Controlling Iodine Deficiency Disorders

Studies for Program Management in Sub-Saharan Africa

BY

STEFAN PETERSON
ABSTRACT


Studies were performed to improve iodine deficiency control programs. Goitre rates and cassava processing practices were compared in three Central African Republic (CAR) populations. Short-cuts in cassava processing were associated with elevated urinary thiocyanate and increased goitre rates, suggesting a goitrogenic effect in one population. While improved cassava processing may be beneficial, the priority is to correct the iodine deficiency.

The use of the urinary iodine/thiocyanate ratio as indicator of goitrogenic effects was explored using data from Tanzania and CAR. As the ratio can be calculated in four mathematically different ways and has physiological shortcomings, its use is discouraged.

Biannual iodised oil capsule (IOC) distribution in a Tanzanian population of 7 million during nine years was studied. Mean distribution coverage was 64%, mean delay of subsequent distribution 1.25 years, and only 43% of targeted person-time was covered. The cost of capsules constituted more than 90% of total program costs. It is cost-effective to invest more funds in communication, support of peripheral staff and supervision.

In a highland Tanzanian village, salt iodine content was highly variable compared to national standards. While school-children had adequate urinary iodine, women at delivery and newborns showed signs of inadequate iodine status. Salt iodine concentrations should be monitored during production and distribution down to household level, and iodine status assessed in all vulnerable groups before adjusting recommended salt iodization levels at production.

WHO's 1994 change in palpation goitre definition considerably lowered specificity and increased measured goitre rates by 25% in Tanzanian school-children compared to the previous system. Ultrasound estimation of thyroid volume under rugged field conditions requires considerable human and material resources yet had a precision only slightly better than palpation. In resource poor settings appropriately trained palpators using the 1960 WHO definition of goitre remain optimal for estimating thyroid size until precision and cost of ultrasound has improved.

Monitoring of process indicators needs to be an ongoing priority activity, separate from periodic evaluations of impact.

Key words: Iodine deficiency, iodized oil, cassava, thiocyanate, iodized salt, cost-effectiveness, epidemiology, monitoring.

Stefan Peterson, Dept of Women's and Children's Health, Section for International Maternal and Child Health, Uppsala University, SE-751 85 Uppsala, Sweden, and the Dept of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden

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“Iodine deficiency is so easy to prevent that it is a crime to let a single child be born mentally handicapped for that reason.”

Labouisse, UNICEF

“We were striving for the best, but it turned out as usual.”

Victor Chernomyrdin, Former Prime Minister of Russia

This study is dedicated to the millions of people still affected by IDD and the people working to reduce these disorders
PAPERS INCLUDED IN THE THESIS

This thesis is based on the following papers, which will be referred to by their Roman numerals:


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ABBREVIATIONS

CAR Central African Republic
ICCIDD International Council for the Control of Iodine Deficiency Disorders
ID Iodine deficiency
IDD Iodine deficiency disorders
IIH Iodine induced hyperthyroidism
I/SCN Iodine / Thiocyanate ratio
IOC Iodized oil capsule
I-salt Iodized salt
MIS Management information system
NCCIDD National Council for the Control of Iodine Deficiency Disorders
NFCC National Food Control Commission
PHC Primary Health Care
PPM Parts per million, corresponds to a concentration of 1 mg per kg
SCN Thiocyanate
T3 Triiodothyronine
T4 Thyroxine
TBG Thyroxine-binding globulin
TFNC Tanzania Food and Nutrition Centre
Tg Thyroglobulin
TRH Thyrotropin-releasing hormone
TSH Thyroid stimulating hormone
UNICEF United Nations Children’s Fund
USD United States dollar
WHO World Health Organization

Iodine terminology:

<table>
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<th>Term</th>
<th>Definition</th>
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<tr>
<td>Iodize</td>
<td>To add iodine, iodide or iodate to e.g. salt</td>
</tr>
<tr>
<td>Iodine</td>
<td>The elemental atom form of iodine</td>
</tr>
<tr>
<td>Iodide</td>
<td>Ion form of iodine, added as potassium iodide (KI)</td>
</tr>
<tr>
<td>Iodate</td>
<td>Oxidized ion form of iodine, added as potassium iodate (KIO₃)</td>
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INTRODUCTION

Iodine Deficiency Disorders (IDD) are a range of health problems and goiter is the visible "marker condition" for more severe disorders. IDD control program activity has increased since the World Health Assembly’s endorsement of the objective of eliminating IDD by the year 2000 (WHO 1992) and the World Development Report’s conclusion that iodine supplementation is one of the interventions "...that would have the highest cost-effectiveness of any health intervention available in the world today" (World Bank 1993). Iodine supplementation programs have started in 90 out of 94 IDD affected developing countries (UNICEF 1995). Several interventions with proven high efficacy are being used. Iodized salt is the main method to combat IDD for long-term control and iodized oil capsules (IOC) a complementary method in areas where iodization of salt for different reasons cannot be implemented or fails to succeed.

Intensive implementation activities have revealed the limited knowledge of how to translate efficacious interventions into effective programs with relevant mechanisms for program monitoring, quality assurance, and impact evaluation. This thesis reports studies of the iodine supplementation program in Tanzania – one of the most developed control programs in Africa – and the early stage of the program in the Central African Republic with goitrogens as a policy issue. Collaborating institutions are the Tanzania Food and Nutrition Center (TFNC) and the Ministère de Santé Publique, Service de Lutte contre les Grandes Éndemies, Central African Republic.

Iodine Physiology

Iodine is essential for normal growth, development, and functioning of the body. Since only minute amounts are required each day, it is known as a micronutrient. Iodine is required for synthesis of the thyroid hormones, thyroxine (T4) and triiodothyronine (T3), which are necessary for the regulation of body metabolism (Hetzel 1989).
The recommended daily iodine intake is 50 µg for infants (<12 months), 90 µg for children up to the age of 6 years, 120 µg for children 7-12 years old, 150 µg for adolescents and adults, and 200 µg for pregnant and lactating women (WHO 1996). The adult human body contains 20-50 mg of iodine, of which 70-80% are stored in the thyroid gland, a remarkable concentration (Hetzel 1989).

In stable iodine intake situations, the amount of iodine excreted in the urine correlates well with the iodine intake and serves as an estimate of iodine intake. Less than 10% of human iodine losses are excreted in the faeces (Choufoer et al. 1963), sweat (Mao et al. 1990), and milk (Vermiglio et al. 1992).

The stomach and the upper small intestine rapidly absorb iodine as either one of two chemical forms: iodide or iodate. Iodate is reduced to iodide, which is transported in the blood to the thyroid gland, where an active transport mechanism pumps it into the thyroid cell. About 60 µg of iodine needs to be trapped per day to maintain an adequate thyroxin level; the efficiency of the trapping mechanism is regulated with the help of TSH depending on the availability of iodine and the gland’s activity. In the gland, iodide is oxidized to iodine, which is bound to tyrosine to form mono- and diiodotyrosine. These are coupled to form triiodothyronine (T3) and thyroxin (T4) in the thyroid epithelial cells. Thyroxin is then stored in colloid follicles bound to thyroglobulin. When needed, the thyroid stimulating hormone (TSH) will stimulate the proteolysis of thyroglobulin in the thyroid cells to release thyroxin into the bloodstream (Hetzel 1989; Passmore & Eastwood 1986).

A feedback system regulates iodine metabolism by using the hypothalamic hormone and the thyrotropin-releasing hormone (TRH), which modulates the secretion of TSH from the hypothalamus. The level of thyroxine (T4) in the blood regulates metabolism. Decreasing T4 levels lead to increasing TSH levels, which serve to increase thyroid iodine uptake as well as the production and release of more T4 and triiodothyronine (T3) into the bloodstream. At high TSH levels the thyroid will preferentially produce the biologically more active T3. Conversely, as thyroid hormone levels rise, TSH secretion falls. Sustained high TSH levels stimulate an increase in the size and number of follicular cells, an increase in vascularization, and
consequently thyroid hypertrophy which leads to better iodine capture. At some stage of hypertrophy the thyroid is regarded a “goitre”. In addition, persistent stimulation may also cause the formation of thyroid nodules (Hetzel 1989).

Thyroid hormones regulate the metabolism of target organs by entering the cells of the peripheral tissues and binding to the nuclear chromatin via a thyroid hormone receptor protein, which in turn affects transcription (Baniahmad et al. 1992). T3 is much more potent than T4. Thyroxin is therefore generally transformed to T3 prior to biological action with the help of the selenium containing enzyme 5′deiodinase (Kohrle 1999). This could explain links between iodine and selenium deficiency (Anonymous 1993; Thilly et al. 1991; Untoro et al. 1999). A recent paper suggests that concurrent iron deficiency anaemia impairs the therapeutic response to iodine supplementation, possibly mediated via decreased T4 to T3 conversion or through decreased thyroxiperidase activity impairing iodide organification (Zimmerman et al. 2000).

**Iodine Deficiency Disorders**

Iodine was originally present in all soils. However, rainfall, glaciation, exposure to wind and floods has leached the soils of iodine, especially in mountainous areas and in flood plains. Although some iodine is returned to the soil by rain, this is insufficient and soils remain iodine deficient (Hetzel & Pandav 1996). Foods and animals grown on such soils will be iodine-deficient. The only rich source of iodine is seafood. If seafood is eaten one to two times per week it provides sufficient iodine intake (Passmore & Eastwood 1986). Iodine-containing animal feeds and antiseptics commonly used in the dairy industry result in iodine rich milk which is an important source of iodine in many countries (Phillips 1997). However, food alone is generally not sufficient to give an adequate iodine intake.

The body’s first reaction to low iodine intake is to increase the uptake efficiency up to four times the normal rate in order to maintain the output of thyroxine. This is evidenced by a reduction in urinary iodine concentrations. If this adaptation is
insufficient, then serum TSH will rise and T4 will fall. The preferential production of the more potent T3 over T4 increases the efficiency of the use of the available iodine. Only when these compensatory mechanisms are exhausted will hypothyroidism occur as thyroxine levels fall below acceptable levels (Hetzel 1989).

The term iodine deficiency disorders (IDD) covers a wide spectrum of clinical conditions (Hetzel 1983). Some disorders are the result of compensation mechanisms, such as thyroid enlargement, goiter. Early abortions, stillbirths, increased perinatal and infant mortality, and mental and growth retardation are some of the other manifestations of iodine deficiency (Lamberg 1991). Some disorders are associated with permanent brain damage that occurs during the first two trimesters of pregnancy (Cao et al. 1994a; Hetzel & Mano 1989; Pharoah & Connolly 1987). The resulting clinical condition, cretinism, is irreversible and it is the most severe and dramatic manifestation of IDD. However, IDD also include a range of more subtle brain damages (Stanbury 1994). Iodine supplementation has been shown to increase iodine deficient children’s intelligence quotient considerably, indicating the suppressive effect of continued iodine deficiency (Bleichrodt & Born 1994). Global estimates of the number of subjects affected by some of the IDD conditions are given in Table 1, (UNICEF 1994b; WHO 1999).

Table 1. Global burden of Iodine Deficiency Disorders.

<table>
<thead>
<tr>
<th>Total population at risk</th>
<th>2.200 million</th>
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<td>Subjects with goiter</td>
<td>740 million</td>
</tr>
<tr>
<td>Subjects with lowered mental ability</td>
<td>300 million</td>
</tr>
<tr>
<td>Cretinism</td>
<td>5.7 million</td>
</tr>
</tbody>
</table>

The effects of iodine deficiency on the foetus and neonate also include increased perinatal and infant mortality (Cobra et al. 1997; DeLong et al. 1997; Hetzel 1989; Pharoah et al. 1976). A sign of iodine deficiency in this period is neonatal hypothyroidism. The incidence rate in iodine deficient areas may
reach up to 1/10, compared to 1/4000 in non-iodine deficient areas (Ermans et al. 1980a; Kochupillai 1992; Kochupillai & Pandav 1987). Even transient hypothyroidism in the neonatal period has been shown to lead to permanent detrimental effects on a child’s intelligence (Calaciura et al. 1995).

During a child’s school-age years, iodine deficiency is an impediment to proper brain functioning, estimated to be 13.5 intelligence quotient points (Bleichrodt & Born 1994). However, the most obvious sign of IDD in this period is thyroid enlargement, goiter. Goiter prevalence rates of 85% and higher have been found in severely iodine deficient areas (Clugston et al. 1987; Eltom et al. 1984). As a sign of hypothyroidism, TSH levels are elevated in large portions of the school aged group (Moreno-Reyes et al. 1993). In adults widespread goiter, hypothyroidism, and reproductive failures contribute to significant human suffering and economic underdevelopment (Hetzel 1989; Hetzel & Pandav 1996).

All the effects of iodine deficiency, encompassed by the concept of IDD, are preventable by increasing the intake of iodine (Burgi et al. 1990). This not only reduces human suffering, but it also brings considerable benefits in terms of improved human and economic development (Li & Wang 1987) and reductions in medical care costs (Gutekunst 1993).

**Goitrogens**

While Iodine Deficiency Disorders (IDD) are primarily caused by insufficient dietary intake of iodine, other substances referred to as goitrogens have been suggested to interfere with the proper functioning of thyroid hormone synthesis and utilization. Many substances have been proposed as potential goitrogens of public health importance but it has been difficult to confirm or reject these hypotheses or to estimate the importance of a goitrogenic effect in any one population.

The pseudo-halide ion thiocyanate (SCN⁻) interferes with the thyroid gland’s uptake and metabolism of iodine through competitive inhibition (Gaitan 1990; Thilly 1992). SCN is formed in the body from glycosides in cabbage, or when cyanide from tobacco smoking or from cyanogenic substances in insufficiently processed cassava is detoxified to SCN during metabolism.
Cassava, a staple for 500 million people, contains naturally occurring cyanogenic glycosides. To avoid cyanide exposure from consumption of roots from bitter cassava varieties, effective processing methods were developed thousands of years ago (Rosling 1988). In Africa, the main steps in the most common processing methods are soaking the root in water (O’Brien et al. 1992), fermenting the grated pulp of the root in sacks, or prolonged drying of the root in the sun (Hahn 1989; Mlingi et al. 1992). Cell disintegration during processing brings an endogenous enzyme in contact with cyanogenic glycosides that break down into cyanohydrins which rapidly yield volatile hydrogen cyanide at pH levels above 6 (Cooke & Maduagwu 1978). However, insufficiently processed bitter roots may contain considerable amounts of cyanogenic glycosides and cyanohydrins that after ingestion may break down and result in significant cyanide exposure (Casadei et al. 1990; Mlingi et al. 1992; O’Brien et al. 1992; Tylleskär 1994; Tylleskär et al. 1992). In the human body most of the cyanide will be enzymatically converted to thiocyanate, which at physiological levels is slowly excreted in the urine. The implication of thiocyanate in IDD has led to calls to reduce cassava consumption (Biassoni et al. 1991; Biassoni et al. 1990a; Biassoni et al. 1990b; Biassoni et al. 1998). Yet, other observations suggest that with adequate iodine intake overt hypothyroidism or goiter will not develop in the presence of high thiocyanate loads (Cliff et al. 1986b; Delange et al. 1994).

The urinary I/SCN ratio (calculated as µg/mg) of a population sample has been recommended as an indicator of the combined effect on the thyroid of low iodine intake and high thiocyanate exposure. Endemic goiter has been found to occur in cassava-eating populations in Zaire when the mean ratio is less than 3, and cretinism has been found to occur when the mean ratio is less than 2 (Hennart et al. 1982). However, this ratio has not been validated with stronger study designs, nor have the programmatic implications for IDD control programs of elevated thiocyanate loads been drawn beyond the drastic proposal to replace cassava as a staple crop.

Another foodstuff for which goitrogenic effects have been postulated is millet (Anonymous 1983; Elnour et al. 1998; Moreno-Reyes et al. 1993). The goitrogenic effects of millet
cannot be overcome by increased intake of iodine (Gaitan & Dunn 1992). High mineral content and bacterial contamination of water may also be goitrogenic. Prolonged boiling inactivates this effect (El Mahdi et al. 1986; Gaitan 1990). An association has also been found between malnutrition and development of goitre which may indicate an enhancement of the effect of goitrogens (Gaitan 1990).

**Analysing urinary thiocyanate**

To assess the possible goitrogenic effects of thiocyanate (SCN) casual urine samples collected for iodine concentration analysis are typically analyzed also for their thiocyanate concentrations. For this procedure a conservant (10% thymol in isopropanol) is added and refrigeration is recommended. Larger urine volumes are also necessary, as another 0.5 ml are needed for the analysis (Lundquist et al. 1979). Thiocyanate values in Swedish non-cassava eating non-smokers is around 40 µmol/l (0.23 mg/dl) (Lundquist et al. 1979) and SCN values of 52 µmol/l (0.3 mg/dl) were found in a Brussels population (Lagasse et al. 1982). Unit conversions scales with indicators of levels of abnormality are given in Figure 1.
Figure 1. Unit conversion scales for Iodine (I) and Thiocyanate (SCN) concentrations in urine with indications of different levels of abnormality.
Iodine Status Indicators

Thyroid size

The size of the thyroid gland in a school-aged child reflects the severity of iodine deficiency the child has experienced in the previous years. The goiter rate in school-aged children has therefore been the most frequently used indicator to assess the degree of iodine-deficiency in a population (Delange et al. 1997; WHO 1994a). School-aged children also reflect a new cohort’s exposure to iodine deficiency in the last few years. Schoolchildren aged 6-12 are often used to approximate the goiter rate in their entire age group. While a school-based survey excludes children suffering from many of the severe complications of IDD such as cretinism and deafness, the goiter rate is deemed representative as long as school attendance in the community is more than 50% (WHO 1994a).

When using the goitre rate to decide whether a population is to be considered iodine deficient or not the decision depends on:

1. the cut-off size at which the thyroid is considered to be a goiter,
2. the precision of thyroid size estimates around that cut-off, and
3. the prevalence of goiter in school-aged children at which iodine deficiency disorders (IDD) are considered a public health problem.

Over the years several definitions of goiter have been used and the acceptable prevalence has changed. In 1960, WHO defined a goiter as “a thyroid gland whose lateral lobes have a volume greater than the terminal phalanxes of the thumbs of the person examined” (Delange et al. 1986; DeMaeyer et al. 1979; Perez et al. 1960). This allowed for a thyroid to be palpable, yet not to be considered a goiter. It was not clear whether it was the combined thyroid volume of both thyroid lobes that had to be larger than the combined volume of both thumbs, or whether it was sufficient that one thyroid lobe was larger than that side’s thumb. Iodine deficiency was defined as a public health problem when more than 10% of school children had goiter (Delange et al. 1986; Hetzel 1988; Perez et al. 1960; Querido et al. 1974).
In 1994 WHO simplified goiter grading by reducing the number of goiter grades from four to two. However, the definition of goiter was simultaneously changed to “an enlarged thyroid that is palpable but not visible”. Although it may not have been a conscious decision the 1994 definition effectively caused all palpable thyroids to be regarded as goiters, see Table 2. In addition, the goiter rate at which IDD is considered a public health problem was lowered from 10% to 5% (WHO 1994a).

Table 2. Simplified classification of goiter according to WHO 1994a.

<table>
<thead>
<tr>
<th>Grade 0:</th>
<th>No palpable or visible goitre.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1:</td>
<td>A mass in the neck that is consistent with an enlarged thyroid that is <em>palpable but not visible</em> 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.</td>
</tr>
<tr>
<td>Grade 2:</td>
<td>A swelling in the neck that is <em>visible when the neck is in a normal position</em> and is consistent with an enlarged thyroid when the neck is palpated</td>
</tr>
</tbody>
</table>

The two WHO classification systems and the effect of the revised definition of goiter are illustrated in Table 3. It is obvious that the new goiter criterion entails a lowering of the threshold at which an individual thyroid is considered a goiter. Furthermore, at the population level the lowering of the acceptable goiter rate to 5% will label new populations as “iodine deficient.” No comparative study on the effect of these changes nor on the precision obtained in goiter surveys using WHO’s 1960 and 1994 criteria for goiter diagnosis was found in the literature.
Table 3. WHO thyroid size classification systems of 1960 with 1986 amendments (Delange et al. 1986; Perez et al. 1960) and the 1994 system (WHO 1994a). Shaded areas indicate the thyroid sizes diagnosed as “goiter” with each system.

<table>
<thead>
<tr>
<th>Criteria for thyroid size estimation</th>
<th>Goiter grades</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WHO1960</td>
<td>WHO1994</td>
<td></td>
</tr>
<tr>
<td>Not palpable</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Palpable lobes ≤ terminal phalanxes of subject’s thumbs</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Palpable lobes &gt; terminal phalanxes of subject’s thumbs</td>
<td>1A</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Visible with neck extended</td>
<td>1B</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Visible with head in normal position</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Visible at a distance</td>
<td>3</td>
<td>2</td>
<td></td>
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</tbody>
</table>

The severity of iodine deficiency is judged by the Total Goiter Rate, which is calculated as the number of children with goiters divided by the total number of children examined. Table 4 gives the benchmarks for grading iodine deficiency. Although goiter rates can also be calculated for Visible Goiter (VGR: children with grade 2 / No of children examined) or, in the old classification, for goiter visible with the neck extended (VGR1B: 1B+2+3 / No of children examined) (Mutamba 1993), these indices have found less widespread use in IDD program management.

Table 4. Epidemiological criteria for assessing the severity of iodine deficiency disorders (IDD) based on the prevalence of goiter in school-age children according to WHO’s 1994 criteria (WHO 1994a).

<table>
<thead>
<tr>
<th>Total Goitre Rate (TGR)</th>
<th>Mild IDD</th>
<th>Moderate IDD</th>
<th>Severe IDD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.0 - 19.9%</td>
<td>20.0 – 29.9%</td>
<td>≥30.0%</td>
</tr>
</tbody>
</table>
The intra-observer (MacLennan et al. 1969) and inter-observer (Tonglet et al. 1994) variation of goiter classification by palpation has been studied and found to be substantial. Some interpretations of this has led to calls to discard palpation in favor of the more costly ultrasound estimation of thyroid volume (Gutekunst et al. 1986; Vitti et al. 1994; WHO 1994a; WHO & ICCIDD 1997). Others have argued that the variations observed reflect random misclassification and have little or no effect at the population level, thus allowing continued reliance on palpation, (Anonymous 1994). The justification given by WHO for the change from palpation to ultrasound is a personal communication by Dr R Gutekunst (WHO 1994a). However, the presented supporting data do not allow determination of the concordance between ultrasound and palpation, nor are they based on the subsequently recommended thyroid volume cut-off values (WHO & ICCIDD 1997).

Studies on the precision of ultrasound estimation of thyroid volume are generally conducted on only a few subjects, and report intra and inter-measurer errors of 2-13% from not clearly deducible statistical procedures (Foo et al. 1999; Özgen et al. 1999; Vitti et al. 1994). The measurement errors reported from ultrasound estimation of thyroid volume are considerably lower than errors for determining the volume of other organs such as the kidney, where the standard deviation of the difference between repeated measurements divided by the mean volume ranges from 14-17% (Emamian et al. 1995). This suggests that different statistical techniques may have been used in the calculation of the errors.

**Urinary iodine**

Most of the iodine absorbed is excreted in the urine making urinary iodine content a good marker of current iodine status. Although 24-hour urine collection accurately determines the amount of iodine excreted, measuring urinary iodine concentrations in casual morning urine samples yields an adequate assessment of whether a population is iodine deficient if at least 40-50 individuals are sampled (Dunn & van der Haar 1990). In a school where 300 children may be examined for goiter, a systematic sub-sample can be sampled for urine; that is,
every 6\textsuperscript{th} child provides a urine sample. To more accurately measure a population’s iodine status in an area a total sample of 200-300 samples is desirable. Collection of casual urine samples is widely practiced because the sampling is acceptable to the research subjects, the volume required for most analysis methods is small (1 ml), the iodine content remains stable, and the samples do not require refrigeration (Benmiloud \textit{et al.} 1994; Dunn & van der Haar 1990; WHO 1994a). An obvious weakness of using casual urine samples is the error introduced from variations in urinary volumes between individual subjects and between different populations.

Using a ratio of urinary iodine and creatinine to compensate for the lack of 24 hour urine collection has been found unnecessary and potentially misleading, especially for individuals who consume very little protein (Dunn \textit{et al.} 1993; Dunn & van der Haar 1990; Furnée \textit{et al.} 1994; WHO 1994a).

Historically iodine concentrations are given as $\mu$g/liter instead of $\mu$mol/liter ($100 \, \mu$g/l = 0.79 $\mu$mol/l), see Figure 1. The analytic procedure that examines iodine concentrations was established by Sandell and Kolthoff in 1937 (Sandell & Kolthoff 1937). The main methods used are still based on the reduction of ceric ammonium sulphate using arsenic containing acids and timed readings in a colorimeter (Dunn \textit{et al.} 1993; May \textit{et al.} 1997). Simpler manual methods for urinary iodine analysis are relatively inexpensive at USD 0.50 - 1.00 per sample (WHO 1994a). However, great care must be taken to avoid contamination with iodine, which is found in household items such as hair shampoo. The method requires special rooms, glassware, reagents, and quality control procedures in reference laboratories (Dunn \textit{et al.} 1993). While there have been attempts to develop analytical methods based on other reactions (Rendl \textit{et al.} 1998), these have so far not been validated in the iodine deficiency concentration range. Because a rapid field test is not yet available, transportation of samples to the laboratory and waiting for the results is necessary.

The severity of iodine deficiency is determined using median urinary iodine concentration values, see Table 5. Recently a suggestion has been made to define the severity of IDD using also the proportion of iodine concentrations below certain cut-off values, and not just from the median value (Karmarkar &
Pandav 1999). This would allow for the identification of situations where a subgroup of the population remains iodine deficient even though the median iodine concentration is sufficient. “Elimination” of iodine deficiency is defined as achieving a median urinary iodine concentration above 100 µg/l with no more than 20% of the specimens registering below 50 µg/l. Assuming a design effect of 3 due to cluster sampling, a sample size of 750 is required to achieve a confidence interval of ∀5% at a prevalence rate of 20% (WHO 1994a).

Table 5. Epidemiological criteria for assessing the severity of iodine deficiency disorders (IDD) based on median urinary iodine levels (WHO 1994a).

<table>
<thead>
<tr>
<th>Median value (µg/l)</th>
<th>Severity of IDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>Severe</td>
</tr>
<tr>
<td>20 – 49</td>
<td>Moderate</td>
</tr>
<tr>
<td>50 – 99</td>
<td>Mild</td>
</tr>
<tr>
<td>≥ 100</td>
<td>No deficiency</td>
</tr>
</tbody>
</table>

**Hormones**

**Thyroid stimulating hormone**

Increasing TSH levels is a compensation mechanism for iodine deficiency. At population level the TSH levels thus indicate iodine deficiency and hypothyroidism. However, use of TSH levels as an indicator beyond the neonatal period has been discouraged because of inconsistent relationships between population TSH levels and iodine status (WHO 1994b).

TSH levels in the foetus and the newborn are of special concern since elevated TSH levels signal insufficient levels of the thyroid hormone. This could cause abnormal brain development (WHO 1994b). In gestational week 11 TSH is first detected in fetal blood. TSH rises sharply at birth up to its maximum at 24 hours after birth and then it falls gradually back over the first 3-4 days as the infant’s T4 levels rise (Thorpe-Beeston et al. 1991). Therefore, it is recommended to sample neonates either from cord blood at birth or only after 72 hours, and then by heel prick (WHO 1994b). TSH levels in neonates can be used to identify congenital hypothyroidism in relatively iodine sufficient environments. Screening all newborns for TSH will identify the
approximately 1 per 4000 neonates (0.275%) that suffer from this condition in populations with adequate iodine intake. This procedure is usually done by blotting whole blood on filter paper, drying it, and sending the sample to a reference laboratory. Children with high TSH levels are then subjected to further testing to confirm their deficiency and if necessary thyroid hormone medication is prescribed (Burrow 1980; Dunn & van der Haar 1990). In countries with universal screening such as Italy an incidence exceeding 1:2000 has been suggested as an indication of mild iodine deficiency (Sorcini et al. 1995).

Measurement of the distribution of TSH levels in a sample of newborns can give a picture of the iodine status in the population (Kochupillai & Pandav 1987; Wächter et al. 1985; WHO 1994a). Table 6 gives the benchmarks for judging the severity of the IDD public health problem based on neonatal hypothyroidism.

Table 6. Epidemiological criteria for assessing the severity of iodine deficiency disorders (IDD) based on prevalence of neonatal hypothyroidism (WHO 1994a).

<table>
<thead>
<tr>
<th>TSH &gt; 5mU/l whole blood in neonates</th>
<th>Mild IDD</th>
<th>Moderate IDD</th>
<th>Severe IDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0-19.9%</td>
<td>20.0-39.9%</td>
<td>40%</td>
<td></td>
</tr>
</tbody>
</table>

**Thyroxine**

Thyroxine (T4) is the primary output of the thyroid gland. Thyroxin is de-iodinated in the peripheral cells to T3 which is thought to be the active hormone (Hetzel 1988). In severe iodine deficiency the T4 levels may decrease, but de-iodination under the influence of increased levels of TSH maintains adequate levels of T3 (Kochupillai et al. 1973). The total T4 level depends on the amount of carrier proteins in the blood. It is therefore preferred to measure the levels of thyroxin that is unbound in the serum, so called free T4. T4 can be used to characterize a finding of an abnormal TSH value in a patient (Todd 1998). However, the use of T4 is not considered as a suitable indicator for population level assessments of iodine deficiency (Benmiloud et al. 1994; WHO 1994a).
Thyroglobulin
Thyroglobulin (Tg) is the storage form of iodine and it is a thyroid hormone precursor. Tg is a glycoprotein found in the follicular colloid of the thyroid gland. Normally small amounts of thyroglobulin leave the follicular cell. Tg is released into the blood when there is an increased turnover of thyroid cells such as in goiter (Todd 1998). Tg is more sensitive than TSH as a measure of iodine status, because Tg changes earlier during iodine deficiency and normalizes sooner during iodine supplementation. Together with thyroid volume Tg has been recommended as a marker of iodine status that is more sensitive than TSH or T4 (Benmiloud et al. 1994; Eltom et al. 2000a; Eltom et al. 2000b).

Iodine supplementation
Although iodine deficiency started appearing as a theory on the cause of goiter as early as the 19th century, many other causative theories persisted into the 20th century. In France, Courtois isolated iodine in 1813 and in 1820 Coindet suggested that iodine could treat goiter. Early attempts to use iodine in this way often produced hyperthyroid effects; its use was therefore not widely adopted. In 1825, Bossingault found that salt used in Guaca, Colombia contained iodine. In 1833, he suggested that iodized salt could prevent goiter. Controlled experiments in France produced Iodine Induced Hyperthyroidism (IIH) which again prevented widespread iodine supplementation (Hetzel 1989). In 1915, the use of sodium iodide tablets in Swiss school children was successful; this led to the introduction of iodized salt in Switzerland in 1922 (Hetzel & Pandav 1996). Marine and Kimball carried out large scale controlled supplementation trials in the United States from 1916 to 1920 that more conclusively demonstrated both the curative and preventive aspects of iodine supplementation. This led up to the community scale use of iodized salt in Michigan in 1924 (Hetzel 1989; Marine & Kimball 1922). In Sweden a pioneering national survey of goiter and cretinism preceded the adoption of salt iodization on a national scale (Höjer 1931). Other pioneer efforts demonstrated that cretinism is caused by iodine deficiency and that supplementation with iodized oil can prevent new cases.
In several countries tremendous social and economic gains have resulted from the control of IDD. In China iodine supplementation led to increased educational achievement, productivity, and quality of life (Li & Wang 1987). A meta-analysis of iodine supplementation trials in areas of mild to moderate deficiency concluded that iodine supplementation raised the intelligence quotient by 13.5 points (Bleichrodt & Born 1994). A 100-year follow up in Switzerland of an initial survey demonstrated the disappearance of cretinism and endemic goiter, as well as reductions in isolated deafness, mental deficiency, and short stature, making iodine supplementation a highly cost-effective intervention for the country (Burgi et al. 1990). Similarly, the World Bank concluded that iodine supplementation is one of the interventions "that would have the highest cost-effectiveness of any health intervention available in the world today" (World Bank 1993). The World Health Assembly endorsed the objective of eliminating IDD by the year 2000 (WHO 1992).

There is overwhelming evidence and resolve to prevent IDD by increasing iodine intake in populations at large. Attempting to reduce IDD through changes in diet is often not practical since most foodstuffs, with the exception of seafood, are poor sources of iodine (Passmore & Eastwood 1986). However, use of iodine-containing animal feeds and disinfectants in the dairy industry have made milk products an important source of iodine in some places (Phillips 1997). The approach generally used to increase the iodine intake countries is either through medicinal supplements or through fortification of widely used foodstuffs such as salt.

**Iodized oil**

Iodized oil was first used as a contrast medium in radiology and later found, in Papua New Guinea, to be an effective control of IDD when injected (McCullagh 1963). Subsequently, it was shown that iodized oil can also be given orally (Eltom 1984). Many countries have since used large amounts of iodized oil in control programs. Outside of China the supply is dominated by...
Laboratoire Guerbet, Paris, France. Their Lipiodol Ultra-Fluid is a x-ray contrast medium conventionally used in radiology; e.g., for lymphography. It is a clear yellow poppyseed-oil based substance containing 480 mg iodine/ml. It is available in 10 ml ampoules for intra-muscular injection as well as in 200 mg capsules and as Oriodol in oral pump-dispensers.

Iodized oil capsules cost about 14 US cents per 200 mg of iodine and the pump-dispensed Oriodol about 4 cents per 200 mg (Hetzel & Pandav 1996). This price is rather substantial compared to e.g. Vitamin A capsules at 2-3 cents each. Subsequently developed cheaper iodised oils have not found their way into the market (Inglenbleek et al. 1997), nor has, to my knowledge, any other producer bid against Guerbet in a tendering process. The Chinese formulation is based on walnut or soybean oil. This formulation has not been formally evaluated for e.g. efficacy, safety and cost against other supplements such as Lipiodol.

**Intra-muscular administration**

In the highland villages of Papua New Guinea, it was demonstrated that a single injection of 2400 mg of iodized oil can maintain normal thyroid function for 3 to 5 years (Buttfield & Hetzel 1967; McCullagh 1963). The long lasting effect is explained by the slow release of the large iodine load from the muscle and its storage in fat tissue. Subsequently, the dose was lowered to 1 ml (480 mg) giving an equally long protective period (Dunn & van der Haar 1990) and large scale injection programs have been implemented in countries such as Papua New Guinea, Nepal, and Democratic Republic of Congo (Zaire). In addition, these injections were reported to be safe for pregnant women (Delange 1996; Pharoah & Connolly 1991). However, the high cost, logistical difficulties, and risks of transmission of diseases such as HIV and hepatitis have switched attention to oral administration of iodized oil.

**Oral administration**

Taking iodised oil orally eliminates many of the disadvantages of injections. There is no risk of transmitting infectious agents via syringes, it requires less skilled staff, and it takes less time. However, since there is no intra-muscular store of iodized oil,
most is excreted within the first few days and the duration of the effect is shorter. An initial study recommended 400 mg every two years (Eltom et al. 1985). In 1987, a review recommended 1 ml (480 mg) for one year’s duration (Dunn 1987b) and in 1990 this was extended to 1-2 years (Dunn & van der Haar 1990). Subsequent prophylactic studies have recommended 240 mg of iodine for a 6-month coverage or 480 mg for 12 months (Benmiloud et al. 1994); a study in Zaire found that 47 mg and 118 mg was sufficient for up to one year (Tonglet et al. 1992). A study in the Sudan found that 200 mg was sufficient to control iodine deficiency in goitrous adults for a 12 month period (Elnagar et al. 1995). Presumably these discrepancies could be explained by different underlying severity of the iodine deficiency, different sampling or evaluation methodologies, influences on iodine absorption/utilization by goitrogens, helminths (Furnée 1994), or iron status (Zimmerman et al. 2000).

It seems clear, however, that the physiologically effective duration of supplementation lasts closer to one year than to two years. This conclusion is an important programmatic disadvantage.

The drawbacks of iodized oil supplementation include the need to make direct contact with every targeted person at the appropriate distribution interval. Intermittent bolus doses are less physiologically effective than a constant dietary supply of iodine, and that, although less than for injections, widespread distribution poses significant logistical challenges. On the positive side, oral iodized oil can be accurately targeted to population groups and individuals. A campaign can also be initiated quickly in a severely iodine deficient area while other control methods are being prepared. Oral iodized oil will thus be targeted for areas with severe to moderate IDD where adequate coverage with iodized salt is unlikely to be achieved in the near future. Depending on the feasibility of introducing iodized salt in an area, oral iodized oil may have to be considered as a medium term control measure when iodine deficiency is severe enough to warrant an intervention (Dunn 1996b).

The target groups for supplementation are, in order of importance: 1) women of childbearing age; 2) children 0-5 years; 3) older children; 4) adult men 15-45 years of age (Dunn 1987b). In people older than 45 years of age, iodized oil is not encouraged
due to increased risks of hyperthyroidism. The same applies to persons with nodular goiter; however, a reduced dose of iodized oil could be considered. A recent review concluded that in areas where iodine deficiency is moderate or severe, iodized oil should also be given during pregnancy (Delange 1996).

The cost of providing iodized oil varies according to the distribution dose, interval, and delivery strategy adopted. The total annual cost of an oil supplementation program has been estimated at USD 0.50 per person and per year (Jamison et al. 1993). However, in spite of the control efforts undertaken using oral iodized oil in several countries, the literature contains no account of the real distribution costs, nor of the actual distribution coverage achieved, and timeliness of repeat distributions.

**Iodized salt**

The first large-scale iodine supplementation programs in the United States and Switzerland used iodized salt. Subsequently other countries in Europe started similar programs. Salt has many advantages. It may be the only foodstuff imported by subsistence agriculture communities. It is consumed in similar amounts by all - even the socioeconomic level of a household has very little influence on its consumption of salt. Furthermore, iodization does not alter the taste or color. In most settings, this makes salt an “ideal” vehicle to deliver a micronutrient like iodine to all individuals in relatively similar daily doses, without even having to contact them individually. An added advantage is that livestock consume salt, benefiting themselves and the consumers of animal products (Mannar 1996).

**Iodizing the salt**

The first countries to embark on salt fortification used potassium iodide (KI). This has been the approach replicated by most countries in temperate climates. However, in tropical humid conditions the evaporation of iodide is substantial. In such settings potassium iodate, KIO₃, provides a less soluble, more stable alternative. Iodate also performs better in salt with impurities. Strictly speaking this is “iodated” salt but it is often referred to as “iodized” as well (Dunn & van der Haar 1990; Hetzel 1989).
In many settings salt production is fairly centralized to a few centers using techniques such as mining, evaporation of salt water or underground brine. This makes it potentially feasible to introduce and control the use of large-scale iodization technology for dry mixing, drip feeding, or spraying the salt with iodine. Thorough mixing of salt is necessary using drum mixers or screw conveyors. The iodization machines most used in sub-Saharan Africa are made in the Indian subcontinent and generally quite simple and rugged. The cost of salt iodization is usually around USD 0.02-0.10 per person per year. However, expressed as a percentage of the retail price of salt, it amounts to about 5% of the total cost of the product (range 2-32%) (Mannar 1996; World Bank 1993).

Iodization levels in salt depend on the average daily salt consumption, the severity of iodine deficiency, and expected iodine evaporation losses during transport, storage, and cooking. Humans usually consume between 5 to 20 grams of salt daily and need a daily iodine intake of 100-200 micrograms. In a warm, moist climate where salt is packaged in large sacks, the recommended iodization levels for the factory were therefore set at 50-100 mg of iodine per kilo of salt, often expressed as part per million (ppm), see Table 7 (WHO 1994a).

Table 7. Salt iodization levels in parts per million recommended at different stages of the distribution chain by WHO in 1994.

<table>
<thead>
<tr>
<th>Daily salt consumption</th>
<th>Factory outside the country</th>
<th>Factory inside the country</th>
<th>Retail level</th>
<th>House hold</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bulk</td>
<td>Small pack</td>
<td>Bulk</td>
<td>Small pack</td>
</tr>
<tr>
<td>5 gr.</td>
<td>100</td>
<td>80</td>
<td>90</td>
<td>70</td>
</tr>
<tr>
<td>10 gr.</td>
<td>50</td>
<td>40</td>
<td>45</td>
<td>35</td>
</tr>
</tbody>
</table>

Iodine induced hyperthyroidism (IIH) was observed in Zimbabwe (Todd et al. 1995) where salt was distributed in small plastic consumer packs minimizing iodine losses. IIH was also reported from Zaire (Bourdoux et al. 1996). This resulted in the recommendation that iodization at the production level should be reduced to 20-40 ppm (Clugston et al. 1996; WHO 1996).
Legislation, quality control, and monitoring
Salt iodization raises the cost of large-scale salt production by about 5%. This may create a situation where both iodized and non-iodized salt can be sold at different prices, alternatively non-iodized salt could falsely be sold as iodized with a larger profit margin. This necessitates legislation requiring universal salt iodization. Moreover, enforcement measures need to be in place to prevent cost competition or fraudulent declarations concerning iodization of salt. In addition it is recommended to increase the popular demand for iodized salt (Dunn & van der Haar 1990).

Quality control of the salt iodization production process is necessary to ensure adherence to the recommended iodization levels. Although government quality control inspections are an essential part of the quality control system, the main responsibility for quality control is left to the producers. Sampling procedures for such quality control have been suggested based on the relatively accurate standard titration method of assessing salt iodine content with intermittent tests using rapid test-kits (Sullivan et al. 1995; WHO 1994a).

In addition, the salt iodine levels need to be monitored along the distribution chain: at point of importation (where applicable), in wholesale warehouses, in retail stores, and in households. One objective of such monitoring is to identify, impound, and discard non-iodized salt. Such activities require a titration assessment of iodine content. Other objectives of iodine content monitoring is to verify assumptions regarding iodine losses due to the effectiveness of packaging materials, storage methods, and retail conditions and develop ways to prevent such losses as well as to study household salt storage. In addition, if rapid test kits are used, peripheral monitoring can serve as a way to educate the public about salt iodization. These kits use the starch-iodine color reaction to detect the presence of either iodide or iodate in a relatively crude way. Where more accurate determination of iodine content is needed, e.g. to quantify losses or as a basis for taking legal action, titration should be used (Dustin & Ecoffey 1978; Sullivan et al. 1995; WHO 1994a).

Quality control and monitoring responsibilities need to be clearly defined. Monitoring criteria for judging the adequacy of the process have been proposed, Table 8. Sampling procedures have

Table 8. Criteria for assessing adequacy of salt iodization programs, their quality control and monitoring (WHO 1994a)

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

* Corrective action systematically taken within 3 hours in 90% of cases using Lot Quality Assurance Methodology
** Monitoring undertaken in 90% of districts in each province at both household and district levels

Limitations
While salt iodization appears to be the main candidate for iodine fortification there are several potential challenges related to getting the iodine onto salt, making iodine stay on salt, ensuring the use of iodized salt, and knowing whether these things occur.

At the iodization stage, challenges include installing iodization machinery, finding a reliable supply mechanism for potassium iodate, and ensuring that production machinery is used and maintained in an effective and consistent manner. This requires a significant initial investment in equipment and training as well as a commitment to continuous external monitoring and quality control. A special difficulty arises in situations where salt originates from many small-scale
Stefan Peterson

producers. Indonesia is one example and Tanzania with its estimated 197 salt producers another (DailyNews 1994). It is even more difficult to monitor quality in the salt produced by an estimated 7,500 women who extract salt from salty soils using evaporation processes in certain rural areas of Tanzania. (ICCIDD 1997b; Momburi 1993). Although small-scale producers only produce about 10% of the total world production (UNICEF 1994a), artisanal salt production is of large importance in geographic areas of severe iodine deficiency. As any one producer is too small to sustain an iodation machine organizing salt iodation viably is difficult. UNICEF has suggested alternative strategies to deal with this situation: organizing small producers into cooperatives that share an iodization machine; sending a mobile salt iodization machine periodically; providing each producer with small scale iodization equipment; and establishing commercial iodization refineries that purchase and iodise the salt from the small producers (UNICEF 1994a). The relative cost of iodizing salt in these ways is likely to be higher than in a large scale operation since more transport and handling of the salt is required. Monitoring salt iodization among small-scale producers is also a logistic challenge.

In countries where the prevailing salt type is crude or coarse salt that has not been crushed and homogenised the large, often impure, salt crystals pose technical challenges to iodization. Iodizing wet salt from salt pans adds further technical complexity.

The difficulties caused by iodine evaporation require adequate wholesale packaging, storage, retail packaging and display mechanisms. Large packaging used for bulk storage and transportation should be lined with polyethylene and consumer packaging should preferably be in sealed plastic bags (Mannar & Dunn 1995). However, often any type of second hand bag is used to pack salt. The salt may not be dry, which allows the iodine to migrate to the bottom of 50 and 100 kg sacks causing iodine levels to be unevenly distributed. Storage may expose the bags to humidity or heat which accelerates iodine loss (Chauhan et al. 1992). At the retail level, it is customary in many places to pour salt out in small heaps left uncovered in the sun causing losses of iodine up to 42% (Kapil et al. 1996). Finally, household storage of the iodized salt may be inadequate and practices such as
washing the salt can further decrease the iodine content before cooking, which results in as much as a 30% iodine loss (WHO 1994a).

Public acceptance and demand for iodized salt is considered a necessary prerequisite of a successful iodization program. This can only be achieved through a massive education effort involving decision makers, salt producers, salt retailers, health workers, citizen groups, and the general public (Dunn 1996a; Dunn & van der Haar 1990). In Germany and other European countries, consumer groups often oppose iodine fortification programs advocating the consumer’s right to choose between iodized and non-iodized products. Similar arguments have been raised in India. In other countries, lack of demand for iodized salt may maintain a market for non-iodized salt, or make the population prefer the cheaper non-iodized salt where both types are available.

Several examples from South Asia and Latin America demonstrate the need for effective monitoring and enforcement mechanisms to achieve and sustain good coverage with adequately iodized salt; (Murdoch et al. 1999; Hetzel 1989; Passmore & Eastwood 1986). Often salt legislation is not enforced. Monitoring and enforcement mechanisms need to be in place at each stage of production and distribution. This will involve several Government agencies and necessitates the setting up of monitoring mechanisms, titration laboratories, and a steady supply of rapid test kits (Dunn 1996a; Sullivan et al. 1995; WHO 1994a).

The combined effect of these difficulties often leads to delays, sometimes for decades, in achieving an effective salt iodization program. Spain is such an example of the long delay in implementing a salt iodization program (Fernandez 1990). Even in the best case it will take a number of years to establish a program. However, even after a successful program has been established there may still be populations without effective access or utilisation of iodised salt, e.g. because of non-iodating small salt producers or local production of salt from salt lakes or “foothill salt” (Momburi 1993). Therefore countries may need to consider complementary supplementation methods where salt iodization is not likely to succeed (Solomons 1998).
Iodization of water, sugar, and other vehicles

Iodized water
Since water has to be consumed daily, it is another vehicle for iodine supplementation. In 1923, the city of Rochester, in New York state, was the first municipality to add iodine to its drinking water. Since then, cities in Thailand, Malaysia, and Sicily have added iodine to their central drinking water. These experiences were largely successful in correcting iodine deficiency and also served to disinfect the water supply provided chemical iodine is used, not iodide or iodate. In Northern Thailand drops of iodine solution are added to school water supplies with good results but requiring constant supervision. However, in many settings drinking water comes from many sources making effective iodization difficult to achieve (Dunn 1987a; Dunn 1996b).

In semi-arid settings people often drink from one or from very few water sources. A system using slow release iodine in silicone matrices has been developed and used in Mali and in the Central African Republic (Fisch et al. 1993; Pichard et al. 1992; Yazipo et al. 1995a; Yazipo et al. 1995b). This method of iodization in hand-pump wells increases water iodine, urinary iodine, and reduces goiter rates. A study from the Sudan confirmed these findings but demonstrated limitations in the effectiveness of the system in traditional wells (Elnagar et al. 1997). The matrices cost around USD 100 each. They need to be changed every year and the per capita cost will depend on how many people draw their drinking water from the same well. Small villages are more expensive to supplement per capita.

In a semi-arid area of Xinjiang, China, iodine absorbed by the crops from iodized irrigation water found its way through the food chain and into people. This method not only normalized iodine deficiency but also reduced infant mortality at an estimated cost of USD 0.05 per capita per year (Cao et al. 1994b; DeLong et al. 1997; DeLong 1998).

Iodized Sugar and Bread
In the Sudan, sugar is a food that is consumed by a large number of people and it is subsidized and rationed. A pilot trial to fortify sugar with iodine was successful in increasing urinary iodine concentrations, in reducing goiter rates, and in improving
thyroid hormone status. Sugar, therefore, is another way to introduce iodine into a population (Eltom et al. 1995).

Iodized bread has been used successfully in Holland, Russia, Australia, and Tasmania but the variations in bread consumption and the unavailability of bread in remote rural areas limit the practicality of this method (Clements et al. 1970; Gandz 1974; Gerasimov et al. 1995). Iodized tea has been suggested as a means of food fortification in Tibet.

Direct supplementation
Direct supplementation can also be done using iodide tablets or solutions. Some of the early supplementation research was done using sodium iodide tablets (Gibson & Backman 1924 cited in Sjöberg & Sundlöf 1971). This supplementation method was used in the Soviet Union and sodium iodide tablets continue to be used in Germany. Iodine solutions such as Lugol’s (6 mg iodine per drop) have been used successfully in controlling iodine deficiency in Bolivia. Direct supplementation, which requires daily, weekly, or perhaps monthly doses, has limited overall effectiveness since its effectiveness depends on individual and systemic responsibility and motivation (Dunn 1996b; Todd & Dunn 1998).

Excess iodine intake

Food, medication, and supplements are sources of iodine. In general, consumption of iodine that exceeds the recommended dosage by as much as ten times is well tolerated by most people. However, some people respond adversely to levels close to the recommended intake (Todd 1998). A dramatic increase in the plasma iodide load causes the thyroid gland to block iodine organification. This transient phenomenon is known as the Wolff-Chaikoff effect (Wolff et al. 1949). Other manifestations of excess iodine include thyroiditis, goiter, hypothyroidism, hyperthyroidism, and sensitivity reactions.

The phenomenon of most relevance for iodine supplementation programs is iodine-induced-hyperthyroidism (IIH). Symptoms are the usual of thyrotoxicosis: anxiety, palpitations, weight loss, muscle weakness, fatigue, diarrhea, sweating, and hot sensations. More serious cardiac effects such as: atrial fibrillation, angina, and heart failure may also occur. In most cases IIH is caused by toxic nodular goiter (Todd 1998).
Following the introduction of iodine supplementation into a previously iodine-deficient population susceptible individuals may develop IIH. In most cases this occurs in women over the age of 40 with nodular goitre (Todd 1998). The most well-known example of this followed the introduction of iodized bread into Tasmania in the 1960’s (Connolly 1971). Recently, in Zimbabwe (Todd et al. 1995) and Zaire (Bourdoux et al. 1996) iodization of salt resulted in cases of IIH. While the condition in any one patient can be serious and requires immediate medical care, IIH is a temporary and rare phenomenon that can be successfully treated if detected. Typically, IIH occurs during the first few years of an iodization program as a result of the many large goiters caused by the previous iodine deficiency, thus making it an iodine deficiency disorder. For a population the benefits of iodine supplementation on balance far outweigh the risks of increased hyperthyroidism (WHO 1997). While IIH cannot be fully avoided it can be minimized by regulating the iodine supply (Todd 1998). Because of this, recommended salt iodization levels were lowered in 1996 to 20-40 ppm (WHO 1996).

Controlling Iodine Deficiency Disorders

Management structure and strategy

Recognizing that it was technically feasible as well as affordable to control IDD, yet effective control programs were not in place, a group of concerned professionals, mostly IDD researchers with a strong representation of endocrinologists, took the initiative to create the International Council for Control of Iodine Deficiency Disorders (ICCIDD). ICCIDD was officially inaugurated in Kathmandu, Nepal in 1986. It has an international executive committee, six regional IDD coordinators and working groups as well as a multidisciplinary network of members. Based on the 1986 World Health Assembly resolution to prevent and control IDD, the ICCIDD has worked closely with multilateral, bilateral, national, and non-governmental organizations to lay out and implement a global strategy for IDD control. This strategy has been endorsed by the UN System’s coordination subcommittee on nutrition (Hetzel 1987a; Hetzel 1988; Hetzel 1996; WHO 1986).

Success in controlling IDD is a complex process involving
political, social, and economic dimensions. This process has been studied in different countries and a model summarizing required program steps and objectives was proposed and updated to its present form based on experiences in South East Asia (Hetzel 1987a). It was adopted immediately as the guiding model by the International Council for Control of Iodine Deficiency Disorders (ICCIDD), and it has remained fairly constant with only minor changes being made. It comprises the following steps which are to be completed in a cyclical fashion by a multi-sectoral National IDD Control Commission (Hetzel 1988):

1. Assessment (collect data, assess situation)
2. Communication (disseminate findings)
3. Planning (develop or update plan of action)
4. Political decision (achieve political support)
5. Implementation
6. Monitoring and evaluation

The latest published version is presented in Figure 2.

Figure 2. The "Social Wheel" of IDD control (Hetzel 1996)
In the following sections selected technical aspects of the IDD “Social Wheel” control cycle as recommended by ICCIDD, WHO and UNICEF are reviewed (WHO 1994a).

Assessing IDD

Many indicators exist for individual iodine deficiency disorders. The selection of indicators for assessment depends on acceptability, technical feasibility, cost, and the indicator’s measurement performance. It is generally recommended to combine at least two indicators, such as thyroid size and urinary iodine concentration. Commonly used indicators are presented in Table 9 together with criteria for judging the severity of the public health problem (WHO 1994a).


<table>
<thead>
<tr>
<th>Indicator</th>
<th>Target Population</th>
<th>Severity of public health problem (prevalence)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mild</td>
</tr>
<tr>
<td>Goiter grade &gt; 0</td>
<td>SACa</td>
<td>5.0-19.9%</td>
</tr>
<tr>
<td>Thyroid volume &gt;97th Centile by ultrasound b</td>
<td>SAC</td>
<td>5.0-19.9%</td>
</tr>
<tr>
<td>Median urinary iodine level (µg/L)</td>
<td>SAC</td>
<td>50-99</td>
</tr>
<tr>
<td>TSH &gt;5mU/L whole blood</td>
<td>Neonates</td>
<td>3.0-19.9%</td>
</tr>
<tr>
<td>Median Tg (ng/ml serum)c</td>
<td>C/Ad</td>
<td>10.0-19.9</td>
</tr>
</tbody>
</table>

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a SAC = school-age children
b Reference values in (WHO & ICCIDD 1997)
c Different assays may have different normal ranges
d C/A = children and adults
The target groups for assessment also merit discussion. While many of the effects of iodine deficiency manifest themselves in neonates and during early childhood, this age-group is not very accessible. Adult women, especially pregnant women, need adequate iodine status to prevent IDD from developing in their foetus. However, this group may not be very appropriate for some indicators since goiters in women do not necessarily reflect recent iodine status. The most commonly studied group is children in schools. This highly accessible and co-operative group is also vulnerable and their thyroid size will reflect the iodine status in the last few years (Aghini-Lombardi et al. 1997). Inference is then made from this group to the others, such as neonates and pregnant women. However, in situations where school attendance is low the children at school may provide a biased estimate as their peers at home may be worse off (WHO 1994a). The construction of sampling frames for school selection must take into account student geographic origin and stratify for presumed different degrees of iodine deficiency.

Communication

The effects of IDD should be communicated to the public and politicians. Topics to communicate include the effects on growth and development, the effects on the brain, the effects on school performance, the effects on productivity, and the effects on quality of life. Widespread understanding of the scope and cause of IDD should result in support and demand for interventions.

Press coverage is assured during launching ceremonies of legislation, iodation plants and major meetings (Daily News 1994; Kwena 2000). In addition, flyers and posters communicate the impact of IDD and encourage the consumption of iodized salt. “Question and answer” booklets have also been produced in some countries. A few countries have made use of “IDD days” to raise awareness. ICCIDD now stresses the need to improve communication at all levels and has produced a communication guide which will be translated into several languages (ICCIDD 1999a; Ling & Reader-Wilstein ).
Plan of action & Achievement of political will

The ICCIDD regional groups serve to promote national programs by coordinating events, providing technical advice, fundraising, and progress monitoring. With their support ICCIDD recommended managerial structures have been re-created in many countries. Thus multisectoral National Control Commissions for IDD implement the strategy and its components in individual countries.

Using an intersectoral commission a plan of action is drawn. This involves a situation analysis of the salt sector and salt consumption as a basis for introducing salt iodization. Recommended groupings such as a salt producers’ association are then formed. In addition, salt producers’ co-operatives are formed to organize small salt producers.

In situations where iodized salt is deemed to be long in coming, other control methods, primarily iodized oil, can be used as temporary control efforts while striving to achieve universal salt iodization.

The international effort to raise awareness and achieve political will has been very successful, as confirmed by the enactment of salt iodization legislation in a growing number of countries. Much operational and financial support for this process has been rendered by UNICEF in light of the goal to eliminate IDD by the year 2000 (Grant 1994). Great strides have been made towards this target but the challenge of achieving full elimination remains.

Implementation

With UNICEF and other donor assistance, salt iodization machinery has been imported and installed in salt producing countries, potassium iodate has been procured, and personnel has been trained. Where control methods other than salt have been used, countries have generally been supported by outside donors.

Monitoring and Evaluation

The initial strategy spelled out monitoring and evaluation as the final step of the “social wheel” (Hetzel 1988). The subsequent
publication of the model talks of evaluation alone and lists indicators such as prevalence of IDD, urinary iodine, and bloodspot TSH, see Figure 2 (Hetzel 1996). Subsequent technical documents also suggest methods and indicators for process monitoring of the intervention, i.e. salt iodization (Sullivan et al. 1995; WHO 1994a).

**IDD in Sub-Saharan Africa**

Iodine deficiency and IDD are widespread in Africa. A third of the total population is considered at risk of IDD and 86 million, 16% of the population, is thought to have goiters. Severe IDD affects large parts of Central, Eastern, and Southern Africa (WHO/UNICEF/ICCIDD 1993). Further details are given below for two severely endemic countries, the Central African Republic and mainland Tanzania.

**Central African Republic**

The Central African Republic is a landlocked country across the Ubangi river from the Ubangi area in the Democratic Republic of Congo (former Zaire). IDD in the Ubangi area was extensively studied by Ermans et al who found severe iodine deficiency and a high prevalence of IDD. Based on findings of increased urinary thiocyanate levels they concluded that cassava was an aggravating factor for IDD (Ermans et al. 1980b; Thilly 1992). In the Central African Republic IDD was found to be highly prevalent both in smaller area surveys (Biassoni et al. 1990b; Mongonou 1982) and in a national survey (Lantum 1991). All parts of the country are highly endemic with total goiter rates between 40 and 90%. Approximately two thirds of the population is affected by IDD (WHO/UNICEF/ICCIDD 1993).

Most of the salt in the country is imported. Salt from Cameroon penetrates the western parts of the country. It is increasingly iodised following the monopolistic producer SELCAM’s successful iodation efforts (Lantum 1992). Other salt sources are located in South Africa, Namibia, and the Sudan in the East. Traditional salts, such as “natron” from Lake Chad and the production of salt by burning grass into ashes, are also
available (ICCIDD 1997a; Thilly 1992). Successful trials have been conducted with iodized water in the more arid parts of the country (Yazipo et al. 1995a; Yazipo et al. 1995b). The national primary health care commission oversees IDD control efforts, which includes monitoring salt imports and monitoring water iodization (Lantum 1992).

Cassava is the main staple crop (Fresco 1986). The thiocyanate load from cassava consumption has been implicated as an aggravator of goiter in CAR (Biassoni et al. 1990a), and reduced consumption suggested as a means to alleviate the problem (Biassoni et al. 1991). Another condition attributed to dietary cyanide-exposure from cassava, is the paralytic disease konzo, which has also been reported in CAR (Peterson 1994; Tylleskär et al. 1994).

**Mainland Tanzania**

Mainland Tanzania has a large landmass with coastline, highlands, mountains, and floodplains. Studies in the southwestern part of the Tanzanian highlands have demonstrated high goiter rates, cretinism, and highly prevalent hypothyroidism in schoolchildren as well as neonates, which were amenable to correction using injections of iodized oil (Wächter et al. 1986; Wächter et al. 1985). Nation-wide systematic surveys of iodine deficiency disorders were gradually conducted in numerous small-scale school goiter-surveys during 1980 through 1990. Total goiter rates between 1 and 88% were found with an estimated 40% of the population affected (WHO/UNICEF/ICCIDD 1993). The summary map of goiter rates by district shows severe IDD in most highland and floodplain regions in Tanzania (NCCIDD-TFNC 1990). Based on the goiter rates established in the school surveys, van der Haar, Kavishe and Gebre-Medhin estimate that 8 million people have goiter, 160,000 cretinism, 450,000 more mildly affected with cretinoidism, and that 30% of total perinatal mortality is caused by iodine deficiency (van der Haar et al. 1988).

The Tanzania Food and Nutrition Center (TFNC) developed a strategy for National IDD control in 1985. The plan called for the use of iodized oil as an interim control method in severely affected areas to prevent further brain damage there, while
working towards a universal salt iodization program. Injection of iodized oil was initially tried in two districts but abandoned due to cost and shortage of trained staff. Instead, iodized oil capsules (IOC) were distributed beginning in 1986. Using an initial criterion of district Visible Goiter Rate >10%, a total of 20 districts were targeted for IOC distribution. Later the criterion was revised to Visible Goiter and grade 1B >10% and 5 more districts were added. Supported by the Swedish International Development Authority, the objective was to distribute two IOC (400mg) every two years to the general public 2-45 years of age, excluding persons with multi-nodular goiter, and one IOC (200mg of iodine) to children aged 12-23 months of age. (ICCIDD 1997b; Sanga 1994).

The efforts to iodize salt in Tanzania began in 1973. However, technical, administrative, and coordination problems among the actors stifled the effort (Sanga 1994). The salt iodization effort should have been re-launched with Dutch support together with the start of the IOC distribution. However, due to several sources of delays it was only in 1991 that UNICEF imported three iodization machines from India and installed them in three major salt works. These first machines were followed by 42 more machines until 1995 (UNICEF 1996). Many of these were smaller rotary drum type mixers provided to 200 or so small-scale salt producers located mainly on the southern coast. These producers were encouraged to form co-operatives and channel all their salt through a centrally located iodization machine. The installed iodization capacity at 150,000 tons per year was theoretically sufficient to satisfy the national need assuming constant salt production throughout the year. Constraints on the program include seasonal salt production and only about 140 salt producers being officially registered. Government has been unwilling to centralize salt production to a few larger producers, presumably for reasons of maintaining job opportunities (Sanga 1994; UNICEF 1996).

In the central parts of the country production of “foothill salt” from salty soils is widespread. Some 7,500 women are believed to be involved. By certain estimates this production is quite substantial amounting up to 40,000 metric tons, although it has yet to be substantiated how widespread exclusive use of the salt is (ICCIDD 1997b; Momburi 1993).
A 1995 law requires all salt for human consumption to be iodized whether produced in the country or imported (some 10,000 metric tons per year) (ICCIDD 1997b). Domestic salt production takes place mainly on the coast and in the extreme west of the country with complex distribution patterns requiring an estimated 4-6 weeks to reach the consumer (TISCO 1992). Consuming an average of 8 grams of salt per day, Tanzanian consumers appear to have strong preferences because of the “taste” and the price for coarse, crudely refined, large-crystal salt distributed in 50 kg reused sacks of different material. The coarse salt is often moist and does not hold iodine very well. Furthermore, it is retailed loose in markets, freely exposed to the sun, providing opportunities for rapid iodine loss. Refined table salt in small 0.5 kg plastic bags is widely available, however, at approximately double the price of the coarse salt. It is mainly used to sprinkle on special foods such as roasted meat. Taking these production, distribution, and retail patterns into account, salt iodization levels were set at 75-100 ppm at the factory so as to achieve household levels of 37 ppm or more (Sanga 1994).

A National Control Commission for IDD (NCCIDD) was organized for all stakeholders. TFNC, under the Ministry of Health, is the secretariat. An association for salt producers has been formed to encourage dialogue, distribution of the UNICEF supplied iodization machines, distribution of potassium iodate, and initially providing appropriate packing materials. Support was also provided for monitoring. The monitoring responsibility is divided among the different actors. These are the Ministry of Water, Energy and Minerals (MOWEM) for the production sites, the National Food Control Commission (NFCC) with their district health assistants for the distribution chain, and TFNC for the household consumption level (ICCIDD 1997b; Sanga 1994). Larger production sites were given a salt titration laboratory. To facilitate production site monitoring, a number of vehicles were supplied to the zonal mining officers in MOWEM. For more accurate quality control and enforcement during the distribution chain, NFCC set up network of regional salt titration laboratories. Peripheral Health Assistants’ and TFNC’s monitoring has largely used rapid field test kits. Altogether the external support for the iodization program amounted to 80% of the budget during the first few years (Sanga 1994).


Figure 3. Location and titles of studies in Africa
AIM OF THE STUDIES

The overall aim of the studies presented in this thesis is to improve the methodologies to assess the severity of iodine deficiency, to monitor the implementation of iodine supplementation programs, and to evaluate program impact. The specific objectives of the five studies are as follows:

- to elucidate whether the thiocyanate load from cassava significantly aggravates the effects of iodine deficiency in three cassava consuming communities of the Central African Republic and draw conclusions for IDD control policy (paper I);

- to analyze the mathematical and physiological properties of the iodine/thiocyanate ratio as an epidemiological indicator for the postulated goitrogenic effects at urinary I/SCN ratios <3 µg/mg using data from Tanzania and the Central African Republic (paper II);

- to estimate the population time supplemented by Iodized Oil Capsule (IOC) distribution over a nine year period in a Tanzanian population of 7 million and to estimate the cost and effectiveness of the three distribution strategies used (paper III);

- to study the relationship among the three main iodine deficiency indicators in three vulnerable groups and to relate this to the iodine content in table salt in a Tanzanian community (paper IV);

- to determine the effects on goiter rate of the WHO 1994 change in palpation criteria for goiter and to compare the relative precision between the old and new palpation systems and ultrasound determined goiter in a school survey in rural Tanzania (paper V).
MATERIALS, METHODS, RESULTS, AND COMMENTS

This thesis consists of several studies, Figure 3. A range of quantitative and qualitative research methods have been used, Table 10. The sections below present the five individual studies grouped into three areas related to their relevance in different stages of the IDD control program cycle. Study I and II relate to the assessment stage, study III to the implementation stage, and study IV and V to the evaluation stage. For each of the three areas material and methods are presented, results summarised and briefly commented on.

Table 10. Summary of research methods used in this thesis.

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</thead>
<tbody>
<tr>
<td>Epidemiology &amp; Biostatistics</td>
<td>✓</td>
<td>✓</td>
<td></td>
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<td>✓</td>
</tr>
<tr>
<td>Biochemical analysis</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Qualitative methods</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost analysis</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Modeling of secondary data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

Assessing Iodine Deficiency and Goitrogenic Effects (paper I,II)

Having arrived in the Central African Republic to study health effects of cassava (Tylleskär et al. 1994), I was struck by finding a goiter in every other child I examined. Since the country is extremely dependent on cassava the potential goitrogenic effects could be considerable as an explanatory factor. The epidemiological indicator urinary I/SCN ratio had been proposed to assess the presence of the potential goitrogenic effects (Delange et al. 1980). A considerable scientific debate has
addressed the issue (Bourdoux et al. 1978; Bourdoux et al. 1980; Cliff et al. 1986a; Delange & Ahluwalia 1983; Delange & Ermans 1971; Delange et al. 1982; Gaitan 1990). However, the question of the goitrogenic effect’s practical importance for iodine deficiency control efforts at population level and the utility of the I/SCN ratio for assessment of potential goitrogenic effects was unclear.

**Materials and Methods**

In study one, cassava processing practices were elucidated in two rural and one urban setting using focus group discussions and participant observation (Khan & Manderson 1992; Scrimshaw & Gleason 1992). A 24 hour dietary recall was made in 20 randomly selected households to establish the importance of cassava in the diet (Cameron & Van Staveren 1988). Casual urine samples were collected for analysis of iodine and thiocyanate in adults in the interviewed households as well as among school children in the local school in each community. Samples were immediately frozen until they were analyzed in Sweden for iodine by a modified Sandell–Kolthoff method (Sandell & Kolthoff 1937) and for thiocyanate (Lundquist et al. 1979), respectively. All goiter gradings were performed independently in triplicate according to Perez et al. (1960). In case of differences, consensus on grade was reached after discussion. The iodine/thiocyanate-ratio (I/SCN) (Delange et al. 1980) was calculated as the mean, median, and mode of the individual samples' ratios obtained through the division of each iodine-concentration (μg/dl) by the same specimen's thiocyanate-concentration (mg/dl).

In study two, a literature review was carried out for use of the I/SCN ratio. The Central African Republic study and additional data from Tanzania were re-analyzed according to the various practices identified in the literature.

**Results**

All three Central African communities studied were iodine deficient, as judged by urinary iodine concentrations. All three study sites depended on bitter cassava as the main staple. Bitter cassava was the dominant staple consumed in all households. However, processing practices differed between the communities,
with a recent introduction of a shortcut processing method in a western village, see Figure 4. In semi-urban Bangui cassava was bought already processed from the village.

![Diagram of cassava processing practices in the two rural areas of CAR.](image)

This change in processing practices resulted in tripled urinary thiocyanate levels compared to the low levels where traditional processing or traded cassava products were consumed. Associated with this was a near doubling of the goiter rate indicating a possible goitrogenic effect, see Table 11.

**Table 11 Cassava processing, urinary iodine and thiocyanate and goiter rates in the studied populations**

<table>
<thead>
<tr>
<th></th>
<th>Western Village</th>
<th>Central Village</th>
<th>Bangui</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cassava processing</td>
<td>shortcut</td>
<td>traditional</td>
<td>traded products</td>
</tr>
<tr>
<td>I µg / dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SEM</td>
<td>6.98±0.73</td>
<td>10.80±2.21</td>
<td>6.30±4.21</td>
</tr>
<tr>
<td>median</td>
<td>5.78</td>
<td>4.57</td>
<td>1.65</td>
</tr>
<tr>
<td>n</td>
<td>48</td>
<td>84</td>
<td>61</td>
</tr>
<tr>
<td>SCN µmol / l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SEM</td>
<td>239±19</td>
<td>231±17</td>
<td>65 ±6</td>
</tr>
<tr>
<td>median</td>
<td>232</td>
<td>186</td>
<td>57</td>
</tr>
<tr>
<td>n</td>
<td>48</td>
<td>84</td>
<td>61</td>
</tr>
<tr>
<td>Crude TGR(%)</td>
<td>51</td>
<td>50</td>
<td>22</td>
</tr>
<tr>
<td>95% Conf.Int.</td>
<td>43-59</td>
<td>38-62</td>
<td>16-28</td>
</tr>
<tr>
<td>n</td>
<td>152</td>
<td>72</td>
<td>184</td>
</tr>
</tbody>
</table>
Figure 5. Distributions of urinary Iodine/Thiocyanate ratios in two groups of Central African schoolchildren.

The mean I/SCN ratio failed to indicate the possible goitrogenic effect in the western area using the postulated cut-off < 3 µg/mg, see Figure 5.
The literature review in paper II revealed that the ratio is poorly defined. It has been calculated in several different ways yielding widely different results, namely as averages of individual ratios:

\[ \text{mean } \frac{I}{SCN} \text{ (Hennart et al. 1982) } \text{ and } \text{median } \frac{I}{SCN} \]

Mathematically expressed as:

\[
\text{mean } \frac{\frac{I_1}{SCN_1} + \ldots + \frac{I_n}{SCN_n}}{n} \quad OR \quad \text{median } \frac{\frac{I_1}{SCN_1} + \ldots + \frac{I_n}{SCN_n}}{n}
\]

and as ratios of group averages:

\[ \text{mean } \frac{I}{\text{mean } SCN} \text{ (Delange 1980) } \text{ and } \text{median } \frac{I}{\text{median } SCN} \text{ (Konde et al. 1994)} \]

Mathematically expressed as:

\[
\frac{\sum (I_{1-n})}{n} \quad OR \quad \frac{\text{median } (I_{1-n})}{\sum (SCN_{1-n})}
\]

Using material from the western part of the Central African Republic and from Tanzania the four different options were calculated, Table 12. These different approaches yield different results varying by a factor of 2 to 4. This is partly explained by the effects of skewed distributions. Furthermore, it can be mathematically shown that the ratio obtained from the group means gives larger weight to the individual ratios with high SCN values, causing this mean to be lower than the mean obtained using individual ratios.
Table 12. Comparisons of urinary I/SCN ratios calculated in different ways for data from the Central African Republic (CAR) and Tanzania.

<table>
<thead>
<tr>
<th></th>
<th>CAR</th>
<th>Tanzania</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=132</td>
<td>n=217</td>
<td></td>
</tr>
<tr>
<td>Averages of individual I/SCN ratios</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean µg/mg (±SEM)</td>
<td>10.1 (±1.7)</td>
<td>35.0 (±10.0)</td>
</tr>
<tr>
<td>Median µg/mg</td>
<td>5.2</td>
<td>9.4</td>
</tr>
<tr>
<td>Ratios of group I/SCN averages</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean µg/mg</td>
<td>6.9</td>
<td>7.5</td>
</tr>
<tr>
<td>Median µg/mg</td>
<td>4.2</td>
<td>8.7</td>
</tr>
<tr>
<td>Crude Goiter Rate</td>
<td>47%</td>
<td>59%</td>
</tr>
<tr>
<td>I (µg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (±SEM)</td>
<td>9.4 (±1.4)</td>
<td>5.6 (±0.4)</td>
</tr>
<tr>
<td>median</td>
<td>4.8</td>
<td>3.6</td>
</tr>
<tr>
<td>SCN (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (±SEM)</td>
<td>1.4 (±0.08)</td>
<td>0.74 (±0.08)</td>
</tr>
<tr>
<td>median</td>
<td>1.1</td>
<td>0.41</td>
</tr>
</tbody>
</table>

There are also physiological limitations in the use of the ratio. Above the kidney threshold for thiocyanate re-absorption around 1.5 mg/dl, the urinary thiocyanate concentrations are not linearly related to the serum concentrations that could exert the possible antithyroid effect (Bourdoux 1995; Rosling 1994). The ratio will also be affected by the 10-12 fold seasonal variation of thiocyanate concentrations (Casadei et al. 1990).

Comments

We found that parts of the Central African Republic are severely to moderately affected by IDD and that goitrogens from insufficient cassava-processing covaries with increased prevalence of goitre (Peterson 1994). This covariation has subsequently been confirmed by others (Biassoni et al. 1998). However, the main cause of the observed goiters is iodine deficiency. Distributing iodine should be the main priority as it can overcome the possible thiocyanate effects (Delange et al. 1994; Gaitan & Dunn 1992). Promotion of effective cassava processing can complement iodine distribution, but it should not
delay the initiation of the iodine supplementation. Effective processing of cassava is associated with much lower urinary thiocyanate levels. This has subsequently also been demonstrated in West Africa (Bilabina et al. 1995). There is no justification to discourage the consumption of cassava from an IDD point of view and continued studies of goitrogens during the assessment stage of an IDD program can detract from the number one priority – to distribute iodine.

The iodine/thiocyanate ratio has mathematical and physiological shortcomings. Its further use should be discouraged. It is recommended to judge absolute iodine and thiocyanate levels independently instead of combining them into a ratio, which obscures the absolute levels (Figure 1).

Distributing Iodine (paper III)

Iodine can be distributed in many ways. Many countries have included IOC in their iodine supplementation programs but Tanzania has to our knowledge had the most extensive experience. While many studies have examined IOC efficacy using different doses and time intervals, the literature does not contain any information on large-scale supplementation programs’ coverage and cost. We set out to determine the proportion of targeted person-time effectively covered according to program objectives, as well as the cost and effectiveness of different strategies to distribute iodised oil capsules to targeted populations.

Materials and Methods

In study three, we examined 57 distribution rounds of iodized oil capsules from 1986 to 1994 in 27 Tanzanian districts with a total population of 7 million. We reviewed IOC distribution reports and administrative records, interviewed past and present program managers, and conducted supervision visits to selected districts. The primary and secondary data was analyzed using a computer spreadsheet model for the proportion of targeted population-time covered as outlined in Figure 6.
From the start of district IOC distribution, the objective was to cover everyone between 1 and 45 years of age every two years. Census data for each district was updated to the year of the analysis, adjusted for the proportion of the population in the target age-group, and used as denominator to calculate the coverage in any one distribution round (Mbalilaki 1988). The mean of individual districts’ distribution coverages was calculated for first and repeat distribution rounds as well as for all combined. Based on the objective to repeat distribution after two years the total population-time covered was calculated (hatched areas in Figure 6). This covered population-time was divided by the total population-time targeted (total area under curve in Figure 6) to yield the population time covered according to program objectives.

For the 20 distribution rounds in 1992-93 a detailed review was done of the distribution strategies planned and finally employed. Costs were determined from a health care provider point of view including opportunity costs of labor and vehicles but excluding overhead cost to the donor as well as direct and indirect costs to the beneficiaries. Cost per dose was determined by dividing the total drug cost and the distribution cost by the number of doses reported ingested. Comparisons were made between the three distribution strategies used.
Results

Reported district distribution coverage ranged from 20% to 96% of the targeted population, with an overall mean coverage of 64%. Coverage declined over subsequent distribution rounds. Multiple linear regression analysis suggested that coverage was significantly and inversely related to distribution round ($p < 0.05$), and positively related (not significantly) to initial visible goiter rate severity ($p = 0.2$).

Repeat distribution was not timely, occurring with a mean delay beyond target of 1.25 years. Taking also this into account, 43% of targeted person-time was covered according to program objectives of distributing at two-year intervals. Of the person-years not covered, 42% were due to less than total coverage and 58% due to delayed repeat distribution beyond the planned two-year interval.

In a sub-study of the 20 distribution rounds between 1991 and 1993, we found that three different distribution strategies had been used to organize mass distribution campaigns in one particular day in each village. Some districts received central funding for fuel and health worker per-diems in addition to receiving the IOC. They set up a “district team” which toured the district using district vehicles to organize and distribute iodine supplements in all villages. Other districts received only the IOC and were told to integrate the distribution into Primary Health Care (PHC). Eight out of the nine districts attempting this distribution strategy did not accomplish the task before the capsules were about to expire. To ensure rapid distribution before expiration date, some of these districts set up a “national district team” to facilitate iodine distribution. Staff from the national program initiated and supported the distribution. These teams, using government cars, were supported with money for fuel and per-diem pay.
Table 13. Mean coverage and cost per ingested dose (2 IOC) in 1992 USD.

<table>
<thead>
<tr>
<th>Distribution strategy</th>
<th>District team</th>
<th>PHC</th>
<th>National+</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of distribution rounds</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>planned</td>
<td>11</td>
<td>9</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>carried out and analyzed</td>
<td>10</td>
<td>1</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Mean coverage</td>
<td>61%</td>
<td>56%</td>
<td>68%</td>
<td>62%</td>
</tr>
<tr>
<td>Cost of 2 IOC</td>
<td>0.30</td>
<td>0.30</td>
<td>0.30</td>
<td>0.30</td>
</tr>
<tr>
<td>Mean cost of unaccounted for IOC / dose reported ingested*</td>
<td>0.16</td>
<td>0.22</td>
<td>0.20</td>
<td>0.18</td>
</tr>
<tr>
<td>Mean management &amp; distribution cost / dose reported ingested</td>
<td>0.05</td>
<td>0.03</td>
<td>0.07</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Mean total cost / dose reported ingested (for 2 year duration)</strong></td>
<td>0.51</td>
<td>0.55</td>
<td>0.56</td>
<td>0.53</td>
</tr>
</tbody>
</table>

The “district team” approach was the most cost effective at 51 cents per dose, corresponding to an annual cost of 26 cents, see Table 13. The analysis was driven by the lower proportion of IOC unaccounted for under this approach. This finding was fairly insensitive to different assumptions on the proportion of unaccounted-for IOC actually wasted. The cost analysis explains this by revealing that the cost of the oil capsules constitute more than 90% of program cost at current coverage levels, Table 14.
Table 14. Cost profiles for iodized oil capsule distribution in a district using "district team" distribution and for the Expanded Program on Immunization.

<table>
<thead>
<tr>
<th>Programs</th>
<th>Iodized oil capsule distribution</th>
<th>Expanded Program on Immunization</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOC/vaccine</td>
<td>92%</td>
<td>10%</td>
</tr>
<tr>
<td>Transport</td>
<td>3%</td>
<td>13%</td>
</tr>
<tr>
<td>Social Mobilization</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Labour</td>
<td>2%</td>
<td>42%</td>
</tr>
<tr>
<td>Equipment</td>
<td>NA</td>
<td>13%</td>
</tr>
<tr>
<td>Building and other costs</td>
<td>NA</td>
<td>5%</td>
</tr>
<tr>
<td>Mgmt, training and supervision</td>
<td>3%</td>
<td>12%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Coverage</td>
<td>63%</td>
<td>80%</td>
</tr>
</tbody>
</table>

NA: Not applicable and therefore not costed.

Comments

The tendency for distribution coverages to decline over subsequent distribution rounds has been observed previously with Vitamin A distribution campaigns (West & Sommer 1987). It is attributed to “program fatigue” among health workers (Greiner 1991) and the emergence of rumors that the IOC was a secretly promoting “family planning” or other schemes to control the population (Magambo et al. 1990). Although the difference was not significant, the tendency towards higher population coverage in places with more visible goiter suggests that population motivation is higher in such places and that IOC, and possibly other direct-contact supplementation methods, will work best where the population is highly motivated. The need for information and communication activities to increase the population’s awareness and motivation in this regard is crucial.

Control of iodine deficiency with IOC requires direct interaction with each recipient at regular but long intervals as there is no “herd immunity”, such as in immunization where an 80% coverage may stop transmission. In contrast, 100% of the population needs to be covered regularly and timely to eliminate IDD. This was not achieved. Distribution coverage was incomplete and delays to repeat distribution common and substantial. In fact, there are bigger potential gains from...
reducing distribution delays than from increasing distribution coverage. This highlights the need for proper and careful planning of iodine distribution in order to avoid administrative delays and to ensure that iodine distribution occurs during an appropriate agricultural season. This has implications for the distribution chain: the donor, the national program, the district, and the local leadership.

More intensive supervision of IOC distribution in more expensive distribution-campaigns is cost-effective compared to unsupervised primary health care distribution, see Table 13. The “district team” approach adds outside funds for distribution expenses to the district and brings coverage rates up, cuts losses of IOC, and lowers the annual cost of supplementation to USD 0.26. The cost analysis explains this finding since more than 90% of the total cost is for the drug. This points out the high cost of the IOC itself at 15 US cents per capsule (1992). By comparison, a Vitamin A capsule costs only 2.8 US cents and the capsules constituted 40% of the total average cost for a large scale distribution program in the Philippines (Loevinsohn et al. 1997). Providing expensive IOC to an underfunded and over-stretched distribution system by “integrating into Primary Health Care” may therefore have been based more on ideology than evidence.

At present drug prices there is scope for increased cost-effectiveness of IOC delivery through investments in distribution, supervision and community mobilisation rather than just delivering an expensive drug to expire on a pharmacy shelf. This lesson should apply also to other high item-cost health interventions with intermittent distribution.

Onchocerciasis control programs that annually distribute ivermectin have proven to be successful when communities direct the treatments themselves. Community directed treatment is organized in endemic areas by explaining program objectives and strategies to the affected population. The population decides on how to organize the distribution and, most importantly, selects its own community-based distributors who are trained on basic principles of the treatment and then organize with their communities to treat everyone during a convenient time of the year. Using village population lists, coverages of 82% rising over the years to 92% have been achieved in Ecuador villages of about 5,000 persons (Guderian et al. 1997). In Uganda an analysis of
the sustainability of the distribution indicated that a significant predictor of sustainable distribution over several years was whether the community had chosen the distributor itself (Katabarwa & Mutabazi 1998). Community ownership, direct and visible effects of the treatment, regular availability of drugs, and community confidence in the initiative are all listed as reasons for the strategy’s success (Tarimo 2000). Lessons to learn for iodized oil capsule distribution include the need to inform communities and let them direct the activity in order to achieve sustainability. However, this success comes at a cost, the per capita distribution cost alone was estimated at USD 0.29 to achieve an 85% coverage in a Ugandan population of 46,000 (Kipp et al. 1998).

Evaluating Program Impact (paper IV,V)

Iodizing salt is the long-term strategy chosen by most countries. WHO and ICCIDD recommended iodization at 100 parts per million for bulk production in warm, moist climates (WHO 1994a). Tanzania adopted this recommendation. Following the reports of iodine induced hyperthyroidism among older subjects with large goiters WHO lowered the recommendation to 20-40 ppm and suggested confirmatory surveys of urinary iodine to ensure a median of 100-200 µg/l (WHO 1996). Such surveys are customarily done in school-children, yet even more vulnerable target groups are the pregnant woman, the foetus and the newborn. However, no biological indicators are usually assessed in these groups of prime beneficiaries due to logistical difficulties (WHO 1997). Yet knowing their status and relation to school-children’s indicators is critical before taking a decision to change salt iodine content. We studied the relation of iodine deficiency indicators in different vulnerable groups in a Tanzanian community with full coverage of salt presumably iodized at 100 ppm at its site of production.

A convenient marker of the last years’ iodine status in a community is the distribution of thyroid sizes in schoolchildren (Aghini-Lombardi et al. 1997). This indicator is then used as a marker for the likely presence of other, more serious disorders.
such as cretinism and infant deaths as well as a summary indicator of the adequacy of the iodine supply (Dulberg 1985). A number of different classification systems exist for grading thyroid size using palpation or ultrasound. In addition to the reduction in number of goitre grades, the 1994 WHO palpation system implies a change in definition of what constitutes a “goiter”. Furthermore, ultrasound estimation of thyroid volume has been recommended as more precise and objective than palpation (WHO 1994a). We studied the implications of the change in palpation goitre definition and compared the obtainable precision using palpation with that of ultrasonic estimation of thyroid volume in a goiter survey in rural Tanzania.

**Material and Methods**

**Relation of outcome indicators and target groups (paper IV)**

We studied the iodized salt distribution coverage and iodine status in different vulnerable groups in Ilembula village in the severely iodine deficient Njombe District (Wächter *et al.* 1986; Wächter *et al.* 1985), where iodized salt had been available for 1-2 years (Sundqvist & Wijetunga 1996). We surveyed village salt iodine content twice during one month using rapid test kits for household and school-children’s samples and titration for retail samples (Sullivan *et al.* 1995). Thyroid size was graded according to Perez *et al.* (1960) in school-children and women in households and delivering at Ilembula Hospital. Two examiners graded independently and settled differences in grade through re-examination and discussion. Urinary iodine concentration was measured in schoolchildren and women at delivery. Cord blood was collected on filter paper from consecutive deliveries and frozen at minus 20 until analysed by the Neonatal Delfia technique at the National Swedish Hypothyroidism laboratory. The iodine deficiency indicators collected in the different groups were evaluated against WHO severity “benchmarks”, see Table 9 (WHO 1994a).
Goiter definition (paper V)
In this study three independent, blinded examiners did double estimation of thyroid size with the old and new palpation classification systems in 225 primary school children in a highland Tanzanian village. Palpation results were compared to double ultrasound estimation of thyroid volume according to Brunn et al. (1981 and Delange et al. (1997). Kappa values were calculated as measures of agreement. Logistic regression was used to study the influence of ultrasonographically determined thyroid size parameters on whether a palpatator considered a child goitrous or not. Using ultrasound “goiter” by WHO cutoff values as gold standard the sensitivity and specificity of the two palpation systems was calculated (WHO & ICCIDD 1997).

Table 15. Iodine deficiency (ID) indicators and WHO severity grading in different population groups (WHO 1994a)

<table>
<thead>
<tr>
<th></th>
<th>School-children</th>
<th>Household Women</th>
<th>Women at Delivery</th>
<th>Neonates</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>60</td>
<td>25</td>
<td>111</td>
<td>123</td>
</tr>
<tr>
<td>Total Goiter Rate (%)</td>
<td>62</td>
<td>52</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>(95% conf int)</td>
<td>(49-74)</td>
<td>(31-73)</td>
<td>(46-64)</td>
<td></td>
</tr>
<tr>
<td>ID severity</td>
<td>severe</td>
<td>severe</td>
<td>severe</td>
<td></td>
</tr>
<tr>
<td>Urinary iodine (µg/l)</td>
<td>Median</td>
<td>140</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>&lt;20 µg/l</td>
<td>0 %</td>
<td>10 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 µg/l</td>
<td>7 %</td>
<td>32 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100 µg/l</td>
<td>28 %</td>
<td>62 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ID severity</td>
<td>none</td>
<td>mild</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH (mU/l whole blood)</td>
<td>Median</td>
<td>1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5 mU/l</td>
<td>25 %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;7.5 mU/l</td>
<td>15 %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;10 mU/l</td>
<td>10 %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ID severity</td>
<td>moderate</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Results

In Ilembula village semiquantitative test-kits indicated that 98% of household salt-samples contained iodine at 25 ppm. Twenty-nine retail samples had a median titration iodine content of 27 ppm (range 11-127), but only 17 % complied with the national recommendation (>37 ppm). Thus almost all salt from households was commercially produced and iodized during the study month, although at relatively low levels. Iodine deficiency indicators and their severity grading are given in Table 15.

Goiter rates indicated “severe“ iodine deficiency in all groups examined suggesting delayed goiter regression since median urinary iodine in the school-children was normal. However, irrespective of whether the delivering women came from the local ward, local or neighbouring district cord-blood TSH and urinary iodine indicated “moderate“ and “mild“ ID, suggesting that the neonates were still at risk of brain damage.

Our comparative study of the two palpation systems and the "gold standard" ultrasound demonstrated that the recent change in goiter definition entailed an increase in estimated goiter rates by up to 25% in the studied population. This is explained by the effective lowering of the cut-off between a normal thyroid and a “goiter”, Table 3. This has major implications for follow-up studies using the new classification system when baseline studies were done with the old system, such as in Tanzania. At global level the number of IDD affected will increase considerably due to the combined effects of lowering the cut-off for goiter and decreasing the acceptable prevalence to 5%. Furthermore, the lowering of the cut-off for goiter decreases specificity to a level of around 30% where it becomes impossible to demonstrate elimination of IDD with the new classification system due to false positives, Figure 7.

There is considerable random misclassification of goiter status upon repeated palpation which, however, results in minimal changes in estimated goiter rates, see Table 16. The level of reclassification in palpation with a kappa value of 0.57 is very close to the result for ultrasound, 0.63 indicating similar precision. Palpation is more influenced by thyroid width than by thyroid length or depth, while ultrasound estimates all three parameters equally. Ultrasound estimation of thyroid volume is demonstrated to be imprecise due to measurement error and lobe shape deviation from the ellipsoid form. This results in a wide confidence interval where the 95% confidence interval for an estimated volume of 10 ml is ±4 ml. Converted to a goiter rate this results in considerable random misclassification making ultrasound, like palpation, unreliable at the individual level but reliable at population level as long as the misclassification is random.
Table 16. Intra-rater variation. Cross-tabulations of repeated palpation (examiner A) and ultrasound determinations of total goitre rate in 225 primary school children in highland Tanzania. Number of children and (Total Goiter Rate).

<table>
<thead>
<tr>
<th>Examination Results</th>
<th>First round Goiter</th>
<th>Second round Goiter</th>
<th>Reclassification</th>
<th>Prevalence</th>
<th>Prevalence Difference</th>
<th>Kappa*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>TOTAL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpator A (WHO'60)</td>
<td>No</td>
<td>90</td>
<td>23</td>
<td>113</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>25</td>
<td>87</td>
<td>112 (50%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TOTAL</td>
<td>115</td>
<td>110</td>
<td>225</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(49%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpator A (WHO'94)</td>
<td>No</td>
<td>33</td>
<td>21</td>
<td>54</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>16</td>
<td>155</td>
<td>171 (76%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TOTAL</td>
<td>49</td>
<td>176</td>
<td>225</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(78%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasound</td>
<td>No</td>
<td>41</td>
<td>17</td>
<td>58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body surface</td>
<td>Yes</td>
<td>14</td>
<td>153</td>
<td>167 (74%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normated</td>
<td>TOTAL</td>
<td>55</td>
<td>170</td>
<td>225</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(76%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Labelling of agreement according to (Altman 1991): kappa <0.2: poor; 0.21-0.4: fair; 0.41-0.6: moderate; 0.61-0.8: good; 0.81-1: very good

Comments

The study of outcome indicators revealed that while all the salt was iodized the iodine concentrations varied greatly at retail level indicating either poor quality of iodation or that large losses of iodine had occurred during transport and storage. We found that, while an assessment of the easily accessible and customarily evaluated school-children showed adequate or even slightly high urinary iodine, other vulnerable groups lagged behind. Women at delivery showed signs of inadequate iodine status and goiter, although the relation between iodine intake and thyroid hormone status in pregnancy is not clearcut and pregnancy-induced changes cannot be ruled out (Elnagar et al. 1998; Eltom et al. 2000b). However, newborns showed signs of thyroid stress indicating a high turnover rate of the little available iodine (Delange 1998). Hypothyroidism, even if
transient, has been linked with negative effects on school achievement and cognition (Huda et al. 1999) and our findings suggest that the important target group of neonates may still be at risk of brain damage at the iodine levels found in the study. The findings could be explained by insufficient time since the introduction of iodized salt, or that current salt iodine levels at household level, while sufficient for school children, may have been inadequate for other vulnerable groups.

In addition our study demonstrated that goiter regression may be delayed in all groups compared to thyroid hormone and urinary iodine levels necessitating longer periods before goiter reassessments to allow time for new "iodine replete" cohorts of school-children to replace the formerly iodine-deficient children (Aghini-Lombardi et al. 1997; Zhao et al. 1999).

It remains to be seen whether universal salt iodization is feasible in countries with widespread small-scale salt production or whether integration with other control methods, such as IOC, will be necessary to achieve elimination of IDD. However, once iodized salt is available in sufficient quantities appropriate monitoring is necessary to adopt international recommendations on salt iodization levels to local circumstances in order to avoid side effects of excess iodine intake. In evaluating the prevalence of iodine induced hyperthyroidism, it should also be noted that already while the iodine deficiency continues the prevalence of IIH is twice that of iodine sufficient communities (Aghini-Lombardi et al. 1999). It is important to monitor salt iodine concentrations during production and distribution down to household level, as well as to assess iodine status with improved indicators in all vulnerable groups in the local setting, before adapting international recommendations on new iodization levels at production. Measures also need to be put in place to reduce variations in salt iodine content during production. Varying salt iodine content may not only be a risk factor for IIH but also to reduce the effectiveness of iodized salt in reducing thyroid volume (Zhao et al. 1999).

For goiter surveys in settings where ultrasound surveys are not feasible, we find that appropriately trained palpators using the old WHO classification of goiter remain "good enough" to monitor elimination of iodine deficiency by the goitre criterion.
However, an allowance for a 10% acceptable prevalence must be made. This 10% cut-off should be applicable for palpation surveys only, to allow for the 10% false positives that result from a specificity of 90% which seems to be the typically attainable performance using the Perez criterion reaches (Smyth et al. 1999). It is, however, not an argument against the lowering of the cutoff for true prevalence of goiter to 5%. However, it should be noted that applying the new palpation criterion and the lower 5% cutoff doubled the estimated number of goitrous individuals in the world from 2-300 million to 686 million. The population considered at risk of iodine deficiency simultaneously rose from 1,000 to 1,600 million (Clugston & Bailey 1996; Dunn & van der Haar 1990; Hetzel 1988; WHO/UNICEF/ICCIDD 1993). Subsequent additions have increased the population considered at risk to 2.2 billion –more than one third of the world’s population– and the number of goitrous to 740 million (WHO 1999).

The differences between 225 repeat ultrasound measurements in our study were larger than errors reported from small validation exercises elsewhere (Foo et al. 1999; Zimmerman et al. 2000). However, the attainable precision in large-scale routine surveys in remote low-income country settings has not been determined before. Our findings in support of the continued utility of palpation are important since ultrasonography is technically difficult and costly to use in the remote highland regions of low-income countries where IDD is likely to linger.

The findings also demonstrate the importance of clarity of definitions in epidemiology and the need to avoid inadvertent oversights, such as the effective lowering of the goiter definition in the 1994 ICCIDD/WHO publication which effectively rendered palpation useless with its low specificity (WHO 1994a). It is suggested that using the research publication process with peer-review to scrutinize major changes may help in this regard.
GENERAL DISCUSSION

Elimination, not Eradication

Joint international and national efforts focusing on salt iodization has made remarkable progress towards reducing iodine deficiency in the last decade. Presently 63 out of 99 reporting countries claim that more than 50% of their households consume iodized salt and in 26 countries the reported level reaches 90% of the households (UNICEF 2000). However, the battle is not won and the issue of sustainability is critical. A nutritional deficiency like IDD will never be eradicated in the same way as smallpox was. Supplementation needs to be sustained forever or else iodine deficiency will return (Dunn 1998). To control iodine deficiency, each and every member of the deficient community needs to be reached regularly with the intervention as, unlike immunizable diseases, no “herd immunity” is provided when the large majority of the target population is covered. Yet another difference between the major infectious and nutritional disorders among poor populations is that nutritional deficiencies constitute no threat to the affluent populations of the world, whereas infectious diseases do.

During the last decade iodine deficiency control programs have been initiated in most low-income countries with considerable external support. In the case of Tanzania, this has amounted to 80% of the program budget (Sanga 1994). Sustaining such high levels of support seems unlikely. The interdependence between countries is not as important for IDD as with infectious diseases such as smallpox, polio, or measles (Dayrit 1998). Over time the manifestations of IDD may also disappear making the perceived need for iodine supplementation less obvious (Alnwick 1998).

The need to build an iodine deficiency control program that is sustainable is crucial no matter what iodine distribution system is set up. This also applies to the communication, monitoring, and enforcement systems. The experience from Tanzania is illuminating in this regard. The responsibility to monitor the program is divided between several ministries. Monitoring the production sites is the responsibility of the Ministry of Water,
Energy and Minerals (MOWEM) and their regional mining officers. However, a 1998 assessment found that they have not been supervised since 1995 (Carlsson et al. 1999). Although both the central Ministry and the zonal officers were supplied with vehicles for site monitoring, these visits were not taking place, except when donor-funded and then at a high cost. A subsequent visit by TFNC to the southern salt producing region revealed that no monitoring was taking place at the production sites and that the supervision vehicle had been sold (Assey et al. 1998).

Monitoring of the distribution process is the responsibility of the National Food Control Commission, Ministry of Health. While this monitoring initially worked relatively well it is now largely not performing, or at least not reporting, since outside funding stopped (Assey et al. 1998). Now only household monitoring continues under the direction of the Tanzania Food and Nutrition Centre, also largely dependent on external funding.

Sustainability issues apply also to the internal monitoring process at the salt factories. While the larger ones were equipped with titration equipment, site visits have not given evidence of regular use of this equipment or regular use of a quality control logbook. Use of rapid test kits seem more widespread but is also less accurate, providing essentially an indication of whether iodine is present or not (Carlsson et al. 1999). In summary, internal and external salt production quality control systems broke down, the distribution monitoring started well but has declined; although household monitoring has partially continued, the monitoring process does not fulfill the adequacy criteria, see Table 8.

As for the actual production of iodized salt, the donation and installation of the iodization machines was the beginning of new procedures. Previous to iodization, salt could be packed directly into sacks on the salt pan and then taken straight for sale or storage. Iodization increases the number of production steps thereby increasing the salt price or decreasing the profit margin. In small salt producing co-operatives, the relative costs for transporting the salt to the iodation plant and producing iodized salt is likely to be even greater than in large operations, perhaps even exceeding the profit. Careful analysis of the economic consequences of salt iodization is crucial for sustainability.

The technical challenges include both installation and
maintenance of the iodization equipment. In many settings machines have never been installed due to expense or technical unsuitability of the equipment. Where installed, upkeep of machines has proven difficult to organize. Following machine breakdowns, new more sustainable ways of iodizing were pioneered using a hand spray pump to put iodine on salt heaps with subsequent manual mixing (Assey et al. 1998). This method seems to be more sustainable for iodization in low cost settings, but the quality of the iodization has yet to be evaluated.

While the Tanzania salt producers’ association was charged with distributing iodization machines, potassium iodate and special lined bags, this body has not functioned well. There is dissatisfaction among producers with the association's functioning as a discussion forum and in giving access to iodization machines and potassium iodate. In fact, the lack of a sustainable source and mechanism for re-supply of potassium iodate is one of the major constraints cited by salt producers. The originally donated stock of labelled, lined polyethylene bags was soon used up and then largely replaced by second-hand unmarked bags (Carlsson et al. 1999). These constraints are shared by salt traders from other countries. A Mombasa workshop for salt producers from 13 Eastern and Southern African countries identified the main barriers to effective salt iodization: the lack of monitoring systems; ineffective enforcement; the existence of taxes and duties on iodine; legal trade barriers between countries; and the large number of small scale salt producers who lack technical skills and resources (Kwena 2000).

Yet Tanzania has made great advances in controlling iodine deficiency. The preliminary findings from schools surveys in 16 endemic districts indicate sufficient to high urinary iodine concentrations in all but 2 districts (Kimboka 2000). While the challenges to uphold and finetune this success are many, this study concurs with a recent evaluation of the IDD program in concluding that the main priority in the current Tanzanian resource-constrained situation is to put a salt iodization production and monitoring system in place, starting in the factories. It was suggested that this will require commitment, accountability, and organizational changes in the concerned government agencies and NCCIDD as well as a more proactive secretariat (Carlsson et al. 1999).
Monitoring does not equal Evaluation

Monitoring and evaluation are presented together as the last step of the global IDD control strategy (Hetzel 1987b; Hetzel 1988). In the latest published version of the IDD “social wheel,” monitoring does not appear, presumably this was inadvertently left out, Figure 2 (Hetzel 1996). Be that as it may, the tendency to see “monitoring and evaluation” as the same is widespread in academic medicine and public health and to the disadvantage of both concepts. Monitoring and evaluation are different activities (Barutwanayo et al. 1993; Rubin 1995; UNICEF 1990), see Box 1.


<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Monitoring</td>
<td>A continuous activity to measure the process of carrying out activities for program implementation (also called implementation evaluation or process evaluation)</td>
</tr>
<tr>
<td>Evaluation</td>
<td>A periodic assessment of a program’s outcomes and impact (effectiveness evaluation). It may also provide information on effectiveness, efficiency, and sustainability</td>
</tr>
<tr>
<td>Effectiveness</td>
<td>A measure of the extent to which original objectives have been achieved</td>
</tr>
<tr>
<td>Efficiency</td>
<td>An economic term measuring the cost at which the objective was achieved</td>
</tr>
<tr>
<td>Efficacy</td>
<td>An intervention’s effect under ideal circumstances, typically determined in controlled clinical trials</td>
</tr>
</tbody>
</table>

It has been suggested that monitoring findings suggesting possibilities of impact should precede any impact evaluation (Greiner 1997). This seems logical. If you have no monitoring data suggesting that the intervention has reached its targeted population, why should you spend resources to evaluate impact? An evaluation, when carried out, should first validate the monitoring findings and second reassess the situation both in terms of outcomes, such as changes in behaviors and laboratory
parameters, and in terms of impact, changes in morbidity and mortality (Barutwanayo et al. 1993). Similarly, for obstetric services it is suggested to monitor availability, utilization, and quality of the service as process indicators before measuring maternal mortality (Koblinsky et al. 1994; Maine et al. 1997). Moreover, the monitoring information will help the interpretation of the impact findings, thus opening up the “black box” research of evaluating impact alone in the absence of any explanatory information on the implementation process (Rossi & Freeman 1993).

**Defining the implementation process**

The widespread practice of confusing monitoring with evaluation and to concentrate on measuring impact indicators may reflect the tendency for nutrition programs to concentrate more on “what to do” than on “how to do it” (Field 1985). There is a need to focus attention on the implementation process since any intervention is dependent on a favorable programmatic context to translate its objectives into community effectiveness. While any one intervention has a certain efficacy under controlled conditions, the process of implementing it in a program has a number of steps that are contingent upon each other to produce the desired outputs, outcomes, and impacts. For curative care these steps have been outlined as a formula (Tugwell et al. 1985). Community effectiveness is the multiplicative combination of conditional probabilities of efficacy, diagnostic accuracy, health provider compliance, patient compliance, and coverage. Assuming independence, Tugwell suggests the following calculation:

\[
\text{Community effectiveness} = \text{Efficacy} \times \text{Diagnostic accuracy} \times \text{Health provider compliance} \times \text{Patient compliance} \times \text{Coverage}
\]

For a supplementation or fortification program applied to an entire population, diagnostic accuracy does not apply. Coverage translates into access to the intervention and health worker compliance translates into quality of the intervention while patient compliance remains. Thus the components:

\[
\text{Community effectiveness} = \text{Efficacy} \times \text{Access} \times \text{Quality} \times \text{Compliance}
\]
This formula demonstrates that even if the efficacy is 100% given 50% access, 50% acceptable quality and 50% compliance, the resulting effectiveness is only 12.5% in spite of the impressive efficacy. An intervention with lower efficacy may even result in better community effectiveness if it is easier to implement and sustain. While the assumption of independence may not fully apply, and the reduction in effect may be overstated, the calculation gives the rationale for focusing on “the how” of an intervention and not just “the what” (Field 1985).

This realization is manifested in the evaluation literature’s recommended practice of describing a program’s “logical model” as a basis for planning and subsequently evaluating an intervention (Goodman 1998; MMWR 1999; Moyer et al. 1997). A logic model describes the complete sequence of events for bringing about change, often in the form of a flowchart. This chart can also spell out infrastructure requirements and interrelationships. The logic model promotes discussion and clarification of the program’s strategies, thus focusing and improving the program design (MMWR 1999).

Box 2. Definition of terms for monitoring and evaluation. Adapted after Bouchet; DiPrete-Brown et al. 1998; Levinson et al. 1999.

<table>
<thead>
<tr>
<th>Input</th>
<th>Funds, materials, goods, training and actions necessary for project activities</th>
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<tbody>
<tr>
<td>Process</td>
<td>The way activities must be carried out to achieve the project outputs</td>
</tr>
<tr>
<td>Output</td>
<td>Provision of project goods and services to the target population; the primary project deliverables</td>
</tr>
<tr>
<td>Outcome</td>
<td>Intermediate change in the condition, behavior or practice of the target population</td>
</tr>
<tr>
<td>Impact</td>
<td>Changes in the occurrence of targeted conditions in the target population</td>
</tr>
<tr>
<td>Benefits</td>
<td>Effects resulting from the impact, usually in combination with other factors</td>
</tr>
</tbody>
</table>
The use of flowcharts or tabulations of steps is also part of the Quality Assurance practice. Quality assurance sets standards and guidelines, communicates them, and then monitors and tries to improve performance in relation to these standards (DiPrete-Brown et al. 1998). Taking a “systems view” of the program standards, indicators and thresholds are set for inputs, processes, outputs, outcomes, and impact, see Box 2 and Figure 8.

**Monitoring**

Monitoring focuses on inputs, processes, and outputs. Using the model in Figure 8, a system for collecting and compiling data needs to be designed as the program’s Management Information System (MIS). By using the MIS to compile required monitoring data, the information can then be analyzed and used to guide program decision-making for improved performance (Bouchet; DiPrete-Brown et al. 1998; Rossi & Freeman 1993). During the analysis it is important to prioritize and focus interventions on the main “bottlenecks” identified in the flowchart or systems model (DiPrete-Brown et al. 1998; Maine et al. 1997).

**Evaluation**

Most interventions aim to influence morbidity and mortality by changing proximate determinants, e.g. to reduce cretinism and goitre by getting all households to regularly consume adequately iodized salt. The program’s outputs to achieve this is iodized salt production and distribution all over the country as well as health education to enlighten consumers on the importance of using iodized salt. It is then assumed that these outputs will translate into outcomes in the form of consumers buying and using iodised salt and getting adequate iodine intake, see Figure 8. Based on the scientific literature, it is also reasonable to make the assumption that adequate iodine intake will then translate to the desired impact in terms of actual morbidity/mortality reductions. Therefore, once monitoring has indicated an adequate output, e.g. good coverage with adequately iodized salt, then the evaluation can be limited to validate the monitoring findings (output) and to evaluate the outcome and impact (Levinson et al. 1999).
Figure 8. A systems view of an iodine fortification / supplementation program with examples of issues for monitoring and evaluation. Outcomes are both biological and behavioral. Adapted from DiPrete-Brown et al. 1998; Levinson et al. 1999 and Bouchet.
However, measuring impacts such as mortality and incidence of cretinism is often more difficult and costly, while evaluation of the more proximate determinants at the outcome stage is generally easier and cheaper to perform. Evaluation of such proximate determinants of impact has therefore been suggested as alternative and complementary evaluation measures (Blecher 1996; Lorenz et al. 1995; Mosley & Chen 1984; van Norren et al. 1989). In the case of iodine deficiency, urinary iodine concentrations is a convenient outcome indicator. For evaluation surveys it can be combined with the most easy to measure impact indicator, thyroid size. However, such measurements have precision problems whether done by palpation or ultrasound (paper V) and goiter regression is delayed after correction of iodine deficiency (paper IV). Other impact indicators, while occasionally necessary to measure for validation studies, require extensive surveys in groups that may be hard to reach (paper IV).

**Modifying the “Social Wheel”**

There is a good case for separating process monitoring from evaluations of outcome and impact. Measurements of the process, outcome, and impact may all be necessary but their periodicity should be different and measurement of process and outcome need to precede, if not replace, the more popular impact evaluations (Schrettenbrunner & Harpham 1993). Impact evaluations are also time-consuming, logistically challenging, expensive and yield results that can only be interpreted together with process indicators (paper IV). Methodological measurement errors may also give spurious results (paper II, V).

The need to first monitor the intervention, i.e. salt iodization, is well reflected in ICCIDD’s current Global Action plan 1999-2001 (ICCIDD 1999a) and in forthcoming WHO monitoring documents (ICCIDD 1999b). It is therefore suggested to stop using “Monitoring and Evaluation” as one concept in IDD strategies in order to recognize that process monitoring is a crucial activity in its own right. Effective monitoring requires appropriate administrative arrangements and practical procedures. The strategy and “social wheel” for IDD control could reflect this by adding a smaller monitoring wheel on to the bigger one at the implementation stage. As this monitoring wheel is a small wheel
turning a big one it has to turn around many times while the big wheel makes one turn, i.e. monitoring has to be done throughout the implementation years while program evaluation could be done at 3-5 year intervals, see Figure 9. The same addition is needed in UNICEF’s “triple A” program cycle (UNICEF 1998).

Figure 9. Modified "Social Wheel" of IDD control for the second and subsequent turns. Superimposed is UNICEF's “Triple A process” and the smaller process monitoring wheel, which turns faster than the larger program wheel. Additional evaluation and updating tasks added. Compare Figure 2.

Adding such a “faster-turning” wheel points out the importance of monitoring as distinct from evaluation. This distinction helps clarify the steps and requirements for successful implementation. This relates particularly to the necessary distinction between the importance and sequencing of measuring
salt iodine content (output) and measuring urinary iodine (outcome). Using rapid test kits or titration on salt is an everyday event at production and distribution level the outcome of which should be monitored at least monthly by the IDD program office. It is part of the monitoring and enforcement process. Salt titration laboratories are required down to factory and regional levels within countries, which is technically feasible since they are relatively simple to manage. Instructions for sampling are available and should be adapted to the specific situation (Sullivan et al. 1995).

Assessing iodine intake by measuring urinary iodine, however, is an intermittent, much more complex activity, which serves to confirm findings of adequate salt iodine content and provide impetus for adjusting salt iodization levels. It therefore has more a characteristic of a periodic evaluation indicator and requires careful elaboration of sampling procedures. Furthermore, the laboratory technology for urinary iodine is complex. Capacity for determining urinary iodine is thus only required at national level for larger countries, or can even be shared among groups of countries, since very few countries will need to run continuous analysis of urinary iodine levels.

The role of the community in iodine control must also be reassessed. Enrolling community based non-governmental organizations in monitoring and advocacy for iodized salt is one promising avenue (Pandav et al. 1995). While public education to create awareness and demand for iodized salt is stressed as a determinant of a successful program (Dunn 1996a), the current placement of communication in the “social wheel” as a step preceding the intervention may need to be revised. The reason is that communication issues also need to become part of the program implementation concurrent with salt iodization. Communication also needs to become more relevant to different contexts. Attention and research needs to be devoted to defining: the different target audiences and the benefits, costs and other barriers that interfere with desired behaviors. These audiences include actors such as the salt workers whom we want to spend the extra energy and money to iodize all salt appropriately. Messages need to be developed that will promote these behaviors most effectively, and the most effective channels of
communication need to be identified for each targeted actor (Cabanero-Verzosa 1999). Use of such strategic communication was highly effective in increasing consumer knowledge of IDD and iodized salt in a campaign in Ecuador (Cabanero-Verzosa 1999). Other target audiences, requiring different messages and channels will include politicians, salt producers, salt factory workers, and salt retailers. This can be achieved by more countries using the available ICCIDD communication strategy (Ling & Reader-Wilstein). An example is the recent press campaign in India to maintain the ban on sale of non-iodised salt (CFAR 2000). Including communication as part of the intervention also implies that its delivery needs to be monitored and its effect evaluated in the last stage of the program cycle.

Reassessing the Situation

The strategy

A combined focus on process monitoring and impact evaluation will assist programs to reassess the feasibility of their control strategies during the evaluation stage. The blueprinted focus on universal salt iodization has been largely successful in most settings (Kavishe 1996). Focusing attention on iodizing the salt has also been wise. Goitrogens do not merit attention until iodine has reached the population (paper I,II). The logistics of distributing iodized oil capsules have also precluded their widespread use for effective mass supplementation (paper III). Most iodine deficiency control programs have now reached maturity and need to reassess the experience of applying this initial strategy. As they set out on the next turn of the control cycle, they may need to be less dogmatic; e.g., they may need to recognize that small scale salt iodation using salt co-operatives and shared iodization machines may not be feasible in all settings. Especially as structural adjustment towards fewer, large-scale salt producers may not be politically acceptable as it may create socio-economic inequalities. Programs need the flexibility to try out new economically and practically viable alternatives for special contexts. One such example is the development in Tanzania of iodization of salt in heaps directly on
the salt pan, using portable pesticide sprayers. Studies on the performance of such methods and other practices in use will be necessary, and form the basis for adapting new international recommendations for iodization levels (paper IV; PAMM 1998; WHO 1996).

Ensuring sustainable and functional monitoring of salt iodization, distribution, and use is crucial to strengthen and sustain the salt iodization program (Pandav et al. 1995; Wang et al. 1997). Adequately iodized salt will then supply the large majority of the population with iodine. The second step is then to identify geographic or socio-economic pockets where iodized salt does not work. For example, iodization may not be a viable alternative when people can access local salt supplies without the use of a producer, when the market is dominated by many small-scale salt producers, or when there are price differences between iodated and non-iodated salt. In such pockets the severity of iodine deficiency needs to be assessed. If severe enough to warrant control efforts, distribution of iodized oil capsules should be considered as an alternative control strategy and monitoring should be developed. Paper III indicated that IOC distribution was most effective where IDD was most severe and especially when local health workers were facilitated to interact with the local communities. The final step is to devote special attention to fine-tuning the supplementation to optimally cover vulnerable groups such as neonates, pregnant women as well as groups with special dietary practices.

**The impact on IDD**

Ultimately programs need to demonstrate their impact in reducing IDD. Some of the impacts may be difficult and costly to measure, such as reduced incidence of cretinism or decreased perinatal death rates. Other impacts are comparatively easy to demonstrate such as reductions in thyroid size and hypothyroidism. However, it is essential to select optimal methods for remote and resource poor environments. The sampling procedures and methods used ultimately depend on the human and financial resources available to conduct the evaluation. In countries with per-capita health expenditures around USD 5 per year these resources are very limited. Research
is needed to validate convenient indicators of outcome and impact (e.g., urinary iodine and thyroid size in school children) against impact in more vulnerable target groups (e.g., pregnant women and newborns) that are harder to reach.

Further developments in this regard could include assessing program impact through studying the distribution of thyroid volumes in a community. While ultrasound measures thyroid volume, the present interpretation of ultrasound data introduces the same dichotomization as “goiter” by making reference to the 97th percentile. This has led to considerable debate on what should be the cutoff (Delange 1999; Foo et al. 1999; Xu et al. 1999; paper V). However, dichotomizing thyroids into “normal” and “goiter” allows no quantification of thyroid size, nor any statement on how far from “normal” a volume is. It is also not possible to merge data across age, body surface area, and sex groups. Similar to anthropometry it is thus suggested to develop thyroid volume z-scores. (Foo & Mafauzy 1999; WHO 1995).

Further study will be required of the practically attainable precision of ultrasound surveys under field-conditions and available budget frames. Standardization of the statistical methodology for assessing ultrasound measurement error will help in that regard. The present findings suggest that due to the combined ultrasound measurement error and error resulting from the assumption of an ellipsoid thyroid shape, the estimated volume will differ considerably from the true volume in any one individual. The apparent precision may thus be largely spurious as long as the ellipsoid approximation method is used (Brunn et al. 1981; paper V) while field adaptations of other, more precise methods could improve the precision (Hegedüs et al. 1983).

The management structure

Most studies in this thesis have focused on biomedical aspects of methods for monitoring and evaluation. However, as programs reach their evaluation stage, it will also be necessary to evaluate the functionality of the institutional arrangements with regards to monitoring and enforcement. This includes the achievements and constraints of partners on the National Control Commission for IDD in fulfilling their envisioned roles. While the NCCIDD was a great step forward in putting all stakeholders around a
table in Tanzania, it does not follow that they have the same objectives. The difference between the health sector and the salt industry is not only one of different educational backgrounds, as often pointed out in the IDD literature, but each has different incentives and goals. The health sector needs to recognize that the salt industry’s primary motive and justification is to make a profit. Effective monitoring, enforcement, and social marketing of iodized salt will assist the serious partners in that regard, while poor enforcement will undercut the collaborating salt industries as non-iodizing competitors will sell 5-10% cheaper (or with a correspondingly larger profit) in the “large volume, small profit margin” salt business. Experience from Tanzania suggests that the institutional arrangements for monitoring need to be rearranged to give a clear and unified responsibility for monitoring of salt iodization to one body. Such unified responsibility for monitoring and management has been identified as an essential requirement in scaling up a project to a program (Greene & Kevany 1994).

Donors need to see the totality of their support, so as not to waste resources overall by attempting to make marginal savings, e.g. on distribution expenses for expensive medications. Similarly when partners agree to co-finance an intervention, provisions must be made to ensure that all necessary ingredients are actually supplied in adequate quality, such as in an arrangement where the donor buys the drug and the government foots the distribution bill. Competitive bidding needs to be used for purchase of inputs and researchers can facilitate this process by evaluating comparative efficacies between interventions, e.g. Chinese and French IOC, rather than merely continuing study the effect of giving different doses of one manufacturer’s product.

The other, equally important requirement is to set up procedures that are within the capacity of national agencies’ financial resources, especially with regards to recurrent costs (Greene & Kevany 1994). Small scale salt producers in Tanzania unable to sustain the cost of iodization machines, thus resorting to spraying and hand-mixing, is one example of inappropriate technology. Another is the inability to sustain factory monitoring of salt iodization in Tanzania in light of the excessive costs to transport officials from several ministries with considerable cost for per-diems for the necessary visits.
Continued modest donor funding also of recurrent costs for IDD control could indeed be justified as very cost-effective utilization of donor funds (World Bank 1993) and in line with what was done for immunization programs. However, if international organizations and donors are careful to support establishment of sustainable procedures in each setting and if appropriate advocacy is done, it could become a national priority to cover the recurrent costs of an IDD control program. At costs around 5-10 US cents per person per year salt iodization is arguably within reach of national resources, even on a 5 dollar per capita health budget. And provide "... the highest cost-effectiveness of any health intervention available in the world today" (World Bank 1993).
CONCLUSIONS

1. We found that studied parts of the Central African Republic are severely to moderately affected by IDD. Goitrogens from insufficient cassava-processing may have aggravated IDD in one area. Although promotion of effective cassava processing may be beneficial, such action should by no means delay the establishment of effective national iodine supplementation.

2. The urinary I/SCN ratio failed to identify the possible goitrogenic effect observed in our Central African study. Furthermore, the ratio was found to be mathematically ill-defined, it has physiological shortcomings, and suffers from seasonal variation. It is recommended to judge absolute urinary iodine and thiocyanate levels independently rather than using a ratio.

3. In IDD endemic areas not covered by iodized salt, iodized oil capsule distribution remains an important tool to achieve elimination of IDD, provided that high coverage is achieved. However, the overall coverage achieved in Tanzania was only 43% of the targeted population time. The attempt to integrate the IOC distribution into primary health care resulted in lower coverage than other strategies in Tanzania. The cost of the IOC constitutes more than 90% of program costs and significant savings can be made from reducing capsule waste. Available funds will be better used if distribution is focused on severely affected communities and a larger proportion of resources is allocated to social mobilization and organisation, labor, training, and supervision. These findings are of general relevance also for campaign distribution of other medications with long distribution intervals in low-income countries.

4. All the salt was iodized in a highland study community. However, the iodine concentrations varied greatly at retail level and indicated that factory quality control was insufficient or that losses of iodine during distribution had been larger than expected. The easily accessible and customarily evaluated school children showed adequate or even slightly high urinary iodine. However,
other vulnerable groups such as women at delivery and newborns showed signs of inadequate iodine status. Goiter regression may be delayed in all groups compared to normalization of thyroid hormone and urinary iodine levels. Local studies are necessary to adapt international recommendations on salt iodization levels to local circumstances. This will help avoid side effects of excess iodine intake such as hyperthyroidism, yet ensure adequate iodine intake in the population. It is recommended to monitor salt iodine concentrations at both production and distribution down to the household level, as well as to assess iodine status in all vulnerable groups as a basis for adapting international recommendations on new iodization levels at production.

5. The WHO 1994 goiter classification system with the 5% prevalence cut-off will due to its low specificity make demonstration of elimination of iodine deficiency by palpation impossible. This will require programs to invest in costly ultrasound equipment and training. However, ultrasound estimation also has considerable errors. Appropriately trained palpators using the 1960 Perez definition of goiter remains optimal for monitoring elimination of iodine deficiency in many resource-poor settings. We recommend a return to palpation with the Perez goiter criterion with a 10% acceptable prevalence for future goiter surveys in resource-poor countries.

6. Under the stewardship of ICCIDD, WHO and UNICEF iodine deficiency control programs across the globe have made remarkable progress over the last decade. They have benefited from large international support and used internationally recommended strategies. As these programs now enter their second cycle of implementation adjustments need to be made to each national context. Methodologies for assessing severity of iodine deficiency and setting up standardized control strategies have been successful. However, monitoring methodologies now need to be strengthened, especially with regards to sustaining and acting on ongoing process monitoring of the implementation. Starting from the salt production stage, monitoring needs to be institutionalized step by step. Appropriate sampling procedures need to be worked out. Once one step is successful monitoring of the next step needs to follow until there is indication of sufficient
implementation to warrant a more refined evaluation. Instituting a quality assurance process with a committed organization responsible for maintaining a management information system and acting on an ongoing monitoring is a top priority. Where iodized salt fails, iodized oil capsule distribution will need considerable strengthening to successfully control IDD through investments in the distribution and monitoring.

For impact evaluation there is need to refine international guidelines for aspects such as evidence based methodology for thyroid size estimation, and the relation of iodine status indicators in different vulnerable groups. In addition to production of these much needed practical guidelines and information materials from international organisations, key methodological developments also need to undergo the peer review process and be published in regular scientific journals.
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