Estimating the burden of disease attributable to vitamin A deficiency in South Africa in 2000

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Objectives. To estimate the burden of disease attributable to vitamin A deficiency in children aged 0 - 4 years and pregnant women aged 15 - 49 years in South Africa in 2000.

Design. The framework adopted for the most recent World Health Organization comparative risk assessment (CRA) methodology was followed. Population-attributable fractions were calculated from South African Vitamin A Consultative Group (SAVACG) survey data on the prevalence of vitamin A deficiency in children and the relative risks of associated health problems, applied to revised burden of disease estimates for South Africa in the year 2000. Small community studies were used to derive the prevalence in pregnant women. Monte Carlo simulation-modelling techniques were used for the uncertainty analysis.

Setting. South Africa.

Subjects. Children under 5 years and pregnant women 15 - 49 years.

Outcome measures. Direct sequelae of vitamin A deficiency, including disability-adjusted life years (DALYs), as well as mortality associated with measles, diarrhoeal diseases and other infections, and mortality and DALYs associated with malaria in children and all-cause maternal mortality.

Results. One-third of children aged 0 - 4 years and 1 - 6% of pregnant women were vitamin A-deficient. Of deaths among young children aged 0 - 4 years in 2000, about 28% of those resulting from diarrhoeal diseases, 23% of those from measles, and 21% of those from malaria were attributed to vitamin A deficiency, accounting for some 3 000 deaths. Overall, about 110 467 (95% uncertainty interval 86 388 - 136 009) healthy years of life lost, or between 0.5% and 0.8% of all DALYs in South Africa in 2000 were attributable to vitamin A deficiency.

Conclusions. The vitamin A supplementation programme for children and the recent food fortification programme introduced in South Africa in 2003 should prevent future morbidity and mortality related to vitamin A deficiency. Monitoring the effectiveness of these interventions is strongly recommended.

S Afr Med J 2007; 97: 748-753.

Vitamin A deficiency continues to be a major public health problem in developing countries, and is estimated to affect about 127 million preschool children and more than 7.2 million pregnant women worldwide.[1] According to the *World Health Report* of 2002,[2] the global prevalence of vitamin A deficiency in children aged 0 - 4 years was about 21% and the prevalence of night blindness in pregnant women 5%, both being highest in Asia and Africa.[2,3]

Vitamin A is essential for maintaining normal vision, gene expression, reproduction, embryonic development, growth and immune function.[4] The clinical manifestation of vitamin A deficiency is xerophthalmia, a collective term for abnormalities that can range from night blindness in its mildest form to permanent blindness in its most severe form.[5] The systemic consequences of vitamin A deficiency, viz. increased rate of infection-related morbidity and mortality, may however begin to occur long before ocular signs of clinical deficiency are evident.[6] In settings where vitamin A deficiency is prevalent, vitamin A supplementation has been shown to result in a 30% reduction in all-cause mortality[7] as well as reductions in morbidity. The morbidity conditions particularly beneficially affected by the amelioration of vitamin A deficiency are diarrhoeal diseases, respiratory disease and measles.[8,9]

The main cause of vitamin A deficiency is a chronic inadequate intake of vitamin A-rich foods such as eggs, milk and liver,[10] as well as the poor bio-availability of β-carotene from dark green and yellow vegetables or fruit.[11] Repeated infections may, however, also contribute towards the depletion of vitamin A stores,[12] especially when accompanied by fever.[13,14] Serum vitamin A levels are also known to be low in individuals infected with HIV.[15] Vitamin A status can also be affected by heavy loads of parasitic infestations such as *Ascaris lumbricoides* and *Giardia lamblia*,[16,17] which may interfere with the absorption of vitamin A.

Serum retinol is the indicator most widely used for assessing vitamin A status. Although there is no direct evidence of

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the level at which functional consequences of vitamin A deficiency (i.e. morbidity and mortality) begin to occur, serum concentrations below 20 µg/dl (0.70 µmol/l) are conventionally used to indicate inadequate status,[18] and serum retinol concentrations below 10 µg/dl (0.35 µmol/l) may be associated with ocular signs of vitamin A deficiency. At a population level vitamin A deficiency is considered to be a significant public health problem when more than 15% of that population present with serum retinol concentrations below 20 µg/dl.[6] However, because clinical and subclinical infection may have a transient lowering effect on serum retinol concentrations, it is recommended that infection status also be measured when vitamin A status is assessed so that overestimation of the prevalence of vitamin A deficiency is avoided.[19]

According to a national survey conducted in 1994/95 (South African Vitamin A Consultative Group (SAVACG)),[20] 33% of children aged 6 - 71 months in South Africa have serum retinol concentrations below 20 µg/dl, which is higher than the global average estimate of 21% for that age group. The prevalence varies from province to province and ranges from 18.5% to 43.5%, with the Limpopo and KwaZulu-Natal provinces being most severely affected. Children living in rural areas and whose mothers are poorly educated are also more affected. There are no national data on the prevalence of vitamin A deficiency in pregnant women. However, *ad hoc* studies suggest that prevalence in this population group ranges from 1% to 6%.[21,22,23] These figures are comparable with global estimates.

The global risk factor assessment found that 0.8 million (1.4%) of deaths worldwide are due to vitamin A deficiency,[2] and that 1.8% of the global burden of disease measured in disability-adjusted life years (DALYs) can be attributable to this deficiency. The aim of the present study was to estimate the burden of disease in South Africa attributable to vitamin A deficiency in children 0 - 4 years of age and pregnant women in 2000.

Methods

Comparative risk assessment (CRA) methodology developed by the World Health Organization (WHO)[2,24] was used. The amount of disease burden attributable to exposure to vitamin A was estimated by comparing the current observed level of vitamin A deficiency with a counterfactual risk factor distribution conferring the lowest possible population risk (the theoretical minimum distribution). For vitamin A deficiency the theoretical minimum was defined by the absence of vitamin A deficiency in the population.[2,3]

Vitamin A deficiency itself appears as an underlying cause of death and disability in the South African burden of disease list.[25] Although there were no deaths in South Africa in 2000 directly ascribed to vitamin A deficiency, a considerable non-fatal component was estimated for this condition, measured in years of life lived with disability (YLDs) through the direct effects of vitamin A deficiency and its sequelae in all age groups. Following the framework developed by Rice *et al*.,[3] the contribution of vitamin A deficiency to child mortality and morbidity can also be measured indirectly through its contribution as a risk factor for several diseases, and added to the direct effects of vitamin A deficiency.

The health outcomes assessed were based on those selected by the WHO international expert collaborating group on vitamin A deficiency.[3] They were restricted to those outcomes included in the 2000 Global Burden of Disease Study,[26,27] and where data were available to quantitatively estimate the relationship with vitamin A deficiency. These included childhood mortality associated with measles, diarrhoeal diseases, malaria and other infectious diseases (which captures the contribution of many low-incidence causes of death under one category), all-cause maternal mortality and childhood morbidity from malaria. HIV/AIDS was excluded as a quantifiable health outcome since the strength of the evidence was considered insufficient to demonstrate a causal link or to estimate the associated risk with this outcome. Blindness was also excluded as a health outcome because vitamin A-related blindness is considered to be a direct functional outcome of the deficiency. Hence, the disability associated with blindness is included in vitamin A deficiency YLDs following the method of Murray *et al*.[26,27]

Prevalence of vitamin A deficiency was defined as low serum retinol concentrations (< 0.70 µmol/l or < 20 µg/dl) among children aged 0 - 4 years and among pregnant women (aged 15 - 49 years).[3] The data source used for prevalence of exposure in children was the SAVACG national survey of 1995, which presented data for a nationally representative sample of children aged 6 - 71 months[20] although white children may have been underrepresented. The SAVACG data were re-analysed to estimate the prevalence of vitamin A deficiency in children 0 - 4 years of age. In the absence of national data, the prevalence of vitamin A deficiency in pregnant women in South Africa was estimated from data from 3 studies: Dannhauser *et al*.[21] (2000), Dhansay *et al*.[22] (2001) and Dhansay *et al*.[23] (1994). In the Dannhauser *et al*.[21] study, a sample of 206 mainly black African women from low-income groups in the second and third trimesters of pregnancy yielded a prevalence of 1% for the whole group. In a cohort of 300 women of mixed ethnic descent at various stages of pregnancy from a low-income suburb of Cape Town, the percentage that were vitamin A-deficient (< 0.70 µmol/l or < 20 µg/dl) was 1.9% at less than 20 weeks' gestation and 1.1% between 28 and 34 weeks' of pregnancy.[22] A cross-sectional study of 105 pregnant women in the third trimester in the same community showed the prevalence of vitamin A deficiency to be 6%.[23] Since the global average prevalence of serum retinol concentrations of < 0.70 µmol/l among pregnant women was estimated at 5.6%,[3] we carried out uncertainty analysis using a range of 1 - 6% for pregnant women (see uncertainty analysis below).

Relative risks (RRs) used for each health outcome were those estimated for the global CRA project[3] based on a comprehensive review of the literature and meta-analyses of randomised placebo-controlled vitamin A supplementation trials in women and children. These are shown in Table I, expressed as the inverse of the protective effect adjusted for baseline prevalence of serum retinol concentrations of < 0.70 µmol/l in trial populations.[28,29] Since RR estimates for child and maternal health outcomes used vitamin A intervention trial data as the starting point, the RRs were adjusted using a 4-step process to take into account the fact that many, but not all, study participants had low serum concentrations at the beginning of the intervention trials.[3]

Population-attributable fractions by age and cause were calculated in MS Excel using the formula:

$$PAF = \frac{P\,(RR-1)}{P\,(RR-1)+1}$$

where P is the prevalence of exposure and RR is the relative risk of disease in the exposed versus unexposed group. The population-attributable fractions were then applied to the revised South African burden of disease estimates for deaths and DALYs for 2000.[25]

Monte Carlo simulation-modelling techniques were used to present uncertainty ranges around point estimates that reflect all the main sources of uncertainty in the calculations. The @ RISK software version 4.5 for Excel[31] was used, which allows multiple recalculations of a spreadsheet each time choosing a value from distributions defined for input variables. The probability distributions around the input variables were based on standard errors of the prevalence for children aged 0 - 4 years from the SAVACG data.[20] For the prevalence of vitamin A deficiency among pregnant women, a uniform probability distribution was specified, with a minimum of 1% and a maximum of 6% (yielding a midpoint estimate of about 3.5%). For the RR input variables a normal distribution was specified, with the natural logarithm of the RR estimates as the entered means of the distribution and standard errors derived from the published 95% confidence intervals.[3] The 95% uncertainty ranges were calculated for the output variables, namely attributable burden as a percentage of total burden in South Africa in 2000 (bounded by the 2.5th and 97.5th percentiles of the 2000 iteration values generated).

Table I. Adjusted relative risks (RRs) of adverse health outcomes associated with vitamin A deficiency

Health outcome	ICD-9 codes[30]	RR* associated with vitamin A deficiency	
		RR	95% CI
Children (0 - 4 years)			
Diarrhoeal disease mortality	001, 002, 004, 006-009	2.15[28]	1.83 - 2.58
Measles mortality	055	1.86[28]	1.32 - 2.59
Malaria incidence	084	1.78[29]	1.43 - 2.19
Malaria mortality	084	1.78[29]	1.43 - 2.19
Selected other infectious disease causes of mortality	003, 005, 020-027, 031, 034, 035, 038†-041, 046-049, 051-054, 057, 060-066, 071-079, 080-083, 087, 088, 100-104,110-118, 121-124, 130-136, 139	1.13[28]	1.01 - 1.32
Pregnant women (15 - 44 years‡)			
All-cause maternal mortality	630-676	4.51[29]	2.91 - 6.94

Source: Adapted from Rice *et al.*[3]
*Adjusted for baseline prevalence of serum retinol concentrations < 0.70 µmol/l in trial population.
†038 Septicaemia; listed separately on the South African burden of disease list but included in this category for this analysis.
‡Attributable fractions calculated for women 15 - 49 years.
ICD-9 = *International Classification of Diseases*, 9th revision.

Table II. Population attributable fractions and burden attributable to vitamin A deficiency in children 0 - 4 years, South Africa, 2000

Related outcomes	PAF (%)	Attributable deaths	Attributable DALYs
Diarrhoeal diseases (mortality)	28	2 972	99 975
Measles (mortality)	23	44	1 488
Other infectious diseases (mortality)	4	45	1 506
Malaria (mortality and morbidity)	21	8	262
Vitamin A deficiency	100	0	460
Total attributable burden		**3 069**	**103 691**

PAF = population-attributable fraction; DALYs = disability-adjusted life years.

Table III. Burden attributable to vitamin A deficiency, South Africa, 2000

Burden	Total		Children aged 0 - 4 years		Females aged 15 - 49 years	
	Burden attributable to vitamin A deficiency	% of total burden	Burden attributable to vitamin A deficiency	% of total children 0 - 4 yrs*	Burden attributable to vitamin A deficiency	% of total females 15 - 49 yrs†
Deaths	**3 290**	**0.6**	**3 069**	**3.2**	**222**	**0.2**
95% uncertainty interval	2 570 - 4 056	0.5 - 0.8	2 379 - 3 806	2.5 - 4.0	66 - 440	0.1 - 0.5
DALYs	**110 467**	**0.7**	**103 691**	**2.5**	**6 776**	**0.2**
95% uncertainty interval	86 388 - 136 009	0.5 - 0.8	80 492 - 128 507	2.0 - 3.1	2 016 - 13 431	0.0 - 0.3

*Burden attributable to vitamin A deficiency in children 0 - 4 years as a % of total burden in children 0 - 4 years in South Africa, 2000.
†Burden attributable to vitamin A deficiency in pregnant women (15 - 49 years) as a % of total burden in females aged 15 - 49 years in South Africa, 2000.
DALYs = disability-adjusted life years.

Results

The prevalence of vitamin A deficiency in South African children aged 0 - 4 years was estimated at 33.8% using the SAVACG national data, which means that 1.8 million children were affected in 2000. For pregnant women, prevalence of vitamin A deficiency was estimated to be fairly low at 1%, but we used a range of 1 - 6% (midpoint 3.5%) for our calculations affecting about 38 500 births.

The population-attributable fractions (PAFs) for the selected health outcomes as well as the estimated number of cause-specific deaths and DALYs attributed to vitamin A deficiency among children aged 0 - 4 years are shown in Table II. PAFs ranged from 4% of mortality from other infectious diseases to 28% of mortality from diarrhoeal diseases. All (100%) vitamin A deficiency YLDs were attributed to vitamin A deficiency. Of 3 069 deaths in children attributed to vitamin A deficiency, the vast majority (N = 2 972) were due to diarrhoeal diseases. Diarrhoeal diseases accounted for 96.9% of all attributable deaths, while malaria (0.2%), other infectious diseases (1.5%) and measles (1.4%) accounted for much smaller proportions of total vitamin A-attributable deaths in children 0 - 4 years of age (Fig. 1).

About 11% of all maternal mortality (222 deaths) was attributed to vitamin A deficiency. In addition to estimating the preventable deaths, attempts were also made to estimate attributable disease burden in children 0 - 4 years of age and pregnant women. Overall, between 86 388 and 136 009 DALYs (0.5 - 0.8% of all healthy years of life lost (YLLs) in South Africa in 2000) were associated with vitamin A deficiency (Table III). Results of the uncertainty analysis are also presented in the table.

Discussion

Vitamin A deficiency is a public health problem among preschool children in South Africa, with 33.8% of children aged 0 - 4 years being vitamin A-deficient. The results of this study suggest that in 2000 about 28% of deaths from diarrhoeal diseases, 23% of those from measles and 21% of those from malaria in children aged 0 - 4 years could be attributed to vitamin A deficiency. In addition, 4% of mortality from other infectious diseases in children aged 0 - 4 years was also attributable to this risk factor.

Vitamin A deficiency accounted for 3 069 deaths in children aged 0 - 4 years (3.2% of all deaths in this age group). Predisposing children to risk of mortality from diarrhoeal diseases is the major consequence of vitamin A deficiency, accounting for 96.9% of the childhood deaths attributable to vitamin A deficiency. This is much higher than the estimated 50% from the global study, in which malaria and measles played a larger role. The burden from measles and malaria is relatively small in South Africa, probably reflecting good disease prevention and control for these conditions.

Despite assuming that women who were vitamin A-deficient had a 4.5-fold increased risk of maternal mortality compared with non-deficient women, only about 11% of maternal mortality in South Africa could be attributed to this risk factor. This is also lower than the estimated 20% of maternal deaths worldwide, and is a result of the relatively low prevalence of vitamin A deficiency among pregnant women in South Africa.

Overall, an estimated 110 467 (95% uncertainty interval 86 388 - 136 009) healthy YLLs, or between 0.5% and 0.8% of all DALYs in South Africa in 2000, are attributable to vitamin A

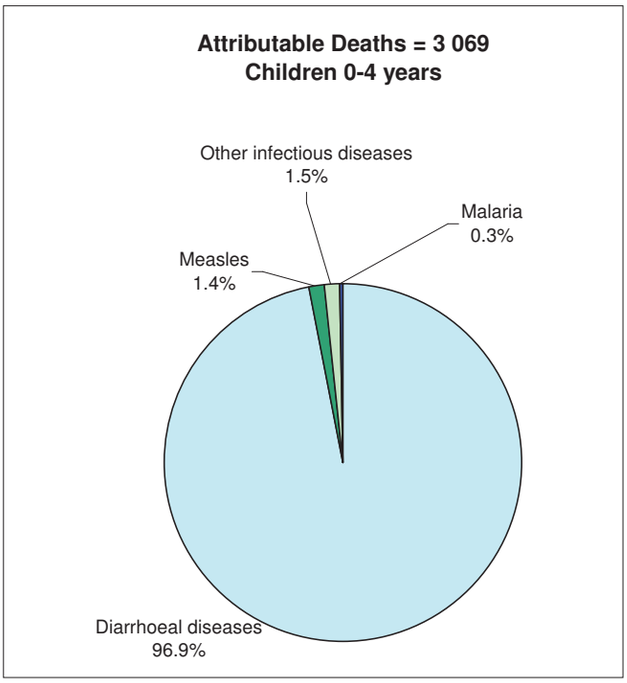

Fig. 1. Deaths attributable to vitamin A deficiency in children 0 - 4 years, South Africa, 2000

deficiency. This risk factor is ranked 14th overall in terms of DALYs for 17 risk factors assessed in South Africa, ranking lower than 'underweight' and other forms of micronutrient deficiencies such as iron-deficiency anaemia. Vitamin A is an important risk factor in children, ranking fourth overall and accounting for 2.5% (2.0 - 3.1%) of all healthy YLLs in children aged 0 - 4 years.

Given the high prevalence of HIV in South Africa, it is important to consider the possible role of vitamin A deficiency in HIV-related morbidity and mortality. Studies have shown that there is increased infant mortality in children born to HIV-positive mothers with vitamin A deficiency, and there is also a strong association between low serum retinol and CD4 counts for both seropositive and seronegative individuals.[32] Although the role of vitamin A supplementation to prevent mother-to-child transmission of HIV is unclear, and WHO guidelines raise concerns about the safety of vitamin A supplementation programmes, data show that vitamin A deficiency is more prevalent among HIV-positive persons than HIV-negative individuals.[33]

Research has shown the importance of optimal nutritional status of an individual in the progression from HIV to AIDS.[33] According to Kafwembe *et al.*,[34] vitamin A concentration is lowered in HIV infection and therefore the depletion of vitamin A appears to increase with progression of the infection leading to AIDS infection, and it delays recovery from other infections. Our estimate is likely to be an underestimation of the attributable burden due to vitamin A deficiency, since we have not quantified this impact. Furthermore, HIV/AIDS accounts for 40% of the total mortality in children aged 0 - 4 years, thus reducing the relative size of other conditions.

A report in 2002[35] showed that nationally, 35% of the clinics routinely administer vitamin A to HIV-positive children, and that of the 130 clinics where vitamin A is dispensed, less than one-quarter prescribe the correct regimen for HIV-infected children. According to the report, vitamin A supplementation in HIV-infected children was associated with reduced morbidity, particularly in relation to diarrhoeal disease, reduced mortality and improved immune function. Whether regular supplementation of vitamin A to the HIV-infected individual can lead to an altered progression to AIDS needs to be explored.[35]

In view of the role of infection in reducing the level of serum retinol,[19] it is possible that survey results overstate the true extent of vitamin A deficiency. This was not considered to be the case in the national SAVACG survey, since children with acute fever were excluded. The burden of disease attributable to vitamin A deficiency estimated in the present study was based on data from the SAVACG study, which were collected in 1994.[20] Since then, however, several interventions have been introduced in South Africa. A high-dose vitamin A supplementation programme targeting all children aged 6 months - 5 years and postpartum women within 4 - 8 weeks of delivery was introduced in 2002.[36,37] A national food fortification programme, whereby maize meal and wheat flour are fortified with several vitamins and minerals including vitamin A, was introduced in 2003.[38] The current levels of vitamin A deficiency could therefore be very different.

A national survey on the micronutrient status of preschool children and women is currently underway, and when these data become available it is suggested that the risk attributed to vitamin A deficiency be recalculated and the situation re-evaluated.

Conclusion and recommendations

Because supplementation and food fortification programmes have already been introduced in South Africa, operational research to monitor the effective implementation of these interventions and assessment of their impact are recommended. The possible negative consequences of blanket supplementation with high-dose vitamin A capsules in children who are not vitamin A-deficient should also be borne in mind.[39]

Another strategy that should not be ignored is that of dietary diversification. This is a long-term approach and should be the ultimate goal of any campaign to control micronutrient deficiencies. A project that focuses on home gardening and encourages the production and consumption of β-carotene-rich foods has, for instance, been successfully implemented in a rural area of KwaZulu-Natal, and was shown to significantly

improve vitamin A status of the preschool children in the area.[40]

The other members of the Burden of Disease Research Unit of the South African Medical Research Council: Pam Groenewald, Nadine Nannan, Michelle Schneider, Desireé Pieterse, Jane Joubert, Karin Barnard and Elize de Kock are thanked for their valuable contribution to the South African Comparative Risk Assessment Project. Ms Leverne Gething is gratefully acknowledged for editing the manuscript. Ms Ria Laubscher and Dr Lize van der Merwe of the MRC Biostatistics Unit made contributions via their statistical expertise and assistance. Dr Robert Black, a member of the Global and Regional Comparative Quantification of Health Risks Assessment Vitamin A Deficiency Team, was extremely helpful in providing advice and guidance and in obtaining relative risks and drafts of the global review chapters. He is also thanked for critically reviewing the manuscripts. Our sincere gratitude is also expressed for the valuable contribution of Associate Professor Theo Vos, University of Queensland School of Population Health. We thank him not only for providing technical expertise and assistance, but also for his enthusiasm and support from the initial planning stages of this project. The other directors of the SAVACG survey (Annemieke van Middelkoop, Anna Coutsoudis, Rudi Eggers, Gregory Hussey and Carl van IJsselmuiden) are thanked for granting us access to the dataset.

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