Vitamin A Administered with Measles Vaccine to Nine-Month-Old Infants Does Not Reduce Vaccine Immunogenicity[1]

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ABSTRACT After a report of reduced seroconversion to measles in infants, aged 6 mo, given vitamin A with their measles vaccination, serious concerns were raised regarding the safety of the WHO's recommendation that infants be supplemented with vitamin A at the time of measles immunization. To determine the impact of coadministered vitamin A on the antibody response to measles vaccine given to infants aged 9 mo, the more common age for immunization in developing countries, we conducted a randomized, double-blind, placebo-controlled trial in an urban slum community in Delhi. Infants (618) were randomly allocated to receive 30 mg vitamin A or a placebo with the measles immunization. Antibodies to measles were measured by ELISA in serum samples obtained at before (baseline) and 12 wk after immunization. Overall, the seroconversion rates did not differ between vitamin A (89.5%) and placebo (87.6%) groups. There were no significant differences in the geometric mean titers in the two groups (ratio of geometric means, 1.19; 95% confidence interval, 0.97–1.46). Among malnourished infants, the geometric mean titer was significantly greater in the vitamin A group compared to the placebo group (ratio of geometric means, 1.57; 95% confidence interval, 1.18–2.0), but seroconversion rates did not differ. There were no differences in seroconversion rates and geometric mean titers in the two study groups among the well-nourished children. These results indicate that 30 mg vitamin A does not reduce the immune response to the coadministered vaccine and, therefore, can be continued to be given safely in public health programs. J. Nutr. 129: 1569–1573, 1999.

KEY WORDS: • *vitamin A* • *measles immunization* • *infants* • *immune response*

Vitamin A supplementation in children 6 mo–5 y of age was shown to reduce childhood mortality by 23–30% (Beaton et al. 1993, Fawzi et al. 1993, Glasziou and Mackerras 1993). Measles immunization given to infants at 9 mo of age provides the first realistic opportunity for supplementation. Semba et al. (1995) reported that 30 mg (100,000 IU) of vitamin A coadministered with a measles immunization at 6 mo of age reduced seroconversion compared to a placebo. This effect was primarily observed in infants who had detectable maternal antibody at baseline. It was hypothesized that immune enhancement by vitamin A may limit the ability of a live-virus vaccine to establish infection, a view supported by the decreased incidence of a vaccine-induced skin rash in the vitamin A group. These observations by Semba et al. (1995) caused serious concerns, in many developing countries, regarding the safety of the coadministration of vitamin A and measles vaccine to infants 9 mo of age, and some critics suggested abandoning this practice in ongoing programs (Ross 1995). In most developing countries, coverage under vitamin A prophylaxis programs is low after the measles immunization contact, this contact is therefore an important opportunity for supplementation.

To determine the impact on the antibody response to the vaccine 12 wk after immunizing infants, at 9 mo of age, with 30 mg of vitamin A coadministered with a standard titer Edmonston-Zagreb measles vaccine, we conducted an individually randomized, double-blind, placebo-controlled trial in a Delhi slum.

METHODS

Study site. The study was conducted in an urban slum of Delhi. In 1–5-y old children seeking treatment at a health facility in a neighboring slum, the prevalence of clinical vitamin A deficiency was ~3.5% and that of subclinical deficiency (serum vitamin A levels of ≤0.7 μmol/L) was 37% (Bhandari et al. 1997).

In a multi-center study conducted in an adjoining area at the same time as the present study, vitamin A status of 9-mo-old infants was assessed by serum retinol and the Modified Relative Dose Response (MRDR)[3] assay (WHO/CHD 1998). The mean serum retinol was 0.89 ± 0.36 μmol/L, 29.6% infants had concentrations ≤0.7 μmol/L, and 57.5% had inadequate vitamin A stores (MRDR > 0.06).

[1] This study was conducted with financial support from the World Health Organization, Indian Council of Medical Research and NUFU.

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[3] Abbreviations used: DPT, diphtheria-pertussis-tetanus; IFN-γ, interferon-gamma; MRDR, modified relative dose response; PRN, plaque reduction neutralization.

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Manuscript received 27 August 1998. Initial review completed 16 February 1999. Revision accepted 10 May 1999.

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Sample size. The a priori hypothesis was that 30 mg of vitamin A coadministered with a measles vaccine to infants at 9 mo of age would, 12 wk after immunization, result in a 10% reduction in seroconversion to measles. Assuming that 92% of controls would seroconvert after the measles immunization (Job et al. 1991), the required sample size was calculated to be 238 infants per cell at 95% confidence level and 90% power (Smith and Morrow 1991). To allow for the possibility of the observed values for the control group being different from those assumed, and for 10% attrition, 309 infants per cell were enrolled.

Enrollment, randomization and study intervention. A household survey was conducted, and ~700 infants between 6 and 9 mo of age were identified. If informed parental consent was available, infants were enrolled when they became 9 mo old. Infants were not included in the study if they had a previous history of measles, contact with a case of measles or measles immunization, or if they had received a dose of vitamin A in the previous 4 mo. This information was ascertained from the caregiver. Infants who had any serious illness requiring hospitalization or had signs of vitamin A deficiency (Bitot's spots, corneal xerosis or keratomalacia) at enrollment were also excluded.

Infants were randomly assigned to receive vitamin A or a placebo by using a simple randomization scheme with random permuted blocks of size eight, i.e., four infants each out of every eight infants enrolled were randomized to receive vitamin A or a placebo. Vitamin A and the placebo were packed in individual dose capsules (courtesy of World Health Organization); the two types of capsules (placebo, vitamin A) were identical in color, shape and size. The active ingredient in the vitamin A capsules was 30 mg of retinol palmitate, whereas the placebo capsules contained soybean oil. Backup doses were provided for each infant in case the infant spat out the allocated supplement.

Infants received two capsules during the study period, one at 9 mo with the measles vaccine and the other at 12 mo of age. Those assigned to receive the placebo at 9 mo of age were given 30 mg vitamin A at 12 mo of age. Infants given the vitamin A supplement at 9 mo of age received the placebo at 12 mo. This scheme ensured that all infants received 30 mg vitamin A by 12 mo of age without interfering with the double-blind design of the study.

The study protocol was reviewed and approved by the All India Institute of Medical Sciences ethics committee.

Immunization and follow up. Subjects were vaccinated with a single dose, standard titer Edmonston-Zagreb measles vaccine (same manufacturing lot, obtained from Swiss Serum Institute, Berne, Switzerland), within 20 min of capsule administration, at 9 mo of age, in the study clinic.

All infants were visited at home by a field worker on post vaccination days 1, 2, 7, 14 and 21 to monitor adverse effects of the vitamin A and measles vaccine. On these visits, the mother was queried about any illness symptoms in the infant since the last visit; the infant was also examined physically, particularly for a measles-like skin rash.

Laboratory tests. About 3 mL venous blood was obtained from all infants prior to measles vaccination and 12 wk thereafter. Serum was separated by centrifugation at 1500 rpm for 10 min within 30–45 min and stored at −20°C.

ELISA was performed to estimate antibody titers by using the modified method of Voller and Bidwell (1976).

The antigen for ELISA was prepared from the same Edmonston-Zagreb vaccine strain of measles vaccine that was used for immunization. Different aliquots were pooled to obtain ~2 L of supernatant, and the virus was partially purified by ultracentrifugation. ELISA was standardized by using the International Standard Anti-Measles Serum (66/202) obtained from the National Institute for Biological Standards and Controls, Blanche Lane, South Mimms, Potters Bar, Hertfordshire, UK. The pre- and post-vaccination samples from one study subject were always tested in the same plate; the samples were coded to ensure that the laboratory staff could not identify pre-immunization from post-immunization samples. All test serums were tested in duplicate with and without the antigen-coated wells. The values of IgG antibodies against measles virus in the test samples was calculated in reference to the standard curve for the same plate.

TABLE 1

Baseline characteristics of enrolled infants in the two intervention groups[1]

	Vitamin A $n = 309$	Placebo $n = 309$
Males	158 (51.1)	163 (52.8)
Height for age Z-score[2]	−1.71 ± 1.03	−1.58 ± 1.01
Infants with HAZ[3] <−2	111 (36.0)	102 (33.0)
Weight for height Z-score[2]	−0.73 ± 0.93	−0.80 ± 0.75
Infants with WHZ[4] <−2	16 (5.2)	18 (5.8)
Mother literate	178 (57.6)	168 (54.4)
Breast feeding		
None	39 (12.6)	37 (12.0)
Partial	268 (87.7)	271 (87.7)
Exclusive	2 (0.6)	1 (0.3)
Immunization status for age		
unimmunized	22 (7.1)	14 (4.5)
partially immunized	65 (21.0)	63 (20.4)
fully immunized	222 (71.8)	232 (75.1)

[1] Values are *n* (%) except those marked [2].
[2] Values are mean ± SD.
[3] Height for age Z-score.
[4] Weight for height Z-score

Analysis. Seroconversion was defined as a four-fold rise in antibody titer over the expected antibody titer caused by the presence of baseline antibody. This titer at the time of obtaining the post immunization sample was calculated assuming a 6-wk half-life of the maternally acquired antibody (Markowitz et al. 1990).

Eighteen (11 in the vitamin A and 7 in the placebo group) infants had evidence of past measles infection at enrollment (pre-immunization antibody titer >2500) although they had no history suggestive of measles infection. Because the objective of the study was to evaluate the impact of vitamin A on the response to primary measles vaccination (previous history of measles was one of the exclusion criteria), it was an a priori decision to exclude infants who had a very high antibody titer at baseline. These 18 infants were therefore excluded from the analysis.

The analysis was performed using EPI INFO version 6 and SPSS for Windows software. Categorical variables were compared using the chi-square test and quantitative outcomes by Student's *t*-test. Differences were considered significant at $P < 0.05$. A multiple linear regression analysis restricted to malnourished infants was performed. In this regression analysis, the outcome variable was the post-immunization measles antibody titer on the logarithmic scale, while vitamin A or placebo treatment, sex, breast feeding, immunization status and presence of baseline measles antibody were explanatory variables.

RESULTS

The baseline characteristics did not differ between the two study groups (**Table 1**). The pre-immunization blood specimen was available from all the 618 enrolled infants, but the post-immunization specimen could not be obtained in 83 of these infants (vitamin A, 39; placebo, 44).

The response to the measles vaccine was assessed by comparing seroconversion rates and geometric mean titers of measles specific antibody 12 wk after immunization in the vitamin A and placebo groups; differences in both outcomes were not significant (**Table 2**).

We found no significant interaction between vitamin A administration impact and presence of baseline measles antibody, ($P > 0.5$). On the other hand, a standard test of interaction (Pocock 1983) suggested a differential impact of vitamin A on the geometric mean antibody titer in infants with weight for age Z-score ≤-2 ($P < 0.01$). A subgroup

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TABLE 2

Antibody response to measles vaccine in infants administered vitamin A or placebo 12 wk after immunization with measles vaccine

	Vitamin A $n = 258$	Placebo $n = 259$	Relative risk of ratio of GM (95% CI)
Seroconversion rate (≥4 fold rise over the expected titer), *n* (%)	231 (89.5)	227 (87.6)	1.02 (0.96–1.09)
Baseline geometric mean antibody titer (95% CI)	27.9 (24.4–31.8)	26.1 (23.3–29.2)	1.07 (0.90–1.27)
Geometric mean antibody titer 12 wk post-immunization (95% CI)	211.8 (182.8–245.5)	178.2 (154.5–205.6)	1.19 (0.97–1.46)
Geometric mean difference between antibody titers 12 wk post-immunization and baseline (95% CI)	116.4 (91.6–147.6)	95.3 (74.8–121.1)	1.22 (0.87–1.71)

analysis was, therefore, performed with infants stratified by weight for age. The geometric mean antibody titer in the subgroup of infants with weight for age Z-score ≤ -2 was significantly greater in the vitamin A group compared to that in the placebo group, but there were no differences in seroconversion rates. Seroconversion rates and geometric mean titers did not differ between the two study groups among the well-nourished children (**Table 3**).

To confirm that the enhanced antibody titer after vitamin A administration in malnourished infants was not due to baseline differences, we performed a multiple linear regression analysis, restricted to malnourished infants, with the logarithm of post-immunization antibody titer as the dependent variable (**Table 4**). Vitamin A treatment was found to significantly improve the antibody titer in the subgroup of malnourished infants, after adjustment for potential confounding factors, including sex, breast feeding, immunization status and presence of baseline measles antibody ($P = 0.009$).

Ten infants (1.6%) developed a measles-like rash within 3 wk of immunization; three of them were in the vitamin A group. Only two subjects had a bulging fontanelle during the 48-h period after immunization and vitamin A administration, both of them in vitamin A group. There were no significant differences in the mean increases in head circumference at 24 or 48 h after vitamin A administration. Other possible adverse effects, including vomiting, drowsiness or irritability, and temperature ≥38°C, did not differ between the two intervention groups (data not shown).

DISCUSSION

The main findings of this study are that vitamin A administered with the measles vaccine to infants at 9 mo of age had no adverse effect on seroconversion or geometric mean titer of measles specific antibody. Our results are consistent with those of a recently published study from Guinea Bissau (Benn et al. 1997).

In the study by Semba et al. (1995), the adverse impact of vitamin A on measles vaccine immunogenicity at 6 mo of age occurred largely in the presence of significant levels of maternally acquired antibody. We did not, however, find an interaction of vitamin A impact with the presence of baseline antibody in the present study. Unlike the findings of the Indonesian study (Semba et al. 1995), we observed no differences in the incidence of a measles-like rash after vaccination.

The improved antibody response to measles vaccine in malnourished infants observed in this study is biologically plausible. Malnourished infants are more likely to have sub-

TABLE 3

Antibody response to measles vaccine in vitamin A and placebo groups in the subgroup of infants with weight for age Z-score (WAZ) ≤ -2

	Vitamin A	Placebo	Relative risk or ratio of GM (95% CI)
Infants with WAZ ≤ -2	$n = 128$	$n = 124$	
Seroconverted, *n* (%)	117 (91.4)	111 (89.5)	1.02 (0.94–1.11)
Baseline geometric mean antibody titer (95% CI)	31.3 (25.2–38.9)	25.5 (22.0–29.4)	1.23 (0.94–1.59)
Geometric mean antibody titer 12 wk post-immunization (95% CI)	251.2 (202.3–311.9)	160.3 (133.3–192.7)	1.57 (1.18–2.08)
Geometric mean difference between antibody titers 12 wk post-immunization and baseline (95% CI)	138.4 (98.9–193.2)	95.3 (65.8–124.4)	1.53 (0.96–2.42)
Infants with WAZ > -2	$n = 130$	$n = 135$	
Seroconverted, *n* (%)	114 (87.7)	116 (85.9)	1.02 (0.93–1.12)
Baseline geometric mean antibody titer (95% CI)	24.9 (21.4–28.9)	26.7 (22.5–31.7)	0.93 (0.74–1.16)
Geometric mean antibody titer 12 wk post-immunization (95% CI)	179.5 (147.6–218.3)	196.3 (158.1–243.8)	0.91 (0.68–1.22)
Geometric mean difference between antibody titers 12 wk post-immunization and baseline (95% CI)	98.2 (69.7–138.0)	99.5 (69.3–142.6)	0.98 (0.6–1.62)

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TABLE 4

Multiple linear regression analysis restricted to infants with weight for age Z-score ≤−2 with logarithm of post immunization measles antibody titer as the outcome variable

Explanatory variable	Regression coefficient (95% CI)	*P*-value
Non breast fed	−0.05 (−0.22, 0.088)	0.402
Not received any dose of DPT[1] & OPV[2]	0.145 (0.062, 0.577)	0.015
Male	−0.084 (−0.203, 0.032)	0.153
Baseline antibody present	0.315 (0.276, 0.604)	<0.001
Vitamin A administered	0.155 (0.039, 0.275)	0.009

[1] Diphtheria-Pertussis-Tetanus vaccine.
[2] Oral Polio vaccine.

clinical vitamin A deficiency. Several human and animal studies have reported increased T-cell help, down-regulation of interferon-gamma (IFN)-γ and isotype switching to IgA and IgG1 after vitamin A supplementation, resulting in an improved humoral response (Friedman et al. 1991, Cantorna et al. 1995, Semba et al. 1993, Tokuyama and Tokuyama 1996). Administration of vitamin A with tetanus toxoid in young children in Bangladesh did not result in an increased antibody response to the vaccine (Brown et al. 1980). Another study in Indonesian children reported an improved antibody response in the vitamin A-treated children compared to those given a placebo, when Diphtheria-Pertussis-Tetanus (DPT) vaccine was given 2 wk after supplementation (Semba et al. 1992). Animal studies have clearly demonstrated that vitamin A repletion of depleted animals causes significantly improved antibody response to protein (T cell-dependent) and polysaccharide (T cell-independent type 2) antigens (Ross 1991).

In the multiple linear regression analysis restricted to malnourished infants, the factors associated with a higher post-immunization antibody titer were vitamin A administration, being not previously immunized with DPT or Oral Polio vaccines, and the presence of baseline measles antibody. There is a plausible explanation for the paradoxical finding of higher antibody titer at the end of the study in those who had baseline antibody. As expected, both seroconversion rate (75.7% vs. 90.6%, $P < 0.001$) and geometric mean difference between the 12-mo and baseline antibody titers (70.3 vs. 112.3, $P = 0.06$) were lower in the infants who had baseline antibody compared to those who had no antibody at baseline. Therefore, we attribute the higher post-immunization antibody titer in these infants to the remaining baseline antibody after decay in 12 wk, despite a poorer response to the measles vaccine.

The observed improvement in vaccine immunogenicity in malnourished infants that were administered vitamin A in this study should be interpreted with caution; this finding is based on a subgroup analysis. Because randomization was not performed at the subgroup level, baseline characteristics of the two intervention groups may have differed. This seems unlikely in the present situation because, in a multiple linear regression model restricted to malnourished infants, the impact of vitamin A on post-immunization antibody titer remained significant even after the adjustment for potentially confounding factors.

Plaque reduction neutralization (PRN), hemagglutination inhibition and ELISA may all be used for measuring the antibody response to measles vaccine. The most meaningful test for the serologic evaluation of immunity status to viral infections including measles is the neutralization test. Several earlier studies have compared the results of PRN with those of ELISA and have shown that ELISA is a sensitive and reliable assay and could represent an alternative to the PRN (Cremer et al. 1985, De Souza et al. 1991, Neumann et al. 1985). Also, the present study was designed to compare the antibody response between the two intervention groups and not for evaluating the absolute protection against measles. Therefore, ELISA was chosen as the more convenient and less expensive assay.

The major implication of these findings is that they set to rest the controversy about the current recommendation of combining vitamin A supplementation with measles immunization of infants at 9 mo of age in public health programs.

ACKNOWLEDGMENTS

We are grateful to Jose Martines, Division of Child Health and Development, WHO, Geneva, for his assistance. We thank Kiran Bhatia for help in the statistical analysis.

LITERATURE CITED

Beaton, G. H., Martorell, R., L'Abbe, K. A., Edmonston, B., McCabe, G., Ross, A. C. & Harvey, B. J. (1993) Effectiveness of vitamin A supplementation in the control of young child morbidity and mortality in developing countries. Final report to CIDA. University of Toronto, Toronto, Canada.

Benn, C. S., Aaby, P., Olsen, J., Michaelsen, K. F., George, E. & Whittle, H. (1997) Randomized trial of effect of vitamin A supplementation on antibody response to measles vaccine in Guinea-Bissau, west Africa. Lancet 350: 101–105.

Bhandari, N., Bahl, R., Sazawal, S. & Bhan, M. K. (1997) Breast-feeding status alters the effect of vitamin A treatment during acute diarrhea in children. J. Nutr. 127: 59–63.

Brown, K. H., Rajan, M. M., Chakraborty, J., Aziz, K.M.A. & Phil, M. (1980) Failure of a large dose of vitamin A to enhance the antibody response to tetanus toxoid in children. Am. J. Clin. Nutr. 33: 212–217.

Cantorna, M. T., Nashold, F. E., Chun, T. Y. & Hayes, C. E. (1995) Vitamin A down-regulation of IFN-γ synthesis in cloned mouse Th1 lymphocytes depends on the CD28 costimulatory pathway. J. Immunol. 156: 2674–2679.

Cremer, N. E., Cossen, C. K., Shell, G., Diggs, J., Gallo, D. & Schmidt, N. J. (1985) Enzyme immunoassay versus plaque neutralization and other methods for determination of immune status to measles and varicella-zoster viruses and complement fixation for serodiagnosis of infections with those viruses. J. Clin. Microbiol. 21: 869–874.

De Souza, V.A.U.F., Pannuti, C. S., Sumita, L. M. & Albrecht, P. (1991) Enzyme-linked immunosorbent assay (ELISA) for measles antibody. A comparison with haemagglutination inhibition, immunofluorescence and plaque neutralization tests. Rev. Inst. Med. Trop. S. Paulo. 33: 32–36.

Fawzi, W. W., Chalmers, T. C., Herrera, M. G. & Mosteller, F. (1993) Vitamin A supplementation and child mortality: A meta-analysis. JAMA 269: 898–903.

Friedman, A., Meidovsky, A., Leitner, G. & Sklan, D. (1991) Decreased resistance and immune response to Escherichia coli infection in chicks with low or high intakes of vitamin A. J. Nutr. 121: 395–400.

Glasziou, P. P. & Mackerras, D.E.M. (1993) Vitamin A supplementation in infectious diseases: a meta-analysis. Br. Med. J. 306: 366–370.

Job, J. S., Halsey, N. A., Boulus, R., Holt, E., Farrell, D., Albrecht, P., Brutus, J. R, Adrien, M., Andre, J., Chan, E., Kissinger, P., Boulos, C. & Cite Soleil/JHU project team. (1991) Successful immunization of infants at 6 months of age with high dose Edmonston-Zagreb measles vaccine. Pediatr. Infect. Dis. J. 10:.303–311.

Markowitz, L. E., Sepulveda, J., Diaz-Ortega, J. L., Valdespino, J. L., Albrecht, P., Zell, E. R., Stewert, J., Zarate, M. L. & Bernier, R. H. (1990) Immunization of six month old infants with different doses of Edmonston-Zagreb and Schwarz measles vaccines. N. Engl. J. Med. 322: 580–587.

Neumann, P. W., Weber, J. M., Jessamine, A. G. & O'Shaughnessey, M. V. (1985) Comparison of measles antihemolysin test, enzyme-linked immunosorbent assay, and hemagglutination inhibition test with neutralization test for determination of immune status. J. Clin. Microbiol. 22: 296–298.

Pocock, S. J. (1983) Clinical Trials: A Practical Approach. John Wiley & Sons, Chichester, UK.

Ross, A. C. (1991) Vitamin A and the immune response. Background document, October. EPI Research and Development Group Meeting Geneva, Switzerland.

Ross, D. (1995) Vitamin A plus measles vaccination: The downside of convenience? Lancet 345: 1317–1318.

Semba, R. D., Munasir, Z,. Beeler, J., Akib A., Muhilal, Audet, S. & Sommer, A. (1995) Reduced seroconversion to measles in infants given vitamin A with measles vaccination. Lancet 345: 1330–1332.

Semba, R. D., Muhilal, Scott, A. L., Natadisastra, G., Wirasamita, S., Mele, L.,

Downloaded from jn.nutrition.org by on August 4, 2010

Ridwan, E., West, K. P. & Sommer A. (1992) Depressed immune response to tetanus in children with vitamin A deficiency. J. Nutr. 122: 101–107.
Semba, R. D., Muhilal, Ward, B. J., Griffin, D. E., Scott, A. L., Natadisastra, G., West, K. P. & Sommer, A. (1993) Abnormal T-cell subset proportions in vitamin-A-deficient children. Lancet 341: 5–8.
Smith, P. G., Morrow, R. H., eds. (1991) Methods for Field Trials of Interventions against Tropical Diseases: "Toolbox." Oxford University Press, Oxford, UK.
Tokuyama, Y. & Tokuyama, H. (1996) Retinoids as Ig isotype switch modulators. The role of retinoids in directing isotype switching to IgA and IgGl (IgE) in association with IL-4 and IL-5. Cell Immunol. 170: 230–234.
Voller, A. & Bidwell, D. E. (1976) Enzyme immunoassays for antibodies in measles, cytomegalovirus, and after rubella vaccination. Br. J. Exp. Pathol. 57: 243–247.
WHO/CHD Immunization-Linked Vitamin A Supplementation Study Group. (1998) Randomized trial to assess benefits and safety of vitamin A supplementation linked to immunization in early infancy. Lancet 352: 1257–1263.

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