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## *Chapter 4*

### VITAMIN A DEFICIENCY

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#### SUMMARY

Vitamin A deficiency is a common form of micronutrient malnutrition affecting 21.1% of preschool-age children and 5.6% of pregnant women worldwide.

The published literature linking vitamin A interventions to cause-specific child mortality due to measles, diarrhoea, malaria and other infectious diseases and to all-cause maternal mortality was comprehensively reviewed. Randomized controlled trial data of vitamin A interventions and survival were used to estimate the risk of mortality associated with vitamin A deficiency. The published relative risks were adjusted for the estimated prevalence of deficiency at study baseline. Summary relative risks were calculated from meta-analyses (for measles, diarrhoea, and other infectious disease causes of child mortality) or from single studies (malaria mortality among children and all-cause maternal mortality).

The estimated relative risks associated with vitamin A deficiency in children were 1.86 (95% CI 1.32–2.59) for measles mortality, 2.15 (95% CI 1.83–2.58) for diarrhoea mortality, 1.78 (95% CI 1.43–2.19) for malaria mortality, 1.13 (95% CI 1.01–1.32) for other infectious disease mortality and 4.51 (95% CI 2.91–6.94) for all-cause maternal mortality.

The available evidence suggests that nearly 800 000 deaths worldwide can be attributed to vitamin A deficiency among women and children. Approximately 20–24% of child mortality from measles, diarrhoea and malaria and 20% of all-cause maternal mortality can be attributed to this preventable condition. Africa and South-East Asia have the highest burden of disease.

## 1. INTRODUCTION

The objective of this chapter is to summarize the available evidence that can be used to *quantitatively* estimate the risk of adverse health outcomes associated with vitamin A deficiency and to calculate the associated burden of disease for different regions of the world. Vitamin A is an essential nutrient required for maintaining immune function, eye health, vision, growth and survival in human beings. Over the years, numerous studies have been conducted to identify the biological functions of vitamin A, the health consequences associated with deficiency, and the mechanisms that explain these relationships. Causal relationships have been clearly demonstrated in some instances and comprehensive reviews on the subject have been published (Sommer and West 1996).

According to World Bank estimates, vitamin A supplementation for preschool-age children is one of the most cost-effective child survival interventions (World Bank 1993). National level public health programmes to prevent and treat vitamin A deficiency are currently being implemented in countries in Asia, Africa and elsewhere. International donors and agencies including the Canadian International Development Agency (CIDA), United Nations Children's Fund (UNICEF), the United States Agency for International Development (USAID), the World Health Organization (WHO) and others have actively supported both national and global level initiatives to raise awareness about the problem of vitamin A deficiency and to promote efforts to implement effective and affordable solutions (Mason et al. 2001). Reducing the prevalence of vitamin A deficiency will lessen disease burden by improving immune function, lowering mortality rates and preventing blindness, especially among children. This chapter will contribute to ongoing efforts to assess the global problem of vitamin A deficiency by using existing data to estimate global prevalence rates, to identify and quantify the adverse health consequences associated with deficiency, and to estimate the future health benefits that could be gained by implementing even more effective control programmes.

## 2. DEFINITION OF MALNUTRITION AND VITAMIN A DEFICIENCY

Malnutrition is a complex phenomenon. Broadly defined, malnutrition refers to the condition of inappropriate nutrition. In the past, discussions of malnutrition in the context of health issues in low-income countries often used this term to refer to the condition of "undernutrition" associated with what was presumed to be protein-energy malnutrition and operationally defined as a deficit in anthropometric status or by the presence of clinical signs such as oedema or altered hair colour. In more recent years, various vitamin and mineral deficiencies, including vitamin A, iron, iodine and zinc have been recognized as discrete types of mal-

nutrition that adversely affect human health and contribute to disease and mortality. Some of these nutrients affect closely related biological systems; for example both vitamin A and zinc play important roles in maintaining different aspects of immune function (Shankar 2001) and both vitamin A and iron affect haemoglobin metabolism (Semba and Bloem 2002). Ecological-level studies have demonstrated that the prevalence of these micronutrient deficiencies are high in many of the same countries, thus many individuals may suffer from multiple micronutrient deficiencies at the same time. However, relatively few data are currently available for quantifying either the joint distribution of multiple deficiencies or the impact that multiple micronutrient deficiencies have on specific health outcomes. Therefore, the comparative risk assessment (CRA) project will estimate the separate contribution of these risk factors to the global burden of disease. Individual reviews are available for the risk factors of iron deficiency (chapter 3), zinc deficiency (chapter 5) and underweight status (chapter 2) in addition to vitamin A deficiency, which is the subject of the current chapter.

Vitamin A is an essential nutrient required for maintaining immune function, eye health, vision, growth and survival in human beings (National Research Council 1989). Although animal studies that identified vitamin A as a necessary factor for rat growth were conducted in the early 1900s and the chemical structure of the vitamin was elucidated over 20 years later, reports describing the link between xerophthalmia (signs in the eye of disease due to a severe lack of the vitamin) and successful treatment with animal liver (a rich source of the vitamin) date back to the medical writings of ancient Egypt (Olson 1996).

At present, vitamin A deficiency remains a widespread public health problem, especially in countries of South Asia and Africa. Globally, preschool-age children and women of reproductive age are the two population groups most commonly recognized to be at risk of this nutritional deficiency and its adverse health consequences. A combination of chronically lower than required dietary intakes of vitamin A-rich foods (eggs, milk, liver, deep orange fruits and dark green leafy vegetables, etc.) combined with malabsorption and increased vitamin A excretion rates associated with some common illnesses places many women and children at risk of developing vitamin A deficiency (Christian et al. 1998b; IVACG 1997; Sommer and West 1996; Stephensen 2001).

No single indicator can be reliably used to assess the full spectrum of vitamin A deficiency. Different aspects of vitamin A status are assessed using clinical indicators, biochemical indicators, functional indicators and histological indicators (WHO 1996). In humans, vitamin A is stored almost exclusively (>90%) in the liver and some investigators propose liver and/or total body stores as a primary indicator of vitamin A status. Although recent isotope dilution techniques to indirectly measure liver vitamin A stores have yielded promising results (Haskell et al. 1999;

Ribaya-Mercado et al. 1999) these techniques have not yet been used in large-scale population-based surveys.

Severe vitamin A deficiency can be identified by the presence of the classical eye signs of xerophthalmia in individuals. However, because severe vitamin A deficiency is relatively rare in most populations, a large number of individuals must be surveyed in order to generate a reliable prevalence estimate. Depending on the severity of vitamin A deficiency in a population, the sample size requirement for a xerophthalmia survey may be nearly ten times higher than what would be required to generate a reliable prevalence estimate for other indicators of vitamin A status, such as low serum retinol concentrations, which may occur more frequently in the same population (Sommer and Davidson 2002; WHO 1996).

Milder vitamin A deficiency is far more common, but the assessment of vitamin A deficiency that does not result in relatively easily observable eye signs is also more problematic. One way to identify milder forms of vitamin A deficiency is to collect blood samples and measure the concentration of circulating serum retinol in an individual. Values  $<0.70\ \mu\text{mol/l}$  have traditionally been considered indicative of deficiency in children, based on empirical data from population-based studies that did not exclude individuals based on measurements of acute phase proteins. In adults, appropriate cut-off levels are less firmly established, but values  $<0.70\ \mu\text{mol/l}$  and  $<1.05\ \mu\text{mol/l}$  have been used for different purposes. Because serum retinol concentrations are transiently depressed during the acute phase response to certain infections, some investigators have questioned the validity of using this indicator to assess the vitamin A status of individuals (Stephensen 2001). However, determining the prevalence of serum retinol concentrations below a defined cut-off point remains one of the most commonly used and widely accepted approaches for assessing the vitamin A status of entire populations (Sommer and Davidson 2002).

At the population level, the prevalence of vitamin A deficiency can be determined based on the prevalence of either: (i) night blindness, usually obtained by verbal recall; (ii) other eye signs of xerophthalmia (Bitot's spots or corneal lesions); or (iii) biochemical indicator values (serum retinol, breast milk retinol, relative dose-response test, modified relative dose-response test, or serum 30-day response), or histological indicator values (conjunctival impression cytology [CIC] that fall below a defined cut-off point (WHO 1996). Until recently the majority of nationally representative, large-scale surveys related to vitamin A deficiency were conducted primarily among preschool-age children. However, in the past few years some large-scale surveys, including recent demographic and health surveys, have also attempted to estimate the prevalence of night blindness among pregnant women. More limited survey findings are available for serum and breast milk retinol concentrations among women. Surveys that included data on any or all of the indicators listed above were used

as a basis for estimating the global prevalence of vitamin A deficiency as a risk factor for the CRA project. The categorical definitions chosen to represent “vitamin A deficiency” among children (aged 0–4 years) and women (aged 15–44 years) for the CRA project are described in the following sections. A description of the data, indicators, and the process used to estimate the current prevalence of vitamin A deficiency among preschool-age children and pregnant women is presented in section 3.5.

## 2.1 DEFINITIONS FOR CHILDREN (0–4 YEARS)

Globally, the most reliable population-based survey data provide estimates of vitamin A deficiency among children aged <5 years, primarily because this is the most well-established high-risk age group for this nutritional risk factor. In the CRA project prevalence estimates have been developed only for the 0–4-year age group, although there is some evidence that slightly older children also suffer from vitamin A deficiency and its adverse health consequences.

In order to calculate the attributable fraction of an adverse health outcome that is due to a risk factor, compatible definitions must be used when estimating the relative risk of the adverse outcome associated with the risk factor and the prevalence of the risk factor itself in a population. This stringent requirement for a compatible definition greatly influenced the data that were suitable for use in the CRA project. The majority of large-scale vitamin A intervention trials involving preschool-age children have been mortality studies that assumed (but did not confirm for all participants) that the children were mildly deficient (i.e. had low serum retinol concentrations). In general, very few participants in those studies exhibited eye signs of xerophthalmia, which is consistent with the expected epidemiological pattern of vitamin A deficiency. Vitamin A receipt was associated with a lower relative risk of adverse outcomes in those trials, even among children who had no eye signs of deficiency.

After considering the availability of intervention trial data and global prevalence data for vitamin A deficiency among preschool-age children, a definition of vitamin A deficiency related to low serum retinol concentrations among children in the 0–4-year age range emerged as the most appropriate choice for use in the CRA project:

- Vitamin A deficient: serum retinol concentration  $<0.70\ \mu\text{mol/l}$ .
- Vitamin A sufficient: serum retinol concentration  $\geq 0.70\ \mu\text{mol/l}$ .

## 2.2 GLOBAL PREVALENCE ESTIMATES FOR CHILDREN

The 1995 WHO report *Global prevalence of vitamin A deficiency* included prevalence estimates of vitamin A deficiency among preschool-age children for two classes of indicators: (i) clinical eye signs of disease (xerophthalmia); and (ii) low serum retinol concentrations. However, data were reported only for the individual countries that met the defini-

tion of a significant public health problem, which was defined as a population prevalence of low serum retinol ( $<0.70\mu\text{mol/l}$ )  $\geq 10\%$ , of night blindness (XN)  $>1\%$ , of Bitot's spots (X1B)  $>0.5\%$ , of corneal xerosis and/or ulceration (X2, X3A, X3B)  $>0.01\%$ , or of xerophthalmia-related corneal scars (XS)  $>0.05\%$  (WHO 1995). Estimates for countries that did not meet those definitions were not incorporated into the global prevalence estimate. A global estimate for the total number of children at risk of vitamin A deficiency (~254 million) was generated by adding the estimated number of children with low serum retinol concentrations (~251 million) and the estimated number with clinical eye signs of vitamin A deficiency (~3 million).

In 1998, the Micronutrient Initiative, UNICEF and Tulane University published a joint report reviewing the recent progress of vitamin A intervention programme activities (Micronutrient Initiative/UNICEF/Tulane University 1998). To generate prevalence estimates for vitamin A deficiency among children, this group used a different approach and developed a modelling process that attempted to take into account the effects of time trends and vitamin A intervention programmes. Data from a subset of countries that had conducted prevalence surveys since the mid-1980s were used to estimate the regional and global prevalence of vitamin A deficiency among children. The number of children affected by low serum retinol concentrations was estimated to range from 75 to 140 million, while the number of children with clinical eye signs of deficiency was estimated as 3 million. The sizeable discrepancy in the estimated prevalence of vitamin A deficiency from these two sources, 254 million and 78 to 143 million children, respectively, was due in part to differences in the data and methodology used, but also to a calculation error in the WHO report (West 2002).

An updated estimate for the global prevalence of vitamin A deficiency in children appears in the 2002 publication *Extent of vitamin A deficiency among preschool children and women of reproductive age* (West 2002), hereafter referred to as the 2002 West report. A brief description of the methodology used in developing the estimate is described in this chapter in section 3.5. Those prevalence data served as the basis for calculating the global burden of disease attributable to vitamin A deficiency among children aged 0–4 years for the CRA project.

### 2.3 DEFINITIONS FOR PREGNANT WOMEN (15–44 YEARS)

In recent years, women of reproductive age have increasingly been recognized as an important group at risk of vitamin A deficiency and the adverse health outcomes associated with this condition (West 2002). However, when compared to preschool-age children, far less information is available to quantitatively estimate the burden of disease among women. Current areas of active research include assessing the magnitude of the problem, investigating the causes of deficiency in women, describing the range of associated adverse health outcomes, and identifying

appropriate interventions for preventing and treating vitamin A deficiency.

Standardized indicators and definitions of vitamin A deficiency among women are only beginning to be developed. To date, relatively few large-scale surveys have been conducted to estimate the prevalence of vitamin A deficiency in women—primarily in Asia and Africa. Although many surveys used the presence of night blindness as an indicator of poor vitamin A status among women, some survey data related to low serum retinol and breast milk vitamin A concentrations are also available. However, very few studies have been conducted to date that quantitatively relate the risk of vitamin A deficiency (defined by any indicator) to adverse health outcomes in women. Despite the inherent limitations in the current data related to vitamin A deficiency in women, the evidence was considered strong enough to generate initial estimates of the related global burden of disease. Further work in this area of research will certainly lead to a refinement of these estimates.

The requirement to have a compatible definition of vitamin A deficiency for estimating the relative risk of adverse health outcomes and the global prevalence of vitamin A deficiency among women determined which data were suitable for use in the CRA project. After considering the availability of intervention trial data and global prevalence data for vitamin A deficiency in women, a definition related to low serum retinol concentrations among pregnant women in the 15–44-year age range emerged as the most appropriate choice for use in the CRA project.

Estimates for the prevalence of vitamin A deficiency have been generated only for pregnant women in the 15–44-year age range primarily because the strongest information is available for this particular group of women. Future projects that quantify the global burden of disease may include non-pregnant and older women as well, if stronger data have become available for quantitatively estimating the prevalence of deficiency and adverse health outcomes in these groups. Vitamin A deficiency in pregnant women aged 15–44 years was operationally defined as:

- Vitamin A deficient: Serum retinol concentration  $<0.70\mu\text{mol/l}$ .
- Vitamin A sufficient: Serum retinol concentration  $\geq 0.70\mu\text{mol/l}$ .

#### 2.4 GLOBAL PREVALENCE ESTIMATES FOR PREGNANT WOMEN

The first comprehensive estimate for the global prevalence of vitamin A deficiency among women of reproductive age appeared in the 2002 West report (West 2002). A brief description of the methodology used in developing the estimate has been described in this chapter in section 3.5. Those prevalence data will serve as the basis for calculating the global burden of disease attributable to vitamin A deficiency among pregnant women aged 15–44 years for the CRA project.

### 3. ADVERSE HEALTH OUTCOMES CONSIDERED FOR REVIEW

Within the framework of the larger Global Burden of Disease (GBD) project, health states (in this case vitamin A deficiency) can contribute directly or indirectly to death and disability. The total amount of death and disability attributed to vitamin A deficiency is therefore a sum of its direct and indirect effects. The direct contribution is measured by estimating the burden associated with the sequelae assigned to vitamin A deficiency as defined by the corresponding chapter in the International Statistical Classification of Diseases and Related Health Problems, tenth revision (ICD-10), whereas the indirect contribution is measured by considering vitamin A deficiency as a risk factor for other causes of death and disability.

Adverse health outcomes generally associated with micronutrient and mineral deficiencies were initially considered for review in relation to vitamin A deficiency. These included blindness; impaired cognitive function; impaired physical work capacity; morbidity (incidence and/or severity) due to diarrhoea, measles, acute respiratory infections, malaria and other infectious diseases; cause-specific mortality related to these diseases; and all-cause mortality. Outcomes potentially associated with vitamin A deficiency in pregnant women included fetal loss, low birth weight, preterm birth, all-cause infant mortality, maternal morbidity and maternal mortality.

#### 3.1 SELECTION CRITERIA FOR ADVERSE HEALTH OUTCOMES

The adverse health outcomes selected for review and inclusion in the CRA project were those that fulfilled the following criteria: (i) a health outcome included in the 2000 GBD study; (ii) a health outcome where data exist to support a probable causal relationship with vitamin A deficiency; and (iii) a health outcome where data were available to *quantitatively* estimate the relationship with vitamin A deficiency.

Blindness and an increased risk of all-cause mortality are two of the most well-established adverse outcomes associated with vitamin A deficiency in preschool-age children (Sommer 1982; Sommer and West 1996). According to recent estimates, vitamin A deficiency that leads to corneal scarring remains one of the most common preventable causes of childhood blindness in developing countries (Gilbert and Foster 2001). In the 1980s, vitamin A supplementation was shown to significantly reduce all-cause child mortality in a series of eight large-scale trials conducted in Asia and Africa. Meta-analyses of those trial data suggest a 23% to 34% reduction in all-cause mortality among children 6 months to 5 years of age (Beaton et al. 1993; Fawzi et al. 1993; Glasziou and Mackerras 1993; Tonascia 1993). Studies that provided vitamin A supplements to newborn infants immediately after birth have also demonstrated a reduction in mortality (Humphrey et al. 1996; Tielsch et al.

2001), although other trials involving vitamin A supplementation of young infants post-neonatally through five months of age have not shown a survival benefit (Anonymous 1998b; Daulaire et al. 1992; West et al. 1995).

Blindness was excluded as a health outcome from the risk factor analysis because in the GBD study, vitamin A-related blindness is considered to be a direct functional outcome of the deficiency, and the disability associated with blindness was measured in this manner (Murray et al. 1996a, 1996b). In the case of child mortality, the contribution of vitamin A deficiency to the global burden of disease was measured primarily through its contribution as a risk factor for several types of cause-specific mortality, rather than as a risk factor for all-cause mortality. However, a small number of child deaths have also been directly attributed to vitamin A deficiency in the GBD database, because vitamin A deficiency itself appears as the underlying cause of death in some vital registration data sets. For this specific cause of death, by definition, the total number of deaths in a subregion<sup>1</sup> was directly assigned the value obtained from the relevant child mortality statistics for that subregion (Murray et al. 2001). Thus, for the CRA project the total number of child deaths attributable to vitamin A deficiency is the sum of those that are directly and indirectly attributed to the deficiency.

Five outcomes potentially associated with maternal vitamin A deficiency during pregnancy were also excluded from the risk factor analysis because the outcomes were not assessed in the 2000 GBD study or the data were insufficient to quantitatively assess the risk of their occurrence. These were fetal loss, low birth weight, preterm birth, all-cause infant mortality and general maternal morbidity (Christian et al. 1998b, 2000, 2001; Katz et al. 2000; Semba et al. 1998). Impaired cognitive function and impaired physical work capacity were excluded from the analysis because there is little evidence to suggest a biologically plausible association with vitamin A deficiency, except for the condition of maternal night blindness, which appears to limit the time for performing household chores to daylight hours (Christian et al. 1998a). Although experimental animal data and observational human data suggest a biologically plausible role for vitamin A deficiency predisposing children to acute respiratory infections (Bloem et al. 1990; Milton et al. 1987; Sommer and West 1996; Sommer et al. 1987), morbidity and cause-specific mortality related to acute respiratory infections were excluded from the analysis because the data from controlled intervention trials in humans have not, to date, consistently revealed measurable effects of vitamin A on incidence, duration or severity of acute respiratory infections (Anonymous 1995).

After excluding those outcomes from the initial list of outcomes under consideration, the following remained for a more detailed review: (i) morbidity and mortality associated with measles in children; (ii) morbidity and mortality associated with diarrhoea in children; (iii) morbid-

ity and mortality related to malaria in children; (iv) selected other infectious disease causes of death in children (other than measles, diarrhoea, malaria or acute respiratory infections); and (v) all-cause maternal mortality. All-cause maternal mortality was a compilation of three separate conditions: maternal sepsis; maternal haemorrhage; and obstructed labour. These last three outcomes related to maternal mortality were selected from the limited number of maternal health conditions that are coded separately in the ICD-10 coding scheme.

The health outcomes selected for children aged <5 years represent the most common preventable causes of death among this age group (Murray et al. 2001). Although some studies have also explored the link between vitamin A and other specific infectious diseases coded as individual cause of death categories in the GBD study (for example helminthic infections and tuberculosis), the strength of the current evidence was considered insufficient to demonstrate a causal link and quantitatively estimate the associated risk with these specific outcomes. HIV/AIDS was also excluded as a quantifiable health outcome for the same reason. The findings relevant to the outcomes that were chosen for inclusion are presented below.

### 3.2 METHODS FOR IDENTIFYING RELEVANT STUDIES AND REVIEW MATERIALS

The following sources were initially consulted to identify relevant materials for this chapter: Medline database; published books about vitamin A, international health, and nutrition; International Vitamin A Consultative Group (IVACG) statements; meeting reports; abstracts and conference proceedings; and other non-peer reviewed literature sources related to vitamin A programme implementation and cost-effectiveness analyses. The Medline database was searched for literature published between 1966 and 2001 in English or with an English language abstract. Combinations of the following keywords were used: vitamin A, vitamin A deficiency, blindness, mortality, acute respiratory infection, pneumonia, diarrhoea, measles, malaria, stillbirth, fetal loss, miscarriage, low birth weight, women.

Abstracts of articles concerning the relationship between vitamin A deficiency in humans, intervention trials, and the health outcomes of interest were reviewed and copies of relevant articles were obtained. Additional publications and reference materials were identified from the citation lists in those sources and through discussions with investigators working in the field.

### 3.3 INCLUSION CRITERIA FOR INDIVIDUAL STUDIES

The individual studies and reports presented in this chapter were restricted to the results of controlled intervention trials because these findings provide strong evidence for a causal relationship and the data

can be used to quantify the risk associated with either documented or suspected vitamin A deficiency (Rothman and Greenland 1998). For the outcomes where published meta-analyses or international consensus statements from IVACG exist, the results from those sources have been included in this chapter rather than a detailed presentation of data from the individual trials.

### 3.4 DESCRIPTION OF EXCLUDED STUDIES

Numerous observational cohort studies, case-control studies, and case-series investigations have been conducted over the years to explore the relationships between vitamin A and morbidity or mortality from specific diseases in children. However, the results of those studies are not presented or discussed in detail in this chapter because such designs provide weaker evidence for a causal relationship as compared to randomized controlled intervention trials. Comprehensive reviews of the numerous cohort studies, case-control studies, and case-series reports related to various adverse health outcomes can be found elsewhere (Bauernfiend 1986; Sommer and West 1996). The findings from intervention studies related to vitamin A deficiency and child morbidity have also been summarized elsewhere (Nalubola and Nestel 1999).

### 3.5 ESTIMATING RISK FACTOR LEVELS

The prevalence of vitamin A deficiency (defined as serum retinol concentrations  $<0.70 \mu\text{mol/l}$ ) among children aged 0–4 years and pregnant women aged 15–44 years was estimated for each of the 14 subregions. This process involved several steps.

First, country-specific prevalence rates were estimated for each one of the 191 WHO Member States. Updated country-specific prevalence rates were obtained from the recent review, 2002 West report (West 2002), which includes the estimated prevalence and number of deficient children and pregnant women in countries where vitamin A deficiency is either documented or presumed to exist, based on non-population-based vitamin A status data or other indirect indicators. Since separate prevalence estimates were not reported for boys and girls, the same prevalence rate was applied to both of these groups in the CRA project analyses. Next, the prevalence of vitamin A deficiency for the countries not included in that review was assumed to be zero. A suitable database was created for analysis and the findings were summarized across the 14 subregions.

A detailed description of the methods used to compile the data for the 2002 West report appears in that document (West 2002), but a brief summary is presented here. In addition, a file that contains a complete listing of the contributing studies and technical notes associated with the 191 countries can be found at <http://www.jhsph.edu/chn/GlobalVAD.html>.

*DATA SOURCES*

A wide variety of data sources related to vitamin A deficiency were reviewed in order to obtain the most current information possible. These included: (i) the 1995 comprehensive survey report compiled by the WHO Micronutrient Deficiency Information System (MDIS) (WHO 1995); (ii) a 2001 update from the MDIS group at WHO that included national survey data published after 1995; (iii) the 1998 report published by the Micronutrient Initiative, UNICEF and Tulane University (Micronutrient Initiative/UNICEF/Tulane University 1998), which incorporated both the 1995 MDIS data and more recent country updates from 107 countries with UNICEF offices and programmes; (iv) published surveys and field studies that reported vitamin A status indicators in women or children; and (v) unpublished reports, meeting presentations and personal communication about recent field surveys and studies not included in other data sources.

*INDICATORS*

The 2002 West report presents prevalence data for xerophthalmia rates and serum retinol concentrations  $<0.70\mu\text{mol/l}$  among children and for night blindness rates and serum retinol concentrations  $<0.70\mu\text{mol/l}$  and  $<1.05\mu\text{mol/l}$  among populations of pregnant women. Since the CRA project only utilized serum retinol data, the methodology used to generate xerophthalmia estimates is not discussed further in this chapter.

In preschool-age children the prevalence of serum retinol concentrations  $<0.70\mu\text{mol/l}$  was directly estimated from survey data whenever possible. When such data were unavailable, the prevalence was assigned a value equivalent to the population prevalence of abnormal CIC results. Survey data referring to children in a narrower age than 0–4 years or surveys that included data that extended slightly beyond the fifth year of life were used as the prevalence estimate for children aged 0–4 years.

For pregnant women the prevalence of serum retinol concentrations  $<0.70\mu\text{mol/l}$  was directly estimated from appropriate survey data whenever possible. When such data were lacking, the prevalence was assigned a value equivalent to the prevalence among non-pregnant or lactating women in the early postpartum period or a value equivalent to the prevalence of breast milk retinol concentrations  $<1.05\mu\text{mol/l}$ . When serological or breast milk data were reported as a mean and SD, rather than as a prevalence rate, the prevalence was derived by assuming the data were normally distributed and calculating the standard normal deviate (*z*-score) and the probability associated with the area under the left tail of the normal curve.

*DATA EXTRAPOLATION*

Separate algorithms were developed for the different subregions of the world to estimate the country-specific prevalence estimates for serum retinol concentrations  $<0.70\mu\text{mol/l}$  among children and pregnant

women (West 2002). In brief, nationally representative survey data, as deduced from individual reports or stated as such from aggregate WHO or other agency reports, were reported whenever possible. In the absence of national level data, results from sub-national or smaller surveys were used and adjustment factors were applied following the precedent of previous analysts (Micronutrient Initiative/UNICEF/Tulane University 1998; WHO 1995), although the subjective weight may have changed from the previous reports owing to new or reinterpreted results for a country. For countries where no data were available, estimates were generated by extrapolation in situations where cultural, dietary, demographic, health and development patterns as well as existing rates of adult and child mortality suggested that vitamin A deficiency is likely to exist. Prevalence rates were extrapolated either by assigning a value from a nearby country with comparable characteristics (primarily in the WHO Region of South-East Asia) or by assigning a median value from neighbouring country national surveys. Prevalence estimates among preschool-age children were also adjusted downwards in countries where the survey data preceded coverage reports from recent vitamin A supplementation programmes that reported coverage rates >75%. The prevalence data for women were not adjusted to account for any potential programmatic impact, because although postpartum maternal vitamin A supplementation programmes are slowly emerging, programmes to prevent vitamin A deficiency during pregnancy are virtually non-existent in the developing world at the present time.

The 2002 West report did not generate prevalence estimates for countries where there was no plausible evidence to suggest the presence of vitamin A deficiency. Therefore, those subregional prevalence estimates do not reflect the contribution of other countries in the world that were assumed to have a 0% prevalence rate of serum retinol concentrations <0.70  $\mu\text{mol/l}$ . Over half of the countries assigned a 0% prevalence rate are located in the subregions classified as EUR-A, EUR-B, EUR-C or AMR-A, where child mortality rates are low (Murray et al. 2001).

The distribution of the 191 countries included in the CRA project is shown in Table 4.1 by the type of survey data used for estimating serum retinol prevalence rates <0.70  $\mu\text{mol/l}$  in children. To calculate subregional prevalence rates of serum retinol concentrations <0.70  $\mu\text{mol/l}$ , the number of affected individuals was totalled for the countries in each subregion and then divided by the subregional population base. For children <5 years of age, the population base was obtained from the *2001 State of the world's children report* (UNICEF 2001), which reported data for the year 1999. For pregnant women the annual number of live births was chosen to represent the population global base for pregnant women, and data were obtained from the same source (UNICEF 2001). The countries that were assigned 0% prevalence accounted for only approximately 17% of the base population of children (Table 4.2) and pregnant women (Table 4.3).

**Table 4.1** Distribution of 191 WHO Member States by population group for which the prevalence of serum retinol concentrations  $<0.70 \mu\text{mol/l}$  was estimated by subregion and type of data used to generate subregional prevalence estimates

Subregion	Population group						No available survey data, assigned 0% prevalence estimate	Imputed prevalence estimates $>0$	No available survey data, assigned 0% prevalence estimate	Imputed prevalence estimates $>0$			
	Children (0–4 years)			Pregnant women (15–44 years)									
	Total	National level data	Sub-national level data	Imputed prevalence estimates $>0$	Total	National level data	Sub-national level data	Imputed prevalence estimates $>0$	Total	National level data	Sub-national level data	Imputed prevalence estimates $>0$	No available survey data, assigned 0% prevalence estimate
AFR-D	26	5	7	14	26	1	5	20	26	1	5	20	0
AFR-E	20	10	7	3	20	3	7	10	20	3	7	10	0
AMR-A	3	0	0	0	3	0	0	0	3	0	0	0	3
AMR-B	26	9	2	0	26	0	2	9	26	0	2	9	15
AMR-D	6	4	1	1	6	0	1	5	6	0	1	5	0
EMR-B	13	1	1	0	13	0	0	0	13	0	0	0	13
EMR-D	9	2	3	4	9	1	3	5	9	1	3	5	0
EUR-A	26	0	0	0	26	0	0	0	26	0	0	0	26
EUR-B	16	1	0	0	16	0	0	0	16	0	0	0	16
EUR-C	9	0	0	0	9	0	0	0	9	0	0	0	9
SEAR-B	3	2	1	0	3	0	3	0	3	0	3	0	0
SEAR-D	7	3	0	3	7	2	2	3	7	2	2	3	0
WPR-A	5	0	0	0	5	0	0	0	5	0	0	0	5
WPR-B	22	5	2	9	22	2	2	12	22	2	2	12	6
World	191	42	24	34	191	9	25	64	191	9	25	64	93

**Table 4.2** Global prevalence of serum retinol concentrations <0.70 µmol/l among children aged <5 years, by subregion

Subregion	Countries with assigned prevalence estimates <sup>a</sup>			Countries with no assigned prevalence estimates (prevalence set to 0%)			Subregional and global totals			
	Countries	Children with serum retinol concentrations <0.70 µmol/l (000s)	Children <5 years (000s)	Prevalence of serum retinol concentrations <0.70 µmol/l (%)	Countries	Children <5 years (000s)	Children with serum retinol concentrations <0.70 µmol/l (000s)	Prevalence of serum retinol concentrations <0.70 µmol/l (%)		
AFR-D	26	13552	47653	28.4	0	NA	26	13552	47653	28.4
AFR-E	20	19853	56281	35.3	0	NA	20	19853	56281	35.3
AMR-A	0	NA	NA	NA	3	21886	3	0	21886	0.0
AMR-B	11	7010	38256	18.3	15	6565	26	7010	44821	15.6
AMR-D	6	1209	9319	13.0	0	NA	6	1209	9319	13.0
EMR-B	2	449	7412	6.1	11	9022	13	449	16434	2.7
EMR-D	9	12215	52406	23.3	0	NA	9	12215	52406	23.3
EUR-A	0	NA	NA	NA	26	21852	26	0	21852	0.0
EUR-B	1	45	152	29.5	15	17935	16	45	18087	0.2
EUR-C	0	NA	NA	NA	9	12565	9	0	12565	0.0
SEAR-B	3	13538	28434	47.6	0	NA	3	13538	28434	47.6
SEAR-D	7	42274	140575	30.1	0	NA	7	42274	140575	30.1
WPR-A	0	NA	NA	NA	5	8019	5	0	8019	0.0
WPR-B	16	17128	122006	14.0	6	3792	22	17128	125798	13.6
World	101	127273	502494	25.3	90	101636	191	127273	604130	21.1

NA Not applicable.

<sup>a</sup> Country-specific data used to estimate subregional prevalence rates were based on the review article "Global prevalence of vitamin A deficiency among preschool children and women of reproductive age" (West 2002). Technical notes and data for individual countries are located at [www.ijhsph.edu/chm/GlobalVAD.html](http://www.ijhsph.edu/chm/GlobalVAD.html). In the review article, the number of children with serum retinol concentrations <0.70 µmol/l in a country was either estimated based on existing survey data or imputed for countries where vitamin A deficiency was likely to exist based on cultural, dietary, demographic, health and development patterns as well as existing rates of child mortality. In order to calculate subregional and global prevalence rates for the CRA project, the prevalence estimate was set to 0% for the remaining 90 countries where no data on preschool child vitamin A deficiency or xerophthalmia were available, but childhood vitamin A deficiency was considered unlikely to exist. These are all classified as "A" or "B" according to the WHO Comparative Risk Assessment Index (WHO 2001): **Region of the Americas** (n = 18) Antigua and Barbuda, Argentina, Bahamas, Barbados, Canada, Chile, Cuba, Grenada, Guyana, Jamaica, Paraguay, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, United States of America and Uruguay; **Eastern Mediterranean Region** (n = 11) Bahrain, Cyprus, Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Qatar, Saudi Arabia, Syria, Tunisia and United Arab Emirates; **European Region** (n = 50) All countries were excluded, except The former Yugoslav Republic of Macedonia; **Western Pacific Region** (n = 11) Australia, Brunei Darussalam, Fiji, Japan, Mongolia, Nauru, New Zealand, Niue, Republic of Korea, Samoa and Singapore.

### 3.6 CHILDREN (0–4 YEARS)

The subregional and global prevalence rates of serum retinol concentrations  $<0.70\mu\text{mol/l}$  among children aged 0–4 years are shown in Table 4.2. The prevalence estimates from the smaller number of countries that contributed to the 2002 West report are compared to the global estimates generated for the CRA project. The results indicate that globally, approximately 21% of all children have serum retinol concentrations  $<0.70\mu\text{mol/l}$ . The highest prevalence rates and the largest number of affected children live in the South-East Asian and African Regions. The estimated number of affected children is similar to what was reported by the Micronutrient Initiative, UNICEF and Tulane University group (Micronutrient Initiative/UNICEF/Tulane University 1998).

### 3.7 PREGNANT WOMEN (15–44 YEARS)

The subregional and global prevalence rates of serum retinol concentrations  $<0.70\mu\text{mol/l}$  among pregnant women aged 15–44 years are shown in Table 4.3. The prevalence estimates from the smaller number of countries that contributed to the 2002 West report are compared to the global estimates generated for the CRA project. The results indicate that globally, approximately 5.6% of all pregnant women have serum retinol concentrations  $<0.70\mu\text{mol/l}$ . Although the prevalence rates among pregnant women are approximately one-fourth those observed in children aged  $<5$  years, a similar risk distribution emerged—with the highest prevalence rates and number of affected women being located in the South-East Asian and African Regions. Although the global prevalence is low, vitamin A deficiency may be an important contributing factor to adverse health outcomes for pregnant women in selected areas of the world.

### 3.8 OTHER GROUPS

There is very little, if any, information available about the global prevalence of vitamin A deficiency and the associated risk in other population groups. Therefore, the prevalence of serum retinol concentrations  $<0.70\mu\text{mol/l}$  among children aged  $\geq 5$  years, among non-pregnant women aged 15–44 years, among men aged 15–44 years, and among adults aged  $\geq 45$  years was not estimated.

## 4. ASSESSING CAUSALITY AND QUANTIFYING RISK FACTOR–DISEASE RELATIONSHIPS

There is often a discrepancy between the problems that motivate a study and the data available for addressing the issue. This applies to the present work, especially when identifying data to be used in estimating the relative risk of adverse health outcomes associated with vitamin A deficiency. Ideally, the results of multiple studies would be available for each outcome of interest from different countries located in different regions

**Table 4.3** Global prevalence of serum retinol concentrations <0.70 µmol/l among pregnant women aged 15–44 years, by subregion

Subregion	Countries with assigned prevalence estimates <sup>a</sup>			Countries with no assigned prevalence estimates (prevalence set to 0%)			Subregional and global totals			
	Countries	Pregnant women with serum retinol concentrations <0.70 µmol/l (000s)	Prevalence of serum retinol concentrations <0.70 µmol/l among pregnant women (%)	Countries	Live births per year (000s)	Prevalence of serum retinol concentrations <0.70 µmol/l among pregnant women (%)	Countries	Pregnant women with serum retinol concentrations <0.70 µmol/l (000s)	Live births per year (000s)	Prevalence of serum retinol concentrations <0.70 µmol/l among pregnant women (%)
AFR-D	26	1 011	9.0	0	NA	9.0	26	1 011	11 185	9.0
AFR-E	20	1 441	10.9	0	NA	10.9	20	1 441	13 240	10.9
AMR-A	0	NA	NA	3	4 238	NA	3	0	4 238	0.0
AMR-B	11	282	3.5	15	1 348	3.5	26	282	9 304	3.0
AMR-D	6	93	4.6	0	NA	4.6	6	93	2 011	4.6
EMR-B	0	NA	NA	13	3 410	NA	13	0	3 410	0.0
EMR-D	9	938	7.8	0	NA	7.8	9	938	12 003	7.8
EUR-A	0	NA	NA	26	4 233	NA	26	0	4 233	0.0
EUR-B	0	NA	NA	16	3 743	NA	16	0	3 743	0.0
EUR-C	0	NA	NA	9	2 527	NA	9	0	2 527	0.0
SEAR-B	3	538	9.1	0	NA	9.1	3	538	5 933	9.1
SEAR-D	7	1 714	5.7	0	NA	5.7	7	1 714	30 279	5.7
WPR-A	0	NA	NA	5	1 629	NA	5	0	1 629	0.0
WPR-B	16	1 240	5.0	6	761	5.0	22	1 240	25 567	4.8
World	98	7 257	6.8	93	21 889	6.8	191	7 257	129 302	5.6

NA Not applicable.

<sup>a</sup> Country-specific data used to estimate regional prevalence rates were based on the review article "Global prevalence of vitamin A deficiency among preschool children and women of reproductive age" (West 2002). Technical notes and data for individual countries are located at [www.jhsph.edu/chn/GlobaIAD.html](http://www.jhsph.edu/chn/GlobaIAD.html). In the review article the number of pregnant women aged 15–45 years with serum retinol concentrations <0.70 µmol/l in a country was either estimated based on existing survey data or imputed for countries where maternal vitamin A deficiency was likely to exist based on cultural, dietary, demographic, health and development patterns as well as existing rates of adult and child mortality. In order to calculate subregional and global prevalence rates for the CRA project, the prevalence estimate was set to 0% for the remaining 93 countries, where no prevalence data on maternal vitamin A deficiency or night blindness were available, but maternal vitamin A deficiency was considered unlikely to exist. These are all classified as "A" or "B" according to the WHO Comparative Risk Assessment Index (WHO 2001): **Region of the Americas** (n = 18) Antigua and Barbuda, Argentina, Bahamas, Barbados, Canada, Chile, Cuba, Grenada, Guyana, Jamaica, Paraguay, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, United States and Uruguay; **Eastern Mediterranean Region** (n = 13) Bahrain, Cyprus, Iran, Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriyah, Oman, Qatar, Saudi Arabia, Syria, Tunisia and United Arab Emirates; **European Region** (n = 51) All countries were excluded; **Western Pacific Region** (n = 11) Australia, Brunei Darussalam, Fiji, Japan, Mongolia, Nauru, New Zealand, Niue, Republic of Korea, Samoa and Singapore.

of the world. This would allow the subregional estimates to be based on empirical data for each location. However, this type of data is simply not available. In the absence of such information the best data possible should be compiled and any important limitations recognized. There are several important limitations of the data and methodology used to estimate risk estimates for this project that deserve comment.

First, no definitive criteria exist for determining with certainty whether or not a particular risk factor is causally related to an adverse health outcome. However, many investigators have adopted the general principles that were originally proposed by Hill for use as guidelines when evaluating potential causal relationships (Hill 1965). A review of vitamin A studies conducted using different designs reveals that many of these general principles hold true when the entire body of evidence is considered together. However, experimental evidence—in this case the demonstration that a vitamin A-related intervention prevents an adverse health outcome—provides some of the strongest evidence for a causal relationship. Therefore, the present review has been restricted to the results of randomized placebo-controlled vitamin A intervention trials conducted in areas with either documented or suspected vitamin A deficiency. The inference commonly made from such a study is that if the vitamin A intervention prevents the occurrence of an adverse health outcome, then vitamin A deficiency is causally associated with it.

The design used for the prospective trials of vitamin A and child mortality was to assign the participants to either a vitamin A or control group, to implement the intervention, and to then follow the participants over time. Aside from observing the presence of clinical eye signs of deficiency, the vitamin A status (serum retinol concentration) of each and every participant was not assessed. The baseline vitamin A status of the populations under study was either inferred from prior survey data gathered in the same subregion or from a subset of the study participants.

Second, the risk estimates reported in the original publications of vitamin A and child mortality represent the *protective* effect of the vitamin A interventions against adverse health outcomes, rather than the relative risk of an adverse outcome associated with vitamin A deficiency *per se*. The risk of an *adverse* outcome was estimated from the original trial results as the inverse of the protective relative risk ( $= 1/\text{protective relative risk}$ ). The following assumptions were made when using the intervention trial data in this manner: (i) that all children participating in the trials were vitamin A deficient at the beginning of the intervention period; and (ii) that the deficiency was corrected in all children assigned to the intervention group, while those in the placebo group remained deficient. Neither of these assumptions is likely to have been met in all of the trials. Thus the unadjusted risk estimates from the trials may underestimate the true relationship between vitamin A deficiency and an adverse health outcome.

Finally, the data from the original intervention trials were analysed on an intention-to-treat basis, rather than on the basis of achieved compliance. In reality both compliance and the biological efficacy of the particular intervention under study would influence the measured relationship between the vitamin A intervention and an adverse health outcome. Secondary analyses from one of the child mortality studies that took actual compliance into account estimated a far greater reduction in all-cause mortality than was observed in the original intention-to-treat analysis (Sommer and Zeger 1991).

On the other hand, the summary risk estimates from the meta-analyses of the individual intervention trials conducted in a variety of countries provide a certain level of built-in control for unmeasured factors that may have differed across sites. The United Nations Administrative Committee on Coordination/Subcommittee on Nutrition (ACC/SCN) meta-analysis of the child mortality trials examined the effect of age and sex on observed mortality and concluded there were no significant differences of vitamin A supplementation on all-cause mortality between males and females or by age category for children between 6 months and 5 years of age (Beaton et al. 1993). In addition, there was no detectable relationship between the effects of the vitamin A intervention and anthropometric status on child mortality.

For the purpose of the CRA project, relative risk estimates for child and maternal health outcomes used vitamin A intervention trial data as the starting point. However, the relative risk estimates were adjusted to take into account the fact that many, but not all, of the study participants had low serum retinol concentrations at the beginning of the intervention trials. The following section describes how the adjustment process was conducted. The same process was applied to data for both the child and maternal health outcomes.

The adjusted relative risks were calculated using a four-step process.

1. A quantitative estimate of the protective effect that a vitamin A intervention had in preventing an adverse health outcome was found in the published literature.
2. The prevalence of serum retinol concentrations  $<0.70 \mu\text{mol/l}$  was estimated among the study population at baseline.
3. An adjusted relative risk was calculated by constructing a hypothetical population of 100 000 individuals and dividing them into two strata using a serum retinol concentration cut-off of  $<0.70 \mu\text{mol/l}$  and the prevalence estimate obtained in the second step. The relative risk of an adverse outcome was then calculated for both strata separately by setting the background incidence rate of the adverse outcome to be equivalent among the following groups: (i) the vitamin A intervention group in the entire study population; (ii) the vitamin A intervention and control groups in the strata with serum retinol con-

centrations  $\geq 0.70 \mu\text{mol/l}$ ; and (iii) the vitamin A intervention group in the stratum with serum retinol concentrations  $< 0.70 \mu\text{mol/l}$ . The relative risk for children in the stratum with serum retinol concentrations  $\geq 0.70 \mu\text{mol/l}$  represents the effect of the vitamin A intervention among children who were not deficient before the trial began. In this stratum the relative risk is 1.0 because those children were not expected to benefit (in terms of reducing all-cause mortality) from the intervention. The relative risk for children in the other stratum is lower than the overall trial estimate (representing a greater protective effect) because those children were deficient when the trial began and all of the observed benefit (in terms of reducing all-cause mortality) associated with the vitamin A intervention was presumably observed among this subgroup of children.

4. The final step in the adjustment process was to calculate the relative risk of all-cause mortality associated with vitamin A deficiency by calculating the inverse of the adjusted protective effect ( $= 1/\text{protective relative risk}$ ). See Table 4.4 for an example calculation based on a 23% reduction in child deaths (protective relative risk of 0.77) associated with a vitamin A intervention and a 41% baseline prevalence rate of serum retinol concentrations  $< 0.70 \mu\text{mol/l}$  in the study population. In this example, the originally reported protective effect associated with the vitamin A intervention is a relative risk of 0.77; the adjusted protective relative risk associated with the vitamin A intervention is 0.58 (equivalent to a 42% reduction in child deaths); and the adjusted relative risk of child death associated with vitamin A deficiency is 1.72.

This adjustment process requires estimates for the baseline serum retinol concentrations  $< 0.70 \mu\text{mol/l}$  for the populations contributing relative risk data to each adverse health outcome. The baseline prevalence estimates are shown in Table 4.5. For some, but not all, adverse health outcomes, baseline prevalence data were directly available from the published reports that contributed relative risk estimates to the adjustment process. In other cases, the prevalence rates were extrapolated accordingly. The process used to derive prevalence rates for each included adverse health outcome is described below.

In order to derive estimates for the measles, diarrhoea, malaria and other infectious disease causes of death and disability in children attributable to vitamin A deficiency, it was necessary to estimate a single underlying prevalence of deficiency that existed in the southern Asian and African populations in which eight large community-based, vitamin A child-mortality intervention trials were conducted. Knowing a single, underlying prevalence of deficiency across these diverse trial populations reveals the background burden of vitamin A deficiency that is understood to account for the overall estimated reduction of 23% in

**Table 4.4** Example of how to calculate the adjusted relative risk of child death associated with vitamin A deficiency assuming a published relative risk of 0.77 for child survival associated with the receipt of vitamin A in a controlled intervention trial and a 41% baseline prevalence rate of ‘vitamin A deficiency’ among the children (defined as serum retinol concentrations  $<0.70 \mu\text{mol/l}$ )

Study population	Died	Survived	Total	Incidence of death	Protective relative risk	% reduction in deaths due to vitamin A intervention
<i>Entire study population</i>						
Vitamin A group	385	49615	50000	0.0077	0.77	23
Control group	500	49500	50000	0.0100		
Total	885	99115	100000			
<i>Children with serum retinol concentrations <math>\geq 0.70 \mu\text{mol/l}</math></i>						
Vitamin A group	227	29273	29500	0.0077	1.00	0
Control group	227	29273	29500	0.0077		
Total	454	58456	59000			
<i>Children with serum retinol concentrations <math>&lt;0.70 \mu\text{mol/l}</math></i>						
Vitamin A group	158	20342	20500	0.0077	0.58 <sup>a</sup>	42
Control group	273	20272	20500	0.0133		
Total	431	40569	41000			

<sup>a</sup> In the example above the relative risk of child death associated with vitamin A deficiency was calculated by using an overall observed relative risk of child survival associated with receipt of vitamin A (0.77) and estimating the relative risk of child survival among the 59% of children who had serum retinol concentrations  $\geq 0.70 \mu\text{mol/l}$  (1.00) and the 41% of children with concentrations below that cut-off (0.58). The relative risk of child death associated with vitamin A deficiency was then calculated as 1.72, which equals the inverse of the protective effect among ‘vitamin A deficient’ children who received vitamin A: 1.72 [1.00/0.58].

**Table 4.5** Estimated baseline prevalence of serum retinol concentrations  $<0.70\ \mu\text{mol/l}$  in the intervention studies used to estimate the relative risk of cause-specific mortality associated with vitamin A deficiency<sup>a</sup>

<i>Cause of death</i>	<i>Estimated baseline prevalence of serum retinol concentrations <math>&lt;0.70\ \mu\text{l}</math> in the intervention trials (%)</i>	<i>Data source</i>
<b>Children</b>		
Diarrhoea	41	See Table 4.6
Measles	41	See Table 4.6
Malaria	55	See Table 1 in Shankar et al. (1999)
Other infectious causes	41	See Table 4.6
<b>Women</b>		
Maternal conditions	19	See Table 2 in West et al. (1999)

<sup>a</sup> The cause of death outcomes were defined using the following GBD codes: measles (U015); diarrhoea (U010); malaria (U020); other infectious causes (U037); all-cause maternal mortality corresponds to the GBD code for maternal conditions (U042).

preschool-age child mortality achieved with vitamin A interventions (Beaton et al. 1993).

An overall background prevalence of serum retinol concentrations  $<0.70\ \mu\text{mol/l}$  was derived by estimating the size and prevalence of vitamin A deficiency for each national or regional population judged to be represented by each intervention trial (Table 4.6). The prevalence rate for each country as available, was applied to the estimated number of preschool-age children in order to estimate the number of vitamin A deficient preschool-age children in each population represented by a trial. These steps resulted in a subjective re-weighting of the sizes of the populations at-risk in each area that were independent of sample sizes for each trial. Finally, numbers of deficient children in each population represented by a trial were summed and divided by the sum of the population estimates of children aged  $<5$  years, resulting in a prevalence that is, roughly, weighted by the sizes of populations at risk that were represented by the trials. This exercise produced prevalence rates of serum retinol  $<0.70\ \mu\text{mol/l}$  that ranged from 28% in the Sudan, to 72% as measured during a vitamin A child mortality trial in Ghana (Ghana VAST Study Team 1993). An estimated 19 million children, or 41%, among the estimated 46.5 million children living in areas at risk of vitamin A deficiency, representing the underlying, local populations of interest, were considered to be vitamin A deficient. In the absence of additional data, this underlying prevalence was further judged to represent the underlying pool of deficient children for whom death from severe episodes of diarrhoea, measles and other non-malarial infectious disease illnesses could be averted each year with vitamin A.

**Table 4.6** Baseline prevalence estimates for serum retinol concentrations  $<0.70 \mu\text{mol/l}$  among populations of children aged  $<5$  years from eight vitamin A intervention trials, by country

Host country	Population $<5$ years of age <sup>a</sup> (000s)	Prevalence of serum retinol concentrations $<0.70 \mu\text{mol/l}$	Number of vitamin A-deficient children (000s)
Ghana, Kitampo	1 063 <sup>b</sup>	0.72 <sup>c</sup>	765
India, Andra Pradesh	8 709 <sup>d</sup>	0.31 <sup>e</sup>	2 700
India, Tamil Nadu	7 143 <sup>d</sup>	0.37 <sup>f</sup>	2 643
Indonesia	22 006 <sup>g</sup>	0.48 <sup>h</sup>	10 563
Nepal	3 485 <sup>i</sup>	0.35 <sup>j</sup>	1 220
Sudan	4 162 <sup>k</sup>	0.28 <sup>l</sup>	1 165
Total/Overall	46 567	0.41 <sup>m</sup>	19 055

<sup>a</sup> Based on Table 1 of the *State of the world's children's report* (UNICEF 2001), unless otherwise noted.

<sup>b</sup> Given that the vitamin A trial in Ghana (Ghana VAST Study Team 1993) was carried out in the central part of the country, which is considered to be at higher risk than the southern, palm-oil consuming areas of the country, only one-third of the Ghanaian child population  $<5$  years of age (3 189 000, UNICEF 2001) was considered to be represented by children in the trial.

<sup>c</sup> D Ross et al., personal communication, 1995, reported in Sommer and West (1996).

<sup>d</sup> Based on government of India census data for 2001 indicating 11.5% of the country's rural population was  $<5$  years, applied to statewide census estimates for both Tamil Nadu and Andra Pradesh; statewide populations were assumed to represent the at-risk population for each trial.

<sup>e</sup> In the absence of serum retinol data from the trial or from representative population surveys of Andra Pradesh, a prevalence of 31% (West 2002) was applied to the state population.

<sup>f</sup> Rahmathullah et al. (1990).

<sup>g</sup> Indonesia is represented by its entire population given that the two mortality trials carried out in Aceh (Sommer et al. 1986) and West Java (Muhilal et al. 1988) were conducted in the north and central parts of the country, respectively.

<sup>h</sup> Prevalence based on the West Java trial (Muhilal et al. 1988) was assumed to represent Aceh and the rest of Indonesia in the early-mid-1980s, amidst evidence of higher subsequent prevalence rates (Kjolhede et al. 1995; West 2002).

<sup>i</sup> Because two population-based trials (Daulaire et al. 1992; West et al. 1991) were conducted in diverse and different parts of the country, the entire population of Nepalese preschool children (UNICEF 2001) was considered to be the underlying population at risk.

<sup>j</sup> In the absence of biochemical data from either child mortality trial in Sarlahi (West et al. 1991) or Jumla (Daulaire et al. 1992), a prevalence of 35% obtained from the 1998 National Micronutrient Survey (Anonymous 1998a) was taken to represent the prevalence during both trials and for the country.

<sup>k</sup> In the absence of risk differentials across different population groups of the Sudan, the entire population was assumed to be represented by children in the trial (Herrera et al. 1992).

<sup>l</sup> Median prevalence (28%) of distribution of 33 national prevalence estimates obtained for African and Eastern Mediterranean Regions was assumed to represent the status of Sudanese preschool children.

<sup>m</sup> Calculated by dividing 19 055 by 46 567.

A prevalence of 55% was assigned for populations of preschool-age children whose risk of death and disability due to *Plasmodium falciparum* malaria could be averted by vitamin A supplementation. This prevalence estimate was based on the data reported in Table 1 from a

single, community-based randomized trial in Papua New Guinea that measured effects of vitamin A supplementation on *P. falciparum* malaria clinic attack rates (Shankar et al. 1999). The assigned prevalence rate was calculated based on the published mean and standard deviation serum retinol concentration for the population at baseline and applying an assumption of normally distributed data.

A prevalence of 19% was assigned to represent populations of pregnant women living in areas of the world where risk of mortality may be reduced by approximately 40% with improved, regular, supplemental intakes of vitamin A, based on the data reported in Table 2 from a single, large randomized community recently conducted in rural Nepal (West et al. 1999). The same overall adjustment process was used to calculate adjusted relative risks of adverse health outcomes for each of the included child and maternal health outcomes. For the child health outcomes, the same adjusted relative risk was reported for children aged 0–4 years (boys and girls) for all regions of the world.

## 5. RISK FACTOR–DISEASE OUTCOME RELATIONSHIPS

The following section describes the individual studies that were used to evaluate and quantify the relative risk of an adverse health outcome associated with vitamin A deficiency. The intervention trials and results are reported separately for children aged 0–4 years and pregnant women aged 15–44 years. Insufficient data were available to quantitatively evaluate the risks of vitamin A deficiency in other population groups. Table 4.7 describes the individual studies that were used to estimate the relative risk of adverse health outcomes for the CRA project with respect to vitamin A. The studies are listed in the same order that the outcomes are discussed in the chapter. Mortality associated with measles and diarrhoeal disease in children appears first, followed by malaria incidence and malaria mortality in children, mortality associated with other infectious causes of death in children, and finally all-cause maternal mortality among pregnant women.

Unless otherwise noted, the risk estimates cited for individual studies are the findings that were originally reported in the literature and represent the *protective* effect of the vitamin A intervention against adverse health outcomes. An adjusted relative risk was calculated from these data to represent the risk of adverse health outcomes associated with vitamin A deficiency following the procedure described in section 4.

### 5.1 RISK ESTIMATES FOR PRESCHOOL CHILDREN (0–4 YEARS)

Preschool-age children have traditionally been considered to be a high-risk group for vitamin A deficiency and its consequences. Most of the large-scale controlled intervention trials that have been conducted were designed to explore the relationships between vitamin A supplementation, morbidity and mortality among children aged <6 years.

**Table 4.7** Studies used to estimate the relative risk of adverse health outcomes for the CRA project, by outcome<sup>a</sup>

Outcome (Reference)	Study design	Location	Study population
<i>Children</i>			
<b>Measles mortality</b> (Beaton et al. 1993)	Meta-analysis of randomized, placebo-controlled vitamin A supplementation trials	4 trials (Ghana; India; Sarlahi, Nepal; Jumla, Nepal)	Children 6–60 months
Original studies included in the meta-analysis: (Ghana VAST Study Team 1993) (Rahmathullah et al. 1990) (West et al. 1991) (Daulaire et al. 1992)	Large dose vitamin A every 4 months RDA of vitamin A in weekly doses Large dose vitamin A every 4 months Large dose vitamin A once with a 5 month follow-up	Ghana India Sarlahi, Nepal Jumla, Nepal	Children 6–90 months Children 6–60 months Children 6–72 months Children 1–59 months
<b>Diarrhoea mortality</b> (Beaton et al. 1993)	Meta-analysis of randomized, placebo-controlled vitamin A supplementation trials	5 trials (Ghana; India; Sarlahi, Nepal; Jumla, Nepal; Sudan)	Children 6–60 months
Original studies included in the meta-analysis: (Ghana VAST Study Team 1993) (Rahmathullah et al. 1990) (West et al. 1991) (Daulaire et al. 1992) (Herrera et al. 1992)	Large dose vitamin A every 4 months RDA of vitamin A in weekly doses Large dose vitamin A every 4 months Large dose vitamin A once with a 5 month follow-up Large dose vitamin A every 4 months	Ghana India Sarlahi, Nepal Jumla, Nepal Sudan	Children 6–90 months Children 6–60 months Children 6–72 months Children 1–59 months Children 9–72 months

*continued*

**Table 4.7** Studies used to estimate the relative risk of adverse health outcomes for the CRA project, by outcome<sup>a</sup> (continued)

Outcome (Reference)	Study design	Location	Study population
<b>Malaria incidence</b> (Shankar et al. 1999)	Randomized, placebo-controlled vitamin A supplementation trial	Papua New Guinea	Children 6–60 months
(Binka et al. 1995)	Large dose vitamin A every 4 months	Ghana	Children 6–90 months
(Study excluded due to non-statistically significant results)			
<b>Malaria mortality</b> (Shankar et al. 1999)	Note: A mortality effect was not assessed in the trial, but the relative risk of malaria mortality was assumed to be equivalent to the observed morbidity effect for the purpose of estimation in the CRA project	Papua New Guinea	Children 6–60 months
<b>Other infectious causes of child mortality</b> (Beaton et al. 1993)	Meta-analysis of randomized, placebo-controlled vitamin A supplementation trials	5 trials (Ghana; India; Sarlahi, Nepal; Jumla, Nepal; Sudan)	Children 6–60 months
Original studies included in the meta-analysis: (Ghana VAST Study Team 1993) (Rahmathullah et al. 1990) (West et al. 1991) (Daulaire et al. 1992) (Herrera et al. 1992)	Large dose vitamin A every 4 months RDA of vitamin A in weekly doses Large dose vitamin A every 4 months Large dose vitamin A once with a 5 month follow-up Large dose vitamin A every 4 months	Ghana India Sarlahi, Nepal Jumla, Nepal Sudan	Children 6–90 months Children 6–60 months Children 6–72 months Children 1–59 months Children 9–72 months
<b>Women</b>			
<b>All-cause maternal mortality</b> (West et al. 1999)	Randomized, placebo-controlled vitamin A/beta-carotene supplementation trial	Sarlahi, Nepal	Married women 13–45 years
RDA Recommended dietary allowance. <sup>a</sup> The outcomes were defined using the following GBD codes: measles (U015); diarrhoea (U010); malaria (U020); other infectious causes (U037); all-cause maternal mortality corresponds to the GBD code for maternal conditions (U042).			

In the early 1990s the ACC/SCN commissioned a review of the existing scientific evidence to assess the effectiveness of vitamin A supplementation on child mortality and morbidity (Beaton et al. 1993). The findings from ten different community-based mortality trials conducted in Africa (Ghana and the Sudan), the Americas (Haiti) and Asia (India, Indonesia and Nepal), and 20 different morbidity trials conducted around the world were considered for inclusion in a formal meta-analysis. Sufficient data were available from five of the mortality trials (Daulaire et al. 1992; Fawzi et al. 1993; Ghana VAST Study Team 1993; Rahmathullah et al. 1990; West et al. 1991) to assess the relationship between vitamin A interventions and cause-specific mortality from measles, diarrhoea and respiratory illness. Separate relative risks were reported in the meta-analysis of these studies for all-cause mortality, mortality attributed to these three specific causes and mortality attributed to all other causes combined.

All five of those mortality trials were conducted in populations where vitamin A deficiency (both clinical and subclinical) was prevalent (assessed either as high rates of xerophthalmia or low serum retinol concentrations). In four of the trials (one in Ghana, two in Nepal and one in the Sudan), the intervention consisted of vitamin A supplementation in age appropriate doses (200 000 IU for children  $\geq 12$  months of age, 100 000 IU for children 6 to 11 months of age and, for one trial in Nepal, 100 000 IU for infants 1 to 11 months of age and 50 000 IU for infants  $< 1$  month of age) every 4–6 months. In India, the intervention was a weekly supplement that contained a weekly RDA of vitamin A. In the Ghana, India and Nepal trials, a statistically significant reduction in all-cause mortality was observed among children in the vitamin A intervention group. No statistically significant effect on all-cause mortality was observed in the Sudan.

### MEASLES

Measles (and thus measles-related mortality) have nearly been eliminated in the Americas due to the implementation of successful measles control programmes over the past ten years (Hersh et al. 2000). At present, the highest rates of measles mortality occur among children aged  $< 1$  year in developing countries. Although unvaccinated children aged  $> 10$  years and adults are also susceptible to measles and measles mortality, estimates for the burden of disease associated with vitamin A deficiency were restricted to children aged 0–4 years for the CRA analysis.

#### *Incidence and morbidity*

Measles is a highly infectious disease caused by the measles virus (Reingold and Phares 2001). Although vitamin A is involved in different aspects of the immune defence system, there is little evidence to suggest that vitamin A status affects the incidence of measles. Therefore,

the relative risk of experiencing a measles episode associated with vitamin A deficiency was not calculated for the CRA analysis.

### *Mortality*

Vitamin A deficiency appears to increase the risk of measles-related mortality. The ACC/SCN meta-analysis of the four prospective community-based trials with information on measles (Ghana, India and two in Nepal) suggests that vitamin A supplementation was associated with a 26% overall reduction in measles mortality (RR = 0.74, 95% CI 0.53–1.04) (Beaton et al. 1993). In the individual trials, the reduction in measles mortality ranged from 18% in Ghana to 75% in Sarlahi, Nepal (Sommer and West 1996). A more recent study from Ghana found no difference in the acute measles case-fatality rate between vitamin A supplemented and placebo groups (Dollimore et al. 1997). Vitamin A supplementation, however, has been found to reduce measles severity. In some (Coutsoudis et al. 1991; Ellison 1932; Hussey and Klein 1990) but not all (Rosales et al. 1996) hospital-based treatment trials, the surviving children who had received vitamin A experienced complications less frequently and recovered faster than their counterparts who received placebo treatment. These findings provide supporting evidence for a causal relationship between vitamin A deficiency and measles mortality.

The relative risk of measles (GBD code U015) mortality among children aged 0–4 years with vitamin A deficiency was estimated for the CRA project from the protective effect of vitamin A interventions (RR = 0.74, 95% CI 0.53–1.04) observed in the ACC/SCN meta-analysis of community-based trials and a 41% estimated baseline prevalence rate of serum retinol concentrations  $<0.70\mu\text{mol/l}$  among those study populations. The adjusted relative risk estimate derived from those data is RR = 1.86 (95% CI 1.32–2.59). The calculations are shown in Table 4.8.

### *DIARRHOEA*

Diarrhoea and diarrhoea-related mortality are prevalent among preschool-age children, particularly in low income countries. The global burden of disease related to diarrhoea mortality is widely distributed around the world.

### *Incidence and morbidity*

Diarrhoeal disease can be caused by a variety of bacterial, viral and parasitic agents (Reingold and Phares 2001). Although vitamin A is involved in different aspects of the immune defence system, including the maintenance of the epithelial cell border in the intestinal tract, there is little evidence from intervention trials to suggest that vitamin A status affects the incidence of diarrhoea. Therefore, the relative risk of experiencing a diarrhoea episode associated with vitamin A deficiency was not calculated. However, there is considerable evidence to link vitamin A status to the severity of diarrhoea episodes (Sommer and West 1996). Children

**Table 4.8** Unadjusted and adjusted relative risks of adverse health outcomes associated with vitamin A deficiency<sup>a</sup>

Outcome	Source of relative risk data	Original trial results (RR of protective effect due to vitamin A intervention)		RR associated with vitamin A deficiency <sup>b</sup>		RR associated with vitamin A deficiency (serum retinol concentrations <0.70 µmol/l) <sup>c</sup>	
		RR	95% CI	RR = [1.00/published protective RR]	95% CI = [1.00/published CI]	RR = [1.00/published protective RR]	95% CI = [1.00/published CI]
<b>Children (0–4 years)</b>							
Diarrhoea mortality	Table 5.10 in Beaton et al. (1993)	0.68	0.57–0.80	1.47	1.25–1.75	2.15	1.83–2.58
Measles mortality	Table 5.10 in Beaton et al. (1993)	0.74	0.53–1.04	1.35	0.96–1.89	1.86	1.32–2.59
Malaria incidence	Table 3 in Shankar et al. (1999)	0.70	0.57–0.87	1.43	1.15–1.75	1.78	1.43–2.19
Malaria mortality	Table 3 in Shankar et al. (1999) using incidence of malaria episodes as a proxy for malaria mortality	0.70	0.57–0.87	1.43	1.15–1.75	1.78	1.43–2.19
Selected other infectious disease causes of mortality	Table 5.10 in Beaton et al. (1993)	0.95	0.81–1.06	1.05	0.94–1.23	1.13	1.01–1.32
<b>Pregnant women (15–44 years)</b>							
All-cause maternal mortality	Text statement about the relative risk for the maternal mortality ratio among vitamin A + beta-carotene vs placebo recipients in West et al. (1999)	0.60	0.39–0.93	1.67	1.08–2.56	4.51	2.91–6.94

<sup>a</sup> The outcomes were defined using the following GBD codes: measles (U015); diarrhoea (U010); malaria (U020); other infectious causes (U037); all-cause maternal mortality corresponds to the GBD code for maternal conditions (U042).

<sup>b</sup> Unadjusted for baseline prevalence of serum retinol concentrations <0.70 µmol/l.

<sup>c</sup> Adjusted for baseline prevalence of serum retinol concentrations <0.70 µmol/l in trial populations.

with poor vitamin A status tend to suffer from more severe and more prolonged episodes of diarrhoea. These findings provide supporting evidence for a causal relationship between vitamin A deficiency and diarrhoea mortality.

### *Mortality*

Vitamin A deficiency does appear to increase the risk of diarrhoea mortality. The ACC/SCN meta-analysis of the five community-based trials with information on diarrhoea (Ghana, India, Nepal [two trials] and the Sudan) suggest that vitamin A supplementation was associated with a 32% reduction in diarrhoea mortality (RR = 0.68, 95% CI 0.57–0.80) (Beaton et al. 1993). In the individual trials that showed a reduction (all but the Sudan), the reduction in diarrhoea mortality ranged from 34% in Ghana to 52% in India (Sommer and West 1996).

The relative risk of diarrhoea (GBD code U010) mortality among children aged 0–4 years with vitamin A deficiency was estimated from the protective effect of vitamin A interventions (RR = 0.68, 95% CI 0.57–0.80) observed in the ACC/SCN meta-analysis of community-based trials and a 41% estimated baseline prevalence rate of serum retinol concentrations  $<0.70\mu\text{mol/l}$  among those study populations. The adjusted relative risk estimate derived from those data is RR = 2.15 (95% CI 1.83–2.56). The calculations are shown in Table 4.8.

### *MALARIA*

Although malaria is endemic in several areas of the world, countries in Africa have particularly high prevalence rates and children aged  $<5$  years experience much of the associated burden of disease.

### *Incidence and morbidity*

Malaria is caused by several species of the protozoa *Plasmodium*, which are transmitted by mosquitoes from one person to another (Reingold and Phares 2001). In humans, *P. falciparum* is the species responsible for the majority of malaria-related morbidity and mortality. Both animal and human studies have implicated specific immune mechanisms for how vitamin A could influence the incidence and severity of malarial disease (Davis et al. 1998; Krishnan et al. 1976; Serghides and Kain 2002; Stoltzfus et al. 1989). In addition, cross-sectional studies have also documented inverse associations between plasma retinol levels and *P. falciparum* parasitaemia in humans (Filteau et al. 1993; Friis et al. 1997; Galan et al. 1990; Samba et al. 1992; Tabone et al. 1992; Thurnham and Singkamani 1991), and one study has reported that low baseline vitamin A status was associated with an increased risk of parasitaemia (Sturchler et al. 1987).

Findings from more recent randomized controlled intervention trials suggest that vitamin A supplementation appears to reduce both the incidence and severity of malaria illness. In Ghana, cohorts of children

received high-dose vitamin A or a placebo every four months as part of either the Child Health (morbidity) or Child Survival (mortality) Study. Blood samples were collected on a monthly basis from different random subsamples of children in a series of cross-sectional surveys conducted over a one-year period. Based on the cross-sectional data, the authors reported no statistically significant differences in the incidence of fever, malaria parasitaemia, parasite density, or probable malaria illness between the two groups and concluded that vitamin A supplementation had no impact on malaria (Binka et al. 1995). However, given the relatively small sample sizes, these studies had limited statistical power and could only detect a statistically significant protective effect of vitamin A supplementation against probable malarial illness that exceeded 70% (Child Survival Study) or 95% (Child Health Study) (Shankar 1995).

A more definitive study of vitamin A supplementation and malaria was recently conducted in Papua New Guinea. In that study children aged 6–60 months received either high-dose vitamin A or a placebo every three months and were followed over a 13-month period. Malaria morbidity was assessed weekly using community-based case detection and surveillance of the patients who reported to the local health centre. Blood smears were prepared for children who had a fever  $>37.5^{\circ}\text{C}$  at the time of the weekly home visit or for any clinic visit and for all children who participated in the three cross-sectional surveys conducted at baseline, at the midpoint, and at the end of the study. Slide-confirmed cases of malaria were followed prospectively and observed for adverse health outcomes. Children in the vitamin A group had a 30% lower frequency of *P. falciparum* febrile illnesses (RR = 0.70, 95% CI 0.57–0.87) and younger children (12–36 months) apparently benefited most from supplementation. The younger children in the vitamin A group also had less severe malaria morbidity, measured as fewer febrile episodes, fewer enlarged spleens and a lower parasite density (Shankar et al. 1999).

The study from Papua New Guinea used a stronger design, evaluated a greater number of disease variables, and had more statistical power to investigate a relationship between vitamin A and malaria morbidity as compared to the Ghana study. Therefore, the findings from Papua New Guinea were used to assess the relative risk of malaria incidence associated with vitamin A deficiency for the CRA project.

### *Mortality*

To date, no randomized trials have demonstrated a significant reduction in malaria mortality associated with the vitamin A supplementation. However, given the recently observed relationship between vitamin A supplementation and malaria severity, an equivalent relative risk was assigned for malaria mortality for the purpose of the CRA project.

The relative risk of malaria incidence (GBD code U020) among children aged 0–4 years with vitamin A deficiency was estimated for the CRA project from the protective effect of the vitamin A intervention

(RR = 0.70, 95% CI 0.57–0.87) observed in the Papua New Guinea trial and a 55% estimated baseline prevalence rate of serum retinol concentrations  $<0.70\mu\text{mol/l}$  in that study population. The adjusted relative risk estimate derived from those data is RR = 1.78 (95% CI 1.43–2.19). The calculations are shown in Table 4.8.

The relative risk of malaria mortality (GBD code U020) among children aged 0–4 years with vitamin A deficiency was estimated by extrapolation for the CRA project from the results of the vitamin A intervention on malaria incidence observed in the community-based trial in Papua New Guinea (RR = 0.70, 95% CI 0.57–0.87) and a 55% estimated baseline prevalence rate of serum retinol concentrations  $<0.70\mu\text{mol/l}$  in that study population. The adjusted relative risk estimate derived from those data is RR = 1.78 (95% CI 1.43–2.19). The calculations are shown in Table 4.8.

#### OTHER INFECTIOUS DISEASES IN CHILDREN

Infectious diseases are a common cause of death among preschool-age children worldwide. The global burden of disease related to the GBD category of “other infectious diseases” among children is widely distributed around the world.

Although acute respiratory infections, diarrhoeal diseases, measles and malaria represent the most common causes of childhood illness and death, many other bacterial, viral and parasitic agents cause disease among children as well. Since vitamin A is involved in a wide variety of different biological processes, vitamin A deficiency may also increase the risk of death due to other less common causes of childhood disease, although studies to date have not specifically quantified those relationships. The GBD study included a group of “other infectious diseases” (GBD code U037) in children that captured the contribution of many low-incidence causes of death under one category. Causes of infectious diseases not explicitly listed in the other GBD categories for children are included under this code (Murray et al. 2001).

#### Mortality

Data from intervention trials among children suggest that vitamin A deficiency increases the risk of mortality from causes other than diarrhoea, measles and malaria. The ACC/SCN meta-analysis of the five community-based trials (Ghana, India, Nepal [two trials] and the Sudan) with information on cause-specific mortality found that vitamin A supplementation was associated with a 5% reduction in mortality from unspecified causes of death (RR = 0.95, 95% CI 0.81–1.06) (Beaton et al. 1993). This risk estimate was used for the purposes of estimation. The relative risk of mortality due to other infectious diseases (GBD code U037) among children aged 0–4 years with vitamin A deficiency was estimated for the CRA project from the protective effect of vitamin A interventions (RR = 0.95, 95% CI 0.81–1.06) observed in the ACC/SCN

meta-analysis of community-based trials and a 41% estimated baseline prevalence rate of serum retinol concentrations  $<0.70\mu\text{mol/l}$  among those study populations. The adjusted relative risk estimate derived from those data is  $\text{RR} = 1.13$  (95% CI 1.01–1.32). The calculations are shown in Table 4.8.

## 5.2 RISK ESTIMATES FOR PREGNANT WOMEN (15–44 YEARS)

Over half a million women around the world die each year from causes associated with pregnancy and childbirth. Most of these maternal deaths occur in the Regions of Africa and South-East Asia.

Although data from either observational or experimental studies relating vitamin A deficiency among women of reproductive age to specific causes of mortality are limited, biologically plausible mechanisms for such relationships do exist (Faisel and Pittrof 2000). A relative risk of maternal mortality was estimated for vitamin A deficiency among pregnant women aged 15–44 years, based on the best data currently available. The risk estimate for these outcomes may be modified in the future when more data that specifically address this issue are available.

To date, the only large-scale randomized controlled trial of vitamin A supplementation among women of reproductive age has been conducted in an area of southern Nepal where high rates of maternal night blindness have been reported (West et al. 1999). More than 44 000 women of reproductive age were randomized to continually receive either vitamin A (7000 $\mu\text{g}$  retinol equivalents), an equivalent amount of beta-carotene, or a placebo capsule on a weekly basis over an approximate three and a half year period; that is, before and during pregnancy, throughout the postpartum period and through any subsequent pregnancy until close-out of the trial. Over 22 000 identified pregnancies were followed. Pregnancy-related mortality (defined as a death during pregnancy or prior to 12 weeks postpartum) was decreased by 40% ( $\text{RR} = 0.60$ , 95% CI 0.37–0.97) in the vitamin A group and by 49% ( $\text{RR} = 0.51$ , 95% CI 0.30–0.86) in the beta-carotene group (West et al. 1999). These findings provide support for a causal relationship between vitamin A deficiency and pregnancy-related mortality.

Data from the study in Nepal were used to estimate the relative risk of maternal mortality associated with vitamin A deficiency. The study presents several sets of mortality results for women stratified by time and cause of death during pregnancy and the postpartum period. The mortality results used for CRA analysis were those that excluded all deaths  $>6$  weeks postpartum and all deaths attributed to reported injury which are the results that most closely conform to the ICD-10 definition of a maternal death (WHO 1992). The combined results for women in the vitamin A and beta-carotene intervention groups were used to represent non-vitamin A deficient women.

The relative risk of maternal mortality among pregnant women with vitamin A deficiency—due to a wide variety of maternal conditions (GBD

code U042)—was estimated for the CRA project from the combined protective effect of the vitamin A and beta-carotene interventions on the maternal mortality ratio (RR = 0.60, 95% CI 0.39–0.93) and a 19% estimated baseline prevalence rate of serum retinol concentrations  $<0.70\mu\text{mol/l}$  observed among women in the Nepal trial (West et al. 1999). In the absence of other studies linking vitamin A deficiency to cause-specific deaths among women, the risk of maternal death (from a wide variety of maternal conditions) was extrapolated from the Nepal study. A maternal mortality ratio of 378 deaths per 100 000 live births among women in the vitamin A and beta-carotene groups combined (West et al. 1999) was used as the starting point for the adjusted relative risk calculations. The adjusted relative risk estimate derived from those data is RR = 4.51 (95% CI 2.91–6.94). The calculations are shown in Table 4.8.

### 5.3 RISK ESTIMATES FOR ALL OTHER GROUPS

Limited information is available about the global prevalence of vitamin A deficiency or its associated adverse health effects in children aged  $\geq 5$  years, in men aged 15–44 years, or in men or women aged  $\geq 45$  years. Therefore, quantitative estimates for the prevalence of vitamin A deficiency and the associated risk of adverse health outcomes were not developed for these groups.

## 6. BURDEN OF DISEASE ASSOCIATED WITH VITAMIN A DEFICIENCY

Summary estimates for three burden of disease measurements are shown in this chapter. The attributable fraction of cause-specific mortality associated with vitamin A deficiency among children aged 0–4 years and pregnant women aged 15–44 years are shown by subregion in Table 4.9. The estimated number of cause-specific deaths and disability-adjusted life years (DALYs) attributed to vitamin A deficiency is shown in Table 4.9 and Table 4.10, respectively.

The attributable fraction results show that worldwide, vitamin A deficiency among children is associated with an estimated 20% of measles-related mortality, 24% of diarrhoea mortality, 20% of malaria incidence and mortality, and 3% of mortality associated with other infectious causes of disease. By definition, the attributable fraction of disease associated with vitamin A deficiency itself is 100%. The attributable fractions vary widely by cause and across the different subregions. In general, the attributable fractions (for disease conditions other than vitamin A deficiency) are highest in the African and South-East Asian Regions, where vitamin A deficiency is most prevalent and child mortality rates for the causes of disease assessed in this chapter are high. Worldwide, vitamin A deficiency (serum retinol concentrations  $<0.70\mu\text{mol/l}$ ) among pregnant women is associated with over 20% of maternal mortality.

**Table 4.9** Attributable fraction of cause-specific mortality (%) due to vitamin A deficiency for measles, diarrhoea, malaria and other infectious diseases among children, for conditions leading to maternal mortality, and for direct sequelae of vitamin A deficiency, by subregion

Subregion	Diseases among children (0–4 years) <sup>a</sup>				Conditions leading to maternal mortality among women (15–44 years) <sup>a</sup>		Direct sequelae of vitamin A deficiency among all age groups and both sexes
	Measles	Diarrhoea	Malaria	Other infectious causes	Maternal causes		
AFR-D	20	25	18	4	24	100	
AFR-E	23	29	22	4	28	100	
AMR-A	b	b	b	b	b	b	
AMR-B	b	15	11	2	10	b	
AMR-D	b	13	9	2	14	b	
EMR-B	2	3	2	b	b	b	
EMR-D	17	21	15	3	22	100	
EUR-A	b	b	b	b	b	b	
EUR-B	b	b	b	b	b	b	
EUR-C	b	b	b	b	b	b	
SEAR-B	29	35	27	6	24	b	
SEAR-D	21	26	19	4	17	100	
WPR-A	b	b	b	b	b	b	
WPR-B	10	14	10	2	14	b	
World	20	24	20	3	22, 21 <sup>c</sup>	100	

<sup>a</sup> The outcomes were defined using the following GBD codes: measles (U015); diarrhoea (U010); malaria (U020); other infectious causes (U037); all-cause maternal mortality corresponds to the GBD code for maternal conditions (U042).

<sup>b</sup> A value for the attributable fraction is not included either because the prevalence of vitamin A deficiency in the subregion was zero or the cause-specific mortality was zero or nearly zero in the associated subregion-age-sex groups.

<sup>c</sup> The global attributable fractions are 22% (for women aged 15–29 years) and 21% (for women aged 30–44 years). They are slightly different because the total number of deaths among women in these age groups differ.

**Table 4.10** Deaths (000s) from measles, malaria, diarrhoea, other infectious diseases among children, from maternal conditions attributable to vitamin A deficiency, and those directly attributed to vitamin A deficiency in vital registration systems, by subregion

Subregion	Cause-specific mortality among children (0–4 years) <sup>a</sup>					Total	Cause-specific mortality among pregnant women (15–44 years) <sup>a</sup>	All-cause mortality directly attributed to vitamin A deficiency in vital registration systems <sup>b</sup>	Total
	Measles	Diarrhoea	Malaria	Other infectious causes					
AFR-D	41	46	79	3	169	24	11	202	
AFR-E	34	93	90	6	223	38	13	271	
AMR-A	0	0	0	0	0	0	0	0	
AMR-B	0	4	0	0	4	2	0	6	
AMR-D	0	2	0	0	2	2	0	4	
EMR-B	0	0	0	0	0	0	0	0	
EMR-D	11	52	7	3	73	14	1	87	
EUR-A	0	0	0	0	0	0	0	0	
EUR-B	0	0	0	0	0	0	0	0	
EUR-C	0	0	0	0	0	0	0	0	
SEAR-B	7	9	1	0	17	5	0	23	
SEAR-D	23	107	10	6	146	21	2	169	
WPR-A	0	0	0	0	0	0	0	0	
WPR-B	2	9	0	1	12	3	0	16	
World	118	323	187	19	647	109	28	778 <sup>c</sup>	

<sup>a</sup> The outcomes were defined using the following GBD codes: measles (U015); diarrhoea (U010); malaria (U020); other infectious causes (U037); all-cause maternal mortality corresponds to the GBD code for maternal conditions (U042).

<sup>b</sup> Among both sexes and all age groups.

<sup>c</sup> Data for the measles, diarrhoea, malaria, other infectious causes, all-cause maternal mortality directly attributed to vitamin A deficiency, and the totals columns were obtained directly from annex results tables. Subregional subtotals for children aged 0–4 years were calculated by adding across disease categories and then totalling those results. Regional subtotals for maternal causes of death were calculated by adding across the 15–29 and 30–44 year-old age categories and then totalling those results. Any discrepancies in the marginal totals in this table are attributed to differences in rounding carried over from the individual columns of the background data tables.

Again, the highest attributable fractions are found in the African and South-East Asian Regions, where vitamin A deficiency and maternal mortality rates are highest.

Worldwide the majority of deaths (see Table 4.10) and DALYs (see Table 4.11) associated with vitamin A deficiency occur in Africa and South-East Asia. However, the relative distribution of deaths and DALYs varies somewhat across subregions for the different causes of disease burden. A higher proportion of the burden of disease from measles, malaria and all-cause maternal mortality occurs in Africa, while South-East Asia has a higher proportion of the disease burden from diarrhoea.

The total number of maternal and child deaths and disease-related morbidity that could potentially be averted if vitamin A deficiency were eliminated depends on several factors: (i) the attributable fraction (determined by the prevalence of vitamin A deficiency and the relative risk of an adverse health outcome); (ii) the global distribution of the adverse health outcomes; and (iii) the estimated number of affected individuals in each subregion. Subregions with a higher attributable fraction but a smaller number of individuals affected by the adverse health outcomes (due to either a small population base or a low prevalence of the condition) may contribute less in absolute terms to the overall global burden of disease when compared to subregions or specific causes of death with lower attributable fractions but a larger total number of affected individuals. Conversely, subregions with similar attributable fractions but different causes of death and/or population bases will contribute different numbers of affected individuals to a global summary.

For example, the AFR-D and SEAR-D subregions have similar attributable fractions of disease for measles (~20%), but the number of deaths attributed to vitamin A deficiency is nearly twice as high in AFR-D (41 000) when compared to SEAR-D (23 000) although the population base of children in the AFR-D subregion is only a third (13.5 million) of the population base of children (42.3 million) in the SEAR-D subregion. For diarrhoea, AFR-D and SEAR-D also have similar attributable fractions of disease (~25%), but in this case the number of deaths attributed to vitamin A deficiency is more than twice as high in SEAR-D (107 000) when compared to AFR-D (46 000). The relative contribution of these different factors (attributable fractions, global distribution of disease and population base) should be kept in mind when comparing the burden of disease attributed to vitamin A deficiency across subregions and specific causes of death.

## 7. DISCUSSION

This chapter generated quantitative estimates of the global burden of disease due to vitamin A deficiency by applying the analytical framework of the CRA project to the best sources of currently available data. The results show, despite decades of achievement in paediatric detection and

**Table 4.11** DALYs (000s) associated with measles, malaria, diarrhoea, and other infectious diseases among children, with maternal conditions attributable to vitamin A deficiency and with direct sequelae of vitamin A deficiency among all age groups, by subregion

Subregion	Children (0–4 years) <sup>a</sup>			Pregnant women (15–44 years) <sup>a</sup>		Total	Both sexes (all age groups) Sequelae directly associated with vitamin A deficiency	Total
	Measles	Diarrhoea	Malaria	Other infectious causes	Maternal causes of morbidity and mortality			
AFR-D	1 432	1 554	2 914	95	662	5 995	378	7 034
AFR-E	1 176	3 131	3 345	189	1 095	7 841	438	9 375
AMR-A	0	0	0	0	0	0	0	0
AMR-B	0	132	2	10	38	144	0	182
AMR-D	0	84	0	3	33	87	0	121
EMR-B	0	15	0	2	0	17	0	17
EMR-D	389	1 746	253	88	401	2 476	40	2 917
EUR-A	0	0	0	0	0	0	0	0
EUR-B	0	1	0	0	0	1	1	2
EUR-C	0	0	0	0	0	0	0	0
SEAR-B	233	314	36	15	152	598	4	754
SEAR-D	790	3 603	368	191	637	4 952	100	5 690
WPR-A	0	0	0	0	0	0	0	0
WPR-B	81	319	11	37	89	448	11	546
World	4 101	10 898	6 931	630	3 106	22 560	972	26 638 <sup>b</sup>

<sup>a</sup> The outcomes were defined using the following GBD codes: measles (U015); diarrhoea (U010); other infectious causes (U037); all-cause maternal mortality corresponds to the GBD code for maternal conditions (U042).

<sup>b</sup> Data for the measles, diarrhoea, malaria, other infectious causes, maternal causes of morbidity and mortality, and sequelae directly attributed to vitamin A deficiency, and the totals columns were obtained directly from the annex results tables. Subregional subtotals for children aged 0–4 years were calculated by adding across disease categories and then totalling those results. Subregional subtotals for maternal conditions were calculated by adding across the 15–29 and 30–44 year-old age categories and then totalling those results. Any discrepancies in the marginal totals in this table are attributed to differences in rounding carried over from the individual columns of the background data tables.

control, that vitamin A deficiency remains a major public health problem among preschool-age children throughout the world. Globally, 21%, or over 127 million children aged <5 years are vitamin A deficient. Twenty per cent to 24% of early childhood deaths due to measles, diarrhoea and malaria are attributable to vitamin A deficiency, plus an additional 3% of deaths due to other infectious causes, accounting for 647 000 deaths of preschool-age children each year. Vitamin A deficiency appears to especially put children at risk of mortality due to diarrhoea, which accounts for 50% of all childhood deaths attributable to vitamin A deficiency.

New to the global view of undernutrition is a previously unrecognized, substantial burden of maternal vitamin A deficiency. Not surprisingly the burden of disease among pregnant women appears to parallel the geographic distribution seen in young children, with Asia and Africa bearing a disproportionate burden. This first attempt to define the problem suggests, conservatively, that 5.6% of all pregnant women, or approximately 7.3 million, are vitamin A deficient in a given year. Vitamin A-deficient women are at a 4.5-fold higher risk of pregnancy-related mortality than non-deficient women. The estimates generated for this project suggest that more than 20% of all maternal deaths in the world may be attributable to vitamin A deficiency. The method used to generate this particular estimate (applying the relative risk of death associated with vitamin A deficiency to all causes of maternal death) may somewhat overestimate the burden of disease related to vitamin A deficiency. It also does not address the prevalence, burden, or potential health consequences of vitamin A deficiency among non-pregnant women of reproductive age, which remain largely unknown.

In addition to estimating the number of preventable deaths, the results from this project suggest that approximately 27 million DALYs are associated with vitamin A deficiency. Given that DALYs provide a composite measure of disease burden associated with both fatal and non-fatal health conditions and that childhood mortality related to infectious diseases is the primary health outcome known to be associated with vitamin A deficiency, it is not surprising that the vast majority of the estimated DALYs (~23 million) are related to infectious disease causes of death in children.

In summary, vitamin A deficiency affects vulnerable populations throughout critical stages of life, as revealed by these estimates of disease burden in young children and pregnant women. Successful efforts to control and reduce vitamin A deficiency have the potential to improve the health and well-being of women and children around the world and to reduce the global burden of disease associated with this nutritional risk factor.

## 8. EXPECTED CHANGES IN THE PREVALENCE OF VITAMIN A DEFICIENCY

Based on the trends observed over the past 20 years, and more specifically on changes over the past 5–10 years, there is reason for optimism and the expectation that the global prevalence of vitamin A deficiency (defined as serum retinol concentrations  $<0.70\mu\text{mol/l}$ ) will decrease in the years leading up to 2030.

Numerous factors contribute to the current situation. In recent years a favourable global policy environment has been created and global partnerships have emerged to help guide activities aimed at the control and prevention of vitamin A deficiency. Various groups have contributed to the positive policy environment including IVACG, international organizations, bilateral agencies and individual country governments around the world.

Although these groups initially focused their attention almost exclusively on the more obvious problem of vitamin A deficiency among children, the situation is now changing. Policy-makers and programme managers are increasingly expanding their efforts in recognition of the fact that vitamin A deficiency is also prevalent among women of reproductive age and has potentially severe health consequences for them as well.

Many countries have already initiated national supplementation programmes for children (most commonly using community-based health services as a routine delivery channel or special vitamin A distribution initiatives combined with national immunization days or child health days or weeks) in an effort to prevent severe vitamin A deficiency among this age group. Although child-based supplementation programmes do not necessarily directly address the problem of vitamin A deficiency among women, other more general approaches may, if the accompanying health messages are modified to specifically encourage women as participants and programme beneficiaries. These include widespread food fortification initiatives, efforts to improve the availability of vitamin A rich foods through agricultural programmes, nutrition education programmes, etc.

Projections for the global prevalence of vitamin A deficiency for the 30-year time period from 2000 to 2030 were developed for the CRA project based on the assumption that the policy and programming environment will remain positive and that prevention and control activities will not only keep pace, but will exceed future population growth.

The global prevalence of 21.1% for serum retinol concentrations  $<0.70\mu\text{mol/l}$  (in preschool-age children) in the year 2000 was used as the baseline prevalence rate. Reductions of 10%, 20% and 30% were projected over the next three decades, resulting in estimated global prevalence rates of 19.0%, 16.9% and 14.8%, in the years 2010, 2020 and 2030, respectively. Although specific programmes to address vitamin A

deficiency in women have started much more recently, the same percentage reductions (10%, 20% and 30%) in prevalence rates were assumed for the purposes of the CRA project. Starting with an assumed baseline rate of 5.6% in 2000, prevalence rates of 5.0%, 4.5% and 3.9% were projected for 2010, 2020 and 2030, respectively.

## ACKNOWLEDGEMENTS

Supported by the Family Health and Child Survival (FHACS) Cooperative Agreement, between the United States Agency for International Development (USAID), Office of Health and Nutrition, and The Johns Hopkins Bloomberg School of Public Health, Department of International Health (JHU), and by the World Health Organization Global Programme on Evidence for Health Policy. The authors thank Maria Andersson and Bruno de Benoist for data used to update the vitamin A deficiency prevalence estimates, and Anuraj H. Shankar for helpful comments on malaria issues. The authors are grateful for the assistance of Steve Fishman, Jeffrey McGuckin and Jonathan Sugimoto in compiling data for the project, and for the valuable insight and advice from other colleagues in the field of international health.

## NOTE

1 See preface for an explanation of this term.

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