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Effects of Vitamin A Supplementation on Immune Responses and Correlation with Clinical Outcomes

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INTRODUCTION

The term vitamin A designates a group of retinoid compounds with the biologic activity of all-*trans*-retinol. Retinoids usually consist of four isoprenoid units with five conjugated carbon-carbon double bonds (141). Preformed vitamin A can be obtained mostly from dietary animal sources (liver, fish liver oils, eggs, and dairy products) as retinyl palmitate, whereas carotenoids that can be converted into retinol are obtained from vegetable foodstuffs (dark-green leafy vegetables and deep-orange fruits). Vitamin A plays an essential role in a large number of physiological functions that encompass vision, growth, reproduction, hematopoiesis, and immunity (143). Despite major advances in the knowledge of vitamin A biology, its deficiency is still a serious public health problem that affects an estimated 127 million preschool children and 7.2 million pregnant women worldwide (153). In children, vitamin A deficiency results in increased risks of mortality and morbidity from measles and diarrheal infections (150), blindness (156), and anemia (125), and among women it is likely to be associated with high mortality related to pregnancy (24, 154). Many of these effects can be linked to the immunological functions of vitamin A.

Vitamin A is one of the most widely studied nutrients in relation to immune function. The first observations that suggested a link between vitamin A and immunity were made even before the structure of vitamin A was deduced in 1931 (70). These included the discoveries that fat in butter improved the outcome of infections in malnourished animals (98) and that vitamin A-deficient rats appeared to be more susceptible to infection (55, 80). In 1932, Joseph B. Ellison discovered that a vitamin A extract reduced the measles case fatality rate in children, and up to 1940, at least 30 therapeutic trials were conducted on the effect of vitamin A on infection-related outcomes (123). After the discovery of antibiotics, research on the mechanisms through which vitamin A improved the immune function was revitalized in the 1960s by the landmark review by Scrimshaw et al. of the interactions between nutrition and infection (119) and later in the 1980s by the finding of protective effects of supplementation on overall child mortality in Indonesia (142), which were confirmed in subsequent large randomized clinical trials (9, 150). More recently, the discovery of the nuclear receptors for the vitamin A active metabolites all-*trans*- and 9-*cis*-retinoic acids (retinoic acid receptor and retinoic X receptor) (53, 87, 101), which regulate gene transcription, provided fundamental evidence for the understanding of the mechanisms through which retinoids affect immunity.

The field of vitamin A immunology has greatly benefited from animal and in vitro experiments. These studies have provided a vast body of knowledge on the cellular and molecular mechanisms by which vitamin A and its metabolites influence the immune function at various levels. Excellent reviews of the available literature on these mechanisms have been recently published (121, 122, 145); however, there are fewer critical

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reviews on the impact of vitamin A supplementation as a preventive or therapeutic intervention on indicators of immunity as measured in population studies. In this paper we present a review of the randomized, controlled clinical trials of vitamin A that have been conducted in humans and which included direct measurements of innate or adaptive aspects of the immune function as study end points. We also provide a correlation of the results from these trials with the effect of supplementation on clinical end points. We consider only the trials in which preformed vitamin A or related retinoids have been tested; trials with pro-vitamin A carotenoids alone are not included in this paper. Results from the human studies reviewed here are interpreted in light of available knowledge from basic research; however, this paper is not aimed at comprehensively reviewing animal or in vitro experimentation.

VITAMIN A SUPPLEMENTATION AND INNATE IMMUNE RESPONSES

Barrier Function and Mucosal Immunity

Vitamin A is fundamental in maintaining the integrity of epithelia. Vitamin A deficiency is associated with pathological alterations in ocular (60, 143), respiratory (91, 160), gastrointestinal (114, 152), and genitourinary (93) epithelial tissues. A number of clinical trials examined the effect of vitamin A supplementation in humans on indicators of mucosal immunity, which included measurements of gut integrity and secretion of immune factors in the genital tract, saliva, and breast milk (Table 1). The lactulose/mannitol (L/M) urinary excretion test was used in some trials as an indicator of gut permeability. One dose of vitamin A administered to Indian children who were hospitalized with diarrhea resulted in a more rapid recovery of intestinal integrity within 30 days after discharge (147); among nonhospitalized children receiving weekly doses, however, there was no effect after 2 months. Vitamin A and β-carotene supplementation to human immunodeficiency virus (HIV)-infected pregnant women in South Africa was associated with lower L/M ratios in their infants at 14 weeks, but only in those who became HIV infected (49). In a nonrandomized, non-placebo-controlled study of children with a history of persistent diarrhea or underweight, supplementation with a single 200,000-IU vitamin A dose (100,000 if <12 mo) was related to a significant decrease in the L/M ratio after 2 weeks compared to the baseline level (22). These children also received 20 mg zinc daily, and therefore it is not possible to ascertain whether the apparent treatment effect could be attributable to vitamin A alone. In the same study, serum retinol was negatively correlated to the urinary L/M ratio, whereas no correlation was found with zinc, which could suggest that if there was a treatment effect, it may have been due to vitamin A. In a small (n = 20), non-placebo-controlled trial of acitretin (a retinoid) in children with severe gastrointestinal mucosal lesions associated with chemotherapy, no effect on the L/M ratio was found after 4 to 5 weeks (75).

Two clinical trials reported the effect of vitamin A supplementation during pregnancy (128) or the early postpartum period (48) on the concentration of mucosal anti-infective proteins in breast milk. No effects were found on secretory immunoglobulin A (IgA), lactoferrin, lysozyme, or interleukin-8 (IL-8). Vitamin A supplementation had no effect on the concentration of immune factors in cervicovaginal fluids of HIV-infected pregnant women, including lactoferrin, lysozyme, and secretory leukocyte proteinase inhibitor, an innate protein produced by mucosal epithelial and acinar cells (102). There was also no effect on the concentration of IL-1β in genital fluids of HIV-infected women in another trial (40). Fecal IL-8 following infections with enterotoxigenic *Escherichia coli* was reduced by vitamin A supplementation according to preliminary results from a trial with Mexican children (82). One noncontrolled trial among children showed an apparent decrease in the concentration of secretory IgA in saliva after 4 weeks of supplementation with 100,000 IU vitamin A with respect to baseline values, but comparisons with children who did not receive vitamin A were not made (16).

In summary, the available evidence indicates a beneficial effect of vitamin A supplementation on intestinal integrity among children suffering from severe infections or who are undernourished. A few supplementation studies have not shown a consistent effect on the concentration of mucosal anti-infective or inflammatory markers in milk, saliva, or genital fluids.

Acute-Phase Response and Complement System

The impact of vitamin A on circulating effectors of innate immunity, including acute-phase response proteins and the complement system, was studied in trials from Ghana, Indonesia, and South Africa (Table 1). In the Ghana study of preschool children, large doses of vitamin A every 4 months for 1 year resulted in significantly increased serum amyloid A and C-reactive protein among children with symptoms of gastrointestinal infections, including severe diarrhea and vomiting (47). By contrast, no significant effect was found on C-reactive protein concentrations after 5 weeks of a single oral dose in the Indonesia study (120). Plasma C3 complement was not affected by four doses of vitamin A administered within a 42-day period to South African children (28).

Monocytes/Macrophages

Experiments in vitro and animal studies suggest that retinoids are important regulators of monocytic differentiation and function. When added to monocytic, myelomonocytic or dendritic cell line cultures, retinoic acid promotes cellular differentiation (19, 52, 69, 92) and influences the secretion of key cytokines produced by macrophages, including tumor necrosis factor (TNF-α), IL-1β, IL-6, and IL-12. All-*trans*-retinoic acid skewed the differentiation of human peripheral blood monocytes to IL-12-secreting dendritic cells in one in vitro study (92), whereas in another it inhibited lipopolysaccharide-induced IL-12 production by mouse macrophages (96). All-*trans*-retinoic acid was shown to decrease secretion of TNF-α in murine peripheral blood mononuclear cells (73) and myelomonocytic (95) and macrophage (88, 94) cell lines. On the other hand, retinoids appear to enhance the secretion of IL-1β (59, 89) and IL-6 (2) by macrophages and monocytes. In rats (61) and in experiments in vitro (35), vitamin A increased the phagocytic capacity of macrophages.

A few supplementation studies with humans included indi-

TABLE 1. Randomized, controlled trials of vitamin A in relation to innate immune responses

Study site (reference[s])	Intervention groups	Population	End point[a]	Result for the indicated measure of effect[b]			*P* value
				Vitamin A		*Placebo*	
India (147)	Vitamin A (200,000 IU) on admission vs 200,000 IU at discharge, vs placebo, single dose	94 infants hospitalized, with diarrhea or respiratory infection	Lactulose/mannitol ratio at 10 and 30 days after discharge	Significantly different in both vitamin A-treated groups compared to control group			<0.05
	Vitamin A (16,700 IU) weekly for 8 wk vs placebo	80 infants	Lactulose/mannitol ratio at 4 and 8 wk	No difference at any time point			
South Africa (49, 115)	Vitamin A (5,000 IU) + β-carotene (30 mg) daily during pregnancy + vitamin A (200,000 IU) at delivery to mothers vs placebo	238 infants born to 728 HIV^+ women	Lactulose/mannitol ratio:	*Vitamin A*		*Placebo*	
			Among HIV^- infants at 14 weeks	0.11		0.09	>0.05
			Among HIV^+ infants at 14 weeks	0.17		0.50	<0.05
			Lactulose/creatinine ratio at:				
			1 wk	Lower		Higher	0.009
			14 wk	Lower		Higher	0.014
		242 infants	Urinary neopterin excretion in infants at 0, 1 wk, 6 wk, 6 mo	No significant effect			
Malawi (128)	Vitamin A (10,000 IU) daily during pregnancy vs placebo	334 HIV^+ pregnant women	Breast milk lactoferrin at 6 wk postpartum	*Vitamin A*		*Placebo*	
				No effect			
Bangladesh (48)	Vitamin A (200,000 IU) single dose vs 7.6 mg β-carotene daily vs placebo started at 1–3 wk postpartum for 9 mo	212 postpartum women	Breast milk immune factors at 3 mo from first dose	*Vitamin A*	β-*Carotene*	*Placebo*	
			Secretory IgA (g/liter)	0.74	0.79	0.86	>0.05
			Lactoferrin (g/liter)	3.06	3.04	3.40	>0.05
			Lysozyme (mg/liter)	118	124	109	>0.05
			IL-8 (ng/liter)	29.6	26.2	33.6	>0.05
South Africa (102)	Vitamin A (5,000 IU) + β-carotene (30 mg) daily during pregnancy + vitamin A (200,000 IU) at delivery vs placebo	60 HIV^+ pregnant women	Immune factors in CVL	*Vitamin A*		*Placebo*	
			Lactoferrin after 6 wk	No effect			
			Lysozyme after 6 wk	No effect			
			SLPI after 6 wk	No effect			
Mexico (82)	Vitamin A (45,000 IU, or 20,000 IU if <12 mo) vs placebo every 2 mo for 1 yr	188 infants, 6–15 mo	Cytokines in stool	*Vitamin A*		*Placebo*	
			IL-4	No significant effect			>0.05
			IL-5	No effect			
			IL-6	Higher during summer in vitamin A group			<0.05
				Lower after enterotoxigenic *E. coli*			<0.05
			IL-8	Lower after enterotoxigenic *E. coli*			<0.05
			IL-10	No effect			
			TNF-α	Higher during summer in vitamin A group			<0.05
			IFN-γ	No effect			
			MCP-1	No significant effect			>0.05

Ghana (47)	Vitamin A (200,000 IU, or 100,000 IU if < 12 mo) vs placebo every 4 mo for 1 yr	329 children age 6–59 mo	Ratio of acute-phase proteins between vitamin A and placebo groups	*Vitamin A*	*Placebo*	
			Serum amyloid A			
			Children with vomiting	2.15		>0.05
			Children with diarrhea	4.20		<0.05
			C-reactive protein			
			Children with vomiting	2.91		<0.05
			Children with diarrhea	2.11		>0.05
			α_1-Glycoprotein			
			Children with vomiting	1.15		>0.05
			Children with diarrhea	1.18		>0.05
Indonesia (120)	Vitamin A (200,000 IU) vs placebo, single dose, 2 wk before antitetanus immunization	236 children age 3–6 yr, 50% xerophtalmic	Change from baseline at 5 wk	*Vitamin A*	*Placebo*	
			α_1-Glycoprotein	No significant differences		
			C-reactive protein	No significant differences		
South Africa (28)	Vitamin A (200,000 IU, or 100,000 IU if <12 mo) vs placebo at days 0, 2, 8, and 42	60 infants age 4–24 mo hospitalized with measles	Plasma complement C3 (g/liter) at days	*Vitamin A*	*Placebo*	
			8	1.25	1.11	>0.05
			42	1.48	1.41	>0.05

[a] SLPI, secretory leukocyte proteinase inhibitor; MCP, macrophage/monocyte chemoattractant protein; CVL, cervicovaginal lavage.
[b] All values presented are means unless noted otherwise. Verbal descriptions of results correspond to those in the indicated references when numerical data were not presented.

rect measures of monocyte and macrophage function, mostly related to cytokine secretion. In a non-placebo-controlled, nonrandomized study of six patients with common variable immunodeficiency who had low serum retinol concentrations, supplementation with vitamin A at 6,500 IU/day for 6 months resulted in decreased concentrations of TNF-α compared to their baseline levels (3). Preliminary results from a trial with Mexican infants showed that the concentration of IL-6 in stool was lower in those who received vitamin A, but this effect appeared to be limited to the period following an infection with enterotoxigenic *Escherichia coli* (82). Vitamin A and β-carotene supplementation to HIV-infected pregnant women had no effect on the concentration of IL-1β in cervicovaginal secretions (40) or on urinary neopterin excretion, an indicator of macrophage activation (115), in studies from Tanzania and South Africa, respectively.

The trials described above suggest that supplementation with preformed vitamin A might down-regulate the secretion of specific proinflammatory cytokines (e.g., TNF-α and IL-6) by macrophages, but seemingly only in response to infections by particular pathogens. Additional, more robust data from human trials would be needed to support this potential mechanism.

Natural Killer Cells and Neutrophils

NK cells are important in the first line of defense against tumors and viral infections. The number of circulating NK cells is reduced during experimental vitamin A deficiency in animals (161). In humans, one cross-sectional study found that children with low serum retinol concentrations had a greater proportion of NK cells than those with higher retinol concentrations (68); however, vitamin A-deficient children were also more likely to be infected with HIV, which is likely to have confounded the association observed. In a clinical trial from South Africa among HIV-infected children, vitamin A supplementation was related to increased number of cells with the CD56 receptor, mostly expressed by NK cells (66).

The development of neutrophils in the bone marrow is controlled by retinoic acid receptor-modulated genes (90), and retinoic acid in cultures accelerates neutrophil maturation (113). Treatment with retinoic acid (162) or vitamin A (62) was shown to restore the number of neutrophils and the superoxide-generating capacity in rats and calves, respectively. There are limited data on the relationship between vitamin A and neutrophil function in humans. In a cross-sectional study of non-HIV-infected pregnant women, low serum retinol concentrations were not predictive of the neutrophil count (54), a very unspecific indicator. A study among preschool children reported no significant differences in neutrophil hydrogen peroxide (H_2O_2) or superoxide (O_2^-) production according to serum retinol concentrations (16). In the same study, the oral administration of 100,000 IU vitamin A was related to a significant increase in H_2O_2 production over baseline values after 4 weeks, but no comparisons with children not receiving supplementation were made.

The apparent benefit of vitamin A supplementation on NK cells among immunosuppressed children deserves confirmation in future investigations.

TABLE 2. Randomized, controlled trials of vitamin A in relation to T-cell function[a]

Study site (reference[s])	Intervention groups	Population	End point	Result for the indicated measure of effect[b]		*P* value
South Africa (28)	Vitamin A (200,000 IU, or 100,000 IU if <12 mo) vs placebo on days 0, 2, 8, and 42	60 infants age 4–24 mo hospitalized with measles	Lymphocyte count (10^9/liter)	*Vitamin A*	*Placebo*	
			Difference at day 42	8.10	6.45	0.05
			Change from day 0 to day 42	3.40	1.96	0.06
			IL-2 (IU/ml) at day:	1.76	1.72	>0.05
			8	1.74	1.70	>0.05
			42			
Indonesia (132)	Vitamin A (200,000 IU) vs placebo, single dose, 2 wk before antitetanus immunization	55 children age 3–6 yr. 30 xerophthalmic	CD4/CD8 ratio at 5 wk from supplementation	*Vitamin A*	*Placebo*	
				1.32	0.97	<0.0001
			% CD4 naive T cells at 5 wk	Higher in vitamin A group		<0.01
			Change in T-cell subsets after 5 wk			
			CD4/CD8 ratio	Significant increase, $P < 0.007$	No significant change	
			% $CD4^+$ $CD45RA^+$	Significant increase, $P < 0.003$	No significant change	
			% $CD4^+$ $CD45RO^+$	No change in any group, no significant difference in change		
			% $CD8^+$ $CD45RA^+$	No change in any group, no significant difference in change		
			% $CD8^+$ $CD45RO^+$	Significant decrease	No significant change	
Guinea-Bissau (13)	Vitamin A (100,000 IU) at age 6 mo vs placebo	276 infants	T-cell subset change between 6 and 9 mo of age	*Vitamin A*	*No vitamin A*	
			% CD4	−0.11	0.45	0.31
			% CD8	1.21	1.61	0.21
			CD4/CD8 ratio	−0.15	−0.07	0.26
	Vitamin A (100,000 IU) at age 6 and 9 mo vs placebo	185 infants	T-cell subset change at 18 mo	*Vitamin A*	*No vitamin A*	
			% CD4	2.50	−2.72	0.07
			% CD8	−1.93	0.49	0.12
			CD4/CD8 ratio	0.28	−0.20	0.06
South Africa (66)	Vitamin A (200,000 IU) on 2 consecutive days vs placebo	75 HIV^+ infants	Absolute lymphocyte count at 4 wk	*Vitamin A*	*Placebo*	
				Increase		0.05
			CD4 cell count at 4 wk	Increase		0.03
			CD56 cell count at 4 wk	Increase		0.05
			CD29 cell count at 4 wk	Increase		0.07
South Africa (76)	Vitamin A (5,000 IU) + β-carotene (30 mg) daily during pregnancy + vitamin A (200,000 IU) at delivery to mothers vs placebo	33 infants born to 728 HIV^+ women	T-helper cell responses to HIV in cord blood (infants)	*Vitamin A*	*Placebo*	
				Slightly more frequent in vitamin A arm but not significant		
Tanzania (40, 44–46)	Vitamin A (5,000 IU) + β-carotene (30 mg) daily during pregnancy and breast feeding to mothers vs placebo	1,078 HIV^+ pregnant women	Woman's T-cell subset counts (/μl)	*Vitamin A*	*Placebo*	
			CD4 at 6 wk postpartum	558	562	0.13
			CD4 at 30 wk postpartum	496	509	0.23
			Overall effect			0.29
			CD8 at 6 wk postpartum	1,061	1,094	0.32
			CD8 at 30 wk postpartum	943	909	0.26
			Overall effect			0.13
			CD3 at 6 wk postpartum	1,698	1,741	0.20
			CD3 at 30 wk postpartum	1,515	1,494	0.68
			Overall effect			0.25

		393 HIV$^+$ pregnant women	IL-1β in CVL (μg/ml)	218[c]	219[c]	0.41
		664 infants born to 1,078 HIV$^+$ women	Infant's CD4 cell count during first 2 yr	No effect		
	Vitamin A (5,000 IU) + β-carotene (30 mg) daily for ≈3–5 yr	1,078 HIV$^+$ women	T-cell subsets (/μl) at >4 yr after enrollment			
			CD4	434	449	0.30
			CD8	920	968	0.07
			CD3	1,425	1,497	0.05
United States (129)	Vitamin A (200,000 IU) single dose vs placebo	120 HIV$^+$ injection drug users		*Vitamin A*	*Placebo*	
			CD4 cells (/μl) at 4 wk			0.17
United States (65)	Vitamin A (300,000 IU) single dose vs placebo	40 HIV$^+$ women		*Vitamin A*	*Placebo*	
			% CD4 at 8 wk			0.56
			% CD8 that are CD38$^+$			>0.05
			Lymphocyte proliferation in response to:			
			PHA			>0.05
			Candida			>0.05
Kenya (5)	Vitamin A (10,000 IU) daily for 6 wk vs placebo	400 HIV$^+$ women	T-cell subsets at 6 wk (/μl)	*Vitamin A*	*Placebo*	
			CD4	272	225	0.04
			CD8	719	581	0.08
Italy (50)	Vitamin A (≈1,500 IU) daily for 3 mo vs. placebo, in both groups, half also received 25 mg zinc zulfate	118 men and women age >65	Total leucocytes (/μl)	*Vitamin A*	*No Vitamin A*	
			Baseline	6,149	6,206	
			Change from baseline	138	361	0.30
			Lymphocytes (/μl)			
			Baseline	1,977	1,942	
			Change from baseline	−73	62	0.05
			CD3$^+$ (/μl)			
			Baseline	1,260	1,123	
			Change from baseline	−109	49	0.01
			CD4$^+$ (/μl)			
			Baseline	712	711	
			Change from baseline	−125	−23	0.01
			CD4$^+$ DR$^+$ (/μl)			
			Baseline	76	70	
			Change from baseline	6	18	0.12
			CD8$^+$ (/μl)			
			Baseline	665	629	
			Change from baseline	−70	30	0.12
			CD8$^+$ DR$^+$ (μl)			
			Baseline	139	116	
			Change from baseline	−0.8	−0.7	0.64
			CD4/CD8 ratio			
			Baseline	1.17	1.16	
			Change from baseline	−0.10	−0.05	0.55
			Cytotoxic T lymphocytes			
			Baseline	70	84	
			Change from baseline	23	51	0.19

Continued on following page

TABLE 2—*Continued*

Study site (reference[s])	Intervention groups	Population	End point	Result for the indicated measure of effect[b]		*P* value
			NK cells (/μl)			
			Baseline	225	252	
			Change from baseline	−4	45	0.11
				Vitamin A	*Control*	
Bangladesh (20)	Vitamin A (200,000 IU intramuscularly) vs no intervention at the time of first of 3 antitetanus immunizations	91 children 1–6 yr	% of positive cutaneous DTH responses (≥5 mm) to a protein derivative and *Candida* after 4 wk	29.5	31.9	>0.05
Zambia (116)	Vitamin A (200,000 IU) single dose vs placebo	200 children age 5 mo–17 yr hospitalized with measles	Cutaneous DTH response at 2 wk	*Vitamin A*	*Placebo*	
			% Children with reactions	44.4	61.3	0.04
			Sum of indurations ≥2 mm	6.9	8.4	0.20
			Mean induration per reaction	4.1	3.9	0.50
			% of children unresponsive to specific antigens			
			Tetanus	82.8	81.0	>0.05
			Diphtheria	81.8	82.5	>0.05
			Tuberculin (PPD)	86.6	72.1	<0.05
			Streptococcus	100.0	90.1	>0.05
			Candida	97.1	85.5	<0.05
			Trichophyton	97.1	92.8	>0.05
			Proteus	97.1	86.8	<0.05
			IL-4, % change from baseline to 2 wk	9.0	35.0	0.18
Bangladesh (106)	Vitamin A (50,000 IU) vs placebo at each time of DPT/OPV vaccination (0, 4, and 8 wk)	120 infants age 6–17 wk	Cutaneous DTH response (% children) after 1 mo after last dose	*Vitamin A*	*Placebo*	
			Tetanus	30.6	32.8	>0.05
			Diphtheria	30.6	22.4	>0.05
			Tuberculin (PPD)	59.7	46.6	>0.05
			Streptococcus	4.8	6.9	>0.05
			Candida	3.2	8.6	>0.05
			Trichophyton	1.6	3.4	>0.05
			Proteus	4.8	1.7	>0.05
			Total (sum induration)	72.6	67.2	>0.05
			Total among children with baseline retinol ≥0.7 μmol/liter	93.3	57.9	0.008
			Avg induration (mm) among children with baseline retinol ≥0.7 μmol/liter	7.0	4.2	0.01
			% Anergic infants	27.4	32.8	>0.05

[a] PHA: phytohemagglutinin; CVL: cervicovaginal lavage; DPT: diphtheria, pertussis, and tetanus vaccine; OPV: oral polio vaccine; PPD: purified protein derivative;
[b] All values presented are means unless noted otherwise. Verbal descriptions of results correspond to those in the indicated references when numerical data were not presented.
[c] Median.

VITAMIN A SUPPLEMENTATION AND ADAPTIVE IMMUNE RESPONSES

T and B Lymphocytes

T-cell immunocompetence can be affected by vitamin A deficiency at various levels, including lymphopoiesis, distribution, expression of surface molecules, and cytokine production. The end points examined in human clinical trials could be grouped into T-lymphocyte counts and function.

T-cell counts. A potential effect of vitamin A on human lymphopoiesis has been suggested in pediatric supplementation trials (Table 2). Among infants from South Africa, vitamin A supplementation significantly increased the total lymphocyte count after 42 days (28), whereas in Indonesia, supplementation was related to a higher proportion of CD4 naive T cells ($CD4^+$ $CD45RA^+$) after 5 weeks, compared to controls (132). In a trial conducted in Guinea-Bissau, vitamin A supplementation at age 6 months was not associated with significant changes in T-cell subpopulations; however, supplementation at both 6 and 9 months resulted in a borderline significant increase in the proportion of CD4 T cells at age 18 months (13). Some trials examined the effect of vitamin A on T-cell counts among HIV-infected children. In South Africa, supplementation in HIV-positive infants was related to a significant increase in total lymphocyte counts as well as specific T-cell subpopulations, including CD4, after 4 weeks (66). By contrast, supplementation in HIV-infected women during pregnancy had no effect on the babies' T lymphocytes in Tanzania (46) or South Africa (76). The comparison between the direct supplementation trial (66) and the maternal supplementation studies (46, 76) is limited not only by the way of administration but also because supplements in the latter trials included β-carotene.

The potential effect of vitamin A on lymphocyte counts in adults has been studied among HIV-infected individuals, who are at high risk of developing profound nutritional deficiencies (51, 71, 135). Single-dose supplementation with vitamin A in nonpregnant HIV-positive women (65) and injection drug users (129) did not have a significant effect on CD4 cell counts; however, daily supplementation with vitamin A during 6 weeks in Kenyan HIV-infected women resulted in a modest, marginally significant greater mean CD4 cell count (5). Daily vitamin A and β-carotene supplementation of Tanzanian HIV-infected women during pregnancy had no effect on their CD4 cell counts (44). In extended analyses of the same study, daily supplementation for >3 years resulted in a statistically significant small negative effect on CD3 and a borderline significant effect on CD8 (45). It is not possible to distinguish whether these effects were due to the preformed vitamin A or the pro-vitamin A carotenoid.

One study among elderly men and women reported an apparent adverse effect of daily vitamin A supplementation on total lymphocyte counts at the expense of CD4 (50). This effect seemed to be ameliorated by the concomitant administration of zinc.

In summary, vitamin A supplementation to children has the potential to increase T-cell counts, particularly of the CD4 subpopulation. Studies have included children who are at high risk of vitamin A deficiency or who are infected with HIV. There is little evidence to support an effect of preformed vitamin A supplementation to adults on lymphopoiesis.

T-cell function. Some evidence is available from human studies regarding the role of vitamin A in lymphocyte immunocompetence. The ex vivo production of gamma interferon (IFN-γ), a Th1 proinflammatory cytokine, was found to be depressed in vitamin A-deficient children from Indonesia (159). In the South African trial among presumably non-HIV-infected infants (28), no vitamin effect was observed on the serum concentration of IL-2, another Th1 cytokine produced mainly by CD4 lymphocytes that plays a key role in proliferation and activation of T, B, and natural killer cells. IL-2 production is transient and peaks after 8 to 12 h after lymphocyte activation (1), and therefore it is unlikely that single measures of serum concentrations accurately reflect a potential treatment effect.

In another study in Zambia among children hospitalized with measles, no effect on the change from baseline in IL-4 concentration after 2 weeks of a single vitamin A dose was noted (116), and a study in Mexico found no differences by treatment arm in IL-4 from stool samples (82). IL-4 is produced mostly by CD4 cells of the Th2 subset.

A number of studies indicate a role for vitamin A in the regulation of IL-10 secretion. IL-10 produced by Th2-helper T cells inhibits the synthesis of proinflammatory Th1-type cytokines, including IFN-γ and IL-2, in both T and NK cells. This mechanism is important in limiting inflammatory responses to some pathogens. Venezuelan children with subclinical vitamin A deficiency had significantly lower circulating concentrations of IL-10 than nondeficient controls in a cross-sectional study (81). In the study of patients with common variable immunodeficiency (3), vitamin A supplementation increased IL-10 concentrations in patients with low serum vitamin A levels. In contrast, preliminary results from a trial of pregnant and lactating women in Ghana suggest that vitamin A supplementation increased the ratios of proinflammatory IFN-γ and TNF-α to IL-10 in the postpartum period (31). The authors speculate that, by reducing IL-10, vitamin A supplementation postpartum could reverse the anti-inflammatory Th2 bias induced by pregnancy and therefore diminish the risk of perinatal infections. This hypothesis would be consistent with studies showing reductions in morbidity from infections and infant mortality in the offspring of mothers supplemented with vitamin A; although some studies suggest a decrease in the incidence of febrile episodes (118), an effect on infant mortality is not apparent (86).

The trial among HIV-infected women from the United States (65) examined the effect of vitamin A supplementation on ex vivo lymphocyte proliferation in response to phytohemagglutinin and *Candida* mitogens and on lymphocyte activation markers ($CD8^+$ $CD38^+$) at 2, 4, and 8 weeks after a single dose; no effect on any of these parameters was observed.

Three studies among children assessed the effect of vitamin A supplementation on the cutaneous delayed-type hypersensitivity (DTH) response, an indicator of T-cell-dependent macrophage activation. There were no differences by treatment arm in the percentage of children with a DTH response to a protein derivative or *Candida* in a non-placebo-controlled trial of intramuscular vitamin A from Bangladesh (20); however, in a different trial among younger infants in the same country,

TABLE 3. Randomized, controlled trials of vitamin A in relation to antibody responses[a]

Study site (reference[s])	Intervention groups	Population	End point	Result for the indicated measure of effect[b]		*P* value
Bangladesh (20)	Vitamin A (200,000 IU intramuscularly) vs no intervention at the time of first of 3 anti tetanus immunizations	95 children 1–6 yr	Anti-tetanus GMT IgG (IU/ml) at 12 wk from first immunization (8 from second immunization)	*Vitamin A*	*Control*	
				0.016	0.011	>0.05
Indonesia (131)	Vitamin A (200,000 IU) vs placebo, single dose, 2 wk before antitetanus immunizations	236 children age 3–6 yr, 50% xerophtalmic	Anti-tetanus GM IgG (μg/liter) change after 3 wk from immunization in:	*Vitamin A*	*Placebo*	
			Tetanus-naive children[c]	62	24	<0.009
			Tetanus-exposed children[c]	1,903	891	<0.07
Turkey (79)	Vitamin A (30,000 IU) for 3 days together with DPT at 2, 3, and 4 mo of age (half also received 150 mg vitamin E one dose at each time	89 infants	Anti-tetanus GMT IgG (mIU/ml) at age:	*Vitamin A only*	*Placebo only*	
			5 mo	1,126.6	880.6	>0.05
			16–18 mo	314.7	314.4	>0.05
			Protective antitetanus titers (≥100 mIU/ml) at age:			
			5 mo	100%	100%	>0.05
			16–18 mo	92%	92%	>0.05
Bangladesh (108)	Vitamin A (50,000 IU) vs placebo at each time of DPT/OPV vaccination (0, 4, and 8 wk)	56 infants	GM IgG (mg/liter) after 1 mo from last dose	*Vitamin A*	*Placebo*	
			Antidiphteria	22.9	11.0	0.029
			Antipertussis	4.1	5.7	>0.05
			Antitetanus	112	119	>0.05
South Africa (28)	Vitamin A (200,000 IU, or 100,000 IU if <12 mo) vs placebo at days 0, 2, 8, and 42	60 infants age 4–24 mo hospitalized with measles	IgG anti-measles nucleocapsid protein (mIU/ml) at day:	*Vitamin A*	*Placebo*	
			8	384.2	222.8	0.01
			42	869.5	654.8	>0.05
Zambia (116)	Vitamin A (200,000 IU) single dose vs placebo	200 children age 5 mo–17 yr hospitalized with measles	GMT IgG anti-measles hemagglutinin protein at 2 wk from vitamin A dose	*Vitamin A* 4.12	*Placebo* 4.30	0.25
Indonesia (133)	Vitamin A (100,000 IU) vs placebo at the time of measles immunization (age 6 mo), single dose	336 infants age 6 mo	Seroconversion to measles[d] after 6 mo from immunization among infants with titer of:	*Vitamin A*	*Placebo*	
			≥8	66.3%	79.3%	<0.04
			<8	100.0%	100.0%	-
			Protective titers (>120) after 6 mo in infants with baseline titers ≥8	61.8%	77.2%	<0.03
			GMT to measles vaccine after:			
			1 mo	25% lower in vitamin A group		0.05
			6 mo	25% lower in vitamin A group		0.09

Guinea-Bissau (10, 11, 14)	Vitamin A (100,000 IU) vs placebo at 2 times of measles immunization (ages 6 and 9 mo)	150 infants age 6 mo	Seroconversion to measles[e]	*Vitamin A*	*Placebo*	
			At age 9 mo			
			Baseline titer ≥32 mIU	20%	20%	>0.05
			Baseline titer <32 mIU	88%	79%	>0.05
			Overall	74%	65%	>0.05
			At age 18 mo	98%	98%	>0.05
			GMT at age 18 mo	1,431	1,768	>0.05
		79 infants followed up	Protective titers (≥125 mIU/liter) at age 6–8 yr	95%	100%	0.36
			GMT at age 6–8 yr	670	783	0.51
	Vitamin A (100,000 IU) vs placebo at the time of measles immunization (age 9 mo only), single dose	312 infants age 9 mo	Seroconversion to measles[e] at age 18 mo	97%	93%	0.15[f]
			GMT at age 18 mo	3704	2439	<0.01
		152 infants followed up	Protective titers (≥125 mIU/liter) at age 6–8 yr	100%	91%	0.0095
			GMT at age 6–8 yr	1,366	1,048	0.09
India (17)	Vitamin A (100,000 IU) vs placebo at the time of measles immunization (9 mo), single dose	100 infants	Seroconversion to measles[g] after 4 wk	*Vitamin A*	*Placebo*	
			Among infants with titers ≥8	83.7%	63.0%	<0.01[h]
			Among infants with titers <8	100.0%	75.0%	>0.05
			Overall	84.0%	64.0%	<0.001[h]
Indonesia (124)	Vitamin A (100,000 IU) vs placebo at the time of measles immunization (age 9 mo)[e] single dose	394 infants age 9 mo	Seroconversion to measles[d] after 1 mo from immunization	*Vitamin A*	*Placebo*	
			Baseline titer <8	98.5%	99.0%	>0.05
			Baseline titer 8–120	100.0%	100.0%	>0.05
			Baseline titer >120	9.5%	9.1%	>0.05
			Protective titer (>120) after 6 mo			
			Baseline titer <8	99.4%	98.7%	>0.05
			Baseline titer 8–120	100.0%	100.0%	>0.05
			Baseline titer >120	100.0%	100.0%	>0.05
			GMT to measles vaccine after:			
			1 mo	1,772	2,298	0.18
			6 mo	1,164	1,900	0.03
				Vitamin A	*Placebo*	
India (7)	Vitamin A (100,000 IU) vs placebo at the time of measles immunization (9 mo), single dose	618 infants	Seroconversion to measles[d] 12 wk postimmunization among infants with titers ≤2,500	89.5%	87.6%	0.50[f]
			GMT 12 wk postimmunization	211.8	178.2	>0.05
			GMT change from baseline to 12 wk postimmunization	116.4	95.3	>0.05
			GMT 12 wk postimmunization among children with low weight	251.2	160.3	<0.05
				Vitamin A	*Placebo*	
India (23)	Vitamin A (100,000 IU) vs placebo at the time of measles immunization (9–12 mo), single dose	395 infants	Seroconversion to measles[i] 1 mo postimmunization	99%	99%	1.00
			Protective titers (>120) after 6 mo	78%	85%	0.14
			GMT to measles vaccine after:			
			1 month	169.6	160.7	0.57
			6 months	187.4	212.8	0.31

Continued on following page

TABLE 3—*Continued*

Study site (reference[s])	Intervention groups	Population	End point	Result for the indicated measure of effect[b]			*P* value
				Vitamin A		*Placebo*	
India (23)	Vitamin A (100,000 IU) vs placebo at the time of measles immunization (9–12 mo), single dose	395 infants	Seroconversion to measles[i] 1 mo postimmunization	99%		99%	1.00
			Protective titers (>120) after 6 mo	78%		85%	0.14
			GMT to measles vaccine after:				
			1 month	169.6		160.7	0.57
			6 months	187.4		212.8	0.31
Bangladesh (107)	Vitamin A (50,000 IU) vs placebo at each time of DPT/OPV vaccination (0, 4, and 8 wk)	57 infants	Seroconversion to OPV[j] after 1 mo from last dose	*Vitamin A*		*Placebo*	
			Type 1	79%		83%	0.76
			Type 2	82%		91%	0.34
			Type 3	82%		87%	0.64
India (15)	Vitamin A (200,000 IU) vs placebo to mothers within 24 h of delivery; all newborns received OPV dose within 72 h of birth	100 mother-infant pairs	Seroconversion to OPV[d] at 6 wk	*Vitamin A*		*Placebo*	
			Type 1	67.3%		77.5%	>0.05
			Type 2	83.6%		79.6%	>0.05
			Type 3	63.3%		65.3%	>0.05
			GMT against poliovirus at 6 wk				
			Type 1	18.4		23.4	>0.05
			Type 2	17.9		21.6	>0.05
			Type 3	9.6		9.7	>0.05
Indonesia (130)	Vitamin A (50,000 IU) vs vitamin A (25,000 IU) vs placebo at each time of OPV vaccination (6, 10, and 14 wk)	467 infants	Seroconversion to OPV[k] at age 9 mo	*Vitamin A, 50,000 IU*	*Vitamin A, 25,000 IU*	*Placebo*	
			Type 1	98.0%	99.1%	98.9%	0.77
			Type 2	100.0%	100.0%	100.0%	1.00
			Type 3	100.0%	100.0%	99.1%	0.99
			Protective titer (≥8) against poliovirus				
			Type 1	93.1%	94.5%	94.5%	0.88
			Type 2	98.3%	98.4%	99.1%	0.84
			Type 3	96.5%	98.3%	95.6%	0.45
			Log_e antibody titers against poliovirus at age 9 mo				
			Type 1	5.32	5.63	5.26	>0.05
			Type 2	5.96	6.02	5.95	>0.05
			Type 3	5.21	5.44	5.36	>0.05
India (6)	Vitamin A (200,000 IL) to mothers between 18 and 28 days postpartum plus 25,000 IU to infants at the time of DPT/OPVI (6, 10, 14 wks) vs placebo to mothers and children	399 mother-infant pairs	Protective titer (≥4) against poliovirus after 12 wk from last dose	*Vitamin A*		*Placebo*	
			Type 1	82.0%		71.2%	0.01[f]
			Type 2	92.3%		93.2%	0.73[f]
			Type 3	84.5%		80.5%	0.29[f]
			GMT against poliovirus				
			Type 1	27.2		17.6	<0.05
			Type 2	287.1		289.1	>0.05
			Type 3	66.5		60.5	>0.05

United States (57)	Vitamin A (200,000 IU) vs placebo on days 0 and 1; all received inactivated influenza vaccine and hemagglutinin antigens on day 14	59 HIV$^+$ children 2–17 yr	Increase in influenza antibodies, GMT (U/liter) day 28	*Vitamin A*	*Placebo*	
			H1N1	19.8	18.9	0.68
			H3N2	28.8	36.4	0.71
			% with titers ≥1:32 after vaccination			
			H1N1	66	50	0.23
			H3N2	66	70	0.71

[a] GMT, geometric mean titers (ln 1/liter); GM, geometric mean; DPT, diphtheria, pertussis, and tetanus vaccine; OPV, oral polio vaccine.
[b] All values presented are means unless noted otherwise. Verbal descriptions of results correspond to those in the indicated references when numerical data were not presented.
[c] Tetanus-naive subjects were children without an immunization history and low baseline anti-tetanus IgG titers (<10 μg/liter). Tetanus-exposed children had a history of tetanus immunization and high baseline titers.
[d] Seroconversion defined as a rise in antibody titer of ≥4-fold over the calculated expected titer.
[e] A positive antibody titer (> 32 mIU) and no record of measles infection.
[f] From χ^2 test calculated with data presented in the reference.
[g] Twofold rise in titers from baseline
[h] *P* value from χ^2 test recalculated with data presented in the reference = 0.02.
[i] Titers of ≥8 in children with no measurable antibodies at baseline, or a rise of ≥4-fold over the calculated expected titer at 4 weeks postimmunization in children with preexisting antibodies.
[j] Antibody titer of ≥16 in a previously negative infant or a ≥4-fold rise over baseline level.
[k] Positive antibody titer (≥2) minus the calculated expected titer of passively acquired maternal antibody, assuming a half-life of 4 weeks for IgG.

monthly oral doses of vitamin A resulted in a significantly greater DTH response, but the effect was limited to the subset of children who had serum retinol concentrations of >0.70 μmol/liter at baseline (106). In the Zambia study among children who had been hospitalized with measles, vitamin A supplements appeared to diminish the proportion of children with DTH responses and seemed to increase the proportion of children who were unresponsive to three antigens (tuberculin [purified protein derivative], *Candida*, and *Proteus*) (116). Children in this study had low mean retinol concentrations at baseline.

In light of the results from several in vitro experiments and animal studies, it has been proposed that vitamin A deficiency induces a shift in the immune response towards Th1-cell-mediated activity whereas vitamin A supplementation would tend to boost Th2-type responses, as recently reviewed by Stephensen (145). Results from trials that examined the effect of vitamin A on clinical outcomes from infections that elicit either a Th1 or a Th2 response suggest that the immunological mechanisms through which vitamin A exerts an effect are pathogen specific and may involve aspects other than the Th1/Th2 balance. Future studies are warranted to assess the role of vitamin A supplementation in humans on differential Th1/Th2 responses according to the baseline vitamin A status of the population and the specific pathogens causing infection.

In summary, there is no conclusive evidence to date for a direct effect of vitamin A supplementation on cytokine production or lymphocyte activation. One of the reasons why the results vary widely across studies is that the potential effect of vitamin A on T-cell function may depend on the specific immune response that each particular pathogen elicits. Also, vitamin A could have transient effects on intermediary markers of T-cell-dependent immunity that may be missed by few and relatively random assessments in population studies.

B cells. There is very little evidence from randomized clinical trials regarding the potential effect of vitamin A supplementation on the proliferation or activation of B lymphocytes. An indirect measure of the potential effects of vitamin A supplementation on B-cell function is the production of antibodies; however, this effect would most likely represent an influence of vitamin A on antigen-presenting cells, as suggested in experiments (33, 63) and human studies reviewed here.

T-Cell-Dependent Humoral Responses

The synthesis of antibodies to T-cell-dependent antigens is typically depressed during vitamin A deficiency, as shown in several animal models (58, 100, 140, 158). The evidence for an association between vitamin A status and T-cell-dependent antibody response is reviewed below.

Tetanus and diphtheria. In two small observational studies, no relationship was found between low retinol concentrations (<0.7 μmol/liter) at the time of immunization with diphtheria and tetanus toxoids and the antibody response after 2 (78) or 4 (16) weeks, respectively. In a vitamin A trial from Indonesia, among children who received a placebo the anti-tetanus toxoid response of xerophthalmic children was the same as that of those who were nonxerophthalmic (131); in that study, both xerophthalmic and nonxerophthalmic children had low serum

retinol concentrations. Low retinol concentrations have been widely used as an indicator of vitamin A deficiency; however, they may also be the result of the acute-phase response during generalized inflammatory states.

The effect of vitamin A on the antibody response to tetanus or diphtheria has been examined in five clinical trials (16, 20, 79, 108, 131), four of which were randomized (20, 79, 108, 131) (Table 3) and three of which (79, 108, 131) used a placebo group as control. In the first trial, conducted among Bangladeshi children 1 to 6 years of age, the intramuscular administration of 200,000 IU vitamin A at the time of the first tetanus immunization was not associated with the vaccine response after 4 or 12 weeks (a second dose of the toxoid had been administered 4 weeks after the first) (20). The intervention was not placebo controlled, and the IgG detection assay seemed to have low sensitivity. In an apparently nonrandomized trial, the oral administration of 100,000 versus 200,000 IU vitamin A to 50 Indian children 1 to 6 years of age at the time of diphtheria and tetanus immunization did not result in significantly different antibody responses to either toxoid after 4 weeks (16). Although no formal comparisons with the response of children who did not receive any vitamin A were made, it seems from the data presented that there was not a significant vitamin effect. In the Indonesian study (131), the oral administration of 200,000 IU vitamin A to tetanus-naive children 3 to 6 years of age resulted in significantly higher titers of anti-tetanus toxoid after immunization compared to those in the placebo group, independent of whether the children were xerophthalmic at baseline or not. It was concluded that, since both xerophthalmic and nonxerophthalmic children had low retinol concentrations at baseline and the vitamin was administered 2 weeks before the toxoid, the correction of vitamin A deficiency may be related to improved antibody responses. Vitamin A had no significant effects on the response to anti-tetanus toxoid in two subsequent clinical trials conducted among younger children (<2 months) in Bangladesh (108) and Turkey (79). The Turkish trial was a two-by-two factorial design with four arms (vitamin A alone, vitamin E alone, vitamins A and E, or placebo), with limited statistical power to make comparisons between separate arms. There appeared to be a higher antibody response in the two arms that received vitamin A (alone or with vitamin E) than in those without vitamin A (placebo or vitamin E only), but a statistical comparison between the arms regrouped in this manner was not presented. Contradictory results between the Indonesian trial and others have been attributed to differences in the underlying prevalence of vitamin A deficiency; however, this would not explain the contrast with the Bangladesh studies (16, 108), in which the concentrations of serum retinol at baseline were similarly low. One alternative explanation is that in the Turkish (79) and the latest Bangladeshi (108) trials subjects were young infants in whom the antibody response to tetanus may have been affected by passive immunity, whereas in Indonesia, children in whom the vitamin effect was observed were older and naive to tetanus. The mean preimmunization concentration of tetanus-specific IgG in the latter study was between 6.0 and 15.1 μg/liter, much lower than that in Bangladesh (between 6.1 and 7.5 mg/liter). It is also possible that the administration of vitamin A some time before the immunization, such as in the Indonesian study, allows for a partial correction of deficiency that may be necessary for an enhanced response to be observed. In the most recent trial from Bangladesh (108), vitamin A had a positive, significant effect on the antibody response to diphtheria toxoid antigen; this effect has not been examined in other randomized trials.

Measles. The effect of vitamin A on the antibody response to measles infection has been studied in a number of clinical trials. Studies in South Africa (28) and Zambia (116) examined the antibody response of children who had been hospitalized with severe measles. In the South African study, the IgG titers to measles virus at day 8 were significantly higher among children who received vitamin A than among those who received a placebo, while no difference was observed at day 42. In the Zambian study, vitamin A had no effect on measles virus antibodies at day 14. The higher dose used in South Africa (twice that in the Zambian trial before the assessment of antibodies) could explain the differences in results.

Other trials assessed the effect of vitamin A supplementation at the time of immunizations on the antibody response. An apparent adverse effect of vitamin A was suggested by a study in Indonesia in which infants who received the supplement at age 6 months together with the Schwarz measles vaccine had a lower seroconversion rate at age 12 months (133). This effect was limited to infants with high antibody titers at baseline, and it was suggested that vitamin A-related enhancement of the immune function together with circulating maternal antibodies could neutralize the vaccine before it induced protective immunity. However, a similar study in Guinea-Bissau did not show a significant effect of vitamin A on measles titers after 3 months (14); it was not possible to compare the effect by levels of maternal antibody concentrations at age 6 months with those in the Indonesian study due to the use of different cutoff points to define baseline titers. It was suggested that the differential effect observed could have been attributed to a higher prevalence of vitamin A deficiency in Indonesia than in Guinea-Bissau (14). In the Guinea-Bissau study, an additional dose of vitamin A administered during a second immunization round at 9 months did not affect seroconversion at age 18 months (10) or the proportion of children with protective titers at age 6 to 8 years (11).

Several other studies have evaluated the impact of vitamin A supplementation simultaneous with measles vaccination at age 9 months only. In a study from Guinea Bissau, the proportion of children who seroconverted to measles virus at age 18 months was not significantly different by treatment arm; however, the geometric mean titer was significantly higher for children given vitamin A supplementation than for those who received a placebo (10) and was particularly higher among boys. In the same study, the proportion of children with protective titers at age 6 to 8 years was significantly higher in those who had received vitamin A together with their measles vaccine at age 9 months (11). In a trial from India among children who received the Edmonston Zagreb strain of measles vaccine at age 9 months, vitamin A resulted in higher seroconversion rates after 1 month (17); however, in two other studies in India (6, 23) and in a trial from Indonesia (124), no effects were observed.

Polio. Vitamin A supplementation has also been studied in relation to poliovirus vaccine seroconversion in Bangladesh, India, and Indonesia. Trials in which vitamin A supplements were administered to infants at each time of oral polio vaccine

vaccination in Bangladesh (107) and Indonesia (130) or to Indian mothers in the early postpartum period (15) showed no effect on titers to any of the three poliovirus types. In the Bangladeshi and Indian trials, seroconversion rates were measured within 2 months of the exposure to vitamin A, whereas in Indonesia the outcomes were assessed about 6 months thereafter. In the latter study, late assessment of seroconversion could have decreased statistical power to detect an effect of treatment, since the rates were close to 100% overall. In a recent trial in India in which the vitamin was administered to both mothers and children, the proportion of children with protective titers against type 1 poliovirus was significantly higher in the experimental group than in the placebo group (6).

Influenza. One study among HIV-infected children found no effect of supplementation on the antibody response to inactivated influenza vaccine (57); further studies with the larger population of non-HIV-infected children are necessary.

In summary, vitamin A may have the potential to increase the antibody response to tetanus toxoid when administered some time before immunization, particularly in children with vitamin A deficiency who have not been exposed to tetanus. Whether a similar effect exists in response to the diphtheria toxoid needs further examination. Vitamin A administered at 9 months of age does not decrease the antibody response to measles virus, but when administered at 6 months together with a dose of measles vaccine that is not to be repeated at 9 months, supplementation could potentially decrease the antibody response. More studies on the effect of vitamin A on the antibody responses to other vaccines are needed.

T-Cell-Independent Humoral Responses

Some animal studies have suggested a role of vitamin A in the antibody response to T-cell-independent antigens such as pneumococcal polysaccharide (100), but a causal link cannot be established with certainty since interventions other than vitamin A repletion may trigger normal antibody responses in animals (99). It would be relevant to examine whether vitamin A supplementation in humans could enhance the response to this and other T-cell-independent antigens from encapsulated bacteria, including meningococcus and *Haemophilus*.

VITAMIN A SUPPLEMENTATION AND CLINICAL OUTCOMES

A major motivation to study the effects of vitamin A on the immune function is the search for mechanistic explanations of the impact of supplementation on mortality and morbidity among children and pregnant women that has been documented in clinical trials (25, 138, 150, 154). Although this review is focused primarily on the effect of vitamin A on immunological parameters, we consider it relevant to briefly correlate the effects on immunity with those on clinical outcomes reported to date.

Vitamin A supplementation after 6 months of age is associated with a reduction in all-cause child mortality of about 23 to 30% (9, 38). Supplementation at birth appeared to decrease mortality in two trials from Indonesia and India (64, 111) but not in a trial from Zimbabwe (86). Supplementation at between 1 and 5 months does not seem to have a beneficial effect (32, 109, 155, 157). The specific immunological mechanisms behind these contrasting effects are not fully understood, and it is likely that they depend on the underlying nutritional and immunological status and the nature of infectious agents causing disease in children. Recently, Benn and colleagues hypothesized that the reason why vitamin A decreases mortality when given to newborns and children at 6 months but not in the 1- to 5-month age bracket is that vitamin A amplifies the nonspecific immune modulation induced by live vaccines (BCG and measles), which are routinely administered at birth and 6 months (12). Additional data to confirm this hypothesis are needed.

The effects of vitamin A supplementation on child morbidity include a reduction in the severity of measles that could be correlated with the enhanced T-cell-dependent antibody production that was observed in the South African study (27, 28). A decrease in the severity of measles morbidity could explain an overall average reduction in measles-specific mortality of about 60% (38) as shown in trials from England (37), South Africa (27, 67), and Tanzania (8). The benefits of vitamin A on measles-related outcomes may go beyond the correction of underlying deficiencies and could actually represent adjuvant therapeutic effects (117).

Vitamin A also appears to decrease the severity of some diarrheal episodes in childhood and their incidence when administered in combination with zinc (110). This outcome could be the consequence of the improvement in gut integrity during severe diarrheal episodes that was documented in South Africa (49) and India (147). Preliminary results from a trial in Mexico indicate that bimonthly vitamin A supplementation reduces the incidence of *Giardia lamblia* infections and diarrheal episodes associated with *Ascaris lumbricoides* (83); the mechanisms are still unknown but could be related to enhanced Th2 immune reactions, which are important in the line of defense against some parasitic infections.

A few studies on the effect of vitamin A supplementation on outcomes related to malaria infection have been conducted. A trial in Ghanaian children found no effect on death from malaria, fever episodes, malaria parasitemia, or probable malaria illness (18); however, statistical power in this study may have been limited. In Papua New Guinea, a trial was conducted to specifically examine the effect of vitamin A supplementation on malaria outcomes. In this trial, supplementation with 200,000 IU at 3-month intervals resulted in a significant 30% reduction in clinical *Plasmodium falciparum* episodes, particularly in children age 12 to 36 months (138). Vitamin A also decreased parasite density and spleen enlargement. In a study of preschool children in Tanzania, vitamin A supplementation every 4 months resulted in a decreased risk of death from malaria (42) and improved weight gain among children who had malaria at baseline (151) but was not associated with the incidence of malaria parasitemia during a 4- to 8-month follow-up period (149). A trial in Mozambique among children admitted to hospital with severe malaria found a non-statistically significant benefit of a single vitamin A dose on hospital death. There were no significant effects on duration of hospital stay, time to resolution of fever, clearance of parasitemia, or development of neurological sequelae (148). A marginally significant reduction of active placental malaria infection at delivery was reported in relation to vitamin A supplementation during pregnancy in a study from Ghana (31). It has been

proposed that the beneficial effects of vitamin A supplementation on malaria could be due to increased phagocytosis of nonopsonized erythrocytes mediated through up-regulation of CD36 cytoadherence receptors and decreased secretion of TNF-α through down-regulation of the peroxisome proliferator activated receptor γ-retinoic X receptor (137).

The effect of vitamin A on respiratory infections has been examined in several randomized clinical trials, with varying results. Most hospital-based studies on vitamin A supplementation and the severity of pneumonia have not shown significant overall effects (36, 41, 74, 97, 139), as recently reviewed by Brown and Roberts (21). In fact, some of the hospital-based studies suggest an apparent increase in indicators of severity associated with vitamin A supplementation (41, 85, 105, 146). A number of community-based trials have also found an apparent increase in respiratory symptoms in relation to vitamin A supplementation (34, 39, 103, 104, 112, 136, 144), particularly among children who are not undernourished. It is not clear whether this apparent increase in respiratory symptoms may be due to a proinflammatory immune response associated with the supplements.

The effect of vitamin A supplementation on tuberculosis outcomes was studied in a clinical trial among hospitalized children who received 200,000 IU vitamin A during two consecutive days or a placebo (56). No effects were found on radiological or other outcomes after 3 months. In a small study of adults in Indonesia, 5,000 IU vitamin A together with 15 mg zinc daily for 6 months resulted in faster sputum conversion and resolution of the X-ray lesion area (72), but it is not possible to attribute the effect to vitamin A alone. Potential effects of vitamin A on tuberculosis could be correlated with the results of trials on DTH responses, but stronger evidence for both clinical and immunological outcomes is lacking.

Vitamin A deficiency is common among HIV-infected persons and appeared to be a predictor of mortality in observational studies (126, 127). A number of clinical trials have examined the effect of vitamin A supplementation on health and survival outcomes in the course of HIV infection. Among HIV-infected children, vitamin A decreases mortality (42, 134) and morbidity from diarrheal disease (26), improves growth (151), and reduces viral load (57); however, among HIV-infected adults, no beneficial effects on mortality, disease progression (45), or viral load (5, 29, 65, 129) have been observed, and only a modest effect on CD4 cell counts has been noted, as reviewed above (5). The effects on child mortality, morbidity from diarrheal disease, and growth could be related in part to the vitamin's action in maintaining the integrity of the intestinal mucosa (49, 147). Positive effects through the enhancement of cellular immunity or antibody production are possible but are not yet consistently supported by results from randomized clinical trials in humans.

When administered daily during pregnancy and lactation, combined vitamin A and β-carotene could increase the risk of mother-to-child transmission (MTCT) of HIV as shown in one study in Tanzania (43). In a smaller study from South Africa, daily administration of vitamin A and β-carotene during pregnancy and at delivery was not significantly related to early MTCT, although the 95% confidence interval included the possibility of a harmful effect (30). In a third trial of daily supplementation during pregnancy in Malawi (77), vitamin A alone had no effect on MTCT. One potential mechanism to explain the adverse effect on MTCT is that vitamin A increases viral shedding in genital secretions, as shown in the Tanzanian trial in which supplementation resulted in greater MTCT (40); in a study of nonpregnant women, there was no effect on genital shedding (5). In one recent study, vitamin A had no effect on genital shedding of herpes simplex virus (4). An alternative mechanism is that retinol may increase the expression of CCR5 receptors in monocytes/macrophages, which would increase the susceptibility of cells to M-type HIV infection (84).

The suggestion that daily vitamin A supplementation to HIV-infected mothers increases MTCT (43) and the recent finding that vitamin A reduces the benefits of multivitamins (B, C, and E) on HIV-related outcomes (45) cast some doubts on the safety of providing vitamin A/β-carotene to HIV-infected adults.

CONCLUSIONS

Vitamin A may have the potential to increase the antibody response to tetanus toxoid when administered some time before immunization; this effect seems to be limited to children with vitamin A deficiency who have not been exposed to tetanus. A similar positive effect in response to the diphtheria toxoid might exist and needs to be confirmed. When administered with the measles vaccine at age 9 months, vitamin A supplementation does not decrease the antibody response and may actually increase it among boys or in children with low weight. However, when administered at 6 months together with a dose of measles vaccine that is not to be repeated at 9 months, vitamin A could potentially decrease the antibody response. Vitamin A supplementation to the child or the mother alone does not appear to affect the antibody response to oral polio vaccine; confirmation of a potential beneficial effect when administered to both the mother and the child is needed. The effect of vitamin A on the immune response to other vaccines, including BCG, polysaccharides from encapsulated bacteria, and hepatitis virus, has not been studied in randomized clinical trials.

In addition to the impact of vitamin A supplementation on antibody production against selected antigens, known effects on cellular immunity are apparent on T-cell lymphopoiesis or lymphocyte differentiation among vitamin A-deficient or HIV-infected children. Effects on cytokine production have not been well documented in clinical trials, and the evidence on lymphocyte activation as measured by the DTH response is mixed. There is limited research on the effects of vitamin A supplementation to adults and the elderly on their immune function; currently available data provide no consistent evidence for beneficial effects. Additional studies with these age groups are needed.

Periodic vitamin A supplementation to children ≥6 months is a useful public health strategy to improve child survival and to decrease the risk of nutritional blindness and of morbidity of infectious origin from measles, severe diarrhea, HIV, and possibly malaria and intestinal helminthiases. The beneficial effects of vitamin A supplementation among children with severe measles could be mediated by a short-term increase in antibody production, possibly as a result of increased lymphocyte

proliferation. The effect on severe diarrhea is likely due to the role of vitamin A in restoring and maintaining gut mucosal integrity. The apparent benefit for survival and growth among HIV-infected children could also be related to the latter, through decreased nutrient losses and improved nutritional status. Other immunological pathways through which vitamin A could exert an effect against severe diarrhea are likely to depend on the causative microorganisms and warrant investigation in future studies. Specific mechanisms for the potential effect of vitamin A on malaria and other parasitic infections are yet to be examined in randomized clinical trials. Similarly, explanatory mechanisms for the apparent harmful impact of vitamin A on respiratory infection among nonundernourished children, MTCT of HIV, and T-cell counts in the elderly deserve further assessment. Data are needed from human trials about the role of vitamin A supplementation in modulating the Th1/Th2 response as a potential explanatory mechanism for the vitamin's observed effects on clinical outcomes.

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