

Vitamin A deficiency and attributable mortality among under-5-year-olds*

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Reported are estimates of the prevalence in developing countries of physiologically significant vitamin A deficiency and the number of attributable deaths. The WHO classification of countries by the severity and extent of xerophthalmia was used to categorize developing countries by likely risk of subclinical vitamin A deficiency. Using vital statistics compiled by UNICEF, we derived population figures and mortality rates for under-5-year-olds. The findings of vitamin A supplementation trials were applied to populations at-risk of endemic vitamin A deficiency to estimate the potential impact of improved vitamin A nutrition in reducing mortality during preschool years. Worldwide, over 124 million children are estimated to be vitamin A deficient. Improved vitamin A nutrition would be expected to prevent approximately 1–2 million deaths annually among children aged 1–4 years. An additional 0.25–0.5 million deaths may be averted if improved vitamin A nutrition can be achieved during the latter half of infancy. Improved vitamin A nutrition alone could prevent 1.3–2.5 million of the nearly 8 million late infancy and preschool-age child deaths that occur each year in the highest-risk developing countries.

Until the past decade, interest in vitamin A deficiency focused on its ocular manifestation, xerophthalmia, the leading cause of childhood blindness in developing countries (1, 2). Beginning in the early 1980s, however, a series of studies in different cultures revealed that even subclinical vitamin A deficiency has broader consequences in developing countries in terms of child morbidity and mortality. Thus, a longitudinal study from West Java, Indonesia, reported a two- to threefold higher risk of respiratory infection and diarrhoea (3) and a fourfold increased risk of mortality among children with mild xerophthalmia (4). Two controlled field trials in northern Sumatra and West Java, Indonesia, reported reductions of 34% and 46%, respectively, in the mortality of preschool-age children administered semiannual vitamin A supplements (5) and fortified commercially distributed monosodium glutamate (6). In India, mortality among preschool-age children was lowered by 54% upon distribution of small, weekly doses of vitamin A (7), while in Nepal, per-

iodic administration of large doses of vitamin A (200 000 IU) reduced mortality by ca. 30% (8, 9). The small reductions reported in some trials (10) indicate that the impact of vitamin A on mortality can be expected to vary within and between regions.

Vitamin A appears to enhance survival during the acute phase of severe infection, as evidenced by studies on measles. Case fatality among children with moderate-to-severe measles has been repeatedly reduced by 50% or more through the use of oral vitamin A therapy on admission to hospital (11–13). In survivors, the severity of acute illness is modulated, and is accompanied by more rapid recovery (13, 14).

These studies have redirected scientific inquiry, increased the funding of vitamin A research and preventive activities, and led to a number of official meetings and statements within the United Nations (15–17)^a and other international agencies (18, 19)^b calling for the prevention and control of vitamin A deficiency.

Estimates of the magnitude of blinding malnutrition published in 1981 (1) have served as a useful basis for international planning purposes. The present article addresses the parallel issue of the

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^a *Prevention and control of vitamin A deficiency: meeting of interested parties. Proposal for a 10-year programme of support to countries.* Unpublished WHO document NUT/84.5, Rev. 1.

^b *Grant, J.P. Ending hidden hunger.* UNICEF, New York, October 1991 (Document No. CF/EXE-IC/1991–032).

likely scale and extent of physiologically significant vitamin A deficiency and the number of childhood deaths directly attributable to this preventable condition.

Methods

Reference data

Based on preliminary assessment reports and data from surveys over the past 25 years, WHO has classified 63 developing countries into three categories, according to the likely severity and extent of blinding vitamin A deficiency.^c Category I includes 23 countries that, according to available data, harbour the highest risk of vitamin A deficiency. Four of these (India, Indonesia, Bangladesh, and the Philippines) have endemic vitamin A deficiency, as indicated by sound, population-based xerophthalmia prevalence data (Table 1). These four countries have provided the basis for the currently accepted estimates of xerophthalmia and blindness from vitamin A deficiency (21). Intervention trials carried out in Indonesia and India (5–7, 10) and in nearby Nepal (8, 9) have reported the impact of vitamin A in reducing preschool-age child mortality. Thus, studies in these four countries (plus Nepal) provide the strongest data and most conservative estimates of the global extent of vitamin A deficiency and its associated mortality.

Category II countries in the WHO classification are those where xerophthalmia is likely to be a public health problem in certain regions but for which there are insufficient national, population-based data. Category III countries are those where the prevalence of xerophthalmia is probably low, although cases have been occasionally observed. Finally, there are "other" developing countries that have not been classified by WHO but which, in view of their high infant and child mortality rates, are likely to harbour vitamin A deficiency. Here, developing countries refer to the 81 nations identified in 1991 by UNICEF to have infant mortality rates exceeding 30 per 1000 live births per year, excluding the USSR and Guyana (22). In this article, category II and III countries have been aggregated with these "other" developing countries and are referred to as "non-category I" countries. Estimates of the number of infant and 1–4-year-old child deaths in category I and non-category I countries are based on 1989 demographic estimates compiled by UNICEF (Table 1) (22).

Standard indicators of vitamin A status

Among the indicators of vitamin A deficiency employed in the studies cited in this article are the following (with diagnostic cut-offs): ocular signs of xerophthalmia (night blindness, conjunctival or corneal xerosis) (23); serum retinol level ($< 20 \mu\text{g/dl}$) (24); the relative dose response (RDR) test ($\geq 20\%$ positivity) (25, 26); and conjunctival impression cytology (CIC-A) (abnormal epithelium) (27). In accord with WHO recommendations (28), dietary data reflecting inadequate vitamin A intake were considered as suggestive that a vitamin A deficiency problem may exist.

Results and discussion

Numbers of children with vitamin A deficiency

In population-based studies in Indonesia (29) and the Philippines (30), half of all clinically normal children had serum vitamin A levels below $20 \mu\text{g/dl}$. A report from Brazil using the RDR test suggests that even children with serum vitamin A levels equal to this cut-off value may have suboptimal vitamin A nutriture (26). Altogether, 86% of children with serum retinol levels of $20\text{--}30 \mu\text{g/dl}$ and 26% of those with serum levels of $30\text{--}40 \mu\text{g/dl}$ were positive in the RDR test. If these rates of RDR positivity are applied to a typical distribution of serum retinol among clinically normal Indonesian children, we would expect 70% to have suboptimal liver stores (J.H. Humphrey et al., unpublished observations, 1991).

Several studies have used CIC-A to detect sub-clinical vitamin A deficiency. Two case-control studies from Indonesia found 22% (31) and 41% (32) of nonxerophthalmic children to be abnormal by this method. Population-based studies in Micronesia (33) and India (34) reported that 42% and 25%, respectively, of clinically normal children were CIC-A abnormal. Allowing for an estimated 5–10% false positivity in CIC-A (27), these studies suggest that 15–40% of clinically normal children in category I countries may have abnormal epithelial differentiation and disturbed physiological function, secondary to vitamin A deficiency.

The combined results of these serological, RDR, and cytological findings indicate conservatively that approximately 40% of children (or 97 million) living in category I countries have physiologically significant vitamin A deficiency (Table 2).

It is more difficult to estimate the extent of sub-clinical deficiency in non-category I developing countries. The above data suggest that where xerophthalmia is a public health problem the number of

^c Global situation — vitamin A deficiency. Based on reports received by WHO as of October, 1988. *Expanded Programme on Immunization Update, December 1988.*

Table 1: Demographic data for WHO-classified category I vitamin A deficient and other non-category I developing countries

	No. of <5-year-olds ^a (x1000)	No. of deaths among 1–4-year-olds (x1000)	No. of deaths among infants aged:	
			<12 months (x1000)	6–11 months ^b (x1000)
Total category I	243 900	3042	5478	1827
Four Asian countries	164 000	1784	3493	1165
India	113 400	1277	2503	834
Indonesia	22 700	134	365	122
Philippines	9100	56	87	29
Bangladesh	18 800	317	540	180
Others	79 900	1258	1985	662
Sub-Saharan Africa ^c	50 800	1024	1497	499
Eastern Mediterranean ^d	4400	76	114	38
Latin America/Caribbean ^e	19 800	109	274	92
Asia ^f	4900	52	100	33
Total non-category I ^g	269 900	1734	3704	1235
Sub-Saharan Africa ^h	39 700	538	934	311
Middle East/North Africa ⁱ	45 900	249	663	221
Latin America/Caribbean ^j	32 600	130	353	118
Asia ^k	151 700	817	1754	585
Total	513 800	4776	9182	3062

^a Derived from ref. 22, Tables 1 and 5.

^b Estimated by assuming that deaths among infants aged 6–11 months represent a third of all deaths among those aged <12 months. Benin, Burkina Faso, Chad, Ethiopia, Ghana, Malawi, Mali, Mauritania, Mozambique, Niger, Nigeria, United Republic of Tanzania, and Zambia.

^c Sudan.

^d Brazil, Haiti.

^e Nepal, Sri Lanka.

^f UNICEF has identified 81 countries with infant mortality rates (IMR) of >30 per 1000 live births (22). All of these countries are included in the non-category I country calculations, except Guyana, for which demographic information was not available, and the USSR. Non-category I countries where vitamin A deficiency is known to exist but where the IMR is ≤30 per 1000 have been excluded from these estimates.

^g Angola, Botswana, Burundi, Cameroon, Central African Republic, Congo, Cote d'Ivoire, Gabon, Guinea, Kenya, Lesotho, Liberia, Madagascar, Namibia, Rwanda, Senegal, Sierra Leone, Somalia, South Africa, Togo, Uganda, Zaire, and Zimbabwe.

^h Algeria, Egypt, Iran, Iraq, Jordan, Lebanon, Libyan Arab Jamahiriya, Morocco, Oman, Saudi Arabia, Syrian Arab Republic, Tunisia, Turkey, and Yemen.

ⁱ Argentina, Bolivia, Colombia, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Paraguay, Peru, and Venezuela.

^j Afghanistan, Bhutan, Cambodia, China, Laos, Mongolia, Myanmar, Pakistan, Papua New Guinea, and Viet Nam.

children with subclinical vitamin A deficiency is 10 times the number with xerophthalmia. Survey data indicate that inadequate dietary intake of vitamin A is widespread (35, 36). In China, where 40% all preschool-age children in non-category I developing countries live, and where 16% of all deaths of 1–4-year-olds occur, the results of four large surveys suggest that 1% of these children may have xerophthalmia (22, 28). Taken together with the above-mentioned tenfold factor this indicates that 10% of Chinese preschool-age children have subclinical

vitamin A deficiency. Applying this same proportion to other non-category I developing countries suggests that nearly 27 million children may suffer from physiological vitamin A deficiency. Worldwide, over 124 million preschool-age children are estimated to be vitamin A deficient (Table 2).

Associated child mortality

Studies that have reported a significant impact of administering vitamin A supplements in category I

Table 2: Estimated percentage and number of preschool-age children with physiologically significant vitamin A deficiency

	No. of <5-year-olds ^a (x1000)	Estimated % with vitamin A deficiency ^b	No. with vitamin A deficiency (x1000)
Total category I	243 900	40	97 200
Four Asian countries ^c	164 000	40	65 600
Others	79 900	40	31 960
Total non-category I	269 900	10	26 990
Total	513 800	—	124 190

^a See Table 1 in ref. 22.^b See text for derivation of proportions.^c India, Indonesia, Philippines, and Bangladesh.

countries have found reductions of 26–54% in the 12-month mortality levels of children aged 1–4 years who received the supplements (5–9). An even greater impact has been projected (41–74% reduction in mortality) for maximum coverage levels (37, 38). Therefore, in category I countries, improved vitamin A nutriture could potentially reduce preschool-age child mortality by an estimated 30–55% (0.91–1.67 million deaths averted per year) (Table 3).

The impact of vitamin A supplementation on child mortality in non-category I countries has not been investigated. Therefore, estimates for these populations have been derived (with several assumptions) from the data for category I countries. Although a longitudinal study of Indonesian children suggested that nearly 20% of all preschool-age deaths in endemic areas could be prevented by controlling xerophthalmia alone (4), most intervention trials have suggested that supplementation can lower mortality among children who are marginally (but not clinically) deficient in vitamin A. Since 10% of children in non-category I developing countries are assumed to have subclinical vitamin A deficiency (compared with 40% in category I countries), it is estimated that the impact of vitamin A on mortality would also be roughly a quarter of that observed in category I countries, i.e., 10–15%. This would account for an additional 173 000–260 000 deaths among children aged 1–4 years in non-category I countries that might be prevented by improved vitamin A nutriture (Table 3).

A “best estimate” range of the potential impact of improved vitamin A nutriture on 1–4-year-old mortality in populations with clinically apparent or subclinical deficiency is 1.09–1.93 million deaths averted per year (Table 3). It should be noted, however, that vitamin A trials have also reported reductions in mortality in the sixth and seventh years of life (5, 8), ages for which demographic esti-

mates of mortality are often not specified. Thus, this range of preventable child deaths is, by definition, conservative.

Associated mortality in late infancy

In developing countries infants may be at risk of vitamin A deficiency because mothers can be deficient in the vitamin during pregnancy (39), may deliver newborns with reduced vitamin A stores (40), and may remain deficient during lactation (41). Nevertheless, breast-feeding appears to be vital in keeping infants adequately nourished with vitamin A (42, 43).

Mortality intervention trials have not adequately addressed the impact of vitamin A on infant mortality. Five studies have reported reductions of 12–72% in mortality when vitamin A supplementation was initiated, on average, at 6 months of age or later in infancy (5–9). This mortality experience was observed over a subsequent 4–12 month period, which tended to overlap into the second year of life. Thus, it is estimated that adequate vitamin A nutriture may reduce mortality among older infants by 10–25% in category I countries (183 000–457 000 deaths averted) (Table 3). Consistent with the above-mentioned assumptions for 1–4-year-olds, we estimate that a quarter of this impact (3–6%) may be observed in non-category I developing countries, i.e., 37 000–74 000 additional deaths averted each year. A total of 220 000–531 000 late infant deaths may be prevented annually by improved vitamin A nutriture (Table 3).

Worldwide, between 1.3 and 2.5 million out of a total of 7.8 million deaths among infants and preschool-age children (late infancy up to age 4 years) could be prevented each year by improving vitamin A nutriture (Table 3). The number of infant deaths prevented may be considerably greater if vitamin A nutriture were truly adequate from conception, and

Table 3. Estimated impact of improving vitamin A nutriture on reducing preschool-age mortality

	No. of deaths/year (x1000)	Low impact ^a		High impact ^a	
		% reduction	No. of deaths averted (x1000)	% reduction	No. of deaths averted (x1000)
<i>Age: 1-4 years (Total)</i>	4776		1085		1933
Total category I	3042	30	912	55	1673
Four Asian countries ^b	1784	30	535	55	981
Others	1258	30	377	55	692
Non-category I	1734	10	173	15	260
<i>Age: 6-11 months (Total)</i>	3062		220		531
Total category I	1827	10	183	25	457
Four Asian countries ^b	1165	10	117	25	291
Others	662	10	66	25	166
Non-category I	1235	3	37	6	74
Total	7838		1305		2464

^a See text for derivation of low and high estimates of impact.

^b India, Indonesia, Philippines, and Bangladesh.

thus had an opportunity to have an impact on fetal wastage and early infant mortality in ways that have not yet been investigated.

Caveats

These estimates were developed systematically, but are based on data of mixed quality and on a number of assumptions.

First, standard demographic projections, as compiled and reported by UNICEF, were used to estimate the annual numbers of births, infant deaths, children under 5 years of age, and deaths that occur each year among 1-4-year-olds. The number of deaths among infants aged ≥ 6 months was assumed to be a third of the published infant mortality rate; errors generated from this process will affect the estimates.

Second, in estimating the ratio of subclinical deficiency to xerophthalmia as 10:1, we have drawn upon the results of different investigators, in different countries, who used a variety of techniques. Thus, this ratio cannot be expected to apply across all populations, but represents a best estimate based on current data. The apparent consistency of this relationship is reassuring, however.

Third, we assumed that the prevalence and severity of vitamin A deficiency in all countries classified as category I by WHO are the same as those in the four well-studied Asian countries from which most data have come, and that the impact of vitamin A supplementation on mortality would be similar to that in the three countries (India, Indonesia, and Nepal) where this has been measured. However,

most of other category I countries were classified on the basis of less tangible evidence.

Fourth, we have not accounted for any potential impact that vitamin A may have in the first half of infancy, as there are insufficient data available from which to derive estimates. It should be noted that the estimates of impact in later infancy represent the effect that could be achieved among infants who receive vitamin A supplements between 6 to 11 months of age.

Finally, we assumed an "average risk" of vitamin-A-related mortality for all provinces in a given country, although, in reality, vitamin A deficiency tends to cluster (i.e., within provinces, districts, or villages) (44).

Despite these limitations, the analyses and estimates obtained provide a useful indication for coming to grips with the probable magnitude of the problem: from 1 in 7 to 1 in 3 deaths involving over-6-month-olds up to preschool-age children in developing countries might be prevented by improving vitamin A nutriture.

One final comment should be noted: vitamin A deficiency is not a proximal determinant of death. Children in developing countries die primarily from infections such as diarrhoea, respiratory disease, and measles (22). Vitamin A deficiency presumably alters the incidence, duration or severity of such infections or the child's ability to withstand their consequences (20, 45). Interventions that reduce the incidence of these infections (e.g., measles immunization) would decrease the net impact of vitamin A supplementation on mortality. However, even well-

organized immunization programmes, with their less-than-complete coverage and efficacy, may leave an important role for improved vitamin A nutrition in reducing the number of infection-related deaths.^d Therefore, until protected water supplies, improved hygiene, universal immunization and other child-survival services are effectively delivered, control of vitamin A deficiency could enhance child health and survival.

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Résumé

Carence en vitamine A et mortalité associée chez les moins de 5 ans

Jusqu'à ces dix dernières années, on s'est surtout intéressé, en ce qui concerne la carence en vitamine A, à la xérophtalmie, cause majeure de cécité de l'enfant dans les pays en développement. Récemment, toutefois, plusieurs études ont montré que même une carence infraclinique en vitamine A peut avoir d'importantes conséquences chez les populations mal desservies par les systèmes de santé. Etant donné le développement croissant des politiques nutritionnelles et des programmes de prévention de la carence en vitamine A, il est urgent de connaître l'ampleur mondiale de ce problème et l'impact potentiel des programmes de supplémentation en vitamine A sur la mortalité chez l'enfant.

La classification OMS des pays selon l'importance de la xérophtalmie et de la cécité d'origine nutritionnelle sur la santé publique, les résultats d'études sur le terrain et d'essais cliniques portant sur la vitamine A, ainsi que les estimations démographiques types de la mortalité juvénile permettent d'évaluer ces paramètres. Dans le présent article, les pays de catégorie I sont ceux dans lesquels la xérophtalmie est présente ou probablement présente, et les pays dits "n'entrant

pas dans la catégorie I" sont 93 autres pays en développement où le risque de carence en vitamine A est plus faible.

En considérant globalement les données sérologiques, la relation dose-réponse et les observations cytologiques, nous estimons que 40% des enfants d'âge préscolaire vivant dans les pays de catégorie I (environ 97 millions d'enfants) présentent une carence en vitamine A significative sur le plan physiologique. S'y ajoutent quelque 10% des enfants des pays n'entrant pas dans la catégorie I (environ 27 millions d'enfants).

La plupart des études qui ont mesuré l'impact de l'administration de vitamine A sur la mortalité juvénile dans les pays d'Asie entrant dans la catégorie I mentionnent des réductions de 31 à 53% lorsque les enfants reçoivent une supplémentation en vitamine A entre 1 et 4 ans. En augmentant la couverture de cette intervention, il est probable que l'impact sera encore plus grand (41 à 74%). Par conséquent, chez les enfants des pays de catégorie I, une amélioration de l'apport de vitamine A devrait pouvoir réduire la mortalité de 30 à 55% chez les enfants de 1 à 4 ans (c'est-à-dire éviter 1,1 à 1,9 million de décès par an).

Dans les pays n'entrant pas dans la catégorie I, on estime que 10% des enfants présentent une carence infraclinique en vitamine A (contre 40% dans les pays de la catégorie I). Comme les essais de supplémentation ont mis en évidence une réduction de la mortalité chez les enfants sans xérophtalmie clinique, on suppose que l'impact de la vitamine A sur la mortalité serait égal à environ un quart de celui observé dans les pays de la catégorie I (soit 10 à 15%). L'amélioration de l'apport de vitamine A pourrait par conséquent prévenir 173 000 à 260 000 décès chez les enfants d'âge préscolaire dans les pays n'entrant pas dans la catégorie I.

Plusieurs études d'intervention font apparaître une réduction potentielle de la mortalité de 12 à 72 % lorsque les suppléments de vitamine A sont donnés dès l'âge de 6 mois. Nous estimons par conséquent qu'un apport suffisant en vitamine A dès cet âge pourrait réduire la mortalité de 10 à 25% dans les pays de la catégorie I (c'est-à-dire éviter 183 000 à 457 000 décès). De même que chez les enfants de 1 à 4 ans, nous estimons que la réduction de la mortalité dans les pays en développement n'entrant pas dans la catégorie I serait égale au quart de celle observée dans les pays de la catégorie I, soit 3 à 6 % (37 000 à 74 000 décès évités si la supplémentation a commencé avant l'âge d'un an).

^d Guidelines for the use of vitamin A in immunization programs: a report of the International Vitamin A Consultative Group (IVACG). Preliminary draft submitted to WHO, September 1990.

En résumé, nous estimons qu'à l'échelle mondiale, plus de 124 millions d'enfants d'âge préscolaire présentent une carence en vitamine A. En améliorant l'apport en vitamine A, 1,1 à 2 millions de décès chez les enfants de 1 à 4 ans, et 0,2 à 0,5 million de décès chez les nourrissons de 6 mois à 1 an, pourraient être évités chaque année.

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