated in vitamin A-deficient populations.

### *THREE-COUNTRY STUDY RECOMMENDATION*

4. The results of the three-country study do not indicate any need to change existing policy to use the EPI distribution system for reducing morbidity and mortality associated with vitamin A deficiency. Additional studies should be conducted to investigate larger and/or more frequent vitamin A doses, particularly to maximize benefits among infants 6 to 9 months of age.

## V. Effect of Vitamin A on the Immune Response

The known effects of vitamin A deficiency and supplementation on the immune response were reviewed. Vitamin A deficiency leads to a downregulation of T-cell and B-cell activation and differentiation.[3, 13 – 15] No impact of vitamin A deficiency on immunologic memory has been noted. Supplemental doses of vitamin A lead to increased CD4 lymphocyte counts by facilitating production of new CD4 cells. Supplementation with 50,000 IU vitamin A simultaneously with each of three doses of DTP and oral poliovirus vaccine (OPV) administered at monthly intervals beginning at 2 – 3 months of age resulted in enhanced delayed-type hypersensitivity to tetanus, diphtheria, and purified protein derivative (PPD), but only in children with adequate baseline vitamin A levels.[16]

**Protein antigens:** The immune response to protein antigens is diminished in vitamin A-deficient animals and humans, and supplementation resulted in increased antibody and T cell responses.[15, 17, 18] In humans, co-administration of vitamin A and immunizations has led to either enhancement or no effect on responses to BCG, tetanus toxoid, diphtheria toxoid, and OPV.[13, 15, 16, 18 – 21] Studies of immunological ontogeny in animals suggest that modulation of the response to certain antigens at early ages can affect the response to other antigens, and that such effects may be modulated by maternal antibodies. This phenomenon has not been well-studied in humans, and the influence of vitamin A on such effects is unknown.

**Carbohydrate antigens:** The immune responses to meningococcal and pneumococcal polysaccharides in rats were substantially decreased during vitamin A deficiency and responses to these antigens were restored following vitamin A supplementation.[14] However, responses to another class of carbohydrate antigen, the lipopolysaccharides, were not affected by vitamin A deficiency. Although both are considered T-independent antigens, T-cells do participate in the response to polysaccharides. A pilot study involving 50 Native American children who received pneumococcal polysaccharide vaccine revealed no apparent effect from vitamin A supplementation (100,000 IU) on the antibody responses to three pneumococcal serotypes (M. Santosham, personal communication). From these results and data on the effects of vitamin A on T-dependent protein antigens, one would not expect deleterious

effects of vitamin A on responses to unconjugated carbohydrate antigens (i.e., meningococcal or pneumococcal polysaccharide vaccine) or protein-carbohydrate conjugates (i.e., Hib and pneumococcal conjugate vaccines) in children.

Meningococcal polysaccharide vaccine has been administered to children, especially during epidemics in the meningitis belt of Africa and during outbreaks in South America. Based upon the enhancement of the response to meningococcal polysaccharide in vitamin A-replete animals, there is no reason to alter plans for vitamin A supplementation with scheduled visits for children who will be receiving meningococcal vaccine.

## VI. The Effect of Vitamin A Supplementation on Specific Vaccines: Polysaccharide conjugate vaccines

Since *Haemophilus influenzae* type b (Hib) and pneumococcal conjugate vaccines are likely to be added to the EPI schedule, additional information on simultaneous vitamin A administration with these vaccines would be useful. There is no animal data available on the effects of vitamin A supplementation on the response to polysaccharide antigens conjugated to proteins.

Theoretically, antigen processing by the immune system might differ from protein vaccines and there could be age-specific differences in the responding B cell network. Although most working group members believe that the effect of vitamin A on this class of vaccines will be similar to protein antigens, additional studies may be warranted.

### SPECIFIC VACCINES RECOMMENDATION

5. Data is pending from studies that evaluate the impact of vitamin A supplementation on Hib conjugate vaccines including polyribosyl ribitol phosphate (PRP) conjugated to meningococcal outer membrane protein (PRP-OMP), tetanus toxoid (PRP-T), and diphtheria toxoid (HbOC). One study is in progress to evaluate the effect of supplementation on HbOC and PRP-OMP in El Salvador (A. Shankar, personal communication).

### HEPATITIS B VACCINE RECOMMENDATION

6. The impact of vitamin A supplementation on the response to hepatitis B vaccine should be evaluated in a vitamin A-deficient population.

### BCG VACCINE RECOMMENDATION

7. Although there is no reason to anticipate a negative effect of vitamin A on the response to BCG, data from one additional study might be useful.

### *Hepatitis B vaccine*

Although the effect of vitamin A supplementation on the response to hepatitis B vaccine should be similar to other protein antigens, the structure of the hepatitis B surface antigen differs from that of tetanus and diphtheria toxoids, suggesting that additional studies may be warranted. There is no need for modifications of existing policy to administer hepatitis B vaccine to all infants regardless of maternal or infant vitamin A supplementation.

### *BCG vaccine*

In Bangladesh where BCG is given at birth, no significant difference in skin test responses to PPD was observed in vitamin A supplemented vs. unsupplemented children, but the responses to PPD were somewhat lower than expected in both groups (50 – 60%) when children were tested at nine months of age.[16] T-cell proliferative responses to BCG were enhanced in Thai children given vitamin A and zinc, but not in children who received zinc alone.[22]

## DTP vaccine

Studies evaluating the impact of vitamin A supplementation on the response to diphtheria and tetanus toxoids have been conducted in animals and humans. Vitamin A-deficient animals and humans had diminished responses to diphtheria and tetanus toxoids.[14,23] Supplementation resulted in marked increases in the antibody response in animals, and one study in humans revealed that vitamin A supplementation (200,000 IU) corrected the response.[14,23,24] A recent study in Bangladesh revealed enhancement of the antibody response to diphtheria toxoid but no effect on tetanus toxoid or pertussis antigen response in children who received 50,000 IU of vitamin A at each of the three visits for primary immunization.[21]

## Measles and rubella vaccines

The current WHO policy recommendation is to provide measles vaccine at 9 months of age. A two-dose measles vaccination regimen at 6 and 9 months is recommended for HIV-infected infants and refugee populations. Studies in several countries reveal that administration of 100,000 IU vitamin A with measles vaccination at 9 months of age is safe without deleterious effect on the immune response to measles vaccine.[25–31] In Guinea-Bissau, no impairment in immune response was seen in the response to the two-dose regimen at 6 and 9 months.[26] These studies lay to rest concerns from an earlier trial involving Indonesian infants that found that seroconversion to measles vaccine was reduced when vitamin A supplementation of 100,000 IU was given along with measles immunization to 6-month-old infants who had maternal antibody at the time of vaccination. Seroconversion was not reduced among infants who did not have detectable maternal antibody.[32] Even when the vaccine is given as early as 6 months, the possibility of a small decrease in antibody response is outweighed by the recognized benefits of vitamin A supplementation on the reduction of mortality associated with measles and other diseases.

Rubella vaccine viruses replicate in the same reticuloendothelial cells as measles vaccine viruses, and the biologic factors affecting immune response to rubella vaccine are analogous to measles vaccine. Based upon data from measles vaccine and vitamin A, no interference is anticipated when rubella vaccine is given with vitamin A. Additional studies might be useful to document these expectations but are not necessary before initiating programs.

## Oral poliovirus vaccine

No adverse effect on the response to oral polio vaccine has been observed.[18, 20]

## Yellow fever vaccine

There are no data evaluating the immune response to yellow fever vaccine in vitamin A-deficient children or animals or the effect of vitamin A supplementation.

### DTP VACCINE RECOMMENDATION

8. Vitamin A supplementation either has no effect or it enhances the immune response to DTP antigens. Therefore, no additional studies are needed before developing policy with regard to administration of vitamin A simultaneously with DTP immunization.

### MEASLES VACCINE RECOMMENDATION

9. Vitamin A supplementation is appropriate for simultaneous administration with measles and/or rubella vaccines at all ages including infants as young as 6 months of age.

### POLIO VACCINE RECOMMENDATION

10. Vitamin A supplementation is appropriate for simultaneous administration with oral polio vaccine at all ages.

### YELLOW FEVER VACCINE RECOMMENDATION

11. Studies to evaluate the effect of vitamin A supplementation on the response to yellow fever vaccine at 6 months and at 9 months of age would be useful.

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# Task Force and Working Group

On July 2, 1998, an IVACG task force held a working group at Johns Hopkins University School of Hygiene and Public Health in Baltimore, Maryland, to discuss and address technical issues regarding the distribution of vitamin A with EPI visits.


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These individuals contributed manuscripts, and some participated in telephone discussions and/or a pre-meeting planning session to review data on the effect of vitamin A on the immune response to EPI antigens.

## About IVACG

Established in 1975, the International Vitamin A Consultative Group guides international activities for reducing vitamin A deficiency in the world. IVACG concentrates its efforts on stimulating and disseminating new knowledge, translating that new knowledge to assist others in its practical application, and providing authoritative policy statements and recommendations that others can use to develop appropriate prevention and control programs.

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This statement was reviewed and approved by the IVACG Steering Committee.

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