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MICRONUTRIENT SERIES

Indicators for assessing Iodine Deficiency Disorders and their control through salt iodization

World Health Organization

United Nations Children's Fund

ICCIDD
International Council for the Control of Iodine Deficiency Disorders

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This document sets out principles governing the use of surveillance indicators in monitoring the epidemiology of iodine deficiency disorders (IDD) and implementing the recommended intervention - salt iodization - to prevent and control them. It includes guidelines on the characteristics and criteria for selection of clinical and biochemical indicators, age and physiological groups, and survey sample size. A simplified three-grade version of the classic five-grade goitre grading system is presented, together with an outline of the principles governing use and interpretation of ultrasound measurements of thyroid size. Also included are recommendations for determining urinary iodine and interpreting thyroid-related hormone estimations; criteria for determining the severity of endemic IDD; recommended levels of salt iodization appropriate for varying climatic conditions, salt-consumption patterns and available packaging; and procedures for monitoring salt iodine content, whether at the factory or importation site, or district and household level. Finally, indicators are presented for monitoring progress towards achieving the goal of eliminating IDD as a significant public health problem by the year 2000. The document, which is intended primarily for managers of national programmes for the prevention and control of micronutrient malnutrition, is the result of a thorough review of the subject undertaken in November 1992 at a joint WHO/UNICEF/ICCIDD consultation. The ensuing report (document WHO/NUT/93.1) served as a review version of the present text; it was distributed widely to participants and other experts in IDD prevention and control, whose helpful comments and suggestions are reflected herein.

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International Council for the Control of Iodine Deficiency Disorders

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Abbreviations

CDD	Control of diarrhoeal diseases
ELISA	Enzyme-linked immunosorbant assay
EPI	Expanded Programme on Immunization
ICCIDD	International Council for the Control of Iodine Deficiency Disorders
IDD	Iodine deficiency disorders
IQ	Intelligence quotient
LQAS	Lot quality assurance sampling
MCH	Maternal and child health
PAMM	Programme Against Micronutrient Malnutrition
ppm	parts per million
PPS	Probability proportionate to size
Tg	Thyroglobulin
TSH	Thyroid stimulating hormone
UNICEF	United Nations Children's Fund
WHO	World Health Organization

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1. Introduction

1.1 Background

1. This document is based on a technical consultation[1] that WHO, in collaboration with ICCIDD and UNICEF, convened in November 1992 (see Annex 1 for list of participants). The three organizations have worked closely for a decade to combat IDD, which is one of the oldest and most insidious of human health scourges.

2. Three factors combine to make reassessment of IDD indicators a timely exercise. First, increasing scientific knowledge about IDD and accumulating experience of related control programmes have made it necessary to review and, in some cases, revise earlier judgements. Secondly, experience from other areas, e.g. quality control procedures used in manufacturing and implementation of immunization programmes, provides new tools that can be applied with advantage to programmes for combating micronutrient malnutrition. Thirdly, the adoption by all governments of the ambitious goal of eliminating IDD as a significant public health problem by the end of the century signals the urgency, even as it provides the impetus, for concerted action.[2]

3. Although indicators for assessing IDD might initially appear to be an uninteresting, even tedious, topic, their review has met with considerable enthusiasm. Building on existing momentum for eliminating IDD as a significant public health problem, participants in the 1992 consultation were unanimous in stressing the importance of having the necessary tools for measuring whether, and when, the decade goal is likely to be reached. They concluded that this can be achieved only by clearly defining appropriate indicators and criteria for assessing both IDD and related control programmes.

4. The consultation was marked by willingness to take a fresh look at the whole subject of IDD indicators, and even WHO's long-standing goitre classification came under critical review! Participants favoured involvement by all who are in a position to identify IDD and to assess, simply but effectively, both its severity and the adequacy of measures to combat it through the recommended intervention, salt iodization.[3] Thus, while participants agreed that the classic five-grade grading of goitres remained valid, they concluded that a simpler three-grade classification system would be a more practical field

[1] Joint WHO/UNICEF/ICCIDD Consultation on the Indicators for Assessing Iodine Deficiency Disorders and their Control through Salt Iodization, 3-5 November 1992, Geneva. The report of the consultation, document WHO/NUT/93.1, was circulated as a review version of the present text.

[2] This goal was formally endorsed by the World Summit for Children (New York, 1990), the World Health Assembly (Geneva, 1991), the Policy Conference on Ending Hidden Hunger (Montreal, 1991), and the International Conference on Nutrition (Rome, 1992).

[3] Considerable progress is now being made towards meeting the goal of universal salt iodization in the majority of countries where IDD is a significant public health problem.

screening device to be used, for example, by school teachers who have been trained for this task.

5. The document provides the most up-to-date internationally agreed outline of practical procedures for verifying the adequacy of salt iodization on a national and local scale. The vexing issue of numbers of subjects and biological specimens required for IDD surveys is creatively handled, in keeping with the various purposes for which surveys are conducted. Thus, sampling methods and sizes are expected to vary according to survey aims. For the first time, clear and epidemiologically adequate guidance is given on this subject, while additional information may be obtained in the works cited.

6. Because of constant evolution in both IDD assessment methodology and the integration of indicators, the document will certainly not be the last word on the subject. Experience in applying the methods and procedures outlined will no doubt permit their further elaboration and refinement. Nevertheless, the document is an important milestone because of the practical yardstick it provides for measuring progress and evaluating the effectiveness of related prevention and control programmes. While the focus for scientific purposes is on clinical and biochemical parameters, the ultimate goal is elimination of the developmental effects of IDD, which are considerably less easily measured.

7. The 1992 consultation was one of a series held for each of the micronutrients for which WHO and UNICEF have adopted specific goals, namely iodine, vitamin A, and iron. While much of the discussion in the first four sections of the present document is also valid for iron and vitamin A, the last two sections are generally specific to iodine only. In view of the increasing interest in micronutrient malnutrition, and the potential benefits from an integrated approach to its monitoring and assessment, it may be feasible eventually to develop guidelines for simultaneous action in respect of all three micronutrient deficiencies. The resulting degree of imprecision would be acceptable if a common sampling frame were to reduce costs significantly and improve logistical capacity to measure progress towards achieving micronutrient goals. There is no point in continuing to amass data when a carefully planned survey covering a minimum number of people produces information that is sufficiently reliable for this purpose. As participants in the 1992 consultation were reminded, it is more important to be roughly right, than precisely wrong.

1.2 Magnitude of the problem

8. Because they are only evidence of a condition, indicators cannot be meaningfully discussed until the condition itself has been clearly identified. Iodine deficiency not only causes goitre; it may also result in irreversible brain damage in the fetus and infant, and retarded psychomotor development in the child. Iodine deficiency is the most common cause of *preventable* mental retardation; it also affects reproductive functions and impedes children's learning ability. The cumulative consequences in iodine-deficient populations spell diminished performance for the entire economy of affected nations. The impact of iodine deficiency on intellectual development and the resulting brake on

socioeconomic development has played a significant role in mobilizing scientists, public health administrators and political leaders the world over to deal effectively with IDD.

9. Knowledge of the global magnitude of IDD, and thus its real significance for health and socioeconomic development, has improved considerably during the last decade. IDD is known to be a significant public health problem in 118 countries.[1] At least 1572 million people worldwide are estimated to be at risk of IDD, i.e. who live in areas where iodine deficiency is prevalent (total goitre rates above 5%), and at least 655 million of these are considered to be affected by goitre. The regional distribution of goitre prevalence, and estimated rates of frank cretinism, are given in Table 1. However, the main motivation behind the current worldwide drive to eliminate IDD as a significant public health problem is the fact that an estimated 43 million people are affected by some degree of mental impairment.[2]

Table 1. Total number of people and percent of regional population living in areas at risk of IDD, or affected by IDD and cretinism (1990)

WHO region	Population (millions)	At risk of IDD		Affected by goitre		Affected by cretinism	
		Millions	% of region	Millions	% of region	Millions	% of region
Africa	550	181	32.8	86	15.6	1.1	0.2
Americas	727	168	23.1	63	8.7	0.6	0.9
Eastern Med	406	173	42.6	93	22.9	0.9	2.3
Europe	847	141	16.7	97	11.4	0.9	1.1
South-East Asia	1 355	486	35.9	176	13.0	3.2	1.3
Western Pacific	1 553	423	27.2	141	9.0	4.5	2.9
TOTAL	5 438	1 572	28.9	655	12.0	11.2	2.0

1.3 Purposes of surveillance

10. IDD surveillance can be used for a number of distinct purposes, including for assessing the magnitude and distribution of IDD prevalence, identifying high-risk populations, evaluating control programmes, and monitoring progress towards achieving long-range goals. The surveillance design employed, indicators used, and the approach to data interpretation will vary according to the specific purpose intended.

11. **Assessing IDD prevalence.** One of the fundamental purposes of IDD surveillance is to determine the magnitude and distribution of IDD within a population. This assessment can provide a baseline for long-term monitoring, serve as an advocacy tool to

[1] ICCIDD/UNICEF/WHO. Global prevalence of iodine deficiency disorders. MDIS Working Paper #1. Micronutrient Deficiency Information System, Geneva, World Health Organization, 1993.

[2] Bailey KV, Clugston GA. Iodine deficiency disorders. In: Murray CJL, Lopez AD, eds. *The global burden of disease and risk factors in 1990.* WHO/World Bank. Geneva, World Health Organization (in preparation).

highlight the extent of IDD problems, and stimulate action including the appropriate allocation of resources for eliminating IDD.

12. **Identifying severely affected areas for intervention**. Identifying severely affected communities is also crucial to IDD programme development. This type of surveillance activity is primarily concerned with identifying priority areas for intervention, thereby ensuring a more efficient use of resources.

13. **Monitoring and evaluating IDD control programmes**. Another fundamental purpose of surveillance is to evaluate implementation and impact of control programmes. Indicators can be measured that assess the extent of a programme activity as well as its impact on specific outcomes.

14. **Measuring progress towards achieving long-term micronutrient goals**. Many countries are working towards the goal of eliminating IDD as a significant public health problem as part of their effort to achieve child health and development goals for the year 2000. Surveillance activities can provide a quantitative basis for assessing progress towards meeting those goals.

2. Selecting target groups

15. A variety of target groups, including neonates, infants, preschool-age and school-age children, and certain groups of adults might serve as the focus for IDD surveillance. Selecting the optimal group or groups depends on a number of considerations, including their vulnerability, representativeness, accessibility, and potential usefulness for surveillance of multiple health problems.

2.1 Selection criteria

16. **Vulnerability**. In order to serve as a sensitive indicator, a target population must be vulnerable to the deficiency. Three aspects of vulnerability are:

- extent of exposure to the deficiency;
- severity of health consequences due to the deficiency;
- degree of clinical or biochemical responsiveness to the deficiency and related interventions.

17. **Representativeness**. The issue of representativeness, or "generalizability" to the wider context of a study, is sometimes referred to as "external validity".

- Is the target group used for surveillance representative of all persons in the same age/sex group in the community? For example, if children are examined in school, are they representative of all school-age children in the community? It may be that children who are in school come from more advantaged or better-educated families, and consequently their risk of IDD may be lower.

- Is the IDD status of the target group representative of the status of the community as a whole? It may be that the apparent prevalence of IDD in the target group leads to an overestimation or underestimation of community prevalence.

18. **Accessibility**. Another criterion for selecting a target population is its accessibility. Easily accessible populations, for example children in school, women in MCH clinics, and neonates in a hospital, may be useful for surveillance purposes. Using these relatively accessible groups will facilitate surveillance and reduce logistic costs, even if the most accessible groups may not always prove to be either fully representative or the most vulnerable.

19. **Usefulness for surveillance of multiple micronutrient malnutrition and other health problems**. It may prove advantageous if the target group selected for IDD surveillance can also be used to assess other nutritional and health problems. For

example, school-based IDD surveillance might also serve for surveillance of iron status or helminth infections. On the other hand, school-age children may be less useful for assessing vitamin A deficiency and child growth using anthropometry.

2.2 Target groups

20. Applying the above criteria to potential target groups makes clear some of their advantages and disadvantages for IDD surveillance. A framework for considering these characteristics in relation to various potential target groups is presented in Table 2.

21. **Neonates.** The use of neonate screening to identify congenital defects is well established in many developed countries and it is being introduced in some less developed countries as well. Regular collection of blood-spot specimens, where this is done, is an important source of information for IDD surveillance given their use in assessing TSH status. Elevated TSH levels, especially during infancy, suggest a deficiency of iodine.

22. Surveillance may also be done practically in iodine-deficient areas by collecting blood-spot specimens from cord blood in a sample of neonates. Blood spots can be collected by trained birth attendants in homes, or at health posts or hospitals. Sample representativeness in this type of surveillance depends on the health system's degree of coverage of neonates. This is a potentially highly effective surveillance design that makes efficient use of existing primary health care infrastructure.

23. **Infants and preschool-age children.** Infants and preschool-age children are also highly vulnerable to IDD and may be useful for surveillance of other health problems as well, for example vitamin A deficiency and anaemia. However, this age group may not be readily accessible except in MCH clinics, where the question of representativeness may arise. Some IDD indicators, e.g. goitre by palpation, may be relatively difficult to assess in this age group. There may be opportunities to coordinate IDD surveillance and iodine supplementation with the immunization programme.

24. **School-age children.** School-age children are a useful target group for IDD surveillance because of their combined high vulnerability, easy access, and usefulness for a variety of surveillance activities. Affected children develop an enlarged thyroid in response to iodine deficiency and can be readily examined in large numbers in school settings. At the same time, other health concerns in this age group, including helminth infections, anaemia, and behavioural factors affecting health, can be assessed and educational interventions implemented. A major concern arising in school-based surveys is that children not attending school are not represented, which possibly leads to biased prevalence estimates. However, on special occasions it may be possible to use school premises for assembling this group together with preschool-age children.

25. **Pregnant women in MCH clinics.** The iodine status of pregnant women is particularly crucial because of the susceptibility of the developing fetus to iodine deficiency. Pregnant women are accessible in primary health care settings, and a wide variety of other health conditions can be assessed concurrently. Representativeness may

be a problem depending upon the level of access to and utilization of health care services by women who are at highest risk.

26. **Adults in households.** Screening adult women and men through household surveys provides an opportunity to establish a sample of a population vulnerable to IDD. However, after age 30, goitre rates are no longer reliable indicators of current iodine intake. Accessibility may be limited because of the expense and logistical constraints associated with performing household surveys. Representativeness depends on the extent to which men and women work outside the home; in particular, it may be difficult to find men at home during the day.

Table 2. Framework for considering target groups for IDD surveillance

	Vulnerability	Representativeness*	Accessibility	Usefulness for other surveillance**
Neonates	High	Intermediate	Intermediate	Intermediate
Preschool-age children in MCH clinics	High	Intermediate/low	Intermediate	High
Preschool-age children in households	High	High	Intermediate	High
Children in schools	High	Intermediate	High	High
Pregnant women in MCH clinics	High	Intermediate	High	High
Adult women in households	Intermediate	Intermediate	Intermediate	Intermediate
Adult men in households	Intermediate	Low	Low	Low

* Level of representativeness depends on access or coverage (see text)

** Usefulness of group for surveillance of other nutrition and health problems

3. Surveillance methods

27. As noted in section 1, IDD surveillance serves several purposes, and data collection methods will vary accordingly. Suggested data-collection schemes are described below. When designing a surveillance system, it is important to decide whether the primary purpose of the survey is to derive a prevalence estimate or to identify high-prevalence areas. Each purpose usually requires a different survey method, and studies that attempt to fulfil both tend to be inefficient and fail to answer adequately either question. In general, the first step is to undertake a prevalence survey. If results show an IDD problem and it is decided that identifying high-prevalence areas is important, a lot quality assurance sampling (LQAS) survey would then be useful.

3.1 Assessing IDD prevalence

28. There are two main requirements in assessing IDD prevalence: collection of the minimal amount of data that are representative of the target population, and provision of a stable prevalence estimate within a desired level of precision. The survey method used depends upon many factors, including the target group (e.g. neonates or school-age children), the survey site (e.g. households or schools), and the size of the geographic area of interest. In large countries, it may be desirable to undertake prevalence surveys by state or province, which can be further refined in selected districts. The number of geographic units to be studied should be kept to the minimum considered necessary to guide interventions.

29. A common method used for immunization and anthropometric household-based surveys is the "probability proportionate to size" (PPS) cluster method.[1] While this method requires up-to-date population census data, where IDD surveys concerning mainly stable populations in rural areas are concerned, outdated census data could be used without undue violation of PPS sampling requirements. In general, all villages and cities are listed and a systematic sampling scheme is used based on the cumulative population. This sampling scheme assures that larger villages and cities are more likely to be selected than smaller ones. The number of individuals to be sampled within each cluster depends upon the prevalence of the condition, the level of precision desired (based on the type and width of the confidence interval), the design effect (a measure of the variability of the prevalence between clusters), whether inference at the cluster level is desirable, and the biological precision of the surveillance method.

[1] Cluster sampling is a sampling process in which sampling units are made up of clusters or groups of study units, e.g. districts, villages and schools.

30. Sample size calculations for prevalence may be based on relative or absolute precision; relative precision is recommended here.[1] The recommended sample size for initial school-based goitre surveys is 1200 children (30 clusters x 40 children per cluster). This sample size is based on an assumed goitre prevalence of 50%, 95% confidence intervals, a design effect of 3, and a relative precision of 10%; or a prevalence of 20% with a relative precision of 20%. As IDD programme interventions proceed and goitre prevalences decline, the critical level of goitre prevalence becomes 5%; larger sample sizes would then be needed to estimate the prevalence rate with the same relative precision, e.g. 5% prevalence with relative precision of 30% would require 3 x 811 = 2400 subjects. As prevalence becomes smaller, estimating prevalence with the same relative precision requires examination of more children. If this is difficult for logistical reasons, one could reduce the precision even further, say to 40%, giving a confidence interval of 3 to 7% in the case of an estimated prevalence of 5%. However, the design effect may also change as interventions proceed. Thirty clusters (schools, households, etc) are intended to ensure a valid prevalence estimate; examining fewer clusters can lead to estimates that differ substantially from the true prevalence.

31. The recommended sample size for the collection of biologic specimens like urine or blood spots is 300 (30 clusters x 10 children per cluster). The sample size for biologic specimens is based on the assumption of a prevalence of abnormal results of 50%, 95% confidence intervals, a design effect of 2,[2] and a relative precision of 16%. This is the appropriate sample size when the results are used for monitoring an intervention's effectiveness, or as the basis for diagnosing endemic IDD. Smaller sample sizes could be adequate when they are used simply to confirm iodine deficiency in a clearly goitrous population.

32. The rationale behind these sample sizes is that palpation is relatively easy and inexpensive to perform, and therefore palpating 40 children per school should pose little problem. Because of the costs involved in collecting, transporting, and analyzing biological specimens, sample size for this purpose should be kept to a minimum. Depending on local conditions and needs, sample sizes may need to be larger or smaller than those recommended above.

33. School surveys could use either PPS or a two-stage cluster approach. The main difference between a PPS survey and a two-stage cluster survey is how schools are selected. With PPS, schools are systematically selected from a cumulative population list; in two-stage cluster sampling they are selected randomly. The PPS survey is self-weighting, whereas in two-stage cluster surveys the school enrolment is required to weight the results. Once schools are chosen, usually a fixed number of pupils are selected to be in the survey, e.g. 40 pupils are palpated while 10 provide urine specimens.

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[1] For more information and sample size tables, see Annex 2.

[2] Note that, generally speaking, the fewer children sampled per cluster, the smaller the design effect.

34. Sampling of neonates may be performed randomly or non-randomly, depending on the purpose of the survey. If neonatal TSH levels are used to track changes in iodine status over time, a random selection procedure should be devised. Particular care is needed in populations with low coverage of assisted deliveries, e.g. rural areas in developing countries.

3.2 Identifying high-prevalence areas

35. In some situations the surveillance goal may be to identify areas of high prevalence in order to focus intervention activities. A difficulty associated with identifying high-prevalence areas is that IDD tends to occur in geographic foci, and a large number of sites may have to be surveyed in order to find the high-prevalence areas. As described in Annex 3 and elsewhere,[1] LQAS is an efficient survey method for screening a large number of sites, for example when school children are chosen as the surveillance target group for identifying areas with high goitre prevalence. In order to find the high-prevalence areas, *every school* within a geographic area would be surveyed, and a sample of children in each would have their thyroid palpated. If a large number of children had goitre, the area would be identified as "high prevalence".

36. To continue the example, suppose that the estimated goitre prevalence among school children in a region is 10%, and the ministry of health (or equivalent) is interested in identifying schools with a severe problem, i.e. a prevalence greater than 30%, in order to focus intervention efforts. How many children would have to be palpated in each school, and at which point would a school be classified as having a severe IDD problem?

37. Using the tables in Annex 3 (and assuming a significance level of 5% and power[2] of 90%), 33 children would need to be randomly selected and palpated in each school. If five or more children had goitre, the school would be classified as having a severe IDD problem (i.e. it would be considered a "rejected" lot). If fewer than five had goitre, the school would be classified as not having a severe problem (i.e. it would be considered an "accepted" lot). There are two possible errors in this connection. A school could be diagnosed as not having a severe IDD problem although it truly has one, or it could be diagnosed as having one although in fact it does not. Using LQAS in this situation is intended to minimize the first error since it may mean *not* intervening in areas that require attention. The second error is of lesser consequence. In the above example, if fewer than five students out of 33 had goitre, there is only a 5% chance that the true prevalence in the school would be greater than 30%.

38. In order to minimize the number of schools to be screened, the study area could be reduced to include only those at high risk of having IDD, such as rural mountainous regions. Since the LQAS-based prevalence estimates for each school would be the result of randomly selected children, a weighted average of the school prevalence estimates

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[1] *World Health Statistics Quarterly*, 1991:44(3), 115-132 and 133-139.

[2] "Power" in this context means the probability of correctly rejecting the null hypothesis when it is false.

would be a valid estimate of the overall area estimate of the prevalence among all school children. The weighting process is accomplished by multiplying the prevalence found in each school (or cluster) in the sample examined by the number of children in the school or cluster.

3.3 Monitoring and evaluating IDD control programmes

39. The main interventions for controlling IDD are fortification of salt with potassium iodate (or iodide) and supplementation with iodized oil. The procedures for monitoring salt iodization programmes are outlined in paragraphs 95-105 while those concerning iodization of other foods and iodized oil are found in paragraphs 106-107.

3.4 Measuring progress towards achieving long-term micronutrient goals

40. Periodic prevalence surveys, as described earlier in this section, are necessary to measure change in prevalence over time. Measuring progress towards achieving long-term micronutrient goals requires that surveys be representative of the population concerned. Because surveys need to be repeated, they should be simple to perform and analyze and based on the minimum number of individuals required to provide stable prevalence estimates within the desired level of precision.

4. Interpreting and presenting results

41. Many IDD parameters are measured on a continuous scale, e.g. urinary iodine levels and TSH, but the results do not have the normal Gaussian distribution. Thus, the use of means and standard deviations is likely to be inappropriate. It may be possible to transform some non-normally distributed data, e.g. by logarithmic means, into a normal distribution and then to calculate means and standard deviations. Transformations may not work for other parameters, and presentation of a median or other centiles, and use of non-parametric statistics, would then be appropriate.

42. It is recommended that the full distribution of results be presented, in addition to a measure of the central tendency (mean or median), and that cut-off points be used to delineate or identify the upper or lower tail of the distribution. The distribution of individuals at the extremes of a distribution can be characterized by using standard cut-off points and tabulating the prevalence of values below or above cut-off values. Several cut-off points may be used to provide an impression of the magnitude of the problem occurring at different levels of the distribution. For example, lower cut-off points may be selected to highlight the most extreme cases of deficiency, while higher cut-off points may be useful in capturing the proportion of the population that may be moderately affected, or at risk of inadequate iodine status.

5. Selecting appropriate indicators

43. There are basically two types of indicators: outcome indicators that provide a measure of IDD status, and process indicators that measure the condition or progress in implementing an IDD control programme. Outcome indicators can be categorized according to whether the assessments are clinical (thyroid size, cretinism) or biochemical (urinary iodine and thyroid-related hormones). Once the target population(s) for assessment are defined, the selection of particular indicators should be based both on the following criteria and the specific surveillance objectives.

5.1 Criteria for indicator selection

44. **Acceptability**. An indicator's acceptability to a given target population is a crucial factor. Some procedures, e.g. assessment of thyroid size by palpation, may be widely acceptable. Others, such as drawing venous blood for biochemical determinations, may be quite unacceptable, especially in certain target groups such as infants and children. Acceptability is also an issue for field staff who perform the tests. Thus, for example, drawing blood specimens in populations having a high prevalence of HIV infection involves some level of risk, or perceived risk, that should be taken into account during indicator selection.

45. **Technical feasibility**. Technical feasibility involves a number of factors including:

- ease of data or specimen collection;
- specimen storage and transport requirements;
- transportability and ruggedness of field equipment;
- availability of personnel to obtain specimens.

46. **Cost**. Costs associated with the use of certain indicators include:

- capital costs for facilities and equipment;
- recurring costs for supplies and reagents;
- maintenance costs;
- training costs;
- personnel, administrative and related costs.

It is useful to estimate the cost per test, but this should still take into account all the above-listed components.

47. **Performance**. Another criterion for indicator selection is performance in identifying IDD status. Useful measures of indicator performance include sensitivity, specificity, and reliability.

48. **Interpretation and availability of reference data**. Interpretation of IDD status depends on availability of reference data. Reference data assist in establishing cut-off values and prevalence levels for use in identifying public health problems. Reference data are useful in selecting indicators and target groups for surveillance, as these will enhance interpretation across different studies.

49. **Using a combination of parameters.** It is generally recommended that at least two indicators be used. No single parameter reflects the entire iodine-deficiency picture and resulting changes in the thyroid. In cases of severe deficiency, initial emphasis may be on lowering rates of goitre and cretinism. As a programme evolves, however, emphasis is likely to shift to ensuring adequate iodine intakes, e.g. by monitoring salt iodization levels and population salt intakes and urinary iodine levels and normal thyroid function, e.g. by measuring TSH levels, especially in neonates. To the extent that resources permit, it is thus desirable for a biochemical baseline to be established at the outset, at least in a sub-sample of the larger population.

5.2 IDD outcome indicators

Clinical indicators

Thyroid size

50. The size of the thyroid gland changes inversely in response to alterations in iodine intake, with a lag of 6 to 12 months in children and young adults (i.e. <30 years of age). The traditional method for determining thyroid size is inspection and palpation. Ultrasonography provides a still more precise and objective method. Both are described below. Issues common to palpation and ultrasound are not repeated in the section on ultrasound.

Palpation

Feasibility

51. Palpation of the thyroid is important in assessing goitre prevalence. Costs are associated with mounting a survey, which is relatively easy to conduct, and training of personnel to do it. Costs will vary depending upon the availability of health care personnel, accessibility of the population, and the sample size. Feasibility and performance vary according to target group.

52. *Neonates*. It is neither feasible nor practical to assess goitre among neonates, whether by palpation or ultrasound. Performance is poor.

53. *Preschool-age and school-age children.* Preferably children 6-12 years of age should be studied. There is a practical reason for not measuring very young age groups: the smaller the child, the smaller the thyroid and the more difficult it is to perform palpation. It is recommended that if the proportion of children attending school is less than 50%, spot surveys should be done on two groups of children of the same age, i.e. those who attend school and those who do not, to ascertain if there is any significant difference between the two. If so, both groups should be studied separately, in all clusters, or an appropriate adjustment should be made in the rate found among school children.

54. *Adults.* Pregnant and lactating women are of particular concern. Pregnant women are a prime target group for IDD control activities because they are especially sensitive to marginal iodine deficiency. Frequently they are relatively accessible given their participation in antenatal clinics.

Interpretation

55. A modification of the previous goitre classification system, which defined five grades, is recommended. The previously used grades 1A and 1B are thus combined into one, and grades 2 and 3 are combined into another (Table 3). Table 4 gives the epidemiologic criteria for establishing IDD severity based on goitre prevalence in school-age children. It should be understood that "mild" is a relative term; it does *not* imply that this category of IDD is of little consequence.

56. It is recommended that a total goitre rate (TGR, goitre grades 1 and 2) of 5% or more in primary school children (age range approximately 6 to 12 years) be used to signal the presence of a public health problem. This recommendation is based on the observation that in a normal, iodine-replete population the prevalence of goitre should be quite low. The cut-off of 5% allows some margin of inaccuracy of goitre assessment and for goitre that may occur in iodine-replete populations due to other causes such as goitrogens and autoimmune thyroid diseases. The previously recommended 10% cut-off level has been revised downwards since it has been shown that goitre prevalence rates between 5% and 10% may be associated with a range of abnormalities, including inadequate urinary iodine excretion and/or sub-normal levels of TSH among adults, children and neonates.

57. For example, in Belgium[1] in 1980 total goitre rates in children aged 6-16 years varied between 2% in the west and 10% in the east, with 3-5% in Brussels. Daily urinary excretion of iodine in Brussels in adults and adolescents averaged 52-80 μg. In such borderline conditions, although there were no changes in the serum concentrations of thyroid hormones and TSH in adults and adolescents, alterations of thyroid function in pregnant and lactating women and neonates required, and were corrected by, iodine

[1] Beckers C et al. Status of iodine nutrition and thyroid function in Belgium. In: Delange F, Dunn JT, Glinoer D, eds. *Iodine deficiency in Europe: a continuing concern.* New York, Plenum Press, 1993:359-362.

supplementation.[1,2,3] Moreover, several recent studies in Asian cities have shown abnormally raised TSH levels (e.g. 32% >5mU/l in Manila, where goitre rates in children aged 7-9 years were 1% and 4% [personal communication from G. Maberly, who is preparing a detailed report on these studies]). In short, even goitre rates 5—10% or lower are no guarantee of normal thyroid function.

58. Finally, the inaccuracy of clinical assessments of grade 1 goitres is increasingly recognized. With more frequent use of ultrasonography (described below), it is known that once the rate of thyroid enlargement exceeds 5%, there is increasing evidence of biochemical abnormality.

59. The specificity and sensitivity of palpation are low in grades 0 and 1 due to a high inter-observer variation. As demonstrated by studies of experienced examiners, misclassification can be as high as 40%. If possible, low goitre rates, especially when found following a sustained intervention, should be confirmed by ultrasound, which provides the only objective measure of thyroid size (see next section). In any case, measurement of urine iodine levels (in an adequate sample) is essential to decide whether an iodine deficiency problem is of public health importance.

Table 3. Simplified classification of goitre

Grade O:	No palpable or visible goitre.
Grade 1:	A mass in the neck that is consistent with an enlarged thyroid that is *palpable but not visible* when the neck is in the normal position. It moves upward in the neck as the subject swallows. Nodular alteration(s) can occur even when the thyroid is not visibly enlarged.
Grade 2:	A swelling in the neck that is *visible when the neck is in a normal position* and is consistent with an enlarged thyroid when the neck is palpated.

[1] Glinoer D. Thyroid regulation during pregnancy. In: Ibid., 181-188.

[2] Delange F. et al. *Neonatal thyroid function in iodine deficiency.* In: Ibid., 199-207.

[3] Delange F. et al. Influence of dietary goitrogens during pregnancy in humans on thyroid function of the newborn. In: *Nutritional factors involved in the goitrogenic action of cassava.* Delange F. et al., eds. IDRC Monograph 184e, Ottawa, International Development Research Centre, 1982:40-50.

Table 4. Epidemiological criteria for assessing the severity of IDD based on the prevalence of goitre in school-age children

	Mild IDD	Moderate IDD	Severe IDD
Prevalence of goitre (TGR)	5.0-19.9%	20.0-29.9%	≥30.0%

Ultrasonography

Feasibility

60. Ultrasonography is a safe, non-invasive specialized technique, which should be performed by trained operators who can perform up to 200 examinations per day. The degree of subjectivity in assessing results, however, points up the importance of developing standardized interpretation criteria. Thyroid volume can be easily calculated using a calculator or a microcomputer during data entry. Portable ultrasound equipment is relatively rugged but requires electricity; it can be operated from a car battery with the aid of a transformer.

Cost

61. Portable ultrasound equipment with a 5 MHz transducer currently costs about US$12 000. Prices are expected to decline with the increasing availability of smaller machines.

Performance

62. Ultrasonography provides a more precise measurement of thyroid volume (Table 5) compared with palpation. This becomes especially significant when the prevalence of visible goitres is small, and in monitoring iodine control programmes where thyroid volumes are expected to decrease over time. For practical reasons, school-age children between 8-10 years should be examined, although this range can be extended to 6-12 years if necessary. The thyroid of younger children is more difficult to examine, especially in children under six years of age. For this purpose a 7.5 MHz transducer is required to obtain adequate resolution.

Table 5. Comparison between palpation and ultrasound in grading small thyroids

	Goitre grade			
	0	1a	1b	2
Number of subjects graded by palpation	105	88	101	10
Subjects with grade confirmed by ultrasound				
Numbers	63	72	89	10
Percentage	60	82	88	100

Source: R. Gutekunst (personal communication)

Interpretation

63. Results of ultrasonography from a study population should be compared to normative data from populations with sufficient iodine intake (average intake >150 μg iodine per person per day and urinary iodine >100 μg/l). In an iodine-replete population, the expected prevalence of thyroid sizes greater than the mean + 2 SD would be 2.3%, and this figure can be compared with the observed prevalence. In addition, the median (50th centile) thyroid volume may be useful. Normative thyroid volume size data from ultrasound on iodine-replete children in Europe are currently being reviewed[1,2] and will be available on request from WHO and ICCIDD about mid-1995. Comparable data for developing countries are not available. There is some evidence of a correlation between thyroid size in adults and body weight.[3] Children in developing countries commonly weight substantially less and are shorter than same-age European children. It is possible that normal thyroid size in such subjects would be smaller. Adequate reference values for children of small body size cannot, therefore, be provided at present.

[1] F. Delange, personal communications.

[2] Vitti P et al. *Thyroid volume measurement by ultrasound in children as a tool for the assessment of mild iodine deficiency.* J. Clin. Endocrin. Metab., 1994, 79:600-603.

[3] Hegedüs et al. *The Determination of Thyroid Volume by Ultrasound and its Relationship to Body Weight, Age, and Sex in Normal Subjects.* J. Clin. Endocr. Metab., 1983, 56:260-263.

Cretinism

Definition

63. Endemic cretinism has been well described and defined by a Pan American Health Organization study group[1] and Delange[2] in terms of three major features:

(a) ***Epidemiology***: Cretinism is associated with endemic goitre and severe iodine deficiency.

(b) ***Clinical manifestations*** of cretinism are mental deficiency and either:

(i) a predominant neurological syndrome consisting of hearing and speech defects and varying degrees of characteristic stance and gait disorders; or

(ii) predominant hypothyroidism and stunted growth.

In some regions, one of the two types may predominate; in others a mixture of the two syndromes will occur.

(c) ***Prevention***: endemic cretinism has been prevented in areas where adequate correction of iodine deficiency has been achieved.

Biological features

64. The typical *neurological cretin*[3] is extremely mentally retarded and most are reduced to a vegetative existence; most are deaf-mute and many have impaired voluntary motor activity, usually involving paresis or paralysis of pyramidal origin, chiefly in the lower limbs, with hypertonia, clonus, and plantar cutaneous reflexes in extension, and occasionally extra-pyramidal signs; spastic or ataxic gait (in severe cases, walking or even standing are impossible); and strabismus (squint). In milder cases there are varying degrees of impaired motor coordination, inability to play games etc. The prevalence of goitre in these cretins is as high as in the non-cretinous population of the areas concerned and they are clinically euthyroid.

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[1] Querido AF et al. Definitions of endemic goitre and cretinism, classification of goitre size and severity of endemias, and survey techniques. In: Dunn JT, Medeiros-Neto, eds. *Endemic goitre and cretinism*. PAHO Scientific Publication No. 292, Washington DC, 1974:266-272.

[2] Delange FM. Anomalies in physical and intellectual development associated with severe endemic goitre. In: Dunn JT et al. *Endemic goitre cretinism, and iodine deficiency*. Pan American Health Organization, Scientific Publication No. 502, Washington DC, 1986:49-67.

[3] Buttfield IH, Hetzel BS. *Endemic cretinism in eastern New Guinea*. Aust. Ann. Med. 1969, 18:217-221.

65. There is less mental retardation among typical *myxoedematous cretins*, as found for example in Zaire, who may be capable of performing simple manual tasks. Signs of long-standing hypothyroidism include dwarfism, myxoedema, dry skin, sparse hair, retarded sexual development, and retarded maturation of body proportions and naso-orbital configuration. Goitre prevalence is much lower than in the non-cretinous population. The clinical picture is confirmed by extremely low levels of serum T4 and T3, low thyroidal uptake of radio-iodine, and very high levels of serum TSH. Lesser degrees of hypothyroidism have fewer clinical signs and biochemical abnormalities. Delong provides additional details of neurological assessment of cretins.[1]

66. In addition to the severe clinical manifestations of frank cretinism, it is clear that iodine deficiency causes a spectrum of milder clinical and subclinical deficits - sensory, motor and intelectual - that may be difficult to identify in a typical field setting. These deficits may be grouped into three main categories: (a) mild multiple features of cretinism (e.g. hearing loss, squint); (b) motor deficits and/or developmental delay; and (c) impaired intellectual performance quantified, for example, by improved IQ scores (5-20 points) in offspring of mothers who received iodized oil during pregnancy.[2] Hetzel[3] also draws attention to impaired cerebral functions that occur in areas of chronic iodine deficiency.

67. In an effort to quantify the prevalence of cretinism and milder clinical and subclinical deficits in iodine deficient populations, Clugston et al.,[4] reviewed available studies from a few countries in Asia, and in Ecuador and Zaire and identified a functional relationship between goitre rates and cretinism prevalence. These studies also indicated that the prevalence of milder clinical and subclinical deficits was approximately 3 times the prevalence of frank cretinism. A recent meta-analysis of effects of iodine deficiency on cognitive and psychomotor development reported an average loss of 13.5 IQ points.

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[1] Delong R. Neurological involvement in iodine deficiency disorders. In: Hetzel et al., eds. *The prevention and control of iodine deficiency disorders*. Amsterdam, Elsevier, 1987:49-63.

[2] Fierro-Benitez R et al. Iodized oil in the prevention of endemic goitre and associated defects in the Andean region of Ecuador. I Program design, effects on goitre prevalence, thyroid function and iodine excretion. In: Stanbury JB, ed. *Endemic goitre*. Washington, World Health Organization/Pan American Health Organization, 1969,193:306-321.

[3] Hetzel B. The story of iodine deficiency: an international challenge in nutrition. Oxford/New Delhi, Oxford University Press, 1989:89-93

[4] Clugston GA et al. Iodine deficiency disorders in South-East Asia. In: Hetzel BS, Dunn JT, Stanbury JS, eds. *The prevention and control of iodine deficiency disorders*. Amsterdam, Elsevier, 1987:273-308. The functional relationship (Fig. 2, p. 280) between total goitre rate and cretinism prevalence was derived by logistic transformation of cretinism prevalence equal to a quadratic form of total goitre rate. The multiple 3.0, relates milder clinical and subclinical deficits to cretinism prevalence, includes those individuals with milder mental, motor and other developmental handicaps (deficits or delays) and those with multiple or single cretinous features which are not identifiable as full cretinism in a typical field study setting. This includes an estimated proportion of persons, in endemic areas, who score below the mean of mental or motor ability tests *in excess* of the proportion of persons who score below the mean in a comparable, but non-endemic, area.

Feasibility

68. Because cretinism is a clinical diagnosis of a disorder with a presentation spectrum from mild to devastatingly severe, it is difficult to identify all of the affected individuals in a population. In fact, the more mildly affected cretins may not be diagnosed except by clinical experts or by using specialized methods, e.g. audiometric or psychometric tests. A significant amount of time may be required to perform the necessary physical examination.

Performance

69. Prevalence of cretinism is not a sensitive indicator of a population's iodine status. As noted above, complete identification of cases is difficult and requires expert clinical skills. The more severely affected cretins, though easily identifiable, probably represent only the 'tip of the iceberg' in terms of IDD case-finding.

Interpretation

70. Clinical examination for signs of cretinism may be most interesting as a historical record of a community's exposure to iodine deficiency, and their prevalence as an initial indication of severe endemic IDD. While cretinism results from iodine deficiency during intrauterine life and early childhood, it is most easily diagnosed in later childhood and adulthood. In a qualitative sense, therefore, the presence of cretins in a community, even if prevalence is very low, is significant because it demonstrates that individuals were exposed to a marked environmental iodine deficiency sometime in the recent past. While this does not necessarily reflect a population's current iodine status, it may have considerable advocacy value. As iodine deficiency decreases, cretins will no longer be born, cretinism will progressively disappear, and the condition will lose its value for monitoring IDD. However, subclinical cretinous manifestations will still have to be taken into account in assessing the disability-burden in areas of severe iodine deficiency.

Biochemical indicators

Urinary iodine

Biological features

71. Since most iodine that is absorbed is excreted in the urine, urinary iodine level is a good marker of a previous day's dietary iodine intake. However, since an individual's level of urinary iodine varies daily and even during a given day, data can be used only for making a population-based estimate. Experience has shown that the iodine concentration in early morning urine specimens (child or adult) provides an adequate assessment of a population's iodine status; 24-hour samples are not necessary. It has been found preferable to express the results per litre of urine[1] rather than per gram of creatinine as was done formerly. Relating urinary iodine to creatinine is cumbersome, expensive, unreliable and unnecessary. Generally speaking, where reports have quoted iodine concentration per gram of creatinine, the same figure may be taken as the concentration per litre of urine. This 1:1 relationship is not always valid, however, particularly where a subject's protein intake, and consequent creatinine excretion, is very low, e.g. as in parts of Zaire and Papua New Guinea.

Feasibility

72. Acceptability is very high and spot urine specimens are easy to obtain. Urinary iodine assay methods are not difficult to learn or use,[2] but meticulous attention is required to avoid contamination with iodine at all stages. Special rooms, glassware and reagents should be set aside solely for this purpose.

73. Small amounts (0.5–1.0 ml) of urine are required.[3] Specimens are collected in tubes, which are tightly sealed with screw tops;[4] they do not require refrigeration or the addition of a preservative. Iodine content remains stable throughout transport to the laboratory. The tightly sealed specimens can be refrigerated in the laboratory for several months before actual determinations are made. Should evaporation occur, iodine concentration will increase.

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[1] 100μg/l is equivalent to 0.79 μmol/l.

[2] Dunn JT et al. Methods for measuring iodine in urine. ICCIDD/UNICEF/WHO, 1993.

[3] However, considerably larger specimens are required if urinary thiocyanate levels are to be measured as well, which is desirable whenever cassava is a major part of the diet. Cyanogenic glucosides are formed from linamarin in cassava, and the thiocyanates impair utilization of iodine by the thyroid. Smoking is also believed to cause varied urinary thiocyanate levels (see Delange F et al. Influence of dietary goitrogens during pregnancy in humans on thyroid function of the newborn. op. cit.).

[4] Such as Sarstedt tubes (manufacturer's reference number 60542).

74. Many analytical techniques are used. The simplest methods, quite adequate for epidemiological surveys, require less than one millilitre of urine. Annex 4 provides a simple method, recommended for use in most circumstances. The specimen is digested in chloric acid and its iodine content is measured by its catalytic action in the reduction of ceric ammonium sulfate (yellow) to the cerous (colourless) form. The result is expressed as a concentration (μg I/l or mmol I/l urine). A trained technician can process 150 specimens per day. Total instrument costs are about US$ 3000, and the total cost per specimen has been estimated to be $ 0.50-1.00, including labour. Other methods digest the urine more completely, but are more complicated, time consuming and costly.

75. Since casual specimens are used, it is desirable to measure about 300 from a given population group to allow for varying degrees of subject hydration and other biological variations between individuals, as well as to obtain a reasonably small confidence interval as already discussed in paragraphs 30-31. A sample of 200 specimens would give a relative precision of 20%, e.g. 50 $\pm$10% below 100μg/l. Smaller sample sizes are adequate to establish at the outset that iodine deficiency is the cause of the endemic goitre.

Performance

76. The recommended methods are able to detect urinary iodine levels as low as 5 to 20 μg/l with a coefficient of variation under 10%. Laboratory techniques require training, but are not difficult to apply. As in all surveys for estimating prevalence, population samples must be representative.

Interpretation

77. Simple modern methods make it feasible to process large numbers of samples at low cost and to characterize the distribution according to different cut-off points and intervals. The cut-off points proposed for classifying iodine deficiency into different degrees of public health significance are shown in Table 6. Frequency distribution curves are necessary for full interpretation, since urinary iodine values from populations are usually not normally distributed, and therefore the median value should be used rather than the mean. The indicator of iodine deficiency "elimination" is a median value for iodine concentration of 100 μg/l, i.e. 50% of the samples should be above 100 μg/l, and not more than 20% of samples should be below 50 μg/l. In principle, the same sample size tables apply as those given for goitre prevalence rates (see Annex 2). The "design effect" applicable for goitre prevalence surveys (see Annex 2), i.e. 3, is also applicable for urinary iodine values, at least in an initial survey, but may decrease over time with implementation of a salt iodization programme. If there are fewer subjects per cluster (e.g. 10), the design effect may be reduced to 2.

78. As an IDD prevention programme progresses, goitre rates become progressively less useful, and urinary iodine levels progressively more useful, as elimination criteria.

Table 6. Epidemiological criteria for assessing severity of IDD based on median urinary iodine levels

Median value (μg/l)	Severity of IDD
< 20	Severe IDD
20-49	Moderate IDD
50-99	Mild IDD
≥ 100	No deficiency

Blood constituents

79. Two blood constituents, TSH and Tg, can be used as surveillance indicators. In a population survey, the collection of a blood spot on filter paper can be used to measure TSH and Tg. Issues common to TSH and Tg will not be repeated in the section on Tg. The thyroid hormones thyroxine (T4) and triiodothyronine (T3) are not discussed, since their measurement is not recommended for surveillance purposes.

TSH

Biological features

80. Iodine is essential for synthesis of thyroid hormones, which are necessary for normal brain and neurological development. The kinetics of the thyroid hormone receptor in the pituitary gland mimic the kinetics of thyroid hormone receptors in the brain. When iodine levels are low, the concentration of thyroid hormones in the pituitary gland stimulates the release of TSH, which is then detectable in blood. Serum or whole blood TSH levels thus directly reflect the availability and adequacy of thyroid hormone. TSH level is the best diagnostic test for determining hypothyroidism. An elevated TSH level in neonate or infant blood is of considerable concern because this indicates an inadequate thyroid hormone level during this crucial stage of brain development. However, if used for purposes of screening, i.e. detecting all hypothyroid neonates, coverage must be *universal* for the screening to be considered adequate. There are limitations in interpreting adult TSH levels, as noted in paragraphs 82 and 87.

Feasibility

81. There is a well-established methodology for determining TSH levels from either dried whole blood spots on filter paper or serum. Whole blood from any site is

acceptable for spotting on to certified grade 1 filter paper. Because only a few drops of whole blood are required, a finger, heel, or earlobe is the most common site for puncture. It is essential that sterile equipment be used - either lancets for blood spot collection, or needles and syringes for collecting whole blood from which the serum is separated. Standard procedures for handling blood products or objects contaminated with blood should be followed. The risk of contracting HIV or hepatitis infection from dried blood spots is extremely low.

82. **Timing.** For neonates, blood specimens can be collected from cord blood at the time of birth, or by heel prick after 3 days (72 hours). Collection from the heel during the first 3 days (<72 hours) of life is not recommended because levels can be elevated as a result of the birth process itself. After the first three days, the timing of specimen collection is no longer crucial. Blood specimens may be obtained from pregnant women during prenatal care visits, or from school-age children during school-based surveys. However, further study of TSH distributions among these older subjects is needed to improve understanding of the specificity of their relationship to iodine deficiency.

83. **Transport.** Blood spots are easy to transport. It is important that the spot be dry before storage or shipment. Filter papers, usually stored in a plastic bag, can be transported using the normal postal system and are stable for periods of up to 6 weeks even in a hostile environment of high temperature and humidity. Customs clearance may be required for international transport of dried blood spots.

84. **TSH assay.** TSH in the blood spot can be measured by commercially available assay kits. The enzyme-linked immunosorbant assay (ELISA) methodology is recommended because of lower equipment cost, longer shelf life of reagents (6 months), and high sensitivity (<2 mU/l)[1]. Direct linkage of the ELISA system to a microcomputer is recommended because this allows a high throughput and facilitates data management for quality assurance and public health decision-making. Laboratory staff may need training in laboratory management and quality assurance. Laboratories should participate in an external quality control programme.[2]

85. **Cost.** Current estimates for the cost of laboratory equipment and reagents are given below. Labour costs for collection and processing will vary depending on local circumstances.

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[1] Miyai K, Ishibashi K, Kawashima M. *Two-site immunoenzymometric assay for thyrotropin in dried blood samples of filter paper.* Clin. Chem. 1981;27 (8):1421-1423; Tseng YC, Burman KD, Baker JR, Wartofsky L. *A rapid, sensitive enzyme-linked immunoassay for human thyrotropin.* Clin. Chem. 1985;31 (7):1131-1134; Waite KV, Maberly GF, Eastman CJ. *Storage conditions and stability of thyrotropin and thyroid hormones on filter paper.* Clin. Chem. 1987;33:853-855; Waite KV, Maberly GF, Ma G, Eastman CJ. *Immunoradiometric assay with use of magnetizable particles: measurement of thyrotropin in blood spots to screen for neonatal hypothyroidism.* Clin. Chem. 1986;32 (19):1966-1968.

[2] The Programme Against Micronutrient Malnutrition (PAMM), which is based at the Emory University School of Public Health, Atlanta, Georgia, USA, supports such a programme.

- TSH ELISA laboratory with state-of-the-art computer-based system and software capable of processing 90,000 tests/year/technologist

  US$ 15 000

- TSH ELISA laboratory hardware and software capable of processing up to 5000 tests/year/technologist

  US$ 5000

- TSH assay kits including titre plate, collection materials (paper & lancets), and reagents procured in the USA

  US$ 0.50-1.00/test.

The same equipment can be used to perform ELISA-based assays for surveillance of various other micronutrients and infectious diseases.

Performance

86. **Sensitivity.** The term 'sensitivity' has two distinct meanings depending on whether it is used in a laboratory or epidemiologic context. In a laboratory context, 'sensitivity' refers to the improved ability of the TSH whole-blood spot-assay kits to detect levels of TSH over the full physiologic range including values as low as 1-2 mU/l. Earlier TSH assay systems were sensitive and reliable only for values over approximately 20 mU/l. The relatively recent commercial availability of the 'sensitive' TSH blood spot assay kit now permits the determination of mild-to-moderate IDD, which may occur when TSH levels are under 20 mU/l.

87. In an epidemiologic context, 'sensitivity' refers to the ability of the TSH assay to identify correctly IDD cases among populations. 'Specificity' refers to a screening test's ability to identify correctly those people who do not have a given condition. The specificity of TSH for IDD screening has not been clearly quantified. However, the number of false negatives — individuals with IDD who test negative — is probably very low. Individuals with mild IDD and mild elevations of TSH can now be detected by using the newer sensitive whole-blood TSH assays. Elevation of TSH values in individuals is associated with all causes of primary hypothyroidism. Causes of TSH elevation other than iodine deficiency include goitrogen ingestion, congenital hypothyroidism (CH), and autoimmune thyroiditis. CH is relatively uncommon, affecting approximately 1 in 4000 neonates (0.275%) worldwide. Autoimmune thyroid disease is less rare, particularly in Western countries. Goitrogen ingestion is usually regional and easily identified in the environment, and in any case results in a relative deficiency of iodine because requirements are greatly increased. IDD screening programmes are not designed to follow-up individuals but to direct population-based interventions. TSH levels are an excellent indicator for hypothyroidism in neonates, but their specificity in older

groups is less certain. In some populations (e.g. in Algeria[1]) there are clear examples of raised goitre rates and inadequate urinary iodine intakes that are associated with TSH levels with the normal range.

Interpretation

88. Reference data for TSH are available among neonates because they are routinely collected as part of neonate congenital hypothyroid screening programmes. TSH values are currently reported in whole blood units or serum units. It is crucial that all reports and discussion of TSH distributions specify the units employed. Congenital hypothyroid screening and IDD surveillance require different TSH cut-off points. A TSH cut-off of 20-25 mU/l whole blood (approximately 40-50 mU/l serum) is commonly used to screen for congenital hypothyroidism. IDD may be present with TSH levels which are only mildly elevated. While further study of iodine-replete populations is needed, a cut-off of 5 mU/l whole blood may be appropriate for epidemiologic studies of IDD. Populations with a substantial proportion of neonates with TSH levels above the cut-off could indicate a significant IDD problem (see Table 7).

Thyroglobulin (Tg)

Biological features

89. Insufficient iodine intake induces a proliferation of thyroid cells, which results in hyperplasia and hypertrophy. This leads to an enhanced turnover of thyroid cells, which release Tg into the serum. Tg in serum changes inversely with iodine intake in all age groups.

Feasibility

90. Acceptability is high, and sample collection and transport are simple, identical to those for TSH (see previous section). The determination technique is similar to that for TSH using a Tg antibody instead of one for TSH, although methods are not yet commercially available. Costs are comparable to those for TSH. Training will be required in laboratory techniques.

Performance

91. Available methods can detect levels as low as 2 ng/ml serum with a coefficient of variation close to 5%. Tg changes rapidly after an alteration of iodine intake in *all* age groups, and may be a more sensitive indicator than TSH, as the following observations

[1] Benmiloud M et al. Oral iodized oil for correcting iodine deficiency: optimal dosing and outcome indicator selection. *J. Clin. Endocr. Metab.* 1994, 79:20-24.

suggest. Tg rises in individuals with an insufficient iodine intake, even under conditions where TSH falls or is suppressed due to functional autonomy, as frequently happens with long-standing iodine deficiency. After iodine depletion, Tg will rise before TSH shifts to higher values and long before goitre develops. Following iodine supplementation, Tg normalizes before thyroid volume has decreased.

Interpretation

92. Individuals (children and adults) with sufficient iodine intake show a median Tg serum level of 10 ng/ml and a normal upper limit, for individuals, of 20 ng/ml in most assay techniques. The results obtained from a survey should be expressed as a median and as the percentage of Tg levels above 20 ng/ml.

Summary of outcome indicators

93. Table 7 provides a summary of cut-off points and prevalences that are considered indicative of a significant public health problem for IDD. As mentioned in paragraph 49, it is highly desirable to have more than one parameter of iodine and thyroid status. Generally speaking, at least two are required. The foregoing pages provide information on which to base a suitable choice of indicators.

Table 7. Summary of IDD prevalence indicators and criteria for a significant public health problem

		Severity of public health problem (prevalence)		
Indicator	Target population	Mild	Moderate	Severe
Goitre grade > 0	SAC[a]	5.0-19.9%	20.0-29.9%	≥30.0%
Thyroid volume > 97th centile by ultrasound[b]	SAC	5.0-19.9%	20.0-29.9%	≥30.0%
Median urinary iodine level (μg/l)	SAC	50-99	20-49	<20
TSH > 5mU/l whole blood	neonates	3.0-19.9%	20.0-39.9%	≥40.0%
Median Tg (ng/ml serum)[c]	C/A[d]	10.0-19.9	20.0-39.9	≥40.0

[a] SAC = school-age children
[b] Normative tyroid volume size values will be available from WHO and ICCIDD in 1995.
[c] Different assays may have different normal ranges.
[d] C/A = children and adults

5.3 Process indicators for IDD control programmes

94. IDD control programmes should have built-in monitoring and education mechanisms. Included in such protocols will be both process indicators associated with programme implementation, and indicators of impact achieved through its implementation as a result. Depending upon the specific characteristics of the IDD control programmes, distinct indicators will need to be considered and different techniques employed to monitor them. Although most countries will use iodized salt[1] as the primary control activity,[2] other programmes, where implemented, will need to be monitored, even if they are used as short-term measures while salt iodization is being established.

Salt iodization programmes

95. All countries with a significant IDD public health problem should undertake a situation analysis of salt available for human and animal consumption, from points of production (or importation) through distribution channels to actual consumption. Such salt is referred to as *food-grade salt,*[3] which includes crude salt for direct edible use by people and livestock; refined salt for edible use; and salt used industrially in processed foods such as bread, biscuits, salted foods, canned foods, and instant foods.

96. The situation analysis should include a list of the major salt producers or importers, production/import/export statistics, and information on salt quality, packaging, transport and storage, retail marketing, prices and household consumption. This information should be updated periodically, e.g. every two years. In addition, periodic monitoring will have to be undertaken at different points along the distribution chain of iodized salt to ensure that iodine-concentration levels are adequate and, if necessary, that corrective action is taken. This could include improvements in packaging, transportation or storage of iodized salt at different points before it reaches the consumer, and modification of iodine level at the factory.

97. Salt iodization involves the addition of a small quantity of iodine (30 to 100 mg of iodine per kg of salt, or parts per million), usually in the form of potassium iodide or

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[1] The term "iodized salt" refers to salt iodinated with any iodine compound - usually potassium iodide (KI) or iodate (KIO_3).

[2] Mannar MGV and Dunn JT. Salt iodization for elimination of iodine deficiency. ICCIDD/MI/UNICEF/WHO, 1995 (in press).

[3] Food-grade salt is a crystalline product destined for human or animal consumption. It should contain at least 97% sodium chloride on a dry-matter basis, excluding additives. All additive should be of food-grade quality. The production, packaging, storage and transportation should be such as to avoid any risk of contamination. Contaminants such as arsenic, copper, lead, cadmium and mercury should not exceed the levels of 0.5, 2, 2, 0.5, and 0.1 mg/kg, respectively, as specified by the FAO/WHO Codex Alimentarius Commission. Codex Alimentarius, Vol. 1, General requirements, section 5.5. Food and Agriculture Organization of the United Nations, Rome, 1992.

potassium iodate.[1] A joint FAO/WHO expert committee noted in 1990 that "potassium iodate has been shown to be a more suitable substance for fortifying salt than potassium iodide, because of its greater stability, particularly in warm, damp or tropical climates".[2]

Techniques for measuring salt iodine levels

98. There are essentially two techniques for measuring iodine levels in salt:

(a) ***Standard titration method.*** It is necessary that this method be conducted in a laboratory. Iodine is liberated using sulphuric acid. The free iodine is titrated with sodium thiosulphate, using starch as an indicator. Slightly different techniques are employed, depending on whether the iodine was in the form of iodate or iodide. Facilities for this method are normally available in most countries in a public health or standards laboratory, but some other laboratory may need to be equipped and helped to develop competence in its operation. The titration method is preferred for checking salt batches produced in factories, or on arrival in the country and in general where accurate testing is required. However, it is too time-consuming and expensive for purposes of routine national monitoring, for which the second method may be more suitable.

(b) ***Rapid-test kits.*** These comprise bottles of starch solution (stabilized), one drop of which is placed on the salt. If the salt is alkaline a neutralizing solution is first applied. The intensity of the blue colour which develops indicates the salt iodine level, up to 50 or 100 ppm, depending on the kit used, with an accuracy of ± 10 ppm. Most of the rapid-test kits presently available can detect the presence of iodate only. Details of available kits may be obtained from WHO, UNICEF or ICCIDD.

Monitoring salt iodine levels

99. Iodization may take place inside the country, at the main production or importation sites, or outside, with salt being imported already iodized. There are inevitably some losses of iodine from salt between production and consumption, and these are often much higher in non-industrialized countries, where packaging, storage and transportation conditions are sub-optimal. Countries should establish the expected iodine content of salt at different points along the distribution system, taking into account climatic conditions, types of packaging, and habitual daily salt consumption. Guidelines are given in Table 8, calculated in each case to provide individuals with 150 μg iodine per day, and allowing

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[1] *Iodine and health: eliminating iodine deficiency disorders safely through salt iodization.* A statement by the World Health Organization. Document WHO/NUT/94.4.

[2] Joint FAO/WHO Expert Committee on Food Additives. Geneva, World Health Organization, 1991 (WHO Technical Report Series, No. 806, Annex 5).

for an average loss of 30% during cooking. The iodine concentration in salt needs to be monitored regularly at two or three levels of the distribution system. The overall responsibility for quality control within a country should be clearly identified. Often it is vested in the ministry of health or equivalent authority through its primary health care unit and regional or provincial and district health departments. At the point of (internal) production, however, the ministry of industry is likely to be involved; at the point of importation, the customs services; and within the marketing system, the ministry of commerce or trade. A bureau of standards may also be responsible for fixing and controlling the level of iodine in iodized salt. Criteria for assuring programme adequacy are provided in Table 9.

Table 8. ICCIDD-UNICEF-WHO recommended levels of iodine in salt

Examples of desirable average levels at various points in the salt distribution chain, depending on climate, salt intake, and conditions affecting packaging and distribution.

Parts of iodine per million parts of salt, i.e. micrograms per gram, milligrams per kilogram or grams per tonne

Climate and daily salt consumption (g/person)	Requirement at factory outside the country		Requirement at factory inside the country		Requirement at retail sale (shop/market)		Requirement at household level
	Packaging						
	Bulk (sack)	Retail pack (<2 kg)	Bulk (sack)	Retail pack (<2kg)	Bulk (sack)	Retail pack (<2 kg)	
Warm moist							
5 g	100	80	90	70	80	60	50
10 g	50	40	45	35	40	30	25
Warm dry or cool moist							
5 g	90	70	80	60	70	50	45
10 g	45	35	40	30	35	25	22.5
Cool dry							
5 g	80	60	70	50	60	45	40
10 g	40	30	35	25	30	22.5	20

Source: Adapted from World Summit for Children - mid-decade goal: iodine deficiency disorders. Geneva, 1994. UNICEF-WHO Joint Committee on Health Policy, document JCHPSS/94/2.7 and document WHO/NUT/93.1.

N.B. 168.6 mg of KIO_3 contains 100 mg of iodine.

N.B. These are indicative initial levels, which should be adjusted in the light of urinary iodine measurement.

Table 9. Criteria for assessing adequacy of salt iodization programmes

Process indicator		Criterion of adequacy
A.	Factory or importer level	
	1. Percent of food-grade salt claimed to be iodized	100%
	2. Percent of food-grade salt effectively iodized	≥90%
	3. Adequacy of internal monitoring process*	≥90%
	4. Adequacy of external monitoring process	10-12 monthly checks per producer/importer, per year
B.	Consumer and district level	
	1. Percent of monitoring sites with adequately iodized salt	
	(i) households (or schools)	Adequate in 90% of samples
	(ii) district headquarters (including major markets)	
	2. Adequacy of monitoring process**	90% or more

* Corrective action systematically taken within 3 hours in 90% of cases using LQAS methodology
** Monitoring undertaken in 90% of districts in each province at both household and district levels.

Monitoring procedures

100. **Factory level.** The responsibility for routine monitoring rests with the factory itself (internal salt monitoring). The recommended procedure is to carry out hourly monitoring with the rapid-test kit, and at least once daily by titration. Observations should be recorded systematically in a register indicating the date, time, batch number and iodine content of the salt. However, the responsible government authority (e.g. ministry of health, industry or commerce, or the standards office or other designated body) should also undertake periodic checks (external salt monitoring) at least once monthly, by titration, and compare results with the factory's own test. During inspection, the manufacturer's records should be verified for adequacy of internal monitoring and variations in iodine levels.

101. **Importation level.** Principles similar to those at factory level apply. Each batch of imported salt should be monitored using rapid-test kits, and periodic checks should also be made using a chemical method. Responsibility for monitoring may be delegated to the customs authorities, ministry of commerce or health, or the standards board. The action

to be taken if the iodine level is too low depends on circumstances and facilities, e.g. if there is no alternative iodation plant in the country, it should not be permitted; if there is another iodation plant, which is desirable, the salt should be sent there for obligatory iodization at the importer's expense. Unless appropriate penalties are defined and rigorously imposed, the whole system will break down. Hence ensuring cooperation in monitoring the system requires the motivation of importers as much as producers. Large quantities of imported salt should be checked at the source by a monitoring agency - several multinational firms undertake such monitoring - to ensure that salt sent from external factories complies with requirements at the source. Imports should be divided into "lots", e.g. train wagons or truckloads, for sampling purposes. LQAS methods apply to this type of sampling.

102. **Wholesale and retail level.** The major distributors should be sensitized to the subject and provided with rapid-test kits to check the salt iodine levels before it is released for retail sale. This is especially important in larger countries or in situations where transportation results in a long time lag between production and consumption. Regular monitoring at three-monthly intervals may be advisable. If there are deficiencies, they should be notified to the provincial or district health authorities.

103. **Community and district level.**[1] Public health inspectors or nurses at district level will often be responsible for this monitoring activity, the objective of which is to verify, using rapid-test kits, that adequate concentrations of iodine are attained in salt, especially when it reaches the consumer. Salt monitoring at the district and community level should be used as an opportunity to disseminate information regarding the importance of consuming iodized salt. When checks at those levels show inadequate salt iodine concentrations, further spot checks should be made at successive levels of the distribution system to identify at what point losses are occurring.

104. Three approaches are recommended for monitoring salt iodization quality at the district level, based on surveys in markets, schools and households. In the first two, more specific information may be obtained about distribution of inadequately iodized salt samples within the district, which may be used to highlight 'hot spots' where problems are likely to be occurring. For schools with an enrolment of 100 to 1000 pupils at least 35 salt samples should be collected and tested to detect if more than 20% of the population served have access to inadequately iodized salt (which is the case if 4 or more samples are found to be inadequate). In monitoring based on household sampling, it will be possible to ascertain whether there is a problem for a district as a whole, but it would not be possible to gain any information about patterns within a district. For each district at least 10 houses in each of 10 remote villages should be randomly selected for spot testing, with a new selection if possible every 4 months.

105. More detailed guidelines on salt monitoring will be included in a salt-monitoring kit, which is being developed by PAMM and others.

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[1] A district is the smallest administrative unit of local government in which all the major government departments are represented.

Other types of IDD control programmes

106. Other potential IDD control programmes include iodization of water, fortification of foods other than salt, and supplementation with iodized oil. If other foods are fortified, then an evaluation of that food, similar to the one described for iodized salt, should be devised. In supplementation programmes, it is important to ensure that the high-risk population is adequately covered. LQAS surveys can be useful (see paragraphs 35-38 and Annex 3).

107. Iodized oil has been widely used in a number of national IDD control programmes. As salt iodization becomes more widespread, iodized oil programmes are likely to be limited to areas that cannot be easily reached by iodized salt distribution. The essential points for monitoring purposes are two: ensuring that normal thyroid function is attained and maintained in the target population; and that operational coverage is adequate, i.e. at least 95% of the at-risk population should receive iodized oil annually, or at an alternative frequency set by programme managers in the light of local conditions. Operational coverage may be determined from health centre or mobile team records, or by rapid cluster-sample surveys to determine the proportion of target groups that actually received the supplement. The latter approach requires that it be possible to identify accurately whether or not an individual received a supplement. In areas where iodized oil is recommended for specific target groups, e.g. young children and women of child-bearing age, LQAS surveys can be useful in determining population coverage. Details of such monitoring are outside the scope of the present document, which focuses on universal salt iodization.

6. Criteria for monitoring progress towards eliminating IDD as a significant public health problem

108. Table 10 presents recommended criteria for use as core indicators in monitoring progress towards the goal of eliminating IDD as a significant public health problem. Criteria include both IDD status indicators and a control programme process indicator since it is important to ensure sustained control of iodine deficiency for an entire population rather than focus on reaching goals based on measuring the IDD status of a single group. Moreover, monitoring salt iodization is a useful first step in tracking progress towards meeting the goal of IDD elimination. Where thyroid size indicators are concerned, a prevalence of thyroid enlargement above 5% signals a public health concern. However, since there are several causes of thyroid enlargement, iodine status should be confirmed by assessing urinary iodine concentration.

Table 10. Criteria for monitoring progress towards eliminating IDD as a public health problem

Indicator	Goal
1. **Salt iodization**	
Proportion of households consuming effectively iodized salt	>90%
2. **Urinary iodine**	
Proportion below 100 μg/l	<50%
Proportion below 50 μg/l	<20%
3. **Thyroid size**	
In school children 6-12 years of age:	
Proportion with enlarged thyroid, by palpation or ultrasound	<5%
4. **Neonatal TSH**	
Proportion with levels > 5mU/l whole blood	<3%

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[1] Joint WHO/UNICEF/ICCIDD Consultation on Indicators for Assessing Iodine Deficiency Disorders and their Control Programmes, 3-5 November 1992, Geneva.

Annex 2 Sample sizes for IDD prevalence surveys

Confidence interval. The interval is determined with a specified level of confidence (or probability) that will include the population parameter being estimated. Thus 95% confidence interval is an interval for which one would be 95% confident that it will include the true prevalence level.

Precision is a measure of how close an estimate is, or is required to be, to the true population value.

Table A2.1 gives the sample sizes in terms of relative precision, i.e. expressed as a proportion of the mean value (ϵ) expected or obtained in the survey. The top row marked "P" gives the anticipated prevalence. For example, 0.05 means a prevalence of 5%; and so on. The first column labelled "ϵ" gives the desired relative precision. For example, a relative precision of 0.10 for an expected prevalence of 0.50 implies a precision of 0.10 x 0.50 = 0.05 (or 5 percentage points) with a minimum sample size of 384 randomly selected individuals to be 95% confident that the range 45% to 55% includes the true prevalence.

Depending on the type and circumstances of a survey, the degree of precision required may vary, e.g. in an initial goitre survey, with expected goitre rates of about 50%, a relative precision of 20% may be appropriate, i.e. 50% $\pm$ 10%. If a salt iodization programme has been implemented for some years and goitre rates are thought likely to be around 5%, a relative precision of 30% (which would mean an eventual "width" of $\pm$ 1.5%) may be adequate.

If the anticipated prevalence is entirely unknown, sample size should be estimated assuming that the result will be at whatever the critical level is for decision-making, i.e. 30% prevalence indicating severe endemicity, or 5% for existence of a public health problem.

Design effect. The figures in Table A2.1 refer to a survey with strict random sampling of a given population. Very often, cluster sampling procedures are used, and are more practical - this is the procedure followed for example in many EPI and CDD surveys, as well as in anthropometric and goitre surveys. For phenomena such as goitre whose distribution is patchy, cluster sampling may produce misleading results - if one happens to fall on clusters of high prevalence, for example. To avoid errors of this sort a larger total number of subjects should be examined. The numbers in the basic Table A2.1 should be multiplied by a factor called the *"design effect"* to allow for this possible lack of homogeneity in the population studied. It is an indication of the variation due to clustering. It is estimated by the ratio of the variance when *cluster sampling* is used, to the variance when *simple random sampling* is used. The design effect has been established at 3 for goitre surveys.

In all cases where the parameter is not normally distributed (i.e. Gaussian distribution), e.g. for urinary iodine excretion values, it is wiser to give median rather than mean values, or another form of presentation of the distribution of values, rather than the mean, as indicated in paragraph 35 of this document.

For other confidence intervals and more details, including guidance on other types of studies than simple prevalence surveys, including lot quality assurance sampling, please see:

S.K. Lwanga & S. Lemeshow (1991) Sample size determination in health studies, a practical manual, WHO Geneva (this book is a practical guide to the subject, with a minimum of background theory).

S. Lemeshow et al. (1990) Adequacy of sample size in health studies, Chichester, John Wiley (this book includes the statistical methodology of sample size determination).

Table A2.1 Estimating a population proportion with specified relative precision

$$n = z^2_{1-\alpha/2}(1-P)/\epsilon^2 P$$

(a) Confidence level 95%

ϵ \ P	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50	0.55	0.60	0.65	0.70	0.75	0.80	0.85	0.90	0.95
0.01	729904	345744	217691	153664	115248	89637	71344	57624	46953	38416	31431	25611	20686	16464	12805	9604	6779	4268	2022
0.02	182476	86436	54423	38416	28812	22409	17836	14406	11738	9604	7858	6403	5171	4116	3201	2401	1695	1067	505
0.03	81100	38416	24188	17074	12805	9960	7927	6403	5217	4268	3492	2846	2298	1829	1423	1067	753	474	225
0.04	45619	21609	13606	9604	7203	5602	4459	3602	2935	2401	1964	1601	1293	1029	800	600	424	267	126
0.05	29196	13830	8708	6147	4610	3585	2854	2305	1878	1537	1257	1024	827	659	512	384	271	171	81
0.06	20275	9604	6047	4268	3201	2490	1982	1601	1304	1067	873	711	575	457	356	267	188	119	56
0.07	14896	7056	4443	3136	2352	1829	1456	1176	958	784	641	523	422	336	261	196	138	87	41
0.08	11405	5402	3401	2401	1801	1401	1115	900	734	600	491	400	323	257	200	150	106	67	32
0.09	9011	4268	2688	1897	1423	1107	881	711	580	474	388	316	255	203	158	119	84	53	25
0.10	7299	3457	2177	1537	1152	896	713	576	470	384	314	256	207	165	128	96	68	43	20
0.15	3244	1537	968	683	512	398	317	256	209	171	140	114	92	73	57	43	30	19	9
0.20	1825	864	544	384	288	224	178	144	117	96	79	64	52	41	32	24	17	11	5
0.25	1168	553	348	246	184	143	114	92	75	61	50	41	33	26	20	15	11	7	•
0.30	811	384	242	171	128	100	79	64	52	43	35	28	23	18	14	11	8	5	•
0.35	596	282	178	125	94	73	58	47	38	31	26	21	17	13	10	8	6	•	•
0.40	456	216	136	96	72	56	45	36	29	24	20	16	13	10	8	6	•	•	•
0.50	292	138	87	61	46	36	29	23	19	15	13	10	8	7	5	•	•	•	•

• = Sample size less than 5

ϵ = relative precision

P = anticipated population proportion (prevalence)

Annex 3 Lot quality assurance sampling

Source: S.K. Lwanga and S. Lemeshow (1991), *Sample size determination in health studies, A practical manual*, pp 15-16 and pp 63-71, WHO, Geneva.

Accepting a population prevalence as not exceeding a specified value

This section outlines how to determine the minimum sample size that should be selected from a given population so that, if a particular characteristic is found in no more than a specified number of sampled individuals, the prevalence of the characteristic in the population can be accepted as not exceeding a certain value.

Required information and notation

(a) Anticipated population prevalence	P
(b) Population size	N
(c) Maximum number of sampled individuals showing characteristic	d*
(d) Confidence level	100(1-x)%

Tables A3.1 present minimum sample sizes for confidence levels of 95% and 90% and values of d* of 0-4.

Example 18

In a school of 2500 children, how many children should be examined so that if no more than two are found to have malaria parasitaemia it can be concluded, with 95% confidence, that the malaria prevalence in the school is no more than 10%?

Solution

(a)	Anticipated population prevalence	10%
(b)	Population size	2500
(c)	Maximum number of malaria cases in the sample	2
(d)	Confidence level	95%

Table A3.1 shows that for P=0.10 and N=2500 a sample size of 61 children would be needed.

Decision rule for "rejecting a lot"

This section applies to studies designed to test whether a "lot" (a sampled population) meets a specified standard. The null hypothesis is that the proportion of individuals in the population with a particular characteristic is equal to a given value, and a one-sided test is set up such that the lot is accepted as meeting the specified standard *only* if the null hypothesis can be rejected. For this purpose a "threshold value" of individuals with the characteristic (d*) is computed as a basis for a decision rule; if the number of sampled individuals found to possess the characteristic does not exceed the threshold, the null hypothesis is rejected (and the lot is accepted), whereas if the threshold is exceeded, the lot is rejected.

Required information and notation

(a)	Test value of the population proportion under the null hypothesis	P_0
(b)	Anticipated value of the population proportion	P_a
(c)	Level of significance	100x%
(d)	Power of the test	100(1-ß)%

Tables A3.2 present minimum sample sizes for a level of significance of 5% and power of 90%, 80% and 50% in one-sided tests.

Example 19

In a large city, the local health authority aims at achieving a vaccination coverage of 90% of all eligible children. In response to concern about outbreaks of certain childhood disease in particular parts of the city, a team of investigators from the health authority is planning a survey to identify areas where vaccination coverage is 50% or less so that appropriate action may be taken. How many children should be studied, as a minimum, in each area and what threshold value should be used if the study is to test the hypothesis that the proportion of children *not* vaccinated is 50% or more, at the 5% level of significance? The investigators wish to be 90% sure of recognizing areas where the target vaccination coverage has been achieved (i.e. where only 10% of children have not been fully vaccinated).

Solution

(a)	Test value of the population proportion	50%
(b)	Anticipated value of the population proportion	10%
(c)	Level of significance	5%
(d)	Power of the test	90%

Because the mistake of accepting groups of children as adequately vaccinated, when in fact the coverage is 50% or less, is the more important, $P_0=0.50$ and $P_a=0.10$. Table A3.2 shows that in this case a sample size of 10 and a threshold value of 2 should be used.

Therefore, a sample of 10 children should be taken from each of the areas under study. If more than 2 children in a sample are found not to have been adequately vaccinated, the lot (the sampled population) should be "rejected", and the health authority may take steps to improve vaccination coverage in that particular area. If, however, only 2 (or fewer) children are found to be inadequately vaccinated, the null hypothesis should be rejected and the group of children may be accepted as not being of immediate priority for an intensified vaccination campaign.

Tables A3.1 Accepting a population prevalence as not exceeding a specified value

The value of n is obtained by solution of the inequality

$$\sum_{x=0}^{d^*} {}^{M}C_x {}^{(N-M)}C_{(n-x)} / {}^{N}C_n < \alpha$$

where $M = N P$, for a finite population; or

$$\text{Prob}\ \{d \leq d^*\} < \alpha$$

i.e.

$$\sum_{d=0}^{d^*} \text{Prob}(d) < \alpha$$

or

$$\sum_{d=0}^{d^*} {}^{n}C_d P^d (1 - P)^{n-d} < \alpha$$

for an infinite population.

(a) Confidence level **95%**, d* = **0**

N \ P	0.90	0.80	0.70	0.60	0.50	0.40	0.30	0.20	0.10	0.05	0.025	0.0125
100	2	2	3	4	5	6	9	13	25	45	82	96
200	2	2	3	4	5	6	9	13	27	51	90	140
1000	2	2	3	4	5	6	9	14	29	57	112	212
2000	2	2	3	4	5	6	9	14	29	58	115	225
2500	2	2	3	4	5	6	9	14	29	58	116	228
5 000	2	2	3	4	5	6	9	14	29	58	118	234
10 000	2	2	3	4	5	6	9	14	29	59	118	236
15 000	2	2	3	4	5	6	9	14	29	59	118	237
20 000	2	2	3	4	5	6	9	14	29	59	118	238
25 000	2	2	3	4	5	6	9	14	29	59	119	238
50 000	2	2	3	4	5	6	9	14	29	59	119	239
Infinite	2	2	3	4	5	6	9	14	29	59	119	239

Table A3.1 (continued)

(b) Confidence level **95%**, d* = **1**

N \ P	0.90	0.80	0.70	0.60	0.50	0.40	0.30	0.20	0.10	0.05	0.025	0.0125
100	3	4	5	6	8	10	14	20	38	64	95	100
200	3	4	5	6	8	10	14	21	42	77	127	191
1 000	3	4	5	6	8	10	14	22	45	90	174	324
2 000	3	4	5	6	8	10	14	22	46	92	181	348
2 500	3	4	5	6	8	10	14	22	46	92	183	356
5 000	3	4	5	6	8	10	14	22	46	93	186	367
10 000	3	4	5	6	8	10	14	22	46	93	187	372
15 000	3	4	5	6	8	10	14	22	46	93	187	374
20 000	3	4	5	6	8	10	14	22	46	93	188	376
25 000	3	4	5	6	8	10	14	22	46	93	188	379
50 000	3	4	5	6	8	10	14	22	46	94	188	379
Infinite	3	4	5	6	8	10	14	22	46	94	188	379

c) Confidence level **95%**, d* = **2**

N \ P	0.90	0.80	0.70	0.60	0.50	0.40	0.30	0.20	0.10	0.05	0.025	0.0125
100	4	6	7	8	10	13	18	27	48	77	100	100
200	5	6	7	8	11	14	19	28	54	98	155	200
1 000	5	6	7	8	11	14	19	29	60	118	227	417
2 000	5	6	7	8	11	14	19	30	61	122	238	455
2 500	5	6	7	8	11	14	19	30	61	122	242	467
5 000	5	6	7	8	11	14	19	30	61	123	246	486
10 000	5	6	7	9	11	14	19	30	61	123	248	493
15 000	5	6	7	9	11	14	19	30	61	124	248	497
20 000	5	6	7	9	11	14	19	30	61	124	251	502
25 000	5	6	7	9	11	14	19	30	62	124	251	502
50 000	5	6	7	9	11	14	19	30	62	125	251	502
Infinite	5	6	7	9	11	14	19	30	62	125	251	502

Table A3.1 (continued)

(d) Confidence level **95%**, d* = **3**

N \ P	0.90	0.80	0.70	0.60	0.50	0.40	0.30	0.20	0.10	0.05	0.025	0.0125
100	6	7	9	10	13	16	22	32	58	88	100	100
200	6	7	9	11	13	17	23	34	66	116	176	200
1 000	6	7	9	11	13	17	24	36	74	145	275	501
2 000	6	7	9	11	13	17	24	37	75	150	291	552
2 500	6	7	9	11	13	17	24	37	75	150	297	571
5 000	6	7	9	11	13	17	24	37	75	152	303	596
10 000	6	7	9	11	13	17	24	37	75	152	305	607
15 000	6	7	9	11	13	17	24	37	75	152	306	610
20 000	6	7	9	11	13	17	24	37	75	153	307	614
25 000	6	7	9	11	13	17	24	37	76	153	307	618
50 000	6	7	9	11	13	17	24	37	76	155	309	619
Infinite	6	7	9	11	13	17	24	37	76	155	309	619

(e) Confidence level **95%**, d* = **4**

N \ P	0.90	0.80	0.70	0.60	0.50	0.40	0.30	0.20	0.10	0.05	0.025	0.0125
100	7	8	10	12	15	19	26	38	66	95	100	100
200	7	9	10	13	16	20	27	41	77	132	191	200
1 000	7	9	10	13	16	20	28	43	87	170	321	578
2 000	7	9	10	13	16	21	28	43	88	176	342	643
2 500	7	9	10	13	16	21	28	43	89	177	349	669
5 000	7	9	10	13	16	21	28	43	89	179	357	701
10 000	7	9	10	13	16	21	28	44	89	180	361	715
15 000	7	9	10	13	16	21	28	44	89	180	361	720
20 000	7	9	10	13	16	21	28	44	89	180	362	724
25 000	7	9	10	13	16	21	28	44	90	181	363	728
50 000	7	9	10	13	16	21	28	44	90	181	363	728
Infinite	7	9	10	13	16	21	28	44	90	181	364	730

Table A3.1 (continued)

(f) Confidence level **90%**, d* = **0**

N \ P	0.90	0.80	0.70	0.60	0.50	0.40	0.30	0.20	0.10	0.05	0.025	0.0125
100	2	2	2	3	4	5	7	10	20	37	78	94
200	2	2	2	3	4	5	7	11	21	41	78	120
1 000	2	2	2	3	4	5	7	11	22	44	87	168
2 000	2	2	2	3	4	5	7	11	22	45	89	175
2 500	2	2	2	3	4	5	7	11	22	45	90	177
5 000	2	2	2	3	4	5	7	11	22	45	91	181
10 000	2	2	2	3	4	5	7	11	22	45	91	182
15 000	2	2	2	3	4	5	7	11	22	45	91	182
20 000	2	2	2	3	4	5	7	11	22	45	91	184
25 000	2	2	2	3	4	5	7	11	23	45	92	184
50 000	2	2	2	3	4	5	7	11	23	46	92	184
Infinite	2	2	2	3	4	5	7	11	23	46	92	184

(g) Confidence level **90%**, d* = **1**

N \ P	0.90	0.80	0.70	0.60	0.50	0.40	0.30	0.20	0.10	0.05	0.025	0.0125
100	3	4	4	5	7	8	11	17	32	56	93	100
200	3	4	4	5	7	9	12	18	35	65	112	188
1 000	3	4	4	5	7	9	12	18	37	74	145	274
2 000	3	4	4	5	7	9	12	18	38	76	149	290
2 500	3	4	4	5	7	9	12	18	38	76	151	296
5 000	3	4	4	5	7	9	12	18	38	76	153	303
10 000	3	4	4	5	7	9	12	19	38	76	154	305
15 000	3	4	4	5	7	9	12	19	38	76	154	308
20 000	3	4	4	5	7	9	12	19	38	76	154	311
25 000	3	4	4	5	7	9	12	19	38	77	155	311
50 000	3	4	4	5	7	9	12	19	38	77	155	311
Infinite	3	4	4	5	7	9	12	19	38	77	155	311

Table A3.1 (continued)

(h) Confidence level **90%**, d* = **2**

N \ P	0.90	0.80	0.70	0.60	0.50	0.40	0.30	0.20	0.10	0.05	0.025	0.0125
100	4	5	6	7	9	12	16	23	43	71	100	100
200	4	5	6	7	9	12	16	24	47	86	141	199
1 000	4	5	6	7	9	12	16	25	51	101	195	366
2 000	4	5	6	7	9	12	16	25	52	104	203	391
2 500	4	5	6	7	9	12	16	25	52	104	206	401
5 000	4	5	6	7	9	12	16	25	52	105	209	414
10 000	4	5	6	7	9	12	16	25	52	105	210	418
15 000	4	5	6	7	9	12	16	25	52	105	211	420
20 000	4	5	6	7	9	12	16	25	52	105	211	426
25 000	4	5	6	8	9	12	17	25	52	105	212	427
50 000	4	5	6	8	9	12	17	25	52	106	212	427
Infinite	4	5	6	8	9	12	17	25	52	106	212	427

(i) Confidence level **90%**, d* = **3**

N \ P	0.90	0.80	0.70	0.60	0.50	0.40	0.30	0.20	0.10	0.05	0.025	0.0125
100	5	6	8	9	11	14	19	29	52	82	100	100
200	5	6	8	9	12	15	20	30	58	104	164	200
1 000	5	6	8	9	12	15	21	32	64	126	241	449
2 000	5	6	8	9	12	15	21	32	65	130	253	484
2 500	5	6	8	9	12	15	21	32	65	130	258	500
5 000	5	6	8	9	12	15	21	32	65	131	262	518
10 000	5	6	8	10	12	15	21	32	65	132	264	526
15 000	5	6	8	10	12	15	21	32	65	132	265	527
20 000	5	6	8	10	12	15	21	32	65	132	265	531
25 000	5	6	8	10	12	15	21	32	66	132	267	535
50 000	5	7	8	10	12	15	21	32	66	135	267	535
Infinite	5	7	8	10	12	15	21	32	66	135	267	535

Table A3.1 (continued)

(j) Confidence level **90%**, d* = **4**

N \ P	0.90	0.80	0.70	0.60	0.50	0.40	0.30	0.20	0.10	0.05	0.025	0.0125
100	7	8	9	11	14	17	23	34	60	90	100	100
200	7	8	9	11	14	18	24	36	69	121	180	200
1 000	7	8	9	11	14	18	25	38	77	150	285	527
2 000	7	8	9	11	14	18	25	38	78	155	302	572
2 500	7	8	9	11	14	18	25	38	78	156	308	595
5 000	7	8	9	11	14	18	25	38	78	157	314	619
10 000	7	8	9	12	14	18	25	38	78	158	316	628
15 000	7	8	10	12	14	18	25	38	78	158	316	628
20 000	7	8	10	12	14	18	25	38	78	158	317	637
25 000	7	8	10	12	14	18	25	38	79	159	318	637
50 000	7	8	10	12	14	18	25	39	79	159	318	637
Infinite	7	8	10	12	14	18	25	39	79	159	318	638

Table A3.2 Decision rule for "rejecting a lot"

$$n = [z_{1-\alpha}\sqrt{\{P_0(1 - P_0)\}} + z_{1-\beta}\sqrt{\{P_a(1 - P_a)\}}]^2/(P_0 - P_a)^2$$

$$d^* = [nP_0 - z_{1-\alpha}\sqrt{\{nP_0(1 - P_0)\}}]$$

The value of d^* is always rounded down to the nearest integer (for example 5.8 would become 5).

(a) Level of significance **5%**, power **90%**, **one-sided** test ($P_a < P_o$)

P_a \ P_o	0.10		0.15		0.20		0.25		0.30		0.35		0.40		0.45		0.0	
	n	d*	n	d*	n	d*	n	d*	n	d*	n	d*	n	d*	n	d*	n	d*
0.05	239	16	76	6	40	3	25	2	18	2	13	1	10	1	8	1	6	0
0.10			378	45	109	14	54	8	33	5	22	4	16	3	12	2	10	2
0.15					498	84	137	25	66	13	39	8	26	5	19	4	14	3
0.20							601	132	161	38	75	19	44	12	29	8	20	6
0.25									686	186	180	52	83	25	48	15	31	10
0.30											753	242	195	66	88	31	50	19
0.35													804	298	205	80	92	38
0.40															837	352	211	93
0.45																	853	402

Table A3.2a (continued)

P_a \ P_o	0.55		0.60		0.65		0.70		0.75		0.80		0.85		0.90		0.95	
	n	d*	n	d*	n	d*	n	d*	n	d*	n	d*	n	d*	n	d*	n	d*
0.05	5	0																
0.10	8	2	6	1	5	1												
0.15	11	3	8	2	7	2	5	1										
0.20	15	5	11	3	9	3	7	2	5	2								
0.25	21	7	16	6	12	5	9	4	7	3	5	2						
0.30	32	12	22	9	16	7	12	5	9	4	7	3	5	2				
0.35	52	22	33	15	22	10	16	8	11	5	8	4	6	3	5	3		
0.40	93	43	52	25	32	16	22	11	15	8	11	6	8	5	6	4		
0.45	212	104	93	48	51	27	31	17	21	12	14	8	10	6	7	4		
0.50	852	444	210	114	91	51	49	29	30	18	19	12	13	8	9	6	5	3
0.55			834	477	203	120	87	53	46	29	27	18	17	12	11	8	7	5
0.60					798	496	191	123	80	53	42	29	24	17	14	10	8	6
0.65							746	501	176	122	72	52	36	27	20	15	11	9
0.70									676	488	156	116	62		30	24	15	12
0.75											589	455	131	48	49	40	21	18
0.80													484	104	102	86	34	30
0.85														398	362	316	67	60
0.90																	221	204

Table A3.2 (continued)

(b) Level of significance **5%**, power **80%**, **one-sided** test ($P_a < P_o$)

P_a \ P_o	0.10		0.15		0.20		0.25		0.30		0.35		0.40		0.45		0.50	
	n	d*	n	d*	n	d*	n	d*	n	d*	n	d*	n	d*	n	d*	n	d*
0.05	184	11	60	4	32	2	21	1	15	1	11	1	8	0	7	0	5	0
0.10			283	32	83	10	42	5	26	2	18	2	13	2	10	1	8	1
0.15					368	60	103	18	50	9	30	6	20	4	14	3	11	2
0.20							441	95	119	27	56	13	33	8	22	6	15	4
0.25									501	133	133	37	61	18	35	10	23	7
0.30											548	173	142	47	65	22	37	13
0.35													583	213	149	57	67	26
0.40															606	252	153	66
0.45																	617	288

P_a \ P_o	0.55		0.60		0.65		0.70		0.75		0.80		0.85		0.90		0.95	
	n	d*	n	d*	n	d*	n	d*	n	d*	n	d*	n	d*	n	d*	n	d*
0.05	5	0																
0.10	6	1	5	1														
0.15	8	2	7	2	5	1												
0.20	11	3	9	2	7	2	5	1										
0.25	16	5	12	4	9	3	7	2	5	2								
0.30	24	9	16	6	12	5	9	4	6	2	5	2						
0.35	38	15	24	10	16	7	11	5	8	3	6	3						
0.40	68	30	38	17	23	11	16	8	11	5	8	4	5	2				
0.45	154	74	67	33	37	19	22	11	15	8	10	5	7	4	5	3		
0.50	615	317	151	80	65	35	35	20	21	12	13	8	9	5	6	4		
0.55			600	340	145	84	62	37	32	19	19	12	12	8	7	4		
0.60					573	353	136	86	57	37	29	19	16	11	10	7	5	3
0.65							534	356	125	85	50	35	25	18	13	9	7	5
0.70									483	346	109	80	43	32	20	15	9	7
0.75											419	321	91	71	33	26	14	11
0.80													342	279	69	58	22	19
0.85															253	219	44	39
0.90																	150	138

Table A3.2 (continued)

(c) Level of significance **5%**, power **50%**, **one-sided** test ($P_a < P_o$)

P_a \ P_o	0.10		0.15		0.20		0.25		0.30		0.35		0.40		0.45		0.50	
	n	d*	n	d*	n	d*	n	d*	n	d*	n	d*	n	d*	n	d*	n	d*
0.05	98	4	35	1	20	1	13	0	10	0	7	0	6	0	5	0		
0.10			138	13	44	4	23	2	15	1	10	1	8	0	6	0	5	0
0.15					174	26	51	7	26	3	16	2	11	1	8	1	6	0
0.20							203	40	57	11	28	5	17	3	11	2	8	1
0.25									228	57	62	15	29	7	17	4	11	2
0.30											247	74	65	19	30	9	17	5
0.35													260	91	67	23	31	10
0.40															268	107	68	27
0.45																	271	121

P_a \ P_o	0.55		0.60		0.65		0.70		0.75		0.80		0.85		0.90		0.95	
	n	d*	n	d*	n	d*	n	d*	n	d*	n	d*	n	d*	n	d*	n	d*
0.05																		
0.10																		
0.15	5	0																
0.20	6	1	5	1														
0.25	8	2	6	1														
0.30	11	3	8	2	6	1												
0.35	17	5	11	3	7	2	5	1										
0.40	30	12	17	6	10	4	7	2	5	2								
0.45	67	30	29	13	16	7	10	4	6	2								
0.50	268	134	65	32	28	14	15	7	9	4	5	2						
0.55			260	143	62	34	26	14	13	7	7	3						
0.60					247	148	57	34	23	13	11	6	6	3				
0.65							228	148	51	33	20	13	9	5				
0.70									203	142	44	30	16	11	7	4		
0.75											174	130	35	26	11	8		
0.80													138	110	25	20	6	4
0.85															98	83	13	11
0.90																	52	46

Annex 4 Recommended method for determining iodine in urine[1]

Brief description. Urine is digested with chloric acid under mild conditions and iodine determined manually by its catalytic role in the reduction of ceric ammonium sulfate in the presence of arsenious acid. The method described is fast and inexpensive, and the digestion is less harsh than some other methods but is usually adequate. This method emphasizes urinary iodine concentrations in the range of 0-150 μg/l (0-1.19 μmol/l) but can be expanded to cover a wider range of values.

Equipment. Heating block, colorimeter (or simple spectrophotometer), vented fume hood with perchloric acid trap (or the simple substitute apparatus described in the text), thermometer, test tubes (13 mm x 100 mm), reagent flasks and bottles, pipettes and a laboratory balance.

Reagents (analytical grade only)

1. $KClO_3$ (potassium chlorate), dry powder
2. $HClO_4$ (perchloric acid, 70%) comes as 70% liquid solution - do not dilute
3. As_2O_3 (arsenic trioxide), dry powder
4. NaCl (sodium chloride), dry powder
5. H_2SO_4 (sulfuric acid, concentrated - 100%, 36 N, liquid)
6. $Ce(NH_4)_4(SO_4)_4 \bullet 2H_2O$ (ceric ammonium sulfate), dry powder
7. H_2O (deionized water — must be free of iodine and other contaminants)
8. KIO_3 (potassium iodate), dry powder

Solutions

1. Chloric acid solution: In a 2000 ml Erlenmeyer flask dissolve with heating 500 g $KClO_3$ in 910 ml H_2O until solubilized. This may take several hours and does not always dissolve completely into solution. Then add slowly (about 15 ml/minute) 375 ml $HClO_4$ (perchloric acid, 70%) while constantly stirring. This preparation is best carried out in a vented fume hood. Store in a freezer overnight. The next day filter with filter paper (Whatman #1 or similar product), preferably on a Büchner funnel. The volume of filtrate is approximately 850 ml. Store in refrigerator (4°).

[1] The method described is a modified version of that developed by Wawshinek O, Eber O, Petek P, Wakonig P and Guraker A, 1985: *Bestimmung der Harnjodaussheidung mittels einer modifizierten Cer-Arsenitmethode.* Berichte der OGKC 8:13-15. This modified method and additional methods are described in: Dunn JT, Crutchfield HE, Gutekunst R, Dunn AD. Methods for measuring iodine in urine. ICCIDD/UNICEF/WHO, 1993; or in: Dunn JT et al. Two simple methods for measuring iodine in urine. Thyroid, 1993, 3:119-123.

2. 5 N H_2SO_4: Slowly add 139 ml concentrated (36 N) H_2SO_4 to about 700 ml deionized water *[careful - this generates heat!]* and when cool, adjust with deionized water to a final volume of 1 litre.

3. Arsenious acid solution: - In a 2000 ml Erlenmeyer flask, place 20 g As_2O_3 and 50 g NaCl, then slowly add 400 ml 5 N H_2SO_4. Add water to about 1 litre, heat gently to dissolve, cool to room temperature, dilute with water to 2 litres, filter, store in dark bottle away from light at room temperature. The solution is stable for months.

4. Ceric ammonium sulfate solution: Dissolve 48 g ceric ammonium sulfate in 1 litre 3.5 N H_2SO_4 (3.5 N H_2SO_4 is made by slowly adding 97 ml concentrated (36 N) H_2SO_4 to about 800 ml deionized water *[careful - this generates heat!],* and when cool, adjusting with deionized water to final volume of 1 litre). Store in a dark bottle away from light at room temperature. The solution is stable for months.

5. Standard iodine solution, 1 μg iodine/ml (7.9 μmol/l): Dissolve 0.168 mg KIO_3 in deionized water to a final volume of 100 ml. (1.68 mg KIO_3 contains 1.0 mg iodine; KIO_3 is preferred over KI because it is more stable, but KI has been used by some laboratories without apparent problems). It may be more convenient to make a more concentrated solution, e.g. 10 or 100 mg iodine/ml, then dilute to 1 μg/ml. Store in a dark bottle. The solution is stable for months.

Standard curves for each assay can either be prepared fresh each time by appropriate dilutions of the 1 μg/ml solution of KIO_3, or individual stock solutions of the desired iodine concentrations can be made. The following are useful standards: 2, 5, 10, 15 μg/dl.

Procedure. Mix the urine sample to suspend evenly any sediment, then pipette 250 μl of each urine sample into a 13 x 100 mm test tube. Prepare standards from the 1 μg/ml (7.9 μmol/l) iodine solution by taking aliquots of 0, 5, 12.5, 25, or 37.5 μl, then add H_2O to a final volume of 250 μl for each tube. This gives iodine standards corresponding to 0, 2, 5, 10, and 15 μg/dl (0, 0.16, 0.40, 0.79 and 1.19 μmol/l, respectively). Additional standards can be prepared if desired.

Add 750 μl of chloric acid solution to each tube (samples, blank and standards), mix gently, and heat all tubes for 50-60 minutes under a heating block at 110-115°C in a fume hood with a perchloric acid trap. (A fume hood can be made using an inverted glass funnel suspended just above all the tubes in the heating block and attached through a water trap to an aspirator suction.) The exact time and temperature are not critical as long as all tubes are heated the same way. Usually there will be very little volume change during heating. If the volume has decreased, make to 1.0 ml with deionized water (pre-marked tubes are useful for this). Some samples may become faintly yellow.

Cool the tubes to room temperature, then add 3.5 ml arsenious acid solution to each tube, mix (by inversion or vortex) and let stand for about 15 minutes.

Add 350 μl of ceric ammonium sulfate solution to each tube and quickly mix by vortex or other means. Use a stopwatch or other precise timer to keep a constant interval

between additions to successive tubes, usually 15-30 seconds (20 seconds is recommended as a convenient interval).

Exactly 20 minutes after addition of ceric ammonium sulfate to the first tube, read its absorbency at 405 μM in a colorimeter (or spectrophotometer), and read successive tubes at the same interval as that used for addition of the ceric ammonium sulfate (i.e. 15-30 seconds, or at 20 seconds as recommended above), so that the time between addition of ceric sulfate and reading is exactly the same for each tube (e.g. 20 minutes).

Calculation of results. Construct a standard curve on graph paper by plotting iodine concentration of each standard on the abscissa against its optical density at 405 μM (OD_{405}) on the ordinate .

For each sample, find its optical density on the standard curve and then locate the corresponding iodine concentration on the abscissa. This is the urinary iodine concentration in μg/dl.

NOTES

1. Since the digestion procedure has no specific end point, it is essential to run blanks and standards with each assay to allow for variations in heating, time, etc.

2. The exact temperature, heating time, and cooling time can vary. However, within each assay, the interval between the time of addition of ceric ammonium sulfate and the time of the reading must be the same for all samples, standards, and blanks.

3. In this procedure it is convenient to run 60 tubes per assay of which 10 are standards (duplicates at concentrations of 0, 2, 5, 10 and 15 μg/dl). An experienced technician can easily process 150 or more samples a day.

4. **Perchloric acid fumes can be toxic and the salts generated may be explosive,** particularly if allowed to dry in a ventilation system. The recommended method releases much less perchloric acid than do harsher digestion methods.

5. The volumes and proportions of sample and reagents can be varied to achieve different concentrations or a different curve shape, if conditions warrant it. If different tube sizes are used, corresponding size holes in the heating block are also needed.

6. If necessary, this method could probably be applied without a heating block, using an oil bath or perhaps a sand bath, but this is not recommended. It is essential that all tubes be uniformly heated and that the temperature be constant within the range described above.

7. Test tubes can be reused if they are carefully washed to eliminate any iodine contamination.

SELECTED WHO PUBLICATIONS AND DOCUMENTATION OF RELATED INTEREST

MICRONUTRIENT MALNUTRITION

Global Prevalence of Iodine Deficiency Disorders. Micronutrient Deficiency Information System, Working Paper No. 1. Geneva, World Health Organization, 1993.

Iodine and Health: eliminating iodine deficiency disorders safely through salt iodization. A Statement by the World Health Organization. Document WHO/NUT/94.4.

Global Prevalence of Vitamin A Deficiency. Report of the WHO Micronutrient Deficiency Information System, Working Paper No. 2, Geneva, World Health Organization, 1994.

Indicators for assessing vitamin A deficiency and their application in monitoring and evaluating intervention programmes. Document NUT/94.7.

Sommer A. Vitamin A deficiency and its consequences: a field guide to their detection and control. Third edition. Geneva, World Health Organization, 1995. Sw.fr. 17.- (11.90).

INFANT AND YOUNG CHILD NUTRITION

Protecting, promoting and supporting breast-feeding: the special role of maternity services. A Joint WHO/UNICEF Statement. Geneva, World Health Organization, 1989. Sw.fr. 6.- (4.20).

Breast-feeding: the technical basis and recommendations for action. Document WHO/NUT/MCH/93.1.

Infant feeding: the physiological basis. Akré, J. (ed.) Supplement to Vol. 67 (1989) of the *Bulletin of the World Health Organization*. Geneva, World Health Organization, 1990. Sw.fr. 20.- (14.-).

International Code of Marketing of Breast-milk Substitutes. Geneva, World Health Organization, 1981. Sw.fr. 4.- (2.80).

NUTRITIONAL ASSESSMENT, MONITORING

Measuring change in nutritional status. Guidelines for assessing the nutritional impact of supplementary feeding programmes for vulnerable groups. Geneva, World Health Organization, 1983. Sw.fr. 14.- (9.80).

An evaluation of infant growth. Summary of analyses performed in preparation for the WHO Expert Committee on physical status and the use and interpretation of anthropometry. Document WHO/NUT/94.8.

de Onis, M. et al. The worldwide magnitude of protein-energy malnutrition: an overview from the WHO Global Database on Child Growth. Bulletin of the World Health Organization, 1993, **71**(6): 703-712.

WHO Working Group on Infant Growth. An evaluation of infant growth: the use and interpretation of anthropometry in infants. *Bulletin of the World Health Organization*, 1995, **73**(2): 165-174.

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This document is intended primarily for managers of national programmes for the prevention and control of micronutrient malnutrition. It sets out principles governing the use of surveillance indicators in monitoring the epidemiology of iodine deficiency disorders (IDD) and implementing the recommended intervention – salt iodization – to prevent and control them. It presents guidelines on the characteristics and criteria for selection of clinical and biochemical indicators; age and physiological groups; survey sample size; and a simplified goitre grading system together with principles of ultrasound measurements of thyroid size. Also included are recommendations for determining urinary iodine and interpreting thryroid-related hormone estimations; criteria for determining the severity of endemic IDD; recommended levels of salt iodization appropriate for varying climatic conditions, salt-consumption patterns and available packaging; and procedures for monitoring salt iodine intake. Lastly, indicators are presented for monitoring progress towards achieving the goal of eliminating IDD as a significant public health problem by the year 2000.