Proceedings of the XX International Vitamin A Consultative Group Meeting

Assessment and Control of Vitamin A Deficiency: The Annecy Accords[1,2]

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ABSTRACT Comprehensive recommendations for the assessment and control of vitamin A deficiency (VAD) were rigorously reviewed and revised by a working group and presented for discussion at the XX International Vitamin A Consultative Group meeting in Hanoi, Vietnam. These recommendations include standardized definitions of VAD and VAD disorders. VAD is defined as liver stores below 20 μg (0.07 μmol) of retinol per gram. VAD disorders are defined as any health and physiologic consequences attributable to VAD, whether clinically evident (xerophthalmia, anemia, growth retardation, increased infectious morbidity and mortality) or not (impaired iron mobilization, disturbed cellular differentiation and depressed immune response). An estimated 140 million preschool-aged children and at least 7.2 million pregnant women are vitamin A deficient, of whom >10 million suffer clinical complications, principally xerophthalmia but also increased mortality, each year. A maternal history of night blindness during a recent pregnancy was added to the clinical criteria for assessing vitamin A status of a population, and the serum retinol criterion for a "public health problem" was revised to 15% or more of children sampled having levels of <20 μg/dL (0.7 μmol/L). Clinical trials and kinetic models indicate that young children in developing countries cannot achieve normal vitamin A status from plant diets alone. Fortification, supplementation, or other means of increasing vitamin A intake are needed to correct widespread deficiency. To improve the status of young infants, the vitamin A supplements provided to mothers during their first 6 wk postpartum and to young infants during their first 6 mo of life should be doubled. J. Nutr. 132: 2845S–2850S, 2002.

KEY WORDS: • *vitamin A deficiency* • *recommendations* • *assessment* • *control*

The XX International Vitamin A Consultative Group (IVACG)[4] meeting in Hanoi was an opportunity to celebrate 25 y of effective gatherings and the first meeting in two decades to comprehensively review and revise policy and programmatic recommendations.

Background

The first modern series of comprehensive recommendations for the control of vitamin A deficiency (VAD) were developed at an international conference held in Jakarta, Indonesia, in 1974 (1). These recommendations were refined and codified at the second IVACG meeting, in Port-au-Prince, Haiti, 2 y later (2). The last comprehensive series of recommendations was issued two decades ago (3). Since then, IVACG and other organizations have periodically issued "policy statements," "guidelines" and "recommendations" on an ad hoc basis.

After the XIX IVACG meeting in Durban, South Africa, IVACG's Steering Committee, chaired by A. Sommer, developed a formal strategy for comprehensively reviewing issues pertinent to the control of VAD, particularly assessment tools and intervention strategies, in light of the large amount of relevant data that had become available over the past 20 y. This coincided with plans by the Food and Nutrition Board of the U.S. Institute of Medicine to issue new dietary guidelines (4) and a decision by the World Health Organization (WHO) to convene a meeting at Yverdon-les-Bains on the appropriate use of vitamin A supplements (5).

[1] Presented at the XX International Vitamin A Consultative Group (IVACG) Meeting, "25 Years of Progress in Controlling Vitamin A Deficiency: Looking to the Future," held 12–15 February 2001 in Hanoi, Vietnam. This meeting was co-hosted by IVACG and the Local Organizing Committee of the Vietnamese Ministry of Health and representatives of United Nations technical agencies, the private sector, multilateral agencies and nongovernmental organizations in Vietnam, with funding from the government of Vietnam. The Office of Health, Infectious Disease and Nutrition, Bureau for Global Health, U.S. Agency for International Development, assumed major responsibility for organizing the meeting. Conference proceedings are published as a supplement to the *Journal of Nutrition*. Guest editors for the supplement publications were Alfred Sommer, Johns Hopkins University, Baltimore, MD; Frances R. Davidson, U.S. Agency for International Development, Washington; Usha Ramakrishnan, Emory University, Atlanta, GA; and Ian Darnton-Hill, Columbia University, New York, NY.

[2] Supported by U.S. Agency for International Development Cooperative Agreement HRN-A-00-97-00015-00, Sight and Life Research Institute and the Bill and Melinda Gates Foundation.

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[4] Abbreviations used: HPLC, high-performance liquid chromatography; IU, international unit; IVACG, International Vitamin A Consultative Group; U5MR, under-five mortality rate; UNICEF, United Nations Children's Fund; USAID, U.S. Agency for International Development; VAD, vitamin A deficiency; VADD, VAD disorders; WHO, World Health Organization; X1B, Bitot's spots; XN, night blindness.

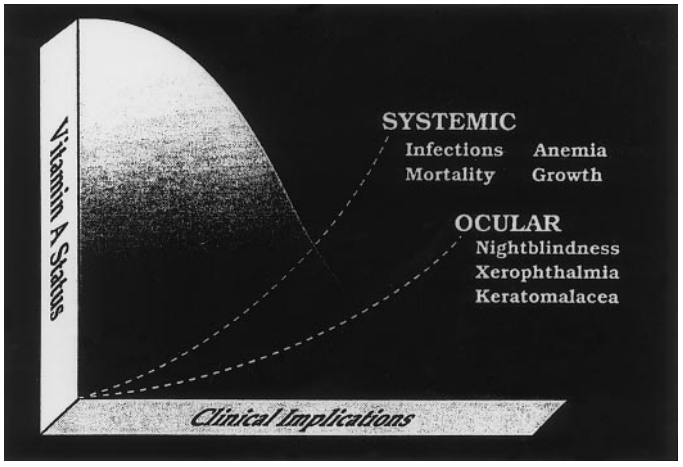

FIGURE 1 As vitamin A status declines, systemic consequences of VAD, including increased mortality, begin to occur even before the appearance of appreciable rates of clinical xerophthalmia.

THE ANNECY ACCORDS

"White papers" were commissioned from leading experts, who assembled at Les Pensieres, Fondation Marcel Mérieux in Annecy, France, for a week's deliberations (Appendix 1). Areas requiring further analysis were referred back to the originators and others, who gathered for final consideration and agreement on February 11, 2001, in Hanoi. These recommendations (the Annecy Accords) were presented for discussion and comment at the main plenary sessions of the XX IVACG meeting.

The IVACG Steering Committee concluded that the revised recommendations, and the rationale upon which they were based, were sufficiently important to warrant formal publication in a citable source, making the information more widely and permanently available than would a stand-alone meeting report.

The principal recommendations and conclusions, summarized below, are sufficiently concise and relevant to be of interest to policy makers and program managers. The background white papers, which are included in this supplement to the *Journal of Nutrition*, provide the rationale and the detailed data upon which they are based. These papers should serve the more demanding needs of scientists and technical advisors.

MAJOR CLARIFICATIONS AND REVISED RECOMMENDATIONS

Definitions and magnitude of the problem

A variety of terms have been used to characterize vitamin A status and its health effects. Three are sufficient to serve that purpose.

VAD: state of inadequate vitamin A nutriture. It is widely accepted that VAD begins when liver stores of vitamin A fall below 20 μg/g (0.07 μmol/g). Serum retinol levels may still be within the homeostatically regulated normal range. By convention, serum retinol levels <20 μg/dL (0.70 μmol/L) are considered deficient, although in most well-nourished populations with "adequate" stores, average serum retinol levels generally exceed 30 μg/dL (1.05 μmol/L) (6,7).

VAD disorders (VADD): physiologic disturbances secondary to VAD. These may be subclinical (e.g., impaired iron mobilization, disturbed cellular differentiation, depressed immune response) or clinical (increased infectious morbidity and mortality, growth retardation, anemia, xerophthalmia). VADD begins long before the onset of xerophthalmia, although the prevalence and severity of these disorders, including increased mortality, increase with the severity of deficiency (**Fig. 1**) (8,9).

Xerophthalmia: clinically evident ocular manifestations of VAD. These include night blindness (XN) through corneal ulceration and keratomalacia (X3) (**Table 1**). For the past 15 y, the nonocular, systemic manifestations of VAD have often been misleadingly referred to as "subclinical." There is nothing subclinical about death, severe infection and anemia. The term "subclinical" should be used only to describe physiologic or cellular disturbances that fit this precise, restricted definition.

Magnitude of the problem

Extrapolations from the best available data suggest that 140 million preschool-aged children and >7 million pregnant women suffer from VAD every year; 1.2–3 million children and significant numbers of women die unnecessarily, and another 4.4 million children and 6.2 million women suffer from xerophthalmia (10). Nearly half of all VAD and xerophthalmia occurs in South and Southeast Asia.

Population assessment

The purpose of population assessment is to determine the extent and severity of VAD in the population. Government officials ultimately must decide when, and at what level of severity, deficiency constitutes "a significant public health problem." In some countries, a single case of keratomalacia presenting to the hospital, or a small cluster of cases of XN, might be sufficient justification for immediate investigation and appropriate intervention. Other countries will desire more compelling, quantitative assessment. WHO and IVACG previously recommended population-based criteria that should elicit a public health response (3,9).

The Annecy and Hanoi Meetings rigorously reviewed candidate criteria with the view to increasing their validity, simplifying assessment and clarifying interpretation. Although the previous criteria remain valid, greater emphasis is placed on a new criterion (XN during pregnancy). Standards for the primary biochemical criterion, plasma retinol concentration, are revised to increase its reliability, and a simple, indirect marker is suggested that can indicate the need to conduct a formal, population-based assessment.

XN during pregnancy

XN during the latter part of pregnancy is exceedingly common in populations known to be vitamin A deficient by

TABLE 1

Xerophthalmia classification (3,9)

XN	Night blindness
X1A	Conjunctival xerosis
X1B	Bitot's spots
X2	Corneal xerosis
X3A	Corneal ulceration/keratomalacia (involving less than one third of the corneal area)
X3B	Corneal ulceration/keratomalacia (involving one third or more of the corneal area)
XS	Corneal scar (from X3)
XF	Xerophthalmic fundus

traditional criteria (11). A woman's history of having experienced XN at some point during her last pregnancy that resulted in a live birth (within the past 3 y) is likely to be even more accurate than questioning parents about XN in their preschool-aged children. In well-nourished populations, the prevalence of a positive history of XN during pregnancy consistently falls well below 3%. Among populations in which deficiency is a problem, the rate exceeds 5% and often 10%. The minimal prevalence criterion for VAD is therefore set at 5% (**Table 2**). The prevalence of XN during a recent pregnancy can be ascertained as part of demographic and health surveys.

Serum retinol

The only biochemical parameter validated and found practical for routine survey use is serum retinol concentration. Even so, reliable results require rigorous techniques and attention to detail.

Because severely depressed serum retinol concentrations (e.g., ≤0.35 μmol/L) are difficult to reproducibly and reliably detect in routine laboratory tests, the index has been raised to <0.70 μmol/L (20 μg/dL), double the concentration originally adopted in 1980 (3). Because more children will have these higher levels, the prevalence criterion has been raised from >5% to >15% (Table 2) (12).

High-performance liquid chromatography (HPLC) is considered the only laboratory technique sufficiently reliable for routine use and reporting. When HPLC is not available, assessment should be limited to clinical criteria.

Appendix 2 details sample size selection and interpretation of prevalence criteria.

Under-five mortality rate (U5MR)

The clinical and biochemical criteria listed above (Table 2) directly reflect vitamin A status. A surrogate indicator may alert countries that have not yet investigated the extent and severity of VAD among their population(s) that they need to do so. U5MR can serve this purpose. It is readily available for most countries and, when studied, populations of countries

TABLE 2

Prevalence criteria indicating significant VAD within a defined population (revised 2001)[1]

Criteria	Prevalence (%)
Clinical[2]	
Children 2–5 y old[3]	
Night blindness (XN)[4]	>1.0
Bitot's spots (X1B)[5]	>0.5
Corneal xerosis (X2) and corneal ulcers (X3)[6]	>0.01
Corneal scars (XS)[6]	>0.05
Women of childbearing age	
XN during recent pregnancy[7]*	>5.0
Biochemical[8]	
Serum retinol <0.70 μmol/L (20 μg/dL)*	>15

* Revised or added in this revision.

[1] A defined population is the group from which the sample surveyed was selected. It may be representative of a group of villages, a region, a province or an entire nation.

[2] In the past, clinical prevalence criteria were restricted to young children. Although these remain valid, the prevalence of a history of night blindness (XN) during a past pregnancy may be more practical, because it is simple to collect, it is reliable and it requires a relatively small sample size (because of its higher prevalence in deficient populations).

[3] The vitamin A status of preschool-aged children is particularly crucial, because very young children are most likely to be deficient and the youngest children experience the highest mortality. Ideally, childhood prevalence criteria should be restricted to children 2–5 y of age. XN is often not apparent in younger children, while Bitot's spots (X1B) in older children are often remnants of previous deficiency. Even the biochemical criterion, serum retinol, is more reliable in this age group: evidence suggests serum retinol levels in neonates may be homeostatistically maintained at lower levels.

[4] In assessing the presence or absence of XN in a child, attempts should be made to identify one or more locally appropriate terms (often translated as "chicken eyes" or "chicken blindness") before resorting to a description of the clinical condition. Where such a term exists, the recognition is likely to be more reliable. Exclude cases from both the numerator and the denominator if they are also said to be "blind" during daylight, because vitamin A deficiency may not be the cause of their "blindness."

[5] X1B are not always responsive to improvement in vitamin A status. In assessing a recent change in vitamin A status in the population, the incidence of new cases is more reliable than a change in prevalence, until such time as those who already had X1B at the baseline assessment have grown too old to remain in the sample. This same caveat is even more true for the prevalence of corneal scars (XS). Because these are permanent, their prevalence can only decline after children with pre-existing scars die or grow too old to remain in the sample.

[6] Corneal xerosis (X2), corneal ulcers (X3), and corneal scars (XS)—the sequelae of X3—are exceedingly rare and unlikely to be discovered in the course of representative population surveys (see Appendix 2). X2 and ulcers are transient conditions, associated with extremely high mortality.

[7] A history of XN during a past pregnancy is obtained from all women of childbearing age. Rates relate to the presence or absence of XN during the women's most recent pregnancy that resulted in a live birth during the past 3 y (since XN is most common during the latter part of pregnancy, only include women who are reliably known to have experienced the third trimester—by having ended their pregnancy in a live birth). Women who have not completed a pregnancy that yielded a live birth within the past 3 y are excluded from the survey, as are women who claim to have been "night blind" **and** "day blind," since the cause of their "blindness" is less certain. The prevalence rate is therefore determined by the number of women who were night blind (and not also day blind) during their most recent pregnancy resulting in a live birth during the past 3 y (numerator), divided by the number of women who experienced a pregnancy ending with a live birth during the past 3 y (denominator). Women who claim to have had difficulty seeing during daylight hours should be excluded from both the numerator and the denominator. (Some African surveys have encountered extremely high rates of "night blindness" combined with "day blindness." The origins of this confusing result require investigation.) Most vitamin A intervention programs target young children. It is therefore possible for a program to be effective in improving children's vitamin A status without changing the prevalence of XN among adult, pregnant women.

[8] Plasma retinol determinations are only valid when carefully analyzed by HPLC.

TABLE 3

Schedule for routine high-dose vitamin A supplementation in vitamin A-deficient populations (5)

Population	Amount of vitamin A to be administered	Time of administration
Infants 0–5 mo	150,000 IU as three doses of 50,000 IU with at least a 1-mo interval between doses	At each DTP contact (6, 10, and 14 wk) (otherwise at other opportunities)
Infants 6–11 mo	100,000 IU as a single dose every 4–6 mo	At any opportunity (e.g., measles immunization)
Children 12 mo and older	200,000 IU as a single dose every 4–6 mo	At any opportunity
Postpartum women	400,000 IU as two doses of 200,000 IU at least 1 d apart	As soon after delivery as possible and not more than 6 wk later
	and/or 10,000 IU daily or 25,000 IU weekly	and/or during the first 6 mo after delivery

with high U5MR invariably prove to have significant VAD (13).

Analyses of existing data suggest that any country (or more localized population) with U5MR >50 is likely to have a vitamin A problem unless proven otherwise. Countries with U5MR between 20 and 50 may have a problem, and its presence or absence needs to be documented.

Physiologic disturbances that can be objectively assessed, especially evidence of abnormal dark adaptation, have shown promise as potentially practical tools for population assessment (14). They await additional field testing and experience.

Intervention programs

Dietary diversification. In theory, dietary strategies are the preferred solution to VAD in young children. But these have proved difficult to implement, and recent data and kinetic modeling indicate it is virtually impossible to correct widespread VAD by diet alone in developing countries where populations remain dependent on conventional plant-based foods.

The U.S. Institute of Medicine recently concluded that the bioavailability of provitamin A β-carotene from plant sources is only half that previously assumed (4). Studies in developing countries estimate that it takes 21 μg of β-carotene from a typical mixed plant diet of vegetables and fruits and 27 μg of β-carotene from green leafy vegetables to yield 1 μg of retinol equivalent. At these rates, it is impossible for young children to consume sufficient quantities of vegetables and seasonal fruits to overcome the inefficiencies of β-carotene conversion. Most developing areas of the world neither produce nor consume adequate β-carotene plant foods to achieve normal vitamin A status (15,16). As shown in calculated models, supplementing both mother and child is necessary to achieve near-normal vitamin A stores by 2 y of age (16).

This is an important conclusion with immense programmatic implications. It does not mean one should not strive to maximize β-carotene consumption by these children and their mothers. Women can eat larger quantities than can young children. Improved maternal vitamin A status will increase vitamin A concentration in breast milk, the single most important source of vitamin A for young children. Maximizing dietary vitamin A intake by children will reduce the amount that needs to be supplemented, but dietary modification is not a strategy that can normalize vitamin A status on its own.

Supplementation and fortification. Wealthy, well nourished populations have achieved vitamin A sufficiency to a significant extent through diets that contain animal (and dairy) products rich in preformed vitamin A, usually augmented by fortification of commonly consumed dietary items and consumption of multivitamin supplements (15,17).

Periodic supplementation is the most widely implemented intervention for controlling VAD in the developing world. A recent WHO-sponsored multicountry study (18) indicated that the currently recommended supplementation schedule for postpartum women and young infants is inadequate to sustain adequate (or even improved) vitamin A status among children beyond 6 mo of age. Clinical trials and kinetic modeling (16,19,20) indicate that supplements in larger doses should increase vitamin A status of infants and young children at minimal risk. IVACG therefore endorses the recommendation (5,21) that the dosing schedule be revised as shown in **Table 3**. New mothers should receive 400,000 international units (IU), split between two doses given at least 1 d apart, within 6 wk of delivery; their infants should receive 50,000 IU at 6, 10 and 14 wk (which can conveniently be given at Expanded Program on Immunization contacts). These doses are entirely safe and may reduce VADD during the first 9 mo of life, but they represent a small amount of the total vitamin A a child needs.

Concerns expressed about possible consequences to older children inadvertently receiving too frequent dosing (e.g., 200,000 IU regularly every 4–6 mo, in addition to doses they may receive when presenting severe protein-energy malnutrition, measles or severe diarrhea) are unwarranted. Kinetic studies indicate that 1-y-olds will not develop toxic levels even if they receive a large dose every month (20). The most common problem is inadequate provision of vitamin A; rarely, if ever, is too frequent dosing a problem.

Fortification of a dietary item commonly consumed by the target group can significantly reduce the prevalence and severity of VAD. However, political, regulatory and trade barriers can prove formidable and require thoughtful attention (22).

Genetically modified crops provide a new approach to increasing β-carotene content and/or bioavailability of vitamin A and provitamin A carotenoids from plant foods. Early attempts to date have provided "proof of concept," but the issue requires a great deal more study and evaluation before this promising technology becomes a viable, additional intervention strategy (23).

Whatever vitamin A intervention programs are selected, they require rigorous and repeated evaluation to ensure they are achieving their goal (24).

CONCLUSION

IVACG's primary mission is to advance global understanding of VAD and enhance efforts for its control. It has had a distinguished 25-y history in helping to achieve this goal (25). This XX IVACG meeting used the best available science to rationalize and simplify existing recommendations for identifying populations with VAD and dealing effectively with the problem. It is hoped that these recommendations will prove

even more practical and helpful than those they replace and make for more effective and efficient control programs.

ACKNOWLEDGMENT

Joanne Katz calculated the sample size requirements of Table 4.

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APPENDIX 1: PARTICIPANTS IN ANNECY WORKSHOP

Participants in Annecy workshop, Les Pensieres, Fondation Marcel Mérieux, October 30 to November 2, 2000

Dr. Lindsay Allen, University of California, Davis
Mr. David Alnwick, United Nations Children's Fund
Dr. Paul Arthur, Kintampo Health Research Center, Ghana
Dr. Martin W. Bloem, Helen Keller International
Dr. Nathan Congdon, Johns Hopkins University
Dr. Omar Dary, Institute of Nutrition for Central America and Panama, Guatemala
Dr. Frances R. Davidson, U.S. Agency for International Development (USAID)
Dr. Saskia de Pee, Helen Keller International/Wageningen University
Dr. Bruno de Benoist, WHO
Dr. Martin Frigg, Task Force Sight and Life
Dr. Duff G. Gillespie, USAID
Dr. Suzanne S. Harris, International Life Sciences Institute
Ms. Cheryl E. Malanick, USAID
Dr. Jose O. Mora, International Science and Technology Institute
Dr. Sonya Rabeneck, United Nations Administrative Committee on Coordination/Subcommittee on Nutrition
Dr. Vinodini Reddy, Hyderabad, India
Dr. David A. Ross, MEMA kwa Vijana Project and Wellcome Trust
Dr. Werner Schultink, United Nations Children's Fund
Mr. Ram K. Shrestha, Nepali Technical Assistance Group
Dr. Suttilak Smitasiri, Mahidol University at Salaya
Dr. Florentino Solon, Nutrition Center of the Philippines
Dr. Alfred Sommer (Chairman), Johns Hopkins University
Mr. Aminuzzaman Talukder, Helen Keller International
Dr. Kraisid Tontisirin, Food and Agriculture Organization
Dr. Anna Verster, WHO/Eastern Mediterranean Regional Office
Dr. Emorn Wasantwisut, Mahidol University, Thailand
Dr. Clive E. West, Wageningen University
Dr. Keith P. West, Jr., Johns Hopkins University
Dr. Stanley H. Zlotkin, The Hospital for Sick Children, Toronto

Participants at concluding session only (November 2, 2000)

Ms. Marion Kelly, U.K. Department for International Development
Dr. Sally Stansfield, Bill and Melinda Gates Foundation
Dr. Shakuntala Thilstead, The Royal Veterinary and Agricultural University, Denmark

Additional participants at Annecy follow-up session (February 11, 2001, Hanoi)

Dr. Parul Christian, Johns Hopkins University
Dr. Nguyen Chi Dung, Scientific Technology Guidance/Ophthalmology
Dr. Jean Humphrey, Johns Hopkins University
Dr. Nguyen Cong Khan, National Institute of Nutrition/Vietnam
Professor Ha Huy Khoi, National Institute of Nutrition/Vietnam
Dr. Roy Miller, MOST Project
Dr. Usha Ramakrishnan, Emory University

APPENDIX 2: POPULATION ASSESSMENT: COLLECTION AND INTERPRETATION OF PREVALENCE DATA

Prevalence surveys are a proven approach to assessing the vitamin A status of a defined population. The population of interest may be a group of villages, a region, a province or an entire nation. Given geographic variations in dietary practices, weather patterns and infectious diseases, vitamin A status may vary considerably within a single political entity.

Ideally, surveys will be targeted to areas at highest risk, with sufficient numbers of participants to detect significant deficiency in localized populations. A cluster of significant deficiency needs to be identified and acted upon, even if other defined groups are better nourished and pooled prevalence rates for the country as a whole do not exceed the recommended prevalence criteria for a significant problem.

Sample size requirements

The number of individuals who need to be surveyed (e.g., sample size) for each defined population of interest depends on the certainty with which one wishes to be able to detect deficiency (if it exists), the prevalence rate established as the criterion and the actual rate in that population (e.g., the rate you would find if you examined every eligible person, instead of a sample of the population).

Table 4 provides an estimate of the number of individuals who need to be examined to have an 80% likelihood of exceeding the recommended prevalence criterion if the actual rate among all eligible participants is "somewhat" or "considerably" greater. For a 90% probability of detecting rates that exceed the prevalence criterion, the number of participants needed (sample size) is larger.

TABLE 4

Sample size requirements for detecting rates exceeding the relevant prevalence criterion

Criterion for deficiency	Actual prevalence anticipated in the population (%)	Sample size required for probability of detection: 80%	Sample size required for probability of detection: 90%
XN among children 2–5 y:			
1.0%	1.50	418	968
	1.75	216	495
X1B among children 2–5 y:			
0.50%	1.00	280	649
	1.50	105	242
Serum retinol <0.70 μmol/L among children 2–5 y:			
15.0%	17	249	578
	20	46	105
XN (by history) during last pregnancy: 5.0%	6.5	191	443
	8.0	58	134

TABLE 5

Suggested criteria and sample sizes for population assessment

Criterion	Sample size
Children 2–5 y: XN (1.0%); X1B (0.5%)	500
Women with completed pregnancy during past 3 y: XN (5%)	130
Children 2–5 y with serum retinol <0.70 μmol/L (15%)	60

For example, if the actual prevalence of XN among all children 2–5 y old were 1.5%, 418 children would need to be examined to be 80% certain the rate detected among this sample was found to be 1.0% or greater. To be 90% certain of exceeding the 1.0% criterion in the sample when the actual rate in the entire eligible population is 1.5%, a sample size of 968 children would need to be examined (Table 4).

Government officials and others considering conducting population assessment surveys will decide which criterion is most useful, which is most practical, and the number and size of the population units for which they would like to estimate vitamin A status (e.g., for each village, district or province, or for the country as a whole). A survey of the required sample size needs to be conducted for each defined population of interest. For example, if information is desired for each of a country's 12 districts, then an adequate sample size is needed for each of the 12 districts (e.g., 418 children ages 2–5 y from each of the 12 districts if childhood XN is chosen as the prevalence criterion).

Although any appropriate sample size might be selected, for the purposes of simplicity and practicality, the following guidelines are suggested (**Table 5**).

1. For clinical criteria among children 2–5 y old, 500 children be included. This will have a reasonable likelihood of exceeding the criterion for XN (the actual prevalence generally exceeds 1.5%) and X1B (the actual prevalence generally exceeds 1.0%).

2. For the serum retinol criterion, at least 60 children should be studied. The prevalence of serum retinol <0.7 μmol/L in affected childhood populations generally exceeds 25%.

3. For XN during a recent pregnancy, 130 women who delivered a live birth within the past 3 y should be included, because the rates in most countries studied usually exceed 7.0%.

As with any sample survey, every effort must be made to ensure that the sample selected is representative of the entire defined population it is meant to reflect.