

Trends and mortality effects of vitamin A deficiency in children in 138 low-income and middle-income countries between 1991 and 2013: a pooled analysis of population-based surveys

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Summary

Background Vitamin A deficiency is a risk factor for blindness and for mortality from measles and diarrhoea in children aged 6–59 months. We aimed to estimate trends in the prevalence of vitamin A deficiency between 1991 and 2013 and its mortality burden in low-income and middle-income countries.

Methods We collated 134 population-representative data sources from 83 countries with measured serum retinol concentration data. We used a Bayesian hierarchical model to estimate the prevalence of vitamin A deficiency, defined as a serum retinol concentration lower than 0.70 µmol/L. We estimated the relative risks (RRs) for the effects of vitamin A deficiency on mortality from measles and diarrhoea by pooling effect sizes from randomised trials of vitamin A supplementation. We used information about prevalences of deficiency, RRs, and number of cause-specific child deaths to estimate deaths attributable to vitamin A deficiency. All analyses included a systematic quantification of uncertainty.

Findings In 1991, 39% (95% credible interval 27–52) of children aged 6–59 months in low-income and middle-income countries were vitamin A deficient. In 2013, the prevalence of deficiency was 29% (17–42; posterior probability [PP] of being a true decline=0.81). Vitamin A deficiency significantly declined in east and southeast Asia and Oceania from 42% (19–70) to 6% (1–16; PP>0.99); a decline in Latin America and the Caribbean from 21% (11–33) to 11% (4–23; PP=0.89) also occurred. In 2013, the prevalence of deficiency was highest in sub-Saharan Africa (48%; 25–75) and south Asia (44%; 13–79). 94 500 (54 200–146 800) deaths from diarrhoea and 11 200 (4300–20 500) deaths from measles were attributable to vitamin A deficiency in 2013, which accounted for 1.7% (1.0–2.6) of all deaths in children younger than 5 years in low-income and middle-income countries. More than 95% of these deaths occurred in sub-Saharan Africa and south Asia.

Interpretation Vitamin A deficiency remains prevalent in south Asia and sub-Saharan Africa. Deaths attributable to this deficiency have decreased over time worldwide, and have been almost eliminated in regions other than south Asia and sub-Saharan Africa. This new evidence for both prevalence and absolute burden of vitamin A deficiency should be used to reconsider, and possibly revise, the list of priority countries for high-dose vitamin A supplementation such that a country's priority status takes into account both the prevalence of deficiency and the expected mortality benefits of supplementation.

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Introduction

Vitamin A deficiency causes xerophthalmia, a range of eye conditions from night blindness to more severe clinical outcomes such as keratomalacia and corneal scars, and permanent blindness. Vitamin A deficiency is also associated with an increased risk of mortality from measles and diarrhoea in children.^{1–3} WHO recommends vitamin A supplementation with a dose of 30 mg retinol equivalents in infants aged 6–11 months and 60 mg retinol equivalents at least twice a year in young children aged 12–59 months living in settings where vitamin A deficiency is a public

health problem,⁴ with up to 100 countries implementing this guidance.⁵ Vitamin A supplementation is also included in international responses to child and maternal undernutrition—eg, in the Scaling-Up Nutrition initiative.⁶

To plan for these programmes, information is needed about the magnitude of vitamin A deficiency in different regions and countries and how it has changed over time while changes in general nutrition of the population have occurred. WHO has compiled data for vitamin A deficiency by country and used the data to make estimates of vitamin A deficiency worldwide and by region, at

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Research in context

Evidence before this study

We searched PubMed without date limits, using the search terms “vitamin A deficiency”, “trend” or “forecasting”, and “spatial” or “subnational”. No language restrictions were applied.

Additionally to indexed articles, many such comparisons are in national and international agency reports, which we also identified and accessed through requests to national and international organisations. For the associations between vitamin A deficiency in children and cause-specific mortality, we used a systematic review and the DEVTA trial, which has been published since the completion of that review.

WHO has compiled data for vitamin A deficiency by country and used the data to make estimates of vitamin A deficiency worldwide and by region, at specific points in time. Other researchers have also reported change across repeated surveys. Researchers, together with the UN Standing Committee on Nutrition, used a regression with time-varying covariates to analyse how vitamin A deficiency has changed in world regions. Studies have also estimated deaths attributable to vitamin A deficiency at one or two timepoints using data for prevalence and relative risks for the effects of vitamin A deficiency on cause-specific mortality.

Added value of the study

Our study advances the international reporting and comparison of vitamin A deficiency and its mortality burden by compiling the latest surveillance data and estimation of trends in deficiency and burden by world region. We estimated that vitamin A deficiency was most prevalent in sub-Saharan Africa and south Asia, where there has been no evidence of a reduction in prevalence since 1991. By contrast, prevalence has decreased in east and southeast Asia and Oceania, and a decline in Latin America and the Caribbean might have also occurred. The absolute mortality burden of vitamin A deficiency has been more than halved since 2000 alone, including major reductions in sub-Saharan Africa and south Asia.

Implications of all the available evidence

This new evidence on both prevalence and absolute burden of vitamin A deficiency should be used to reconsider, and possibly revise, priority countries for vitamin A supplementation. Improved data for vitamin A deficiency in high-prevalence regions are also needed.

specific points in time.^{7,8} Other researchers have also reported change across repeated surveys.^{9–11} Researchers, together with the UN Standing Committee on Nutrition, used a regression with time-varying covariates to analyse how vitamin A deficiency has changed in world regions.^{9,11}

Some studies have also estimated deaths attributable to vitamin A deficiency at one or two timepoints using data for prevalence and relative risks (RRs) for the effects of vitamin A deficiency on cause-specific mortality.^{12–16} In the past few decades, child mortality has decreased substantially in most countries,¹⁷ with lower mortality from diarrhoea, an important contributor to this decline.¹⁸ Mortality from measles, another disease affected by vitamin A deficiency, has also decreased faster than overall child mortality.¹⁸ Therefore, mortality attributable to vitamin A deficiency might have changed above and beyond what is due to a change in the prevalence of deficiency. We aimed to estimate trends in the prevalence of vitamin A deficiency and the number of child deaths attributable to this risk factor during a period in which both the prevalence of deficiency and cause-specific child mortality are likely to have changed.

Methods

Study design

Our aim was to estimate the prevalence of vitamin A deficiency and the number of child deaths attributed to vitamin A deficiency for every low-income and middle-income country over time. Our analysis had three components: first, we gathered data for the prevalence of vitamin A deficiency and the RRs for the association

between vitamin A deficiency and mortality. Second, we synthesised these data to generate estimates of trends in vitamin A deficiency prevalence, in children aged 6–59 months, and pooled RRs for its effects on specific causes of child death. Third, we calculated the number of deaths attributable to vitamin A deficiency. We did all calculations by country for 138 low-income and middle-income countries; we grouped countries into five regions for modelling and presentation (appendix).

Data sources

Our data search and access strategy was designed to obtain as many sources as possible while ensuring that the sources were representative of the population at the national level or at least a first administrative unit within the country. We included data from the WHO Vitamin and Mineral Nutrition Information System Micronutrients Database,¹⁹ data reported by other agencies, and those in the published scientific literature. Additional details about our data search, data access, inclusion criteria, flow chart of data access, and data sources are in the appendix.

We used serum retinol concentration as an indicator of vitamin A deficiency because it is the most commonly used biomarker for assessment of subclinical vitamin A deficiency at the population level.^{19,20} Vitamin A deficiency was defined as serum retinol concentrations lower than 0.70 µmol/L. We did not use data for clinical indicators of vitamin A deficiency—namely, xerophthalmia (eg, night blindness, corneal scarring, and Bitot’s spots). We took this approach because night blindness and corneal

See [Online](#) for appendix

scarring are not usually measured in children younger than 2 years of age. We attempted to convert prevalence of Bitot's spots, which is measured more commonly in children,¹⁹ to prevalence of low serum retinol concentration but the association between the two variables was weak and heterogeneous (appendix), and hence did not allow robust conversion. This might be because Bitot's spots are sometimes associated with previous versus current vitamin A deficiency.²¹ Some surveys²² have used retinol-binding protein as an indicator of vitamin A status instead of serum retinol because its measurement is less costly. However, we identified very few sources that had measured both serum retinol and retinol-binding protein and hence could not develop a statistical model to convert retinol-binding protein to serum retinol.

We obtained RRs for the effects of vitamin A deficiency on mortality from measles and diarrhoea from randomised trials of vitamin A supplementation (appendix). Most of these trials were summarised in systematic reviews and meta-analyses.^{1,2} The DEVTA trial³ has been published since these reviews were completed and was included here. Consistent with the conclusions of systematic reviews,^{1,2} we restricted the mortality effects to ages 6–59 months, the age range in which trials have collectively identified an effect. The number of deaths in children aged 1–59 months by cause for 2000–13 was obtained from WHO and the Child Health Epidemiology Reference Group, with data sources and methods described in detail elsewhere.¹⁸ Following the analyses used in the *Lancet* Series on Maternal and Child Undernutrition published in 2013,¹⁴ we estimated that 79% of postneonatal child diarrhoea deaths occur in children aged 6–59 months,²³ and that all post-neonatal child measles deaths occur in children aged 6–59 months of age; this estimate is based on an analysis of verbal autopsy data by age group (Li Liu, John Hopkins University, personal communication).

Statistical analysis

Nine (7%) of the 134 data sources reported mean serum retinol or prevalence of deficiency based on serum retinol concentrations less than 0.35 $\mu\text{mol/L}$ or serum retinol concentrations less than 1.05 $\mu\text{mol/L}$ (appendix). We used data sources that had reported both prevalence of serum retinol concentrations less than 0.70 $\mu\text{mol/L}$ and any of the other three metrics to develop regression models to estimate serum retinol. This approach has been successfully used to convert between prevalence of diabetes, hypertension, or obesity and mean blood glucose, blood pressure, or body-mass index,^{24–26} and to convert between severity cutoffs used to define blindness and impaired vision.²⁷ We accounted for the additional uncertainty associated with this conversion by combining the regression uncertainty with that caused by sampling.

The statistical methods are described in detail in a previous publication.²⁸ Briefly, we used a Bayesian hierarchical probit model, which uses all available data to make estimates for each country-year. In the hierarchical

model, estimates for each country-year were informed by data from that country-year itself, if available, and by data from other years in the same country and in other countries, especially those in the same region with data from similar time periods. The hierarchical model shares information to a greater degree where data are non-existent or weakly informative (ie, have large uncertainty), and to a lesser degree in countries or regions and in years with more data. We modelled trends over time as a linear trend. We did not include a non-linear term, as done for stunting, underweight, or anaemia,^{28–30} because fewer countries had several data sources for vitamin A deficiency than for other nutritional indicators; this data scarcity limits robust estimation of non-linear trends. The estimates were also informed by covariates that might help to predict vitamin A deficiency at the population level, including national income (logarithm of per-person gross domestic product [GDP] in inflation-adjusted international dollars), maternal education, proportion of population that lived in urban areas, mean weight-for-age Z score, and an aggregate metric of availability of calories and animal-source foods.^{31,32} The model included a variance term that accounted for unobserved design factors (sample design, season, retinol measurement method, etc) that led to variability in the data beyond that expected because of sample size. Finally, the model accounted for the fact that subnational data might have larger variation than national data by including an additional, empirically estimated, random effect for subnational data.

The uncertainties of our estimates incorporate the sampling error in each data source; non-sampling error arising from issues in sample design and measurement that affects the variability of reported prevalences; additional error associated with subnational data; uncertainty associated with converting from mean serum retinol, prevalence of serum retinol concentrations lower than 0.35 $\mu\text{mol/L}$, or prevalence of serum retinol concentrations lower than 1.05 $\mu\text{mol/L}$ to the primary outcome; and uncertainty due to making estimates by country and year when data were missing.

We fitted the Bayesian model using the Markov chain Monte Carlo (MCMC) algorithm and obtained 1000 samples of the model variables, which were used to obtain 1000 posterior samples of vitamin A deficiency for each country-year. Prevalences for regions and the world were calculated as population-weighted averages of those of the constituent countries. All reported credible intervals represent the 2.5th–97.5th percentiles of the MCMC draws. We report the posterior probability (PP) that an estimated increase or decrease in prevalence represents a truly decreasing trend. The PP would be 0.50 when a decrease is statistically indistinguishable from an increase, a PP larger than 0.50 indicates more certainty about a decreasing trend, and a PP smaller than 0.50 indicates more certainty about an increasing trend.

We obtained RRs for the association between vitamin A deficiency and cause-specific mortality by pooling RRs of

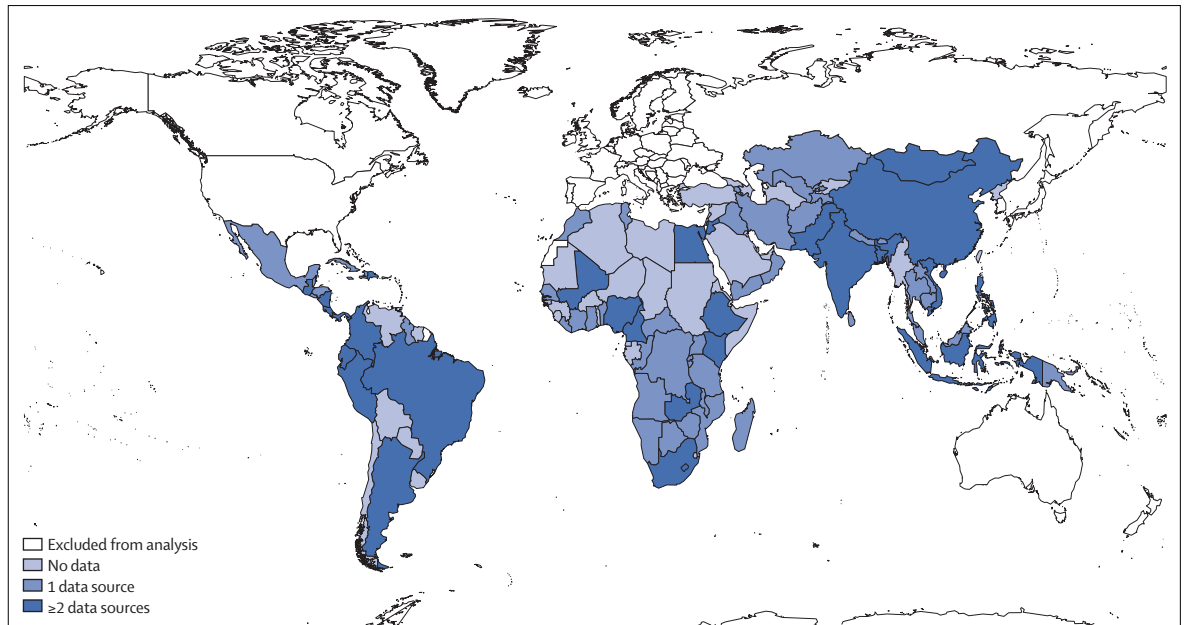


Figure 1: Number of data sources used in the analysis, by country

	Prevalence in 1991 (%)	Prevalence in 2000 (%)	Prevalence in 2013 (%)	PP of decrease
Central Asia, Middle East, and north Africa	19% (5–40)	14% (7–23)	11% (2–27)	0.76
East and southeast Asia and Oceania	42% (19–70)	21% (14–30)	6% (1–16)	0.99
Latin America and the Caribbean	21% (11–33)	15% (10–22)	11% (4–23)	0.89
South Asia	47% (14–78)	46% (28–62)	44% (13–79)	0.54
Sub-Saharan Africa	45% (29–60)	49% (40–58)	48% (25–75)	0.45
All low-income and middle-income countries	39% (27–52)	33% (27–39)	29% (17–42)	0.81

Data are % (95% CrI), unless otherwise specified. Tabulations by WHO, UNICEF, and UN regions are presented in the appendix. A PP greater than 0.50 indicates a decrease and a PP smaller than 0.50 indicates an increase in deficiency. PP=posterior probability. CrI=credible interval.

Table 1: Estimated prevalence of vitamin A deficiency by region in 1991, 2000, and 2013, and the PP that the reported decrease is a true decrease

randomised intervention studies. The participants of randomised vitamin A supplementation trials might be a mix of children who were vitamin A deficient and those who had adequate vitamin A intake. Supplementation benefits the deficient participants to the extent that it compensates for inadequate dietary intake. For this reason, and following previous analyses of vitamin A deficiency and anaemia,^{12,33} we adjusted trial RRs for background prevalence of deficiency to calculate the reduction in risk in the deficient group (appendix). We used background prevalence in the trial participants when available, and the estimated national prevalence from our own analysis when the trial had not measured baseline serum retinol. We then pooled the adjusted RRs using a random-effects model.³⁴

We calculated the population attributable fraction (PAF), which is the proportional reduction in deaths from diarrhoea and measles that would occur if vitamin A

deficiency had been eliminated.¹⁵ We calculated the number of deaths from diarrhoea and measles attributable to vitamin A deficiency by multiplying their corresponding PAF by total deaths from that disease. To calculate the uncertainties of the number of deaths attributable to vitamin A deficiency, we used 1000 draws from the uncertainty distributions of each input (prevalence, RR, and total number of cause-specific deaths), and repeated the calculations using these draws. The resulting distribution characterised the uncertainty distributions of the number of deaths attributable to vitamin A deficiency.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. GAS and JEB had full access to the data. ME had final responsibility for the decision to submit for publication.

Results

We collated 134 population-representative data sources from 83 countries with measured serum retinol concentration data (appendix). Of these, 70 were from the 1990s and 64 were from 2000 or later. 90 (67%) were nationally representative. 29 countries had two or more data sources, and 54 countries had only one data source. 55 countries had no data (figure 1). Because of limited availability and large within-region and within-country variations in measured prevalences, the estimated prevalences had large uncertainty compared with other risk factors,^{24–26,28,29,35} even at the regional level (table 1).

In 1991, 39% (95% credible interval [CrI] 27–52) of children in low-income and middle-income countries

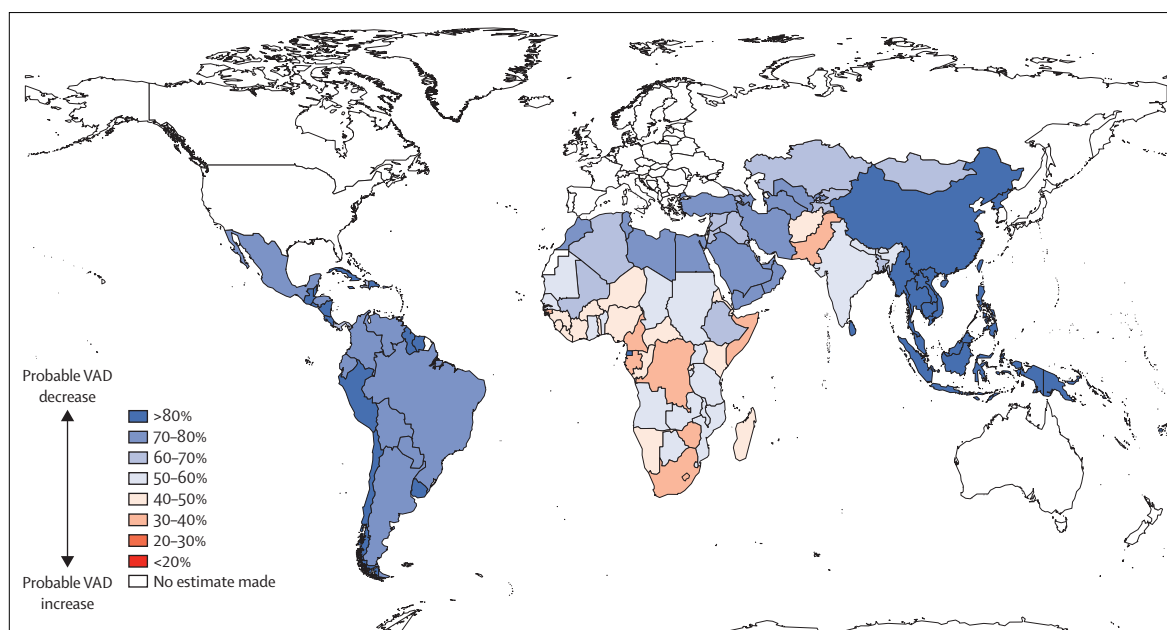


Figure 2: The posterior probability that vitamin A deficiency decreased from 1991 to 2013
VAD=vitamin A deficiency.

were vitamin A deficient (table 1). Regional prevalences in 1991 ranged from more than 40% in sub-Saharan Africa, south Asia, and east and southeast Asia and Oceania, to less than 25% in Latin America and the Caribbean, and in the region of central Asia, the Middle East, and north Africa. Nationally, the prevalence of vitamin A deficiency was at least 8% in every country; 100 countries had a prevalence of at least 20%, and hence would be classified as having a public health problem by WHO.

Trends in the prevalence of deficiency from 1991 to 2013 varied by region, with a slight improvement at the worldwide level to 29% (17–42; PP of being a true decline=0·81). Deficiency significantly decreased in only one region: east and southeast Asia and Oceania, from 42% (19–70) to 6% (1–16; PP=0·99). The prevalence of deficiency might have decreased in Latin America and the Caribbean to 11% (4–23) in 2013 (PP=0·89) and in central Asia, Middle East, and north Africa to 11% (2–27) in 2013 (PP=0·76). In sub-Saharan Africa and south Asia, little change in prevalence occurred during the analysis period; both regions had prevalences of more than 40% for all years during the analysis period.

The prevalence of vitamin A deficiency decreased by more than 20 percentage points in 24 countries: 23 of these countries were in east and southeast Asia and Oceania and one was in sub-Saharan Africa; the PPs for declines in these countries ranged between 0·86 and greater than 0·99 (figure 2). Many countries in south Asia and sub-Saharan Africa had no improvement and some might even have had a deterioration in vitamin A status during this period. By 2013, the prevalence of

vitamin A deficiency was between 3% and 9% in 47 countries: 21 in Latin America and the Caribbean, 12 in east and southeast Asia and Oceania, and 14 in central Asia, north Africa, and the Middle East (figure 3). Prevalence was 20% or higher in 56 countries, and was more than 40% in three south Asian and 40 African countries.

In the pooled analysis of randomised trials, vitamin A supplementation was associated with a 24% (95% CI 7–38) reduction in the risk of dying from diarrhoea and a 14% (–8 to 32) reduction in the risk of dying from measles (appendix). After adjustment for background prevalences, being vitamin A deficient was associated with a RR of 1·69 (1·17–2·45) for death from diarrhoea and 1·26 (0·84–1·87) for death from measles.

94 500 (95% CrI 54 200–146 800) deaths from diarrhoea and 11 200 (4300–20 500) deaths from measles were attributable to vitamin A deficiency in 2013 (table 2). These figures amount to 1·7% (1·0–2·6) of all deaths in children younger than 5 years in low-income and middle-income countries. The number of deaths attributable to vitamin A deficiency in 2013 was less than half of those in 2000, when the number of attributable deaths was 266 200 (188 800–334 700). By comparison, the share of deaths in children younger than 5 years attributable to this deficiency was somewhat similar in the two periods: 2·7% (1·9–3·5) in 2000 and 1·7% (1·0–2·6) in 2013. In view of the fact that little reduction occurred in the prevalence of deficiency in the highest-burden regions (south Asia and sub-Saharan Africa), the worldwide decrease in vitamin-A-deficiency-attributable deaths was mainly due to reduced deaths from diarrhoea and

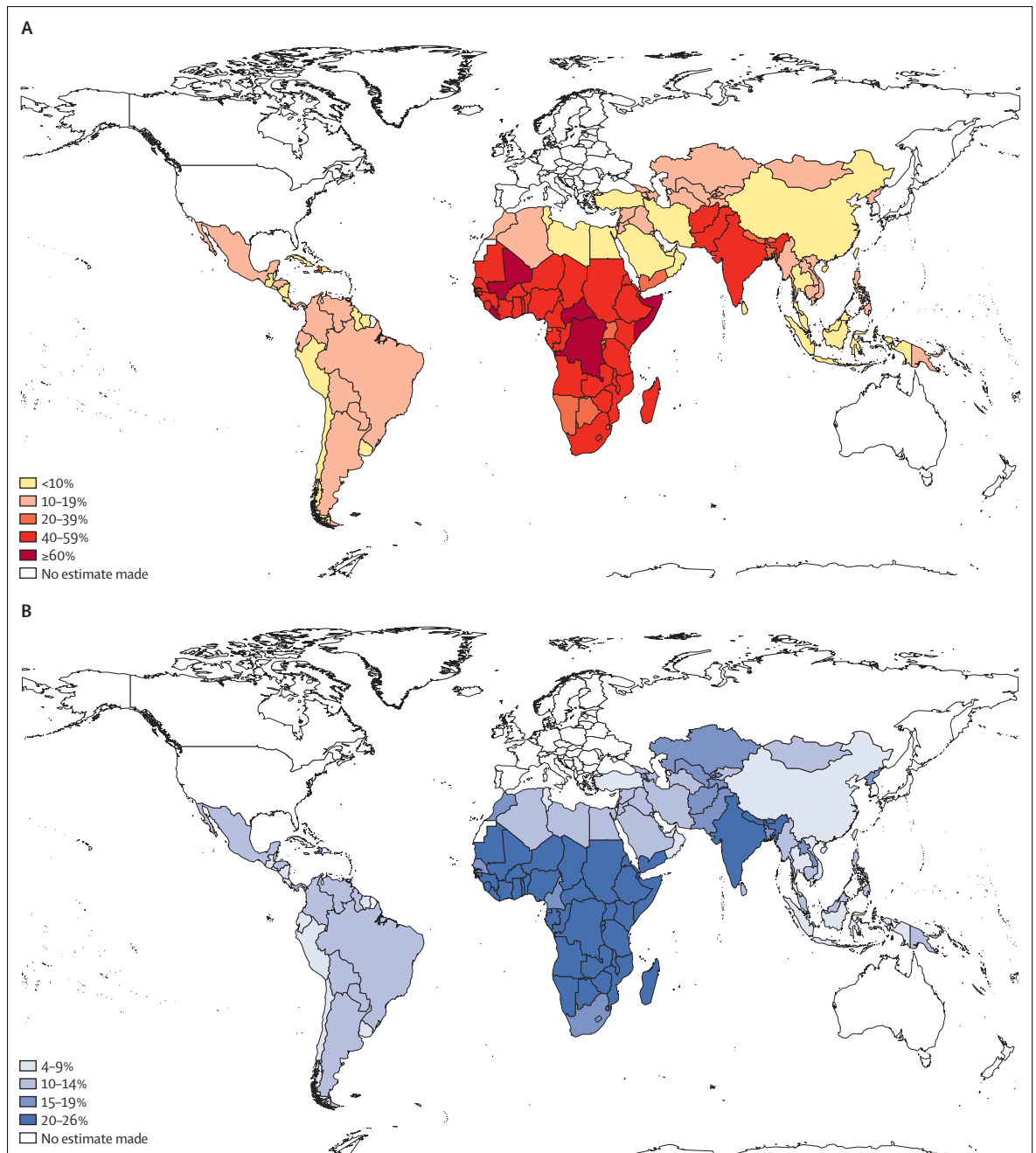


Figure 3: Estimated prevalence of vitamin A deficiency in children aged 6 to 59 months by country in 2013 (A) and the posterior standard deviation (analogous to standard error in non-Bayesian analysis) of the estimates (B)

measles in south Asia and sub-Saharan Africa. In 2013, more than 95% of deaths attributable to vitamin A deficiency occurred in sub-Saharan Africa and south Asia, where both the prevalence of deficiency and child mortality are high. In these regions, vitamin A deficiency accounted for 2.0% (1.0–3.4) of all deaths in children younger than 5 years in sub-Saharan Africa and 2.0% (0.7–3.5) of all deaths in children younger than 5 years in south Asia.

Discussion

Our estimates of the prevalence of vitamin A deficiency in developing countries using population-based data suggest that deficiency is highest in south Asia and sub-Saharan Africa, where our results indicate little change during the past two decades; however, our estimates are very uncertain because of data limitations. We noted evidence of improvement in east and southeast Asia and Oceania, and suggestion of improvement in Latin

	Diarrhoea		Measles		All causes	
	Number (in thousands)	Proportion of all deaths (%)	Number (in thousands)	Proportion of all deaths (%)	Number (in thousands)	Proportion of all deaths (%)
2000						
Central Asia, Middle East, and north Africa	3.7 (1.6–5.9)	8.2% (3.7–13.3)	0.4 (0.0–0.9)	5.0% (0.8–12.3)	4.1 (1.8–6.5)	0.9% (0.4–1.4)
East and southeast Asia and Oceania	11.5 (7.1–17.6)	10.5% (6.7–15.5)	2.3 (0.5–4.8)	7.2% (1.9–16.2)	13.9 (8.5–20.6)	1.2% (0.7–1.7)
Latin America and the Caribbean	2.5 (1.4–3.8)	7.6% (4.5–11.7)	0	NA*	2.5 (1.4–3.8)	0.6% (0.4–1.0)
South Asia	90.9 (40.9–143.3)	18.0% (8.4–28.3)	12.3 (1.9–24.6)	11.2% (1.9–24.7)	103.2 (49.1–156.7)	3.0% (1.4–4.6)
Sub-Saharan Africa	102.8 (69.9–142.8)	19.0% (15.0–23.7)	39.7 (14.1–66.2)	11.5% (5.1–21.1)	142.5 (96.2–189.4)	3.4% (2.3–4.5)
All low-income and middle-income countries	211.4 (147.6–279.0)	17.2% (12.7–21.6)	54.8 (24.0–85.0)	11.0% (5.8–18.4)	266.2 (188.8–334.7)	2.7% (1.9–3.5)
2013						
Central Asia, Middle East, and north Africa	1.2 (0.2–2.8)	6.5% (1.4–14.7)	0.0 (0.0–0.1)	4.3% (0.3–16.6)	1.2 (0.2–2.9)	0.4% (0.1–0.9)
East and southeast Asia and Oceania	1.4 (0.4–3.2)	4.1% (1.1–9.0)	0.2 (0.0–0.6)	2.0% (0.3–6.0)	1.6 (0.4–3.6)	0.3% (0.1–0.6)
Latin America and the Caribbean	0.5 (0.2–1.1)	5.9% (1.9–11.9)	0	NA*	0.5 (0.2–1.1)	0.3% (0.1–0.5)
South Asia	34.8 (11.1–61.7)	17.0% (5.8–31.0)	5.1 (0.5–13.6)	11.1% (1.2–30.1)	39.9 (13.0–69.2)	2.0% (0.7–3.5)
Sub-Saharan Africa	56.6 (28.7–100.6)	18.4% (10.5–26.6)	5.9 (2.2–11.0)	13.0% (4.8–23.8)	62.5 (32.9–107.0)	2.0% (1.0–3.4)
All low-income and middle-income countries	94.5 (54.2–146.8)	16.5% (10.1–23.4)	11.2 (4.3–20.5)	11.0% (4.3–20.2)	105.7 (60.8–163.7)	1.7% (1.0–2.6)
Data in parentheses are 95% CrI. Tabulations by WHO, UNICEF, and UN regions are presented in the appendix. CrI=credible interval. NA=not available. *A population attributable fraction was not calculated because no measles deaths occurred in the Latin America and Caribbean region during this time period.						
Table 2: Number (in thousands) and proportion (%) of child deaths attributable to vitamin A deficiency by region in 2000 and 2013						

America and the Caribbean and central Asia, the Middle East, and north Africa. The persistent high prevalence of vitamin A deficiency in south Asia and sub-Saharan Africa might be due to insufficient dietary diversification, unsuccessful food fortification, and the restricted effect of vitamin A capsule delivery on serum retinol. Frequent exposure to infections,²³ which increase the risk of subclinical deficiency and decrease serum retinol concentrations in children with adequate liver stores,³⁶ might have also contributed to persistent vitamin A deficiency in regions with high infection burden.

The number of deaths attributable to vitamin A deficiency, about 100 000, was substantially smaller than the mortality effects of suboptimal growth,¹⁴ which increases the risk of dying from a range of infectious diseases.³⁷ Nonetheless, in the two worst-off regions of south Asia and sub-Saharan Africa, vitamin A deficiency accounted for around 2% of child deaths. The number of deaths attributable to this risk factor has decreased by more than 50% since 2000, mainly because child deaths from diarrhoea and measles have declined. These decreases are probably because of improvements in general nutritional status and water and sanitation (for diarrhoea),²³ and vaccinations (for measles),³⁸ although vitamin A supplementation might have played a part.

Our estimated prevalence for the year 2000 of 33% (95% CrI 27–39) in 138 low-income and middle-income countries coincides with the 33% (31–35) reported by the

WHO for 1995–2005 in countries with a 2005 GDP per person of less than or equal to US\$15 000.⁷ Our CrIs also overlap with estimates published by the UN Standing Committee on Nutrition, as do our estimates of a moderate decline in deficiency since 1990 worldwide.⁹ The number of deaths attributable to vitamin A deficiency is also consistent with the 120 000–160 000 deaths estimated in the GBD 2010 study¹⁶ and in the *Lancet* Series on Maternal and Child Undernutrition.¹⁴ All these estimates are substantially lower than those of the Comparative Risk Assessment Study¹² and the *Lancet* Series on Maternal and Child Undernutrition published in 2008.¹³ This downward adjustment occurred because trials led to the exclusion of malaria as an outcome of vitamin A deficiency, lowering of RRs for other outcomes, and changing the age range of analysis from 1–59 months to 6–59 months. Had we only used the trials included in the 2010 Cochrane systematic review¹ (ie, excluding the large DEVTA trial which had somewhat small effects),^{2,39} the number of deaths attributable to vitamin A deficiency in children aged 6–59 months would be about 50% higher than presented. In relation to age group, trial evidence does not collectively provide evidence of effects in infants younger than 6 months of age.^{14,40–43}

The strengths of our study are our extensive data search and rigorous criteria for inclusion of sources; estimation of trends; and systematic estimation and reporting of uncertainty to show the extent of data scarcity. The main

limitation of our analysis is that, despite the extensive data search and access, fewer data were available for biological markers of vitamin A deficiency than for other nutritional conditions, including anthropometric status and anaemia,^{28,29} which are easier to measure in population-based surveys. Data shortage was exacerbated by the fact that it was not possible to predict the prevalence of deficiency on the basis of serum retinol from the more recently available retinol-binding protein data; nonetheless, some recent surveys with serum retinol were accessed and used in the analysis. In regions where deficiency remains prevalent, specifically south Asia and sub-Saharan Africa, investment in surveillance using consistent methods would help provide improved information for both intervention priorities and to assess the effects of programmes and overall changes in nutrition on the prevalence of deficiency. We did not estimate the prevalence of vitamin A deficiency in women of reproductive age and in children younger than 6 months of age because the pooled effect of randomised trials of maternal vitamin A supplementation does not suggest benefit in terms of reduction of maternal mortality or mortality before 6 months of age.^{1,2,44} However, night blindness caused by deficiency might be a source of disability in women. Finally, cross-sectional health and nutrition surveys do not allow establishment of whether low serum retinol is due to insufficient intake or due to the temporary effects of infection and accompanying inflammatory response; because deficient children are more at risk of infection, decoupling the role of the two factors can only be done in trial and longitudinal data. Further research is needed to establish a standard method for adjusting serum retinol measurements for those with increased acute-phase reactants.

The large reductions in child mortality in initial trials of vitamin A supplementation led to efforts to scale up high dose vitamin A supplementation in low-income and middle-income countries, despite some controversy about how large the benefits of these programmes might be.^{45–47} According to UNICEF's summary of administrative data,⁵ more than two-thirds of children in the developing world now receive vitamin A supplementation, with most receiving the recommended two annual doses; in the late 1990s, only half received any supplementation and less than 20% received two doses per year.⁵ Despite these efforts, the prevalence of vitamin A deficiency does not seem to have changed in these regions. The persistently high levels of deficiency might be because supplementation, by contrast with regular dietary intake, increases serum retinol over short periods of 8 to 12 weeks,⁴⁸ although sparseness of data might also have made it difficult to spot their effects. Supplementation nonetheless might have contributed to mortality reduction based on the results of randomised trials.^{1–3,39} At the same time, we have noted downward revisions of the mortality burden of vitamin A deficiency with the most detailed and up-to-date analysis presented in this paper.

The reported trends in the prevalence and the mortality burden in different regions have two implications. The first is that improvement of vitamin A status in south Asia and sub-Saharan Africa to replicate the reductions in deficiency seen in east and southeast Asia and in Latin America and the Caribbean will probably need an improvement in the overall nutrition of the population, including through dietary diversification and improved access to vitamin-rich foods, and improved access to treatment for infectious diseases. Until this happens, large scale or targeted supplementation or fortification strategies will probably have some beneficial effect on mortality in these regions.⁴⁷ Data to identify subnational populations at risk of vitamin A deficiency are also needed to guide targeting of interventions in a more effective way. The second implication is that supplementation needs in east and southeast Asia and in Latin America and the Caribbean, where the prevalence of deficiency and child mortality are both quite low compared with south Asia and sub-Saharan Africa, should be reconsidered, possibly leading to a revised and shorter list of priority countries.

Contributors

ME designed the study concept. GAS, LMD-R, LR, S-PO, RG, ZAB, and AT-P collated country data and checked data sources, with contributions from other authors. JEB and MMF developed statistical methods with input from GAS, QH, GL, SRF, and ME. YL, GD, WF, REB, GAS, and ME developed the approach for pooling trials. GAS, JEB, QH, YL, GL, RAW, and SRF analysed the data and prepared the results. GAS and ME wrote the first draft of the report and all other authors contributed to subsequent drafts.

Declaration of interests

LMD-R is a staff member of the Micronutrient Initiative, an international non-governmental organisation that implements micronutrient programmes worldwide, some of which deliver vitamin A supplements to children. GAS and LR are staff members of the WHO. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions, policy, or views of the WHO.

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