4 Indicators of impact

4.1 Overview

Assessment of thyroid size by palpation is the time-honoured method of assessing IDD prevalence. However, because of the lack of sensitivity to acute changes in iodine intake, this method is of limited usefulness in assessing the impact of programmes once salt iodization has commenced. In this case, urinary iodine is the most useful indicator because it is reflective of the current intake of iodine in the diet (*23*).

Since most countries have now started to implement IDD control programmes, urinary iodine rather than thyroid size is emphasized in this manual as the principal indicator of impact. Thyroid size is more useful in baseline assessments of the severity of IDD, and also has a role in the assessment of the long-term impact of control programmes.

The introduction of ultrasonography for the assessment of thyroid size has been a significant development. In areas of mild to moderate IDD, measurement of thyroid volume using ultrasound is preferable to palpation for grading goitre. New international reference values for thyroid volume by ultrasound have recently become available and can be used for goitre screening in the context of IDD monitoring (*24*).

Two other indicators are included in this chapter: thyroid stimulating hormone (TSH), and thyroglobulin (Tg). While TSH levels in neonates are particularly sensitive to iodine deficiency, and although difficulties in interpretation remain, there is a potential future for the use of neonatal TSH in the identification of IDD and their control; although the cost of implementing a TSH screening programme is too high for most developing countries. Measurement of Tg in children is a sensitive indicator of iodine status and improving thyroid function after iodine repletion. A standardized dried blood spot Tg assay has been developed and can be used for assessing and monitoring iodine nutrition in the field (*25*).

4.2 Urinary iodine

Biological features

Most iodine absorbed in the body eventually appears in the urine. Therefore, urinary iodine excretion is a good marker of very recent dietary

iodine intake. In individuals, urinary iodine excretion can vary somewhat from day to day and even within a given day. However, this variation tends to even out among populations.

Studies have convincingly demonstrated that a profile of iodine concentrations in morning or other casual urine specimens (child or adult) provides an adequate assessment of a population's iodine nutrition, provided a sufficient number of specimens are collected. Round the clock urine samples are difficult to obtain and are not necessary.

Relating urinary iodine to creatinine, as has been done in the past, is cumbersome, expensive, and unnecessary. Indeed, urinary iodine/creatinine ratios are unreliable, particularly when protein intake – and consequently creatinine excretion – is low.

Feasibility

Acceptance of this indicator is very high, and casual urine specimens are easy to obtain. Urinary iodine assay methods are not difficult to learn or use, but meticulous attention is required to avoid contamination with iodine at all stages. Special laboratory areas, glassware, and reagents should be set aside solely for this determination.

In general, only small amounts (0.5–1.0 ml) of urine are required, although the exact volume depends on the method. Some urine should also be kept in reserve for replicate testing or for external quality control. Samples are collected in small cups and transferred to tubes, which should be tightly sealed with screw tops. They do not require refrigeration, addition of preservative, or immediate determination in most methods. They can be kept in the laboratory for months or more, preferably in a refrigerator to avoid unpleasant odour.

Evaporation should be avoided, because this process artificially increases the concentration. Samples may safely be frozen and refrozen, but must be completely defrosted before aliquots are taken for analysis.

Many analytical techniques exist, varying from very precise measurement with highly sophisticated instruments, to semi-quantitative 'low tech' methods that can be used in regional, country, or local laboratories. Most methods depend on iodide's role as a catalyst in the reduction of ceric ammonium sulfate (yellow colour) to the cerous form (colourless) in the presence of arsenious acid (the Sandell-Kolthoff reaction). A digestion or other purification step using ammonium persulfate or chloric acid is necessary before carrying out this reaction, to rid the urine of interfering contaminants.

A brief description of some of the methods introduced in this section is presented in the following pages.

Methods with ammonium persulfate (method A)

Small samples of urine (0.25–0.5 ml) are digested with ammonium persulfate at 90–110 °C; arsenious acid and ceric ammonium sulfate are then added. The decrease in yellow colour over a fixed time period is then measured by a spectrophotometer and plotted against a standard curve constructed with known amounts of iodine (*26*). This method requires a heating block and a spectrophotometer, which are both inexpensive instruments. About 100–150 subject samples can be run in a day by one experienced technician. Several versions of this method exist and details of one of these are given in Annex 3.

Methods with chloric acid (method B)

Chloric acid can be substituted for ammonium persulfate in the digestion step, and the colorimetric determination carried out as for method A (*27*). A disadvantage is the safety concern, because the chemical mixture can be explosive if residues dry in ventilating systems. Handling these chemicals in a fume cupboard and using a chloric acid trap when performing sample digestion is strongly recommended (see Annex 3).

Other methods

A modification of method B uses the redox indicator ferroin and a stopwatch instead of a spectrophotometer to measure colour change (*28*). Urine is digested with chloric acid and colour changes in batches of samples measured relative to standards of known iodine content. This places samples in categories (e.g., below 50 µg/l, 50–100 µg/l, 100–200 µg/l, etc.) that can be adjusted to desired levels. This method is currently being adapted to ammonium persulfate digestion.

Another, semi-quantitative method is based on the iodide-catalysed oxidation of 3,3',5,5'-tetramethylbenzidine by peracetic acid/H2O2 to yield coloured products that are recognized on a colour strip indicating three ranges: <100 µg/l, 100–300 µg/l, and > 300 µg/l (*29*). Interfering substances are removed by pre-packed columns with activated charcoal. Analyses must be run within two hours, and the procedure requires the manufacturer's pre-packed columns.

In still another method, samples are digested with ammonium persulfate on microplates enclosed in specially designed sealed cassettes and heated to 110 °C (*30*). Samples are then transferred to another microplate and the ceric ammonium sulfate reduction reaction carried out and read on a microplate reader. Field tests are promising: up to 400 urine samples can be analysed in one day, depending on manufacturers' supplies.

Choice of method

Criteria for assessing urinary iodine methods are reliability, speed, technical demands, complexity of instrumentation, independence from sole-source suppliers, availability of high quality reagents, safety, and cost. The choice among the above and other methods depends on local needs and resources. Large central laboratories processing many samples may prefer 'high-tech' methods, while smaller operations closer to the field may find the simplest methods more practical.

Due to the potential hazards of chloric acid, method A (see Annex 3) using ammonium persulfate is currently recommended. It can adequately replace the chloric acid method, since the main difference is the substitution of ammonium persulfate for chloric acid in the digestion step. Results are comparable.

The other methods described above show promise but are not yet fully tested.

Quality control and reference laboratories

All laboratories should have clearly defined internal quality control procedures in place, and should be opened to external audit. In addition, all laboratories should participate in an external quality control programme in conjunction with a recognized reference laboratory. This is important because unrecognized iodine contamination has been a common occurrence in UI laboratories. An international network of resource laboratories (IRLI[1]) was established to fill this need. It closely collaborates with the Programme for Ensuring the Quality of Iodine Procedures (EQUIP) run by the Centers for Disease Control of the United States of America.[2]

Active efforts are now in progress, both to define performance criteria for laboratories and to develop a global system of reference laboratories. These reference laboratories will provide reliable measurements of urinary iodine, and will conduct technical training and supervision. This initiative is a major priority for ensuring sustainability of iodine sufficiency.

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[1] IRLI Network was jointly established by CDC, WHO, UNICEF, ICCIDD and MI to identify laboratories to serve as effective resources for their regions, thus strengthening the capacity of laboratories throughout the world to accurately measure iodine in urine and salt. The network currently includes 12 laboratories (Australia, Belgium, Bulgaria, Cameroon, China, Guatemala, India, Indonesia, Kazakhstan, Peru, the Russian Federation, South Africa). http://iodinenetwork.net/Resources_Lab.htm

[2] EQUIP uses laboratory quality assurance as a tool for eliminating IDD worldwide. It is a CDC standardization program designed to provide urinary iodine laboratories with an independent assessment of their analytical performance. The program assists laboratories to monitor the degree of variability and bias in their urinary iodine assay. IRLI laboratories are invited to participate in the EQUIP program. http://www.cdc.gov/nceh/globalhealth/projects/labactivites.htm

Performance

Most of the above methods perform reliably, although some of the newer ones need further testing as of this date. With appropriate dilutions, they can be extended upward to examine whatever range is desired. The coefficient of variation is generally under 10% for all methods. Proper training is necessary but not complicated.

Since casual specimens are used, it is desirable to measure a sufficient number from a given population to allow for varying degrees of subject hydration and other biological variations among individuals, as well as to obtain a reasonably narrow confidence interval (see Annex 4). In general, 30 urine determinations from a defined sampling group are sufficient.

Interpretation

Simple modern methods make it feasible to process large numbers of samples at a low cost and to characterize the distribution according to different cut-off points and intervals. The cut-off points proposed for classifying iodine nutrition into different degrees of public health significance are shown in Table 4 and Table 5.

The median value for the sampled population is the most commonly assessed indicator. Urinary iodine values from populations are usually not normally distributed. Therefore, the median rather than the mean should be used as the measure of central tendency. Likewise, percentiles rather than standard deviations should be used as measures of spread. Frequency distribution curves can also be very useful for full interpretation, particularly if there is salt iodine level data available for the same population.

In children and non-pregnant women, median urinary iodine concentrations of between 100 µg/l and 299 µg/l define a population which has no iodine deficiency.[1] In addition, not more than 20% of samples should be below 50 µg/l. In non-pregnant, non-lactating women, a urinary iodine concentration of 100 µg/l corresponds roughly to a daily iodine intake of about 150 µg under steady-state conditions.

During pregnancy, median urinary iodine concentrations of between 150 µg/l and 249 µg/l define a population which has no iodine deficiency (*6*).

Establishing the ideal range of values for urinary iodine is difficult. Historically, schoolchildren were assessed by palpation, establishing a pre-intervention baseline for the prevalence of IDD. This population

[1] By definition, when the median is 100 µg/l, at least 50% of the samples will be lower than 100 µg/l.

Table 4 Epidemiological criteria for assessing iodine nutrition based on median urinary iodine concentrations of school-age children (≥6 years)[a]

MEDIAN URINARY IODINE (µg/l)	IODINE INTAKE	IODINE STATUS
< 20	Insufficient	Severe iodine deficiency
20–49	Insufficient	Moderate iodine deficiency
50–99	Insufficient	Mild iodine deficiency
100–199	Adequate	Adequate iodine nutrition
200–299	Above requirements	Likely to provide adequate intake for pregnant/lactating women, but may pose a slight risk of more than adequate intake in the overall population
≥300	Excessive	Risk of adverse health consequences (iodine-induced hyperthyroidism, autoimmune thyroid diseases)

[a] Applies to adults, but not to pregnant and lactating women.

Table 5 Epidemiological criteria for assessing iodine nutrition based on the median or range in urinary iodine concentrations of pregnant women[a]

POPULATION GROUP	MEDIAN URINARY IODINE CONCENTRATION (µg/l)	IODINE INTAKE
Pregnant women	< 150	Insufficient
	150–249	Adequate
	250–499	Above requirements
	≥ 500	Excessive[b]

[a] For lactating women and children <2 years of age a median urinary iodine concentration of 100 µg/l can be used to define adequate iodine intake, but no other categories of iodine intake are defined. Although lactating women have the same requirement as pregnant women, the median urinary iodine is lower because iodine is excreted in breast milk (*6*).

[b] The term "excessive" means in excess of the amount required to prevent and control iodine deficiency.

was also sampled for urinary iodine, thus establishing a normal range. This normal range has been extrapolated to the full population. It may be more logical to sample women of reproductive age, or adolescent girls – thus providing more information on populations that may include those with or on the verge of greater need. The upper limit of the recommended range for these populations reflects concern about the risk of hyperthyroidism when high levels are introduced to a previously endemic population.

Recent data have suggested that the normal range for pregnant and lactating women should reflect their additional need and the risk that these needs may not be met if population levels are too low. However, this leaves a relatively narrow range for a median UI level that will both meet the needs for pregnant/lactating women, and not be excessive for

the remainder of the population. This guide provides the best current estimates for the optimal values to meet the overall population needs.

Urinary iodine concentration is currently the most practical biochemical marker for iodine nutrition when carried out with appropriate technology and sampling. This approach assesses iodine nutrition only at the time of measurement, whereas thyroid size reflects iodine nutrition over months or years. Therefore, even though populations may have attained iodine sufficiency on the basis of median urinary iodine concentration, goitre may persist, even in children.

With rapid global progress in correcting iodine deficiency, examples of iodine excess are being recognized, particularly when salt iodization is excessive and poorly monitored (*20*). Tolerance to high doses of iodine is quite variable, and many individuals ingest amounts of several milligrams or more per day without apparent problems. The major epidemiological consequence of iodine excess is iodine-induced hyperthyroidism (IIH) (*24*,*31*). This occurs more commonly in older subjects with preexisting nodular goitres, and may occur even when iodine intake is within the normal range.

Iodine intakes above 300 μg/l per day should generally be discouraged, particularly in areas where iodine deficiency has previously existed. In these situations, more individuals may be vulnerable to adverse health consequences, including iodine-induced hyperthyroidism and autoimmune thyroid diseases.

In populations characterized by long-standing iodine deficiency and a rapid increase in iodine intake, median value(s) for urinary iodine above 200 μg/l (and in pregnant women, above 250 μg/l) are not recommended because of the possible risk of iodine-induced hyperthyroidism. This adverse condition can occur during the 5 to 10 years following the introduction of iodized salt (*24*,*31*). Beyond this period of time, median values up to 300 μg/l have not demonstrated side-effects, at least not in populations with adequately iodized salt. In schoolchildren, urinary iodine concentrations >500 μg/l are associated with increasing thyroid volume, which reflects the adverse effects of chronic iodine excess (*32*).

4.3 Thyroid size

The traditional method for determining thyroid size is inspection and palpation. Ultrasonography provides a more precise and objective method.

Both methods are described below. Issues common to palpation and ultrasound are not repeated in the section on ultrasound.

4.3.1 Thyroid size by palpation

The size of the thyroid gland changes inversely in response to alterations in iodine intake, with a lag interval that varies from a few months to several years, depending on many factors. These include the severity and duration of iodine deficiency, the type and effectiveness of iodine supplementation, age, sex, and possible additional goitrogenic factors.

The term "goitre" refers to a thyroid gland that is enlarged. The statement that "a thyroid gland each of whose lobes have a volume greater than the terminal phalanges of the thumb of the person examined will be considered goitrous" is empiric, but has been used in most epidemiological studies of endemic goitre and is still recommended (see Table 6).

Feasibility

Palpation of the thyroid is particularly useful in assessing goitre prevalence before the introduction of any intervention to control IDD, but much less so in determining impact. Costs are associated with mounting a survey, which is relatively easy to conduct, and training of personnel. These costs will vary depending upon the availability of health care personnel, accessibility of the population, and sample size. Feasibility and performance vary according to target groups, as follows:

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

School-age children (6–12 years): This is the preferred group, as it is usually easily accessible. However, the highest prevalence of goitre occurs during puberty and childbearing age. Some studies have focused on children 8 to 10 years of age.

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.

If the proportion of children attending school is low, schoolchildren may not be representative (Annex 4). In these cases, spot surveys should be conducted among those who attend school and those who do not, to ascertain if there is any significant difference between the two.

Alternatively, children can be surveyed in households. For further discussion, see Chapter 5 on survey methods.

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. Often they are relatively accessible given their participation in antenatal clinics. Women of childbearing age – 15 to 44 years – may be surveyed in households.

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 high.

Technique

The subject to be examined stands in front of the examiner, who looks carefully at the neck for any sign of visible thyroid enlargement. The subject is then asked to look up and thereby to fully extend the neck. This pushes the thyroid forward and makes any enlargement more obvious.

Finally, the examiner palpates the thyroid by gently sliding their own thumb along the side of the trachea (wind-pipe) between the cricoid cartilage and the top of the sternum. Both sides of the trachea are checked. The size and consistency of the thyroid gland are carefully noted.

If necessary, the subject is asked to swallow (e.g. some water) when being examined – the thyroid moves up on swallowing. The size of each lobe of the thyroid is compared to the size of the tip (terminal phalanx) of the thumb of the subject being examined.[1] Goitre is graded according to the classification presented in Table 6.

Table 6 Simplified classification of goitre[a] by palpation

Grade 0	No palpable or visible goitre
Grade 1	A goitre that is palpable but not visible when the neck is in the normal position (i.e., the thyroid is not visibly enlarged) Thyroid nodules in a thyroid which is otherwise not enlarged fall into this category
Grade 2	A swelling in the neck that is clearly visible when the neck is in a normal position and is consistent with an enlarged thyroid when the neck is palpated

[a] A thyroid gland will be considered goitrous when each lateral lobe has a volume greater than the terminal phalanx of the thumbs of the subject being examined.

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 high.

Interpretation

Table 7 gives the epidemiological criteria for establishing IDD severity, based on goitre prevalence in school-age children. The terms mild, moderate, and severe are relative and should be interpreted in context with information from other indicators.

[1] Another method is to stand behind the subject with the neck in the neutral position and hold the fingers (not thumb) over the area of the gland. The person is asked to swallow and the gland is palpated by the fingers as it glides up. This is repeated on each side of the neck.

It is recommended that a total goitre rate or TGR (number with goitres of grades 1 and 2 divided by total examined) of 5% or more in school-children 6 to 12 years of age be used to signal the presence of a public health problem. This recommendation is based on the observation that in normal, iodine-replete populations, the prevalence of goitre should be quite low. The cut-off point of 5% allows both for some margin of error of goitre assessment, and for goitre that may occur in iodine-replete populations due to other causes such as goitrogens and autoimmune thyroid diseases.

Table 7 Epidemiological criteria for assessing the severity of IDD based on the prevalence of goitre in school-age children[a]

	DEGREES OF IDD, EXPRESSED AS PERCENTAGE OF THE TOTAL OF THE NUMBER OF CHILDREN SURVEYED			
Total goitre rate (TGR)	None	Mild	Moderate	Severe
	0.0–4.9%	5.0–19.9%	20.0–29.9%	≥ 30%

[a] Goitre prevalence responds slowly to changes in iodine intake.

Finally, in this context it is emphasized that thyroid size in the community may not return to normal for months or years after correction of iodine deficiency.

4.3.2 Thyroid size by ultrasonography

In areas of mild to moderate IDD, the sensitivity and specificity of palpation are poor and measurement of thyroid size using ultrasound is preferable. Ultrasonography is a safe, non-invasive, specialized technique that can be quickly done (2–3 minutes per subject) and is feasible even in remote areas using portable equipment. Ultrasonography provides a more precise measurement of thyroid volume 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. The technical aspects of thyroid ultrasonography are reported in Annex 2.

Feasibility

Portable (weight 12–15 kg) ultrasound equipment with a 7.5 MHz transducer currently costs about US $15 000. A source of electricity is needed, and the operator needs to be specially trained in the technique. Differences in technique (e.g. the pressure applied with the transducer) and estimation of thyroid anatomy (e.g. inclusion of the thyroid isthmus and/or capsule thickness) can result in high interobserver variability.

Interpretation

Results of ultrasonography from a study population should be compared with reference data (*33*). Reference values for thyroid volume measured by ultrasonography in schoolchildren of iodine-sufficient populations are shown in Table 8. These are presented as a function of age, sex, and body surface area (BSA) in order to take into account the differences in body development among children of the same age in different countries. This approach is potentially useful in countries with a high prevalence of child growth retardation due to malnutrition with both stunting (low height-for-age) and underweight (low weight-for-age).

An advantage of the thyroid volume-for-BSA is that the age of the child is not required, which in some populations is not known with certainty. A limitation of the thyroid volume-for-BSA is that it requires the collection of weights and heights: in severely malnourished populations of schoolchildren, 10% or more may have a BSA below the lowest BSA cut-off of 0.7.

The thyroid volume references proposed here are applicable for goitre screening only if thyroid volume is determined by the standardized method described in Annex 2.

Table 8 Gender-specific 97th percentile (P97) of thyroid volume (ml) by age and body surface area (BSA) measured by ultrasound in iodine-sufficient 6–12 yr-old children[a]

	BOYS	GIRLS		BOYS	GIRLS
AGE (yrs)	P97	P97	BSA (m^2)	P97	P97
6	2.91	2.84	0.7	2.62	2.56
7	3.29	3.26	0.8	2.95	2.91
8	3.71	3.76	0.9	3.32	3.32
9	4.19	4.32	1.0	3.73	3.79
10	4.73	4.98	1.1	4.2	4.32
11	5.34	5.73	1.2	4.73	4.92
12	6.03	6.59	1.3	5.32	5.61
	1.4	5.98	6.40		
	1.5	6.73	7.29		
	1.6	7.57	8.32		

[a] MB Zimmermann, 2004 (*33*).

4.4 Blood constituents

Two blood constituents, TSH and Tg, can serve as surveillance indicators. In a population survey, blood spots on filter paper or serum samples can be used to measure TSH and/or Tg.

Determining serum concentrations of the thyroid hormones, thyroxin (T4) and triiodothyronine (T3), is usually not recommended for monitoring iodine nutrition, because these tests are more cumbersome, more expensive, and less sensitive indicators.

In iodine deficiency, the serum T4 is typically lower and the serum T3 higher than in normal populations. However, the overlap is large enough to make these tests impractical for ordinary epidemiological purposes.

4.4.1 Thyroid stimulating hormone (TSH)

Biological features

The pituitary secretes TSH in response to circulating levels of T4. Serum TSH rises when serum T4 concentrations are low, and falls when they are high. Iodine deficiency lowers circulating T4 and raises the serum TSH, so iodine-deficient populations generally have higher serum TSH concentrations than do iodine-sufficient groups.

However, the difference is not great and much overlap occurs between individual TSH values. Therefore, the blood TSH concentration in school-age children and adults is not a practical marker for iodine deficiency, and its routine use in school-based surveys is not recommended.

In contrast, TSH in neonates is a valuable indicator for iodine deficiency. The neonatal thyroid has a low iodine content compared to that of the adult, and hence iodine turnover is much higher. This high turnover, which is exaggerated in iodine deficiency, requires increased stimulation by TSH. Hence, TSH levels are increased in iodine-deficient populations for the first few weeks of life – this phenomenon is called transient hyperthyrotopinemia (*25*).

The prevalence of neonates with elevated TSH levels is therefore a valuable indicator of the severity of iodine deficiency in a given population. It has the additional advantage of highlighting the fact that iodine deficiency directly affects the developing brain.

In iodine-sufficient populations, about one in 4000 neonates has congenital hypothyroidism, usually because of thyroid dysplasia. Prompt correction with thyroid hormone is essential to avoid permanent mental retardation.

Thyroid hormone affects proper development of the central nervous system, particularly its myelination; a process that is very active in the perinatal period. To detect congenital hypothyroidism and initiate rapid treatment, most developed countries conduct universal screening of neonates with bloodspot TSH taken on filter papers, or occasionally with blood spot T4 followed by TSH.

While screening in developed countries is directed at detecting

neonates with TSH elevations which are 20 mIU/l whole blood or higher, the availability of TSH assays sensitive to 5 mlU/l permits detection of mild elevations above normal. This permits detection of transient hyperthyrotopinemia. To be broadly applicable in a population, the screening must be universal, and not omit children born in remote or impoverished areas. For countries and regions that already have a system of universal neonatal screening with a sensitive TSH assay in place, the data can be examined and transient iodine deficiency recognized, usually without further surveying.

Feasibility

Serum TSH is widely used in the field of thyroidology as a sensitive marker for both hypothyroidism and hyperthyroidism. Methods for determining TSH concentrations, from either dried whole blood spots on filter paper or from serum, are well established and widely available. Typically, a few drops of whole blood are collected on filter paper from the cord or by prick of the heel or other site.

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.

Some experimental data suggest normal values for cord blood are higher than those for heel prick blood. Blood spots, once dried, are stable. They can be stored in a plastic bag and transported even through normal postal systems and are usually stable for up to six weeks.

It must be emphasized that the primary purpose of screening programmes is to detect congenital hypothyroidism, and its use as an indicator of iodine nutrition will be a spin-off. Hence, the only additional cost will be for data analysis. It is not recommended that a neonatal screening programme be set up solely to assess community iodine deficiency. Less expensive means for obtaining this information exist.

TSH screening is inappropriate for developing countries where health budgets are low. In such countries, mortality among children under five is high due to nutritional deficiencies and infectious diseases, and screening programmes for congenital hypothyroidism are not cost effective.

Performance

A variety of kits for measuring TSH are available commercially in developed countries. Most have been carefully standardized, and perform adequately. Assays that utilize monoclonal antibodies, which can detect

TSH as low as 5 mIU/l in whole blood spots, are more useful for recognizing iodine deficiency.

Interpretation

Permanent sporadic congenital hypothyroidism, with extremely elevated neonatal TSH, occurs in approximately one of 4000 births in iodine-sufficient countries. Other than infrequent cases of goitrogen exposure, iodine deficiency is the only significant factor to increase this incidence.

The increase in the number of neonates with moderately elevated TSH concentrations (above 5 mlU/l whole blood) is proportional to the degree of iodine deficiency during pregnancy. It may be higher than 40% in severe endemic areas. When a sensitive TSH assay is used on samples collected three to four days after birth, a <3% frequency of TSH values >5 mlU/l indicates iodine sufficiency in a population (*34*).

Interpretation is complicated when antiseptics containing beta-iodine, such as povidone iodine (Betadine™), are used for cleaning the perineum prior to delivery or even the umbilical area of the baby. Beta-iodine increases TSH levels in the neonate in both cord blood and heel prick specimens.

4.4.2 Thyroglobulin (Tg)

Biological features

Tg is a thyroid protein that is a precursor in the synthesis of thyroid hormone, and small amounts of Tg can be detected in the blood of all healthy individuals. The thyroid hyperplasia and goitre characteristic of iodine deficiency increases serum Tg levels, and, in this setting, serum Tg reflects iodine nutrition over a period of months or years. This contrasts to urinary iodine concentration, which assesses more immediate iodine intake. A serum Tg assay has recently been adapted for use on dried whole blood spots (DBS) (*35*,*36*). The assay makes sampling practical even in remote areas. Measurement of DBS Tg in school-age children is a sensitive indicator of iodine status in a population and can be used to monitor improving thyroid function after iodine repletion.

Interpretation

Standard reference material for the DBS Tg assay is now available from WHO. It is stable when stored for up to one year at temperatures ≤ -20 °C. An international reference range for DBS Tg has been established in iodine-sufficient five to 14 year-old children that can be used for monitoring iodine nutrition. The DBS Tg reference interval for iodine-sufficient school-age children is 4–40 μg/l.

Performance

DBS Tg correlates well with urinary iodine and thyroid size (*35*,*36*), the other recommended indicators for monitoring iodine status in populations. It complements these tests, and can be used in conjunction with urinary iodine to measure recent iodine intake, and thyroid volume to assess long-term anatomic response.

Feasibility

The method is simple and robust. A drop of whole blood from a finger stick (or a venipuncture sample) is spotted directly onto good-quality filter paper.[1] The spots are allowed to dry at room temperature (≈20 °C), and then stored in sealed low-density polyethylene bags; preferably refrigerated at 4 °C, but they also can be stored for several weeks at cool, dry room temperatures, before analysis.

[1] An example of the type of paper that can be used is Grade 903 Filter Paper produced by Schleicher & Schuell; Einbeck, Germany.

Table 9 Indicators of impact at population level: summary

MONITORING INDICATOR (UNITS)	AGE GROUP FOR ASSESSMENT	ADVANTAGES	DISADVANTAGES
Median urinary iodine concentration (µg/l)	School-age children and pregnant women	– Spot urine specimens are easy to obtain – The most practical biochemical marker for iodine nutrition, when carried out with appropriate technology and sampling – Feasible to process large numbers of samples at low cost – Cut-off points proposed for classifying iodine nutrition into different degrees of public health significance are well established – External quality control program in place	– Assesses iodine intake only over the past few days – Meticulous laboratory practice is required to avoid contamination with iodine – A sufficiently large number of samples must be collected to allow for varying degrees of subject hydration and other biological variations among individuals – Not valuable for individual assessment
Goitre rate assessed by palpation (%)	School-age children	– Simple and rapid screening test – Requires no specialized equipment	– Specificity and sensitivity of palpation are low in grades 0 and 1 due to a high inter-observer variation – Responds slowly to changes in iodine intake
Goitre rate assessed by ultrasound (%)	School-age children	– A more precise measurement of thyroid volume compared with palpation – Safe, non-invasive – International reference values for thyroid volume in schoolchildren are available as a function of age, sex, and body surface area	– Expensive equipment and a source of electricity is needed – operator needs to be specially trained in the technique – Responds slowly to changes in iodine intake
TSH (mIU/l)	Newborns	– Measures thyroid function at a vulnerable age when iodine deficiency directly affects the developing brain – If screening programs to detect congenital hypothyroidism is in place then only additional cost will be for data analysis – Collection by heel stick and storage on filter paper is simple – Blood spots can be stored for several weeks at cool, dry room temperatures	– Not recommended to be set up solely to assess community iodine deficiency due to expense – Cannot be used when antiseptics containing iodine are used during delivery – Requires use of a standardized, sensitive assay – Should be taken either from the cord at delivery or by heel prick at least 48 hours after birth to avoid physiological newborn surge
Tg (µg/l)	School-age children	– Collection by finger stick and storage on filter paper is simple – Can be stored for several weeks at cool, dry room temperatures, so sampling practical even in remote areas – Measures improving thyroid function within several months after iodine repletion – Standard reference material is now available, but needs to be validated – An international reference range has been established	– Expensive immunoassay – Requires laboratory infrastructure