BELLAGIO BRIEF ON VITAMIN A DEFICIENCY

The 1986 report, "State of the World's Children," 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" 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 "Bellagio Declaration" and the "Summit on the Rights of Children" for worldwide control or elimination of vitamin A deficiency and the recent spate of published scientific data, a meeting of concerned scientists, health officials and policy makers was convened on February 3-7, 1992, at the Rockefeller Study Center in Bellagio, Italy to examine the role of vitamin A status on the health of Third World children and reach clear and appropriate conclusions where warranted; and to consider policy implications arising from these conclusions that might guide programme managers and decision makers.

The group considered data concerning the biochemistry and molecular biology of vitamin A; its role in immunity and cellular differentiation; 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.

Conclusions

1. Vitamin A is essential for normal health and survival.
2. Vitamin A deficiency increases mortality among children 6 months through 6 years of age; improving the vitamin A status of deficient children dramatically increases their chance of survival.
3. Vitamin A deficiency increases the severity, complications and risk of death from mealses. Improving vitamin A status before the onset of measles (prophylaxis), or after measles occurs (treatment), reduces the severity of complications and associated mortality.
4. 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.
5. Vitamin A is essential for normal and ocular function. Deficiency results in nightblindness and other manifestations of xerophthalmia, including corneal destruction (keratomalacia) and blindness.
6. 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.

7. Tens of millions of the world's children are vitamin A deficient; a million or more needlessly die or go blind every year.
8. 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. Improving the vitamin A status of deficient children is an important component of a comprehensive child survival strategy.

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 first discovered, progressive depletion of vitamin A in animals has been shown to result in alterations in immune function, histologic and functional abnormalities in cells throughout the body, wasting, severe infection, death, and in those animals that survive, blindness. The more severe the vitamin A deficiency, the more common, and severe, the consequences.

For over 60 years physicians have reported increased rates of infection and greater severity of measles in children who were vitamin A deficient; abnormalities that could be cured or prevented with vitamin A. In each of three hospital-based, randomized, controlled treatment trials (one in London in 1930; two in the past decade in Africa), children who received vitamin A died at less than half the rate of children who received routine therapy. The African measles mortality studies, and a recent African measles morbidity trial, examined the increase and severity of measles complications. All found these were reduced in children receiving vitamin A. Community-based observational and intervention trials, particularly a just-completed morbidity trial in Ghana, 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 4000 preschool-age Indonesian children seven times over an 18-month period. Other factors being equal, there was a close, statistically significant dose-response relationship between the severity of vitamin A deficiency and the risk of infectious episodes and death.

The observation that the presence and severity of vitamin A deficiency had a direct relationship with mortality suggested the possibility that improvement in vitamin A status of children in communities in which vitamin A deficiency was prevalent might reduce childhood (age 6 months to 6 years) mortality. A series of controlled, community-based prophylaxis trials were carried out over the past decade in which 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, India and Nepal) have been published. In all six trials, the vitamin A group experienced lower mortality. Pooling the six trials (over 10,000 children and 1,000 deaths) using meta-analytic methods indicates that conservatively, vitamin A supplementation programmes 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 $p = >0.32$). The probability that vitamin A programmes 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 differences in the design and conduct of the trials.

Cause-specific mortality was examined in three of the community-wide mortality intervention trials; in all three, there were dramatic reductions in deaths associated with diarrhea (the major cause of death in children over 5 months of age) and measles.

These same intervention trials, and at least two directed at the impact on xerophthalmia, 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, and which in turn affect cellular differentiation, the integrity of epithelial lining 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 consistency of animal models with the clinical reports, observational studies, community-based prevention and hospital treatment trials, and their biologic plausibility, all support the generalizability of the clinical findings. 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 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 cents. In one intervention study (Jumla, Nepal) with high underlying mortality, the cost per death averted was only $11 US. The costs associated with improving vitamin A status will be minimized when such programmes 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 in the vitamin A trials and hospital studies occurred in children with only marginal pre-existing deficiency. In most trials, study children were without xerophthalmia, as those with ocular disease were excluded at baseline. In others, xerophthalmia was rarely, if ever, encountered in the population.

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