IVACG Policy Statement on Vitamin A, Diarrhea, and Measles

Scientific evidence accumulated in the last decade has led to consensus about the protective role of vitamin A supplementation on childhood mortality. In populations where vitamin A deficiency is endemic, a 23-34% reduction in mortality is expected when vitamin A status is raised to normal values. Community trials achieved this impact within a brief (4-6-month) period through universal periodic supplementation in the form of either megadoses, small weekly doses, or vitamin A-fortified foods. This reduction was due in large part to a fall in diarrheal and measles-related deaths in the supplemented children. Clinical trials of children hospitalized with measles showed that large-dose vitamin A had a beneficial effect on mortality in previously deficient children, with case-fatality ratios reduced on average by 66%. In addition, there is growing evidence of the impact of improved vitamin A status in reducing the duration, severity, and complications associated with both measles and diarrhea. Given that diarrhea and measles are still leading causes of infant and childhood morbidity and mortality in developing countries, and considering the body of evidence, members of the IVACG Steering Committee strongly recommend that vitamin A supplements be included in all child survival programs as an effective strategy to reduce the consequences of these diseases.

Scientific Basis for the Relationship Between Vitamin A Supplementation, Diarrhea, and Measles

The impact of vitamin A supplementation on mortality of children 6 months to 5 years of age has been the subject of numerous studies in the past decade. Eight major randomized, placebo-controlled intervention trials were conducted in Asia and Africa. In six of these trials significant reductions in overall child mortality, ranging from 19% to 54%, occurred in the supplemented group (Sommer et al. 1986, Muhilal et al. 1988, Rahmathullah et al. 1990, West et al. 1991, Daulaire et al. 1992, Ghana VAST Study Team 1993). In the other two studies no effect was found (Vijayaraghavan et al. 1990, Herrera et al. 1992). Four independent meta-analyses were performed with data derived from these trials. The results of all four meta-analyses indicated average reductions in mortality of 23% (Beaton et al. 1993), 30% (Fawzi et al. 1993, Glaziou and Mackerras 1993), and 34% (Tonascia 1993).

The prevalence of xerophthalmia at baseline or other variables, such as baseline anthropometric status of children and control group mortality rates (used as a proxy for baseline mortality rates), could not predict the magnitude of beneficial impact (Beaton et al. 1993). The different periodicities and doses of vitamin A supplied during the six trials with a positive effect on mortality seemed to be equally effective. Two trials delivered megadoses every 6 months, two every 4 months, one delivered small weekly doses, and in another, daily vitamin A doses were supplied by fortified MSG (monosodium glutamate). Given these differences in supplementation, it is highly unlikely that vitamin A supplementation had a nonspecific "pharmacological" effect dependent on a very high potency dose (Beaton et al. 1993).

Cause-specific mortality, as determined by verbal autopsy data from five of the six trials with significant effects on mortality, were pooled in a meta-analysis. There was a statistically significant 32% reduction in deaths from diarrhea (RR=0.68, 95% CI = 0.57-0.80) (Beaton et al.

1993). In one of the studies, death by diarrhea included "acute gastroenteritis" plus "chronic diarrhea and malnutrition" (Ghana VAST Study Team 1993).

Vitamin A supplementation does not appear to prevent clinically apparent infection. Apart from two small-scale studies (Bloem 1990, Lie 1993), most of the well-designed morbidity trials showed either a small but significant reduction in overall incidence (RR=0.94, 95% CI=0.90-0.98) (Barreto et al. 1994) or no significant reductions in either incidence or mean daily prevalence of diarrhea (Abjeljaber et al. 1991, Rahmathullah et al. 1991, Ghana VAST Study Team 1993, Biswas et al. 1994, Bhandari et al. 1994).

However, there is considerable evidence of a significant impact of improved vitamin A status on the severity of diarrhea. In one trial, supplementation was associated with a 9% reduction in the frequency of moderate diarrhea (3 or more days of 4 or fewer liquid or semiliquid stools per 24 hours) (RR=0.91, 95% CI=0.85-0.98) and a 20% reduction in the incidence of severe diarrhea (3 or more days of 5 or more liquid or semiliquid stools per 24 hours) (RR=0.80, 95% CI=0.65-0.98) (Barreto et al. 1994). The more severe the diarrhea, the greater the impact of vitamin A supplementation; for _4, _5, or _6 stools per 24 hours, the odds ratios for supplemented children were 0.90 (p=0.049), 0.80 (p=0.005), and 0.77 (p=0.006), respectively. In another study, there was a 36% reduction in the mean daily prevalence of diarrhea (associated with fever) among vitamin A-supplemented children older than 23 months (Bhandari et al. 1994). In another trial there was a significant difference ($p<0.05$) in the average duration of diarrhea per episode (2.1 versus 3.0 days) between the supplemented and control groups (Biswas et al. 1994). In yet another large study, there were 15% fewer signs and symptoms of dehydration in the supplemented compared with the placebo groups (RR=0.85, $p<0.001$) as well as a 12% lower clinic attendance (RR=0.88, $p<0.02$) and a 38% reduction in the frequency of diarrhea-related hospital admissions (RR=0.62, $p<0.02$) (Arthur et al. 1992, Ghana VAST Study Team 1993).

Three of four randomized placebo-controlled trials of children hospitalized with measles studied mortality. In all three there were statistically significant reductions in case-fatality ratios of generally 50% or more (50%, Barclay et al. 1987; 80%, Hussey and Klein 1990; 45%, Ellison 1932). Meta-analysis suggested an average reduction in mortality of 66% (OR=0.34,95% CI=0.15-0.77) (Glaziou and Mackerras 1993). Two trials had either a small sample size or lower baseline mortality (Coutsoudis et al. 1991, Ogaro et al. 1993). In all five trials, the incidence and/or severity of at least one of the major complications of measles, such as diarrhea, pneumonia, croup, or otitis media, was significantly reduced. In addition, there was evidence that vitamin A-supplemented children spent fewer days at the hospital (Hussey and Klein 1990, Ogaro et al. 1993), clinically recovered in less than 8 days (Coutsoudis et al. 1991, 1992), exhibited enhanced immune response, and had fewer postmeasles complications (Coutsoudis et al. 1991, 1992).

Given that diarrhea and measles are still leading causes of infant morbidity and mortality in developing countries and considering the body of evidence, members of the IVACG Steering Committee strongly recommend that vitamin A supplements be included in all child survival programs in areas of endemic vitamin A deficiency as an effective prophylactic (and, for measles, treatment) strategy to lessen the consequences of these diseases.

References

Abjeljaber MH, Monto AS, Tilden RL, Schork MA, Tarwotjo I. The impact of vitamin A supplementation on morbidity: a randomized community intervention trial. Am J Public Health 1991;81:1654-1656

Arthur P, Kirkwood B, Ross D, Morris S, Gyapong J, Tomkins A, Addy H. Letter: Impact of vitamin A supplementation on childhood morbidity in northern Ghana. Lancet 1992;339:361-362

Barclay AJ, Foster A, Sommer A. Vitamin A supplements and mortality related to measles: a randomized clinical trial. BMJ 1987;294:294-296

Barreto ML, Santos LMP, Assis AMO, Araujo MP, Farenzena GH, Santos PAB, Fiaconne RL. Effect of vitamin A supplementation on diarrhoea and acute lower respiratory infection in young children in Brazil. Lancet 1994;344:228-231

Beaton GH, Martorell R, L'Abbe KA, et al. Effectiveness of vitamin A supplementation in the control of young child morbidity and mortality in developing countries. Final report to CIDA. Toronto: University of Toronto, 1993

Bhandari N, Bhan NK, Sazawal S. Impact of massive dose of vitamin A given to preschool children with acute diarrhoea on subsequent respiratory and diarrhoeal morbidity. BMJ 1994; 309:1404-1407

Biswas R, Biswas AB, Manna B, Bhattacharya SK, Dey R, Sarkar S. Effect of vitamin A supplementation on diarrhoea and acute lower respiratory tract infection in children. Eur J Epidemiol 1994;10:57-61

Bloem MW, Wedel M, Egger RJ, Speek AJ, Schrijver J, Saowakontha S, Schreurs WHP. Mild vitamin A deficiency and risk of respiratory tract diseases and diarrhea in preschool and school children in northeastern Thailand. Am J Epidemiol 1990;131:332-339

Coutsoudis A, Broughton M, Coovadia HM. Vitamin A supplementation reduces measles morbidity in young African children: a randomized, placebo-controlled double-blind trial. Am J Clin Nutr 1991;54:890-895

Coutsoudis A, Kiepiela P, Coovadia HM, Broughton M. Vitamin A supplementation enhances specific IgG antibody levels and total lymphocyte numbers while improving morbidity in measles. Pediatr Infect Dis J 1992;11:203-209

Daulaire NMP, Starbuck ES, Houston RM, et al. Childhood mortality after a high dose of vitamin A in a high risk population. BMJ 1992;304:207-210

Ellison JB. Intensive vitamin A therapy in measles. BMJ 1932;2:708-711

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

Ghana VAST Study Team. Vitamin A supplementation in northern Ghana: effects on clinic attendances, hospital admissions, and child mortality. Lancet 1993;342:7-12

Glaziou PP, Mackerras DEM. Vitamin A supplementation and infectious disease: a meta-analysis. BMJ 1993;306:366-370

Herrera HG, Nestel P, El Amin A, et al. Vitamin A supplementation and child survival. Lancet 1992;340:267-271

Hussey GD, Klein M. A randomised, controlled trial of vitamin A in children with severe measles. N Engl J Med 1990;323:160-164

Lie C, Ying C, Wang E-L, Brun T, Geissler C. Impact of large dose vitamin A supplementation on childhood diarrhoea, respiratory disease and growth. Eur J Clin Nutr 1993;47:88-96

Muhilal, Permeisih D, Idjradinata YR, et al. Vitamin A fortified monosodium glutamate and health, growth and survival of children: a controlled field trial. Am J Clin Nutr 1988;48:1271-1276

Ogaro FO, Orinda VA, Onyango FE, Black RE. Effect of vitamin A on diarrhoeal and respiratory complications of measles. Trop Geogr Med 1993;45:283-286

Rahmathullah L, Underwood BA, Thulasiraj RD, et al. Reduced mortality among children in southern India receiving a small weekly dose of vitamin A. N Engl J Med 1990;323:929-935

Rahmathullah L, Underwood BA, Thulasiraj RD, Milton RC. Diarrhoea, respiratory infections and growth are not affected by a weekly low-dose vitamin A supplement: a masked controlled field trial in children in southern India. Am J Clin Nutr 1991;54:568-577

Sommer A, Tarwotjo I, Djunaedi E, et al. Impact of vitamin A supplementation on childhood mortality: a randomized controlled community trial. Lancet 1986;1:1169-1173

Tonascia JA. Meta-analysis of published community trials: impact of vitamin A on mortality. Proceedings of the Bellagio Meeting on vitamin A deficiency and childhood mortality. New York: Helen Keller International, 1993

Vijayaraghavan K, Radhaiah G, Prakasam BS, Sarma KVR, Reddy V. Effect of massive dose vitamin A on morbidity and mortality in Indian children. Lancet 1990;336:1342-1345

West KP, Pokherel RP, Katz J, et al. Efficacy of vitamin A in reducing child mortality in Nepal. Lancet 1991;338:67-71