METHODOLOGICAL APPROACHES TO ESTIMATING GLOBAL AND REGIONAL PREVALENCES OF VITAMIN AND MINERAL DEFICIENCIES

Report on the Joint World Health Organization US Centers for Disease Control and Prevention Technical Consultation

Atlanta, USA 7–9 December 2010

World Health Organization

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Abbreviations

CDC	US Centers for Disease Control and Prevention
CHERG	Child Health Epidemiology Reference Group
CI	confidence interval
DALY	disability-adjusted life year
DHS	Demographic and Health Surveys
ETH	Swiss Federal Institute of Technology
FAO	Food and Agriculture Organization
GBD	global burden of disease
GDP	gross domestic product
HDI	Human Development Index
HHI	hidden hunger index
IDD	iodine-deficiency disorder
IMR	infant mortality rate
IQ	intelligence quotient
MDIS	Micronutrient Deficiency Information System
MICS	Multiple Indicator Cluster Survey
ppt	percentage point
SD	standard deviation
TSH	thyroid-stimulating hormone
UIC	urinary iodine concentration
UNICEF	United Nations Children's Fund
UNSCN	United Nations System Standing Committee on Nutrition
US	United States
USA	United States of America
VMNIS	Vitamin and Mineral Nutrition Information System
WHO	World Health Organization
WHOSIS	WHO Statistical Information System

INTRODUCTION
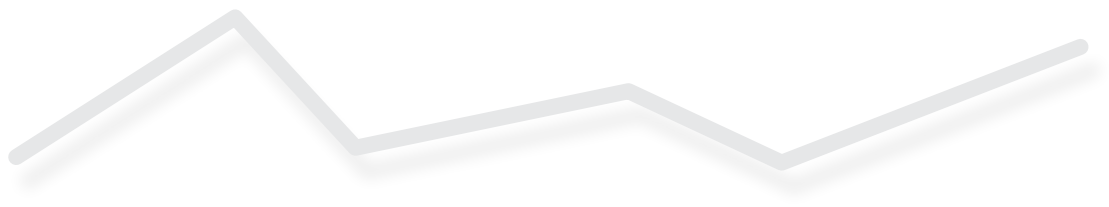
The World Health Organization (WHO) Vitamin and Mineral Nutrition Information System (VMNIS), formerly known as the Micronutrient Deficiency Information System (MDIS), was established in 1991 following a request by the World Health Assembly to "establish, as part of the health and nutrition monitoring system, a micronutrient monitoring and evaluation system capable of assessing the magnitude and distribution of vitamin A and iron deficiency disorders and monitor the implementation and impact of control programmes" *(1)*.

The VMNIS micronutrient database collates information at national and first administrative (state) levels on various biomarkers of vitamin and mineral status. The initial efforts were focused on collecting data on anaemia, and vitamin A and iodine deficiencies *(2–4)*. However, evaluations of epidemiological and informatics capabilities of the system in 2009 guided upgrade of the VMNIS database to include more micronutrients. This information system was also expanded to incorporate additional resources and tools for vitamin and mineral nutrition surveillance, to:

- provide Member States and their partners with up-to-date national, regional and global assessments of the magnitude and distribution of vitamin and mineral status in populations;

- track progress towards the goal of eliminating major vitamin and mineral deficiencies;

- identify high-priority areas for targeting and implementing nutrition interventions;

- assess the influence of vitamin and mineral deficiencies as risk factors in the overall global burden of disease (GBD);

- provide tools and resources to support efforts of Member States and their partners to assess vitamin and mineral nutritional status in populations.

The WHO Department of Nutrition for Health and Development has published global estimates of the prevalence of anaemia for the period 1993–2005 *(5)*, for vitamin A deficiency for the period 1995–2005 *(6)*, and for iodine-deficiency disorders (IDDs) for the periods 1993–2003 *(7)* and 2004–2007 *(8)*. The VMNIS micronutrients database data, along with data from other WHO databases, have also been used by the WHO Mortality Burden of Disease study to assess the comparative importance of iron, zinc and vitamin A deficiencies in causing premature death, loss of health and disability in different populations *(9)*.

WHO has a mandate from the World Health Assembly to produce global estimates of vitamin and mineral deficiencies, but it is not the only body working in this area. Multiple groups have produced global estimates for different purposes, including advocacy, targeting of resources at a global level, monitoring progress over time, understanding the GBD, and country comparisons. These groups used different methodological approaches to develop these estimates of the global burden of vitamin and mineral deficiencies; see, for example, references *(5, 9–13)*. The differences in the published estimates for a given micronutrient may be related to the availability of data for priority

target groups; differences in the timing of data analysis; variations in geographical distribution of the data; underlying assumptions of the statistical approaches; and the different purposes for which the estimates were made. The inconsistency between the methods and estimates generated has frequently raised questions among Member States and their stakeholders on the most appropriate values to use to describe global or national micronutrient status.

In view of the above, a joint WHO/United States (US) Centers for Disease Control and prevention (CDC) technical consultation was held from 7 to 9 December 2010 in Atlanta, Georgia, United States of America (USA), with the following objectives:

1. to review various methodological approaches to estimate global vitamin and mineral deficiencies and their underlying assumptions;

2. to review available sources of data, taking into account their strengths and limitations;

3. to review and discuss the statistical methods used to evaluate the precision, accuracy and uncertainty of the estimates;

4. to discuss the most appropriate methods for estimating global vitamin and mineral deficiencies, and trends by micronutrient and subpopulation;

5. to discuss the role of nutritional deficiency estimates in calculation of the GBD.

Meeting format and agenda

Individuals with expertise in statistical methods and micronutrient surveillance were invited to the consultation (see Annex 1). Some of these individuals who were experienced in producing global estimates of micronutrient deficiencies and assessing their relevance as risk factors for other conditions were also invited to prepare a background paper describing their methodological approach (see Annex 2) and to present it at the technical consultation, to facilitate the discussions.

The meeting lasted for three days and the agenda was organized to enable participants first to understand and discuss the methods and considerations that have been used to produce global estimates of vitamin and mineral deficiencies. It was expected that this would prepare them for the discussions centred on developing estimates for anaemia and other specific vitamin and mineral deficiencies that took place on the second and third days.

On the first day, the authors presented their background papers, and each presentation was followed by a group discussion. The participants also discussed the role of WHO and others in creating global estimates of deficiencies; whether those estimates should be national or regional; and whether they should be cross-sectional or represent trends over time. The second day focused on a review of the VMNIS update, covariates and data sources available to include in statistical models; and methods for statistical models. The remainder of the second day and the third day of the meeting

focused on discussions for developing global estimates for anaemia, and deficiencies in vitamin A, iodine, zinc, folate and iron. For these discussions, the group considered the available data, methods, assumptions and covariates. There was more time allotted in the agenda for discussions about developing estimates for anaemia, vitamin A and iodine deficiencies, as global surveillance has historically focused on these conditions and, as a result, there are more data available. All meeting attendees were allowed to participate in all discussions, which were facilitated by a chairperson. This meeting report presents brief summaries of each presentation and the discussions that took place at the consultation.

SUMMARY OF MEETING PRESENTATIONS

Developing comparable international health parameters for WHO

Presented by Gretchen Stevens
Department of Health Statistics and Informatics, WHO, Geneva, Switzerland

WHO produces comparable estimates of health parameters, such as risk-factor prevalence, disease incidence or mortality rates, at country or regional level, allowing Member States to appropriately benchmark their health status against others in their region or worldwide. General guidance on generating comparable estimates of health parameters includes: (i) gather the best available data, through a systematic review, country consultation, or review of WHO and other databases; (ii) correct for major known biases to improve validity and cross-population comparability; (iii) predict values for populations with incomplete or no data; and (iv) evaluate and communicate major sources of uncertainty. Before starting the data-gathering exercise, clear definitions should be established and documented for each disease or risk to be reviewed, and exclusion and inclusion criteria should be established. Generally, data gathering should focus on population-level sources rather than clinical populations. Comparable health statistics are based on corrected statistics (corrected for known biases and adjusted to be internally consistent) and predicted statistics. Before publication, each WHO Member State is consulted to ensure that the estimates have taken account of all recent, relevant information and to allow Member States to understand the methods and data sources used to produce comparable estimates, and to comment on those methods.

(See Annex 2)

Statistical methods for WHO estimates of the global prevalence of anaemia and vitamin A and iodine deficiency

Presented by Lisa M Rogers
Department of Nutrition for Health and Development, WHO, Geneva, Switzerland

Part of WHO's mandate is to provide information on the health status of the population at the global level. WHO maintains the VMNIS micronutrients database, a tool for collating information on the population status of various nutrients globally. Based on this information, WHO has published global estimates of the prevalence of anaemia, and of vitamin A and iodine deficiency. To develop these estimates, data from the most recent national survey were used in preference to those from subnational surveys. For the countries that did not have survey data, WHO calculated their prevalence by developing a regression model using indicators of population health status as covariates. A high proportion of the population was covered by surveys for anaemia (69% to 76%) and iodine (91%), but the proportion varied greatly for vitamin A (19% to 76%). While the regression-based models explained a large amount of the variation in the prevalence of anaemia among countries with survey data (32% to 58%), they only explained 13% to 46% of the variation in the prevalence of vitamin A deficiency. There is a need for more data on key indicators, to generate more precise estimates. Although there may be technical and financial challenges, countries without survey data may consider collecting data for key vitamins and minerals on a more frequent basis (every 3–5 years).

(See Annex 3)

Methods for estimating trends in micronutrient deficiencies: the United Nations System Standing Committee on Nutrition sixth report

Presented by Peter Horjus
Consultant, New Orleans, USA
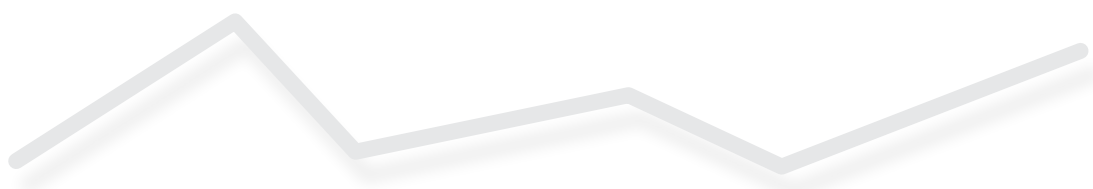
Methods for estimating trends in vitamin A deficiency, anaemia and IDDs are described as used in the United Nations System Standing Committee on Nutrition (UNSCN) *6th report on the world nutrition situation (12)* and earlier reports. The first method (method A) involves comparing repeated survey estimates (after data cleaning and standardization), country-by-country, through time. In the second method (method B), regression models are developed from existing survey results, using independent variables available for all countries and years; then, using the coefficients, the models are applied to all countries and specified years, to predict expected prevalences over time. For vitamin A and anaemia, correlations with common variables such as national income or education are used; for IDDs, a two-stage process is used, estimating pre-iodization IDD levels and then changes with iodized salt. For vitamin A and anaemia, the methods are very similar to those used by WHO. These methods give apparently reasonable estimates of trends and for cross-sectional comparisons of countries (e.g. for ranking need), and thus provide some information for an overview of policies. The results can neither ascribe causality nor give information on effectiveness, and hence give no evidence on what to do about the problems described.

(See Annex 4)

Development of a new framework to estimate the global burden of disease due to iodine deficiency

Presented by Michael B Zimmermann
Laboratory for Human Nutrition, Swiss Federal Institute of Technology (ETH), Zürich, Switzerland

Deficiencies of micronutrients contribute to the GBD, and interventions to prevent these deficiencies are highly cost-effective strategies for public health action. A decade has passed since the last estimate of the GBD due to iodine deficiency. Because of progress in the control of iodine deficiency worldwide, and the development of new assessment methods, the Child Health Epidemiology Reference Group (CHERG) reassessed the contribution of iodine deficiency to the GBD. This task was given to an expert group at ETH Zürich, which took a stepwise approach following guidelines from the 2009 update of the GBD study operations manual *(14)*. First, the expert group completed a systematic literature search on the effects of iodine deficiency. Then, using these data, a new IDD model was defined. It included the GBD 1990 *(10)* and 2000 *(11)* sequelae of goitre and cretinism, but added sequelae such as hyperthyroidism, and borderline, mild and moderate intellectual impairment. The model was refined by including three levels of severity of iodine deficiency, as defined by the WHO criteria for the median urinary iodine concentration (UIC): mild iodine deficiency, median UIC = 50–99 µg/L; moderate iodine deficiency, median UIC = 20–49 µg/L, and severe iodine deficiency, median UIC = 0–19 µg/L. Then, to accurately define the proportion of the global and regional population affected by these levels of iodine deficiency, the WHO VMNIS global

database was thoroughly reviewed and updated to produce new global and regional estimates of the prevalence of iodine deficiency in 2010. Currently, analytic approaches are being developed to produce new estimates of how iodine deficiency results in loss of intelligence quotient (IQ) points in populations, and to estimate the resulting intellectual impairment.

(See Annex 5)

The global hidden hunger indices and maps: methodology and findings

Presented by Jee-Hyun Rah
Sight and Life, Basel, Switzerland

Unified global efforts to mitigate widespread deficiencies of multiple micronutrients in high-burden countries are crucial to the achievement of most of the Millennium Development Goals. Indices and maps of global hidden hunger have been developed, to help prioritize programme assistance and to use as an evidence-based approach to develop a global advocacy tool. Two types of hidden hunger indices (HHIs) and maps were created, based on the (i) national prevalence data on stunting, anaemia due to iron deficiency, and low serum retinol levels among preschool-age children in 149 countries; and (ii) estimates of disability-adjusted life years (DALYs) attributed to micronutrient deficiencies for 36 high-burden countries. A number of countries in sub-Saharan Africa, as well as Afghanistan and India, had an alarmingly high level of hidden hunger, with stunting, iron-deficiency anaemia and vitamin A deficiency all being highly prevalent. In the 36 high-risk countries, deficiencies of micronutrients were responsible for 2% to 12% of the total DALYs. The total DALY rates per 100 000 population attributed to micronutrient deficiencies were highest in sub-Saharan African countries. In general, micronutrient deficiencies overlap within countries, with the exception of iodine, which presented a different pattern and magnitude of deficiency. The current indices and maps provide crucial evidence for appropriate prioritization of programme assistance aiming to tackle global multiple micronutrient deficiencies. Moreover, the indices and maps are believed to serve as useful tools to call for unified efforts to stimulate relevant global advocacy efforts *(15)*.

Vitamin and mineral deficiencies in the Global Burden of Diseases, Injuries and Risk Factors study

Presented by Majid Ezzati
Imperial College London, London, United Kingdom of Great Britain and Northern Ireland

Detailed description of the level and distribution of diseases and injuries, and their causes, are important inputs to public health policies and programmes. Following the original GBD study (1990) *(10)*, methodological improvements, and more extensive data collection, the Comparative Risk Assessment study used standardized concepts and approaches to quantify the individual and combined (joint) burden of disease attributable to over 25 risk factors, which included iron, vitamin A and zinc deficiencies. The results were published in 2002 *(16)*. Despite the considerable efforts made and the methodological improvements achieved, more work was required because of the
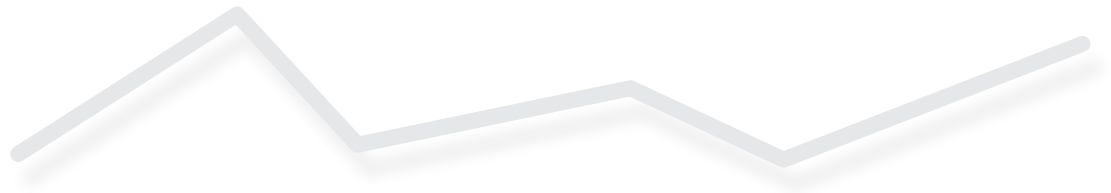
availability of newer sources of primary data, and development of new methods for estimating adult mortality and population-based methods for calculating disability weights. The GBD 2010 study *(17)* commenced in 2007, with the aims of: (i) conducting a complete systematic assessment of the data on all diseases and injuries, to produce comprehensive and comparable estimates of the burden of diseases, injuries and risk factors for 1990, 2005, and 2010; and (ii) developing a series of tools for use by specific audiences, to standardize and broaden the burden of disease research and analysis. Tailored publications will help policy-makers and non-research audiences to interpret GBD concepts and utilize study results. The publications from the GBD 2010 study include estimates on growth retardation as well as iron, vitamin A, zinc and iodine deficiencies, and possibly folate deficiency. There are several methods and models currently being used to quantify the burden of disease attributable to risk factors, including the use of counterfactual exposure distributions and population attribution fractions.

SUMMARY OF
THE DISCUSSIONS

The meeting participants discussed the presentations and some of the challenges in developing global estimates of micronutrient deficiencies. The intention was not to reach consensus but to discuss relevant issues that could help communicate the needs in this area, to move it forward. As some of the issues discussed were recurrent, they are summarized by main topic below.

The role of WHO and its partners in the surveillance of micronutrient deficiencies

An important and unique role for WHO is to develop and maintain a user-friendly database for indicators of the vitamin and mineral status of populations worldwide. This helps to maintain an efficient infrastructure that everyone can access as a starting point for analysis, instead of each group working independently and duplicating efforts to search, collect, compile and use the same data at the start of each project. The upgrade of the WHO VMNIS database represents a valuable contribution to this process, as more data are available in an efficient and easy-to-use format *(18)*.
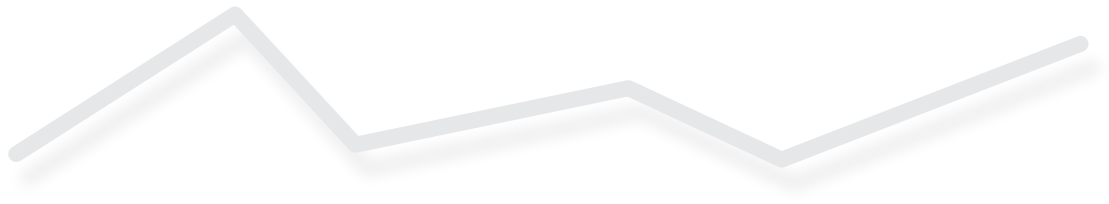
Methodological approaches: challenges, assumptions, covariates and uncertainty

Estimates with different levels of representativeness are required for different purposes by different audiences. For example:

- national-level data may be more meaningful and useful for national planning to trigger micronutrient interventions;

- United Nations agencies and other organizations responsible for creating global or regional policies may need United Nations region-specific or global estimates.

Independent of the level of representativeness, there are several challenges in developing estimates of vitamin and mineral deficiencies: data may be sparse or absent, not representative, or just not available in the desired metric. Different analytical methods for modelling have been used to overcome these challenges. They have traditionally been parametric, but as data frequently do not follow a bell-shaped curve, the use of nonparametric or semi-parametric methods – such as Bayesian methods – is becoming more frequent, to fit the shape of the distribution. Meeting participants highlighted the need for a clear description of an estimate's objective and the methodological approach used, to allow others to understand any differences when making comparisons between estimates.

An important topic discussed was what to do when data are sparse; i.e. how to impute data when there is no information for the indicator of choice, for the country of choice, for the subpopulation of choice, or for the year of choice. Where national-level data are lacking, often national estimates are imputed using data from other countries, from national covariates associated with micronutrient status, or from surveys that are representative of geographic areas that are below the first administrative (state) level. Although original data collected in each country are preferable, imputed data could sometimes be used if only poor-quality national-level data are available or the required data are not available. There was some debate about whether data from surveys carried

out below the first administrative level, or collected outside of the time period of interest, should be incorporated into model building. Some participants suggested that all data points can contribute useful information and that error could be accounted for with variance estimation. Other participants stated that models should be built only on data that meet the inclusion criteria in terms of the time period of interest, and should be representative of at least the first administrative level.

Although data imputation is useful, some participants were concerned that the development of estimates for countries that do not collect data could discourage them from carrying out periodic national micronutrient surveys. The general hope was that, instead, it may catalyse countries to begin a pattern of collecting and using original data on a regular basis. All participants agreed that imputed data need to be clearly identified in reports.

Regarding the development of estimates for world regions, it was discussed that different audiences prefer and use estimates at different levels for different purposes. For example, national-level data may be more meaningful and useful for national planning, compared to regional-level data; consequently, countries may prefer to use national-level data or even report that regional data do not represent the situation in their specific country. In comparison, United Nations agencies and other international organizations may need, or prefer, regional estimates to direct their actions. It was highlighted that, for developing regional estimates, it is necessary to start with national estimates to avoid the assumptions that places without data are identical to those with data, and that there are zero uncertainties. If these assumptions are not taken into account, then it is very likely that both the mean regional estimate and its uncertainty will be incorrect. It was also pointed out that a caveat of the regional estimates is that the comparability across agencies and organizations is currently limited, as the different definitions of world regions vary across agencies and organizations. An important consideration when developing regional estimates is that they may dilute significant problems across countries and limit the ability to identify and track problems at the national level. Also, some countries do not easily fit into a single regional category and data from large countries may overpower those from the other countries within a region. To overcome this issue, some meeting participants involved in the development of estimates have categorized countries into more rather than fewer regions.

It was highlighted that a conceptual framework is useful to help understand the underlying factors and processes that are expected to influence estimates. The use of such conceptual frameworks requires flexibility to allow for the inclusion of biological, behavioural, or health-care system covariates, at both study and country level, that reasonably might be related to micronutrient deficiencies. However, there is a risk in making the analytic models increasingly complex. Even if covariates conceptually make sense, their use may be limited by the quality of the data across countries and their availability. However, some participants expressed that the use of covariates in an analytic model may not need to be limited to those for which there is evidence of causality, from well-conducted studies of individuals, if they improve the predictive ability of the estimates. Participants discussed that it may be acceptable to have a broader scope, especially when working with ecological data, as long as there is a certain reasonableness associated with the use of the data. There are cases where
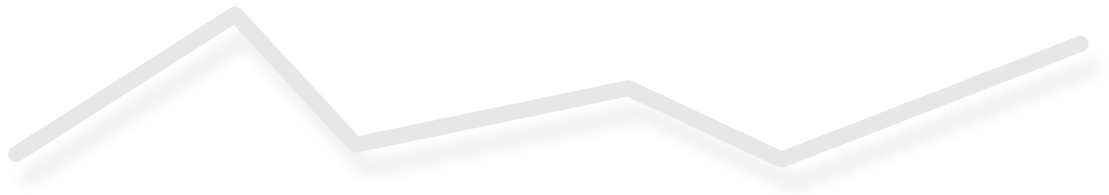
covariates that regularly show no relationship in studies with individuals are retained in the global estimates of micronutrient-deficiency models, such as latitude, as they improve the model fit. Some participants felt that the use of external validity tests is the only criterion that should be used to probe that a predictive model is correct (i.e. the estimate from new surveys falls into the predicted uncertainty of the estimate). A word of caution pointed out by one participant is that it is not appropriate to impute covariates and then use these imputed values to impute prevalence estimates.

Although most of the methods used to estimate micronutrient deficiencies include the most recent survey of each country (cross-sectional approach), it was mentioned that producing trend estimates would be a powerful advocacy resource and could be used to advocate for changes at the country level. The World Health Assembly requires WHO to provide updates on some micronutrients every 3 to 5 years, but the lack of data has historically influenced the ability to generate trend information. Estimates over different time points need to be developed using comparable methods (not two separate points in time using different methods). It is also preferable to avoid large time spans, as many interventions and changes may have taken place during such a time period. There is a need to further explore change in covariates over time. While some covariates are stable (e.g. genetics) or change slowly over time (e.g. maternal education), others may change very rapidly (e.g. coverage of an intervention). The degree of change needs to be considered, to appropriately inform the estimates. If yearly estimates are produced, then the rapidly changing covariates should be included for every year of the analysis. This, nonetheless, may limit the number of covariates included in the model.

An important consideration throughout the discussion was that estimates are often not calculated in isolation; they are accompanied by their uncertainty, and it is important to consider this uncertainty in the interpretation of results.

Methods for future estimations of vitamin and mineral deficiencies

Anaemia

There are currently six target populations traditionally included in reports on anaemia: children aged 6 to 59 months, children aged 60 months to 12 years (school-age children), children aged 12 to 15 years, non-pregnant women (women of reproductive age), pregnant women, and men. Since young children and pregnant women represent the intervention groups of highest interest, most data are collected for these groups and there is minimal information available for the other groups.

Participants expressed that obtaining data that exactly match these categories is a challenge. For example, not all the reports separate non-pregnant and pregnant women (or document the number of weeks of pregnancy). Similarly, reported data for children sometimes do not disaggregate younger children from older children, which may increase the risk of underestimating the prevalence of anaemia in the most vulnerable group (i.e. children aged 6 to 23 months, when the sample includes children up to 59 months of age). Conversely, although there are currently limited data available for lactating women only, it may not be necessary to generate estimates for this population, because after 3 months postpartum their haemoglobin concentrations (and anaemia prevalence) tend to be similar to those of non-pregnant women *(19)*. If survey planners
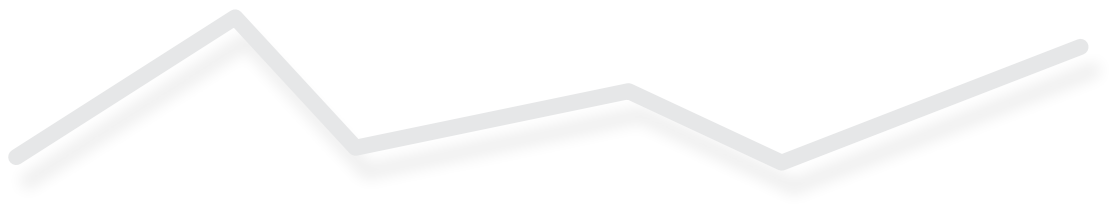
decide to assess this group separately, it would be useful to collect information on how long the women have been lactating and, if they are lactating, whether they are breastfeeding their infants exclusively.

An important consideration when developing global estimates is assessment of the data quality for haemoglobin, as it frequently varies across surveys. Not all surveys report the adjustments or exclusions for smoking, altitude or implausible data points. All data should be treated the same in the statistical model, regardless of the laboratory assessment method, and should also be described carefully for transparency. There are, however, some methodological questions that still need further discussion, such as the use of non-normally distributed data and the issue of data that use cut-off values other than those recommended by WHO.

Although haemoglobin is the most frequently collected biomarker, there are still insufficient data for all countries. It was reiterated that WHO should continue to produce national estimates for those countries with no data showing the uncertainty in the estimate (e.g. prevalence with confidence interval) and, if possible, trends over time.

Covariates can be used to impute missing data on anaemia. It is difficult to find relevant covariates available for all countries. When developing estimates for anaemia, the following covariates could be used if enough data are available: altitude, smoking, malaria infection, hookworm infestation, blood disorders, low birth weight, prematurity, child nutritional status, total fertility, health utilization, immunization coverage, maternal education, education, economic status, and population density.

Among covariates that are widely available, there may be problems with the type or quality of some of the data. For example, some covariates are only available as dichotomous data (yes or no), when other types of discrete or continuous data would be more useful. Such is the case for malaria parasite density (continuous), knowledge of which may be more useful than just knowing whether malaria infection is endemic in the country (dichotomous).

Iron deficiency

Currently there are no direct global estimates of iron deficiency. The WHO VMNIS *(18)* has only just started collecting these data. The use of data on anaemia to derive information about iron deficiency may be discouraged because of concerns about the assumptions relating to how much of anaemia is attributable to iron deficiency compared to other causes in all settings.

There is an ongoing debate on the use of biochemical indicators of iron status rather than on functional indicators for producing estimates of iron deficiency. There are more than 15 biochemical indicators of iron status and since they measure different stages of iron metabolism, the estimated prevalence of iron deficiency can change dramatically, depending on the indicator used, as well as the adjustments for indicators of infection and/or inflammation or other factors. Serum or plasma ferritin is the most frequently reported indicator of iron status, but there are still very few countries with data on plasma ferritin and almost none include information on indicators of inflammation to allow better interpretation of the data. Participants highlighted the relevance of collecting, in addition to serum ferritin status, data on serum transferrin

receptors, zinc protoporphyrin, erythrocyte protophyrin and transferrin saturation, as these are the most useful indicators to assess whether a subject is iron deficient. More research would be needed to determine whether any of those indicators is useful for assessing iron status at population level and whether they are reported frequently enough in surveys to allow the development of estimates. The usefulness of combining different indicators (e.g. ferritin and transferrin) to assess iron status at the population level is being explored.

Vitamin A deficiency

The discussion started with a brief overview of the available information in the WHO VMNIS. The number of surveys conducted at the first administrative level or higher shows a decreasing trend over time for both biochemical and, mainly, clinical indicators. Although there are data from studies at local or district levels, most of the participants expressed that they may not be informative for national estimates. The hope is that, as analytical methods become more widely available (i.e. high-pressure liquid chromatography), there will be more national surveys measuring serum retinol, which is currently the vitamin A biomarker with the most data points. While all surveys collecting biological samples should use laboratories participating in external quality assurance programmes, such as the CDC's Vitamin A Laboratory External Quality Assurance (VITAL-EQA) programme for nutritional biomarkers *(20),* this is especially important for analysis of serum retinol, where there is wide variability across laboratories.

One of the current challenges for the development of estimates is the adjustment of data for infection and/or inflammation, as only some surveys with individual data adjust for or exclude these variables, and fewer include in their report the data both with and without adjustment/exclusion for infection and/or inflammation. It is unclear how to adjust for inflammation and infection at the individual level and how to use these data when developing global estimates.

Other potential variables to consider when developing estimates of vitamin A deficiency include: seasonality related to vitamin A-rich foods; vaccination; and biannual coverage of vitamin A supplementation. In addition to serum retinol, retinol-binding protein is emerging as an indicator for the assessment of vitamin A status at the population level in some nutrition surveys; this is a result of a wider availability of field-friendly and inexpensive methods of measuring it. There are also challenges associated with the use of this indicator, as it is influenced by the amount of adipose tissue and the presence of inflammation.

Although the discussion gave most attention to biochemical indicators, it was mentioned that clinical indicators of vitamin A deficiency may be useful to generate global estimates of deficiency, and, in fact, they have been used for that purpose. Assessment of night blindness is non-invasive and a relatively easy indicator to collect for the priority populations of pregnant women and young children. The assessment should ask whether subjects can see during the day, as well as during the night. The presence of Bitot's spots may be an indicator that is difficult to collect and, owing to its low prevalence, it may not be useful for developing global estimates of vitamin A deficiency.

Iodine deficiency

Both goitre and urinary iodine levels are the most common indicators assessed for iodine status. The main populations of interest are women of reproductive age, pregnant women and infants, although most of the available data are collected in convenience samples of preschool- and school-age children and are not always nationally representative or of use to extrapolate to other age groups, such as pregnant women.

Since 2003, urinary iodine concentration has become the main indicator of iodine status, rather than the incidence of goitre. Some participants suggested that if a country has not introduced iodized salt or does not have an iodine intervention programme in place, presenting both indicators side by side may be counterproductive, because populations tend to have residual goitre; this is especially true in populations other than young children. A problem with reporting urinary iodine, however, is that it is an indicator for characterizing populations rather than individuals (i.e. it is not appropriate to present a prevalence below a given cut-off value used for the median of the population). The messages in the estimates report need to be accurate, to avoid misinterpretations that could potentially lead to excessive iodine consumption by individuals.

According to the participants, it would be desirable that, in addition to school-age children, WHO produce estimates for infants, women of reproductive age and pregnant women. Typically, infants are at higher risk of iodine deficiency if they are not fed complementary foods containing iodine (i.e. prepared with iodized salt); they are a priority group, given the importance of iodine in children's brain development, but there are no data available at the first administrative level or higher to develop global estimates. For women of reproductive age and pregnant women, WHO could explore development of estimates for these populations in the future, if the number of surveys increases.

In these models, some covariates and environmental indicators (e.g. percentage of the population within 200 miles of the ocean, or measures of the ability of the soil to retain minerals) can be used to predict goitre but are not useful for predicting urinary iodine. Some participants mentioned that seasonality may be an important variable for models, as some studies have shown that urinary iodine content varies substantially through the year, regardless of the status of iodization programmes in countries. The iodine content of water may also be useful for predicting excess intakes. A better understanding of the use and coverage of iodized salt would also be informative, both for estimates of iodine status and for national programmes.

Zinc deficiency and folate deficiency and insufficiency

There are three commonly used indicators for assessment of zinc: serum zinc, dietary data, and stunting (height-for-age<2 SD). Serum zinc is the most appropriate biomarker to assess zinc status, but there are limited user-friendly methods to adequately collect and analyse the samples from national surveys (i.e. several precautions are needed to avoid contamination of samples and the samples must be processed within 2 hours of collection). As of 2010, approximately 14 countries had reported serum zinc concentrations in populations from nationally representative surveys conducted during the previous 20 years. In the absence of data on serum zinc, some academic groups are using data from the Food and Agriculture Organization of the USA United Nations to examine the
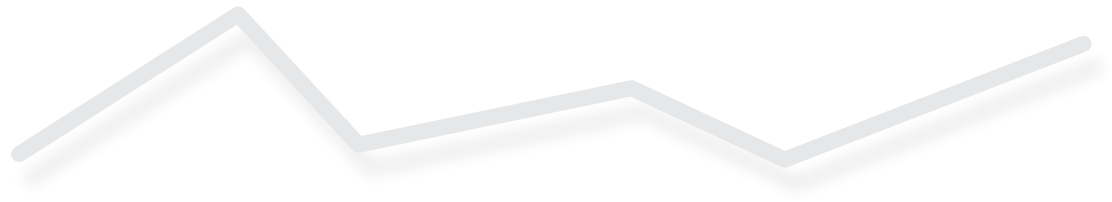
bioavailable zinc in the diet of different populations, with the aim of estimating the proportion of populations that are zinc deficient. This could be useful information, but this method may not be appropriate for estimating zinc deficiency for age-specific groups. Stunting has been used as a predictor variable in various models. Data on stunting in children are widely available from national surveys, but may not serve as a useful proxy for zinc deficiency, as other factors also affect stunting. The use of data on stunting to develop global estimates of deficiency was discouraged by several participants.

With regard to folate nutritional status, red blood cell folate and serum (or plasma) folate are indicators used in cross-sectional surveys. Although red blood cell folate and serum folate are useful for assessing status, there is debate about the appropriate cut-off values in women of reproductive age, particularly the values associated with prevention of neural tube defects. Some participants stated that the potential exists to use data on neural tube defects in order to back-calculate folate deficiency or folate insufficiency on a global basis, but there is insufficient understanding about how such models would work.

Countries are encouraged to collect data on folate in national surveys, but the costs of assessing red blood cell folate and serum (or plasma) folate may be relatively high, particularly for microbiological assay. It is not uncommon that folate status is only measured in a subsample, which may limit the availability of nationally representative data, depending on the sampling method. There is a need to develop field-friendly, inexpensive methods to assess levels of red blood cell and serum (or plasma) folate.

There are limited data available from national surveys for WHO to develop global estimates on zinc and folate deficiency or insufficiency. Researchers are encouraged to work on models with the existing data from all other levels.

Conclusion

Although it is clear that each indicator of vitamin or mineral status has its own particularities, participants highlighted the relevance of collecting clinical and biochemical indicators of micronutrient status in national surveys, particularly for iron, vitamin A, iodine, zinc and folate, in order to better understand the micronutrient situation in countries and worldwide, and to support the implementation of public health programmes aimed at improving micronutrient status and health.

The WHO Department of Nutrition for Health and Development will continue its workplan to review and update the cut-off values for iron and vitamin A status. Where survey data seem sufficient, WHO will evaluate whether trend analyses are feasible and work with partners on their development. If data are insufficient, there is value in displaying those few data points to encourage the measurement and adequate reporting of such indicators. For this purpose, WHO will work on a web-based, user-friendly dissemination platform.

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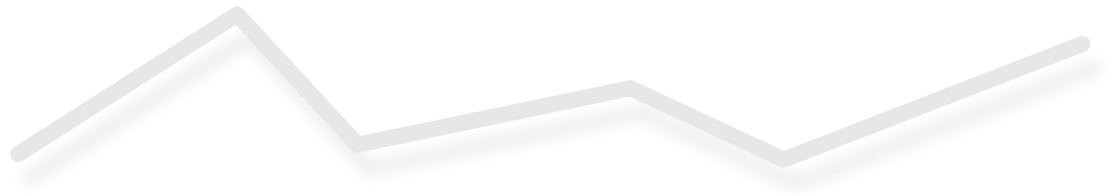
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ANNEX 1
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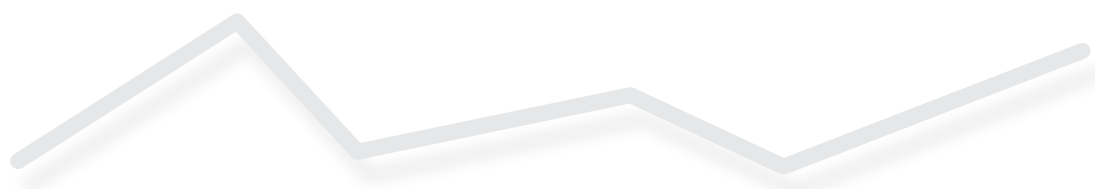
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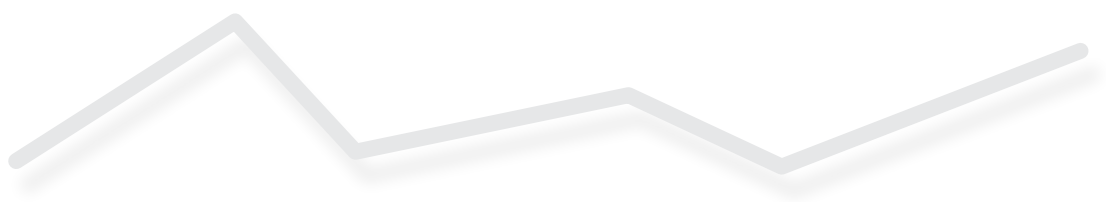
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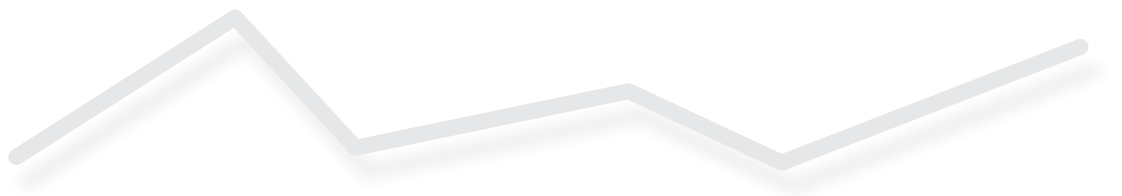
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ANNEX 2

**Developing comparable
international health parameters for WHO**

Annex 2 Developing comparable international health parameters for WHO

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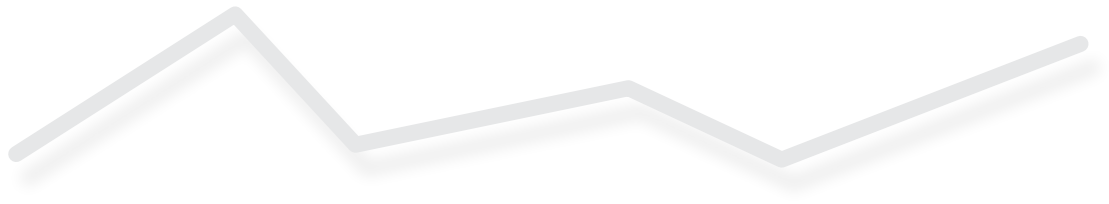
Abstract

The World Health Organization (WHO) produces comparable estimates of health parameters such as risk-factor prevalence, disease incidence, or mortality rates at country or regional level, allowing Member States to appropriately benchmark their health status against others in their region or worldwide. This paper outlines the options and general guidance to generate comparable estimates of health parameters: (i) gather the best available data, through a systematic review, country consultation, or review of WHO and other databases; (ii) correct for major known biases to improve validity and cross-population comparability; (iii) predict values for populations with incomplete or no data; and (iv) evaluate and communicate major sources of uncertainty. Before starting the data-gathering exercise, clear definitions should be established and documented for each disease or risk to be reviewed, and exclusion and inclusion criteria should be established. Generally, data gathering should focus on population-level sources rather than clinical populations. Comparable health statistics are based on corrected statistics (corrected for known biases and adjusted to be internally consistent) and predicted statistics (forecasts from earlier studies, or "farcasts" from other populations). Where country estimates are involved, a country consultation should be carried out with WHO Member States.

Introduction

The World Health Organization (WHO) produces comparable estimates of health parameters such as risk factor prevalence, disease incidence or mortality rates, at country or regional level. This is an important input to WHO technical advice to Member States on health priorities and responses. It also allows countries to appropriately benchmark their health status against others in their region or income level. The WHO approach to health statistics is based on the premise that the best estimates of incidence, prevalence and mortality can be generated by carefully analysing all available sources of information in a country or region, correcting for bias, and generating estimates where they are missing. Broadly, the steps to generate comparable estimates of health parameters are as follows:

1. gather the best available data, through a systematic review, country consultation, or review of WHO and other databases;

2. correct for major known biases to improve validity and cross-population comparability;

3. predict values for populations with incomplete or no data;

4. evaluate and communicate major sources of uncertainty.

This paper provides an overview of options and general guidance for carrying out each of these steps.

Step 1: Gathering the best available data

Data may be gathered directly from routine Member State reports, disease/injury registries, health information systems, comparable surveys (such as the Demographic and Health Surveys [DHS] or Multiple Indicator Cluster Survey [MICS]), health databases and/or systematic literature reviews. All applicable data sources, including, where relevant, both published and unpublished studies, should be reviewed to identify the data sources to be used for the preparation of estimates. As a minimum, all data sources used should be identified and referenced, but ideally the data sources to be used should be placed in the public domain (e.g. as a dataset of extracted information, together with references to all sources).

In general, data gathering should focus on population-level sources rather than clinical populations (see discussion of bias below). Some considerations in gathering and evaluating data sources are listed next.

Documenting case definitions

Before starting the data-gathering exercise, clear definitions should be established and documented for each disease or risk to be reviewed. Case definitions should be based on widely accepted, standard definitions in the literature and should include confirmation with laboratory or radiological diagnoses, where tests are available. A case definition used for a systematic literature review may differ from the case definition used to process centralized data sources, and thus documentation is critical. Risk-factor reviews should present the exact definition of exposure to the risk prior to the review process, balancing available epidemiological evidence and data on population-based exposure.

Establishing and documenting inclusion and exclusion criteria

One may wish to be more inclusive if few data are available, or include only high-quality data if more data are available. Exclusion criteria usually include a consideration of how data were gathered, as well as measurement considerations for each specific health parameter. For example, the following criteria were used for a systematic review of high blood pressure *(1)*:

- population-based or community-based studies with randomized samples (simple random, one-stage or multi-stage stratified sampling) would be included;

- studies not reporting their sampling method would be excluded;

- any study with a non-probability or convenience sample would be excluded (e.g. volunteers, employees, health centre patients).

  Examples of excluded studies were:

- studies on high-risk populations (e.g. hypertensive, uninsured, at high risk of cardiovascular disease);

- studies on patients with hypertension (treatment, monitoring, management, care);

- studies on specific ethnic minorities or immigrants;

- studies that select participants based on socioeconomic status.

Characteristics of included data sources

For each data source, the information listed next should be collected.

1. Citation – bibliographic reference to the publication or data source, specifying authors, type of publication, publication year, URLs for publications or datasets vailable on the internet, including date accessed.

2. Study population descriptions (national, subnational or other subpopulation). It is also important to specify subpopulation strata for which study results are available (e.g. urban/rural), particularly for population characteristics that are used to adjust for bias or missing data. For cases where information cannot be obtained from the study, DHS or national/regional consensus data may be used to generalize with regard to basic population characteristics.

3. Sample size, by age and sex and strata.

4. Study design and setting (community cross-sectional survey, longitudinal survey; household or facility based, etc.).

5. Sampling strategy (simple random, cluster sampling, etc.; include design factor if relevant).

6. Time period of data collection.

7. Sexes covered (male, female, or persons not further categorized by sex).

8. Age range covered, and its units.

9. Case definition and measurement technique.

10. Additional known biases for which adjustments were or will be made (e.g. altitude, smoking).

Step 2: Correcting for bias

Murray has classified health statistics into three types: crude, corrected and predicted *(2)*.

- Crude health statistics are measurements of indicators that come directly from primary data-collection platforms, with no adjustments or corrections. These figures may be subject to many problems, including incomplete ascertainment, non-representativeness, instrument bias, misclassification and distortion. Crude health statistics typically should be corrected. The exception is when they are generated from complete enumeration of cases in a population without systematic measurement error (e.g. all-cause mortality for a death-registration system that captures all deaths).

- Corrected health statistics are measurements of indicators where two types of analytical efforts may have been undertaken: mapping into the quantity of interest and correction for a range of known biases. Mapping into the quantity of interest from an indirect correlate or consequence is based on specific assumptions and models, and introduces uncertainty. Correcting for known bias ranges from routine procedures, such as using sample weights in household survey analysis, to more complex procedures, which may involve analytical models. Correcting for known bias is extremely important if valid, reliable and comparable health statistics are to be generated; it does, however, introduce significant scope for legitimate disagreement between analysts.

- Predicted health statistics are values for health statistics that are based on a model relating the quantity of interest to covariates. Two types of predicted statistics are widely used: forecasts, which are predictions for time periods for which data are not yet available, and "farcasts", where the prediction is out of sample but in the same time period. Forecasts and farcasts are often used to estimate missing data for populations. Predicted statistics have uncertainty resulting from model choice, unexplained variance in the model, and model parameter uncertainty.

In most cases, comparable health statistics are based on corrected statistics (corrected for known biases and adjusted to be internally consistent) and predicted statistics (forecasts from earlier studies, or farcasts from other populations). When preparing comparable health statistics, the first step is to consider and correct for known biases. A summary of major common sources of bias follows.

Inconsistent case definitions

An important first step to avoid bias is to ensure that there is a clear definition for the exposure and outcome of interest.

- Data with non-standard definitions can be used if they can be mapped to the standard definition.

- Models or methods may be developed to map from a proxy or indirect measure of the disease/risk to the true quantity of interest, e.g. from PPD (purified protein derivative) skin test for tuberculosis to tuberculosis incidence.

Incomplete population-based surveillance

In order for estimates to be comparable, it is necessary to correct for incomplete coverage of surveillance systems (i.e. get data for the whole population). Crude data that come from notifications, health service contacts, or diagnoses made by specific
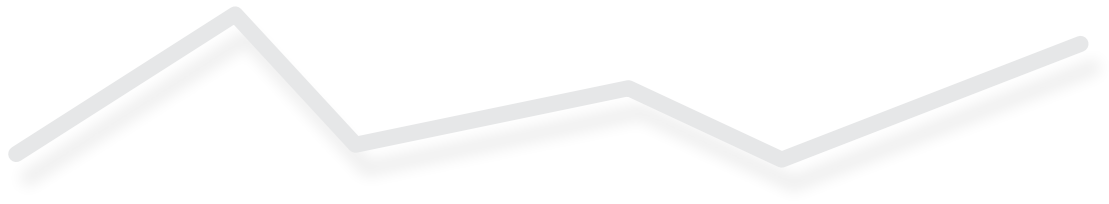
sectors of the health system (e.g. publicly funded clinics) are usually incomplete and will provide epidemiological estimates that are biased. Very often, it is the poor and other disadvantaged groups with the greatest health problems whose data do not get captured in these systems. In some cases, this may be correctable, e.g. if additional information is available on the completeness of recorded or notified cases and the potential difference in incidence or prevalence between the subpopulations captured and not captured by the data-collections system.

Measurement instrument bias

If there are systematic known biases in the measurement instrument, these must be quantified and the results adjusted accordingly. For example, the prevalence of self-reported asthma based on symptom-based questions tends to be two to three times higher than if the case definition requires a positive airway hyper-reactiveness test. In contrast, the prevalence of self-reported diabetes ("Have you ever been diagnosed by a doctor or nurse with diabetes?" or "Do you suffer from diabetes?") is typically an underestimate. Even in high-income countries such as the United Kingdom of Great Britain and Northern Ireland (UK) or the United States of America (USA), between 40% and 50% of people with diabetes are undiagnosed, according to health-examination survey data.

An important type of measurement bias is social desirability bias, where survey respondents provide responses that are socially acceptable rather than accurate. Measurement bias, especially self-report bias, may vary systematically by populations. Therefore, a correction factor that is valid for one population may not be valid for another. Special efforts should be made to establish the comparability of figures for the quantities of interest, from studies in different regions.

Particular care must be taken when using self-report data collected using questions with unanchored response categories (e.g. "How much difficulty do you have in walking around: none/mild/moderate/severe/cannot do"). The use of subjective response categories by respondents with the same level of difficulty typically varies within and across populations, and it can be difficult to develop comparable estimates from such data.

Non-representative population bias

For household surveys or other sampled data, non-representativeness can be a profound problem, e.g. when data are collected from clinic attendees or samples of volunteers; when data pertain to urban or rural groups only; or when there is a bias in socioeconomic status or language. Other important forms of non-representativeness may relate to the time period from which the studies are drawn. If it is known that there is a time trend in the quantity of interest, this may need to be taken into account to avoid producing a biased estimate for the target time period. If there were significant changes in effectiveness, access or availability of treatment during or after the time period of the studies, this may also need to be explicitly addressed, e.g. the scale-up of use of insecticide-treated nets in recent years in malaria-endemic areas. Seasonality may also be an issue for some causes/exposures.

Some non-representative population data should be excluded, while some can be corrected for, before or during modelling. Whether data should be excluded or attempts
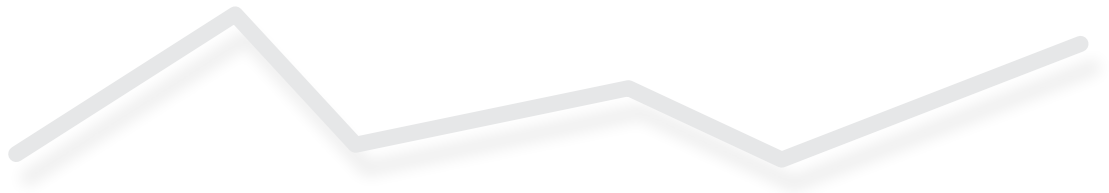
made to correct them will partly depend on the amount and quality of data that are available (i.e. more strict criteria can be applied if more data are available).

If the quantity of interest is known, or suspected, to vary across the factor on which the sample is non-representative, then any non-representative study data must be adjusted to estimate the quantity for the whole population. This adjustment can be made using known distributions or relationships in the same country, or in other countries of the region, or, in some cases, from an analysis of all data. For instance, if there is a systematic difference between urban and rural prevalence of diabetes, and there are some countries or regions with only urban studies, it would be advisable to quantify the relationship and use the urban studies to estimate rural and whole-population prevalences. If there is a known relationship to one or more covariates, the estimates can be adjusted to be more appropriate for the larger population. Typically, if survey data are available, covariates such as socioeconomic status, percentage of the population living in a rural area, level of schooling, or ethnicity may be used at the individual level. Alternatively, aggregate data at the level of subpopulations in a country can be used in a predictive model, with covariates reflecting average levels of schooling, wealth (e.g. gross domestic product [GDP]), or the proportion of the population living in cities for that specific subpopulation.

Study/publication bias

An additional form of non-representativeness that cannot be as easily addressed is study population or publication selection bias, based on the level of the quantity of interest. For many diseases or risk factors, evidence may only be available from a limited number of local studies. Community studies, however, are often conducted in settings where the investigators anticipate finding larger or smaller amounts of the disease or risk factor than expected. This is a particular problem for focal diseases such as some of the nutritional deficiencies or neglected tropical diseases. Overall, this creates a real prospect of selection bias when no national data are available. This problem is so common that efforts should be made to use more robust techniques to predict when selection bias is an issue. One strategy for dealing with this issue is to stratify populations into exposure risk groups and then apply data from strata-specific studies for each of these risk strata.

Consistency analysis

An important strategy for dealing with unknown bias is to examine the internal or external consistency of estimates. Internal consistency (within a disease or injury topic) involves comparison of estimates for different quantities such as cause-specific incidence, prevalence and mortality estimates, to ensure consistency at the population level. Another form of internal consistency checking involves triangulation of estimates for the same quantity derived from different starting points with different models/assumptions. For example, do the direct estimates of cause-specific deaths derived from population-level surveillance using verbal autopsy methods tally with estimates of deaths derived from incidence and case-fatality estimates? External consistency involves comparison or explicit adjustment to ensure consistency with "envelope" estimates. For example, are cause-specific estimates for a major cause of death in a population consistent with estimates derived from other sources of the level of all-cause mortality? Single-cause studies are well known to overestimate quantities of interest, owing to

the focus on identification of the single cause, resulting in over-inclusion of events that investigators who are interested in multiple causes may well assign to another cause.

Step 3: Predicting values for populations with incomplete or no data

This section provides guidelines for addressing the lack of data for some countries or years when regional and global estimates are being produced. The strategy will depend on the amount of available data (for how many populations in how many regions) and on the availability of evidence/data on predictors of variations in the quantities of interest. Missing subpopulations, such as missing age/sex groups or missing urban or rural data, can be predicted prior to this step or in this step.

Selecting covariates

A first modelling step is to select covariates that might predict the parameter of interest. A typical strategy is to brainstorm a comprehensive list of covariates, and then narrow it down based on data availability, as comprehensive global datasets exist for few covariates. Three core covariates are often considered:

- wealth, as measured by GDP per capita or log GDP per capita;

- mortality rates, as measured by child mortality rates, life expectancy or adult mortality *(3)*;

- education, as measured by mean years of schooling or literacy rates.

   Special attention should be paid to how data for covariates are generated: some comprehensive indices, such as the Human Development Index *(4),* are simple combinations of wealth, mortality and educational attainment. It is better to determine which of the original data best predict the health parameter of interest, rather than using a combined index.

Selecting and fitting a predictive model

Once covariates have been selected and assembled, model fitting can begin. At this stage, the help of a statistician is usually enlisted. General suggestions regarding useful model types are given below; however, the precise statistical model used will depend on the type of data available and the specific purpose of the modelling exercise.

Regression modelling

- Look for a quantifiable relationship with relevant covariates using regression methods. If a relevant set of covariates can be found that explain a substantial component of the variance and perform well in leave-one-out analyses, then use the regression model and predict values for missing countries.

- Region effects can be accounted for using multilevel/hierarchical modelling (which allows for region-specific constants or coefficients, such as coefficients determining sex patterns).

- It may be appropriate to include, in the same regression models, covariates to adjust for non-representativeness, non-standard definitions or other forms of bias.

Matching and data imputing

- In some cases, it is not possible to fit a regression model that can satisfactorily predict the parameter of interest (i.e. available covariates do not explain the parameter). Another option is to match populations with no data to populations for which data are available, based on world region, income or other parameters. Average parameter estimates for populations with missing data can be calculated from statistics for the matched populations. Match criteria should be transparent and replicable (i.e. it is not advisable to match based on expert opinion rather than on well-documented criteria).

- This method can only be used when many data are available, and it does not provide estimates of uncertainty.

The data analysis should be described in such detail that, given access to the same data, the estimates could be regenerated. Regardless of the model type used, the following issues should be considered:

- For many epidemiological parameters, such as hearing loss, a strong age pattern is observed. In that case, it is typically best to only collect data that are disaggregated by age, as it is difficult statistically to correct for wide age ranges. When strong age patterns are observed, parameters for wide age groups are difficult to combine. Parameters may be influenced by the average age within the age group, which is typically younger in low- and middle-income countries. In addition, if inconsistent age ranges are used, it is rarely possible to combine wide age-range data.

- As with age, some health parameters show a strong trend over time. In addition, it is often useful for programmes to have information on trends in parameters of interest. However, the ability to make inferences about trends depends on the amount of data available, over what time period. For parameters that have changed substantially in recent years (owing to programme interventions or other secular trends), time trends should be explicitly accounted for, either by restricting observations to a limited time period or by modelling changes over time and predicting for a specific point in time.

- It is good practice to develop estimates by sex.

- Adjustment for known biases should be carried out, either before model fitting, or by using a covariate within the model.

It is important to validate a predictive model. In general, the analyst should confirm that the predicted values approximate observations, when available, and that predictions for missing countries are consistent with any indirect sources of information. A useful way to validate a model is to fit a model excluding a subset of observations, and then compare the model's prediction to the observed data (so-called leave-one-out analyses).

What if data are sparse?

Often, data are particularly sparse or even missing in some region(s) of the world. In a typical case, only one or two studies are available for a given region. These studies show a particularly high or low disease or risk-factor prevalence, and the researcher

should be cautious in relying on these studies alone to make regional estimates. Instead, one should assess how much studies vary within other regions, and consider whether the studies in the region with sparse data may have particularly high or low estimates that are primarily due to bias or stochastic variation rather than a real epidemiological pattern. Hierarchical models may be useful in this case. They compare variability in study observations within regions versus across regions, to determine how much weight should be given to data from sparse regions. Hierarchical models typically produce estimates that are between global means and that are based only on data from the region.

Step 4: Evaluating and communicating major sources of uncertainty

Typically, when comparable estimates are generated, they include regions with limited, incomplete and uncertain data. It is thus important to provide some analysis and guidance on levels of uncertainty in the estimates, to allow the user of the information to assess whether the information's uncertainty range is compatible with the purpose at hand. For example, highly uncertain data may be adequate for determining general health priorities, but not for analysis of trends.

Uncertainty in estimates is generally difficult to quantify, since, apart from the large number and disparate nature of the data sources used, there is often limited information or knowledge of the quality and potential biases in the data. Uncertainty may arise from several important sources:

- stochastic variation (e.g. when estimates for a population are based on observations from a sample);

- systematic (non-random) biases (e.g. how representative for the whole population are the estimates from the study of a subgroup; how validly does the survey instrument address the quantity of interest); disagreements between sources may often be an indication of systematic bias in one or several sources;

- use of models when there are missing data. Uncertainty from using models to estimate missing values can be divided into three components:

    o specification uncertainty from the choice of which model to use;

    o parameter uncertainty, owing to the uncertainty in the coefficients estimated for a given model;

    o fundamental uncertainty – the component of variation that is not explained by a given model.

Stochastic variation is generally straightforward to quantify and is often the only source of uncertainty quoted in studies. Systematic biases are usually difficult to quantify, but should, as a minimum, be discussed qualitatively. Model uncertainty can be quantified by comparing estimates from different statistical models, and by directly calculating prediction uncertainty from the final model.

Transparency and accountability

Crude statistics (input data) should be fully documented, ideally in the public domain. While a documented list of studies or data sources is a good start, ideally the extracted and summarized dataset used for analysis should be placed in the public domain, e.g. through provision of a database or dataset on a website.

Peer-reviewed published methods should be used, or a paper should be subjected to expert review. Ideally, these are published in sufficient detail to allow replication of analysis and results. All key assumptions and inputs should be documented. Where country estimates are involved, a country consultation should be carried out with WHO Member States. The purpose of this consultation is threefold:

1. to ensure that the estimates have taken account of all recent, relevant information for each Member State;

2. to allow Member States to understand the methods and data sources used, to produce comparable estimates, and to comment on those methods;

3. to give Member States advance notice of estimates that will be published for their country. Where Member States produce official estimates that differ, either because of different but generally valid methods, or because of differences in approach to definitions and bias adjustment, it may be appropriate to include a statement such as the following with the results: "Figures have been computed by WHO to ensure comparability; thus, they are not necessarily the official statistics of Member States, which may use alternative rigorous methods".

Note that country consultation does not require that WHO and an individual Member State reach consensus on the final results. This is often not possible, as Member States may use a range of methods and assumptions, and differing approaches to bias adjustment.

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ANNEX 3

Statistical methods for WHO estimates of the global prevalence of anaemia and vitamin A and iodine deficiency

Annex 3 Statistical methods for WHO estimates of the global prevalence of anaemia and vitamin A and iodine deficiency

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Abstract

Part of the World Health Organization's (WHO's) mandate is to provide information on the health status of the population at the global level. WHO maintains the Vitamin and Mineral Nutrition Information System (VMNIS) micronutrients database, a tool for collating information on the population status of various nutrients globally. Based on this information, WHO has published global estimates of the prevalence of anaemia, and of vitamin A and iodine deficiency. Data from the most recent national survey were used in preference to subnational surveys. For the countries that did not have survey data, WHO calculated their prevalence by developing a regression model using indicators of population health status as covariates. A high proportion of the population was covered by surveys for anaemia (69% to 76%) and iodine (91%), but the proportion varied greatly for vitamin A (19% to 76%). While the regression-based models explained a large amount of the variation in the prevalence of anaemia among countries with survey data (32% to 58%), they only explained 13% to 46% of the variation in the prevalence of vitamin A deficiency. Countries without survey data are strongly encouraged to make efforts to collect data for key vitamins and minerals on a regular basis (every 3–5 years).

Introduction

Part of the World Health Organization's (WHO) mandate is to provide information on the health status of populations at the global level. In the 45th World Health Assembly, held in 1992, Member States were urged to "establish, as part of the health and nutrition monitoring system, a micronutrient monitoring and evaluation system capable of assessing the magnitude and distribution of vitamin A and iron deficiency disorders and monitor the implementation and impact of control programmes" *(1)*. As this request has not been fulfilled by all Member States, WHO produces global estimates of vitamin and mineral deficiencies, to identify high-priority areas to target and in which to implement micronutrient interventions; to advocate for resource allocation; and to assess the influence of vitamin and mineral deficiencies as risk factors for the overall global burden of disease. Furthermore, in 2005, the World Health Assembly adopted a resolution that
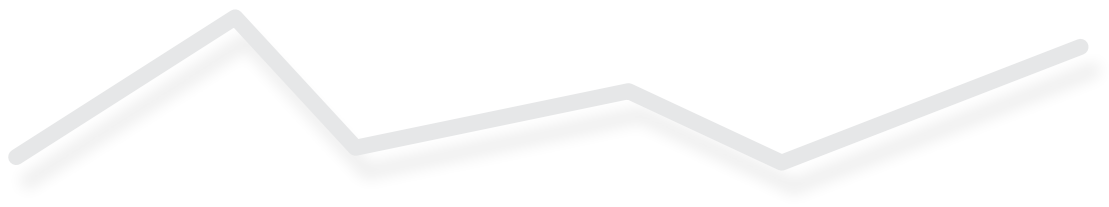
WHO Member States should report on the global situation of iodine deficiency every 3 years *(2)*.

Since 1991, the WHO Department of Nutrition for Health and Development has been maintaining the WHO Vitamin and Mineral Nutrition Information System (VMNIS). VMNIS currently collates information at the national, regional, state and local levels, on various indicators of vitamin and mineral status, including anaemia, and vitamin A and iodine deficiency. Based on this information, WHO has published global estimates of the prevalence of anaemia, vitamin A deficiency and iodine deficiency. The most recent of these reports include the global prevalence of anaemia from 1993 to 2005 *(3)*, of vitamin A deficiency from 1995 to 2005 *(4)*, and of iodine deficiency from 1993 to 2006 *(5)*.

Methods for developing vitamin and mineral estimates

Data sources

The most recent reports utilized data from the VMNIS micronutrients database on anaemia, vitamin A deficiency, and iodine deficiency.

Data were obtained from the scientific literature and through collaborators, including WHO regional and country offices, United Nations organizations, ministries of health, research and academic institutions, and nongovernmental organizations. MEDLINE and WHO regional databases (African Index Medicus, Index Medicus for the WHO Eastern Mediterranean Region, Latin American and Caribbean Center on Health Sciences Information, Index Medicus for South-East Asia Region) were also systematically searched. These resources were augmented by manual searching of articles published in non-indexed medical and professional journals. Data were extracted from reports written in any language.

For inclusion in the database, a complete and original survey report, providing details of the sampling method used, was necessary. Data were included in the database if they were representative of any administrative level in the country, including nationally representative data, surveys that were representative of a region within a country, and surveys conducted at the first administrative (state) level. Surveys conducted at the second administrative level boundary, or local surveys, were also included.

Data selection

Surveys for use in the development of global estimates of deficiency were selected according to the year of survey, the administrative level they represented, and the population group surveyed. Data from the most recent national survey were used in preference to subnational surveys. When two or more subnational surveys had been carried out in different locations of the country, data were pooled and weighted by the sample size of the survey.

In general, surveys with prevalence data based on a sample size of less than 100 subjects were excluded. However, national surveys with a sample size of less than 100, but greater than 50, were considered as nationally representative when the results were being applied to a total population of less than 500 000 people or to pregnant women, since the numbers in this group are frequently small, especially in populations with a lower fertility rate.
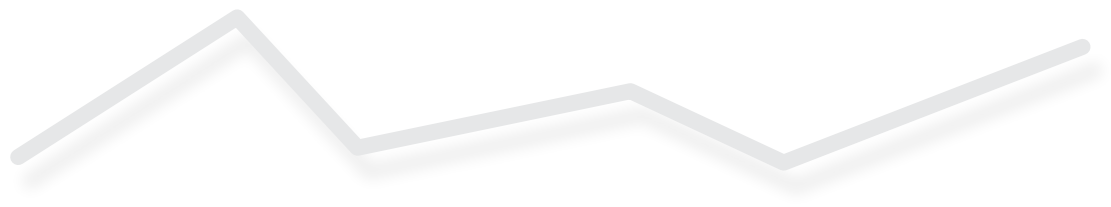
Anaemia

The most recent estimates covered the time frame from 1993 to 2005 and assessed anaemia as defined by haemoglobin concentrations in the following population groups: preschool-age children (<5 years), school-age children (5–14 years), pregnant women (no age range defined), non-pregnant women of reproductive age (15–49 years), men (15–59 years), and elderly men and women (>60 years). Wherever possible, children aged <6 months were excluded from the estimates for preschool-age children, since the cut-off value for anaemia is not defined for this age group.

WHO-recommended cut-off values were used to classify those individuals with anaemia (6). If two or more national surveys were available during the specified time period, the most recent survey was used. In the absence of national data on anaemia, surveys that were representative of at least the first administrative level were used, if two or more surveys at this level were available for the population group and country concerned within the acceptable time frame.

Vitamin A deficiency

The most recent estimates covered the time frame from 1995 to 2005 and assessed night blindness and serum/plasma concentrations in both preschool-age children (<5 years) and pregnant women (no age range defined). Where possible, children younger than 6 months of age were excluded from the estimates for vitamin A deficiency based on serum/plasma retinol, and children younger than 2 years of age were excluded from the estimates based on night blindness in preschool-age children, since cut-off values are not defined for this age group. For pregnant women, all ages and trimesters of pregnancy were included for data on serum/plasma retinol.

WHO-recommended cut-off values for serum/plasma retinol were used to classify those at risk of biochemical vitamin A deficiency (retinol <0.70 µmol/L). Data on current night blindness were used for preschool-age children. However, for pregnant women, the majority of surveys included in the estimates were conducted by Measure Demographic and Health Surveys (DHS), and reported women's history of night blindness during their most recent pregnancy in the previous 3–5 years that ended in a live birth. All prevalence figures for pregnant women that were unadjusted for daytime visual problems were used. All surveys in pregnant women that provided only an adjusted value or a figure for current night blindness, rather than a history of night blindness, were excluded. As with anaemia, in the absence of national data on vitamin A deficiency, data that were representative of at least the first administrative level were used, if they were available for two or more regions or states for the population group and country concerned, within the acceptable time frame. There were a few exceptions to this general principle: the use of district-level surveys for Ghana and Sao Tome and Principe, and the use of first administrative-level surveys representing only one state for Tajikistan and Uzbekistan.

Iodine deficiency

The 2003 estimates of iodine deficiency used urinary iodine data for school-age children (6–12 years) collected between 1993 and 2003. In the absence of data for school-age children, data on the next closest age group were used. In 2007, only data on urinary

iodine for school-age children collected in the previous 10 years (1997–2006), that were not available for the estimates produced in 2003, were used to update the estimates *(7, 8)*.

In 2003, data from the most recent national survey were used in preference to subnational data; if a national survey was more than 5 years old, and more recent subnational data were available, preference was given to the subnational data, to reflect current recommendations for salt iodization and recent changes in iodine status. The 2007 estimates only used new national urinary iodine data. For countries with no new data, the 2003 estimates (based only on survey data) were retained.

WHO-recommended cut-off values were used to classify populations with insufficient iodine intake (proportion of the population with a urinary iodine concentration <100 µg/L).

Statistical analysis

Estimated prevalence of anaemia and vitamin A deficiency

Data available from surveys were extracted from publications and reports that present data in inconsistent formats and with varying degrees of analysis. Equations were developed to standardize the data and derive one measure from another when the WHO-recommended cut-off value was not reported, and these are potential sources of error. For example, when the prevalence of anaemia or vitamin A deficiency was either not reported, or was reported for a non-WHO cut-off value, the prevalence was estimated by one of the following methods, in order of preference.

1. When the mean and standard deviation (SD) of haemoglobin/retinol concentration were available, the prevalence was calculated using these variables and assuming that the haemoglobin/retinol concentration is normally distributed.

2. When the SD was not provided, but the prevalence for a non-WHO cut-off value and the mean were provided, these two figures were used to calculate the SD by assuming a normal distribution within the population and using the Z score. The Z score was derived using the proportion of values below a provided cut-off value. The mean was subtracted from the provided cut-off value and the resulting absolute value divided by the absolute value of the Z score. This provided an estimate of the SD in the population. Following this calculation, the mean and SD were used, as above, to derive the prevalence for the non-WHO cut-off value.

3. When the mean, SD or prevalence for a WHO-recommended cut-off value were not reported, but an alternative cut-off value was provided, a SD of 0.35 µmol/L retinol was assumed, based on the literature, and the mean SD of the haemoglobin concentration for each population group was calculated from other surveys included in the estimates for each of the population groups (preschool-age children, SD = 13.8 g/L; school-age children, SD = 11.3 g/L; non-pregnant women, SD = 13.7 g/L; pregnant women, SD = 14.0 g/L; and men, SD = 14.5 g/L). The prevalence of deficiency was then estimated using the reported alternative prevalence and the assumed SD, using the above methodology.

For iodine, some survey reports provided only one measure of iodine nutrition: the percentage of the population with a urinary iodine <100 µg/L, the median urinary iodine concentration, or, in some cases, the mean instead of the median urinary iodine

concentration. In these cases, equations to derive one measure from another were developed with the use of data from the database (see references *(5)* and *(8)* for details).

Some countries did not have any survey data that met the inclusion criteria. Therefore, a multiple regression model was developed using data from countries with a reported prevalence of anaemia or vitamin A deficiency and indicators of population health status, so that the prevalence of anaemia or vitamin A deficiency could be predicted for the countries without data. The indicators of population health status considered in the regression model included the following:

- Human Development Index (HDI), 2002 (anaemia and vitamin A) *(9)*;

- individual components of HDI (vitamin A):

    o life expectancy at birth; adult literacy rate; the combined primary, secondary, and tertiary gross enrolment ratio (education); and gross domestic product (GDP) per capita *(10)*;

- under-5 mortality rate, 2003 (vitamin A) *(11)*;

- adult female mortality rate, 2003 (vitamin A) *(11)*;

- measles immunization coverage rates, 2003 (vitamin A) *(12)*;

- stunting, 2004[1] (vitamin A);

- wasting, 2004[1] (vitamin A);

- population growth rates (vitamin A) *(13)*;

- health indicators from the World Health Statistics database (anaemia) *(12)*;

- regional indicator variable (anaemia and vitamin A);

- any interaction term between the regional indicator variable and the remaining variables (anaemia and vitamin A).

Some countries (Afghanistan, Cook Islands, Democratic People's Republic of Korea, Iraq, Kiribati, Liberia, Marshall Islands, Micronesia, Montenegro, Nauru, Niue, Palau, Serbia, Somalia, Tuvalu) did not have an HDI value; therefore, their HDI values were estimated with a regression model using two of the same components and one proxy indicator for education (average years of schooling in adults instead of adult literacy and gross enrolment in school), fitted to the group of countries with HDI estimates. This was used to derive and estimate the HDI data for these countries.

Separate prediction equations for each indicator (haemoglobin – for anaemia; retinol – for vitamin A deficiency; night blindness – for vitamin A deficiency) and each population group were derived (see Tables 1 and 2). The prevalences of anaemia, biochemical vitamin A deficiency and night blindness were estimated by using the

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[1] Based on analysis of 388 nationally representative studies for 139 countries from the WHO Global Database on Child Growth and Malnutrition *(14)*. These were used to estimate the prevalence of child stunting and wasting for each country in the world, according to the new *WHO Child Growth Standards (15)*.

prediction equations in countries where no information was available and only explanatory variables were known. For regression-based estimates, a point estimate and 95% prediction interval were computed by using the logit transformations in the regression models and then back-transforming them to the original scale *(16, 17)*.

Table 1. Prediction equations used to generate estimates of anaemia for countries without survey data

Population group[a]	Number of countries	Equation	R^2	P value for model
Preschool-age children	82	= 3.5979 – 4.9093*HDIb – 0.0657*Exp on health – 0.0003*Exp on health per capita – 0.0009*Adult female mortality	0.550	<0.0001
School-age children	35	= 1.4248 – 2.6894*HDI + 0.0087*Urban population – 0.0129*Imm Measles – 0.0005*Exp on health per capita	0.583	<0.0001
Non-pregnant women	79	= 0.9475 – 2.3447*HDI + 0.1643*Population growth rate – 0.0697 Exp on health	0.453	<0.0001
Pregnant women	60	= 2.7783 – 2.8352*HDI – 0.0085*Imm DTP3 – 0.0004*Exp on health per capita – 0.0017*Adult male mortality	0.323	<0.0001
Men	32	= 0.0991 – 4.6160*HDI + 0.0209*Imm DTP3 – 0.0828*Gov Exp on health	0.577	<0.0001
Elderly	13	= –1.6693 + 0.2872*HDI – 0.1359*Exp on health + 0.0047*Adult male mortality	0.385	0.0627

Exp: expenditure; Gov: government; HDI: United Nations Human Development Index; Imm DTP3: immunization for diphtheria, tetanus and pertussis.

[a]Population subgroups: preschool-age children (<5 years), pregnant women (no age range defined), non-pregnant women (15–49 years), school-age children (5–14 years), men (15–59 years), elderly (≥60 years).

Table 2. Prediction equations used to generate biochemical vitamin A deficiency estimates for countries without survey data in populations at risk of vitamin A deficiency

Population group[a]	Number of countries	Equation	R^2	P value for model
Preschool-age children	64	= –1.41497 – 0.00012074 GDP + 0.01128 Under-5 mortality – 0.25813 Population growth rate	0.334	<0.0001
Pregnant women	16	= –3.6887 – 0.01450 Stunting + 2.6583 Africa indicator + 2.68685 Asia indicator	0.461	0.0150

GDP: gross domestic product.

[a]Population subgroups: preschool-age children (<5 years), pregnant women (no age range defined).
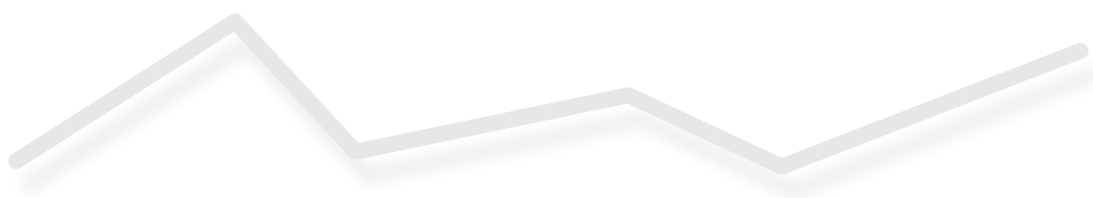
In the case of iodine deficiency, no estimates were derived by using a prediction equation for countries in which these were missing.

Combining national estimates

Country estimates were combined to provide estimates at the global level, as well as by WHO and United Nations regions for specific population groups (anaemia: school-age children, pregnant women, non-pregnant women; vitamin A: preschool-age children and pregnant women; iodine: school-age children), by pooling the data and weighting them by the population that each estimate represented. Then, using the estimated variance of the weighted average, 95% confidence intervals (CIs) were constructed. The population figures were the 2006 projection from the 2004 or 2006 revision of the United Nations population estimates *(13, 18)*. Population figures for pregnant women were derived from the annual total number of births (time period 2005–2010). For 14 countries with small total populations (0.01% of all women), birth data were not provided in the tabulations of the United Nations Population Division, and the number of pregnant women was estimated by applying a WHO regional average of births per reproductive-age woman (15–49 years) to the total number of reproductive-age women.

Only the global prevalence of anaemia was calculated for school-age children, men and elderly people (regional estimates were not produced). All population groups (preschool-age children, pregnant women, non-pregnant women, school-age children, men and elderly) were combined to calculate the overall prevalence of anaemia, which covered the entire population except for one segment (women 50–59 years of age). The estimate of anaemia prevalence in the elderly was applied to this segment of the population.

For vitamin A, only country estimates for the 156 Member States with a 2005 GDP lower than US$ 15 000 were combined, to provide estimates at the global level, as well as by WHO and United Nations regions, as it is unlikely that there is vitamin A deficiency in countries with a higher income. The number of individuals with vitamin A deficiency was estimated for both indicators (retinol and night blindness), for each country considered to be at risk of deficiency.

Estimates of the global prevalence of insufficient iodine intake are based on the proportion of the population with a urinary iodine concentration below 100 μg/L. For each country, the proportion is applied to the total national population of both school-age children and the general population, and then pooled for regional and global estimates.

Assumptions

These estimates were made based on a number of assumptions.

1. All surveys were treated equally, although their methodological quality varied greatly. For example, most surveys used multi-stage cluster sampling proportionate to the population size within the country, but not all did, and in some national surveys, specific areas had to be left out because of security or accessibility issues.

2. For some population groups (e.g. children aged 0.5–4.9 years), the population sampled covered only a portion of the desired age range (e.g. 1–2 years), or covered ages outside the age range (0.5–6 years). For the purpose of the analysis, these surveys were considered equivalent to those that covered only the desired age range in full. However, an estimate from individuals equally distributed among the age ranges would be more appropriate.

3. While the use of subnational data was kept to a minimum, it was assumed that they represented the national population, and this may result in an over- or underestimation of the prevalence of deficiency for those countries.

4. Each prevalence estimate from survey data was considered to be representative of the entire country, whether from a national or subnational sample, and the variance of the estimate was calculated using the logit transformation. Since most surveys utilized a cluster sampling design, variance estimates were adjusted using a design effect of 2. From the point estimate of the prevalence and its variance, a 95% CI was generated in logit scale and then transformed to the original scale *(19, 20)*.

5. The estimates for anaemia and biochemical vitamin A deficiency (retinol <0.70 µmol/L) for pregnant women did not take account of the trimester of pregnancy, since this information is not routinely reported in publications. Prevalence would be expected to vary by trimester, and thus the estimates for pregnant women may have been biased if there was not an even distribution of women at various stages of pregnancy.

6. For vitamin A, an arbitrary assumption was made that all countries with a 2005 GDP ≥US$ 15 000 were free from vitamin A deficiency of public health significance in preschool-age children and pregnant women, and these countries were therefore excluded. None of these 37 countries had data on retinol or night blindness reported for preschool-age children or pregnant women. Although there are few survey data available in these countries to support this assumption, the exclusion is supported by the usual tendency for risk of vitamin A deficiency to decline with rising socioeconomic status, which is most clearly evident in its association with xerophthalmia *(21–24)*. A second reason for excluding higher-income countries from the analyses was to improve the predictability of the regression models and to keep the focus on areas where vitamin A deficiency is likely to be of public health significance.

Results

Data coverage

The population covered by the survey data was calculated by dividing the sum of the number of individuals in the population group in countries with survey data by the total number of individuals in the population group worldwide, or, in the case of vitamin A deficiency, the number of individuals in the population group in the countries identified at risk of vitamin A deficiency (GDP <US$ 15 000) worldwide. The 37 countries with GDP ≥US$ 15 000, representing 8–9% of the total global population of preschool-age children and pregnant women, were assumed not to have vitamin A deficiency of public health significance and were excluded from further analysis.

The proportion of the population covered by anaemia survey data was high for preschool-age children (76.1%) and pregnant (69.0%) and non-pregnant women (73.5%), but lower for school-age children (33.0%), men (40.2%), and elderly people (39.1%) (see Table 3). Globally, the proportion of preschool-age children and pregnant women covered by survey data for night blindness was 54.0% and 55.0%, respectively, and by survey data for serum retinol, 75.7% and 18.9%, respectively (see Table 4). Global estimates of iodine deficiency were based on data from 130 countries, covering 91.1% of the world's population of school-age children (see Table 5). For the 63 countries without urinary iodine data, estimates were not made.

Table 3. Number of countries and percentage of population covered by anaemia prevalence surveys (national or subnational) conducted between 1993 and 2005, by WHO region

WHO region (number of countries)	Population subgroup[a], *n* in millions (%)						
	PreSAC	PW	NPW	SAC	Men	Elderly	All
African Region (46)[b]	74.6 (26)	65.8 (22)	61.4 (23)	13.2 (8)	21.9 (11)	0.0 (0)	40.7
Region of the Americas (35)	76.7 (16)	53.8 (15)	56.2 (13)	47.1 (9)	34.3 (2)	47.6 (1)	58.0
South-East Asia Region (11)	85.1 (9)	85.6 (8)	85.4 (10)	13.6 (3)	4.1 (2)	5.2 (1)	14.9
European Region (52)	26.5 (12)	8.3 (4)	28.0 (12)	9.3 (3)	14.1 (3)	8.0 (2)	22.9
Eastern Mediterranean Region (21)	67.4 (11)	58.7 (7)	73.5 (11)	15.5 (6)	27.5 (6)	3.2 (3)	84.3
Western Pacific Region (27)	90.4 (10)	90.2 (8)	96.9 (13)	83.1 (7)	96.2 (10)	93.3 (6)	13.8
Global (192)	76.1 (84)	69.0 (64)	73.5 (82)	33.0 (36)	40.2 (34)	39.1 (13)	48.8

[a]Population subgroups: PreSAC, preschool-age children (<5 years); PW, pregnant women (no age range defined); NPW, non-pregnant women (15–49 years); SAC, school-age children (5–14 years); men (15–59 years); elderly (≥60 years).

[b]Total number of countries with data; no figure is provided for "All", since each country may be partially covered by some population groups, but few countries have data on all six population groups and no countries have data for women 50–59 years of age.

Table 4. Number of countries and percentage of population covered by night blindness and serum retinol prevalence surveys (national or subnational) conducted between 1995 and 2005, by WHO region in countries at risk of vitamin A deficiency[a]

WHO region (number of countries)	Population subgroup, *n* in millions (%)			
	Preschool-age children[b]		Pregnant women[b]	
	Night blindness	Retinol	Night blindness	Retinol
African Region (46)	14 (30.3)	24 (78.8)	24 (69.8)	8 (30.9)
Region of the Americas (32)	0 (0.0)	16 (49.8)	6 (14.9)	4 (0.6)
South-East Asia Region (11)	5 (82.4)	6 (82.4)	8 (96.8)	3 (14.7)
European Region (29)	2 (1.0)	5 (17.8)	2 (1.3)	0 (0.0)
Eastern Mediterranean Region (17)	4 (33.8)	6 (58.4)	2 (34.4)	2 (39.8)
Western Pacific Region (21)	7 (87.3)	10 (99.8)	3 (12.4)	2 (10.3)
Global (156)	32 (54.0)	67 (75.7)	45 (55.0)	19 (18.9)

[a]Excludes countries with a 2005 gross domestic product ≥US$ 15 000.
[b]Population subgroups: preschool-age children (<5 years); pregnant women (no age range defined).

Table 5. Number of countries and percentage of population covered by urinary iodine (UI) surveys (national or subnational) conducted in school-age children (6–12 years) between 1993 and 2006, by WHO region

WHO region[b]	Number of school-age children (millions)[c]	Data coverage for school-age children[a]		
		Urinary iodine		
		Countries (*n*)	Total number (millions)	Proportion (%)
African Region	141.3	36	126.8	89.7
Region of the Americas	109.1	21	100.4	92.1
South-East Asia Region	241.4	9	238.5	98.8
European Region	73.8	38	63.4	85.8
Eastern Mediterranean Region	88.7	16	77.6	87.5
Western Pacific Region	183.2	10	155.9	85.1
Total	837.5	130	762.6	91.1

Source: revised, with permission, from reference *(5)*.
[a]School-age children: 5–14 years.
[a]193 WHO Member States.
[b]Based on population estimates for the year 2006 (2004 revision) *(13)*.

Proportion of population and number of individuals affected by anaemia, and vitamin A and iodine deficiency

Anaemia affects 1.62 billion people (95% CI = 1.50 billion to 1.74 billion) worldwide, which corresponds to 24.8% of the population (95% CI = 22.9% to 26.7%; see Table 6). The highest prevalence is in preschool-age children (47.4%, 95% CI = 45.7% to 49.1%), and the lowest prevalence is in men (12.7%, 95% CI = 8.6% to 16.9%). However, the population group with the greatest number of individuals affected is non-pregnant women (468 million, 95% CI = 446 million to 491 million).

Table 6. Global anaemia prevalence 1993–2005 and number of individuals affected

Population group[a]	Prevalence of anaemia		Population affected	
	%	95% CI (%)	*n* (millions)	95% CI
Preschool-age children	47.4	45.7 to 49.1	293	283 to 303
School-age children	25.4	19.9 to 30.9	305	238 to 371
Pregnant women	41.8	39.9 to 43.8	56	54 to 59
Non-pregnant women	30.2	28.7 to 31.6	468	446 to 491
Men	12.7	8.6 to 16.9	260	175 to 345
Elderly	23.9	18.3 to 29.4	164	126 to 202
Total population	24.8	22.9 to 26.7	1620	1500 to 1740

CI: confidence interval.

[a]Population subgroups: preschool-age children (<5 years); school-age children (5–14 years); pregnant women (no age range defined); NPW, non-pregnant women (15–49 years); men (15–59 years); elderly (≥60 years).

Night blindness affects 5.17 million preschool-age children (95% CI = 1.99 million to 8.38 million) and 9.75 million pregnant women (95% CI = 8.7 million to 10.8 million) worldwide, which corresponds to 0.9% and 7.8% of the population group at risk of vitamin A deficiency, respectively (see Table 7). Low serum retinol concentrations (<0.70 µmol/L) affect an estimated 190 million preschool-age children (95% CI = 178 million to 202 million) and 19.1 million pregnant women (95% CI = 9.30 million to 29.0 million). This corresponds to 33.3% of the preschool-age population and 15.3% of pregnant women in populations at risk of vitamin A deficiency globally (see Table 7).

Table 7. Global prevalence of night blindness, serum retinol concentrations <0.70 μmol/L, and number of individuals affected in populations of countries at risk of vitamin A deficiency, 1995–2005

| Population group[a] | Night blindness | | | | Serum retinol <0.70 μmol/L | | | |
| | Prevalence | | Population affected | | Prevalence | | Population affected | |
	%[b]	95% CI (%)	n (millions)	95% CI	%[b]	95% CI (%)	n (millions)	95% CI
Preschool-age children	0.9	0.3 to 1.5	5.17	1.99 to 8.38	33.3	31.1 to 35.4	190	178 to 202
Pregnant women	7.8	7.0 to 8.7	9.75	8.70 to 10.8	15.3	7.4 to 23.2	19.1	9.30 to 29.0

CI: confidence interval.
[a]Population subgroups: preschool-age children (<5 years); pregnant women (no age range defined).
[b]Numerator and denominator exclude countries with a 2005 gross domestic product ≥US$ 15 000.

Based on the 2007 estimates, the iodine intake of 31.5% (266.0 million) of school-age children worldwide is insufficient (defined as a median urinary iodine concentration <100 μg/L) (see Table 8).

Table 8. Global prevalence and number of individuals with insufficient iodine intake in school-age children (6–12 years) and in the general population (all age groups), by WHO region, 2007

| WHO region[a] | Insufficient iodine intake (UI <100 μg/L) | | | | |
| | School-age children[b] | | | General population | |
	Countries (n)	Proportion (%)	Total number (millions)[c]	Proportion (%)	Total number (millions)[c]
African Region	13	40.8	57.7	41.5	312.9
Region of the Americas	3	10.6	11.6	11.0	98.6
South-East Asia Region	0	30.3	73.1	30.0	503.6
European Region	19	52.4	38.7	52.0	459.7
Eastern Mediterranean Region	7	48.8	43.3	47.2	259.3
Western Pacific Region	5	22.7	41.6	21.2	374.7
Global	47	31.5	266.0	30.6	2008.8

Source: reproduced, with permission, from reference *(5)*.
UI: urinary iodine.
[a]193 WHO Member States.
[b]School-age children (5–14 years).
[c]Based on population estimates for the year 2006 (2004 revision) *(13)*.

Discussion

There is high population coverage for anaemia survey data for the three population groups considered to be the most vulnerable: preschool-age children, pregnant women and non-pregnant women of childbearing age. Additionally, nationally representative data covered more than two thirds of the population in each of these groups, reducing the bias from using local data. However, there were fewer survey data available for school-age children, men and the elderly, and for some countries there were no data for an entire region; therefore, the country-level estimates for these population groups were not presented. For the countries without anaemia survey data, regression-based estimates were used, which were able to explain a large amount of the variation in anaemia prevalence among countries with survey data (32% to 58%).

Preschool-age children and pregnant women are the population groups most at risk for vitamin A deficiency, owing to their increased demands for vitamin A and the potential health consequences associated with vitamin A deficiency during these life stages. About half of the global populations of both preschool-age children and pregnant women considered to be at risk of vitamin A deficiency were covered by survey data for night blindness. For serum retinol, however, coverage (76%) was considerably greater in preschool-age children than in pregnant women (19%). Although the majority of the survey data were collected in nationally representative samples, the regression-based estimates could only explain 13% to 46% of the variation in the prevalence of vitamin A deficiency among countries with survey data.

Pregnant women and young children living in communities that are unlikely to have access to iodized salt are the population groups most susceptible to iodine deficiency. Over 90% of the world's population of school-age children was covered by survey data for this report, representing 130 countries. However, only approximately half of the countries had nationally representative data, representing 60% of the world's population. The remainder had only one or more subnational surveys, or had no data. Subnational data represented approximately 30% of the populations covered by these estimates. In 2009, an assessment of the number of national surveys on urinary iodine concentrations for school-age children found that, within the 5-year period of 2004–2008, only 37 of WHO's 193 Member States had nationally representative data, covering just 36.3% of the world's school-age population *(25)*. In contrast, 47 national surveys were conducted in the previous 5-year period (1993–2003). With only 37 Member States reporting national urinary iodine data for school-age children between 2004 and 2008, it would be difficult to generate a global estimate of iodine deficiency based on national data alone. Additionally, there are very few data on women of reproductive age, including pregnant women, and countries should be encouraged to include this population group in national surveys, as these women are an important target population for preventing iodine deficiency.

Given the public health importance of these deficiencies, it is surprising that numerous countries lack national prevalence data. In order for the WHO VMNIS to reach its full potential, data should be collected on all vulnerable population groups, and surveys should more inclusive and collect information on all important indicators.

Conclusions

The estimates developed by WHO of the extent and severity of anaemia, and of vitamin A and iodine deficiency, have practical limitations imposed by the absence, untimely, partially representative, or uncertain technical quality of data. For anaemia and vitamin A deficiency, estimates for countries without survey data have been derived from regression models employing available covariates that have been shown to be predictive in countries with data. Also, a number of countries in specific regions had no data or very few data for one of the indicators. In this respect, modelled estimates of the prevalence of deficiency should be interpreted with caution, since they are based primarily on regression analyses. These figures should be considered "place holders" until measured survey data become available, and serve to emphasize the "work-in-progress" nature of these reports.

Countries without survey data are strongly encouraged to collect data on a regular basis (every 3–5 years). Regression-based estimates are appropriate at regional and global levels, but may not accurately reflect the situation in an individual country, given the variation explained by the current models. National data are critical for global assessments, but it is also important to ensure that there is adequate representation from the different geographical regions within a country. Some micronutrient deficiencies may cluster in specific areas, even when there is no problem evident at the national level.

The maintenance of the VMNIS micronutrients database, and the periodic generation of estimates of deficiency, provide valuable tools for tracking the global progress in the elimination of anaemia and vitamin A and iodine deficiencies, and the effectiveness of the current strategies for their control. Hopefully, these estimates will encourage countries to plan routine surveys that assess the prevalence of deficiency and the factors that may be contributing to their development, including the incidence of infectious diseases.

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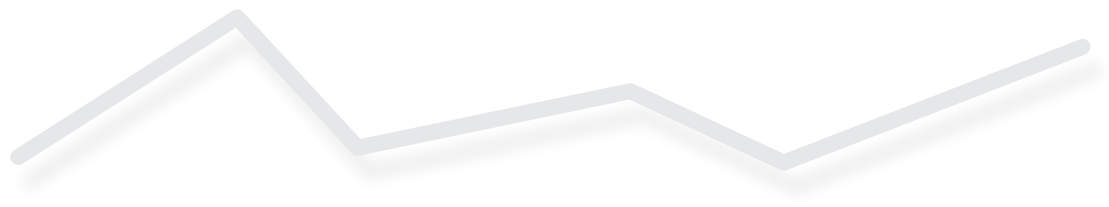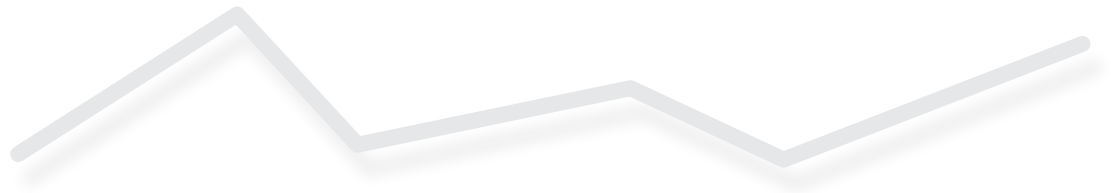
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ANNEX 4

Methods for estimating trends in micronutrient deficiencies: the United Nations Standing Committee on Nutrition sixth report

Annex 4 **Methods for estimating trends in micronutrient deficiencies: the United Nations Standing Committee on Nutrition sixth report**

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Abstract

Methods for estimating trends in vitamin A deficiency, anaemia and iodine deficiency disorders (IDDs) are described as used in the United Nations System Standing Committee on Nutrition (UNSCN) 6th report on the world nutrition situation and earlier reports. The first method (method A) involves comparing repeated survey estimates (after data cleaning and standardization) country-by-country through time. In the second method (method B), regression models are developed from existing survey results, using independent variables available for all countries and years; then, using the coefficients, the models are applied to all countries and specified years, to predict expected prevalences. Aggregating by regional groups, allowing for population numbers, provides regional estimates in specified years, and hence an estimate of trends. For vitamin A and anaemia, correlations with common variables such as national income or education are used; for IDDs, a two-stage process is used, estimating pre-iodization IDD levels and then changes with iodized salt. For vitamin A and anaemia, the methods are very similar to those used by the World Health Organization (WHO). These methods give apparently reasonable estimates of trends and for cross-sectional comparisons of countries (e.g. for ranking need), and thus provide some information for an overview of policies. The results can neither ascribe causality nor give information on effectiveness, and hence give no evidence on what to do about the problems described. More attention to evaluation data is now also suggested, to guide policy.

Introduction

The methods described here were developed over many iterations, starting with the United Nations System Standing Committee on Nutrition (UNSCN) reports on the world nutrition situation (for underweight), then used in 2001 for micronutrients in *The micronutrient report (1)*; in 2005 in *Recent trends in malnutrition in developing regions (2)*; and the UNSCN's recent (2010) *6th report on the world nutrition situation (3)*. The first two were supported by the Micronutrient Initiative and the latter by UNSCN. Full details of the publications are given in references *(1–3)*.
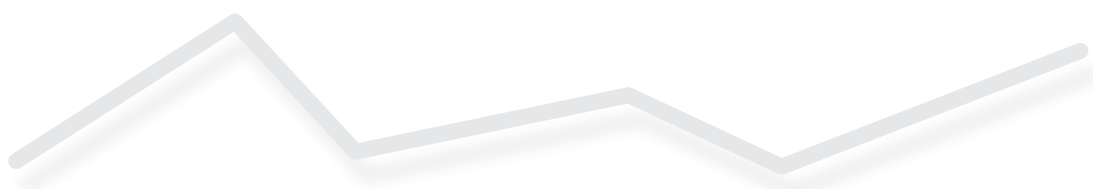
Reasons for estimating trends

Cross-sectional levels (usually prevalences) of micronutrient deficiencies are commonly used for ranking countries in terms of need, and for defining the severity of problems. Trend estimates can expand this by defining deficiencies by level and trend, e.g. bad/getting worse through to good/getting better. This is generally more useful for assessing priorities and the required policies. Different estimates of levels and trends may be appropriate for different purposes. In nutritional surveillance, these purposes are usually defined as for: long-term planning; programme monitoring and evaluation; and timely warning. While the implication is that the first of these is the priority, the other two should perhaps also be kept in mind. Generally, methods applied for large-scale trends are only broadly relevant (e.g. highlighting the ineffectiveness of periodic distribution of vitamin A capsules in affecting global vitamin A deficiency).

Levels are meaningful by region, for advocacy and description, but do not need to be very accurate. Often country prevalence estimates are needed; but these need only put countries in a category, and again do not need to be very precise. This was done for seven indicators for 2000 (see reference *(2)*, Annex 2), as best guesses by country (underweight, xerophthalmia, low serum retinol, anaemia [children, pregnant and non-pregnant women], and iodine deficiency disorders [IDDs]), and, for example, in the *6th report on the world nutrition situation (3)*, to classify countries by prevalence of vitamin A deficiency.

Estimating trends is a completely different story. Each estimate by country or region has to be comparable with others through time for the same country/region; moreover, rates of change are small compared with likely errors – for instance a change of one percentage point (ppt)/year is a high rate. Since this is the more difficult estimate, and trends are usually of more interest, most effort has gone into estimating trends.

Methods used by UNSCN for micronutrients

The UNSCN methods use direct and indirect comparisons to estimate trends. The models used for indirect estimates are similar to those used by the World Health Organization (WHO), but produce estimates for various regional groupings, and are adjusted to a defined year. WHO uses a range of years, e.g. 1993–2005 for anaemia. This paper aims to describe methods and related issues, (i) generally as they apply to all the nutrient deficiencies, and then (ii) for aspects that are specific to vitamin A, anaemia and iodine.

Measures of outcome, cut-off points, indicators and meaning/interpretation

Indicators should, if possible, reflect function (e.g. eye function would be preferable, in principle, to serum retinol), but the choice of indicators is usually driven by availability. Where indicators change, this can affect ability to estimate trends. Measures with reasonable prevalence are needed (e.g. xerophthalmia is too low to be very useful).
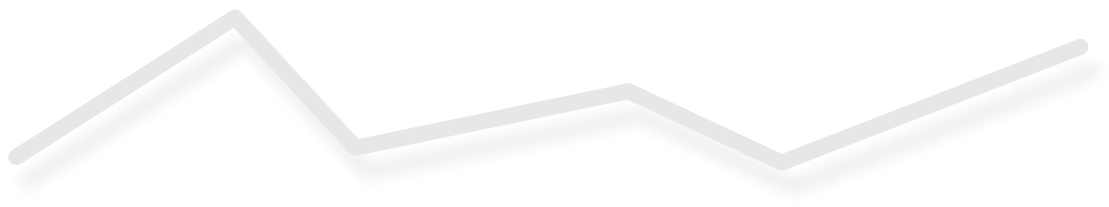
Measures and cut-off points

Anaemia

The only measure that is widely used to measure iron deficiency is haemoglobin. Among the common national surveys, such as the Multiple Indicator Cluster Survey (MICS) and Demographic and Health Surveys (DHS), only the DHS began to measure haemoglobin in the 1990s (although most national surveys that include haemoglobin measurements have taken place in the past decade). The DHS have included haemoglobin measurements in 55 countries, consistently measuring levels in children (usually 6 months to 5 years of age), with 51 of these surveys also measuring them in women (15–49 years old). The DHS define anaemia in children and women as mild, moderate or severe, using the thresholds shown in Table 1. Total anaemia prevalence is the combination of all three groups (all cases <10.0 g/dL haemoglobin).

Table 1. DHS definitions of anaemia in children and women

	Anaemia (g/dL haemoglobin)			
	Mild	**Moderate**	**Severe**	**Any anaemia**
Children	10.0–10.9	7.0–9.9	<7.0	<11
Non-pregnant women	10.0–11.9	7.0–9.9	<7.0	<12.0
Pregnant women	10.0–10.9	7.0–9.9	<7.0	<11.0

Anaemia is reported for more age groups and populations than other indicators of vitamin and mineral status, and conventionally it is estimated separately for children, pregnant women and non-pregnant women of reproductive age. It should be noted that the cut-off points, such as those given in Table 1, are not necessarily comparable between groups (e.g. 11 g/dL in pregnant women may not represent the same risk or disability as 12 g/dL in non-pregnant women). It could be argued that multiple cut-off points would be better (moderate, severe, as in anthropometry), but for the present, even getting the prevalences for a single cut-off point poses sufficient challenge. Moreover, in poor populations, much lower cut-off points are used clinically, so there is an issue that the prevalence of, for example, <12g/ dL, is unconvincing in relation to the extent and seriousness of the anaemia.

A major constraint for the surveys is the requirement for taking blood. In addition, there is the question of how accurate the point-of-care test for haemoglobin (i.e. Hemocue) measure is. Surveillance from routine assessment is sometimes used, but this has not, so far, been done systematically and it remains an open question as to whether this could be done. However, assessment by observing pallor is far too subjective, and no standardization of this measure is available. Again, it is questionable whether this is feasible.

Vitamin A deficiency

The prevalence of xerophthalmia is generally too low (usually below 1%) for the clinical signs to be accurately measured in a population. Very large samples are required to obtain reliable estimates; moreover, it is difficult to standardize measurement of xerophthalmia and this marker of vitamin A deficiency is now being replaced by serum retinol. However, measurement of retinol requires drawing blood and complex laboratory procedures, such as high-performance liquid chromatography. It may be possible, in the future, to use blood spots instead.

The drawbacks of using serum retinol include arbitrary cut-off points (e.g. 20 μg/dL); this may be too low, as increases in serum retinol are seen even in populations with serum retinol between 20 μg/dL and 30 μg/dL. As far as the authors know, cut-off points have not been related to risk or function. Interpretation of low serum retinol as a measure of vitamin A deficiency is therefore uncertain. It does not respond to periodic large doses of vitamin A.

Other methods for assessing vitamin A deficiency, such as eye response to dim light, seem promising in principle but unlikely in practice. Low serum retinol will probably continue to be used in the near future.

Iodine-deficiency disorders

Goitre has the longest recorded trend over time and is still potentially useful for measurement of IDD, as it is a measure of function, whereas urinary iodine is a measure of recent intake. Since goitre is closer to a functional measure, it could be argued that this should be retained. Cord-blood thyroid-stimulating hormone (TSH) at delivery would be potentially useful as a measure of thyroid adequacy in the fetus. This is a crucial consideration, as low thyroid hormone in utero leads to significant risk to cognitive development.

Data sources, data standardization and data cleaning

General data sources

The data used in the *6th report on the world nutrition situation (3)* to estimate the levels and trends of nutrition indicators were developed over several iterations and decades, including earlier UNSCN reports on the world nutrition situation, and an extensive update and analysis in 2004, supported by the Micronutrient Initiative and the United Nations Children's Fund (UNICEF) *(2)*. These compilations drew most of their data from WHO databases and from DHS, UNICEF (the State of the World's Children reports *(4)*, ChildInfo *(5)*) and similar sources. For the *6th report on the world nutrition situation (3)*, which was based on updates of the databases and estimates in the 2005 report *(2)*, new outcome data were sought, introduced primarily from current WHO databases, and added to the existing files; other sources were also used. Almost all the outcome data used were in the WHO Statistical Information System (WHOSIS) or the WHO Vitamin and Mineral Nutrition Information System (VMNIS) database, and were selected or adjusted for age band and other characteristics.

The methods used to identify the independent variables for the regression models for vitamin A deficiency, IDDs, anaemia, and underweight and stunting, for 1990, 1995 and 2000, have been previously described *(2)*, and in most cases these were updated with more recent data. New data for the 2005 and 2007 estimates were primarily obtained from the United Nation Population Division, an online database that includes country-level data from population-based surveys such as the MICS and DHS, as well as data collected by national governments and United Nations agencies. These data are compiled by the United Nations data system for domains of interest (i.e. education, health, etc.) as well as Millennium Development Goal indicators. Additional data were downloaded from the World Bank, UNICEF and the Food and Agriculture Organization (FAO); more details on the specific independent variables used for each outcome are given in the *6th report on the world nutrition situation (3)*.

In a few instances (e.g. estimating anaemia in pregnant women), subnational surveys were used, particularly where there was a lack of national-level data, although this was rare.

General standardization and data-cleaning issues

The most rigorous need is for comparison within countries over time. To achieve this, it was found helpful, if tedious, to lay out the data points available as a matrix – years as columns and countries as rows (see reference *(2)*, Annex 1) – which can include the model-derived estimates as complete columns. This allows a quick view of where there are data, and, to an extent, which cases may be outliers. WHOSIS now uses a similar format for its survey data.

The four factors that need to be established are as listed next.

- **Sample**: what population does it represent; how was it sampled; what is the design effect (usually not known and, regrettably, ignored), etc.? The sample size should be recorded and the minimum established (this usually only applies to subnational surveys).

- **Age band/sex/pregnant or non-pregnant**: standardization of age bands is important, and usually 6–59 months is the most common; for anthropometry, an adjustment factor was used (from ratios derived from survey results) that allowed correction to a standard age band. This was not done for other deficiencies, but should be, and research is needed in this area. Otherwise it is crucial to identify and record the biological status; sex was not distinguished (except for anaemia) but perhaps it should be done in future. Note that this also means that, particularly for anaemia, several cases can be obtained from one survey, coded by biological status/age band. The most important thing is to ensure that, when estimating changes within a country through time, identical groups are being compared; it is best that these are the standardized groups (e.g. 6–59 months); next best is the same age bands but not the standardized ones (e.g. 0–36 months); if there are no comparable age bands between two surveys, then this comparison cannot be made. The adjustment is acceptable for the general database (for modelling, method B) but not for direct comparison (method A).

- **Seasonality**: this has not been taken into account in the estimates for these purposes (deficiencies can be affected by season, e.g. wasting) and not much is known about the effect of seasonality. This is an area for future research.

- **Indicators**: occasionally there is a diversity of cut-off points (e.g. for anaemia); this needs to be checked for reported prevalence values and if these differ over time then comparisons cannot be made. No corrections have been tried, except to go from median urinary iodine excretion to prevalences, using WHO algorithms. Differences between assessment methods are also of concern, e.g. Hemocue versus laboratory estimates, but these have not, so far, been investigated.

Decisions on the plausibility of doubtful values during the development of these models draws on comparison of reported values with the model-derived country–year estimates, as well as observation of the data points that are outliers.

Specific issues

Anaemia

Representative surveys often include several biological groups; thus, one survey can generate a number of cases, distinguished as being different groups (the data structure codes each such group as a separate case [row]). The data on anaemia show more variation than for other deficiencies, with a higher proportion of subnational surveys among the available data. The model-derived estimates are particularly useful here, in considering the plausibility of individual points. In some estimates for the 2005 publication *(2)*, subnational data were included in deriving the models. For the *6th report on the world nutrition situation (3)*, only national data were used.

For doubtful country–year prevalences, the estimates for pregnant and non-pregnant women were compared with each other and with the model estimates, to further identify likely outliers.

Vitamin A deficiency

National surveys of xerophthalmia are now quite rare – only seven new cases were added to the database between 2005 and 2009 – and with the low prevalences of xerophthalmia (about 1–2%), this is not an ideal measure. However, xerophthalmia does represent a serious clinical condition and it is probably of interest to continue reporting, even if with many provisos.

The usual reports are of Bitot's spots (X1B) or night blindness (X1N). These two were combined for the indicator used *(3)*, and used for method A but not for modelling in the 2010 publication *(3)*, although they were used in 2005 *(2)*.

Estimates of low serum retinol (<20 µg/dL or 0.7 µmol/L) are increasingly available, and only national estimates were used for the *6th report on the world nutrition situation (3)*. Although there is probably some relation to age, any age group between 0 and

72 months was treated as the same and no adjustments were made; since the effect of age is considerable, the options for adjusting for age should be further investigated and applied, if feasible. Outliers of >70% prevalence were excluded, and otherwise the same checks from model estimates as described above were used to assess plausibility.

Iodine-deficiency disorders

The most commonly used measures of IDDs is goitre, which has the longest recorded trend over time and is useful as a measure of function. WHO classifies goitre into two grades *(6)*, with total goitre being the combined prevalence of the two.

- **Grade 1**: a goitre that is palpable but not visible when the neck is in the normal position, even when the thyroid is not visibly enlarged. Thyroid nodules in a thyroid that is otherwise not enlarged fall into this category.

- **Grade 2**: a swelling in the neck that is clearly visible when the neck is in a normal position and is consistent with an enlarged thyroid when the neck is palpated.

Data on goitre have the disadvantage of being harder to collect in standardized way (as compared with urinary iodine); there are examples of discrepancies within and between surveys in diagnosis of goitre. However, goitre has the most data points available for meta-analysis use (there were 197 data points for total goitre rate in the *6th report on the world nutrition situation (3)*).

The second commonly used measure of IDDs is urinary iodine, which is more likely to be a measure of recent rather than long-term intake. Urinary iodine is reported by at least one of the following categories:

- **distribution**: the percentage of the population falling within the categories <20 µg/L, 20–49 µg/L, 50–99 µg/L, 100–299 µg/L, >300 µg/L;

- **prevalence**: the percentage of the population falling below the cut-off level of 100 µg/L;

- **median** and/or **mean** (µg/L, µg/g creatinine or µg/24 h).

Urinary iodine is less subject to measurement bias (misdiagnosis) than is goitre. However, it has fewer available data points for meta-analysis (there were 91 data points for low urinary iodine prevalence in the *6th report on the world nutrition situation (3)*). Some of these prevalence data points were computed from the mean urinary iodine levels, using an equation very similar to that recommended by WHO (2004) *(7)*.

It should be noted that there is no algorithm to convert between prevalence of goitre and urinary iodine, and, as they measure two indicators that change at different rates, such a conversion is not likely to be correct.

Another alternative, but less commonly used, measure of IDDs – TSH levels measured on neonatal cord blood – should be explored, but is rarely reported at present. Diagnostic strips using immunoassay are available.

The choice is then whether to base regional and global levels on the prevalence of low urinary iodine or of total goitre. The arguments to use total goitre prevalence include those listed next.

- Despite the disadvantage of poor quality of data on goitre, there is greater availability of this indicator (more data points).

- The use of endogenous (endemic) IDD levels in predictive modelling allows estimates of trends. This is only available as total goitre in most cases (see the description and use of this indicator below).

- Urinary iodine would provide a better estimate of current iodine access than goitre. However, data on goitre reach back further in time, so if the aim is to track trends over a decade or more – over the time in which coverage of iodized salt has been expanding – then at present goitre provides the only practical choice. However, in the future, it should be feasible to shift towards use of urinary iodine, as WHO has done in recent reports.

- Goitre is also nearer to a measure of function, rather than short-term access to iodine. TSH would probably be better still (e.g. in cord blood). It needs to be borne in mind that the main concern is thyroid function, in utero and postnatally, and monitoring should aim to cover this issue.

Independent variables

The sources and handling of independent variables, for developing multivariate interpolation models are described in references *(2)* and *(3)*. The principle is that variables associated with the outcome indicators that are available for each country and year need to be identified, so that they can be used to infer prevalences for defined years. These have all been taken from the various global databases, usually maintained by United Nations organizations. Where series have a few missing values, these are linearly interpolated. The main issue arises when the definition of the indicator, and/or its estimate, changes. The most common independent variable used is national income (gross domestic product, gross national product, gross national income, producer price index, and so on), and when a new estimate supersedes an earlier one, the series back in time has to be re-entered. Population estimates are also needed, for aggregation, and these may also change between those available (including back in time) in, for example, 2009 and 2004. Again, the series just has to be re-entered. Estimates that are less easily available, such as numbers of pregnant women, are derived by calculation, as described in reference *(3)*.

Predictive regression models and calculation of population prevalences and numbers affected

Three methods of assessing trends have been used, starting with estimates at country–year level (i.e. for a specified country and specified year). These methods are described and were used in the 2001 *(1)*, 2005 *(2)*, and 2010 *(3)* reports.

The first ("method A") involves comparing pairs of surveys to estimate the direction (and rate) of change, country-by-country. A further use of surveys stratified by region was to make a rough estimate, included to be in line with WHO practice at the time, by averaging available data points (unweighted) by region and band of years – examples are shown in Table 2 in the *6th report on the world nutrition situation (3)* and Table 4 in the 2005 paper *(2)*. While this method is useful to get a quick look at levels and possible trends, it is probably not worth continuing and will not be further discussed here. The second method ("method B") uses the database established as described above to estimate missing country–year values for standardized years, by fitting regression models using predictive independent variables. This is described in detail later.

Method A: comparing national surveys

When national survey results are considered comparable (see earlier), straightforward comparison of trends for those countries with repeated surveys gives a general picture of the way the situation is changing. It is roughly estimated that 2 ppt change is likely to be significant, given usual sample sizes. Note that prevalences and not means are compared, being quicker, but means (e.g. mean serum retinol or haemoglobin) would be an advance to consider for the future.

The balance between improvement, no change and deterioration, for example, by region, then gives a view of likely overall changes; the model-derived trend estimates should at least be in line, or, if not, this flags where to look again. The rate of change (in ppt/year) can also be viewed from these comparisons; again, the model-derived estimates should not be greatly out of line with these.

Note that the rule of thumb of 2 ppt difference being interpreted as change is independent of time, as the comparison between surveys does not depend on the time between them.

Method B: estimating country–year prevalences for specified years to give trends

The interpolation model method has been used for many of the UNSCN reports and for the 2001, 2005 and 2010 papers *(1–3)*. It is necessary because any other method of estimating trends is vulnerable to errors introduced by country data points appearing at one time but not another; also, it avoids forcing a linear (or other algorithmic) trend through time. Therefore, it has been considered unavoidable to make estimates for each country at specified times, and to use these as the basic data for then estimating trends. As these estimates fit within the time frame studied, and do not try to extrapolate into the future, they are referred to as interpolation models; they can also be called "prediction"; they refer to a use of regression that makes no attempt to infer causality.
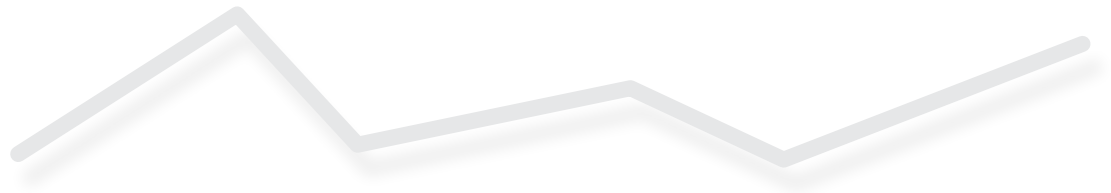
For each outcome variable, the datasets are set up as described above: the unit of analysis is the country–year, where there is a valid survey result. Independent (potential) predictor variables are entered for the country and year, to match the outcome data. A view of the available outcome data can conveniently be seen, as shown in Annex 1 of reference *(2)*; this was not done for 2010.

A range of potential independent predictor variables was explored for the 2005 paper, and these are listed in the methodology description, before selecting those included in the final models. For the *6th report on the world nutrition situation (3)*, the models were based on similar independent variables and the full potential range was not explored again (fewer resources were available for the analyses for this report). Regional dummies were used, generally matching the regional groupings. Interactions, notably but not only with regional dummies, were explored systematically for the 2005 paper *(2)*, less so for the 2010 paper *(3)*. A variable for year was tested and was always not significant (except for IDDs); that is, the change through time was being captured by the independent variables, such as gross national income.

Further details of the model development, test criteria (e.g. examining and generally minimizing standard deviations of residuals) and treatment of outliers are given in the reports. Note that the models were fitted to the full set of data through time, so that the estimates for earlier years were redone. This procedure established "best" models for vitamin A deficiency and anaemia (and underweight, not discussed here). For IDDs, a different approach is used. The R2 values (a rough guide to fit) were about 0.5 (for underweight, for comparison, the value was 0.8). More relevant here, around 70% of the residuals were less than about 9 ppt, in the best models, which gives a view as to the fit: it is not that reliable for individual countries (a 70% chance that the interpolated value is within 9 ppt of the reported, or presumed actual unmeasured, value), although this is likely to balance out when aggregated.

Once the coefficients are estimated, the relevant independent values for the specified years (e.g. 1990, 1995, 2000, 2005, 2007 in the *6th report on the world nutrition situation (3)*) are looked up for each country and inserted into Excel spreadsheets. The equation estimated by regression is then used in Excel to calculate the predicted prevalences for each country for the specified year.

Population estimates are entered by country for the specified years; hence, the numbers of people affected (e.g. pregnant women with anaemia) are calculated. The countries are sorted into regions or subregions, the numbers affected and total population numbers summed and divided, and the weighted prevalence obtained. It should be noted that this method is more flexible and safer than using population weights themselves, but gives the same result.

The predicted values by country and specified year provide the basis. However, for critical countries with large populations, notably, but not only, China and India, predicted values are carefully compared with actual survey results, and on occasions the values used are based on the survey results, trended to be compatible through time,
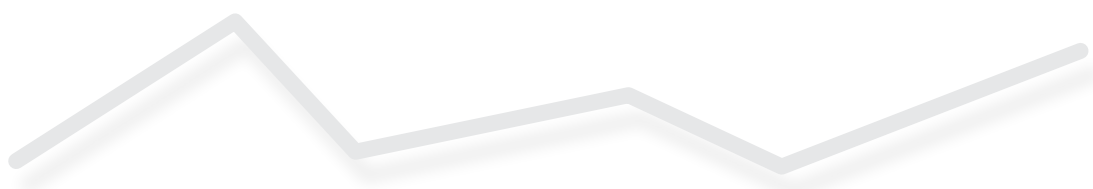
using the model-derived trend. This is similar to making the "best guess" cross-sectional estimates (see below). The type of country–year matrices presented in Annex 1 of the *6th report on the world nutrition situation (3)* are useful for this.

Making "best guess" estimates for comparisons at country level for a base year, applying method B

Annex 2 of reference *(2)* gives estimates of seven outcome indicators for 2000. This was the basis for the Micronutrient Initiative/UNICEF's report *(1)*. Clearly the model-derived estimates alone are not sufficiently accurate to compare across countries. However, they can be adjusted in many cases, using survey results at near points in time.

This requires evolution of a set of rules for interpolating to a base year. A detailed description of the procedure is given in reference *(2)*. These estimates are relevant to the present exercise, as estimating trends is an important feature.

Methods specific to vitamin A deficiency and anaemia

These have been covered above. The models are given in references *(2)* and *(3)*.

Methods for IDDs

The methodology for estimating country-level IDDs follows the "method B" approach, as with iodine and vitamin A: by using the established database to estimate missing country–year values for standardized years, by fitting regression models using predictive independent variables. However, unlike vitamin A and iron, IDDs are more closely associated with environmental factors (which influence the iodine soil content), and the use of iodized salt, rather than socioeconomic or development indicators. In this sense, the methodology for IDD approaches (without claiming to be) a causal model, as well as a predictive model.

Following this, in order to estimate regional and national levels of IDDs, a regression model was created to predict the level of endogenous (endemic) goitre. Values for endogenous total goitre rate were taken from previous estimates, derived from research linking endogenous goitre prevalences to soil characteristics (from FAO data) and other factors *(2)*, and then imputing endogenous rates from these characteristics to fill in missing data. Fig.1 illustrates a separate analysis that compares a map from circa 1990, showing areas known to have higher levels of IDDs, and a map displaying geographical data combining areas with high rainfall (which can leach soils of iodine) and certain soil types that are less likely to retain iodine. Very similar patterns can be seen in both maps, indicating the relationship between environmental factors and IDDs.

Fig. 1. Comparison of IDD (total goitre) prevalences and areas predicted to have iodine-deficient soils. (a) Geographical distribution of IDDs, from surveys circa 1990 *(8)*. (b) Estimates from FAO rainfall and soil maps, using Geographic Information System overlaying

a

■ Areas with known iodine deficiency

b

■ Iodine-deficient soils
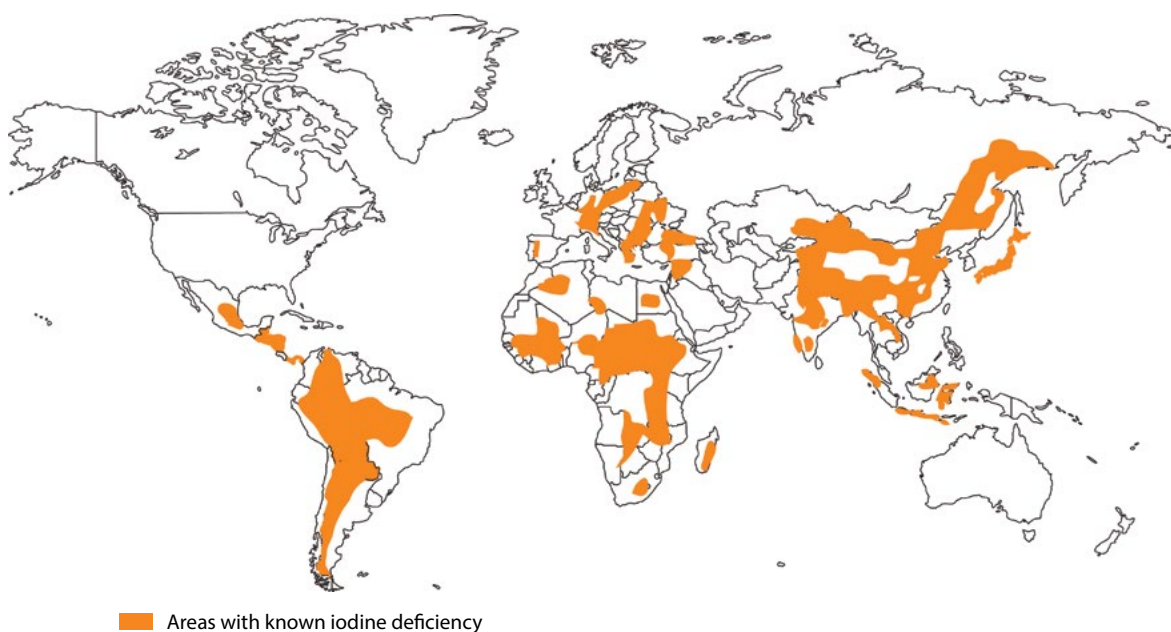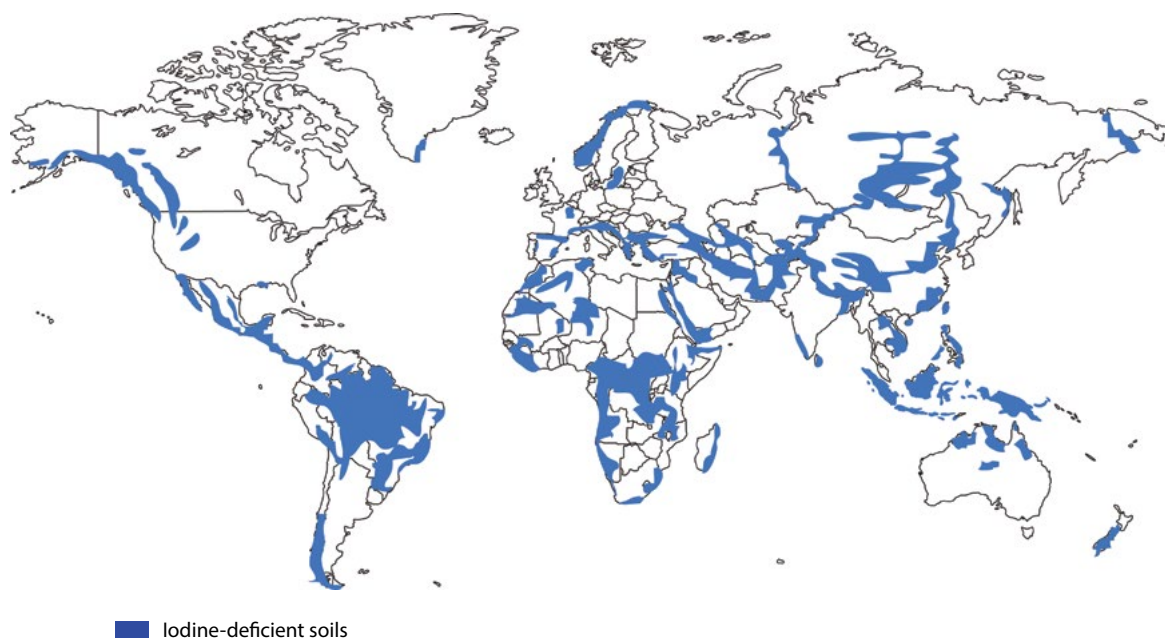
A regression model was then run with current goitre as the outcome variable, and prevalence of iodized salt use, years since iodization began in the country, and endogenous goitre levels (as calculated in the first regression model). Some models in previous reports *(2)* excluded the years since iodization but included the interaction term between percentage of households using iodized salt and endogenous goitre. For urinary iodine, a simpler approach was used, with urinary iodine as the outcome variable, and the percentage of households with iodized salt, a regional dummy variable for the Americas, and years since iodization began as the dependent variables. The level of endemic goitre was not used in this model. As with vitamin A and anaemia, these regression model equations for low urinary iodine and total goitre rate were then applied to data from the specified years, to calculate predicted prevalences for each country for the specified year.

The population estimates follow the same methodology as for vitamin A and anaemia.

Discussion

For the purposes suggested in the introduction to this paper – to identify priority areas, resource needs, and global and regional trends – specifying where and for whom deficiencies are bad/worsening, bad/improving, better/worsening (unusual) and better/improving is probably what is needed. The methods described here, as used by the UNSCN, and very similar ones used by WHO, are about adequate. Some areas for improvement and research have been indicated.

However, trends and differentials do not themselves indicate the policies and programmes needed. Cross-country data such as the ones discussed in this paper are not ideal for evaluation or for assessing causes, but some glaring points are obvious. For example, while it has been observed that vitamin A deficiency is only decreasing at about 0.4 ppt/year – 4 ppt/decade – despite the fact that about 60% claimed "full coverage" of periodic distribution of massive-dose vitamin A capsules, in contrast, IDDs (as goitre) have more than halved over a similar period (see reference *(3)* Fig. 7). Taken together, these observations should lead to an immediate review and follow-up.

So, relating these trends to causes needs to be prioritized, as does interpreting them in terms of policy implications. At the same time, but beyond the scope of this paper, carefully designed evaluations are crucial to aid the interpretation of trends, and to guide policy decisions.

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ANNEX 5

Development of a new framework to estimate the global burden of disease due to iodine deficiency

Annex 4 Development of a new framework to estimate the global burden of disease due to iodine deficiency

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Abstract

Deficiencies of micronutrients contribute to the global burden of disease (GBD), and interventions to prevent these deficiencies are highly cost-effective strategies for public health action. A decade has passed since the last estimate of the GBD due to iodine deficiency. Because of progress in the control of iodine deficiency worldwide, and the development of new assessment methods, the Child Health Epidemiology Reference Group (CHERG) reassessed the contribution of iodine deficiency to the GBD. This task was given to an expert group at the Swiss Federal Institute of Technology (ETH) Zürich, which took a stepwise approach following guidelines from the 2009 update of the GBD study operations manual. First, the expert group completed a systematic literature search on the effects of iodine deficiency. Then, using these data, a new iodine-deficiency disease model was defined. It included the GBD 1990 and 2000 sequelae of goitre and cretinism, but added sequelae such as hyperthyroidism, and borderline, mild and moderate intellectual impairment. The model was refined by including three levels of iodine deficiency severity as defined by the World Health Organization (WHO) criteria for the median urinary iodine concentration (UIC): mild iodine deficiency, median UIC = 50–99 µg/L; moderate iodine deficiency, median UIC = 20–49 µg/L, and severe iodine deficiency, median UIC = 0–19 µg/L. Then, to accurately define the proportion of the global and regional population affected by these iodine-deficiency levels, the WHO Vitamin and Mineral Nutrition Information System (VMNIS) global database was thoroughly reviewed and updated to produce new global and regional estimates of the prevalence of iodine deficiency in 2010. Currently, analytic approaches are being developed to produce new estimates of how iodine deficiency results in loss of intelligence quotient (IQ) points in populations, and estimate the resulting intellectual impairment.

Introduction

Iodine deficiency leads to inadequate production of thyroid hormone, which has multiple adverse effects on growth, development and health in humans. These

effects are collectively termed the iodine-deficiency disorders (IDDs) and are one of the most common human diseases *(1, 2)*. Approximately 2 billion people are at risk of iodine deficiency worldwide, owing to inadequate dietary intake. Iodine deficiency was estimated to be the 77th leading cause of disease burden in the world in 1990, accounting for 0.1% of the total disability-adjusted life-years (DALYs) *(3)*. The sequelae and disability weights in the *Global burden of disease 2000* (GBD 2000) *(4, 5)* estimate for iodine deficiency are shown in Table 1; they included goitre, cretinism and intellectual disability. The total global DALYs (in thousands) attributed to iodine deficiency were 3529 in GBD 2000 *(5)*, compared with 1562 in GBD 1990 *(3)*.

Table 1. Sequelae definitions and their disability weights for iodine deficiency used in the Global burden of disease 2000 *(4, 5)*

Cause category	GBD 2000 code	ICD-9 codes	ICD-10 codes
Iodine-deficiency disorders	UO55	243	E00–E02
Case/sequelae	Definition		Disability weight (DW)
Total goitre rate (TGR) (G1 + G2)	A mass in the neck consistent with an enlarged thyroid: • Grade 1 (G1) = palpable but not visible • Grade 2 (G2) = visible in neutral neck position		<0.001 G1 (DW 0.000) and G2 (DW 0.001) were merged into TGR for the final estimates
Mild developmental disability	Any of the following due to iodine deficiency: bilateral hearing loss, delay of walking ability, mild intellectual impairment		0.006
Cretinism	Hypothyroid cretinism: hypothyroidism and stunting as a result of iodine deficiency Neurological cretinism: mental deficiency (IQ below 70), deaf-mutism, and spastic paralysis as a result of iodine deficiency		0.804
Cretinoidism	Some but not all features of full cretinism as a result of iodine deficiency		0.255

GBD: Global burden of disease. ICD: International Classification of Diseases *(6)*. IQ: intelligence quotient.

Until the 1990s, total goitre prevalence was used as the primary indicator for the assessment of population iodine deficiency. However, inspection and palpation of goitre in areas of mild iodine deficiency has poor sensitivity and specificity. Moreover, in areas of endemic goitre, although thyroid size predictably decreases in response to increases in iodine intake, it may not return to normal for months or years, even after correction of the iodine deficiency *(7)*. During this transition period, the goitre rate is difficult to interpret, because it reflects both a population's history of iodine nutrition and its present status.

Urinary iodine concentration (UIC) is a more sensitive indicator of recent changes in iodine intake, is more objective and has become the recommended indicator for assessing iodine nutrition in the population *(8)*. Since 2003, the World Health Organization (WHO) has used nationally representative data on UIC in school-age children (6–12 years) to update country, global and regional estimates of iodine nutrition. The median UIC, based on the ranges shown in Table 2, is used to classify the severity of iodine deficiency in populations. In place of the goitre rates used in the estimates of the GBD 1990 and 2000, in the current estimates, the UIC should be used as the indicator of iodine deficiency.

Table 2. Severity of iodine deficiency based on median urinary iodine concentration and the total goitre rate

|	None	Mild	Moderate	Severe
Median urinary iodine concentration (µg/L)	>100	50–99	20–49	<20
Total goitre rate (%)	0–4.9	5.0–19.9	20.0–29.9	≥30

Source: adapted from reference *(7)*.

Methods

Owing to the progress in the control of iodine deficiency worldwide and the development of new assessment methods, the Child Health Epidemiology Reference Group (CHERG) decided to reassess the contribution of iodine deficiency to the GBD. This task was given to an expert group at ETH Zürich, which took a stepwise approach following guidelines from the 2009 update of the GBD study operations manual *(9)*. First, the expert group completed a systematic literature search on the effects of iodine deficiency. Then, using these data, a new IDD model was defined

Systematic literature review on the health impacts of iodine deficiency

The expert group carried out a systematic literature review of the effects of iodine deficiency in humans. The inclusion criteria defined prior to the review were original studies or meta-analyses, including: cross-sectional population-based studies and randomized controlled intervention trials; health outcomes of mild, moderate and severe iodine deficiency; and UIC and/or goitre as indicators for iodine deficiency. PubMed, Current Contents Connect and ISI Web of Science were searched for articles in English, French, German and Spanish, with the combinations of the keywords: "iodine", "iodine deficiency", "iodized salt", "goitre/goiter", "cretinism", "nutrition", "thyroid", "supplementation", and "fortification". The reference lists of articles identified by this search strategy were also searched, and those that fulfilled the predefined criteria were selected (see Fig. 1). Papers that described health outcomes of iodine deficiency beyond goitre and cretinism were focused on, because the links between iodine deficiency and these sequelae had previously been comprehensively reviewed in GBD 1990 and 2000 *(3, 5, 10, 11)*.

Fig. 1. Literature review and data abstraction flow diagram
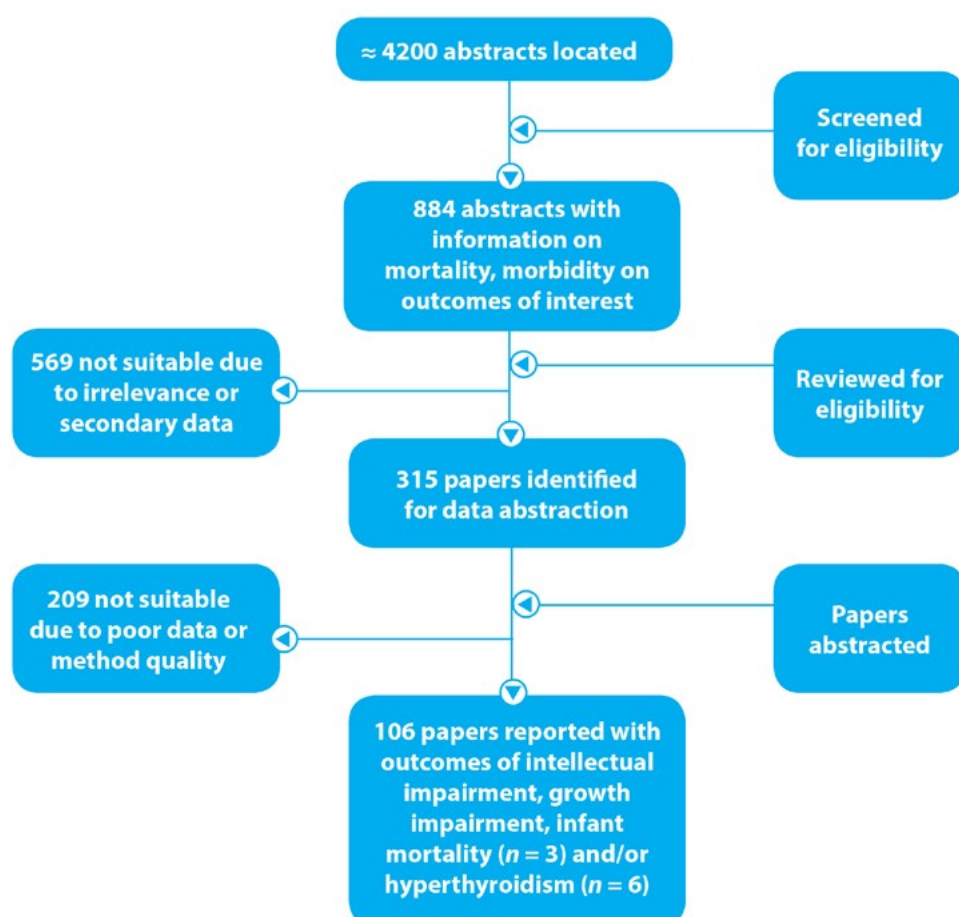
Updating the global prevalence of iodine deficiency in 2010

The global prevalence of iodine deficiency was last reviewed in 2003 *(12)* and 2007 *(13)*. To estimate the present situation of iodine deficiency, the last estimate of the global prevalence of iodine deficiency was updated by conducting a systematic literature review of epidemiological prevalence studies. Data compiled in the WHO Vitamin and Mineral Nutrition Information System (VMNIS) database on iodine deficiency *(14)* were used, and an extensive literature search in PubMed, Current Contents Connect and ISI Web of Science was conducted, for articles in English, French, German, Spanish and Russian; correspondence was also carried out with iodine experts around the world.

The inclusion criteria were: studies using a cross-sectional population-based sample frame; studies using standard UIC assay techniques; and studies presenting the data as median UIC or proportion (%) of the population with UIC <100 μg/L. For each country, the most recent national survey in school-age children (if not available for preschool children, adolescents or adults) within 10 years (1999–2009) was selected. For countries where a national survey was not available, the data were prioritized as

follows: (i) subnational data, 1999–2009; (ii) nationally representative data, 1993–1998; and (iii) subnational data, 1993–1998. For subnational country estimates, all eligible subnational studies carried out within the selected study frame were pooled and presented as a weighted national estimate.

In 2010, surveys covered approximately 95% of all school-age children worldwide. Working with the support of WHO, new global and regional estimates of the prevalence of iodine deficiency in 2010 were produced (see Table 3). The severity of iodine deficiency at the country level was defined by presenting the proportion of the population with mild iodine deficiency (median UIC = 50–99 μg/L), moderate iodine deficiency (median UIC = 20–49 μg/L) and severe iodine deficiency (median UIC = 0–19 μg/L). For countries where the distribution of UIC was missing for one or more of the severity categories, existing national data worldwide were used to develop predictive equations based on regression analysis to impute missing data points. The results are positive overall: the number of countries with inadequate iodine intake decreased from 54 in 2003 to 47 in 2007 and 37 in 2009. The proportion (%) of school-age children worldwide with inadequate intake is 30.3% in 2009, with a decrease in the total number of school-age children with insufficient iodine intake from 285 million in 2003 to 266 million in 2007 and 246 million in 2009.

Table 3. Number of countries, proportion of population, and number of individuals with insufficient iodine intake in school-age children (6–12 years) and in the general population (all age groups), by WHO region, 2010

| WHO region[a]	Insufficient iodine intake (UIC <100 μg/L)				
	School-age children			General population	
	Countries (*n*)	Proportion (%)	Total number (millions)[b]	Proportion (%)	Total number (millions)[c]
African Region	12	40.1	58.2	440.8	323.4
Region of the Americas	2	12.2	12.9	11.7	103.9
South-East Asia Region	0	31.9	77.0	31.7	535.4
European Region	14	43.6	28.6	43.9	359.9
Eastern Mediterranean Region	5	45.5	37.0	43.3	230.6
Western Pacific Region	4	18.5	31.8	17.3	300.3
Total	37	30.3	245.5	28.7	1853.4

[a]193 WHO Member States.
[b]Based on population estimates for the year 2009 *(15)*.
Preliminary data as of November 2010.

Defining the disease model

Based on the literature review on the health impacts of iodine deficiency, and considering both the GBD 1990 and 2000 disease models *(3, 5)*, the iodine-deficiency sequelae and disease model were defined (see Fig. 2). The disease model was based on three levels of severity, as defined by WHO UIC criteria (see Table 2). The contribution of iodine deficiency to the GBD is twofold: exposure in utero during pregnancy and current exposure. Country and regional data on iodine deficiency defined above are generally available for school-age children and these data constitute a proxy for the general population. The prevalence of current iodine deficiency was treated as a lifelong condition that affects the entire general population, including pregnant women, so these estimates include a contribution from in utero exposure. A male to female ratio of 1:1 was assumed for all conditions. The data available on UIC for time-series analysis are scarce and limited by the heterogeneous patterns of gradual introduction and/or relapse in salt iodization programmes. Thus, a time-series component was not included.

Fig. 2. Disease model and sequelae for iodine deficiency. UIC: urinary iodine concentration
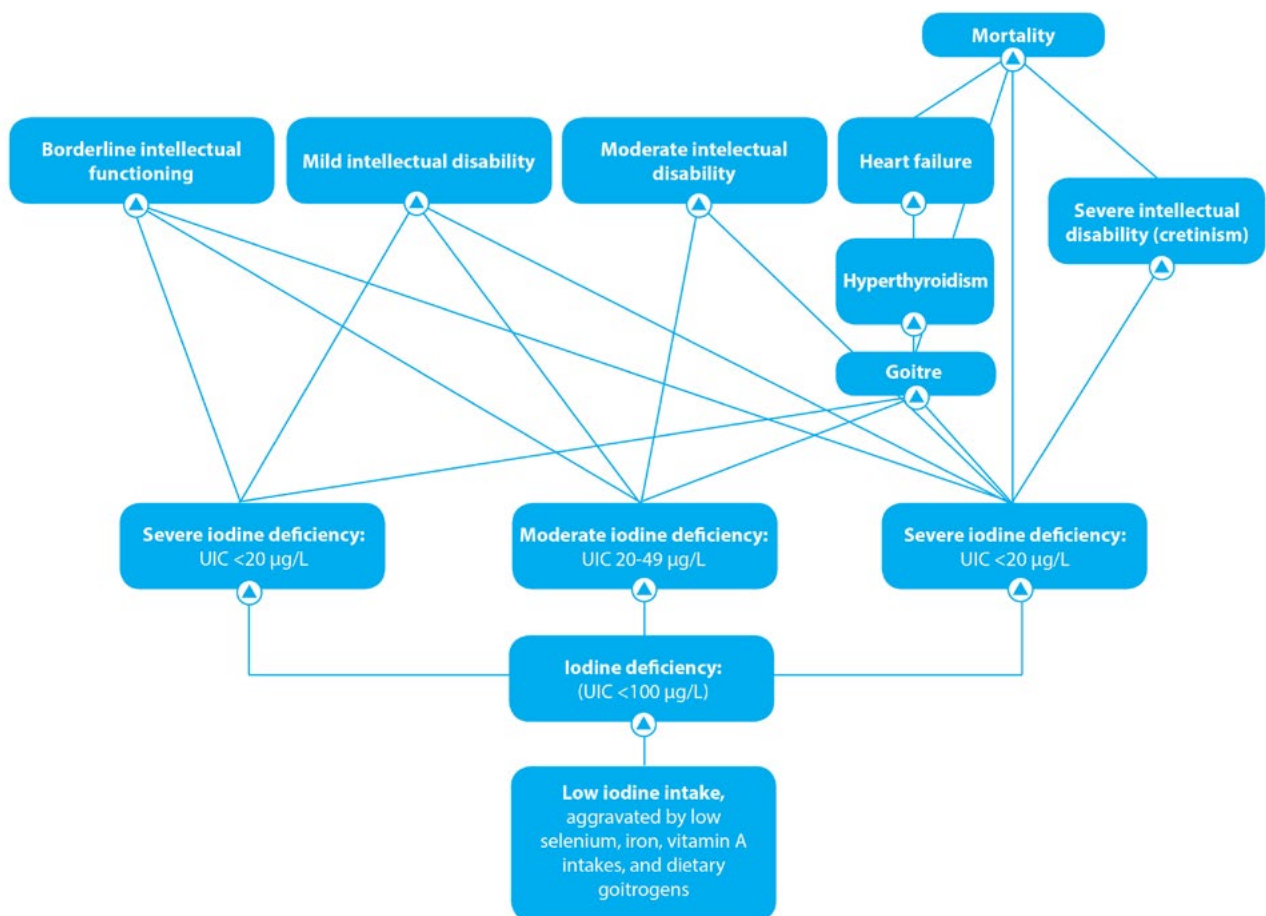
Defining the sequelae of iodine deficiency

Goitre

Goitre prevalence is no longer routinely measured in national studies of iodine status. The prevalence of goitre was therefore estimated from the UIC distribution. The proportion of the population with mild, moderate or severe iodine deficiency, based on UIC ranges, was assigned a corresponding goitre prevalence, as outlined in the final row of Table 2. Thus, the sequela of goitre (SS167, see Table 4) was applied to 5%, 20% and 30% of the population with mild, moderate and severe iodine deficiency, respectively *(8)*. This was applied to the entire population in each country.

Table 4. Sequelae used in the current disease model for iodine deficiency

GBD code	Sequelae	Definition	Lay description
SS167	Iodine-deficiency goitre		This person has a large mass in the front of the neck. They sometimes have weakness and fatigue, constipation and weight gain
SS140	Congestive heart failure		This person has symptoms of chronic cardiac insufficiency graded mild and greater (Killip scale k2 to k4)
SS82	Generic uncomplicated disease: worry and daily medication (hyperthyroidism)		This person has a chronic disease that requires daily medication and causes some worry, but minimal interference with daily activities
SS163	Borderline intellectual functioning	ICD-10 definition, IQ range 70–84	This person does not do well in school, has some difficulty doing complex or unfamiliar tasks and has trouble concentrating. The person may also have behavioural problems
SS161	Mild intellectual disability/mental retardation	ICD-10 definition, IQ range 50–69	This person has low intelligence and is slow in learning at school. As an adult, the person can work at simple supervised jobs and live independently, but often needs help to raise children
SS162	Moderate intellectual disability/mental retardation	ICD-10 definition, IQ range 35–49	This person has low intelligence and is slow in learning to speak and do simple tasks. As an adult, the person requires a lot of support to work productively, live independently and raise children
SS164	Severe intellectual disability/mental retardation (cretinism)	ICD-10 definition, IQ range 20–34	This person has low intelligence and cannot speak more than a few words, needs help with most basic daily activities and can do only simple tasks under close supervision

Source: personal communication, CHERG group and C Mathers, 23 July 2009.
ICD: International Classification of Diseases *(6)*. IQ: intelligence quotient.

Hyperthyroidism and heart failure

Hyperthyroidism occurs in iodine deficiency because of the development of autonomous nodules in goitrous thyroid glands, which produce excess thyroid hormone *(2)*. The crude incidence rate of overt hyperthyroidism in a population with mild iodine deficiency is approximately 65/100 000 per year, and in moderate and severe iodine deficiency it is approximately 93/100 000 per year *(16)*. Nearly all cases are in the age group >50 years. About 6% of hyperthyroid individuals who are untreated will develop symptoms of heart failure *(17, 18)*. Therefore, the prevalence of congestive heart failure was estimated to be 5.58/100 000 in moderate and severe iodine deficiency and 3.9/100 000 in mild iodine deficiency. The disability weight for congestive heart failure (SS140, see Table 4) is 0.201, range 0.186 to 0.206, GBD 2000 *(4)*. This will only apply to the population group ≥50 years. For the remainder of the cases of hyperthyroidism, the sequela of generic uncomplicated disease (SS82, see Table 4) was applied to the same population (≥50 years).

Cretinism/stunting

Cretinism is an irreversible conditions occurring in situations of moderate and severe iodine deficiency. The method used in GBD 2000 was followed, to estimate the rate of cretinism in school-age children (5–14 years) from the goitre rate in a population *(5)*. It was assumed that new incident cretinism cases only occur in countries with median UIC <50 µg/L. Because a total goitre rate of 20% was assumed for these countries (see above), the proportion G1 to G2 (see Table 1) was estimated, based on data from the Micronutrient Deficiency Information System (MDIS) in countries before introduction of iodine prophylaxis *(19)*. The multiple logistic regression formula below provides the best-fitting relationship between cretinism and total goitre, based on actual data from Ecuador, Zaire and several countries in Asia *(11)*. The functional relationship between cretinism (C) and goitre rate (G1 and G2, see Table 1) was established using multivariate analysis and logistic modelling, where:
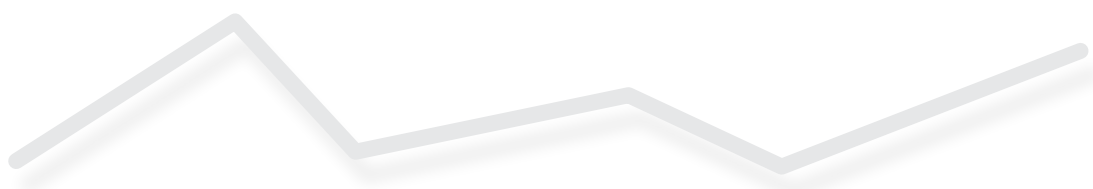
$$\mathrm{Ln}(C/[1-C]) = b_0 + b_1 G1 + b_2 G2$$

and

$$b_0 = -9.3939, \quad b_1 = 15.796, \quad b_2 = -8.8026$$

Intellectual disability

The body of evidence on the link between iodine deficiency in early life and a decrease in intelligence quotient (IQ) score strongly suggests the relationship is causal, with different degrees of intellectual disability for each of the severity categories mild, moderate and severe. Two studies have estimated the intellectual disability in severe iodine deficiency. A meta-analysis by Bleichrodt *(20)* included 21 observational and experimental studies and a control group on the effect of iodine deficiency on mental development. Bleichrodt estimated that severe iodine deficiency was associated with a mean loss of 13.5 IQ points, in studies including both school-age children and adults. Another meta-analysis *(21)* included 2214 participants (mainly children) and IQ was used as the main outcome measure. The studies were all done in areas of severe iodine deficiency. The IQ of the non-iodine-deficient groups was, on average, 13.5 IQ points higher than that of the iodine-deficient groups. The data on the effects of moderate to

mild iodine deficiency on IQ are less robust. They are based on two recent double-blind randomized controlled studies in school-age children in areas of moderate and mild iodine deficiency *(22, 23)*. These suggest that the loss of IQ points in school-age children with a median UIC of 65 μg/L (mild iodine deficiency) is 1–2 points and in moderate iodine deficiency (median UIC 44 μg/L) is 3–4 points.

These data were used to quantify the loss of IQ points associated with varying degrees of severity of iodine deficiency. Iodine sufficiency was defined as a median UIC in a population of >100 μg/L. In populations with severe iodine deficiency (median UIC <20 μg/L), a loss of 13.5 IQ points was assumed. It was also assumed that a population with moderate iodine deficiency (median UIC of 20–49 μg/L) showed a loss of 3–4 IQ points (midpoint of 3.5 IQ points) and a population with mild iodine deficiency (median UIC of 50–99 μg/L) showed a loss of 1–2 IQ points (midpoint of 1.5 IQ points).

A loss of IQ points per se is not a disease in the International Classification of Diseases (ICD) *(6)* system, so IQ loss was converted into degree of intellectual impairment, based on the defined sequelae in Table 4. Loss of IQ may increase the risk for other diseases and injuries *(24)*, but no attempt was made to quantify these extremely heterogeneous relationships.

A reduction in IQ points was defined as a disease burden when it resulted in mild or moderate intellectual impairment, which was defined as having an IQ score in the ranges given in Table 4. In human populations, intelligence generally approximates a normal distribution *(25)*, with a mean IQ score of 100 and a standard deviation of 15. To estimate the global and regional prevalence of intellectual impairment resulting from IQ reduction attributable to iodine deficiency, the proportion of children within the normal distribution with IQ scores near the thresholds in Table 4, for whom the loss of 1.5, 2.5 or 13.5 IQ points would result in a total IQ point score less than the cut-off values defined in the table, was first estimated. Thus, the proportion of borderline intellectual impairment attributable to iodine deficiency was estimated as the proportion of children losing a number of IQ points (i.e. ratio of children with UIC within the intervals 0–20 μg/L, 20–49 μg/L and 50–99 μg/L, multiplied by the fraction of children with >84 IQ points for whom a loss of *x* points results in a final IQ score of ≤84 IQ points. A similar method was used in GBD 2000 to estimate the IQ deficit associated with ranges of blood lead *(26)*.

Prevalence rates of mild mental retardation in high-income countries are lower than those in low- and middle-income countries *(27)*, and it is assumed that most of these differences are explained by non-congenital causes. Because the normal distributions of IQ scores were established from data from high-income countries, the number of additional cases of intellectual impairment likely to be observed in low- and middle-income countries that result from additional risks besides iodine deficiency needs to be taken into account. Several risk factors and diseases occur more frequently in low- and middle-income countries and result in intellectual impairment. The detailed estimates of the global burden of disease listed in the *World health report 2001 (28)* provide prevalences of cognitive impairment as a consequence of anaemia, lead exposure, meningitis, pertussis, encephalitis, hookworm infection, ascariasis and trichuriasis, for the 14 subregions *(3)*. Based on the prevalence of intellectual impairment from known, non-congenital causes other than iodine deficiency, values from high-income and from low- and middle-income countries were compared, and an "adjustment ratio" to account
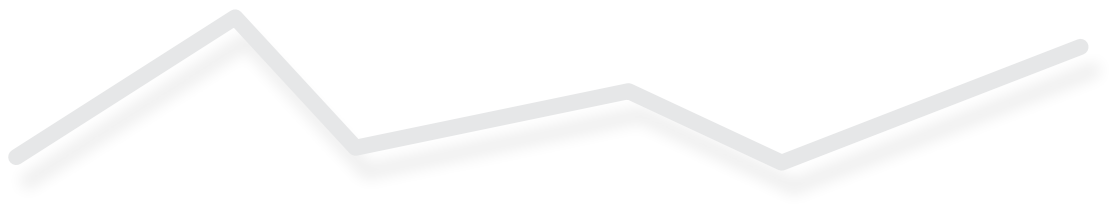
for the increased risk of impairment in low- and middle-income countries was estimated. It was assumed that the adjustment ratio applies for the considered ranges of IQ, and the estimated prevalence rates per 1000 people affected by iodine-deficiency-induced intellectual impairment were multiplied by these subregion-specific adjustment ratios.

Mortality

Mortality is also associated with cretinism. As in GBD 2000 *(5)*, this study used a relative risk for mortality for severe mental retardation of 6.33 *(29),* multiplied by the region-specific background mortality rate (in the 5–14 years age group), to estimate the number of deaths. Mortality rates for congestive heart failure were calculated in the overall GBD estimates.

Large controlled studies have reported reductions in the infant mortality rate (IMR) when severe iodine deficiency is corrected *(30–34)*. DeLong et al. *(30)* corrected severe iodine deficiency in a Chinese population with iodine-fortified water and found a large reduction in both neonatal and infant mortality. Iodized oil given to iodine-deficient pregnant women in Zaire at ~28 weeks of gestation decreased the IMR *(31)*. In Algeria, rates of abortion, stillbirth and prematurity were significantly lower among women given oral iodized oil 1–3 months before conception or during pregnancy, than among untreated women *(32)*. A randomized, placebo-controlled trial of oral iodized oil in Indonesia reduced the IMR *(34)*. In a large cross-sectional study in Indonesia, use of adequately iodized salt was associated with a lower IMR *(33)*. Taken together, these results suggest iodine prophylaxis in severe iodine deficiency reduces infant mortality. The expert group reviewed these data for potential inclusion in the estimate.

Discussion and conclusions

Data on the adverse health effects of iodine deficiency have extensively increased since GBD 1990 *(3)*. At that time, most studies making up the evidence for disability due to iodine deficiency were based on studies carried out in populations with moderate and severe iodine deficiency. Recent studies have also investigated the health effects in mild iodine deficiency, beyond goitre and cretinism. The expanded use of more sensitive indicators of iodine deficiency has led to more studies investigating the effects specifically due to mild, moderate and severe iodine deficiency. The spectrum of evidence for the consequences of iodine deficiency has broadened since GBD 1990, allowing the expert group to develop a more comprehensive disease model. This disease model includes additional sequelae of iodine deficiency that had not been included in previous GBD estimates.

A major advance in the current model is the use of the UIC as the indicator of severity of iodine deficiency, rather than the goitre rate. UIC is a more specific and sensitive indicator of current iodine status in populations than the goitre rate; this is particularly important now, when many countries introduced (with varying success) an iodine-deficiency control programme, and residual goitre rates may reflect a history of iodine deficiency. But this GBD estimate also retains several analyses used in both the 1990 *(3)* and 2000 *(5)* estimates, including the relationship between goitre and cretinism in severe iodine deficiency, as well as the estimation of increased mortality in large goitre and cretinism.
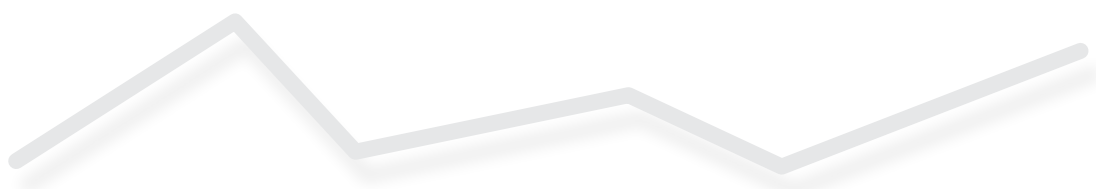
A limitation of the present model is the small number of studies contributing the evidence for mild and moderate intellectual disability. More data on the effects on intellect of mild-to-moderate iodine deficiency would likely improve this estimate. Another weakness is the lack of data on the prevalence of iodine deficiency in pregnant women, which means specific estimation of the contribution from in utero exposure is not yet possible. Unfortunately, it was not possible to include a time-series component, as data available on UIC for time-series analysis were scarce and limited by the heterogeneous patterns of gradual introduction and/or relapse in universal salt iodization programmes. This may be insurmountable, and it is likely that, in future estimates, the large residual disease burden due to exposure to iodine deficiency early in life, which exists in most countries that have recently introduced iodine prophylaxis, will need to be ignored. Finally, in some large countries, such as China and India, varying regional coverage of iodized salt has resulted in small pockets of iodine deficiency that are not captured by estimates based on subnational and national data. For example, cretinism still occurs in remote areas of western China *(35)*, despite an overall adequate national iodine status.

The new model includes three levels of severity of iodine deficiency, based on the UIC in populations. The estimate of the intellectual impairment caused by iodine deficiency has been sharpened by using these three levels and a new approach based on the population shift in the IQ distribution derived from estimation of the GBD due to ranges of blood lead concentrations *(26)*. The proportion of the population affected by mild, moderate and severe iodine deficiency, based on ranges of UIC, is used to predict the loss of IQ points. This is extrapolated to the normal distribution of IQ, adjusted for developing regions, and it quantifies the population in which iodine deficiency results in an IQ shift into the defined ranges of borderline and mild intellectual impairment.

The thorough update of the WHO VMNIS global database as part of this project comprehensively redefined the global and regional prevalences of iodine deficiency for 2010. The current estimates show that iodine status worldwide has improved over the past decades. Taken together, these reforms should improve the accuracy of the current estimate of the GBD due to iodine deficiency and thereby better inform public policy in regional and national health programmes to prevent iodine deficiency.

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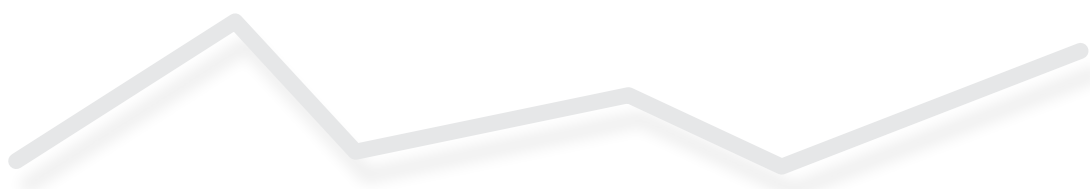
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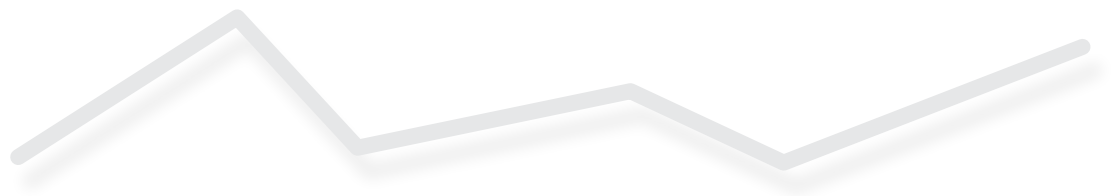
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