

Abstracts and Reports



Bellagio Brief: Vitamin A Deficiency and Childhood Mortality

The 1986 UNICEF report, *State of the World's Children* (1), drew attention to emerging observations suggesting that improving vitamin A status might have great potential for reducing childhood mortality. The 1990 report of the Commission on Health Research for Development (2) noted gathering confirmation of the potential impact of vitamin A deficiency on child health and survival, and declared that "if these findings are confirmed, the strategic implications would be astounding. . . ."

In light of recent calls by the World Summit for Children (3) and the "Bellagio Declaration" (4) [which stemmed from an international meeting on hunger held in Bellagio, Italy, in 1989] for worldwide control or elimination of vitamin A deficiency,¹ and the recent spate of published scientific data, a meeting of concerned scientists, health officials, and policy makers was convened on 3–7 February 1992 at the Rockefeller Study and Conference Center in Bellagio, Italy. The

purpose was to examine the role of vitamin A status on the health of children in developing countries, to reach clear and appropriate conclusions where warranted, and to consider policy implications arising from these conclusions that might guide program managers and decision makers.

The group considered published data concerning the biochemistry and molecular biology of vitamin A; its role in cellular differentiation and immunity; animal models and clinical case reports of vitamin A deficiency; the epidemiology of vitamin A deficiency in human populations and the environment in which it arises; prospective observational field investigations; hospital treatment studies; and controlled, community-based prophylaxis trials.

The meeting was supported by the Charles A. Dana Foundation, organized by Helen Keller International, and chaired by Professor Abraham Horwitz.²

CONCLUSIONS

- Vitamin A is essential for normal health and survival.
- Vitamin A deficiency increases mortality among children 6 months through

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¹In this regard, the Pan American Health Organization has drawn up a plan of action for the elimination of vitamin A deficiency from the Americas (Document CD36/15), which was ratified by the Member Governments at the XXXVI Meeting of the Directing Council in September 1992.

²Director Emeritus of PAHO.

6 years of age; improving the vitamin A status of deficient children dramatically increases their chance of survival.

- Vitamin A deficiency increases the severity, complications, and risk of death from measles. Improving vitamin A status before the onset of measles (prophylaxis), or after measles occurs (treatment), markedly reduces the severity of complications and associated mortality.
- Vitamin A deficiency increases childhood morbidity, particularly the severity of infectious episodes (e.g., diarrhea, pneumonia). Improvement of vitamin A status reduces the severity of infectious episodes.
- Vitamin A is essential for normal vision and ocular function. Deficiency results in nightblindness and other manifestations of xerophthalmia, including corneal destruction (keratomalacia) and blindness.
- Increased morbidity and mortality occur at levels of vitamin A deficiency less severe and chronic than required for nightblindness and xerophthalmia. *Therefore, the definition of vitamin A deficiency for public health purposes must be revised and made more sensitive to milder degrees of deficiency.*
- Tens of millions of the world's children are vitamin A deficient; one million or more needlessly die or go blind every year.
- Improving the vitamin A status of deficient children and treating all cases of measles with vitamin A, even in populations in which xerophthalmia is rare, can substantially reduce childhood disease and mortality.
- Increasing the vitamin A intake of deficient children through diet or supplementation is an important component of a comprehensive child survival strategy.

SCIENTIFIC RATIONALE

The evidence that vitamin A deficiency increases childhood morbidity and mortality and that this can be prevented by improving vitamin A status is overwhelming.

Since 1913, when vitamin A was discovered (5, 6), progressive depletion of vitamin A in animals has been shown to result in histologic and functional abnormalities in cells throughout the body (7), alterations in immune function (8–12), wasting (1, 2, 13, 14), severe infection (15, 16), death (17, 18), and in those animals that survive, blindness (6, 17). The more severe the vitamin A deficiency, the more common, and severe, are the consequences.

For over 60 years physicians have reported the same histologic changes (19), increased rates of infection (19–21), and greater severity of measles (22) in children who were vitamin A deficient—all conditions which could be cured or prevented with vitamin A. In each of three hospital-based, randomized, controlled trials on the treatment of measles [one in London in 1930 (22); two in the past decade in Africa (23, 24)], children who received vitamin A died at less than half the rate of children who received routine therapy. The African measles mortality trials (23, 24) and a recent African trial (25) on measles morbidity also examined the incidence and severity of measles complications. All found that measles complications, both incidence and severity, were reduced in children who received vitamin A. Other community-based observational studies (26–28) and intervention trials, particularly a just-completed morbidity trial in Ghana (29), indicate that better vitamin A status reduces the risk of other severe infections as well, particularly diarrhea and pneumonia.

In 1983 a community-based observational study re-examined 4 000 pre-

school-age Indonesian children seven times over an 18-month period. Other factors being equal, a close, statistically significant dose-response relationship existed between the severity of vitamin A deficiency and the risk of infectious episodes (26) and death (30). That the presence and severity of vitamin A deficiency had a direct relationship with mortality suggested the possibility that improving the vitamin A status of children in communities where vitamin A deficiency was prevalent might reduce childhood (age 6 months to 6 years) mortality.

Over the past decade a series of controlled, community-based prophylaxis trials have been conducted in order to verify this potential reduction in mortality. In each trial, mortality among children randomly assigned to receive supplemental vitamin A was compared with that of their concurrent controls. The results of six such trials [two each in Indonesia (31, 32), India (33, 34), and Nepal (35–36)] have been published. In all six trials, the vitamin A group experienced lower mortality. Pooling the data of the six trials (approximately 100 000 children and 1 000 deaths) by using meta-analytic methods indicated that, on average, vitamin A supplementation programs can reduce childhood mortality by 34%. The size of the impact observed in each of the six trials was consistent with the 34% overall reduction (heterogeneity, $p \geq 0.32$). The probability that the vitamin A programs reduced childhood mortality was highly significant ($p < 10^{-9}$). The consistency of these findings is particularly persuasive given variations in the underlying mortality and other health indices of the study populations and the differences in the design and conduct of the trials.

Cause-specific mortality was examined in three of the community-based prophylaxis trials (33, 35, 36). In all three, dramatic reductions were found in deaths

associated with diarrhea (the major cause of death in children over 5 months of age) and measles.

These same trials, and at least two other trials directed at the impact on xerophthalmia (37, 38), confirm that improvement of vitamin A status in deficient children will prevent even the most severe forms of xerophthalmia, including keratomalacia and blindness.

Modern molecular biology has begun to unravel the mechanisms by which vitamin A exerts its powerful, pervasive effects. It is now known that vitamin A directly affects the expression of at least 300 different genes—a number that is likely to grow—which in turn affect cellular differentiation, the integrity of epithelial structures, and immunologic function. While the precise mechanisms by which vitamin A manifests its impact are yet to be delineated, the biological plausibility of those effects is well established.

The generalizability of the clinical findings is supported by the consistency of animal models with clinical reports, the results of observational studies, community-based prevention and hospital treatment trials, and their biological plausibility. Given the weight of existing evidence, additional trials that withhold vitamin A from deficient children 6 months of age and older would appear to be unwarranted.

The reduction in child mortality achieved by prophylactic community-wide improvement of vitamin A status and vitamin A treatment of measles cases is comparable to the impact of the most effective of the other child survival strategies. Methods for improving vitamin A status include periodic distribution of large-dose capsules appropriate for age, fortification of readily consumed dietary staples, and increased intake of vitamin A-rich foods, alone or in combination. The cost of a large dose of vitamin A from UNICEF delivered to any country is only

2–4¢ US. In one intervention study in Nepal (36) with high underlying mortality, the cost per death averted was only US\$ 11. The costs associated with improving vitamin A status will be minimized when such programs are integrated, as appropriate, with other child survival strategies, attempts to control other relevant micronutrient deficiencies, and as part of existing community health activities.

Much of the mortality reduction found in both community and hospital-based trials occurred in children with only marginal pre-existing deficiency. In most trials, study children were without xerophthalmia, as those children with ocular disease were excluded at baseline. In others, xerophthalmia was rarely, if ever, encountered in the population. Increased morbidity and mortality occur at levels of vitamin A deficiency less severe and chronic than required for nightblindness and xerophthalmia. Thus, it is imperative that programs to improve vitamin A status be targeted toward populations which may be marginally or mildly deficient.

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ANNEX. Participants in the meeting on vitamin A deficiency and childhood mortality, Bellagio, Italy, February 1992.

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 Dr. Jon Rohde, Senior Adviser, UNICEF
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Balancing Microbial and Chemical Risks in Disinfection of Drinking Water: The Pan American Perspective

The following is an abridged version of the keynote speech delivered by Dr. Carlyle Guerra de Macedo, Director of PAHO, at the First International Conference on the Safety of Water Disinfection: Balancing Microbial and Chemical Risks. The conference was held from 31 August to 3 September 1992 in Washington, D.C., and was cosponsored by the International Life Sciences Institute, United States Environmental Protection Agency, United States Food and Drug Administration, American Water Works Association, Pan American Health Organization, and World Health Organization.

In prescribing medication, the physician is acutely aware of the need to weigh chemical and biological risks, because virtually every medication has both benefits and potentially negative physiological side-effects. In simple terms, the physician's objective is to do the most good and to cause the least harm. The process of deciding on a course of treatment can be straightforward or quite complex, depending on the severity of

the disease, the condition of the patient, the pharmacokinetic activity of the medicine, and, most importantly, previous experience. A number of parallels can be drawn between balancing microbial and chemical risks in the treatment of infectious and parasitic diseases and the topic of this conference, particularly with regard to factors governing the decision-making process in developed and developing countries.